Studies on Chiral Allenyl and Vinyl Anions

A Thesis submitted for the Degree of

Doctor of Philosophy

by

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in the

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of the

Department of Chemistry

at the

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To Mum and Dad

STATEMENT

The accompanying thesis submitted for the degree of Ph.D. entitled "Studies on Chiral Allenyl and Vinyl Anions" is based on work conducted by the author in the Department of Chemistry of the University of Leicester between the period October 1985 and September 1988.

All the work recorded in this thesis is original unless otherwise acknowledged in the text or by references. None of the work has been submitted for another degree in this or any other university.

Signed: ..... S. House ..... Date: .....10/6/89....

Part of this work has been published as a communication;

Asymmetric Induction in the Reaction of a Chiral Lithiated Sulphoxide and Aldehydes

S. House, P. R. Jenkins, J. Fawcett and D. R. Russell, J. Chem. Soc., Chem. Commun., 1987, 1844.

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Finally, I want to thank my mother and father and my four strapping brothers for their encouragement and unfaltering faith and confidence in me throughout my studies.

ABBREVIATIONS

m-CPBA	-	meta-chloroperbenzoic acid
de	-	diastereomeric excess
DIBAL-H	-	diisobutylaluminium hydride
DME	-	dimethoxyethane
DMF	-	dimethylformamide
DMSO	-	dimethylsulphoxide
ee	-	enantiomeric excess
g.l.c.	-	gas liquid chromatography
h.p.l.c.	-	high performance liquid chromatography
LDA	-	lithium diisopropylamide
NBS	-	N-bromosuccinimide
n.m.r.	-	nuclear magnetic resonance
TBAF	-	tert-butyl ammonium fluoride
THF	-	tetrahydrofuran
t.l.c.	-	thin layer chromatography

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CHAPTER 1

Introduction

1.1 ASYMMETRIC SYNTHESIS

Asymmetric reactions have proven to be of great synthetic value to the organic chemist, asymmetric carbon-carbon bond forming reactions, in particular, being important in the synthesis of a wide range of optically active compounds.[1] An asymmetric synthesis is one in which an achiral unit is converted into a chiral unit so that the stereomeric products are formed in unequal amounts; usually from a synthetic point of view, the more unequal the ratio of products formed, then the more useful is the reaction. Such asymmetric reactions can normally be rationalized in terms of steric and electronic interactions which stereochemically control the course of the reaction. The work detailed in the following chapters concentrates on the applications of chiral heteroatomic stabilized carbanions, in which the carbanionic centre is derived from an sp^2 hybridized carbon atom, to carbon-carbon bond formation in potential asymmetric syntheses.

1.2 α-HETEROATOMIC STABILIZED CARBANIONS[2]

The stability of a carbanion is directly related to the strength of its conjugate acid; the weaker the acid, the greater the base strength and the lower the stability of the carbanion. For simple hydrocarbons, acetylenic protons are more acidic than vinylic protons which, in turn, are more acidic than alkyl protons; this is a result of the carbanion stability.

$$RC\equiv\overset{\ominus}{C} > R_2C=\overset{\ominus}{C}H > R_3C-\overset{\ominus}{C}H_2$$

Stability of carbanions

The higher the s-character at the carbanionic centre ($sp > sp^2 > sp^3$), the closer are the electrons to the nucleus resulting in a lowering of their energy and hence greater stabilization of the carbanion. But

acetylenes, alkenes and alkanes are all relatively weak acids with pKa values of ca. 25, 44 and 50 respectively (cf. RCOOH, pKa 4-5). However, the relative kinetic and thermodynamic acidities of a compound can be enhanced by the introduction of a heteroatom α to the respective proton. This enhancement is due to an increase in the stability of the resulting carbanion by the inductive effect and, in the case of sulphur and phosphorus, an effect disputedly caused by $p\pi$-$d\pi$ bonding or by the polarizibility of the atom.

An illustration of the effect of different heteroatoms on the kinetic acidity of α-protons is shown in Table 1, where f is the ratio of the deuterium exchange rate for a given C-D bond in the compound compared with that for the C-D bond in benzene (i.e. the rate of dedeuteration of the compound with a deuterium atom previously introduced was determined).[3]

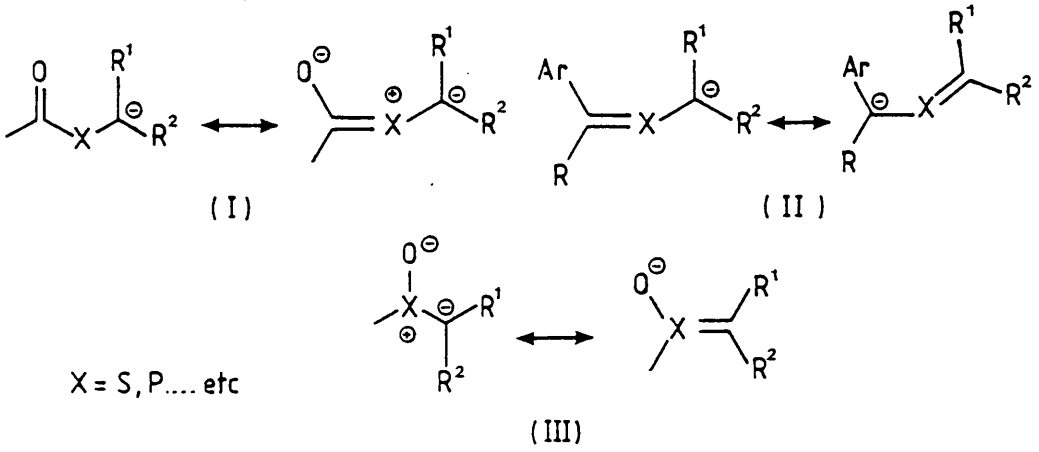
The ease of formation of the α-heterostabilized carbanion depends on the actual nature of the heteroatom moiety and the position the heteroatom occupies in a row and column of the Periodic Table. The formation is usually easier when the heteroatom is further to the right of a row and when the atom is in the third rather than second or fourth rows.

	f	f_{rel}
$C_6H_5SCH_3$	$1x10^6$	$2x10^8$
$C_6H_5SeCH_3$	$1x10^5$	$2x10^7$
$C_6H_5OCH_3$	0.22	$4x10^1$
$C_6H_5P(CH_3)_2$	140	$3x10^4$
$C_6H_5N(CH_3)_2$	0.005	1

TABLE 1

Modifications of the heteroatom leading to stabilization of the resulting carbanion include: the attachment of an electron-withdrawing group to the heteroatom; the presence of a charge-dipole interaction,

Fig. 1 (I); the ability to delocalize the negative charge, Fig. 1 (II); the heteroatom being a partially or fully charged heterocentre, e.g. phosphonyl, sulphinyl, Fig. 1 (III).



(I) (II) (III)

Fig. 1

The presence of alkyl groups attached to the carbanionic centre lowers the stabilization whilst the attachment of electron-withdrawing groups or the presence of a second heteroatom enhances the stabilization of the carbanion.

The relative inductive stabilizing effect of heteroatoms on carbanions is not in doubt, but the controversy between the $p\pi$-$d\pi$ orbital theory and the polarization theory to explain the difference in carbanion stabilization by heteroatoms lying in the same column of the Periodic Table has not been resolved. The "d-orbital" theory explains the higher acidity of compounds bearing heteroatoms possessing 3d or 4d unoccupied orbitals by the stabilization of the carbanion by delocalization of the charge in the relatively low-lying orbitals. This allows carbanion $2p\pi$-heteroatom $d\pi$ overlap which should be better with 3d than 4d orbitals, Fig. 2.

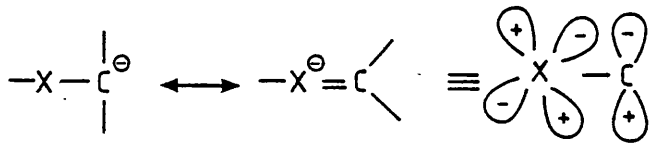


Fig. 2

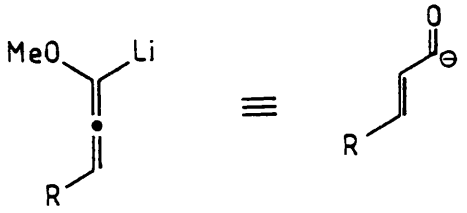
The "polarization theory" is mainly related to the results of theoretical calculations which stress the unimportance of $d\pi$-$p\pi$ overlap to explain the higher stabilization of carbanions bearing a heteroatom belonging to the second or third row of the Periodic Table. All theoretical results are explained in terms of the polarizibility of the heteroatom, a property related to the electronegativity and refractive index which measures the degree of diffusion of the carbanionic lone pair into the carbon framework. Analogous to the $d\pi$-$p\pi$ orbital theory, the polarization theory also explains the greater acidity of compounds in which the heteroatom belongs to the third row of the Periodic Table.

CHAPTER 2

Chiral α-Alkoxyallenyl Carbanions

2.1 INTRODUCTION

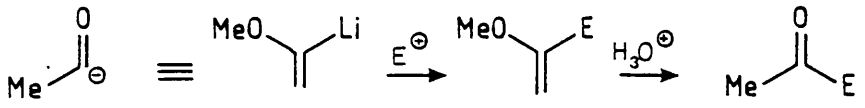
The importance of functionalizing aldehydes and ketones has led to the development of a range of synthetically equivalent reagents that enable the carbonyl group to be derivatized or elaborated at positions where the normal reactivity (polarity) is reversed (umpolung).[4] The use that α-lithio-α-methoxyallene (1) has seen in this respect, as an acrolein (R = H) or crotonaldehyde (R = CH_3) carbanion equivalent (2), led to considerations that development of an analogous reagent containing a chiral alkoxy group would lead to the preparation of optically active α-hydroxy-vinylketones.



(1) (2)

2.2 METHOXYVINYLLITHIUM AND ITS ANALOGUES

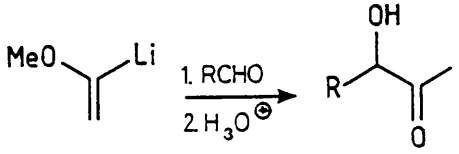
The use of methoxyvinyllithium (3) as a synthetic equivalent of the acyl carbanion (4)[5a] was reported by Baldwin et al.,[5b] in 1974. Reaction of (3) with electrophiles and subsequent acid hydrolysis of the product gave the corresponding carbonyl compounds in high yield, Scheme 1.



(4) (3)

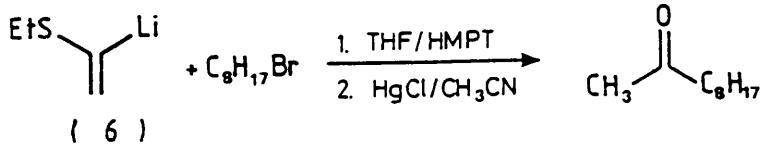
Scheme 1

The reaction of (3) with aldehydes and ketones gave α-ketols (5) after hydrolysis.

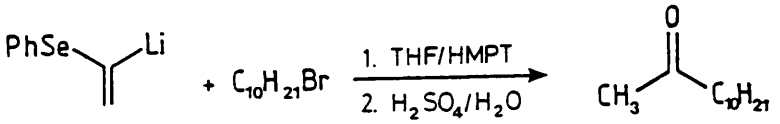


(3) (5)

The analogous thio- (6) and selenoethers (7) behave in a similar manner as masked acyl anion equivalents.[2]

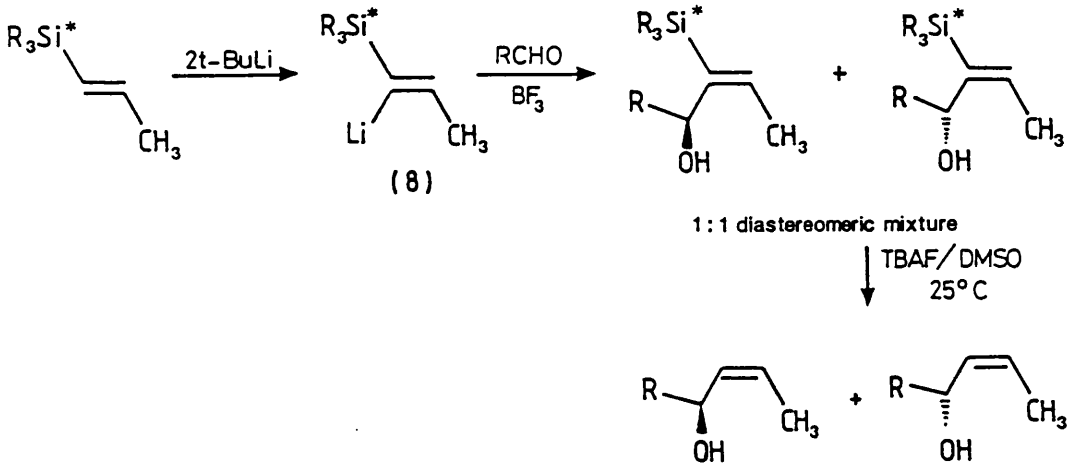


(6)



(7)

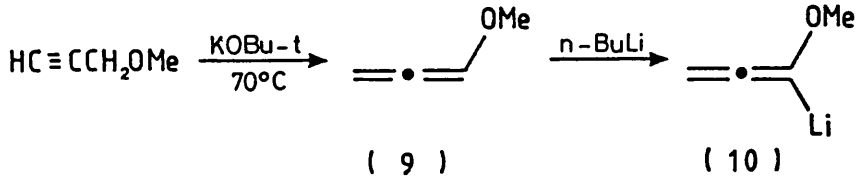
Recently a chiral silicon analogue (8) (where Si^* = chiral silicon centre and R_3 represents three different groups) of (3) was prepared by Torres et al.[6] and reacted with a range of aldehydes. Although the resulting diastereoisomers could be separated and the silicon moiety removed by protiodesilylation, the selectivity of the addition was poor, ca. 1:1, Scheme 2.



Scheme 2

2.3 METHOXYALLENE AND ITS USE IN SYNTHESIS

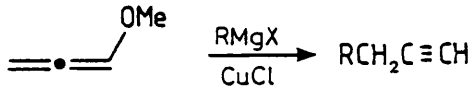
The preparation of methoxyallene (9) and the generation of its α-lithio-derivative (10) was first reported by Hoff et al.[7a] in 1968.



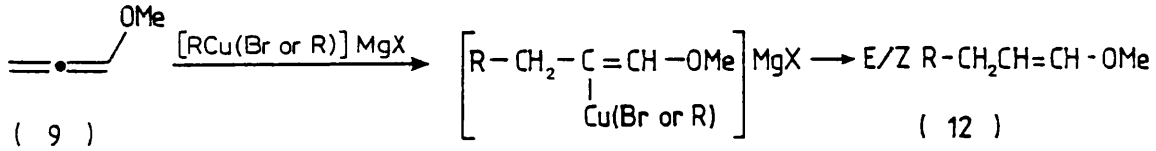
(9) (10)

In the following period the reactions of (9) and (10) were investigated and subsequently (10) has played a vital rôle in the synthesis of a number of natural products. (10) can be alkylated,[7] reacted with aldehydes and ketones[8] and further synthetically useful reactions of (10) are detailed in Scheme 3. Acid hydrolysis is the final step in many examples leading to the formation of the carbonyl compound; clearly in such cases (10) behaves as the carbanion equivalent (2).

Addition of Grignard reagents to methoxyallene in the presence of copper(I) halides yields the 1-alkyne[18] as the 1,3-substitution product (11) whilst the addition of organocopper reagents gives vinylic ethers (12).[19]



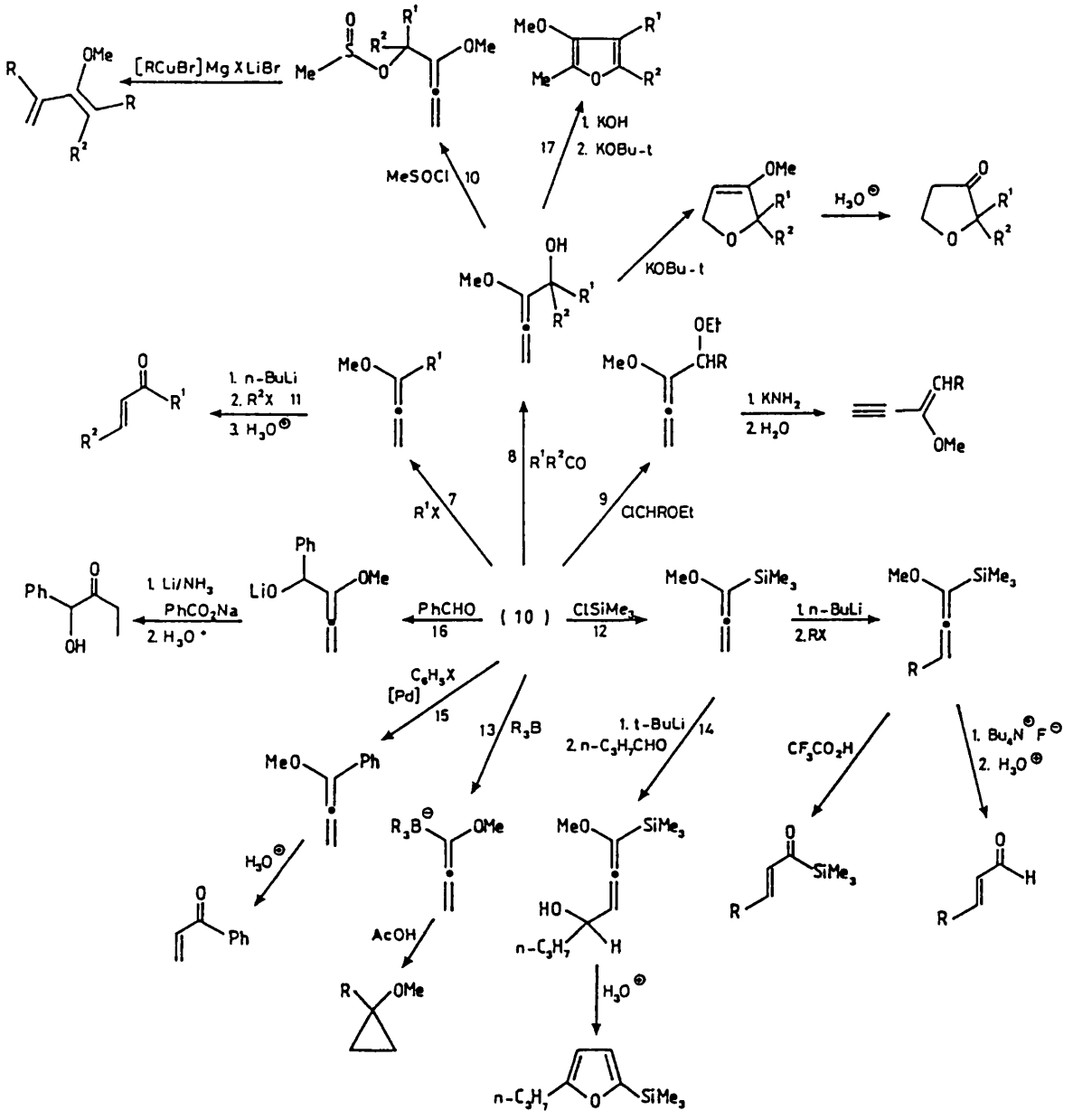
(9) (11)



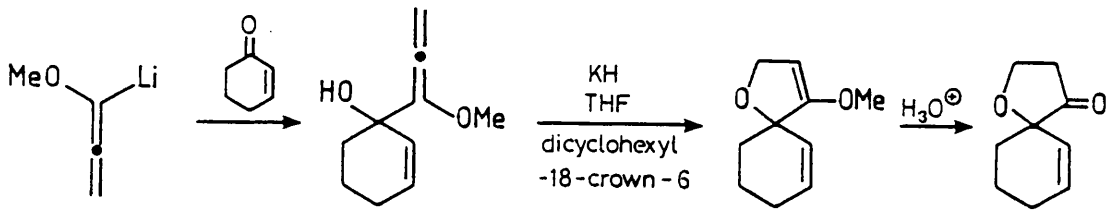
(9) (12)

(9) also participates in a Wittig-type reaction to yield either 1-methoxy-1,3-butadienes or on hydrolysis α,β-unsaturated aldehydes.[20a] An additional synthesis of butadienes was reported[20b] which involved isomerization of the alkylated methoxyallene to the conjugated diene using pyridinium p-toluenesulphonate in dichloromethane.

The participation of (10) in the synthesis of spirohydrofuran-3(2H)-ones, present in the muscarine alkaloids, was reported by Magnus.[21] The reaction of cyclohex-2-enone with (10) followed by cyclization and hydrolysis gave the spirohydrofuran-3(2H)-one (13) in 40% overall yield, Scheme 4.



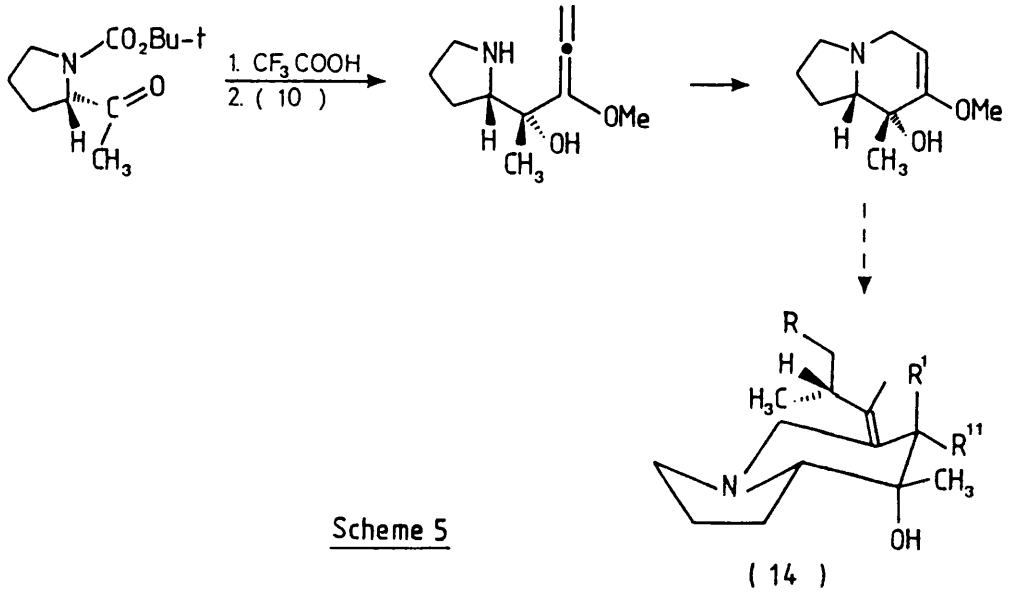
Scheme 3



(10) (13)

Scheme 4

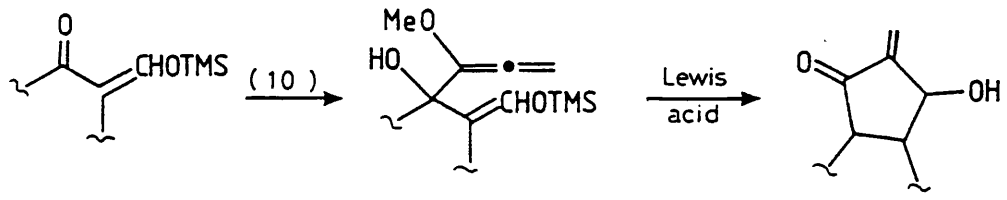
This strategy was extended to the synthesis of helixanes (polyoxa-polyspiroalkanones)[22] and was also used successfully in the synthetic approach to Bruceantin.[23] The use of (10) in the stereocontrolled synthesis of the allopumiliotoxin A alkaloids (14) was fundamental in the construction of the bicyclic ring system,[24] Scheme 5.



Scheme 5

(14)

The addition of (10) to a carbonyl group was used in the synthesis of a highly functionalized cyclopentenone via a cyclopentannelation, a reaction considered important in the synthesis of the methylenomycin series of compounds,[25] Scheme 6.



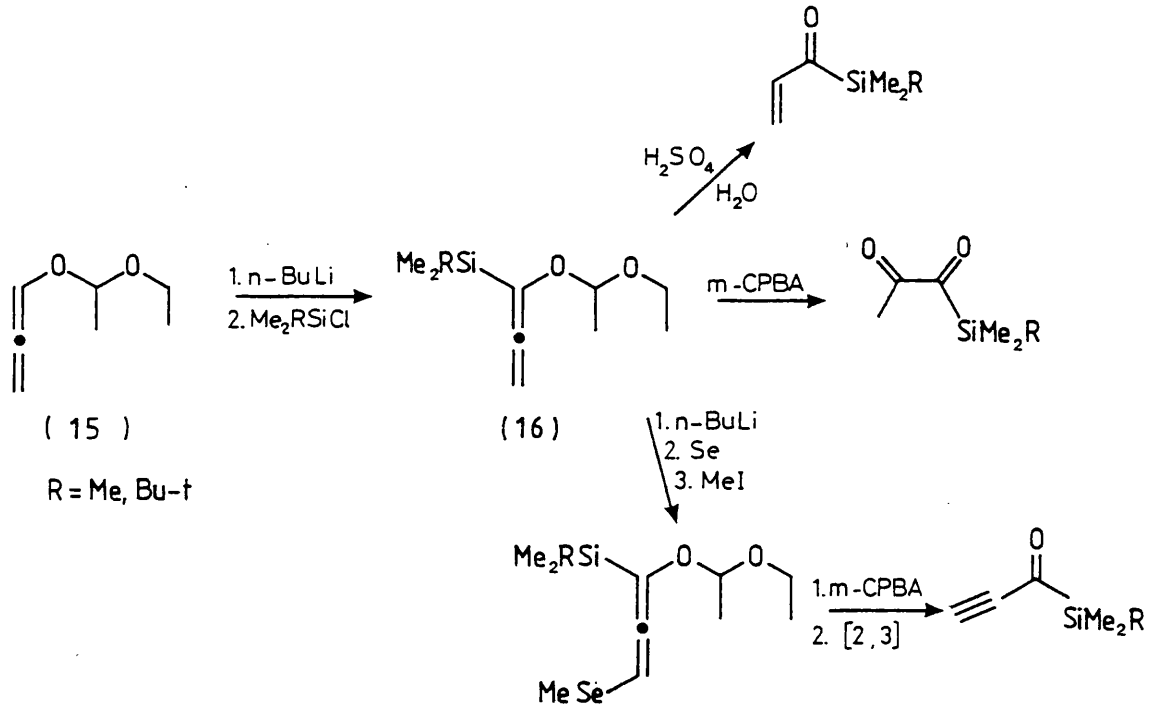
Scheme 6

Furthermore, the key intermediate in the synthetic approach to quassimarin via an intramolecular Diels-Alder reaction, reported by Shishido et al.,[26] was formed from the addition of (10) to an α,β-dialkoxy ketone.

2.4 OTHER ALLENYL ETHERS

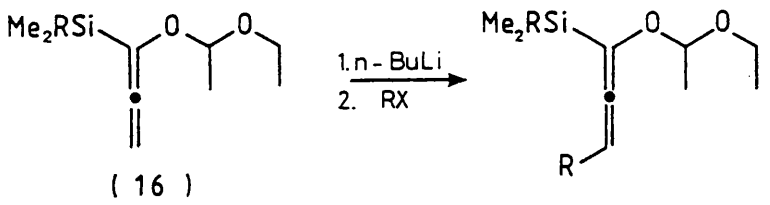
Based on the precedent set by the reactions of methoxyallene, other related allenyl ethers have been used as synthetic tools.

Reich et al.[27] used the ethoxyethyl allenyl ether (15) to prepare a variety of vinyl, ethynyl and acyl silyl ketones,[27a] Scheme 7.



Scheme 7

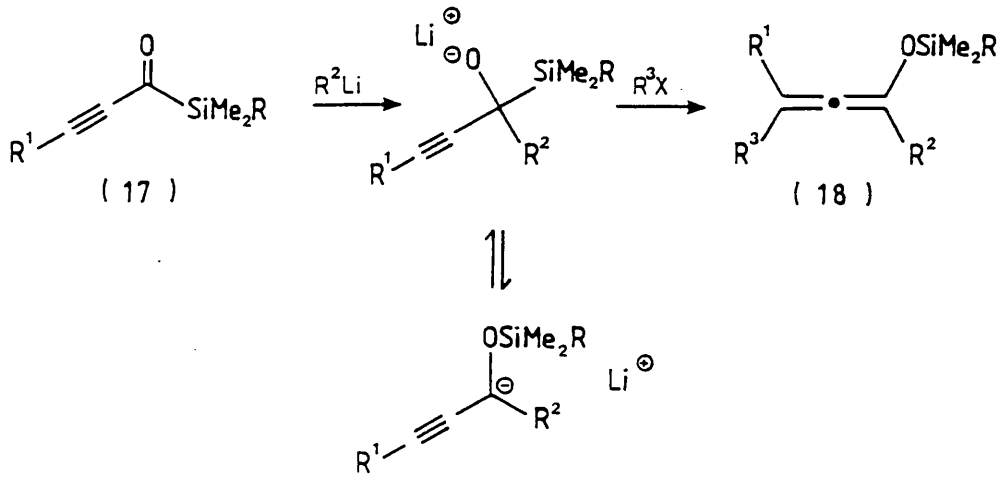
The preferred use of (15) aided isolation and purification, it being less volatile and less prone to polymerization than (9). The silylated allenyl ethers (16) could be stored for long periods at freezer temperatures under nitrogen provided a trace amount of radical inhibitor was present. Metallation and reaction of (16) with electrophiles gave a 1:1 mixture of diastereoisomers (chiral centre in ethoxyethyl group).



(16)

1 : 1 diastereomeric mixture

γ-Lithiated (16) also reacted with carbonyl compounds but gave adducts that were unstable and not easily convertible to silyl enones. The acetylenic silyl ketones (17) were subsequently converted to silyl allenyl ethers (18),[27b] Scheme 8.



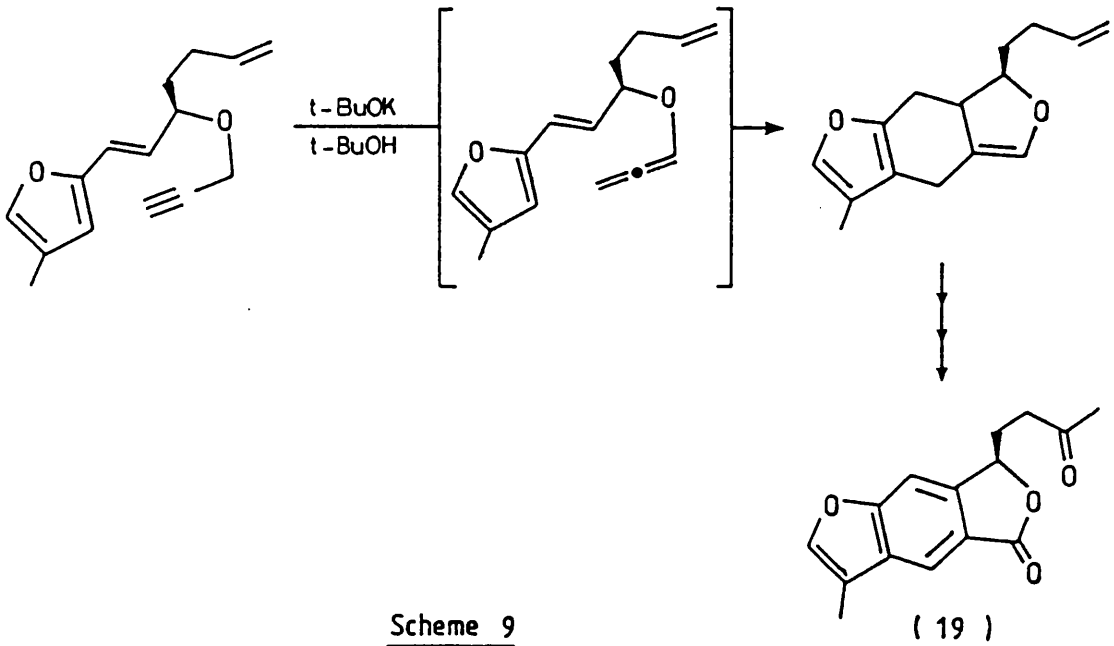
(17)

(18)

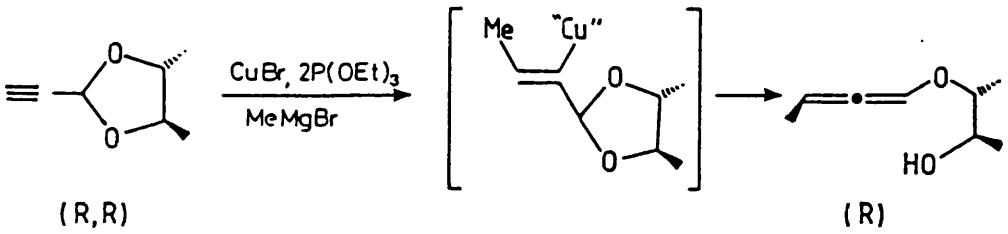
Scheme 8

The ethoxyethyl allenyl ether (15) was also utilized by Stork in the total synthesis of cytochalasins[28] and the analogous use of an alkoxy allene in an intramolecular cycloaddition was employed by Kanematsu et al.[29] in the total synthesis of a carbolactone system (19), Scheme 9.

Alexakis et al.[30] prepared a number of optically active alkoxy allenes, derived from chiral acetylenic acetals, by the diastereoselective β-elimination reaction of the transient organometallic species, Scheme 10.



Scheme 9 (19)



(R,R) (R)

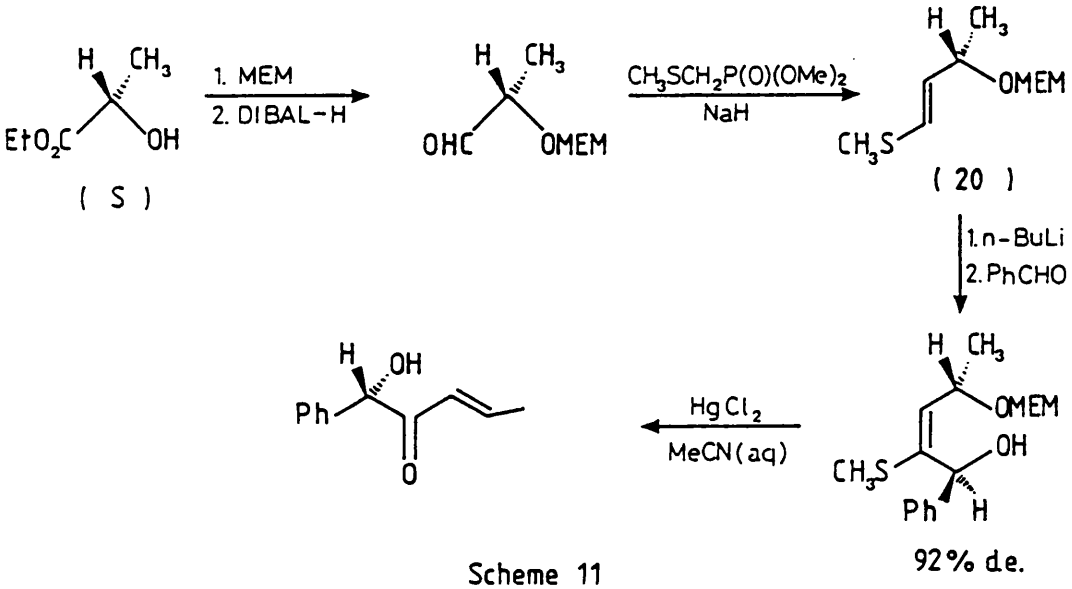
100% de 78%

Scheme 10

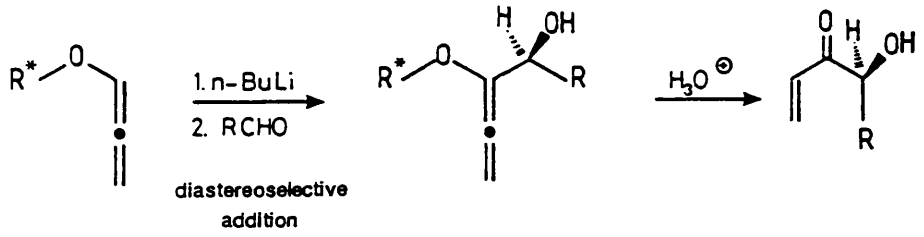
2.5 RESULTS AND DISCUSSION

Complementary to the work of Braun et al.[31] who reported the highly stereoselective addition of a crotonaldehyde synthon (20) to benzaldehyde, Scheme 11, the proposed use of a chiral α-lithiated α-alkoxyallene as an analogous synthon would provide the potential for similar methodology, Scheme 12.

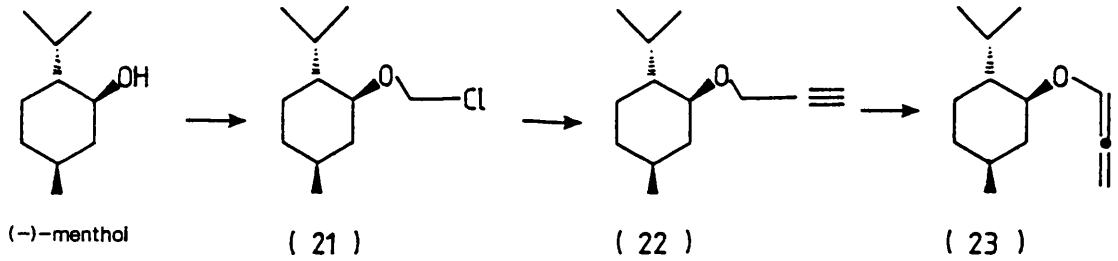
The initial objective was to use the method of Brandsma et al.[7a] to prepare a chiral alkoxyallene by isomerization of the corresponding propargyl ether. It was recognised that a chiral alcohol would provide access to the propargyl ether and (-)-menthol had all the prerequisites to be an ideal R* group (chiral auxiliary), Scheme 13.



Scheme 11

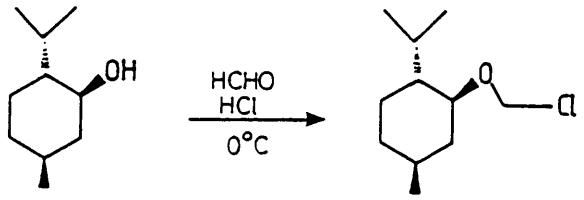


Scheme 12



Scheme 13

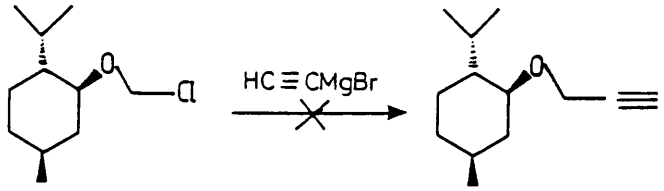
Dry hydrogen chloride gas was passed over a mixture of (-)-menthol and paraformaldehyde at 0°C for eight hours to give crude chloromenthoxymethane (21) as a colourless liquid in 61% yield.[7a] Although the ^{1}H n.m.r. spectrum and t.l.c. indicated the presence of menthol, the chloroether (21) was used crude in the next stage.



(21)

The chloromethylene protons were shown to be diastereotopic by the 300 MHz ^{1}H n.m.r. spectrum, the signal for each proton being a doublet (J = 12.5 Hz) at δ5.57 and δ5.59.

The attempted reaction of (21) with ethynyl magnesium chloride[32] failed to give the required product (22) with only the recovery of menthol.

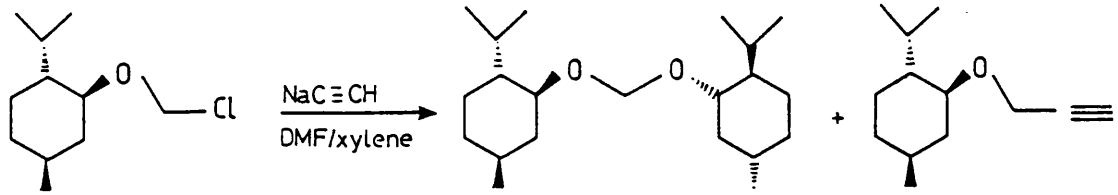


(21) (22)

The addition of sodium acetylide to (21) in a 1:1 DMF/xylene mixture gave a white solid whose t.l.c. showed a major component with a trace of a second product. After subjecting the crude sample to 5 mmHg pressure to remove volatile impurities, the presence of the minor product was no longer apparent by t.l.c. Initial thoughts that the white solid was the required product (22) were dispelled; although the 90 MHz ^{1}H n.m.r. spectrum was consistent with the solid being (22) with a singlet at δ4.85 for the acetylenic methylene protons, the integration for these protons was inconsistent with that of the rest of the spectrum. The fact that the integration was erroneous for the product being (22), that the 'apparent' acetylenic methylene protons were non-diastereotopic by 300 MHz ^{1}H n.m.r., that no signal for the terminal actylenic proton was seen (although it was possibly masked by the menthol ring protons) and that the mass spectrum gave a molecular ion (M^+) $^m/_z$ 324, suggested that

the white solid was a dimeric species.

Repeating the sodium acetylide addition but not subjecting the crude sample to 5 mmHg pressure, gave a solid whose 90 MHz ^{1}H n.m.r. spectrum was identical to before but with additional signals at δ4.2 (doublet) and at δ2.3 (triplet). The white solid was distilled to give a colourless oil in 12% yield whose spectral characteristics were consistent with it being (22) and a white distillation residue which after recrystallization from ethanol had the spectral characteristics of the dimer (24).



Major product

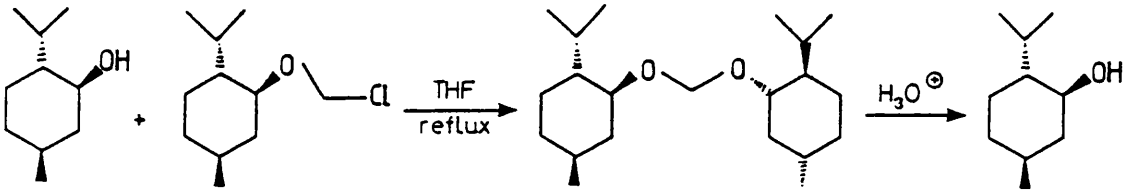
Minor product

(21) (24) (22)

In agreement with the literature,[33] the dioxymethylene protons of (24) appeared as a sharp singlet at δ4.81 in the ^{1}H n.m.r. spectrum, whilst the analogous methylene protons of (22) appeared as two identifiable doublet of doublets with J = 15.8 Hz and 2.4 Hz at δ4.14 and δ4.22. The terminal acetylenic proton was seen as a triplet at δ2.37 with J = 2.4 Hz.

Coupling of the chloroether (21) with (-)-menthol (present as the contaminant in the crude starting material) to give the dimer (24) was obviously assisted by the presence of the acetylide anion in deprotonating the alcohol. In fact, refluxing molar equivalents of (-)-menthol and (21) in THF overnight, gave the dimer (24) in 66% yield with spectral characteristics consistent with those obtained previously. Acid hydrolysis of (24) gave menthol as the expected product, Scheme 14.

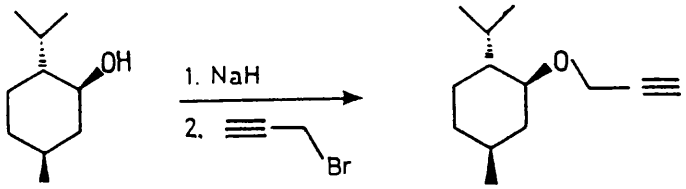
The unsatisfactorily low yield of (22) from the described method



(21) (24)

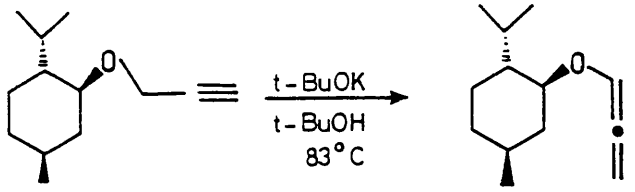
Scheme 14

above, prompted the search for a more efficient synthesis of the propargyl ether (22). Adaptation of a method used by Wilson and Cram[34] involving the addition of propargyl bromide to a solution of sodium menthoxide in DMF gave the required propargyl ether (22) in 47% yield after flash chromatography, with spectral data identical to that recorded for the ether prepared previously. [The oil obtained after purification by chromatography could be further purified by Kugelröhr distillation.]



(22)

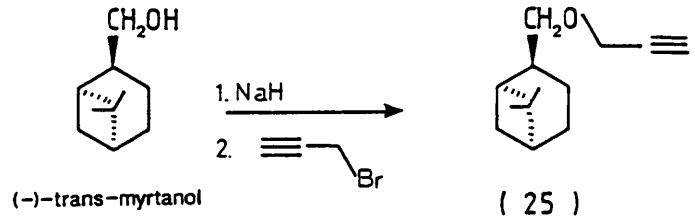
The isomerization of (22) to the allene (23) was achieved by heating a solution of the propargyl ether (22) in tert-butyl alcohol with a slight excess of freshly sublimed potassium tert-butoxide at 83°C for six hours; the allene was obtained in 74% yield. The 90 MHz ^{1}H n.m.r. spectrum showed the terminal allenyl protons as a doublet at δ5.35 (J = 6 Hz) and the allenyl proton adjacent to the menthoxy group as a triplet at δ6.55 (J = 6 Hz).



(22) (23)

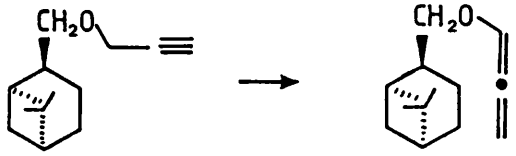
However, the crude allene could neither be purified by distillation nor silica gel flash chromatography, the latter technique causing significant decomposition of the product. In fact the allene (23) proved to be very unstable even at temperatures of -30°C overnight, when again decomposition was observed. Consequently the attempted lithiation and reaction of the lithiated derivative of (23) with electrophiles proved too difficult to control and monitor due to the instability of the menthoxyallene. In an attempt to improve the stability of the allene, it was decided to change the nature of the chiral group by using an alternative chiral alcohol. The primary alcohol (-)-trans-myrtanol was chosen as a suitable replacement although the ultimate generation of the new chiral centre would see it form one carbon more distant from the existing one in comparison with (-)-menthol, (1,5- cf. 1,4-asymmetric induction).

Alkylation, adopting the same procedure used for the alkylation of (-)-menthol by the addition of propargyl bromide to a solution of sodium myrtoxide in DMF, gave the corresponding propargyl ether (25) in 38% yield after distillation and flash chromatography.



(-)-trans-myrtanol (25)

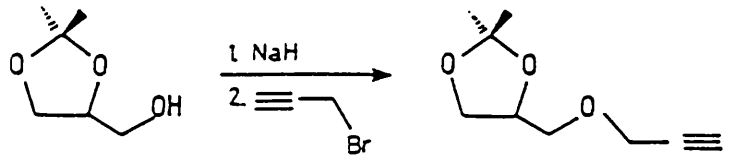
Isomerization of (25) to the allene (26) using potassium tert-butoxide in tert-butyl alcohol at 83°C gave the product in 83% yield.



(25) (26)

However, the frustratingly low stability of (26) to chromatographic purification techniques and distillation coupled with its high instability to storage made the attempts at lithiation using n-butyllithium in THF and DME and quenching with benzaldehyde and D_2O somewhat frivolous, decomposition products being the end result.

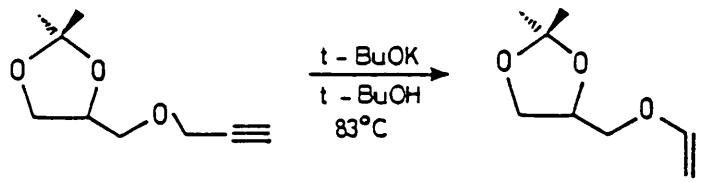
Without pursuing this apparent "lost case" any further a third chiral alcohol was alkylated via addition of propargyl bromide to its alkoxy anion in DMF. Hence racemic 1,2-O-isopropylidene-1,2,3-trihydroxypropane gave the corresponding propargyl ether (27) as a colourless oil in 45% yield, after distillation of the crude brown reaction mixture.



1,2-O-isopropylidine
1,2,3-trihydroxypropane

(27)

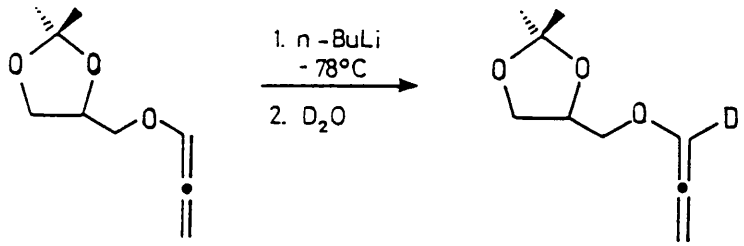
Isomerization to the allene (28) was achieved using the standard method of heating a solution of (27) in tert-butyl alcohol containing an excess of potassium tert-butoxide at 83°C until t.l.c. had indicated the complete disappearance of starting material. The allene was obtained in 56% yield as an oil.



(27) (28)

(28) proved to be of a higher stability than (23) or (26) prepared previously and was subjected to Kugelröhr distillation and flash chromatography with only a small amount of decomposition resulting.

Addition of n-butyllithium to a solution of (28) in THF at -78°C, gave a yellow solution which after ninety minutes at this temperature was quenched with a solution of D_2O in THF. The 90 MHz ^1H n.m.r. spectrum of the crude reaction mixture indicated that (28) had been successfully lithiated and deuterated giving (29); the doublet at δ5.45 and the triplet at δ6.75 were replaced by a singlet at δ5.45 with an integration for two protons.



(28) (29)

The stability of the α-lithioallene could be attributed to the chelating ability of one of the ring oxygen atoms giving rise to a stable chair-like structure, Fig. 3.

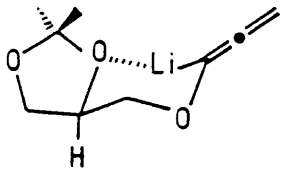
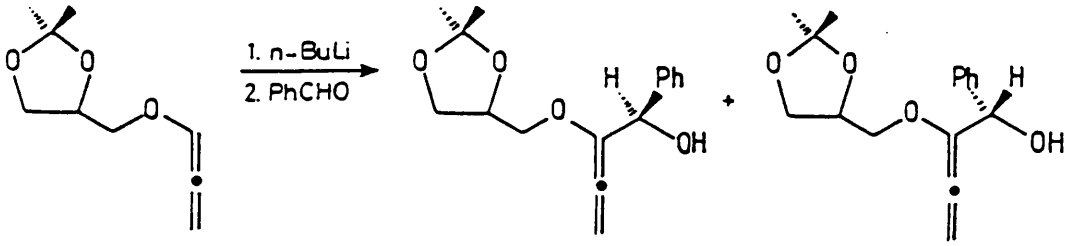


Fig. 3

Generation of the anion and quenching with benzaldehyde gave a reaction mixture whose t.l.c. indicated the presence of a trace of starting material but also a major product. Work-up afforded a crude reaction mixture which was purified by flash chromatography to give a mixture of the required diastereoisomers (30a) and (30b) in 72% overall yield. The pair of isomers was one spot by t.l.c. and consequently not separable. [A small amount of decomposition occurred during chromatographic purification and the mixture would not distil.]

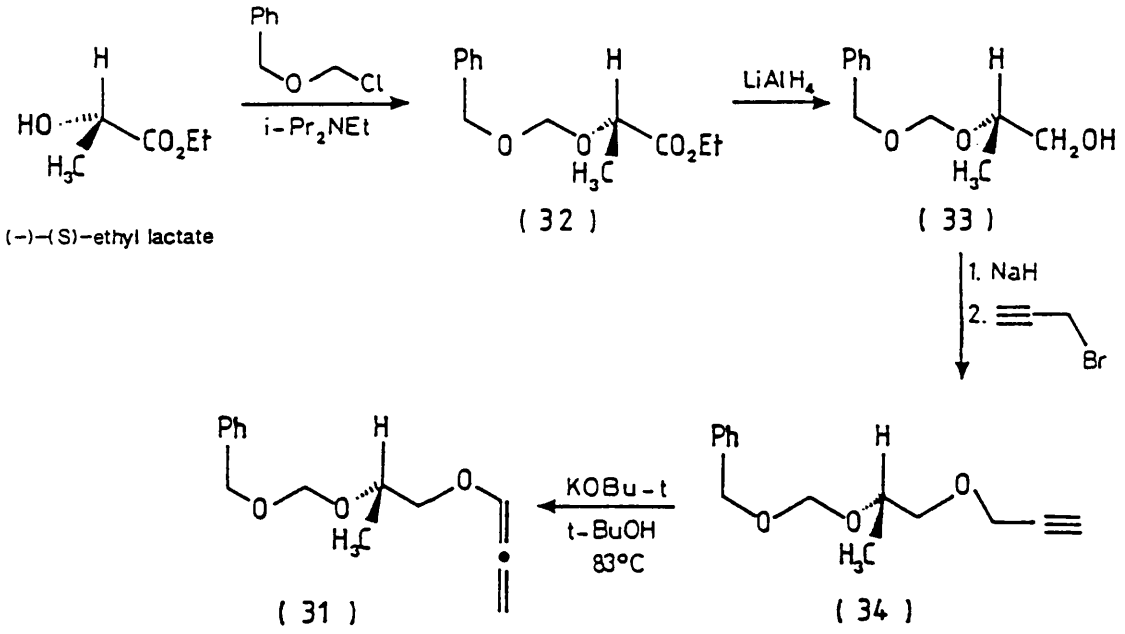
The crude reaction mixture had to be analysed immediately to



(28) (30a) (30b)

determine the diastereomeric ratio as decomposition of the products was dramatic even at -30°C overnight. By ^{13}C n.m.r., the diastereomeric ratio was measured at ca. 1:1; to confirm this measurement, a g.l.c. of the crude product was obtained but similar to the t.l.c., no separation of the isomers could be achieved.

The limited success of using (28) as an asymmetric precursor prompted the use of a similar oxygenated (-)-(S)-ethyl lactate derived alkoxyallene (31) prepared in the same manner as (28), Scheme 15.



Scheme 15

Yields of 65%, 77%, 47% and 80% were obtained for (32), (33), (34) and (31) respectively. The allene (31) again proved to be of reasonable stability although a small amount of decomposition occurred on the flash column during purification. Analogous to the oxygen chelated lithio-

structure, Fig. 3, a similar stabilized lithiospecies was postulated for α-lithio (31), Fig. 4.

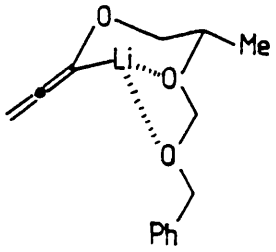


Fig. 4

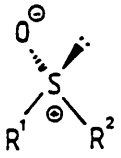
However, lithiation of (31) and quenching of the anion with benzaldehyde proved to be very frustrating with no evidence of diastereomeric products being obtained, only the isolation of decomposition products. In fact, attempted lithiation and reaction with methyl iodide failed to give the methylated product and it appeared that the formation/stability of the lithiated allene was the limiting factor.

CHAPTER 3

Chiral α-Sulphinylvinyl Carbanions

3.1 INTRODUCTION

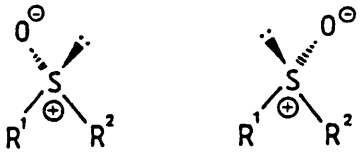
The synthetic utility of the chiral sulphoxide group (35a) in asymmetric reactions has received much attention over the last two decades.[35-40]



(35a)

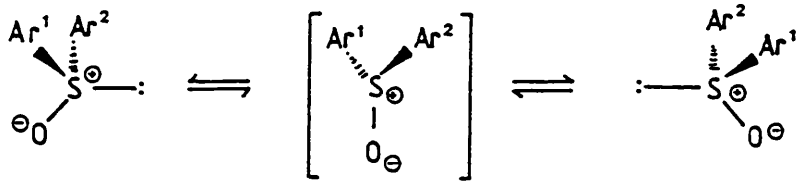
The chirality at the tri-coordinate sulphur atom arises, because the sulphur lone pair of electrons give it, its tetrahedral shape. The sulphinyl group is peculiar, with respect to other chiral groups, because of the very different stereoelectronic nature of the attached ligands; two alkyl/aryl groups, the oxygen atom and the lone pair of electrons.

The properties of the sulphoxide group are well documented.[35,41,42] At room temperature, the group does not undergo pyramidal inversion and it is because of this fact that enantiomeric sulphoxides exist, e.g. (35a) and (35b).



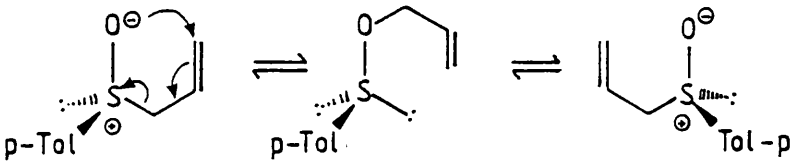
(35a) (35b)

Only at temperatures above 200°C does the optical stability waver. Diaryl and aryl methyl sulphoxides racemize at this temperature (in solvent) via a pyramidal inversion mechanism, Scheme 16.



Scheme 16

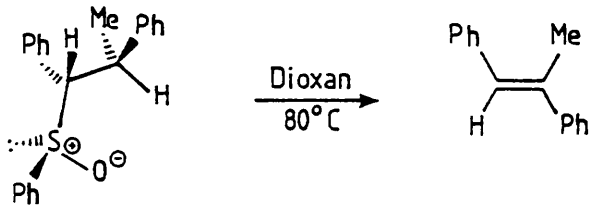
Benzylic sulphoxides racemize at temperatures of 130-150°C via a homolytic mechanism whilst allylic sulphoxides are prone to racemization relatively easily at 50-70°C via a [2,3] sigmatropic rearrangement,[35] Scheme 17.



Scheme 17

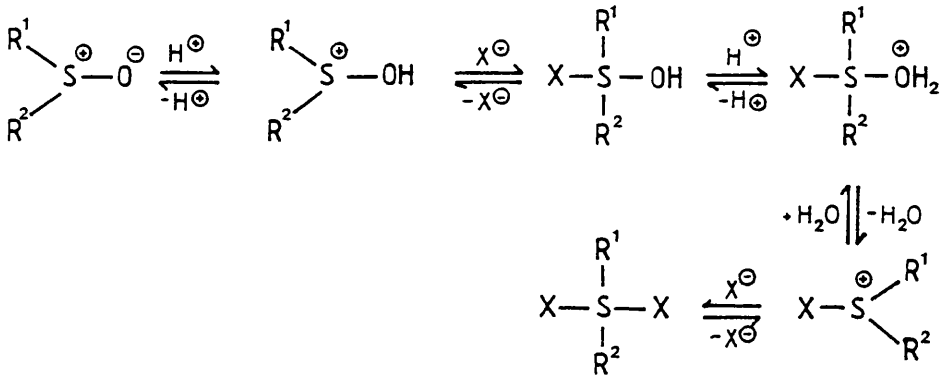
This allylic sulphoxide-sulphenate ester rearrangement tends to dominate much of the chemistry of the allylic sulphoxides.

In some instances, however, an elimination can occur at or below the racemization temperature. Alkyl sulphoxides containing a β-hydrogen atom usually undergo pyrolysis by a cis-elimination to give olefins, e.g. (36) to (37).[35]



(36) (37)

Racemization at sulphur can also be propagated by acid catalysis,[43] Scheme 18.



Scheme 18

Use is made of this acid catalysed racemization in the preparation

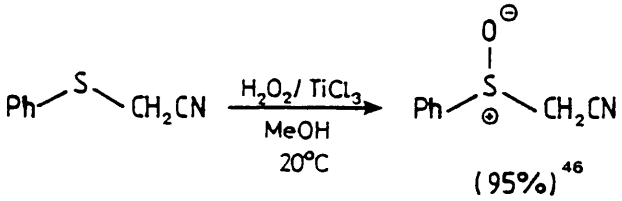
of certain diastereomerically pure sulphinate esters (see p.28). Basic conditions do not racemize sulphoxides but care must be taken when using certain organolithium reagents as group exchange can occur.[35,44] Photochemical racemization is also possible but is not usually a problem under normal conditions.[35]

3.2 PREPARATION OF OPTICALLY ACTIVE SULPHOXIDES

3.2.1 The Oxidation of Sulphides

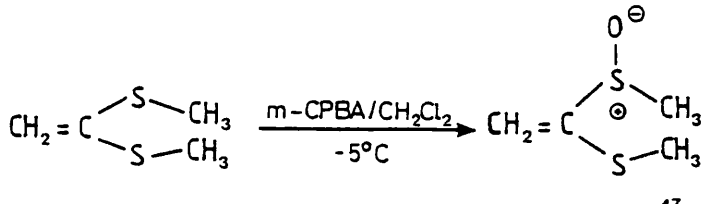
There are numerous methods for the oxidation of sulphides to sulphoxides.[45] In general, many of the classical methods give racemic sulphoxides and it is only recently that developments in the field of asymmetric oxidation have occurred.

Hydrogen peroxide, either alone or associated with various solvents or catalysts, is the commonest of the classical methods, although over-oxidation to the sulphone is not uncommon, e.g.



(95%)[46]

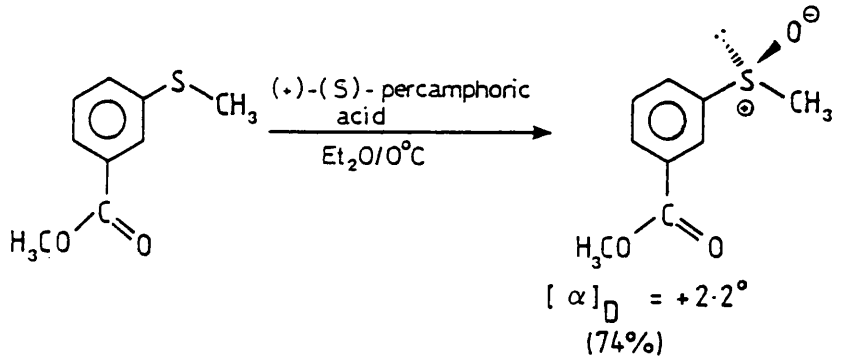
Other common oxidants include tert-butyl hydroperoxide, m-chloroperbenzoic acid (m-CPBA), sodium metaperiodate and a variety of other halogen containing oxidants including hypochlorites and bromites, e.g.



(85%)[47]

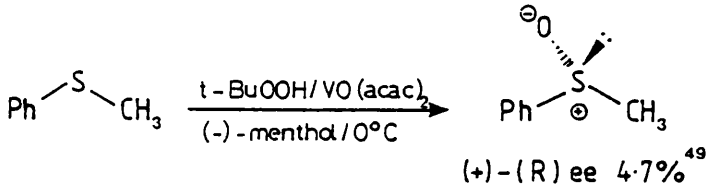
Asymmetric oxidations can be achieved by chemical or microbiological methods. The first example of a synthesis of an optically active

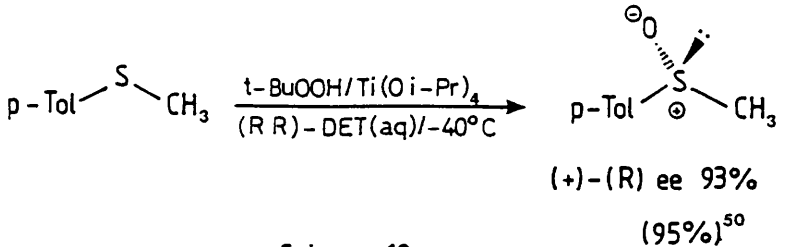
sulphoxide was reported by Balenovic et al.[48] in 1960, using (+)-(S)-percamphoric acid as the oxidant.



A variety of other chiral peracids were developed and used successfully, e.g. monoperglutaric acids, (+)-α-cyclohexyl perpropionic acid.[45]

Oxidation by tert-butyl hydroperoxide activated by a catalyst in a chiral solvent yields a mixture of chiral sulphoxides but the ee of the favoured sulphoxide is always small.[49] The induction is improved if the tert-butyl hydroperoxide is associated with titanium tetraisopropoxide in an aqueous solution of (R,R)-diethyl tartrate,[50] Scheme 19.

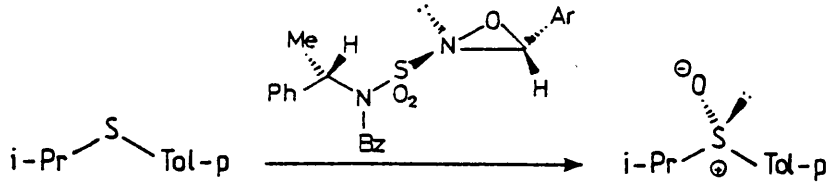




Scheme 19

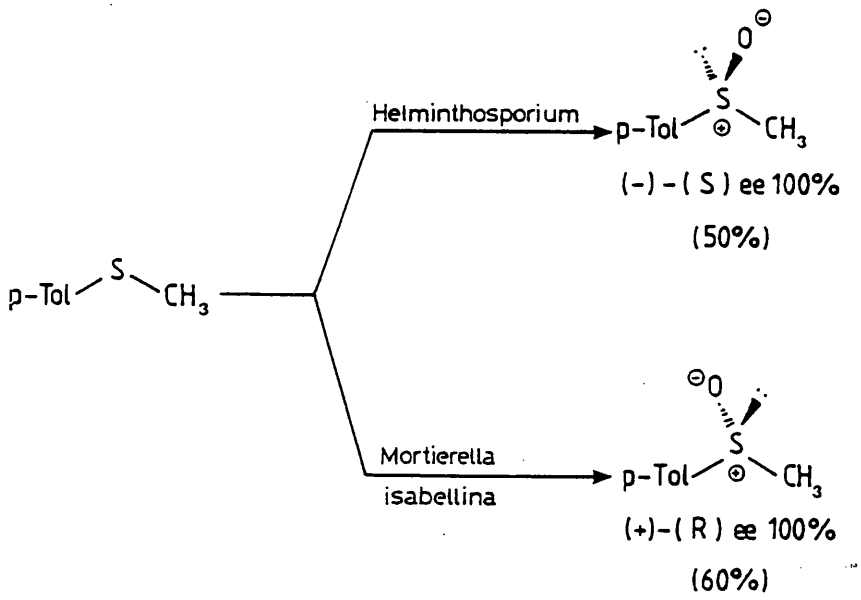
Other chemical methods include the use of 1-chlorobenzotriazole in (-)-menthol,[45] sodium metaperiodate on an alumina support or in the presence of bovine serum albumin[45] and of chiral derivatives of 2-sulphonyl and 2-sulphamyloxaziridines,[51] when the enantioselectivity is

dependent on the chiral oxaziridine used and the sulphide being oxidized, e.g.



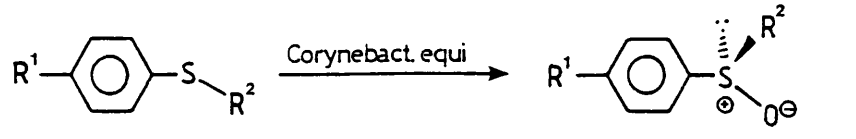
ee 65%
(90%)[51]

The use of microbiological oxidants produces the respective sulphoxides in a state of higher optical purity. Numerous strains of fungi have been developed and extensively used to perform a variety of sulphoxidations.[45] For example, the (R) and (S)-isomers of methyl p-tolyl sulphoxide can be isolated in 100% optical purity after microbiological oxidation using different fungi,[52] Scheme 20.



Scheme 20

More recently the use of Corynebacterium equi. as an oxidant has been reported.[53]

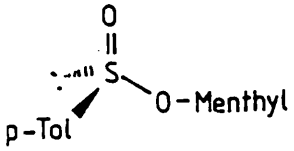


(+)-(R) ee 87-100%
(7-100%)

[For a more extensive summary of sulphide to sulphoxide oxidations, see Ref. 45.]

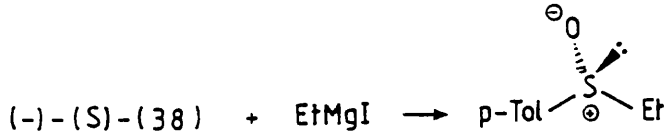
3.2.2 Nucleophilic Substitution at Sulphur

Nucleophilic substitution at sulphur, involving organometallic addition to optically pure tri-coordinate sulphur compounds, affords the most accessible route to optically active sulphoxides. The commonest sulphinyl containing precursors are the sulphinate esters, the first example of an optically active ester being reported by Phillips in 1925,[54] (-)-menthyl (S)-p-toluenesulphinate, (38).



(-)-(S)-(38)

However, it was not for thirty-six years that an optically active sulphinate ester was treated with a Grignard reagent to afford an optically active sulphoxide. Andersen[55] prepared (+)-(R)-ethyl p-tolyl sulphoxide (39) from the sulphinate ester (38) and ethyl Grignard.

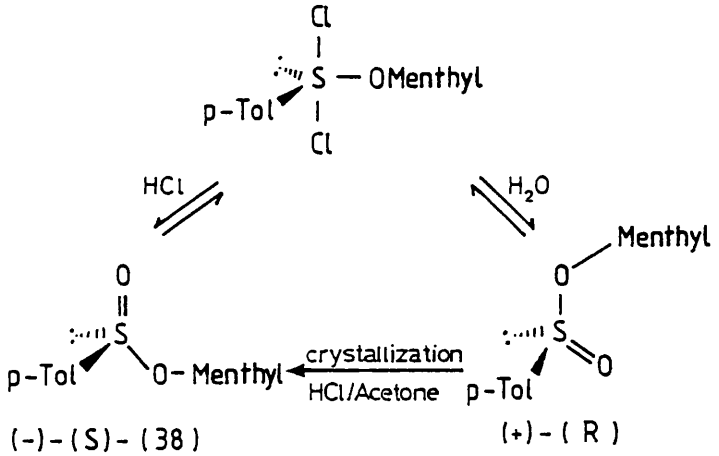


(+)-(R)-(39)

The Andersen synthesis was subsequently used fairly generally and underwent various adaptations to produce a variety of optically active sulphoxides.[35] The stereochemical course of the addition was also firmly established, there being an inversion of configuration at the sulphur atom.[56]

The sulphinate esters are usually the menthyl ones of arenesulphinic acids (particularly p-tolylsulphinic acid). The (S)-isomer is usually

crystalline and can be obtained in good to moderate yield from the reaction of the arenesulphinyl chloride and the appropriate alcohol followed by recrystallization from solvent containing a few drops of conc. hydrochloric acid. Because only the (S)-isomer is crystalline, this can be removed by filtration. Racemization at sulphur (the reaction shows no particular diastereoselectivity) is propagated by acid catalysis and hence redissolving the residue in acidic solvent causes more of the required isomer to crystallise out. In this way, a high yield of the (S)-isomer can be obtained, Scheme 21.

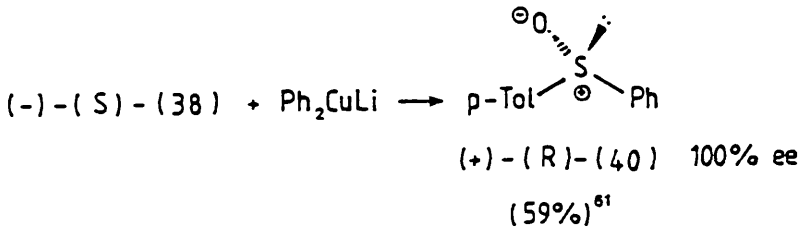


Scheme 21

A stumbling block of the Andersen synthesis is the inability to produce dialkyl sulphoxides from menthyl sulphinate esters because the diastereomeric menthyl alkanesulphinates are obtained as inseparable mixtures of oils. [Ridley and Smal[57] encountered similar problems when preparing sugar based sulphinate esters.] However, Andersen et al.[58] prepared a cholesteryl methane-equivalent of (38) where both isomers were crystalline and easily separable. Treatment with an alkyl Grignard gave the corresponding alkylmethyl sulphoxide of high optical purity. Dialkyl sulphoxides can also be prepared by the reaction of optically active aryl alkyl sulphoxides with alkyllithiums but this procedure can result in group exchange and/or racemization.[44]

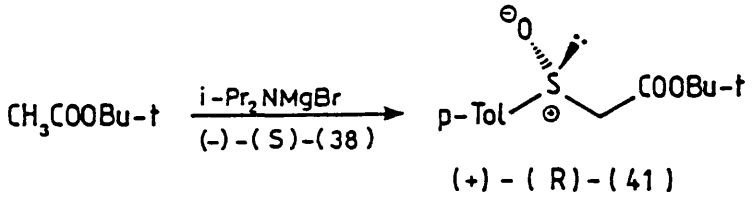
More recently the preparation of a variety of menthyl sulphinate esters from sulphonyl chlorides[59] and the enantioselective synthesis of alkyl tert-butylsulphinates from sulphites[60] have been described; both methods complementing the existing procedures but also opening routes to more varied optically active sulphoxides.

The classical Andersen synthesis used ether or THF as the solvent for the Grignard addition but Harpp et al.[61] found that under these conditions unacceptable amounts of the corresponding sulphides were formed. The alternative use of organocopper lithium reagents gave sulphoxides of high optical purity in moderate to good yields, e.g. the preparation of phenyl p-tolyl sulphoxide (40) from (38).

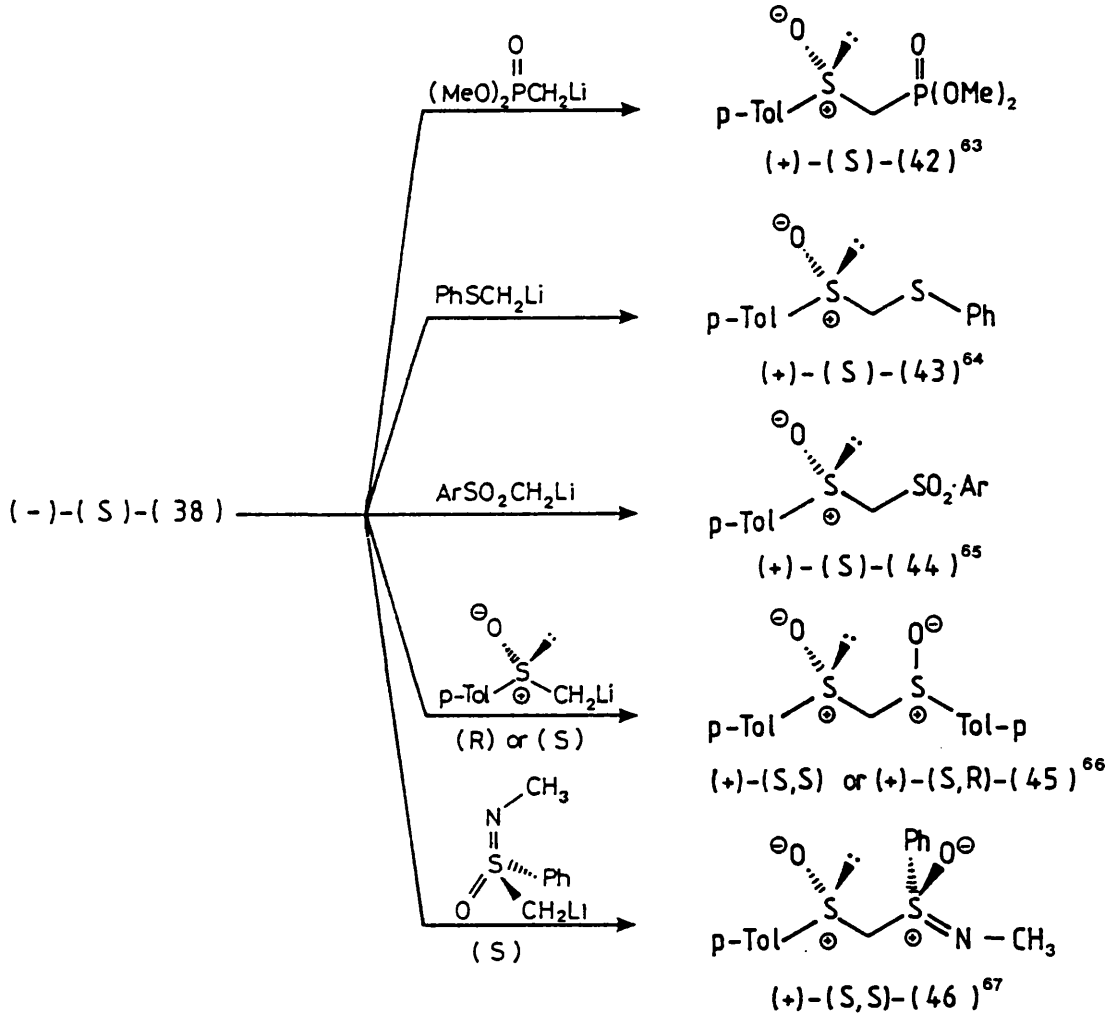


However, it was reported that the yields for the normal Andersen synthesis could be increased if the solvent for the addition was changed to benzene[62] [yield of (+)-(R) methyl p-tolyl sulphoxide (89.5% ee) increased from 55%[61] to 82%[62]].

Providing the sulphoxide with extra functionality has been achieved in a number of ways but all encompass nucleophilic substitution at sulphur. Hence addition of a mixture of tert-butyl acetate and (-)-(S)-(38) to a THF/ether solution of diisopropylamide magnesium bromide gave (+)-(R)-tert-butyl-p-toluenesulphinylacetate (41) in 90% yield.[35] The synthetic utility of (+)-(R)-(41) will be discussed later.

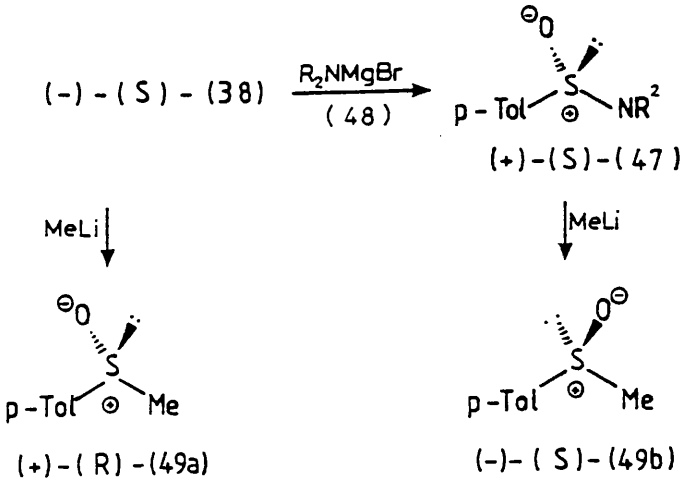


The nucleophilic addition to (-)-(S)-(38) by reagents other than Grignards has resulted in the formation of a variety of optically active sulphoxides with added functionality, Scheme 22.



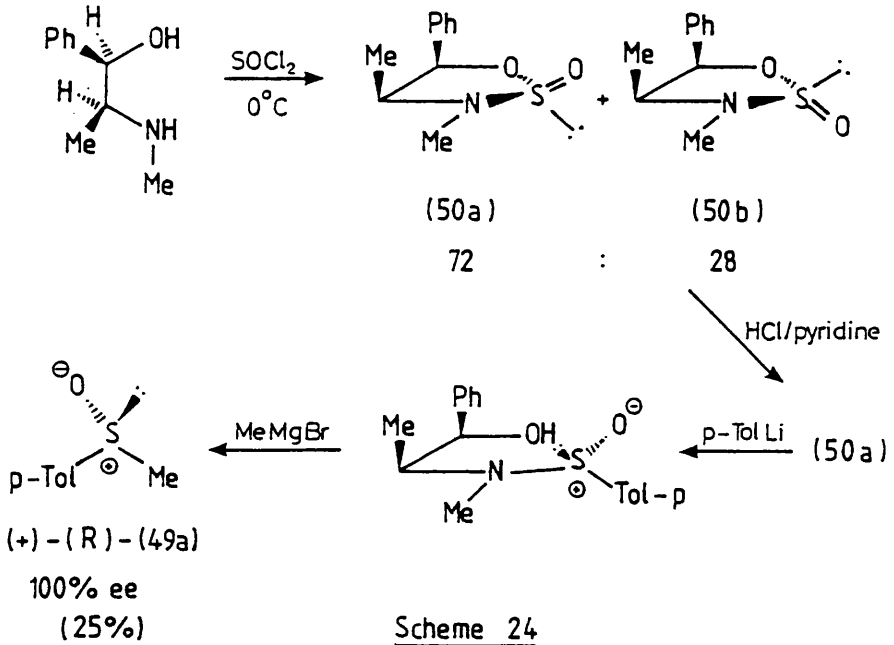
Scheme 22

Optically active sulphinamides (47) can be prepared by the reaction of (38) with the appropriate Grignard (48) and hence permits the preparation of enantiomeric sulphoxides (49) by subsequent reaction with methyllithium.[68] Although the sulphinamide (47) can be prepared optically pure, the sulphoxide obtained on reaction of (47) with methyllithium may not be so, due to possible racemization,[44] Scheme 23.



Scheme 23

An extension of this method was developed which used the chiral 1,2,3-oxathiazolidin-2-oxide (50),[69] Scheme 24.

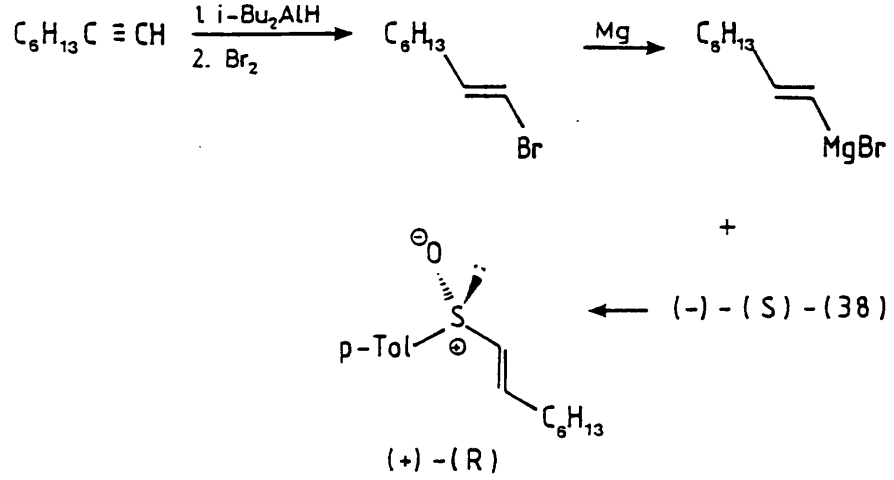


Scheme 24

Many of the methods used to prepare optically active diaryl, aryl/alkyl and dialkyl sulphoxides can similarly be used to prepare alkenyl sulphoxides.

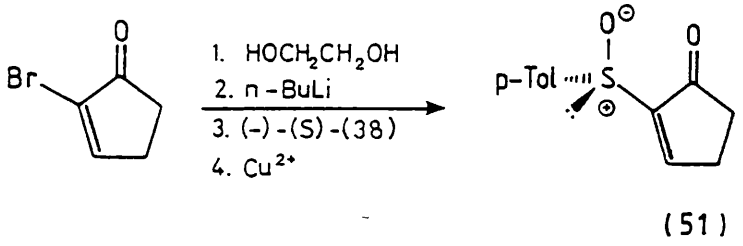
One of the early syntheses of a 1-alkenyl sulphoxide was by Stirling[70] who used the Andersen method of adding the appropriate vinyl Grignard to a solution of (-)-(S)-(38). Further examples were provided

by Stirling et al.,[71] a few years later, using similar methods. The stereocontrolled synthesis of (E)-1-alkenyl sulphoxides reported by Posner and Tang[72] provided these compounds in good yield, with negligible sulphide formation, and of high optical purity, Scheme 25.



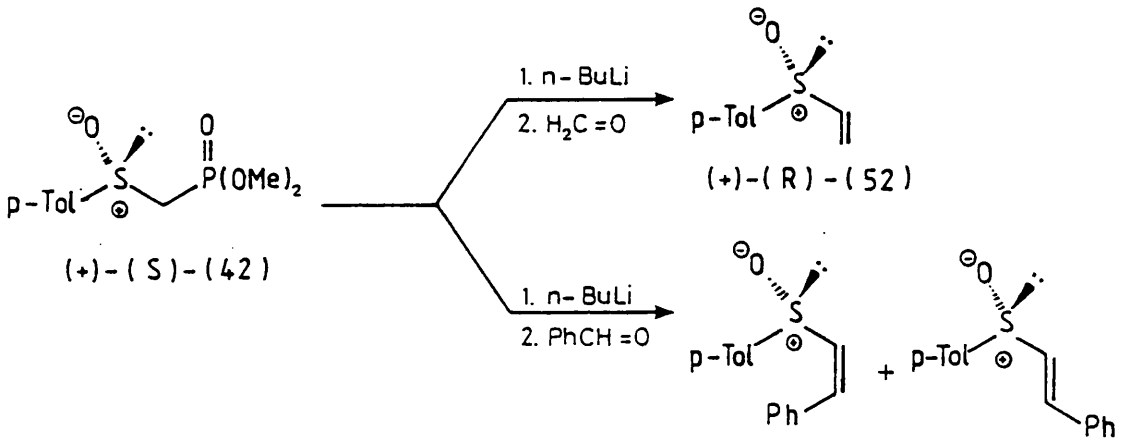
Scheme 25

Posner et al.[73] also reported the synthesis of (+)-(S)-2-(p-tolylsulphinyl)-2-cyclopentenone (51), a key compound in the chiral synthesis of natural products.



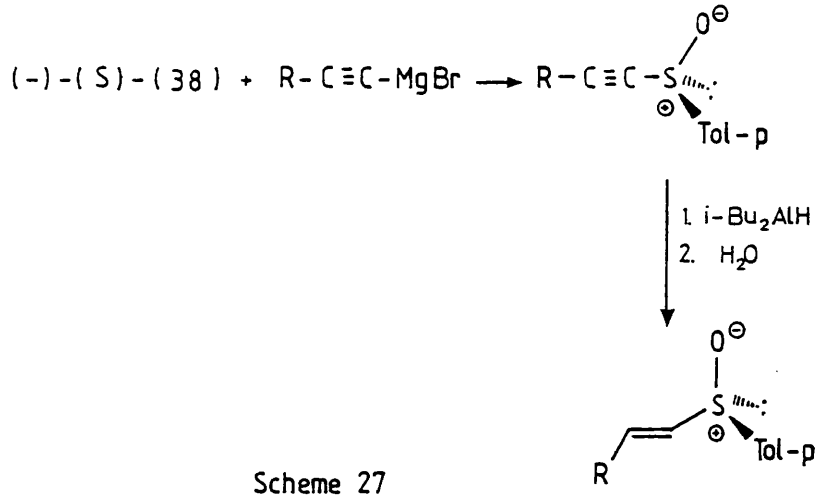
A different approach, by Mikolajczyk et al.,[63] utilized the compound (42) in the Horner-Wittig reaction, Scheme 26.

However, the reaction often gives mixtures of (E) and (Z)-isomers and sometimes results in the formation of unwanted allylic sulphoxides as by-products.



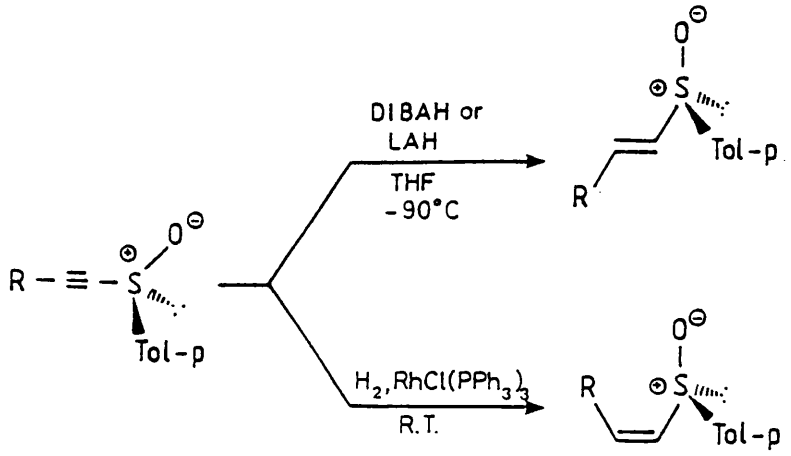
Scheme 26

Because of the difficulty in obtaining pure halovinyl compounds for use in the Andersen synthesis and because of the problems in controlling the (E)/(Z) isomer ratio in the Horner-Wittig reaction, Kosugi et al.[74] prepared (E)-1-alkenyl p-tolyl sulphoxides from the stereoselective hydro-alumination of 1-alkynyl p-tolyl sulphoxides, Scheme 27.



Scheme 27

Furthermore, Kosugi et al.[75] have extended the idea to produce both (E) and (Z)-isomers by selective reduction using different reagents, Scheme 28.



Scheme 28

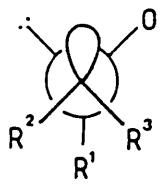
3.3 OPTICALLY ACTIVE α-SULPHINYL CARBANIONS IN ASYMMETRIC SYNTHESES

3.3.1 Introduction

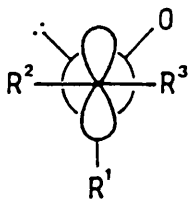
The formation of α-sulphinyl carbanions and their reaction with prochiral reagents can give rise to product(s) rich in one diastereoisomer. Because they can cause asymmetric induction in C-C bond formation and because the sulphinyl function is subsequently easily removed, α-sulphinyl carbanions have become versatile reagents for the asymmetric synthesis of many naturally occurring products.

The stereochemical course by which an electrophile becomes attached to the α-carbon atom of α-lithiosulphinyl carbanions depends in a complex way on the choice of solvent, nature and origin of the initial lithiating agent, the presence of added lithium salts and of complexing agents and the nature of the quenching reaction. Despite this complex situation, the trapping of α-sulphinyl carbanions in a stereochemical manner is often very useful synthetically.

Although the carbanions retain their chirality, the conformation of the α-lithio species has been subject to debate - whether they are pyramidal (54) or planar (55), the unsymmetrical nature of the carbanion is not in doubt.



(54)



(55)

3.3.2 Stereochemistry of α-Sulphinyl Carbanions

The chiral sulphinyl function attached directly to the carbanionic centre gives α-sulphinyl carbanions their diastereomeric character, a property highlighted by the different relative rate of H/D exchange of the two methylene protons of benzyl methyl sulphoxide with D_2O/NaOH.[35] The relative ease of H/D exchange of these methylene protons is influenced markedly by the nature of the base and the solvent and because of the theoretical interest this topic has aroused, there have been a large number of studies on the stereochemistry of α-sulphinyl carbanions.[35]

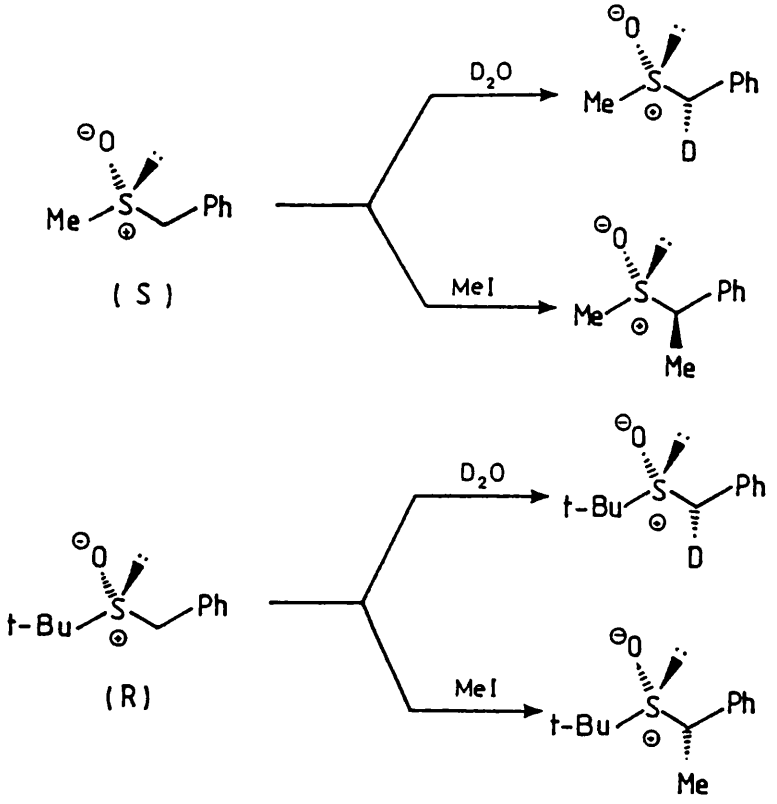
Table 2 shows the reaction of four different α-lithiosulphoxides with a range of electrophiles. Although the stereochemistry is depend-

Lithiosulphoxide	Electrophile	Yield (%)	Diastereomeric ratio
$PhCH(Li)S(O)CH_3$	D_2O	85	15:1
	Acetone	75	15:1
	Cyclohexanone	72	15:1
	Methyl iodide	76	15:1
$PhCH(Li)S(O)Bu\text{-}t$	D_2O	90	99:1
	Acetone	77	99:1
	Methyl iodide	95	99:1
$PhCH(Li)S(O)Ph$	D_2O	80	1.5:1
	Cyclohexanone	85	1.5:1
	Methyl iodide	79	1.5:1
$CH_3CH(Li)S(O)Ph$	Acetone	81	13:1
	Benzophenone	73	12:2

TABLE 2

ent on the substituent at the sulphinyl function, the diastereomeric ratio remains the same regardless of the electrophile used for quenching each carbanion.

However, it was concluded that the absolute configuration at the carbon atom of the major diastereoisomer changed with the electrophile; retention of configuration when carbonylated or deuteriated but inversion of configuration on methylation.[35] But more recently Itaka et al.[76] found, using neutron diffraction crystallography, that the absolute configuration of monodeuteriated benzyl tert-butyl sulphoxide had been erroneously assigned in the earlier work and further confirmation by Ohno et al.[77] pointed to the fact that the stereochemical pathways for deuteriation and methylation of the tert-butyl sulphoxide are the same. However, there remains no convincing rationale for the origin of the stereoselectivity or for the difference between the methyl and tert-butyl series, Scheme 29.

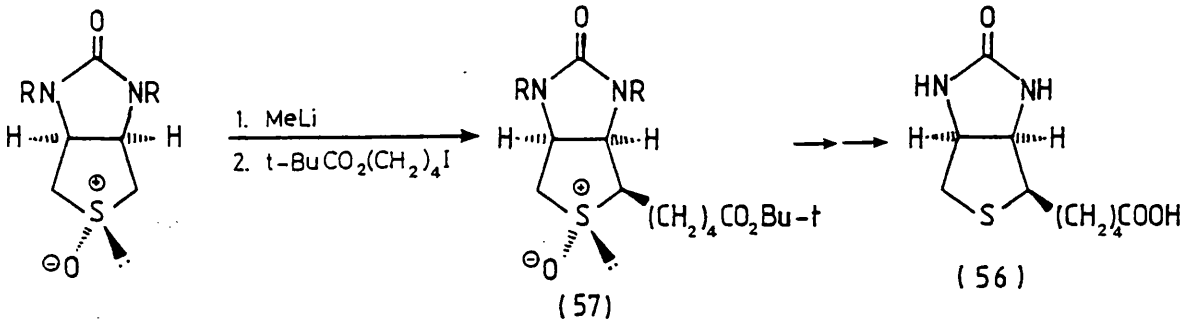


Scheme 29

3.3.3 Alkylation

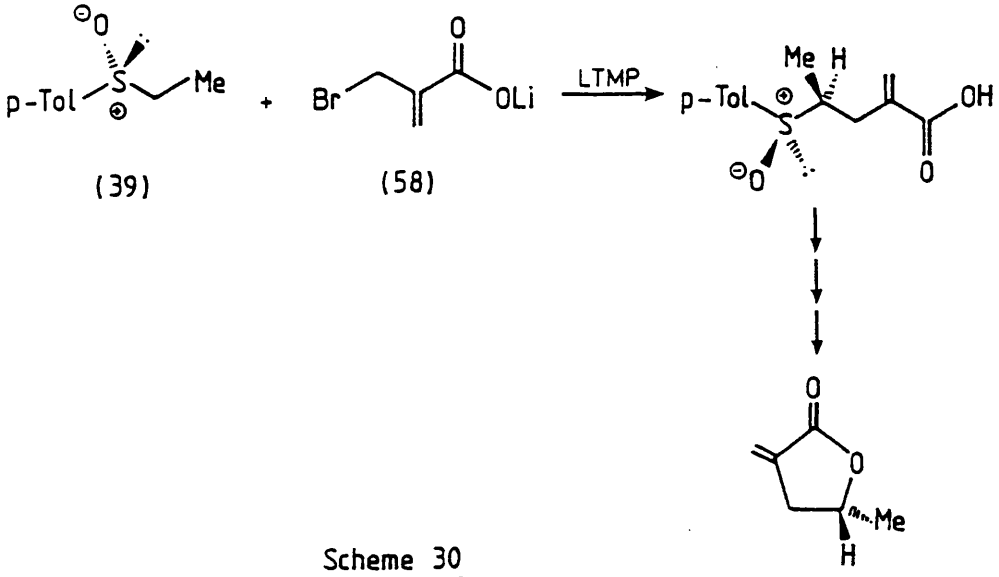
α-Sulphinyl carbanions are readily alkylated by a variety of electrophiles.

An interesting application was reported by Marquet et al.[78] in the total synthesis of (±)-biotin (56). The carbanion was alkylated with tert-butyl ω-iodovalerate to give a single isomer (57). It was found that the choice of base and solvent was crucial for the alkylation yield.



(57) (56)

More recently a high degree of diastereoselection (90%) was achieved when quenching (+)-(R)-ethyl p-tolyl sulphoxide (39) with lithium α-bromomethyl acrylate (58) using lithium tetramethylpiperidine (LTMP) as the base,[79] Scheme 30.

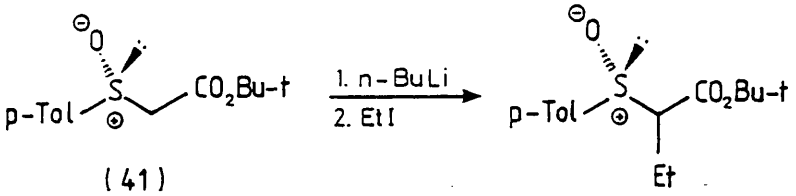


(39) (58)

Scheme 30

In contrast to the highly stereospecific behaviour of the methylene

protons of benzyl methyl sulphoxide, the reactivity of the analogous protons in arylsulphinyl acetates was found to be comparable. Solladié et al.[80] reported that the alkylation of (+)-(R)-tert-butyl-p-toluene-sulphinyl acetate (41) with methyl iodide, ethyl iodide or benzyl bromide using n- or t-butyllithium as base proceeded with poor diastereoselectivity (best diastereomeric ratio, 3:2 for quenching with ethyl iodide).



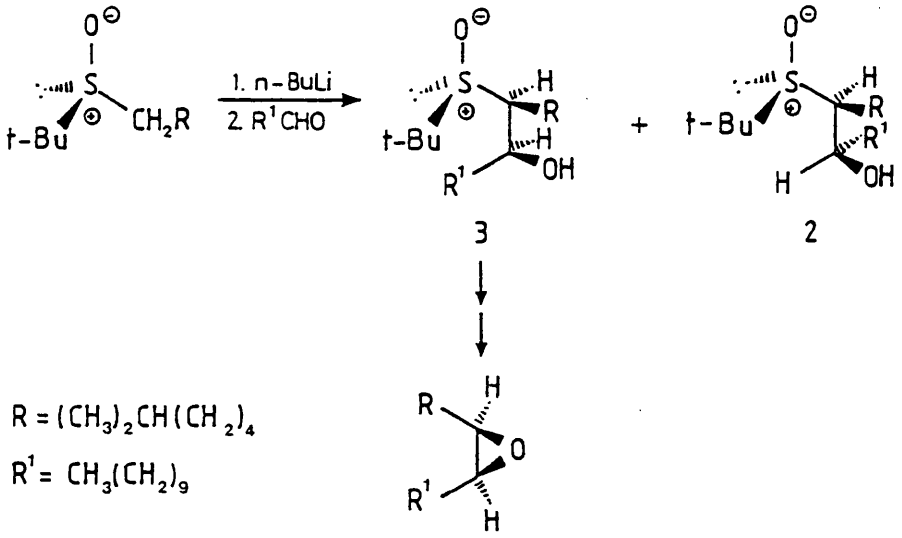
(41)

3 : 2 ratio

3.3.4 Addition to Carbonyl Compounds

α-Sulphinyl carbanions undergo an aldol-type condensation with carbonyl compounds affording β-hydroxyalkyl sulphoxides. The first reports of asymmetric reactions were not impressive; Johnson and Schroek[81] reported the addition of carbanionic (+)-(S) methyl n-butyl sulphoxide to benzaldehyde and fractional crystallization of the major isomer, but no indication of diastereoselectivity was given. Tsuchihashi et al.[82a] reported that the additions proceeded with poor stereoselectivity, a result confirmed by Kunieda et al.[82b] Kingsbury[83] quenched anionic racemic benzyl phenyl sulphoxide with benzaldehyde and obtained the four diastereomeric products in 40% overall yield and in a ratio of 41:19:8:32 as measured from the relative yields. Despite the low selectivity of the additions, the condensation of optically active alkyl tert-butyl sulphoxides with aldehydes, which gave the major pair of diastereoisomers in a ratio of 3:2, was used in the stereospecific synthesis of optically active oxiranes, among them the sex-attractant

(+)-disparlure (59),[84] Scheme 31.

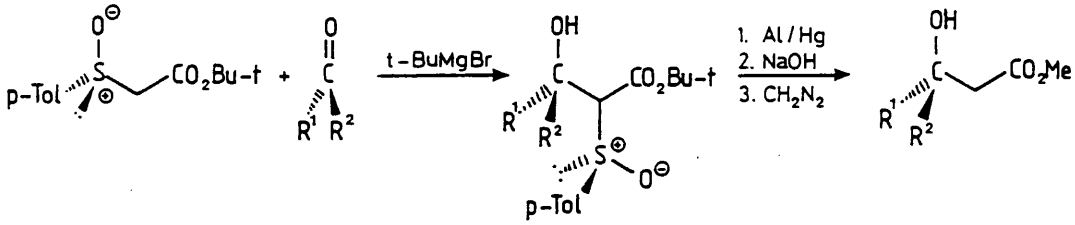


(59)

Scheme 31

The number of asymmetric syntheses of this type, however, has increased somewhat over the last few years, resulting in the formation of synthetically useful intermediates.

(+)-(R)-tert-Butyl-p-toluenesulphinyl acetate (41), in the presence of base, reacts with prochiral carbonyls with varying degrees of asymmetric induction depending on the nature of the substituents at the carbonyl group,[85] Scheme 32.



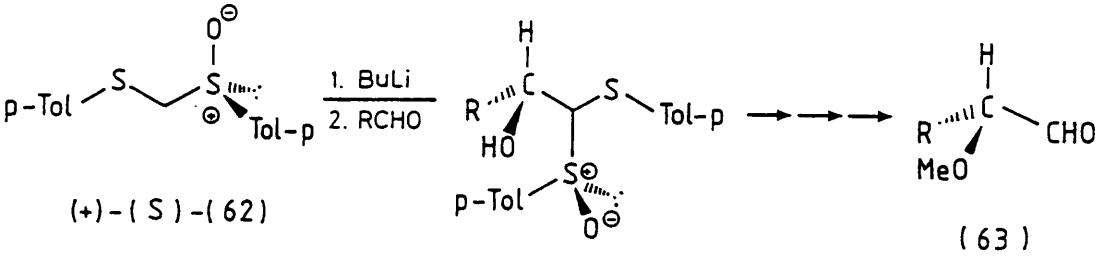
(41) (60) (61)

R¹	R²	Yield (60)	ee (%) (61)
H	Ph	85	91
Me	Ph	75	68
Ph	CF_3	75	20
H	n-C_7H_{15}	80	86
Me	cyclohexyl	88	95

Scheme 32

This method of introducing chirality has been applied successfully to the synthesis of optically active lactones,[86a] in the total synthesis of maytansine[86b] and in the synthesis of chiral α-hydroxyalkyl acrylates.[86c]

The acidity of the methylene protons α to the sulphinyl group is increased by the presence of a second sulphur substituent β to the original sulphur containing moiety. The reaction of carbanionic (+)-(S)-p-tolyl p-tolylthiomethyl sulphoxide (62) with benzaldehyde and phenylacetaldehyde gave (after methylation, reduction and hydrolysis) the corresponding α-methoxy aldehydes (63) in 70 and 46% ee respectively,[87] Scheme 33.

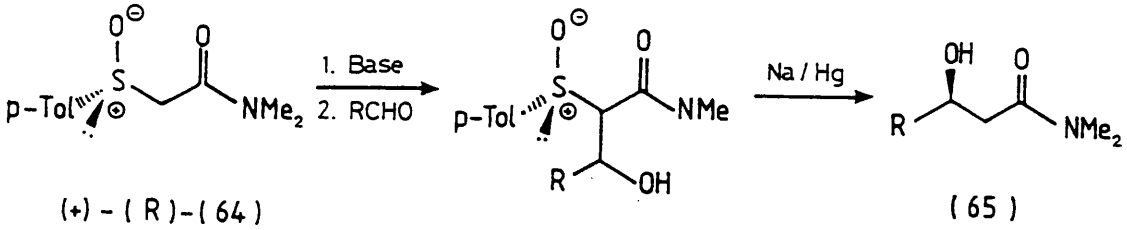


(+)-(S)-(62) (63)

R = Ph, $PhCH_2$

Scheme 33

The reaction of the lithium enolate of (+)-(R)-p-tolylsulphinyl-N,N-dimethylacetamide (64) with aldehydes gave the corresponding β-hydroxyacetamides (65) in moderate optical yields (R = Me, ee 47%), after reductive desulphurization,[88] Scheme 34.



(+)-(R)-(64) (65)

Scheme 34

However, the use of n-butyl magnesium bromide as base resulted in

the formation of (65) in a much higher optically pure state (R = Me, ee >99%), via the chelated transition state, Fig. 5.

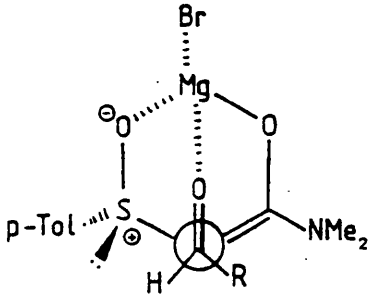
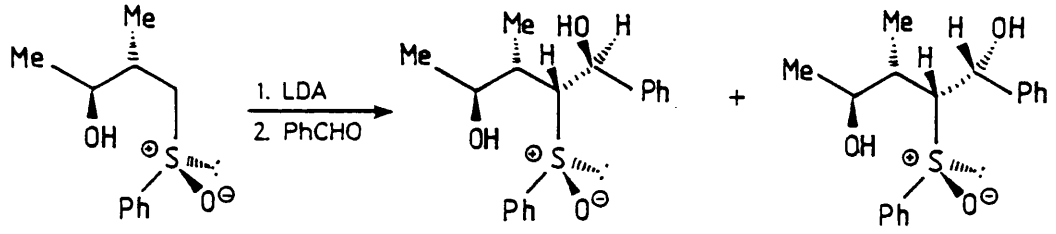


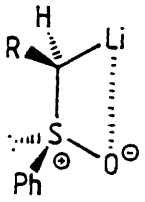
Fig. 5

Williams et al.[89] reported the reaction of aldehydes with the α-sulphinyl carbanion generated from γ-hydroxyalkyl sulphoxides, having three chiral centres provided useful methodology for the generation of 1,2- and 1,3-asymmetry. Deprotonation of (66) with LDA and reaction with benzaldehyde gave a 91:9 diastereomeric mixture of isomers.

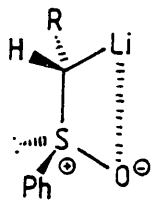


(66) 91 9

The stereogenic atom β to the sulphoxide group and the potential co-ordination of the heteroatom affect the carbanionic configuration. The same reaction with the compound diastereomeric at sulphur gave a mixture of four stereoisomers in a 67:17:13:3 ratio, indicating the carbanion configuration was dependent on the asymmetry at the β-position as well as the chirality at sulphur. The results were explained in terms of a model assuming a tetrahedral carbanion with intramolecular co-ordination of the lithium atom and so the possibility of diastereomeric carbanions (67a) and (67b).



(67a)

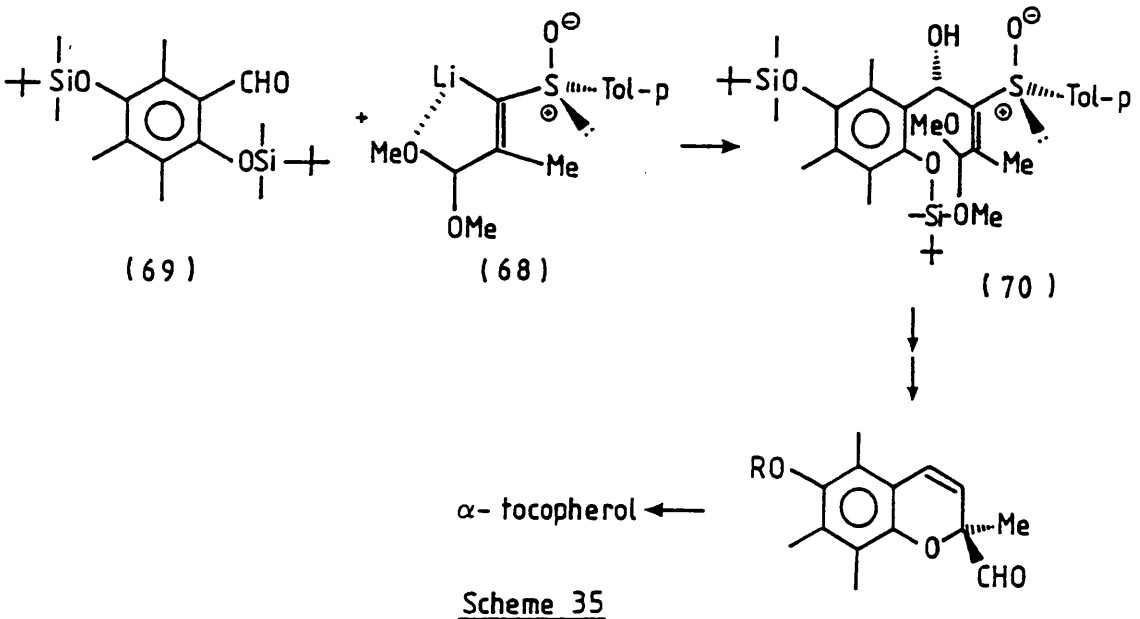


(67b)

Although sterically, (67b) may be more stable than (67a), both faces of the carbanion are hindered and so (67a), having one face with only a proton and the sulphur lone pair should be more reactive towards aldehydes. This model can be used to explain the selectivity with variations in R.[89]

1-Alkenyl aryl sulphoxides can be effectively α-lithiated by LDA at low temperatures and reacted with a range of electrophiles to give 1-substituted 1-alkenyl sulphoxides in high yield.[90] There have been limited studies on the reactions of α-lithio-1-alkenyl sulphoxides with carbonyl compounds. Okamura et al.[90a] reacted a small number of α-lithio-vinyl-sulphinyl carbanions with benzaldehyde and methyl phenyl ketone but reported no diastereoselectivity. Posner et al.[91] reported 20-25% asymmetric induction for a similar system, including studies on variations in solvent, base, reaction temperature, aldehyde structure and metal salt additives. The only successful application to synthesis was described by Solladié and Moine[92] in the enantiospecific formation of the chroman ring of α-tocopherol by the addition of the vinyllithio-sulphinyl reagent (68) to the aldehyde (69), to afford the allylic alcohol (70) in 75% yield as a single diastereoisomer, Scheme 35.

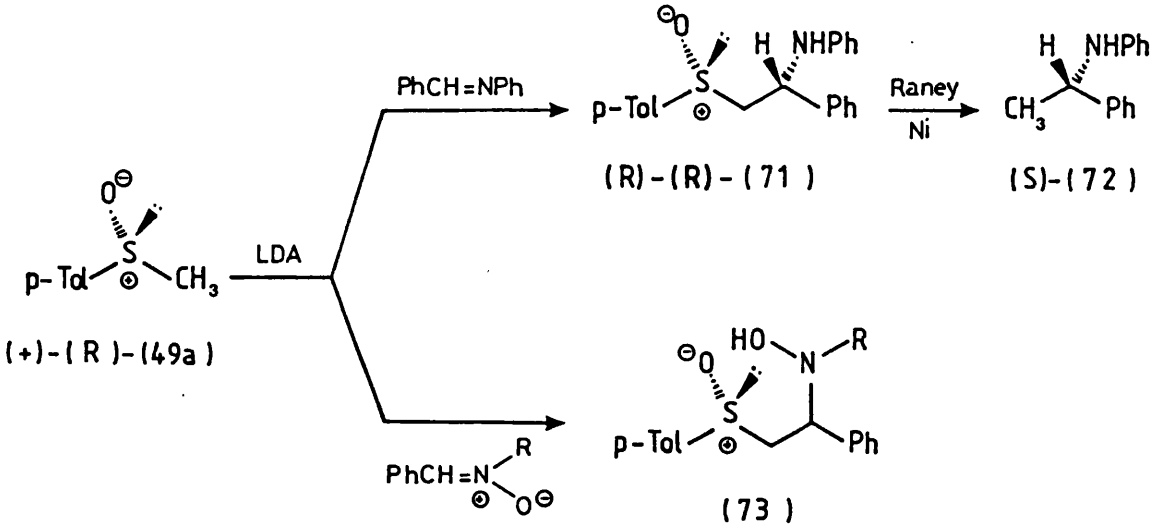
The addition of benzaldehyde to the anion generated from aryl allyl sulphoxides gives a mixture of products resulting from α- and γ-attack as described by Antonjuk et al.[93] α-Attack yields all four possible diastereoisomers whilst γ-attack yields the products having the (E)-configuration in a greater than 2:1 diastereomeric mixture.



Scheme 35

3.3.5 Aminoalkylation

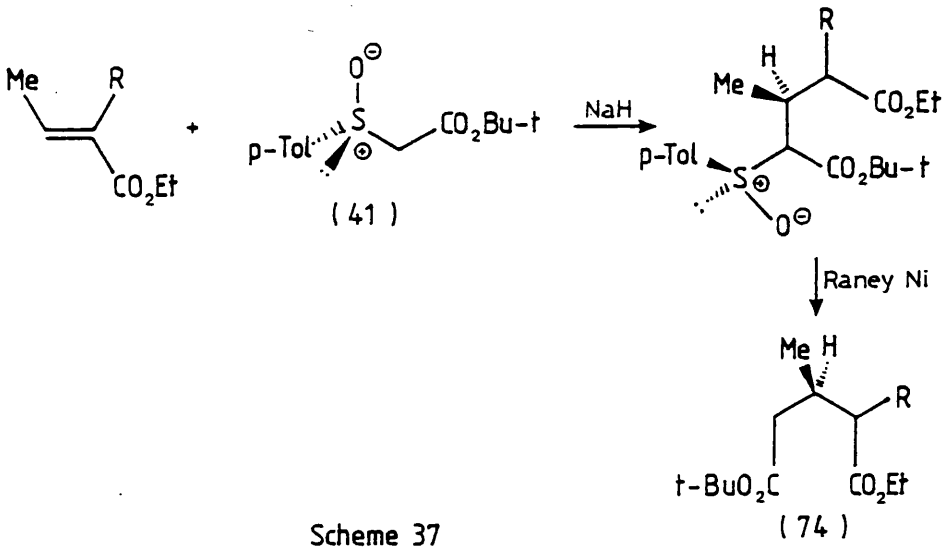
(+)-(R)-Methyl p-tolyl sulphoxide (49a) reacts with benzylidene aniline, in the presence of base, to give the corresponding β-anilino-sulphoxide (71) with high asymmetric induction. Reductive desulphurization leads to the enantiomerically pure amine (72).[94a] The same carbanion reacts with nitrones to give optically active hydroxylamines (73) with varying degrees of induction[94b] (100:0 diastereomeric ratio when R = t-Bu), Scheme 36.



Scheme 36

3.3.6 Michael Additions

The enolate generated from (+)-(R)-tert-butyl-p-toluenesulphinyl acetate (41) adds to α,β-unsaturated esters to give, after reductive desulphurization, the corresponding diesters (74) in 12% (R = H) and 24% (R = CO_2Et) ee,[95] Scheme 37.

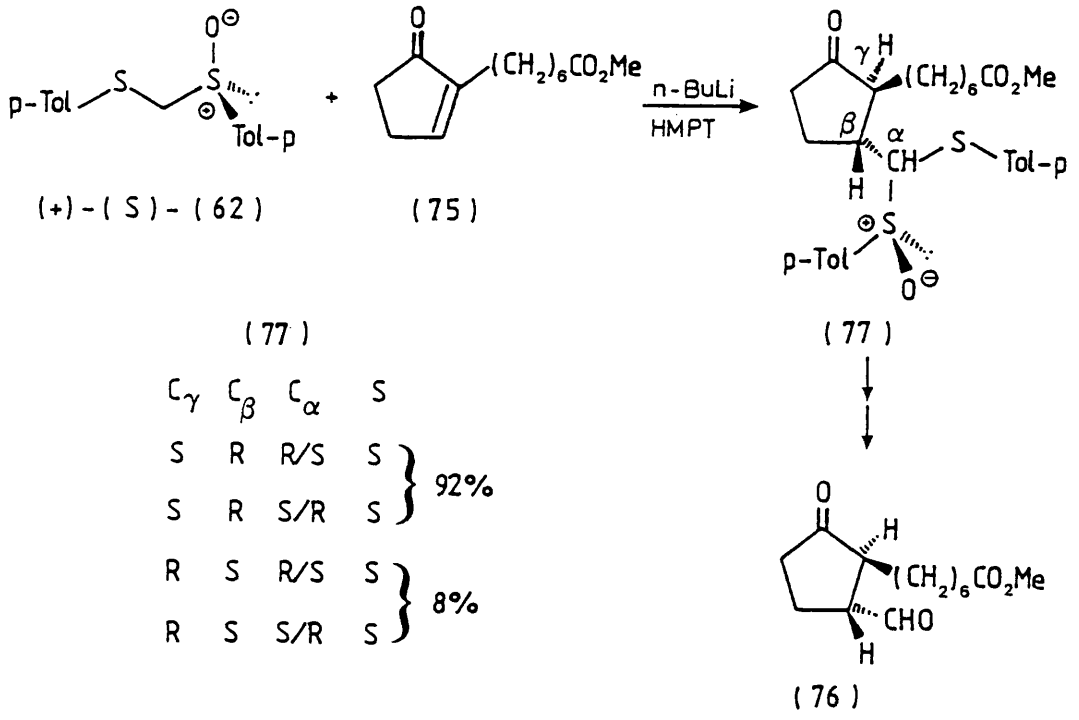


(41)

(74)

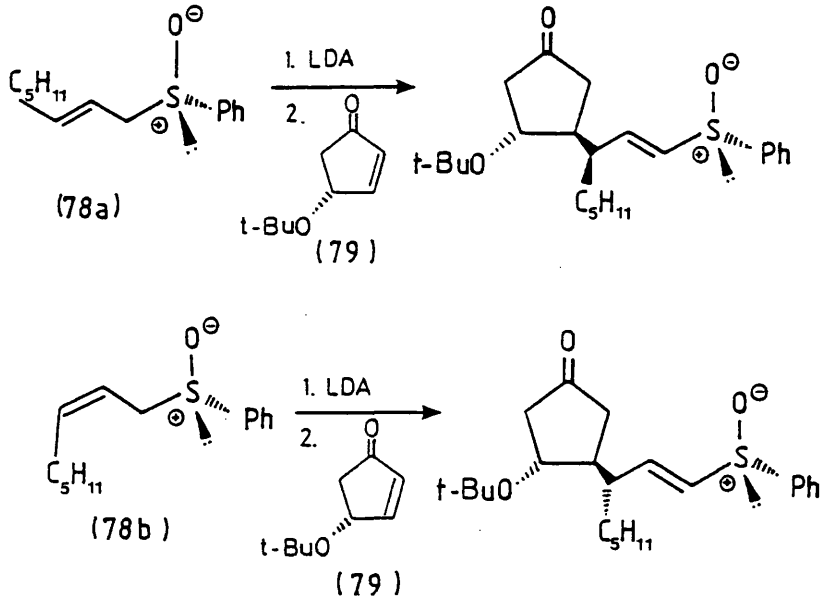
Scheme 37

The addition of (+)-(S)-p-tolyl p-tolylthiomethyl sulphoxide (62) to the substituted cyclopentenone (75), in the presence of n-BuLi-HMPT, gave a mixture of four diastereoisomers with the side chains having the thermodynamically more stable trans arrangement and with high β- and γ-induction (92%) but poor α-stereoselection (52:48).[96] Reduction and hydrolysis leads to the important prostaglandin precursor (76) in an optically active form, Scheme 38.



Scheme 38

More recently, Binns et al.[97a] reported that the conjugate addition of the carbanions from (E) and (Z)-1-phenylsulphinyl-2-octene (78a) and (78b) to 4-tert-butoxycyclopent-2-en-1-one (79) proceeded stereoselectively forming (E)-vinylic sulphoxides as single isomers.



Similar work by Hua et al.[97b] on the regio and stereochemical aspects of the reaction of carbanionic (+)-(R)-allyl p-tolyl sulphoxide with a variety of cyclic enones has proved important in the asymmetric synthesis of (+)-hirsutene.

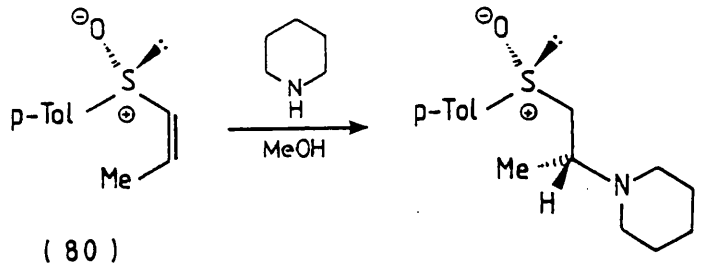
3.4 REACTIONS OF OPTICALLY ACTIVE VINYL SULPHOXIDES

3.4.1 Electrophilic Addition

Halogens add to α,β-unsaturated sulphoxides to give α,β-dihalogeno-sulphoxides.[71] Similarly NBS reacts with (+)-(R)-(E)-β-styryl p-tolyl sulphoxide in water or methanol to give diastereomeric mixtures of α-bromo-β-hydroxy (or methoxy) sulphoxides in a high diastereomeric ratio.[98]

3.4.2 Nucleophilic Addition

Amines add to vinyl sulphoxides to give β-aminosulphoxides. The addition of piperidine to (-)-(R)-(Z)-propenyl p-tolyl sulphoxide (80) gave a quantitative mixture of the diastereomeric adduct with 74% asymmetric induction.[71]

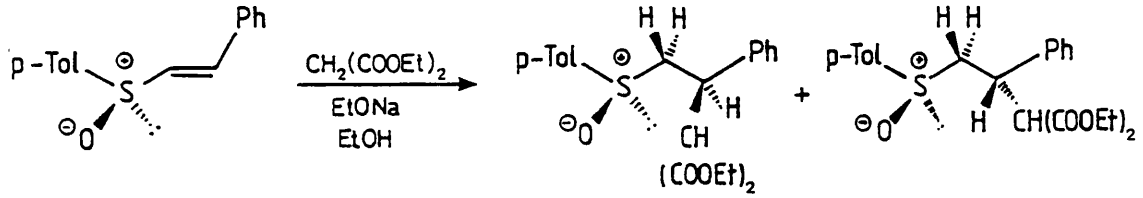


(80)

Major diastereoisomer

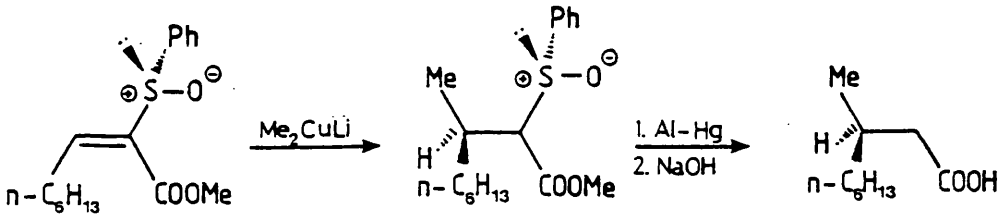
Tsuchihashi et al.[99] reported the Michael addition of diethyl malonate and ethyl acetoacetate to p-tolyl vinyl sulphoxides in the presence of base. (+)-(R)-(E)-β-Styryl p-tolyl sulphoxide was found to afford (R)-(R)-(81a) and (R)-(S)-(81b) in a 80:20 ratio of diastereo-isomers when treated with diethyl malonate. The stereoselectivity is

dependent on the relative stability of the carbanionic species formed after addition of the malonate anion.



(81a) (81b)

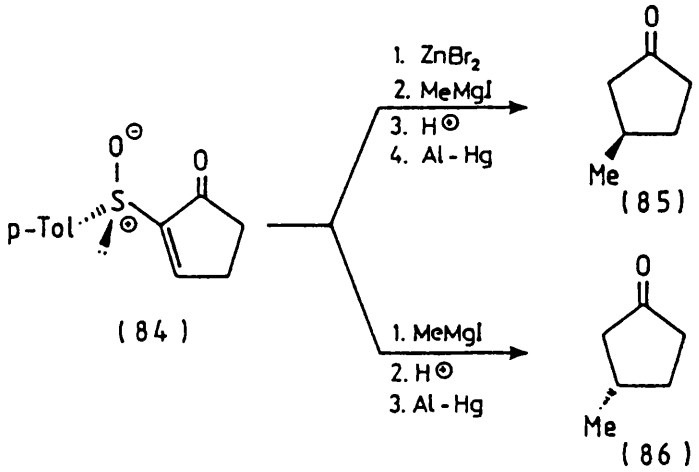
Posner has published a large number of papers based on the nucleophilic addition of organometallic reagents to α,β-unsaturated sulphoxides.[37,100] Dialkyl cuprates add to vinyl sulphoxides giving the 1,4-addition product. For example, the (E)-1-octenyl sulphoxide (82) reacted with dimethylcopperlithium to give the acid (83) in 65% optical yield after reduction and saponification.[100a]



(82) (83)

The addition of methylmagnesium iodide to enantiomerically pure (+)-(S)-2-(p-tolylsulphinyl)cyclopentenone (84), in the presence of zinc bromide, gave (+)-(R)-3-methylcyclopentanone (85) in 72% ee after reductive desulphurization. The addition in the absence of the metal bromide gave the cyclopentanone (86) with the opposite configuration at C-3,[37] Scheme 39.

This was rationalized in terms of chelated and non-chelated structures [Fig. 6 (I) and (II)]. In the presence of metal ions the sulphoxide assumes a chelated structure and alkylation occurs from the side of the non-bonding electron pair. In the absence of metal ions, the dipoles of the sulphinyl and carbonyl functions would be in opposite



Scheme 39

directions as would the electron lone pair and so attack from the opposite face would occur.

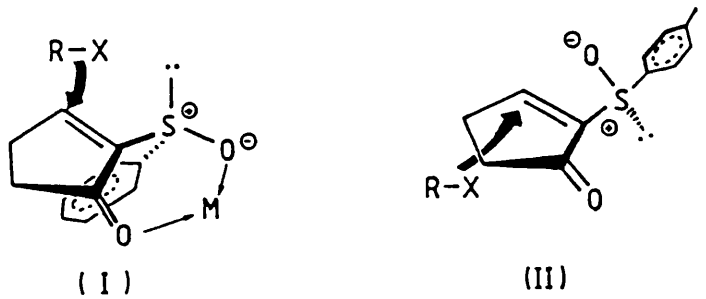


Fig. 6

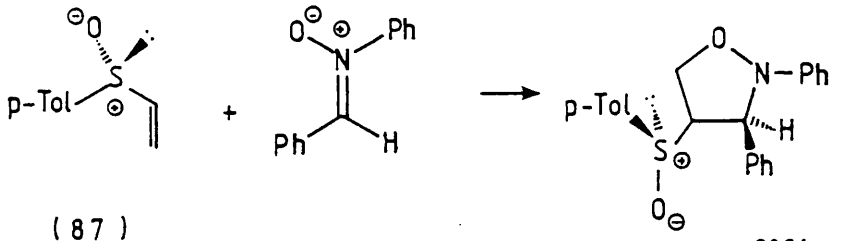
3.4.3 Diels-Alder Cycloadditions

Enantiomerically pure, doubly activated α,β-olefinic sulphoxides undergo highly diastereoselective cycloadditions with cyclopentadiene and other selected dienes.[101] Olefins singly activated by only a sulphinyl group do not usually act as effective parties in the cycloadditions. The use of butadienyl phenyl sulphoxide as a diene[102] and an example of an inverse electron demand (2+4) cycloaddition involving a pyrone sulphoxide[103] have also been reported.

3.4.4 1,3-Dipolar Cycloadditions

The cycloaddition of nitrile oxides to vinyl sulphoxides usually produces a mixture of regio- and diastereoisomers. The ratios are dependent on the nitrile oxide used and the configuration of the olefinic sulphoxide double bond.[104]

High asymmetric induction was reported by Koizumi et al.[105] in the 1,3-dipolar cycloaddition of (+)-(R)-p-tolyl vinyl sulphoxide (87) with acyclic nitrones.



(87)

ee > 90%

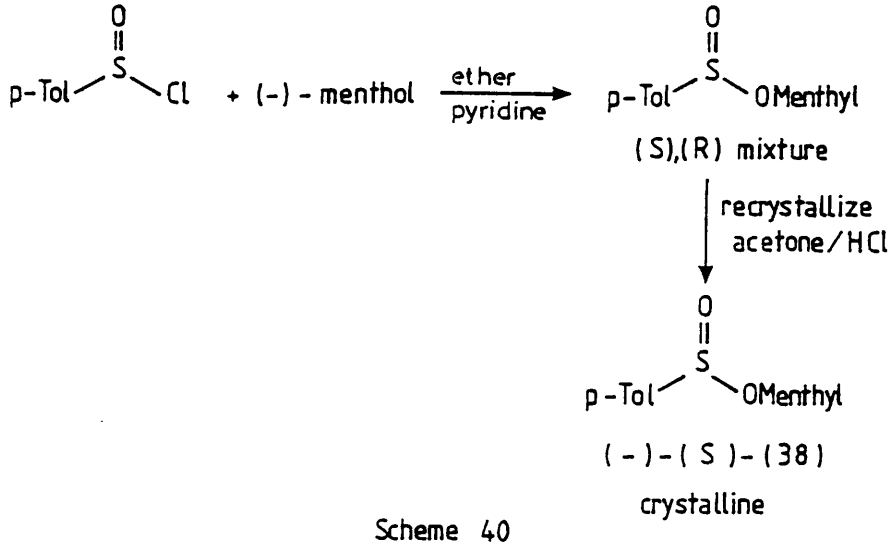
3.5 RESULTS AND DISCUSSION

Previous reports[90a,91,92] on the diastereoselectivity in the reaction between optically pure lithiated vinyl sulphoxides and aldehydes have been limited and the observed selectivity low. We initially set out to prepare a variety of optically pure vinyl sulphoxide anions and to study their reaction with aldehydes paying particular attention to diastereoselectivity. Our proposed route to the vinyl sulphoxides was via the Andersen synthesis by adaptations of the work of Stirling[71] and Posner.[72]

Initial attempts to prepare diastereomerically pure menthyl benzenesulphinate from benzenesulphinyl chloride and (-)-menthol were not successful. Despite the literature precedent[72] for the reaction, the required (S)-isomer proved very difficult to crystallize at room temperature - only at temperatures of ca. -40°C was the crystalline diastereoisomer stable in petroleum ether. Consequently, the yield of

(-)-menthyl (-)-(S)-benzenesulphinate as a crystalline solid was negligible.

However, the preparation of (-)-menthyl (-)-(S)-p-toluenesulphinate (38) was straightforward in accordance with the literature,[35] and the sulphinate ester was obtained as a white crystalline solid with acceptable melting point and optical rotation, Scheme 40.

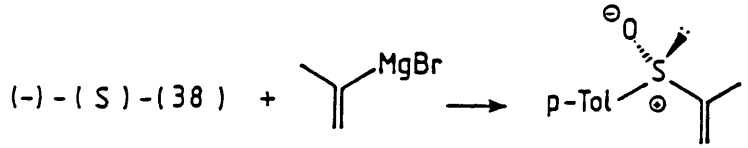


Scheme 40

The yield of (-)-(S)-(38) was optimized by recrystallizing the crude mixture from acetone containing a few drops of concentrated hydrochloric acid to effect epimerization at sulphur (Scheme 21, p.28).

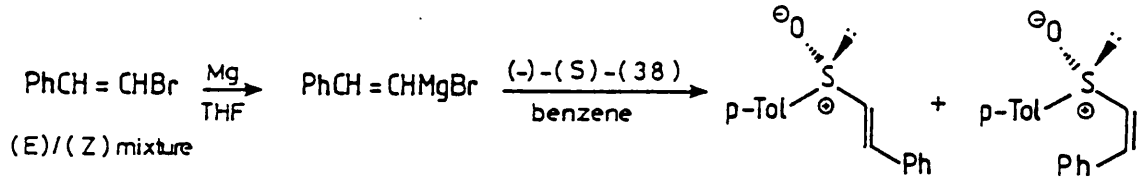
As previously mentioned, one of the problems of preparing vinyl sulphoxides using the Andersen synthesis, is the unavailability of pure (E) or (Z)-vinyl halides. Most commercially available vinyl halides are mixtures of the two geometrical isomers; the (E)-isomer being the major component. Cheaply available β-bromostyrene was shown to be a ca. 11:1, (E)/(Z) mixture of isomers as measured by g.l.c. Before preparing the corresponding Grignard reagent from this halide mixture, it was considered worthwhile preparing (-)-2-[(R)-p-tolylsulphinyl]-propene (88) from 2-propenyl magnesium bromide and (-)-(S)-(38) to become familiarised with the reaction conditions. Hence (88) was prepared in

47% yield (lit.[72] 75%) as an oil.



(88)

Consequently, the Grignard reagent of β-bromostyrene was prepared in THF, using iodine as a reaction initiator, and added dropwise to a solution of (-)-(S)-(38) in benzene. T.l.c. of the crude reaction mixture showed there to be two major products which were easily separable by flash chromatography. These were the (E) and (Z)-isomers (53b) and (53a) which had δ_H data and optical rotations consistent with the literature,[63] Scheme 41.



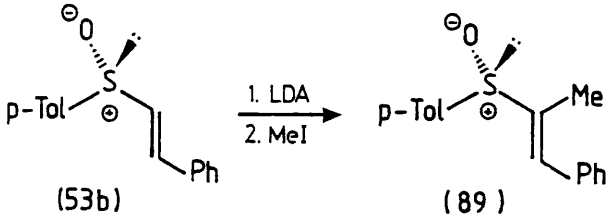
(53b) (53a)

Scheme 41

The yields of (53b) and (53a) were 49% and 14.5% respectively indicating that the formation of the Grignard reagent was not completely stereospecific. Yoshino et al.[106] had reported that the formation of Grignard reagents from (E) and (Z)-β-bromostyrenes in THF, proceeded with a high degree of retention of double bond configuration, especially in the presence of ethyl bromide. However, the use of iodine as a reaction initiator tended to give greater degrees of isomerization. The result was therefore in agreement with this report.

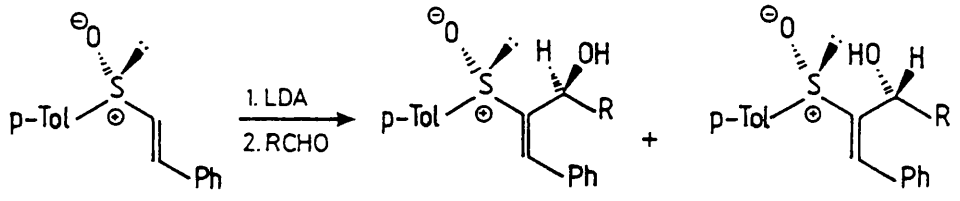
The generation of α-lithio-1-alkenyl sulphoxides can be achieved by using a slight excess of LDA at -78°C.[90] Accordingly, (+)-(E)-2-phenyl-1-[(R)-p-tolylsulphinyl]-ethylene (53b) was α-lithiated with LDA and the anion quenched with methyl iodide to give the methylated product (89) in

56% yield as a white solid.



(53b) (89)

Having successfully lithiated and methylated (53b), an attempt was made to quench the α-lithiosulphoxide with the prochiral carbonyl compound benzaldehyde. After deprotonation of (53b) and the addition of benzaldehyde, the t.l.c. of the reaction mixture showed the formation of two products with a small ΔR_f. Separation by flash chromatography gave two major fractions; an upper fraction consisting of one probable diastereomeric product and an impurity in a 1:1 mixture and a lower fraction, the ^1H n.m.r. suggesting it to be the other diastereoisomer. However, neither fraction could be further purified and because analysis by h.p.l.c. showed the probable diastereomeric ratio to be ca. 1:1, it was decided to change the nature of the aldehyde in order to obtain a higher selectivity and a more satisfactory result. The lithiated (E)-sulphoxide (53b) was consequently quenched with acetaldehyde (MeCHO), isobutyraldehyde (Me_2CHCHO) and trimethylacetaldehyde (Me_3CCHO), each reaction resulting in the formation of a pair of diastereomeric alcohols (90a) and (90b).



(53b) (90a) (90b)

R = Me, Me_2CH, Me_3C

Unlike the reaction products resulting from the benzaldehyde quench, the diastereomeric pair could be easily separated by use of a 'chromato-

tron' and no difficulty with impurity contamination was encountered. The diastereomeric ratio was determined from the crude reaction mixture using h.p.l.c., the diastereoselectivity increasing with an increase in the bulk of R, Table 3.

Aldehyde	Diastereomeric ratio (90b) : (90a)	Yield (%) (90b)	Yield (%) (90a)	$[\alpha]_D(^o)$ (90b)	$CHCl_3$ (90a)
MeCHO	45 : 55	18	34	+101	+11.5
Me_2CHCHO	34 : 66	16	44	+35	+24
Me_3CCHO	15 : 85		59[a]	-52	+142

[a] Total yield of both isomers.

TABLE 3

The assignment of that particular diastereoisomer to that particular set of experimental data is an arbitrary one, except in the case of the trimethylacetaldehyde product, where significant asymmetric induction was observed (ca. 6:1 diastereoselectivity). The major isomer was purified and an X-ray crystal structure determination performed to establish the configuration at the new chiral centre. Fig. 7 [see also Appendix 1] shows the result of this determination, indicating the major isomer has the (S)-configuration at the new asymmetric centre.

A third product, with a greater polarity than (90a) or (90b) was also obtained in 2%, 4% and negligible yield, for R = Me, Me_2CH and Me_3C respectively. The white solid had spectroscopic properties (^1H, ^{13}C n.m.r., mass spec.) which showed it to be the dimeric species (91), presumably formed by the 'Michael-type' addition of the α-lithiosulphinyl carbanion to the starting material.

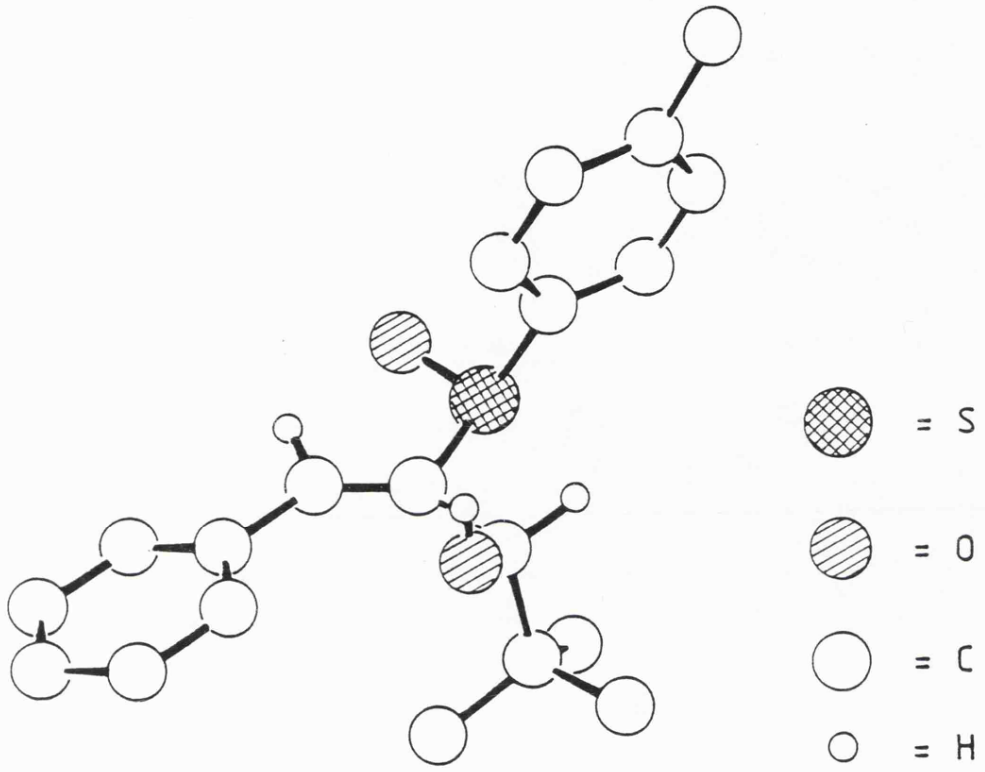
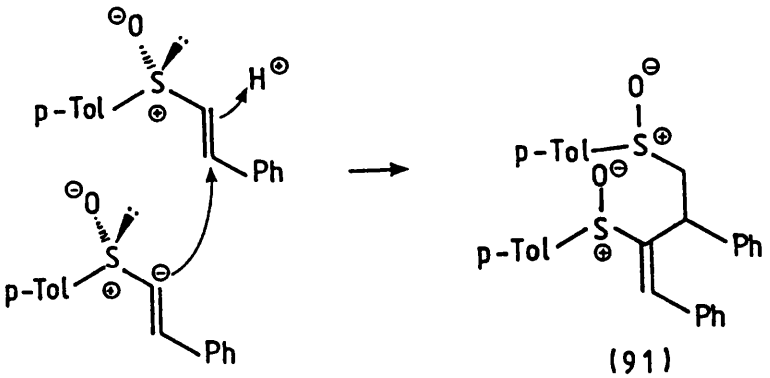


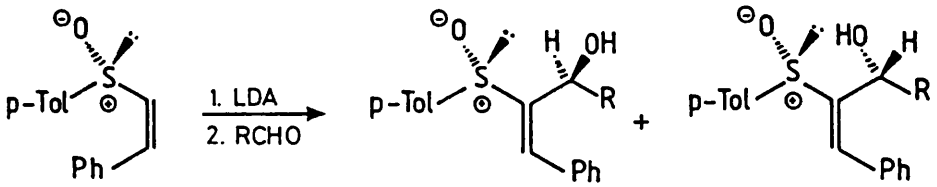
Figure 7

X-ray Crystal Structure of (+)-(S)-(E)-4,4-Dimethyl-2-[(S)-p-tolylsulphinyl]-1-penten-3-ol (94a).



(91)

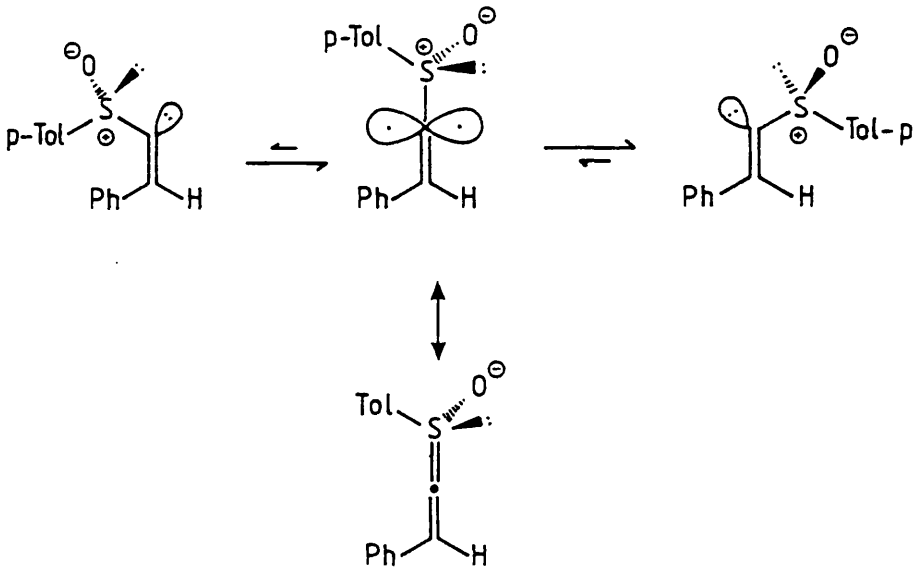
In accordance with the work of Okamura et al.[90a] and Posner et al.,[90b] the same pair of diastereoisomers was obtained from the (-)-(R)-(Z)-isomer (53a) as from the (+)-(R)-(E)-isomer (53b).



(53a) (90a) (90b)

R = Me, Me_2CH, Me_3C

The diastereomeric products had identical spectral properties to those prepared previously from (53b). Usually vinyl anions exhibit a high degree of configurational stability[107] although the stability can depend on the degree of substitution at the double bond as well as the nature of the substituents.[107b,108] The (Z) to (E) isomerization described above can be considered to be caused by the steric repulsion between the p-tolylsulphinyl group and the phenyl substituent on C-2, and the fact that the p-tolylsulphinyl group may lower the energy barrier for isomerization,[90a] Scheme 42.



Scheme 42

The degree of diastereoselectivity for the reaction was almost identical and the yields comparable with those obtained previously, Table 4.

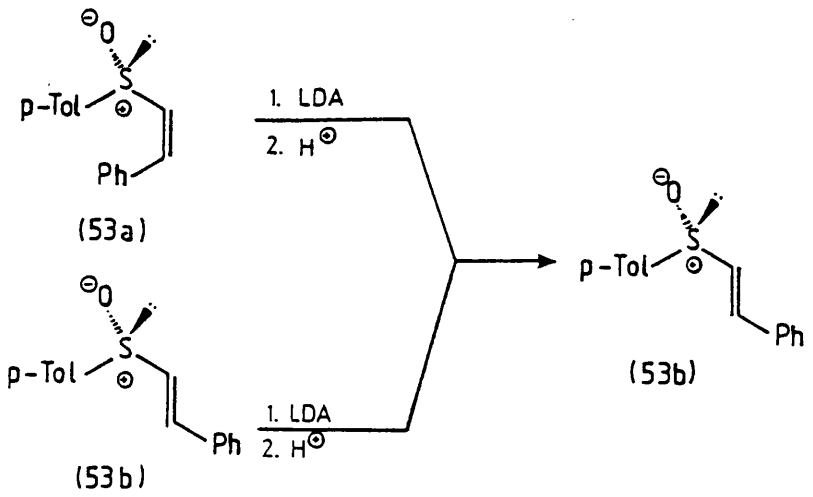
Aldehyde	Diastereomeric ratio (90b) : (90a)	Yield (%) (90b)	(90a)	$[\alpha]_D(^o)$ (90b)	$CHCl_3$ (90a)
MeCHO	47 : 53	18	25	+100	+9
Me_2CHCHO	41 : 59	25	35	+ 35	+23
Me_3CCHO	14 : 86	71[a]		-	-

[a] Total yield of both isomers.

TABLE 4

Because of the (Z) to (E)-isomerization, it was possible that a degree of racemization was occurring.[37b] However, fears were dismissed when deprotonation followed by reprotonation of (53a) gave (53b) of the same optical purity as an original sample, Scheme 43.

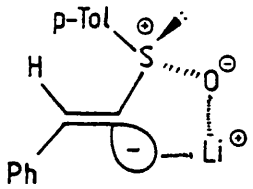
This was reinforced by the fact that the diastereomeric pairs obtained from (Z)-(53a) had, within estimated experimental error, the



Scheme 43

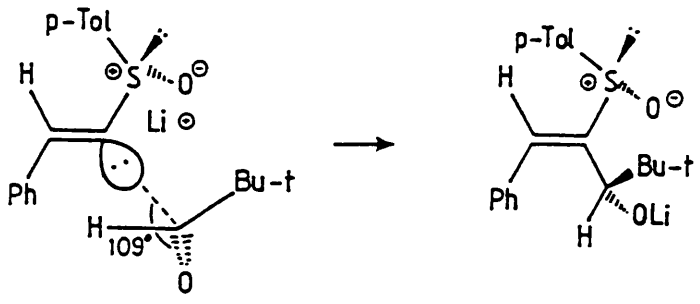
same respective optical rotations as those obtained from (E)-(53b). [Compare $[\alpha]_D$, Table 4 with $[\alpha]_D$, Table 3]. Additionally, as before, a sample of the dimer (91) was also isolated in 5%, 7% and negligible yield, for R = Me, Me_2CH and Me_3C respectively.

The X-ray crystal structure (Fig. 7) shows the new carbon-carbon bond and the sulphur-oxygen bond of the sulphoxide moiety to be in an anti arrangement. However, it would be reasonable to assume the anion to exist mainly in conformation (92), where the sulphur lone electron pair can overlap with the double bond and the sulphoxide oxygen is close enough to interact with the lithium species.



(92)

Bearing in mind the direction of approach of a nucleophile to a carbonyl group, we initially proposed the transition state (93) to explain the diastereoselectivity of the addition.

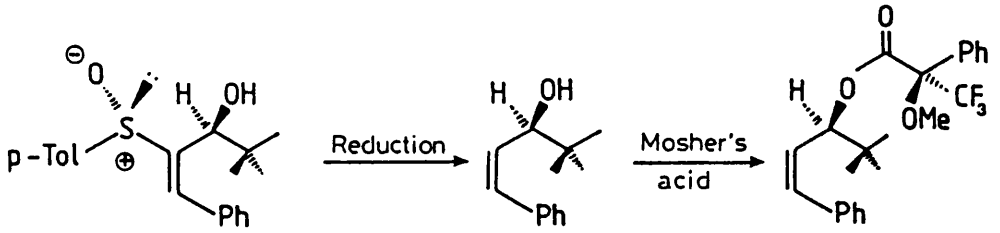


(93)

In this model, the plane of the alkene atoms and the plane of the carbonyl atoms approach each other at the tetrahedral angle, the approach of the aldehyde to the anion occurring so that the bulky tert-butyl group is on the less hindered side away from the phenyl ring.

The highly hindered 1-adamantyl methyl ketone failed to react with the α-lithiated vinyl sulphoxide (53b) and so provided no further evidence as to the nature of the stereoselectivity.

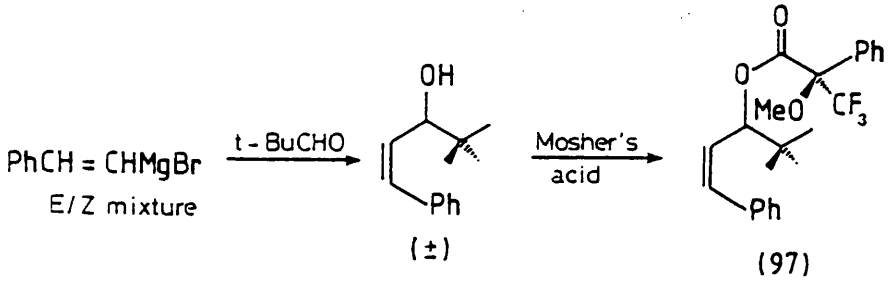
The next objective was to reduce the diastereomerically pure (+)-(S,S)- (94a) and hence provide a route to an enantiomerically pure allylic alcohol (S)-(95) whose optical purity could be confirmed by its reaction with Mosher's acid, Scheme 44, and the comparison of the ^{19}F n.m.r. of the resulting diastereomerically pure ester (96) with that of a racemic mixture (97) prepared by an alternative route, Scheme 45.



(+)-(S,S)-(94a) (R)-(95) (96)

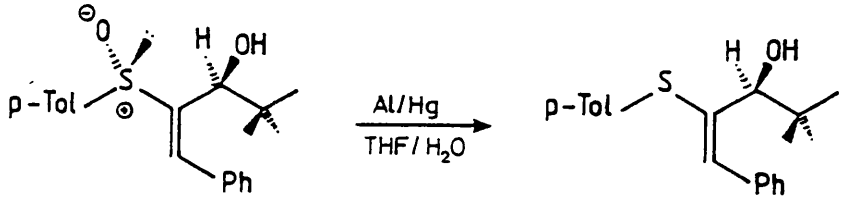
Scheme 44

The methods available in the literature for reductive desulphurisation are numerous.[109] (+)-(S,S)-(94a) was subjected to reductive conditions using sodium amalgam, but the reaction mixture yielded only

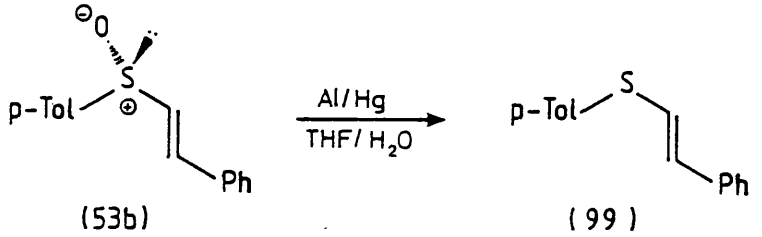


Scheme 45

starting material and decomposition products. Similarly, the addition of activated zinc to a solution of (+)-(S,S)-(94a) in THF gave only starting material as the recovered yield. The use of Raney Nickel (freshly prepared or commercially available reagent) caused severe decomposition of (+)-(S,S)-(94a), t.l.c. showing a number of products, none of which could be easily isolated. Aluminium amalgam added to a THF/H_2O solution of (+)-(S,S)-(94a) did reduce the sulphoxide moiety, but only to the sulphide (98).



Despite the continued addition of amalgam and extension of the reaction time, the sulphide (98) could not be reduced further. Analogously, the (+)-(R)-(E)-sulphoxide (53b) was subjected to aluminium amalgam reduction and it too was reduced only to the sulphide (99).



The formation of the sulphides from their respective sulphoxides could be followed easily by t.l.c; the reaction was very clean and ΔR_f

large [R_f (ether) (94a) 0.39, (98) 0.68]. Confirmation that the sulphide was being formed was provided by low resolution ammonia chemical ionization mass spectroscopy [for (99)].

Because of the apparent inertness of (+)-(S,S)-(94a) to the attempted methods of reductive desulphurization, it was decided to return to this problem later and instead concentrate on the proposed transition state for the aldehyde addition to α-lithiovinyl sulphoxides. To improve diastereoselectivity and also to validate the transition state, it was decided to change the nature of the groups R and R^1, Fig. 8 (originally R = p-tolyl and R^1 = phenyl).

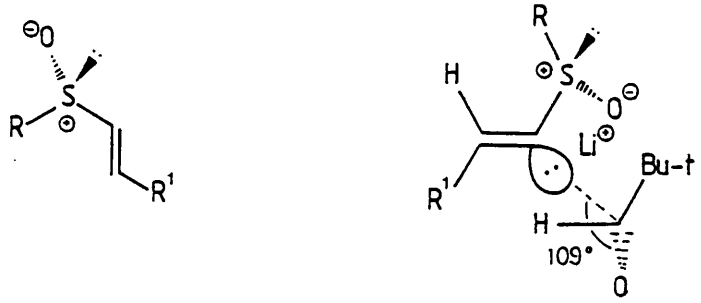
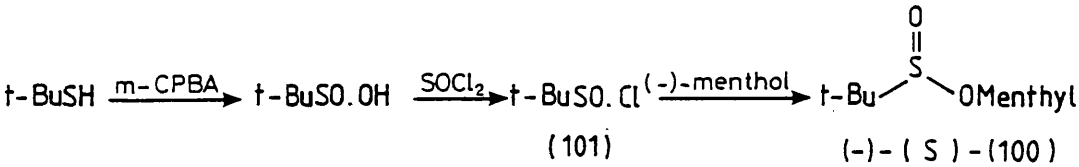


Fig. 8

To maximise steric influences it was decided to introduce R and R^1 = t-butyl in separate schemes and observe the effect on the diastereoselectivity.

Posner and Tang[72] had described the preparation of the diastereomerically pure (-)-menthyl (-)-(S)-tert-butylsulphinate (100) in an analogous method to the preparation of (-)-(S)-(38), Scheme 46.

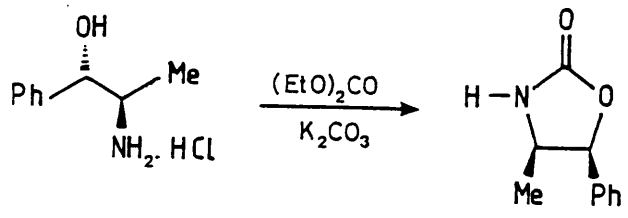


Scheme 46

The esterification step, however, caused some concern. Unlike (-)-(S)-(38) which is crystalline and separable from the liquid (+)-(R)-

isomer by recrystallization (see p.28), (-)-(S)-(100) was described as a liquid and no indication was given of how the ester was obtained diastereomerically pure. The esterification shows no particular diastereoselectivity and because no separation of isomers was described, there were doubts over the reported optical purity of (-)-(S)-(100). Suspicions were confirmed when tert-butylsulphinyl chloride (101) was reacted with (-)-menthol; the esterification product was purified by flash chromatography and analysed. Although appearing as one spot by t.l.c., ^{13}C n.m.r. and g.l.c. showed the liquid product to be a mixture of diastereomers. [A ratio of 1.6:1 as measured by g.l.c.]

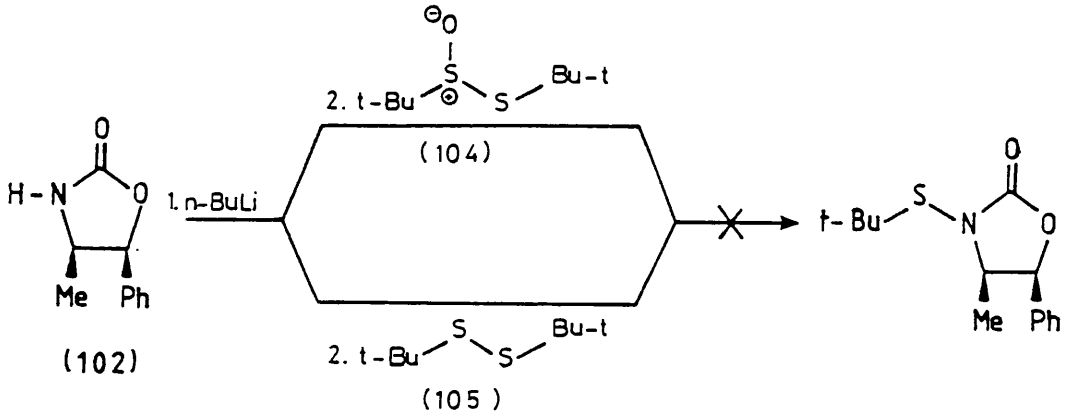
The need for an optically pure diastereomeric centre at sulphur was imperative. Because the tert-butylsulphinate ester route, using (-)-menthol as the chiral auxiliary, did not fulfill this need, the strategy was altered to enable separable tert-butylsulphinyl compounds to be obtained using a different chiral auxiliary. The use of the chiral 2-oxazolidinone (102) as an auxiliary in asymmetric syntheses had been reported by Evans et al.[110] and was hence prepared in good yield (62%) from the ephedrine free base of (+)-norephedrine hydrochloride (103) and diethyl carbonate, as a white crystalline solid after recrystallization (m.p. and $[\alpha]_D$ consistent with the literature[110]).



(103) (102)

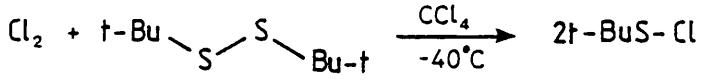
The strategy was to attach the sulphur containing moiety to the oxazolidinone nitrogen atom and utilize the asymmetry of the ring to prepare diastereomeric sulphur compounds. However, initial attempts to

attach an appropriate sulphur-containing group failed. 2-Methyl-2[{(2-methylpropyl)sulphinyl}thio]propane (104) was prepared in 71% yield as a colourless liquid by the oxidation of di-tert-butyl disulphide (105) using hydrogen peroxide according to the method of Field and Khim.[111] A solution of (104) in THF was added dropwise to the lithium enolate[112] of (102) but work-up gave the recovery of starting materials only. Similarly, the attempted reaction of di-tert-butyl disulphide (105) with lithiated (102) also resulted in the recovery of starting materials, Scheme 47.

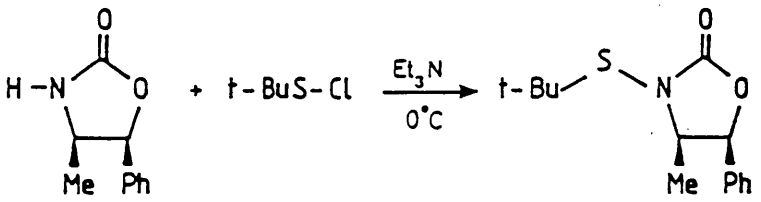


Scheme 47

Analogous to the preparation of other aliphatic sulphenyl halides,[113] one mole of chlorine was added to an equivalent of di-tert-butyl disulphide (105) in carbon tetrachloride, at -40°C, to give a product in moderate yield. Not expecting any complications, the product was assumed to be the tert-butylsulphenyl chloride (106).

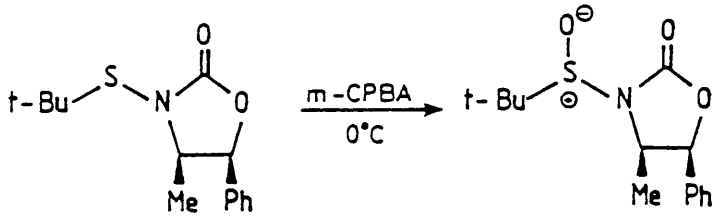


A solution of the 2-oxazolidinone (102) and triethylamine was added to the suspected (106) to give a single product in good yield. All spectral data of the white solid suggested that it was the required 3-(tert-butylthio)-2-oxazolidinone (107).



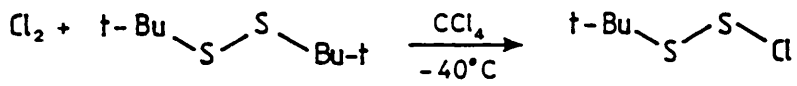
(102) (106) (107)

Oxidation of (107) with m-CPBA in chloroform, at 0°C, gave a white crystalline product in good yield, which was one spot by t.l.c. but which ^{1}H and ^{13}C n.m.r. showed to be a ca. 1:1 mixture of diastereoisomers. From this evidence it was reasonable to assume that we had a 1:1 unseparated mixture of the diastereoisomers of (108).



(107) (108)

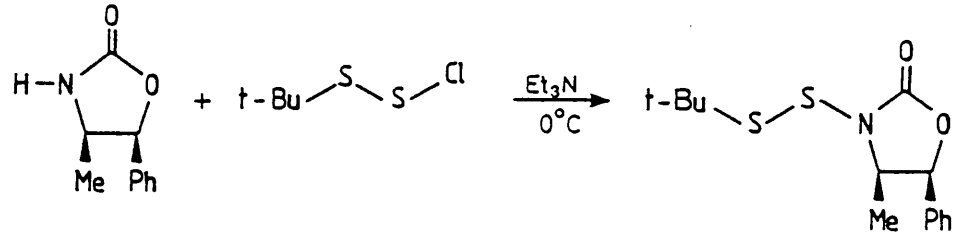
However, initial frustrations proved to be unfounded. Subsequent preparation of the two diastereoisomers of (108) (see p.66) by an alternative route showed them to be distinguishable, separable compounds by t.l.c. Additionally, analytical data on (107) and (108) was erroneous by a much greater factor than would normally be expected, even for an impure sample. A literature search clarified the problem. It had been reported[114] that at temperatures above -30°F (ca. -35°C), the chlorination of the disulphide (105) gave the sulphenyl chloride (106). However, at temperatures below this, the major product was the tert-butyl thiosulphenyl chloride (109) not (106) as believed.



(105) (109)

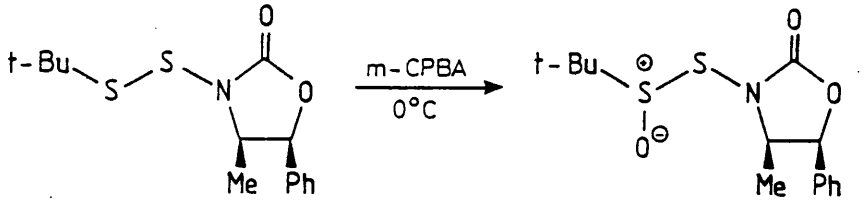
Hence reaction of (109) with the 2-oxazolidinone (102) in the

presence of triethylamine gave the tert-butylsulphenylthio compound (110).



(102) (109) (110)

Subsequent oxidation of (110) by m-CPBA gave the 1:1 diastereomeric mixture of (111) where presumably the oxygen becomes attached to the more nucleophilic sulphur atom.



(110) (111)

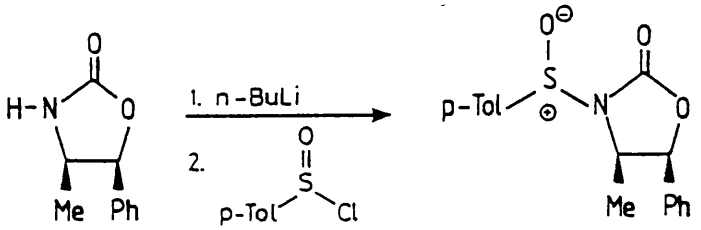
1:1 diastereomeric mixture

The analytical data calculated for (110) and (111) then proved to be correct.

An alternative approach was considered which would involve the direct reaction between the 2-oxazolidinone (102) and tert-butylsulphinyl chloride (101). To test the suitability of this method, an initial run using p-tolyl-sulphinyl chloride was performed. [The main reason for this was the difficulty in preparing tert-butylsulphinyl chloride. The reaction conditions for the preparation described by Youn and Herrman[115] proved difficult to control and the method described earlier by Posner and Tang[72] was problematic and involved the use of tert-butyl mercaptan.]

p-Tolylsulphinyl chloride was added dropwise to lithiated (102) at -78°C to give, after work-up, the required 3-(p-tolylsulphinyl)-2-

oxazolidinone (112) as a white solid and a 4:1 mixture of diastereoisomers.

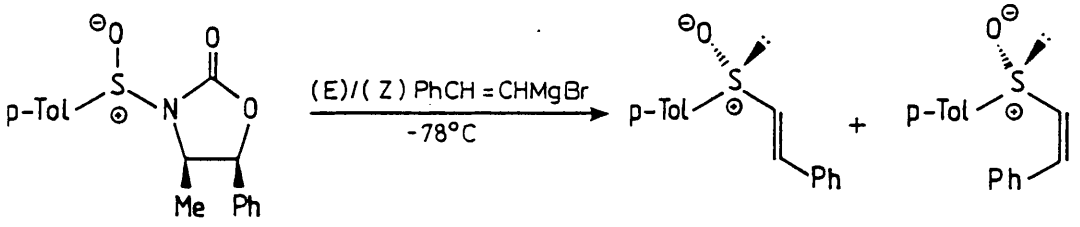


(102) (112)

4 : 1 diastereomeric mixture

The major isomer was obtained by recrystallization of the white solid from a 2:1 ethyl acetate-petroleum ether mixture. [The mixture could not be separated by chromatography.] Two recrystallizations gave (112) diastereomerically pure by ^{1}H n.m.r.

The displacement of the chiral auxiliary by the Grignard reagent addition of (E)/(Z)-styryl magnesium bromide resulted in the formation of the isomeric (+)-(R)-(E)-(53b) and (-)-(R)-(Z)-(53a), prepared previously from (-)-(S)-(38), in 66% and 20% yields respectively.



(112) (53b) (53a)

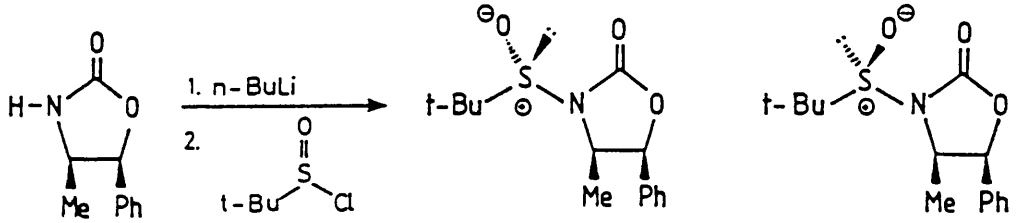
Diastereomerically pure

A sample of the crude (E)-isomer (53b) was recrystallized from petroleum ether to constant rotation ($[\alpha]_D$ = +160°) indicating that the configuration at the sulphur atom was (R). Assuming that the addition of the Grignard reagent to (112) proceeds with inversion of configuration (a precedent set by other sulphinic acid derivatives), then the major isomer of (112) must also have the (R) configuration at sulphur.

Having established a working route to enantiomerically pure p-tolyl sulphoxides via the 2-oxazolidinone (102) and the respective sulphinyl

chloride, the analogous preparation of the required tert-butyl sulphoxides was attempted.

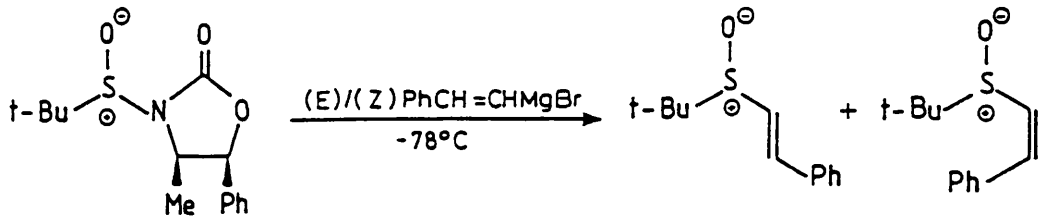
Tert-butylsulphinyl chloride prepared according to the method of Posner and Tang,[72] was added dropwise to lithiated (102) at -78°C. T.l.c. of the crude reaction mixture showed the presence of two products which were separated by flash chromatography. Spectral data showed them to be the required 3-(tert-butylsulphinyl)-2-oxazolidinone diastereoisomers (113a) and (113b), obtained in 41% and 24% yield respectively.



(102) (113a) (113b)

The assignment of the configuration at sulphur in each isomer as shown is arbitrary.

(E)/(Z)-Styryl magnesium bromide was added dropwise to a stirred solution of the major isomer of (113) at -78°C and consistent with the products yielded from the p-tolyl derivative (112), purification by 'chromatotron' gave the (E) and (Z)-isomers (114a) and (114b) as a white solid and yellow oil in 61% and 8% yield respectively.

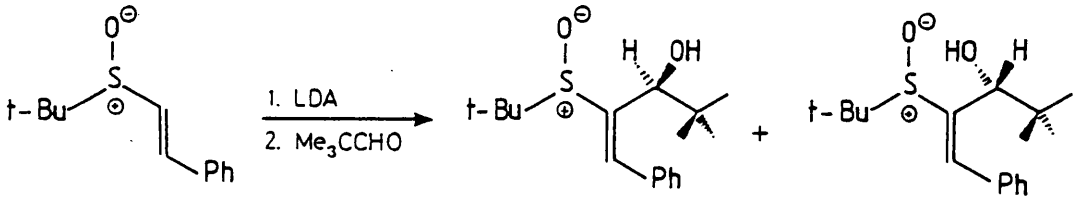


(113) (114a) (114b)

No comment on the sulphur configuration in (114a) and (114b) can be made because the configuration at sulphur in the major isomer of (113) is not known.

The (E)-isomer (114a) was lithiated in the standard way followed by

trimethylacetaldehyde quenching as before. The diastereomeric ratio as determined by h.p.l.c. was measured at 1:4.6 from the crude reaction mixture. Subsequent purification of the mixture by a 'chromatotron' gave the respective sulphinyl allylic alcohols (115a) and (115b) as white solids in 48% and 7% yield.



(114a) (115a) (115b)

[Again, the assignment of the new chiral centre is an arbitrary one.]

The diastereomeric ratio obtained is consistent with the proposed transition state, bearing in mind the ratio obtained using the p-tolyl sulphoxide (53b). The nature of the group R would not be considered to be having any great influence on the way in which the anion approaches the carbonyl group, Fig. 9. Hence the comparable ratios when R = p-tol and t-Bu.

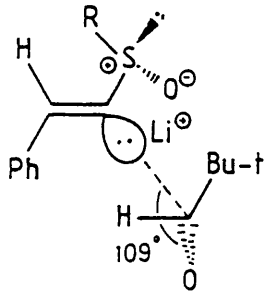
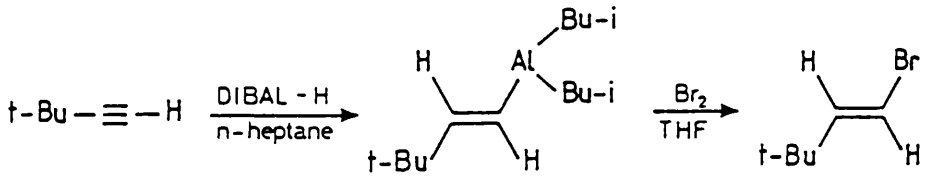


Fig. 9

Having studied the effect of changing the aldehyde and of replacing the p-tolyl group with the bulkier tert-butyl group on the sulphinyl moiety, it was tentatively concluded that the nature of the group attached at the β-vinyl position was most influential in determining the ratio of diastereomeric alcohols formed. The next objective was to

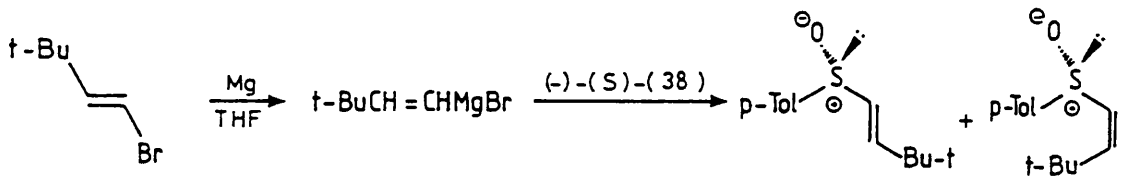
design and synthesise a molecule to test this hypothesis. The aim was to replace the phenyl group in the vinyl sulphoxide with a larger substituent, for example a tert-butyl group. The synthesis of this molecule is now described.

(E)-1-Bromo-3,3-dimethyl-1-butene (116) was prepared using the method of Zweifel and Whitney[116] by the successive addition of DIBAL-H and bromine to the butyne precursor (117).



(117) (116)

The preparation of the Grignard reagent from (116) proved more difficult than the preparation of the corresponding styryl equivalent. The bromide (116) was refluxed for several hours with magnesium in THF until sufficient magnesium had been consumed. The cooled Grignard reagent was then added dropwise to (-)-(S)-(38) to give the (E) and (Z)-isomers (118a) and (118b) as a white solid and yellow oil in 17% and 15% yield respectively after flash chromatography.

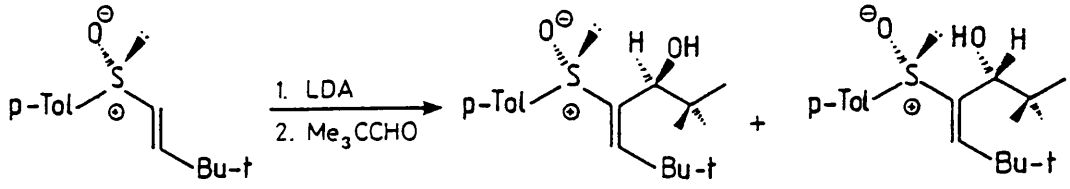


(116) (E)/(Z) mixture (118a) (118b)

The low yields reflect the difficulty experienced in forming the Grignard reagent. Although the (E)-vinyl bromide (116) was isomerically pure, the formation of the Grignard reagent is thought to proceed via a radical mechanism in a non-stereospecific manner with the degree of retention of configuration dependent on the substituents.[117] Méchin and Naulet[117] reported that for the (E)-vinyl bromide (116), the degree of

retention of configuration was 60-62%. In the presence of iodine (cf. styryl magnesium bromide) the degree of retention could be even lower.

The (E)-isomer (118a) was lithiated (the anion left to form over 1h) with LDA at -78°C and quenched with trimethylacetaldehyde. Using h.p.l.c. the diastereomeric ratio was measured at 1:1.2 from the crude reaction mixture and purification subsequently gave the sulphinyl allylic alcohols (119a) and (119b) as white solids in 45% and 37% yield respectively.

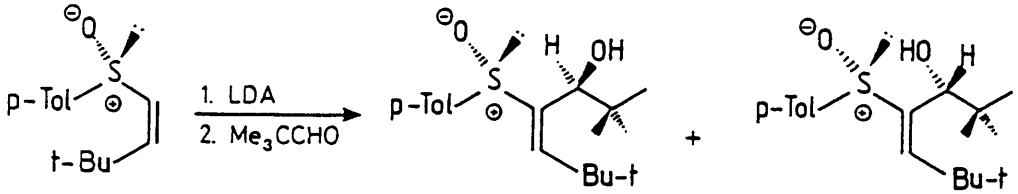


(118a) (119a) (119b)

[The assignment of the new chiral centre is an arbitrary one.]

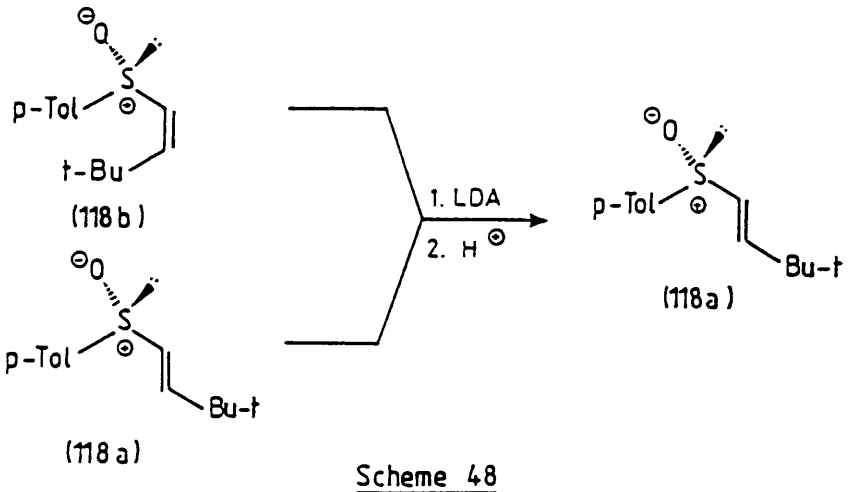
The diastereomeric pair (119a) and (119b) exhibited a great difference in polarity, a fact which helped in their separation (ΔR_f = 0.25) and emphasised by their very different solubilities in a range of solvents.

Analogous deprotonation and quenching of the (Z)-isomer (118b), gave the same pair of diastereoisomers (119a) and (119b) and in the same ratio.



(118b) (119a) (119b)

This was consistent with previous results and confirmation of the cis to trans isomerization of the α-lithiosulphoxide was obtained by deprotonation and reprotonation of the (Z)-(118b) and (E)-(118a) isomers, Scheme 48.



Scheme 48

The rather poor diastereoselectivity observed in the formation of (119a) and (119b) was very disappointing and not in accord with previously obtained results explained by the transition state, Fig. 8.

Until now, the reaction of the vinyl anion with trimethylacetaldehyde has been treated in a rather simplistic way, but one which fulfills requirements, i.e. the lithiated vinyl sulphoxide has been treated as a monomeric carbanionic species. This oversimplified picture seems to break down when trying to rationalize the formation of (119a) and (119b) as a 1:1 diastereomeric mixture and in reality, the lithiated anion's behaviour depends to a great extent on its actual structure, the degree of aggregation and the extent and nature of solvation.

The crystal structure of ethyl lithium in the solid phase is tetrameric.[118] The lithium atoms form a tetrahedron with each face of the tetrahedron having a carbon atom of the ethyl group sitting above it, Fig. 10.

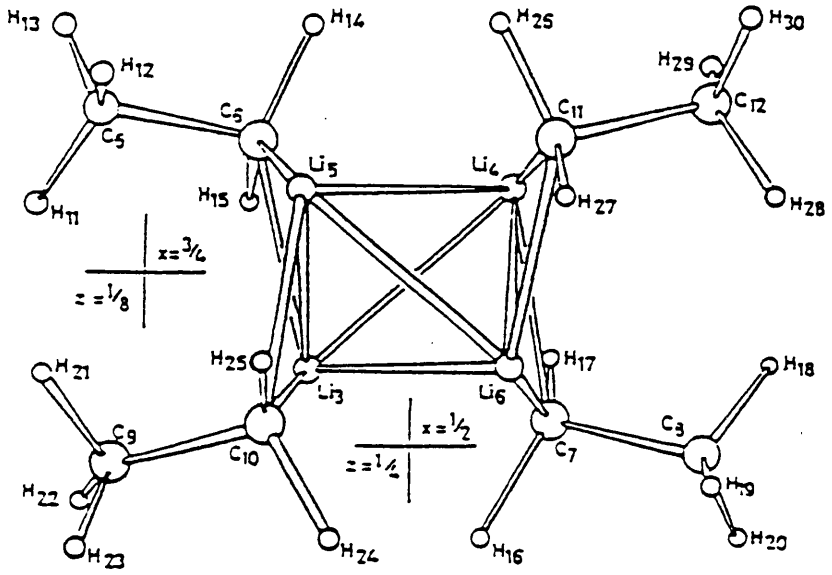


Fig.10

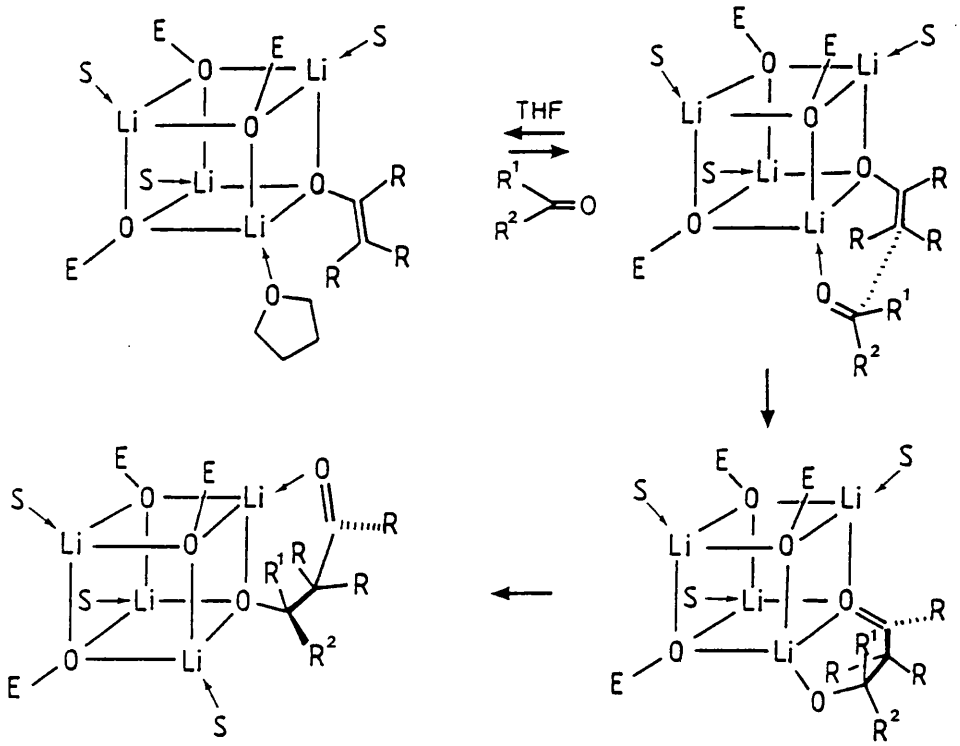
n-Butyllithium in a non-polar hydrocarbon solvent exists as the hexamer, but Ogle et al.[119] have demonstrated an equilibration between tetrameric and dimeric n-butyllithium in a co-ordinating solvent such as THF.

$$(BuLi)_4.4THF + 4THF \rightleftharpoons 2(BuLi)_2.4THF$$

Ogle et al.[119b] demonstrated the relative rates of reaction of the two species with benzaldehyde, the dimeric species being ca. 10x more reactive. Although their work gave no confirmation of the existence of a monomeric species, its presence could not be totally dismissed and the existence of other analogous monomeric lithio species is not improbable. Conversely, the existence of higher oligomeric species cannot be ruled out.

$$(RLi)_x.Solvent \rightleftharpoons (RLi)_4.Solvent \rightleftharpoons (RLi)_2.Solvent \rightleftharpoons RLi.Solvent$$

Seebach et al.[120] reported that lithium enolates can exist as tetrameric cubic structures in the solid state and also postulated that the tetrameric structures were the reactive species in solution, Scheme 49.



Scheme 49

Initially one of the four complexing solvent molecules is displaced by the electrophile and reaction follows. The environment met by an incoming substrate, however, suggests that the stereochemical course of the reaction is not a simple 1:1 relationship between enolate and electrophile but depends on the influence of all three adjacent enolates. This suggests a rather complex situation.

These ideas can be extrapolated to explain the different stereoselectivity in the reaction of (53b), (114a) and (118a) with trimethylacetaldehyde. Hybridization of these models leads to a structure for the lithiovinyl sulphoxide anion in a THF solution, where the anion sits above each face of a tetrahedron of lithium atoms, Fig. 11.

Only two of the four anionic species (R) are shown in full for simplicity. Replacement of the appropriate solvent molecule by tri-

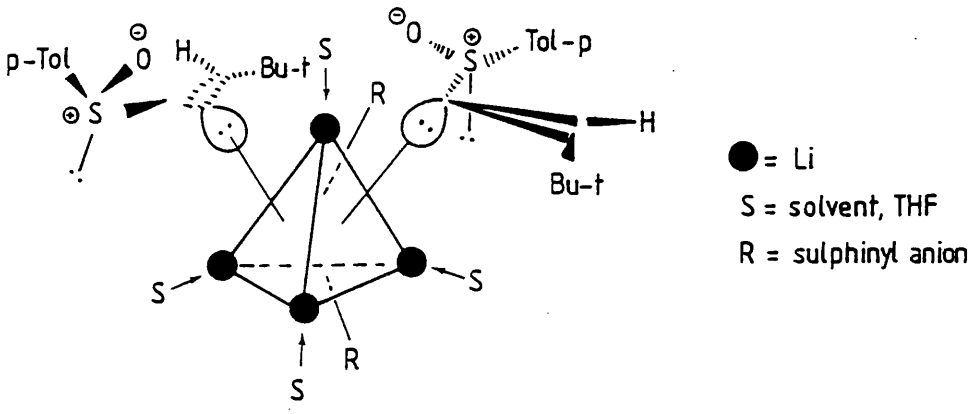


Fig. 11

methylacetaldehyde makes it possible for the anion to attack either face of the aldehyde in a non-stereoselective manner, leading to a 1:1 diastereomeric mixture, Fig. 12. This model involving the tetrameric anionic species works well for the vinyl sulphoxide (118a) and helps to explain the non-stereoselectivity of the addition. The earlier model utilizes the idea of monomeric anionic species for the vinyl sulphoxides (53b) and (114a) in their addition to trimethylacetaldehyde.

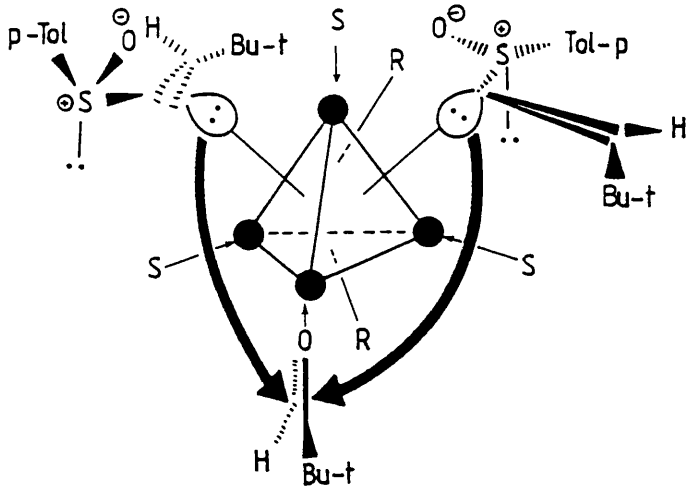
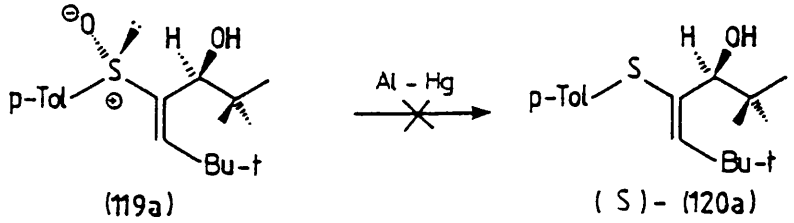


Fig. 12

Reduction of (119a) and (119b) to the corresponding enantiomeric sulphides, analogous to the reduction of (94a) using aluminium amalgam, would confirm the diastereomeric relationship between (119a) and (119b).

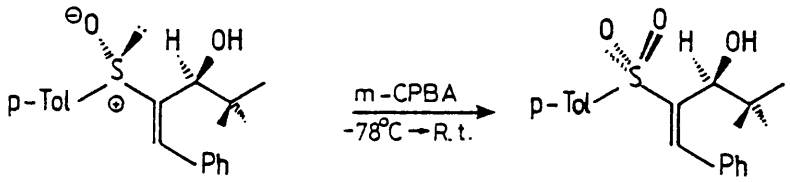
However, the attempted reduction of (119a) and (119b), using the same method as for the reduction of (94a), with prolonged reaction time, gave only the recovery of starting material in either case.



(119a) (S)- (120a)

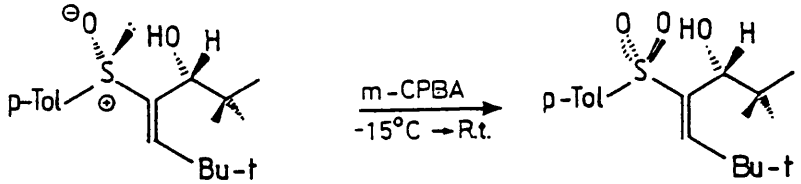
(119b) (R)- (120b)

However, oxidation of (94a) using m-CPBA in dichloromethane, allowing the solution to warm from -78°C to room temperature, gave the corresponding sulphone (121) in good yield (64%) as white crystals.



(94a) (121)

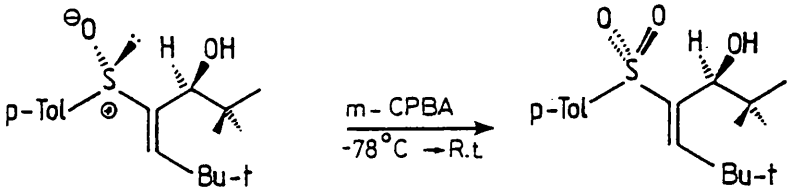
Accordingly, adopting the same procedure, the more polar diastereoisomer (119b) [arbitrarily assigned] was oxidized to the sulphone (122b) in 61% yield as a white solid and had an optical rotation measured at +21.3° (2.1 in $CHCl_3$).



(119b) (122b)

Similarly, the less polar diastereoisomer (119a) was oxidized to the sulphone (122a) in 46% yield, the portion of m-CPBA being added at a

temperature of -15°C and the reaction mixture allowed to warm slowly to room temperature. [At temperatures below -15°C, the solid precipitated out of solution.]



(119a) (122a)

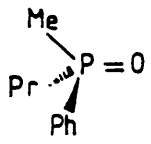
The optical rotation was measured at -20.8° (2.0 in $CHCl_3$) confirming that (122a) and (122b) were enantiomeric and that the diastereomeric sulphinyl allylic alcohols (119a) and (119b) had opposite configurations at the chiral carbon atom.

CHAPTER 4

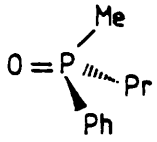
Chiral Vinyl Phosphorus Reagents

4.1 INTRODUCTION

The chemistry of carbanions generated α to a phosphorus moiety is dominated by the Wittig reaction and modifications of it.[121,123] This chapter concentrates on the generation and reaction of chiral Wittig-like carbanions of five valent four co-ordinate phosphinic acid derivatives. The stability of phosphorus ylids has already been discussed (see p.2) and the existence of compounds having a chiral phosphorus centre is well known, e.g. the enantiomeric phosphine oxides (123a) and (123b).



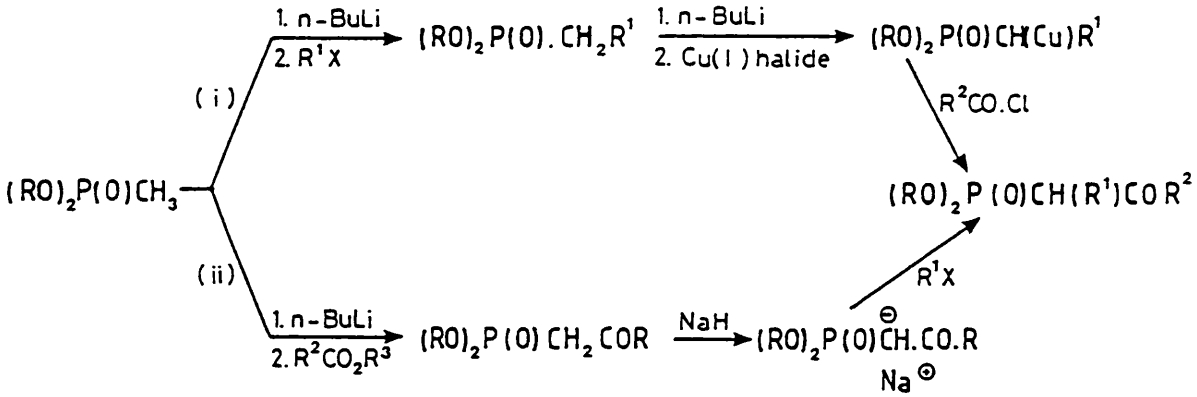
(-)-(S)-(123a)



(+)-(R)-(123b)

4.2 ALKYLATION AND ACYLATION OF PHOSPHINIC ACID DERIVATIVES

O,O'-Dialkyl alkylphosphonate esters can be readily alkylated and acylated at the carbon centre α to phosphorus,[122] Scheme 50.



Scheme 50

For pathway (i), the use of normal alkyl halides (R^1X) gives better results when X = I rather than when X = Br whilst for more reactive halides (e.g. allylic), bromides prove more satisfactory than chlorides. Because they are more stable in a basic medium, diethyl esters (R = Et)

are used in preference to dimethyl esters.

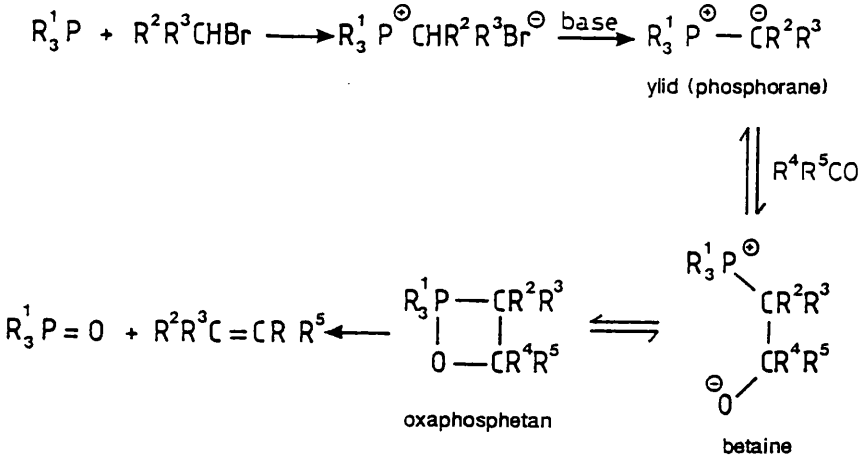
For pathway (ii), R^1X must be a reactive halide (e.g. allylic, acetylenic) as normal alkyl halides fail to react with the sodium enolate although the use of the more reactive potassium enolate can give satisfactory results when R^1 = Me and Et.

4.3 THE WITTIG REACTION[123]

The synthetic importance of converting an aldehyde or ketone into an alkene where the position of the olefinic double bond is unambiguous is obvious. The alkene double bond is formed by the reaction of the aldehyde or ketone with a phosphorus ylid (phosphorane), Fig. 13.

Fig. 13

Usually, the ylid is formed by the deprotonation of a phosphonium salt prepared from a triaryl (or trialkyl) phosphine and an alkyl halide. Scheme 51 shows the complete reaction sequence.

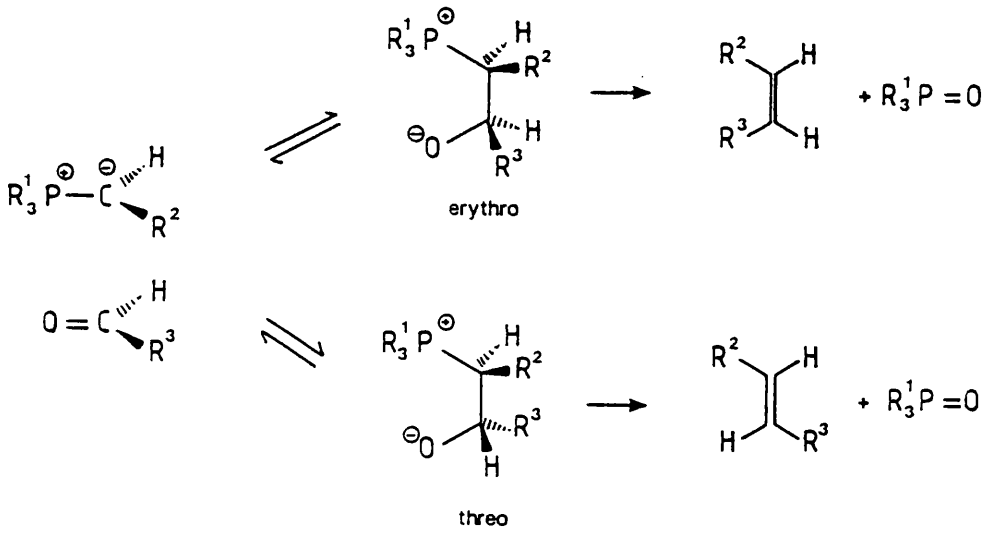


Scheme 51

The reactivity of the ylid and the rate determining step are governed by the nature of R^1, R^2 and R^3. Alkylidene trialkylphosphor-

anes (R^1, R^2 and R^3 are alkyl groups) are more reactive than alkylidene triphenylphosphoranes (R^1 = Ph) in the formation of the betaine because the positive charge on phosphorus is lessened by the inductive effect of the alkyl groups (R^1). However, for similar reasons the decomposition of the betaine becomes more difficult. If R^2 and R^3 are electron withdrawing groups, the negative charge on the ylid is stabilized and the reactivity towards the carbonyl group decreases. For these reagents the rate determining step is therefore the formation of the betaine. [Evidence for the formation of the betaine has been provided by the isolation of compounds of this type *via* trapping by protonation or complex formation with lithium salts.] The more electrophilic the carbonyl group, the more readily does the reaction proceed. If R^2 and R^3 are alkyl groups then the ylids are markedly nucleophilic and react readily with carbonyl groups making the decomposition of the betaine the rate determining step. Because the polarity of the carbonyl group is of little consequence in the step, these reagents react well with both aldehydes and ketones.

Resonance stabilized ylids react with aldehydes to give the (E)-alkene as the predominant product whilst non-stabilized ylids usually give more of the (Z)-alkene. With stabilized ylids the formation of the intermediate betaines is reversible allowing interconversion to the more stable threo form which collapses to the (E)-alkene (thermodynamic product), Scheme 52. With the non-stabilized ylid, the betaine formation is irreversible and conversion into the alkene proceeds mainly from the kinetically favoured erythro betaine.



Scheme 52

4.4 MODIFIED WITTIG REACTIONS[121,123]

Modifications using carbanions derived from phosphine oxides (124) and phosphonate esters (125) were developed to compensate for limitations of the normal Wittig reaction.

$$(Ph)_2P(O)CH_2R^1 \xrightarrow{base} (Ph)_2P(O)\overset{\ominus}{C}HR^1 \xrightarrow{R^2R^3CO} R^2R^3C{=}CHR^1 + (Ph)_2PO_2^{\ominus}$$

(124)

R^1 = alkyl, alkoxycarbonyl etc.

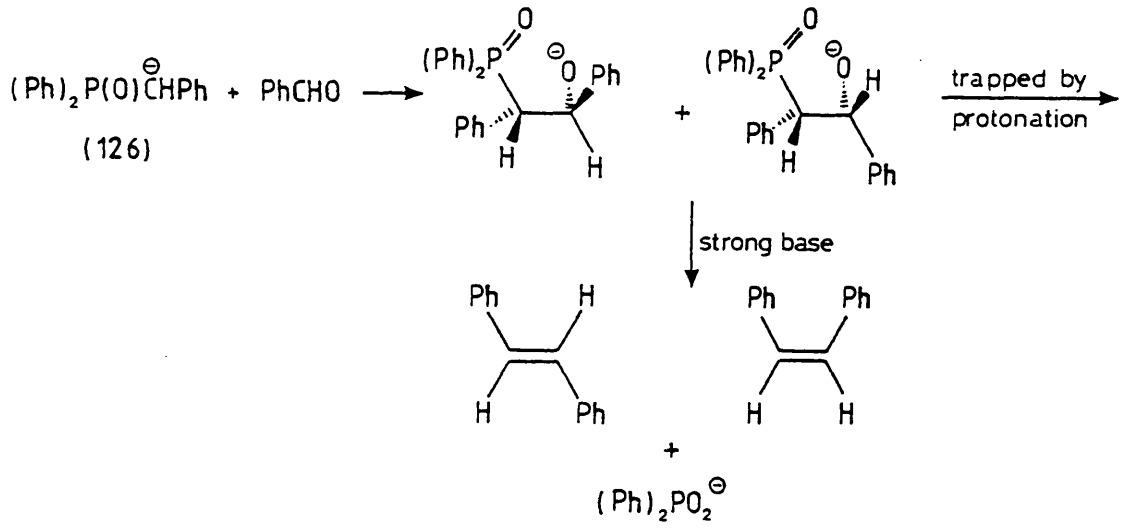
$$(RO)_2P(O)CH_2R^1 \xrightarrow{base} (RO)_2P(O)\overset{\ominus}{C}HR^1 \xrightarrow{R^2R^3CO} R^2R^3C{=}CHR^1 + (RO)_2PO_2^{\ominus}$$

(125) (127)

R = alkyl, phenyl, R^1 = resonance stabilizing group

Reaction of phosphine oxide derived carbanions (126) with an aldehyde leads to diastereomeric adducts which can be trapped by protonation or treated with a strong base to give the alkene and the phosphinate anion, Scheme 53.

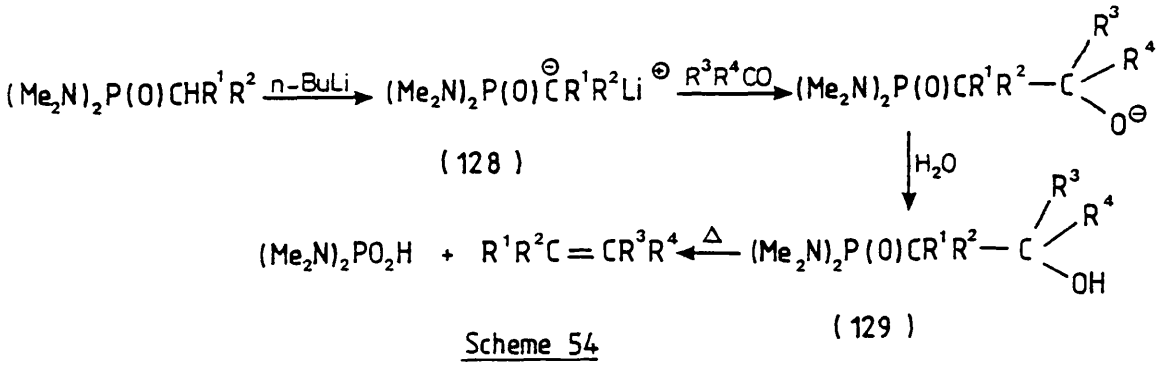
The phosphonate carbanions (127) are more nucleophilic than phosphonium ylids and react with greater ease and under milder conditions with carbonyls. This enhanced reactivity allows alkylation of the



Scheme 53

of the carbon α to phosphorus unlike the phosphonium ylids of the normal Wittig reaction. Additionally, the water soluble phosphate ions allow much easier separation from the olefin and the ready availability of phosphonates from the Arbuzov reaction makes it advantageous to use phosphonate esters.

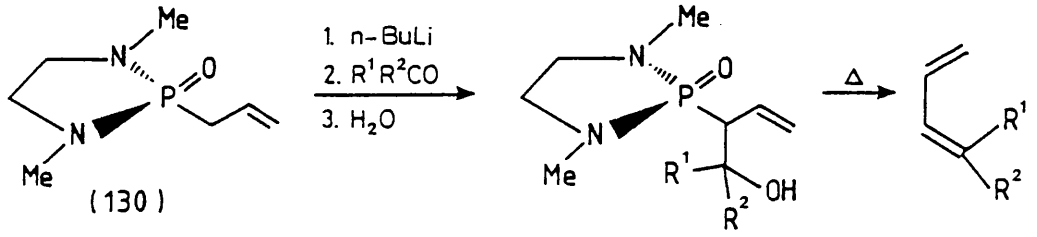
Other variations have included the use of the α-lithium derivatives of phosphonic acid bisamides (128). The initially formed β-hydroxy phosphonamide (129) can be isolated and purified and subsequent thermal decomposition leads to the olefin. Because the pure diastereomeric phosphonamides (129) can be isolated and separated, control of the olefin geometry is achieved,[124] Scheme 54.



Scheme 54

The use of the β-hydroxy phosphonamides for olefin synthesis was

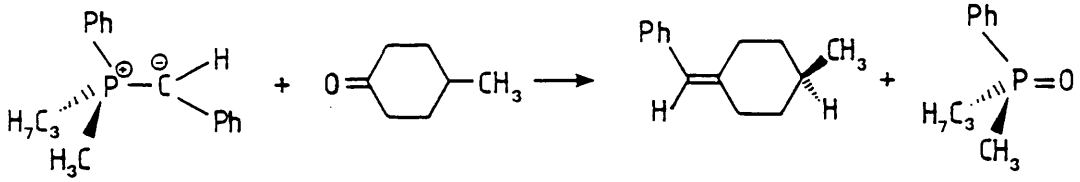
extended to diene synthesis by Corey,[124] using an allyl diazaphospholidine species (130), Scheme 55.



Scheme 55

4.5 CHIRAL PHOSPHORUS CARBANIONS

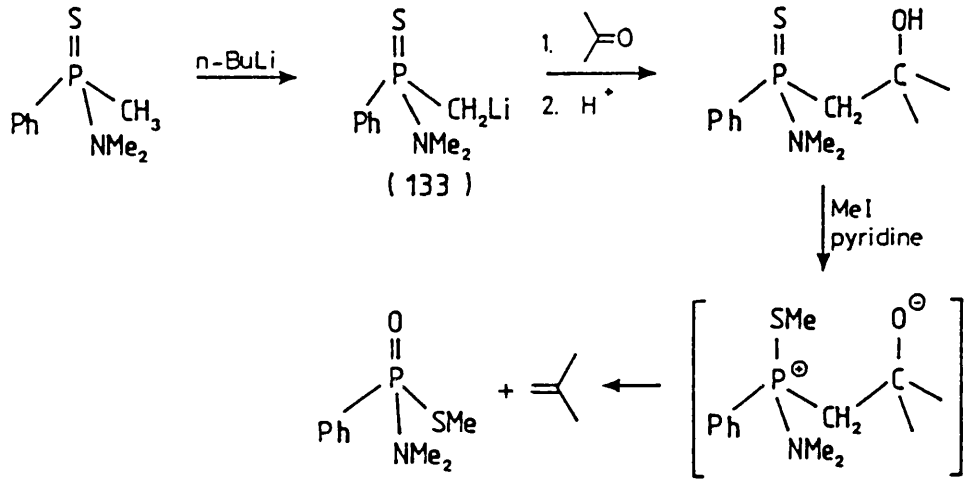
The use of an optically active phosphorus ylid to obtain partial asymmetric synthesis in the preparation of a number of chiral cyclohexanes containing an exocyclic double bond was demonstrated by Lienert.[125] The optically active ylid (R)-(131) prepared from (+)-(S)-benzylmethylphenylpropylphosphonium bromide reacted with 4-methylcyclohexanone to give (+)-(S)-benzylidene-4-methylcyclohexanone (132) in 43% optical yield.



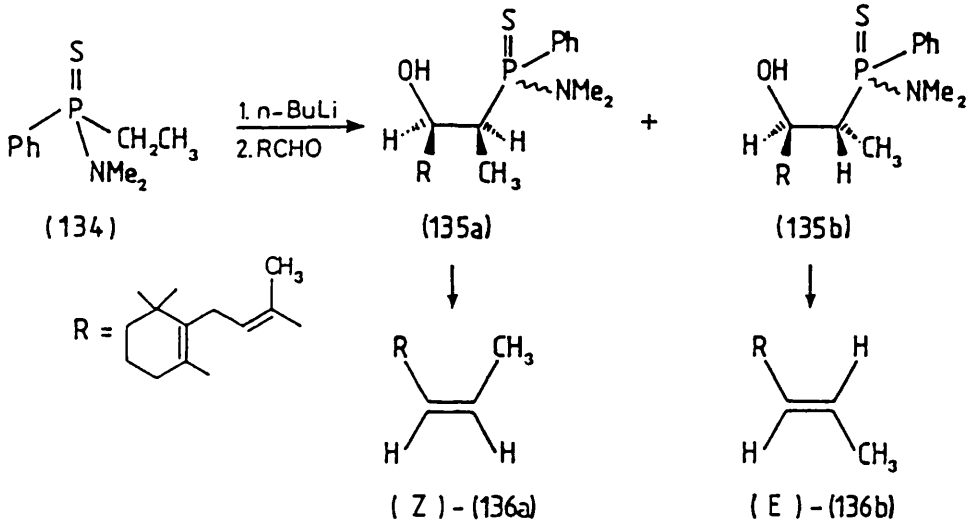
(R)-(131) (+)-(S)-(132)

More recently, Johnson[126] described a method for the alkylidenation of ketones and selected aldehydes using a chiral P-(α-lithioalkyl)-phosphinothioic amide (133), Scheme 56.

The anion (133) could be smoothly alkylated using methyl iodide, n-butyl bromide and benzyl bromide. Deprotonation of the racemic methylated adduct (134) and reaction with a prochiral carbonyl substrate (RCHO) gave a diastereomeric mixture of four components, Scheme 57.



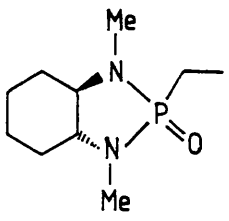
Scheme 56



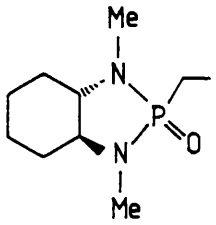
Scheme 57

The relative R_f's of the diastereoisomers were more sensitive to the relative configuration at carbon than at phosphorus and so the diastereomeric pair (135a) was easily separated from the other pair (135b). Treatment with methyl iodide and pyridine gave the corresponding (Z)-(136a) and (E)-(136b) alkenes.

Hanessian et al.[127] reported the formation of optically active olefins from achiral ketones by use of the enantiomeric bicyclic phosphonamides (137) and (138).

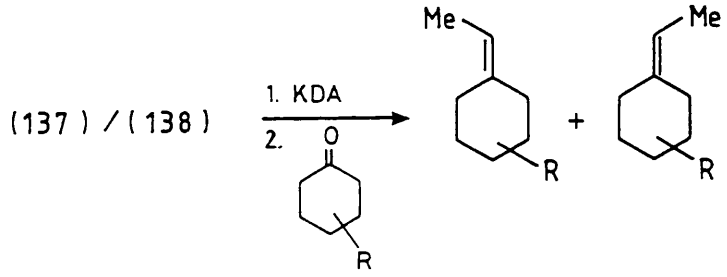


(R,R)-(137)

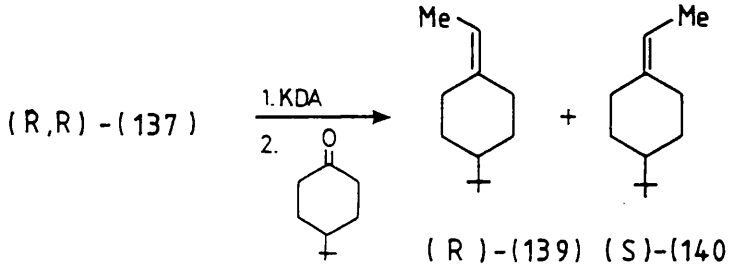


(S,S)-(138)

Deprotonation of (137)/(138) and quenching with a substituted cyclohexanone gave a mixture of diastereoisomers with optical purity ranging from 69-90%.



For example, quenching carbanionic (R,R)-(137) with 4-tert-butylcyclohexanone gave the corresponding (R)-(4-tert-butylcyclohexylidene)-ethane (139) in 82% yield and 90% optical purity.



(R)-(139) (S)-(140)

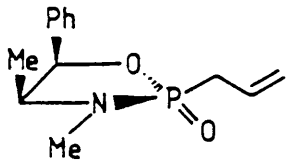
95 5

Nucleophilic attack occurs from the more accessible face of the anion, the high degree of asymmetric olefination in the example above being attributed to attack from the equatorial side of the carbonyl group by the pro-R face of the anion.

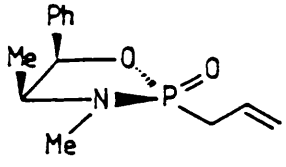
Reaction of carbanionic (137)/(138) with alkyl halides gave 80% of one diastereoisomer because easier access by the bulky base to the pro-R hydrogen in the (R,R)-(137) reagent leads to a carbanion that shows high

diastereofacial bias.

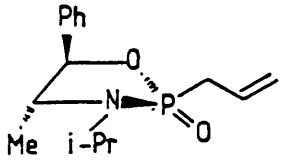
To complement the work of Haynes[128] who reported the formation of a single product from the reaction of allyl diphenyl phosphine oxide with cyclopentenones and analogous to the chiral cyclic phosphorus carbanion used by Hanessian,[127] Hua et al.[129] reported the use of the chiral allyl phosphorus species (141)-(144) to obtain good enantioselectivity in the 1,4-addition of the anion to cyclic enones.



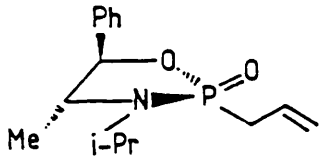
(141)



(142)

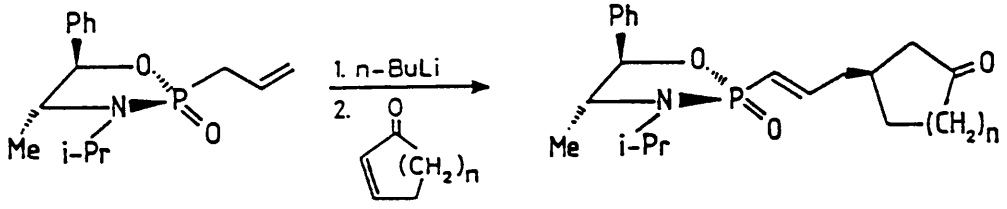


(143)



(144)

The use of (141) and (142) gave products of 70-74% ee but the use of (143) gave excellent optical yields. The presence of i-Pr at nitrogen prevents chelation of the lithium ion with the O=P-N side of the molecule. Hence, carbanionic (143) reacts with cyclo-pentenone, -hexenone and -heptenone to give the 1,4-adduct in 98, 88 and 95% ee.

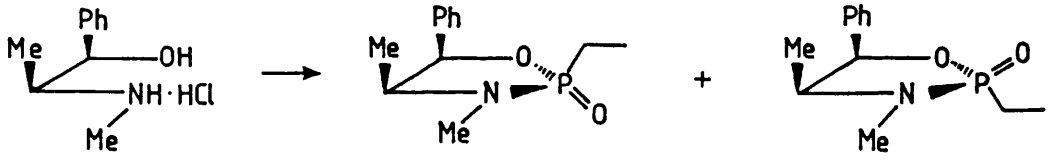


(143)

4.6 RESULTS AND DISCUSSION

Hanessian's use of the enantiomeric bicyclic phosphonamides (137) and (138) in asymmetric alkylation[127] suggested that related chiral cyclic phosphorus compounds might behave similarly. The objective was to synthesise such related compounds and study their reaction with electrophiles in the presence of base. A small amount of work had already been performed in this department (Dr. M. R. Selim, Ph.D. Thesis, 'Studies on Asymmetric Induction', 1987) and reproduction and extension of this experimentation was the initial aim.

Based on the work of Inch et al.,[130] the chiral 1,3,2-oxazaphospholidin-2-ones (145a) and (145b) were prepared from (-)-ephedrine hydrochloride (146) and ethylphosphonic dichloride (147) in benzene containing triethylamine. [(147) was prepared by the addition of phosphorus pentachloride to diethyl ethanephosphonate.]



(146) (145a) (145b)

The two isomers were easily separable by flash chromatography and were obtained as white solids, (145a) in 32% yield and (145b) in 28% yield. Full spectral data and analyses on both isomers were recorded. [The previous work[131] had given 90 MHz ^{1}H δ_H and 24 MHz ^{31}P δ_P for (145a) and 300 MHz ^{1}H δ_H, 75 MHz ^{13}C δ_C, 24 MHz ^{31}P δ_P and m/z for (145b).] The assignment of the configuration at phosphorus was based on the comparative downfield shift of H-5 in each isomer in the ^{1}H n.m.r. spectra. For (145a) the H-5 proton has a 1,3-cis-relationship with the P=O group and is deshielded relative to H-5 in (145b).[130,131]

Deprotonation of (145a) and (145b) proved difficult and no direct evidence for the formation of an α-phospholidinocarbanion was obtained. Attempted deprotonation with LDA and n-butyllithium at temperatures ranging from -78°C to room temperature and over periods ranging from 1h to 20h failed to give the ethylated or deuterated products on quenching with ethyl iodide and D_2O respectively. In all cases, only the recovery of starting material and isolation of decomposition products resulted. [This was contradictory to ref. (131) where the deprotonation of (145a) and (145b) with n-butyllithium and ethylation gave diastereomeric products in ratios of 19:1 and 1:1.2 respectively. Unfortunately, no experimental data was provided!]

However, the continuing interest in α-heteroatomic vinylic compounds led to the preparation of the vinyl 1,3,2-oxazaphospholidin-2-ones (148a) and (148b) from styrylphosphonic dichloride (149). (149) was prepared by the procedure of Schmutzler[132] from the addition of a styrene solution in benzene to phosphorus pentachloride and decomposition of the resulting salt with sulphur dioxide, Scheme 58.

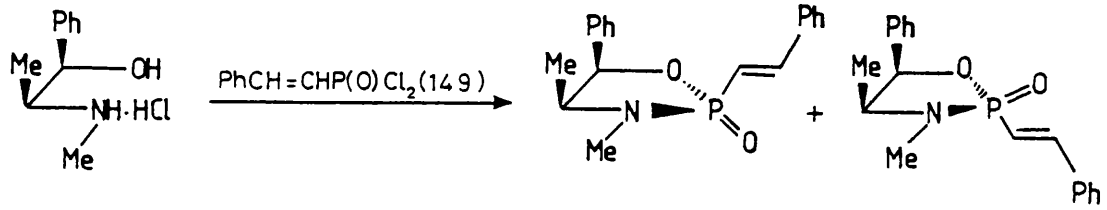
$$PhCH{=}CH_2 \xrightarrow{2PCl_5} PhCH{=}CH\overset{\oplus}{P}Cl_3\overset{\ominus}{P}Cl_6 \xrightarrow{2SO_2} PhCH{=}CHP(O)Cl_2$$

(149)

Scheme 58

Analogous to the preparation of (145a) and (145b), the addition of (-)-ephedrine hydrochloride (146) to a solution of (149) in benzene containing triethylamine gave the vinyl 1,3,2-oxazaphospholidin-2-ones (148a) and (148b) as crystalline white solids in 41% and 39% yields respectively after flash chromatography. Both isomers gave 300 MHz ^1H δ_H and 24 MHz ^{31}P δ_P values consistent with the literature.[133]

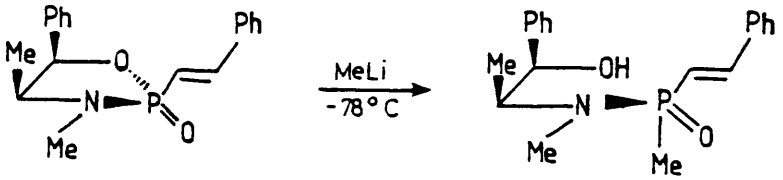
As before, the configuration at phosphorus of each isomer was determined by the relative downfield shift of the H-5 proton in the ^1H n.m.r.



(146) (148a) (148b)

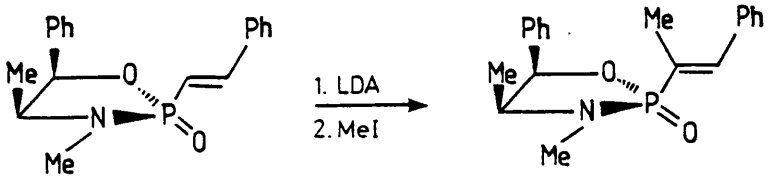
spectra.

The removal of the more acidic vinylic proton on the carbon centre α to phosphorus was achieved using LDA as the base. [The addition of methyllithium to (148a) at -78°C resulted in the opening of the oxaza-phospholidinone ring by cleavage of the P-O bond to form the ring opened product (150).]



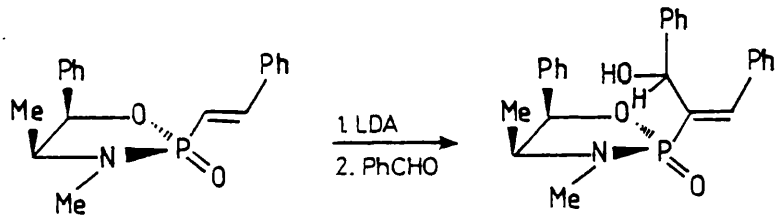
(148a) (150)

Hence, a solution of (148a) in THF was added to an LDA solution at -78°C and after 15 min. quenched with methyl iodide. The ^{31}P n.m.r. spectrum of the crude product showed a single peak [proton decoupled spectrum) at δ_p 35.09 [δ_p 30.25 for (148a)], whilst the 90 MHz ^1H n.m.r. indicated that the product was the methylated compound (151); the signal for the new methyl group appeared as a doublet of doublets at δ_H 2.1 with J_p ca. 15 Hz and a further smaller coupling due to the proton in the allylic position.



(148a) (151)

Purification of (151), however, proved difficult; it would not distil and flash chromatography failed to yield a purer sample. Furthermore, the reaction of lithiated (148a) with benzaldehyde proved as frustrating. The vinyl carbanion was generated as before with LDA and subsequently quenched with benzaldehyde. The ^{31}P n.m.r. spectrum of the crude reaction mixture showed the presence of four products as well as starting material (148a) in a ratio of 1 (starting material): 2.97:1.01:1.88:2.51. Separation by flash chromatography gave three major fractions; the first fraction consisted of a mixture of decomposition products whilst the other two fractions were assigned the structures (152a) and (152b), from the ^{1}H n.m.r. spectra, diastereomeric at the new chiral centre.

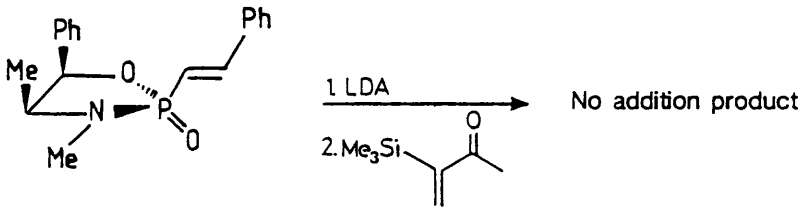


(148a) (152a) and (152b)

However, the reaction was not deemed a success because the diastereomeric ratio was measured at 1:1.18, with a total yield of (152a) and (152b) of only 35% and separation by flash chromatography on a silica gel column resulting in partial decomposition of the products.

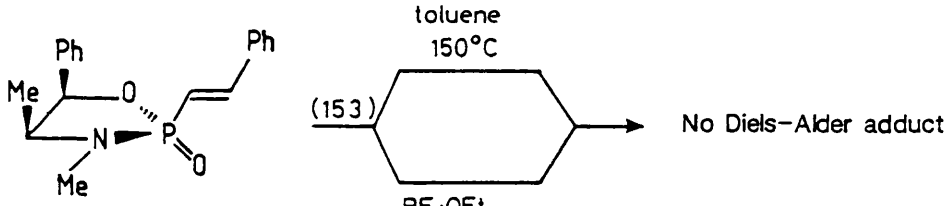
The use of lithiated (148a) in the attempted Michael addition to 3-trimethylsilyl-3-buten-2-one at -78°C and temperatures up to room temperature also failed to give a satisfactory result with only the isolation of recovered starting material.

The use of (148a) as a dienophile in the Diels-Alder reaction was also investigated. The thermal reaction of (148a) and 1-methoxy-3-(trimethylsiloxy)-1,3-butadiene[134] (Danishefsky's diene) (153) in toluene at



(148 a)

150°C gave only starting material as indicated by t.l.c. Similarly, the Lewis acid ($BF_3.OEt_2$) catalysed Diels-Alder reaction in dichloromethane at -78°C gave only the recovery of starting material.



(148a)

Despite the lack of positive results in the use of the described chiral oxazaphospholidinones, it is felt that their use in asymmetric reactions warrants further investigation.

EXPERIMENTAL

EXPERIMENTAL

All 90 MHz ^{1}H n.m.r. spectra were recorded on a Varian EM-390 spectrometer and all ^{31}P n.m.r. (24 MHz) on a Jeol JNM-FX-60 spectrometer. High-field ^{1}H n.m.r. (300 MHz) and ^{13}C n.m.r. (75 MHz) spectra were recorded on a Bruker AM-300 spectrometer at the University of Leicester. ^{1}H n.m.r. (400 MHz) and ^{13}C n.m.r. (100 MHz) spectra were recorded using the high-field n.m.r. service at the University of Warwick.

Accurate mass measurements were made at the SERC mass spectrometry centre, University College of Swansea and standard mass spectra were recorded on a Micromass 16B spectrometer. Elemental analysis was carried out by C.H.N. Analysis, Wigston, Leicester or Butterworth Laboratories, Teddington, Middlesex. Optical rotations were recorded on a Perkin-Elmer 141 polarimeter and infra-red spectra on a Perkin-Elmer 298 spectrometer. Melting points were determined on a Kofler hot-stage and are uncorrected.

Flash chromatography was carried out according to the method of Still *et al.*[†] using silica gel manufactured by Merck & Co., Kiesel 60, 230-400 mesh (ASTM). Purifications by chromatotron were performed using model 7924T and Merck & Co. Kieselgel 60 PF 254 silica plates. T.l.c. was conducted on precoated aluminium sheets (60F-254) with a 0.2 mm layer thickness, manufactured by Merck & Co. Preparative layer chromatography was conducted on precoated glass plates (60F-254), also manufactured by Merck & Co.

G.l.c. was carried out on a Pye Unicam PU 4500 capillary chromatograph and h.p.l.c. on a Shimadzu LC-4A liquid chromatograph.

The concentration of the n-butyllithium was determined by back titra-

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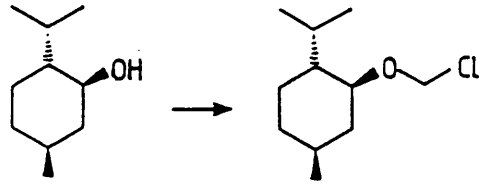
[†] W. C. Still, M. Kahn and A. Mitra, J. Org. Chem., 1978, 43, 2923.

tion with 0.5M hydrochloric acid from solutions in dibromoethane and water using phenolphthalein as an indicator.

Petroleum ether refers to the 40-60°C fraction and all petroleum ether, petroleum ether 60-80°C and ethyl acetate was distilled prior to use. THF, toluene and benzene were distilled from sodium metal in the presence of benzophenone. Ether refers to diethyl ether and was distilled from lithium aluminium hydride. Dichloromethane, triethylamine and pyridine were distilled from powdered calcium hydride. Methanol and ethanol were distilled from magnesium and iodine. Purification of less frequently used solvents will be described as the text requires.

Superscripts in the experimental text refer to notes at the end of the experiment and <u>not</u> to the main references.

Preparation of Chloromenthoxymethane (21)[1]



(21)

(-)-Menthol (15.6g, 0.10 mol) and paraformaldehyde (9.0g, 0.10 mol) were mixed together and poured into the reaction flask. A stream of dry hydrogen chloride gas[2] was passed over the stirred mixture, at 0°C, and after a short time the solids fused into a thick liquid. After 8h, the viscous liquid was extracted into ether and the small volume of water separated. The solution was dried (anhydrous $CaCl_2$) and the solvent and any excess hydrogen chloride gas removed in vacuo to give chloromenthoxymethane (21) as a colourless liquid[3] (12.5g, 61%).

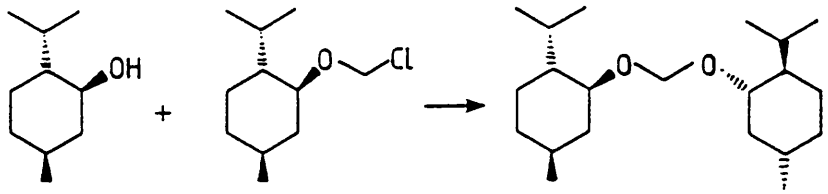
δ_H (300 MHz; $CDCl_3$) 0.68-1.49 (17H, m),[4] 1.60-1.71 (2H, m), 2.07-2.20 (2H, m), 3.53 (1H, td, J = 10.7, 4.4 Hz, H-1'), 5.57 (1H, d, J = 12.5 Hz, H-1), 5.59 (1H, d, J = 12.5 Hz, H-1);

δ_C (75 MHz; $CDCl_3$) 15.96(q), 21.04(q), 22.24(q), 23.04(t), 25.15(d), 31.42(d), 34.20(t), 39.93(t), 47.84(d), 78.80(d), 81.19(t).

Notes

1. Known compound see Ref. 135. Literature procedure see Ref. 7(a).
2. Hydrogen chloride gas dried by passing through concentrated sulphuric acid.
3. The liquid was not distilled but used crude in the next stage.
4. Should be 14H (probable menthol contamination).

Preparation of Methylenedioxybis-(2-isopropyl-5-methyl-cyclohexane) (24)[1]



(21) (24)

(-)-Menthol (0.78g, 5 mmol) and chloromenthoxymethane (21) (1.02g, 5 mmol) were dissolved in THF (10 ml) and refluxed, overnight, under nitrogen. The reaction mixture was poured into water (30 ml), the aqueous solution extracted with ether (2 x 50 ml), the combined extracts washed with water (50 ml) and dried ($MgSO_4$). Removal of the solvent *in vacuo* followed by flash chromatography (9:1 petroleum ether-ether) gave methylenedioxybis-(2-isopropyl-5-methyl-cyclohexane) (24) as a white solid (1.07g, 66%), m.p. 52-55°C (m.p. recorded after recrystallisation from ethanol).

R_f 0.52 (9:1 petroleum ether-ether);

δ_H (300 MHz; $CDCl_3$) 0.75-1.66 (32H, m), 2.13-2.23 (4H, m), 3.26 (2H, td, J = 10.5, 4.3 Hz, H-1'), 4.81 (2H, s, H-1);

δ_C (75 MHz; $CDCl_3$) 16.12, 21.22, 22.31, 23.17, 25.34, 31.67, 34.43, 42.46, 48.64, 79.11, 95.27;

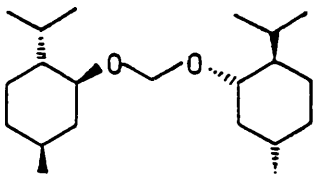
$C_{21}H_{40}O_2$ requires 324.3028

found 324.3021.[2]

Notes

1. Known compound see Ref. 33.
2. Ammonia chemical ionization conditions used which showed $(M+NH_4^+)$ molecular ion.

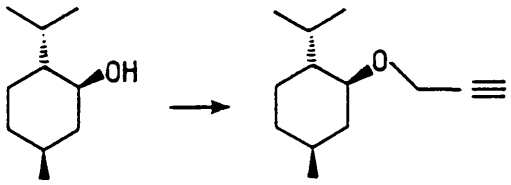
Hydrolysis of Methylenedioxybis-(2-isopropyl-5-methyl-cyclohexane) (24)



(24)

A solution of methylenedioxybis-(2-isopropyl-5-methyl-cyclohexane) (24) (65 mg, 0.2 mmol) in THF (4 ml) and hydrochloric acid (0.5M) (2 ml) was refluxed overnight. T.l.c. showed the complete disappearance of starting material. The reaction mixture was diluted with ether (10 ml), extracted, and the aqueous solution re-extracted with a further volume of ether (2 x 10 ml). The combined ether extracts were washed with saturated aqueous sodium hydrogen carbonate solution (30 ml), water (30 ml) and dried ($MgSO_4$). Removal of the solvent in vacuo afforded a white solid in quantitative yield which t.l.c. and ^1H n.m.r. showed to be menthol.

Preparation of 3-Menthoxypropyne (22)[1]



(22)

(-)-Menthol (6.0g, 38 mmol) was added to a suspension of sodium hydride[2] (1.14g, 38 mmol) in DMF[3] (15 ml), under nitrogen. The mixture was stirred until the evolution of hydrogen had ceased and was then warmed to 50°C over 1h, followed by stirring for a further 2h at this temperature. After this time, propargyl bromide (3.9 ml, 35 mmol) in DMF (6 ml) was added dropwise, when an immediate brown colouration was observed. The reaction mixture was stirred for 5h at 50°C, then poured into water (100 ml) and acidified. The aqueous solution was extracted with ether (3 x 100 ml), the combined ether extracts were filtered, washed successively with water (300 ml), sodium thiosulphate solution (300 ml), brine (300 ml), water (300 ml) and dried ($MgSO_4$). The solvent was removed in vacuo and after flash chromatography (7:3 petroleum ether-ether), 3-menthoxypropyne (22) was obtained as an oil (3.48g, 47%). [Further purification by Kugelröhr distillation (110°C at 5 mmHg) yielded a colourless oil.]

R_f 0.59 (7:3 petroleum ether-ether);

$C_{13}H_{22}O$ requires C 80.35%, H 11.41%, N 0.00%,

found C 80.26%, H 11.35%, N 0.00%.

δ_H (300 MHz; $CDCl_3$) 0.73-1.68 (16H, m), 2.08-2.28 (2H, m), 2.37 (1H, t, J = 2.4 Hz, H-1),[4] 3.27 (1H, td, J = 10.5, 4.2 Hz, H-1'), 4.14 (1H, dd, J = 15.8, 2.4 Hz, H-3), 4.22 (1H, dd, J = 15.8, 2.4 Hz, H-3);

δ_C (75 MHz; $CDCl_3$) 16.24, 21.00, 22.33, 23.34, 25.43, 31.50, 34.50,

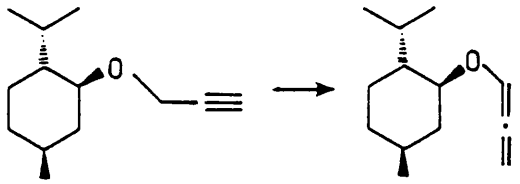
39.85, 48.23, 55.24, 73.46, 78.06.

M/Z 194 (M^+), 138(52), 123(27), 109(100).

Notes

1. Adapted literature procedure see Ref. 34.
2. The sodium hydride was washed free of oil using petroleum ether 60-80°C.
3. Distilled at reduced pressure, prior to use.
4. Decoupling at δ2.37 caused the signals at δ4.14 and δ4.22 to collapse to doublets.

Preparation of Menthoxy-1,2-propadiene (23)[1]



(22) (23)

Freshly sublimed potassium tert-butoxide (0.90g, 8 mmol) was added to a solution of 3-menthoxypropyne (22) (1.38g, 7.1 mmol) in tert-butyl alcohol[2] (20 ml), under nitrogen, and the mixture stirred at 83°C, for 6h, after which time t.l.c. showed the complete disappearance of starting material. The mixture was poured into water (50 ml) and the aqueous solution extracted with ether (4 x 40 ml). The combined ether extracts were dried ($MgSO_4$), and the solvent removed in vacuo to give menthoxy-1,2-propadiene (23) as a yellow oil (1.02g, 74%).[3]

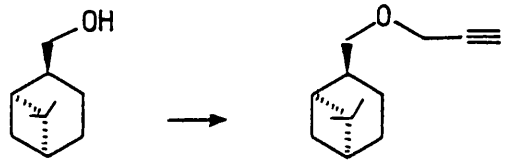
R_f 0.69 (7:3 petroleum ether-ether);

δ_H (90 MHz; $CDCl_3$) 0.55-2.35 (21H, m),[4] 3.45 (1H, td, J = 10.5, 4.5 Hz, H-1'), 5.35 (2H, d, J = 6 Hz, H-3), 6.55 (1H, t, J = 6 Hz, H-1);

Notes

1. See Ref. 29.
2. Distilled from magnesium and iodine prior to use.
3. The crude yield is quoted as the allene could not be distilled and decomposed on a silica gel flash chromatography column. It proved to be very unstable, even at a temperature of -30°C, overnight.
4. Should be 18H.

Preparation of 3-Myrtoxypropyne (25)



(25)

Using the same procedure as for the preparation of (22),[1] (-)-trans-myrtanol (2.07 ml, 13 mmol) was added to sodium hydride (0.39g, 13 mmol) in DMF (15 ml) and quenched with propargyl bromide (1.3 ml, 11 mmol) in DMF (3 ml). Work-up afforded a brown viscous oil which after distillation (170°C at 0.4 mmHg) and flash chromatography (19:1 petroleum ether-ether) gave 3-myrtoxypropyne (25) as a colourless oil (0.94g, 38%).

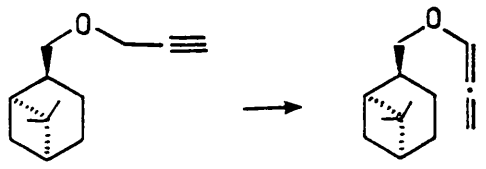
R_f 0.65 (7:3 petroleum ether-ether);

δ_H (90 MHz; $CDCl_3$) 0.85 (3H, s, CH_3), 1.00-2.35 (16H, m),[2] 2.4 (1H, t, J *ca.* 2 Hz, H-1), 3.3 (2H, d, J *ca.* 7.5 Hz, H-1'), 4.05 (2H, d, J *ca.* 2 Hz, H-3).

Notes

1. See p.95.
2. Should be 13H.

Preparation of Myrtoxy-1,2-propadiene (26)



(25) (26)

Using the same procedure as for the preparation of (23),[1] freshly sublimed potassium tert-butoxide (0.60g, 5.4 mmol) was added to a solution of 3-myrtoxypropyne (25) (0.94g, 4.9 mmol) in tert-butyl alcohol (15 ml). After stirring, at 83°C, under nitrogen, until t.l.c. indicated the disappearance of starting material, the reaction mixture was subjected to work-up to give myrtoxy-1,2-propadiene (26) as an oil (0.78g, 83%).[2]

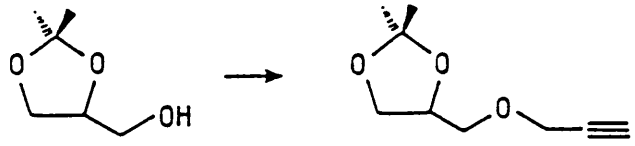
R_f 0.76 (7:3 petroleum ether-ether);

δ_H (90 MHz; $CDCl_3$) 0.85 (3H, s, CH_3), 1.15-2.6 (17H, m),[3] 3.35 (2H, d, J *ca.* 7.5 Hz, H-1'), 5.35 (2H, d, J *ca.* 6 Hz, H-3), 6.65 (1H, t, J *ca.* 6 Hz, H-1).

Notes

1. See p.97.
2. The allene was unstable to purification techniques - it decomposed on a silica gel flash chromatography column and on distillation.
3. Should be 13H.

Preparation of 1,2-O-Isopropylidene-1,2-dihydroxy-3-(2-propynyl-1-oxy)-propane (27)



(27)

Using the same procedure as for the preparation of (22),[1] 1,2-O-isopropylidene-1,2,3-trihydroxy-propane[2] (10g, 76 mmol) in DMF (15 ml) was added to sodium hydride (2.28g, 76 mmol) in DMF (20 ml)[3] and quenched with propargyl bromide (8.4 ml, 76 mmol) in DMF (10 ml). Work-up afforded a brown oil which after Kugelrohr distillation (*ca.* 16 mmHg) gave 1,2-O-isopropylidene-1,2-dihydroxy-3-(2-propynyl-1-oxy)-propane (27) as a colourless liquid (5.8g, 45%).

R_f 0.63 (ether);

δ_H (300 MHz; $CDCl_3$) 1.36 (3H, d, J = 0.6 Hz, CH_3), 1.43 (3H, d, J = 0.5 Hz, CH_3), 2.46 (1H, t, J = 2.4 Hz, H-3'), 3.57 (1H, dd, J = 9.7, 5.4 Hz), 3.61 (1H, dd, J = 9.7, 5.7 Hz), 3.75 (1H, dd, J = 8.3, 6.3 Hz), 4.07 (1H, dd, J = 8.3, 6.4 Hz), 4.19 (1H, dd, J = 15.8, 2.4 Hz, H-1'), 4.24 (1H, dd, J = 15.8, 2.4 Hz, H-1'), 4.30 (1H, m, H-2);

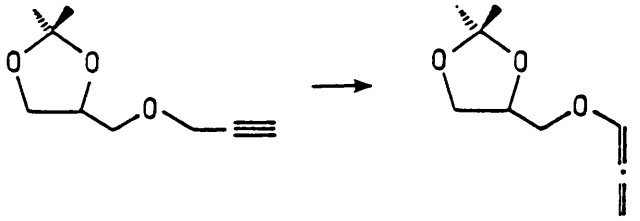
δ_C (75 MHz; $CDCl_3$) 25.4(q), 26.7(q), 58.6(t), 66.6(t), 70.7(t), 74.4(s), 74.7(d), 79.3(d), 109.4(s);

M/Z 171 (M^+ + 1, 4), 155(81), 117(25), 101(100).

Notes

1. See p.95.
2. The alcohol is racemic. Prepared by Dr. M. R. Selim who kindly left this compound after completing his work, see Ref. 136.
3. Procedure altered in that the reaction mixture was heated to 70°C rather than 50°C.

Preparation of 1,2-O-Isopropylidene-1,2-dihydroxy-3-(1,2-propadienyl-1-oxy)-propane (28)



(27) (28)

Using the same procedure as for the preparation of (23),[1] freshly sublimed potassium tert-butoxide (1.51g, 13.5 mmol) was added to a solution of 1,2-O-isopropylidene-1,2-dihydroxy-3-(2-propynyl-1-oxy)-propane (27) in tert-butyl alcohol (20 ml). After stirring, at 83°C, under nitrogen, until t.l.c. indicated the disappearance of starting material, the reaction mixture was subjected to work-up to give the crude allene. Kugelröhr distillation (125°C at 15 mmHg) afforded a pale yellow liquid (1.70g, 85%) which after further purification by flash chromatography (1:1 petroleum ether-ether) gave 1,2-O-isopropylidene-1,2-dihydroxy-3-(1,2-propadienyl-1-oxy)-propane (28) as a colourless liquid (1.12g, 56%).[2]

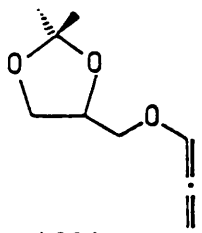
R_f 0.75 (ether);

δ_H (90 MHz; $CDCl_3$) 1.35 (3H, s, CH_3), 1.45 (3H, s, CH_3), 3.5-4.5 (5H, m), 5.45 (2H, d, J *ca.* 6 Hz, H-3'), 6.75 (1H, t, J *ca.* 6 Hz, H-1').

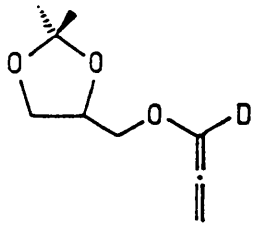
Notes

1. See p.97.
2. The allene proved to be more stable than (23) and (26) prepared previously, although distillation and flash chromatography did not completely purify it.

Deuteration of 1,2-O-Isopropylidene-1,2-dihydroxy-3-(1,2-propadienyl-1-oxy)-propane (28)



(28)



(29)

n-Butyllithium[1] (190 µl, 0.5 mmol) was added dropwise to a solution of 1,2-O-isopropylidene-1,2-dihydroxy-3-(2-propynyl-1-oxy)-propane (28) (56 mg, 0.3 mmol) in THF (1 ml), under nitrogen, at -78°C. The yellow solution was left stirring at this temperature for 1½ h and then quenched with a 1:1 D_2O/THF mixture. After allowing to warm to room temperature over 1h, the solution was poured into water and the aqueous solution extracted with ether (2 x 10 ml). The combined ether extracts were dried ($MgSO_4$) and the solvent removed in vacuo to leave the crude deuterated product.[2]

R_f 0.73 (ether);

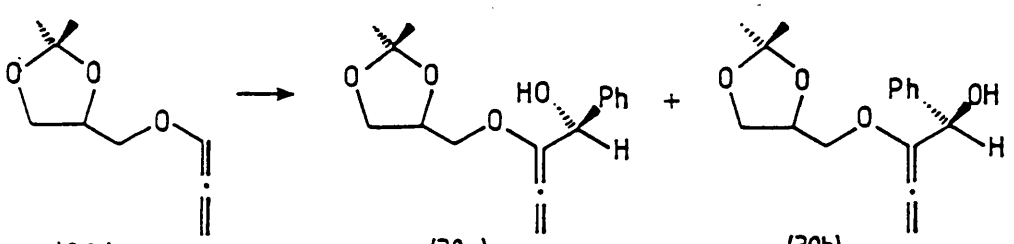
δ_H (90 MHz; $CDCl_3$) 1.35 (3H, s, CH_3), 1.45 (3H, s, CH_3), 3.5-4.5 (5H, m), 5.45 (2H, s, H-3').

Notes

1. n-Butyllithium was 2.6M by titration.

2. No purification was attempted.

Preparation of Diastereoisomers (30a) and (30b)[1]



(28) (30a) (30b)

n-Butyllithium[2] (1.13 ml, 29 mmol) was added dropwise to a solution of 1,2-O-isopropylidene-1,2-dihydroxy-3-(1,2-propadienyl-1-oxy)-propane (28) (500 mg, 29 mmol) in THF (2½ ml), under nitrogen, at -78°C. After stirring for 1½ h at this temperature, benzaldehyde (0.3 ml, 29 mmol)[3] in THF (½ ml) was added and the mixture slowly allowed to warm to room temperature. After 1h, the reaction mixture was quenched with water, the aqueous solution extracted with ether (2 x 15 ml), the combined ether extracts dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was purified by flash chromatography (1:1 petroleum ether-ether) to give the diastereoisomers (30a) and (30b) as an oil (583 mg, 72%) and a (1:1) mixture.[4,5]

R_f 0.26 (1:1 petroleum ether-ether);

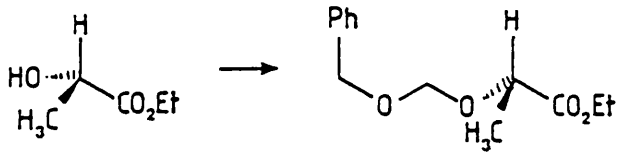
δ_H (300 MHz; $CDCl_3$) 1.30 (6H, s, CH_3),[6] 1.34 (6H, s, CH_3),[6] 3.20 (1H, brd, J ca. 5 Hz, OH), 3.25 (1H, brd, J ca. 5.5 Hz, OH), 3.52 (1H, dd, J = 5.8, 3.1 Hz), 3.55 (1H, dd, J = 5.8, 3.0 Hz), 3.59-3.66 (4H, m),[6] 3.90 (1H, dd, J = 8.3, 6.6 Hz), 3.91 (1H, dd, J = 8.4, 6.5 Hz), 4.23 (2H, br.quin, J ca. 5.8 Hz, H-2),[6] 5.22 (2H, brs),[6] 5.49 (4H, 2d, J ca. 2 Hz), 7.21-7.40 (10H, m, C_6H_5);[6]

δ_C (75 MHz; $CDCl_3$) 25.22(q),[6] 26.61(q),[6] 66.46(t),[6] 69.41(t),[6] 72.75(d), 72.91(d), 73.61(d),[6] 92.76(t), 93.03(t), 109.43(s),[6] 126.54(d),[6] 127.64(d),[6] 127.98(d),[6] 134.75(s), 135.00(s), 140.94(s),[6] 196.86(s), 196.98(s).

Notes

1. The diastereoisomers are arbitrarily assigned (30a) and (30b).
2. n-Butyllithium was 2.6M by titration.
3. Washed with aqueous sodium hydrogen carbonate, dried ($MgSO_4$), then distilled prior to use.
4. The ratio of diastereoisomers in the crude reaction mixture was 1:1 as measured from the ^{13}C n.m.r. spectrum.
5. Some decomposition occurred on the silica gel flash column.
6. Signals common to both diastereoisomers.

Preparation of (-)-(S)-Ethyl-2-[(phenylmethoxy)methoxy]-propanoate (32)[1]



(32)

Chloromethyl benzyl ether (26.5g, 0.17 mol) was added to a stirred solution of (-)-(S)-ethyl lactate (10g, 85 mmol) and N,N-diisopropyl ethylamine (43.7g, 0.34 mol) in dichloromethane (70 ml), under nitrogen. After 20h at room temperature, the mixture was poured into ice cold molar hydrochloric acid and the organic layer separated. The aqueous layer was washed with dichloromethane (3 x 70 ml), and the combined extracts washed successively with sodium hydrogen carbonate solution (150 ml), brine (150 ml) and dried ($MgSO_4$). Removal of the solvent in vacuo afforded a colourless oil which after flash chromatography (9:1 petroleum ether-ether) gave (-)-(S)-ethyl-2-[(phenylmethoxy)methoxy]-propanoate (32) as a colourless oil (13.1g, 65%).

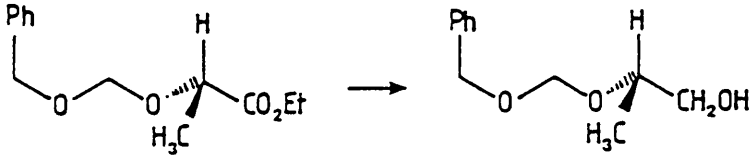
R_f 0.23 (9:1 petroleum ether-ether);

δ_H (90 MHz; $CDCl_3$) 1.25 (3H, t, J *ca.* 6 Hz, $CO_2CH_2\underline{CH_3}$), 1.40 (3H, d, J *ca.* 7 Hz, CH_3), 4.15 (2H, q, J *ca.* 7 Hz, $CO_2\underline{CH_2}CH_3$), 4.25 (1H, q, J *ca.* 7 Hz, H-2), 4.6 (2H, s, $\underline{CH_2}Ph$), 4.8 (2H, s, $\underline{CH_2}OCH_2Ph$), 7.25 (5H, s, C_6H_5).

Notes

1. Known compound and literature procedure see Ref. 137.

Preparation of (S)-2-[(phenylmethoxy)methoxy]-propan-1-ol (33)[1]



(32) (33)

A solution of (-)-(S)-ethyl-2-[(phenylmethoxy)methoxy]-propanoate (32) (8.7g, 36 mmol) in ether was added to a stirred suspension of lithium aluminium hydride (1.37g, 36 mmol) in ether (40 ml), under nitrogen, so as to maintain a gentle reflux. After a further 1h of refluxing, the reaction mixture was cooled and a saturated aqueous solution of sodium carbonate was added until the effervescence ceased. The dense, white solid was filtered and after careful washing with ether (60 ml), it gave a colourless solution which was washed successively with cold hydrochloric acid (80 ml), sodium hydrogen carbonate solution (80 ml), brine (80 ml) and dried ($MgSO_4$). The solvent was removed in vacuo to give an oil, which after flash chromatography (1:1 petroleum ether-ether), gave (S)-2-[(phenylmethoxy)methoxy]-propan-1-ol (33) as a colourless oil (5.5g, 77%).

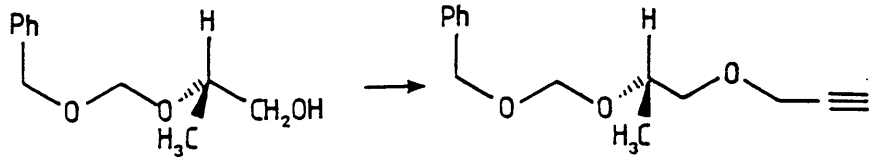
R_f 0.38 (1:1 petroleum ether-ether);

δ_H (90 MHz; $CDCl_3$) 1.15 (3H, d, J *ca.* 6 Hz, CH_3), 2.50 (1H, brs, OH), 3.5 (2H, brd, J *ca.* 6 Hz, $\underline{CH_2}OH$), 3.65-3.90 (1H, m, H-2), 4.6 (2H, s, $Ph\underline{CH_2}$), 4.8 (2H, s, $\underline{CH_2}OCH_2Ph$), 7.3 (5H, s, C_6H_5).

Notes

1. Known compound and literature procedure see Ref. 137.

Preparation of 3-[2-[(Phenylmethoxy)methoxy]propoxy]-propyne (34)



(33) (34)

Using the same procedure as for the preparation of (22),[1] (S)-2-[(phenylmethoxy)methoxy]-propan-1-ol (33) (7.11g, 36 mmol) in DMF (10 ml) was added to sodium hydride (1.05g, 35 mmol) in DMF (15 ml) and quenched with propargyl bromide (3.9 ml, 35 mmol) in DMF (10 ml). Work-up afforded the crude product which after purification by flash chromatography (3:2 petroleum ether-ether) and Kugelrohr distillation (160°C at 0.4 mmHg) gave 3-[2-[(phenylmethoxy)methoxy]propoxy]-propyne (34) as a colourless liquid (4.01g, 47%).

R_f 0.48 (3:2 petroleum ether-ether);

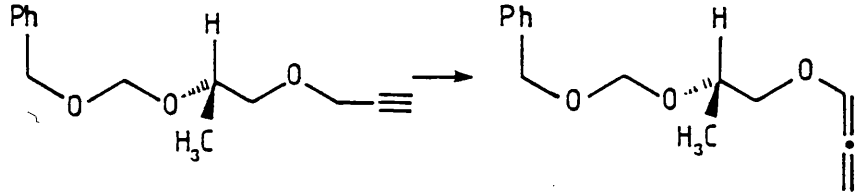
δ_H (300 MHz; $CDCl_3$) 1.22 (3H, d, J = 6.4 Hz, CH_3), 2.42 (1H, t, J = 2.4 Hz, H-1), 3.54 (2H, d, J = 5.1 Hz, H-1'), 3.99 (1H, m, H-2'), 4.17 (1H, dd, J = 15.5, 2.4 Hz, H-3), 4.22 (1H, dd, J = 15.5, 2.4 Hz, H-3), 4.61 (1H, d, J = 11.7 Hz, $PhCH_2$), 4.66 (1H, d, J = 11.7 Hz, $PhCH_2$), 4.84 (2H, s, CH_2OCH_2Ph), 7.28-7.36 (5H, m, C_6H_5);

δ_C (75 MHz; $CDCl_3$) 17.35(q), 58.61(t), 69.34(t), 71.87(d), 73.72(t), 74.45(d), 79.66(s), 93.36(t), 127.59(d), 127.87(d), 128.35(d), 137.93(s).

Notes

1. See p.95.

Preparation of 1-[2-[(Phenylmethoxy)methoxy]propoxy]-1,2-propadiene (31)



(34) (31)

Using the same procedure as for the preparation of (23),[1] freshly sublimed potassium tert-butoxide (1.08g, 9.6 mmol) was added to a solution of 3-[2-[(phenylmethoxy)methoxy]propoxy]-propyne (34) (2g, 8.5 mmol) in tert-butyl alcohol (15 ml). After stirring, at 83°C, under nitrogen, until t.l.c. had indicated the disappearance of starting material, the reaction mixture was subjected to work-up. The crude product was purified by flash chromatography (3:2 petroleum ether-ether) to give 1-[2-[(phenylmethoxy)-methoxy]propoxy]-1,2-propadiene (31) as a colourless liquid (1.6g, 80%).[2]

R_f 0.54 (3:2 petroleum ether-ether);

δ_H (90 MHz; $CDCl_3$) 1.2 (3H, d, J *ca.* 6 Hz, CH_3), 3.55 (2H, d, J *ca.* 6 Hz, H-1'), 4.05 (1H, m, H-2'), 4.55 (2H, s, $Ph\underline{CH_2}$), 4.8 (2H, s, $\underline{CH_2}OCH_2Ph$), 5.4 (2H, d, J *ca.* 6 Hz, H-3), 6.85 (1H, t, J *ca.* 6 Hz, H-1), 7.25 (5H, s, C_6H_5).

Notes

1. See p.97.

2. Some decomposition occurred whilst on the silica gel flash column.

Preparation of Benzenesulphinyl chloride[1]

The sodium salt of benzenesulphinic acid (21.9g, 0.13 mol) was added portionwise to thionyl chloride[2] (73 ml, 1 mol), with the exclusion of moisture at room temperature. The resulting yellow, viscous oil was stirred for 2h and the excess thionyl chloride removed in vacuo. After the addition of ether (30 ml) and the filtration of the inorganic material under a 'nitrogen blanket' the solvent was removed in vacuo to give benzenesulphinyl chloride as a pale yellow oil[3] (12.5g, 60%).

Notes

1. Known compound and literature procedure see Ref. 72.
2. Freshly distilled from linseed oil.
3. Used crude in the next stage.

Attempted Preparation of (-)-Menthyl (-)-(S)-benzenesulphinate[1]

Pyridine (12.7 ml, 157 mmol) and a solution of (-)-menthol (12.01g, 77 mmol) in ether (125 ml) was added to a solution of benzenesulphinyl chloride (12.5g, 78 mmol) in ether (125 ml) and the mixture stirred at room temperature overnight. The pyridinium hydrochloride was filtered and washed with ether and the filtrate washed consecutively with water (4 x 50 ml), 10% hydrochloric acid (4 x 50 ml), water (2 x 50 ml) and dried ($MgSO_4$). The solvent was removed in vacuo to give a colourless oil. The oil, however, proved almost impossible to crystallize using a variety of techniques, and only a small yield of (-)-menthyl (-)-(S)-benzenesulphinate was obtained in the crystalline form.

Notes

1. Known compound and literature procedure, see Ref. 72.

Preparation of p-Tolylsulphinyl chloride[1]

Thionyl chloride[2] (104 ml, 1.43 mol) was dissolved in an equal volume of ether and the sodium salt of p-toluenesulphinic acid (40g, 0.19 mol) added portionwise, under a nitrogen atmosphere. After the addition was complete, the reaction mixture was warmed gently over a period of 2h, with stirring, after which time the evolution of gases had stopped. The excess thionyl chloride and solvent were removed *in vacuo* and the residue redissolved in petroleum ether then filtered to remove any inorganic solids. The solvent was removed *in vacuo* to give p-tolylsulphinyl chloride as a yellow oil[3] (25.8g, 78%).

Notes

1. Known compound and adapted literature procedure, see Ref. 138.
2. Freshly distilled from linseed oil.
3. Used crude for next stage.

Preparation of (-)-Menthyl (-)-(S)-p-toluenesulphinate (38)[1]

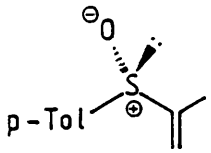
A solution of p-tolylsulphinyl chloride (30g, 172 mmol) in ether (75 ml) was added dropwise to a stirred solution of (-)-menthol (22.6g, 145 mmol) and pyridine (21 ml, 260 mmol) in ether (150 ml), at 0°C, under nitrogen. Once the addition was complete, the mixture was allowed to warm to room temperature and left stirring overnight. After decomposition with water (100 ml), the organic layer was separated, washed with 20% aqueous hydrochloric acid (3 x 50 ml), water (100 ml) and dried ($MgSO_4$). Removal of the solvent *in vacuo* gave a solid which was recrystallized from hot acetone as colourless crystals. The mother liquor was concentrated and redissolved in hot acetone with 3-4 drops of concentrated hydrochloric acid and again cooled to afford additional crystals. This process was repeated twice and the combined crystals were recrystallized from 15% aqueous acetone to give (-)-menthyl (-)-(S)-p-toluenesulphinate (38) as colourless needles (17.8g, 41.8%) m.p. 106-107°C (lit.[72] 108°C);

$[\alpha]_D$ -198° (2.0 in acetone) (lit.[72] -200°).

Notes

1. Known compound and adapted literature procedure, see Refs. 35 and 72.

Preparation of (-)-2-[(R)-p-Tolylsulphinyl]-propene (88)[1]



(88)

Magnesium turnings (67 mg, 2.8 mmol) and a crystal of iodine were covered with the minimum of THF, under nitrogen. 2-Bromopropene (240 μl, 2.7 mmol) was added so as to maintain a steady reflux, followed by a further volume of THF (10 ml) and the reaction mixture refluxed for 1h. (-)-Menthyl (-)-(S)-p-toluenesulphinate (38) (600 mg, 2.04 mmol) in THF (8 ml) was added to the formed Grignard reagent and the mixture left to stir at room temperature for 20h, followed by a reflux for 11h. The reaction mixture was then quenched with saturated aqueous ammonium chloride solution, the aqueous solution extracted with ether (2 x 40 ml), and the combined extracts dried (K_2CO_3). Removal of the solvent <u>in vacuo</u> followed by purification by flash chromatography (7:3 ether-petroleum ether) gave (-)-2-[(R)-p-tolylsulphinyl]-propene (88) as an oil (171 mg, 47%) (lit.[72] 75%).

R_f 0.25 (7:3 ether-petroleum ether);

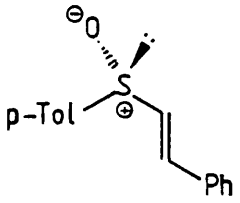
δ_H[2] (90 MHz; $CDCl_3$) 1.7 (3H, s, CH_3), 2.35 (3H, s, CH_3), 5.5 (1H, s with fine coupling, H-1), 5.9 (1H, s, H-1), 7.15-7.5 (4H, q, C_6H_4).

Notes

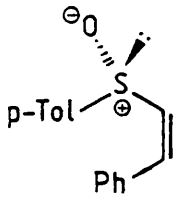
1. Known compound and literature procedure, see Ref. 72.

2. Values consistent with literature, see Ref. 72.

Preparation of (+)-(E) and (-)-(Z)-2-Phenyl-1-[(R)-p-tolylsulphinyl]-ethylene (53b)[1] and (53a)[1] respectively[2]



(53b)



(53a)

Magnesium turnings (0.46g, 19 mmol) and a crystal of iodine were covered by the minimum of THF, under nitrogen. β-Bromostyrene[3] (0.6 ml, 4.7 mmol) was added dropwise, and an immediate reaction was evident. The remainder of the halide (1.7 ml, 13.3 mmol) was added in THF (10 ml) so as to maintain a gentle reflux, after which time a further volume of THF (10 ml) was added. The mixture was stirred under reflux for a further 3h. After allowing to cool, the formed Grignard reagent was added dropwise to a solution of (-)-menthyl (-)-(S)-p-toluenesulphinate (38) (4.2g, 14 mmol) in benzene (25 ml). After stirring at room temperature, for 2h, the reaction mixture was quenched with saturated aqueous ammonium chloride solution, the solution extracted with chloroform (3 x 75 ml), the combined chloroform extracts dried ($MgSO_4$) and the solvent removed in vacuo to give a crude solid. Flash chromatography (4:1 ether-petroleum ether) and recrystallization[4] (both isomers from petroleum ether), gave (+)-(E)-2-phenyl-1-[(R)-p-tolylsulphinyl]-ethylene (53b) as a white solid (1.66g, 49%) m.p. 78-79°C (lit.[63] 82°C) and (-)-(Z)-2-phenyl-1-[(R)-p-tolylsulphinyl]-ethylene (53a) as yellow needles (0.49g, 14.5%) m.p. 48-51°C (lit.[63] 52-52.5°C).

(53b)

$[\alpha]_D$ = +162.5° (2.1 in $CHCl_3$); (lit.[63] +166°);

R_f 0.36 (4:1 ether-petroleum ether);

ν_{max} (CH_2Cl_2) 3030w, 2970w, 2860w, 1610w, 1595w, 1575w, 1490m, 1445m, 1255m, 1175w, 1085s, 1045brs (S=0), 1015m, 965s, 895w, 870m, 810s, 790m, 690brs, 620w;

δ_H (300 MHz; $CDCl_3$) 2.40 (3H, s, CH_3), 6.81 (1H, d, J_{trans} = 15.5 Hz, H-1), 7.25-7.59 (10H, m);

δ_C (75 MHz; $CDCl_3$) 21.39(q), 124.84(d), 127.67(d), 128.81(d), 129.67(d), 130.08(d), 133.04(d), 133.75(s), 135.89(d), 140.66(s), 141.67(s);

M/Z 242 (M^+), 226(100), 211(45), 194(31), 179(21), 178(34), 166(12), 135(22), 121(22), 103(16).

(53a)

$[\alpha]_D$ = -700° (2.06 in $CHCl_3$); (lit.[63] -736°);

R_f 0.26 (4:1 ether-petroleum ether);

ν_{max} (CH_2Cl_2) 3020m, 2970m, 2860w, 1605s, 1595s, 1575m, 1490s, 1445m, 1395m, 1300w, 1205m, 1175m, 1085s, 1045brs (S=0), 1015s, 920m, 810s, 720brs;

δ_H (300 MHz; $CDCl_3$) 2.39 (3H, s, CH_3), 6.43 (1H, d, J_{cis} = 10.6 Hz, C<u>H</u>=CH), 7.08 (1H, d, J_{cis} = 10.6 Hz, CH=C<u>H</u>), 7.26-7.58 (9H, m);

δ_C (75 MHz; $CDCl_3$) 21.34(q), 124.32(d), 128.60(d), 129.41(d), 129.73(d), 130.04(d), 133.83(s), 137.09(d), 138.34(d), 141.34(s), 141.48(s);

M/Z 242 (M^+), 226(100), 211(46), 194(35), 179(23), 178(35), 166(13), 135(25), 121(24), 103(20).

<u>Notes</u>

1. Known compounds, see Ref. 63 (^1H n.m.r., m.p. and $[\alpha]_D$ consistent with the literature.

2. Adapted procedure, see Ref. 71.
3. Obtained from Aldrich as a (11:1) mixture of (E):(Z) isomers as measured by g.l.c.
4. An initial recrystallization from isopropyl ether (passed through an alumina column) was sometimes necessary.

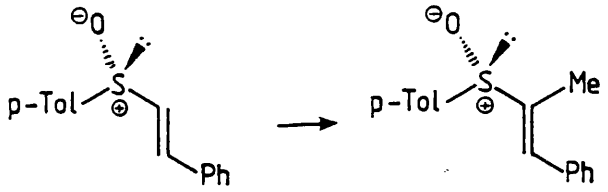
General Procedure for the Generation of LDA[1]

Diisopropylamine[2] (210 μl, 1.5 mmol) was added to a flask containing THF (7 ml) under a nitrogen atmosphere, at 0-5°C. n-Butyllithium[3] (600 μl, 1.5 mmol) was added dropwise to the solution, with stirring. The LDA solution was left stirring for 20 mins at 0-5°C before use.[4]

Notes

1. Literature procedure, see Ref. 139.
2. Distilled from sodium hydroxide pellets, prior to use.
3. n-Butyllithium was 2.5M by titration.
4. Unless stated otherwise, the LDA solution was cooled to -78°C and the reagent to be deprotonated added dropwise to it.

Preparation of (E)-1-Phenyl-2-[(R)-p-tolylsulphinyl]-propene (89)



(53b) (89)

(+)-(E)-2-Phenyl-1-[(R)-p-tolylsulphinyl]-ethylene (53b) (200 mg, 0.83 mmol) in THF (5 ml) was added dropwise to a preformed solution of LDA[1] (1.0 mmol) in THF (5 ml), under nitrogen, at -78°C. An immediate brown colouration was observed and after only a few minutes methyl iodide (260 μl, 4.2 mmol) in THF (1 ml) was added. The reaction was stirred for a further 2h at -78°C, quenched with saturated aqueous ammonium chloride solution, extracted with chloroform (3 x 25 ml), and the combined chloroform extracts dried ($MgSO_4$). The solvent was removed in vacuo and after flash chromatography (ether) and recrystallization[2] (petroleum ether), (E)-1-phenyl-2-[(R)-p-tolylsulphinyl]-propene (89) was obtained as a white solid (118 mg, 56%), m.p. 74-76°C.

R_f 0.39 (4:1 ether-petroleum ether);

$C_{16}H_{16}OS$ requires C 74.96%, H 6.29%, N 0.00%,

found C 75.00%, H 6.02%, N 0.20%.

ν_{max} (CH_2Cl_2) 3050s, 2980s, 1595m, 1490s, 1445s, 1420s, 1265brs, 1210m, 1180m, 1100m, 1080s, 1055s (S=O), 1015s, 960m, 925m, 895s, 810s, 735brs;

δ_H (300 MHz; $CDCl_3$) 1.89 (3H, d, J = 1.4 Hz, CH_3), 2.39 (3H, s, CH_3), 7.26-7.56 (10H, m);

δ_C (75 MHz; $CDCl_3$) 10.47(q), 21.24(q), 125.10(d), 128.24(d), 128.40(d), 129.14(d), 129.70(d), 131.64(d), 134.62(s), 139.52(s), 141.27(s), 142.11(s);

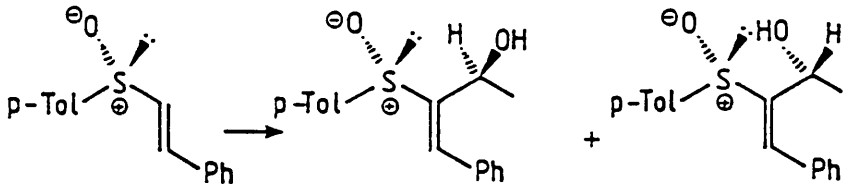
M/Z 256 (M^+), 240(72), 225(25), 208(27), 181(29), 140(20), 124(15), 117(45), 115(100).

Notes

1. See p.115.

2. An initial recrystallization from isopropyl ether may be necessary.

Preparation of (+)-(S)-(E) and (+)-(R)-(E)-4-Phenyl-3-[(S)-p-tolyl-sulphinyl]-3-buten-2-ol (153a) and (153b)[1] from (53b)



(53b) (153a) (153b)

Using the same procedure as for the preparation of (89)[2] (+)-(E)-2-phenyl-1-[(R)-p-tolylsulphinyl]-ethylene (53b) (200 mg, 0.83 mmol) was deprotonated with LDA (1.0 mmol) and quenched with acetaldehyde[3] (280 μl, 5.0 mmol). After standard work-up, the crude reaction mixture[4] was purified by use of a 'chromatotron' (1:1 ethyl acetate-petroleum ether) to give (+)-(S)-(E) and (+)-(R)-(E)-4-phenyl-3-[(S)-p-tolylsulphinyl]-3-buten-2-ol (153a) and (153b) as colourless oils (80 mg, 34%) and (43 mg, 18%)[5] respectively.

(153a)

$[\alpha]_D$ = +11.5° (1.6 in $CHCl_3$);

R_f 0.31 (ether);

ν_{max} (CH_2Cl_2) 3320brm (OH), 3020w, 2970m, 2920m, 1595m, 1490m, 1445m, 1370m, 1110m, 1080s, 1030brs (S=O), 1010s, 925m, 880m, 810s, 620m;

δ_H (300 MHz; $CDCl_3$) 0.91 (3H, d, J = 6.7 Hz, CH_3), 2.39 (3H, s, CH_3), 3.42 (1H, brs, OH), 5.07 (1H, brm, H-3), 7.25-7.72 (10H, m);

δ_C (75 MHz; $CDCl_3$) 21.46(q), 22.16(q), 65.46(d), 126.15(d), 128.58(d),[6] 129.69(d), 129.90(d), 131.25(d), 134.06(s), 140.54(s), 141.89(s), 148.90(s);

H.p.l.c.; R_t (Partisil PXS 10/25, 7:3 petroleum ether-ethyl acetate, 3 cm^3 min^{-1}) 8.3 mins;

$C_{17}H_{18}O_2S$ requires 286.1027

found 286.1029.[7]

(153b)

$[\alpha]_D$ = +101 (1.9 in $CHCl_3$);

R_f 0.33 (ether);

ν_{max} (CH_2Cl_2) 3360brw (OH), 2970w, 2920w, 1595w, 1490m, 1450w, 1375w, 1250m, 1110m, 1075s, 1035brs (S=O), 1010s, 880w, 810s, 690brs;

δ_H (300 MHz; $CDCl_3$) 1.36 (3H, d, J = 6.7 Hz, CH_3), 2.37 (3H, s, CH_3), 2.60 (1H, brs, OH), 5.02 (1H, brm, H-3), 7.20-7.64 (10H, m);

δ_C (75 MHz; $CDCl_3$) 21.42(q), 22.42(q), 65.86(d), 125.61(d), 128.61(d), 128.78(d), 129.55(d), 130.00(d), 132.57(d), 133.91(s), 141.09(s), 141.72(s), 147.58(s);

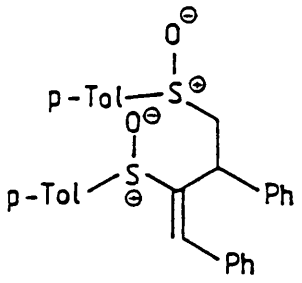
H.p.l.c.; R_t (Partisil PXS 10/25, 7:3 petroleum ether-ethyl acetate, 3 cm^3 min^{-1}) 6.4 mins;

$C_{17}H_{18}O_2S$ requires 286.1027

found 286.1014.[7]

Notes

1. The assignment of the diastereoisomer shown to that particular set of experimental data is arbitrary.
2. See p.116.
3. Fractionally distilled under nitrogen prior to use.
4. The diastereomeric ratio as measured from the crude reaction mixture by h.p.l.c. was (153b):(153a), 1:1.2.
5. (8 mg, 2%) of the dimer (91) were also isolated as a white solid.



(91)

R_f 0.17 (ether);

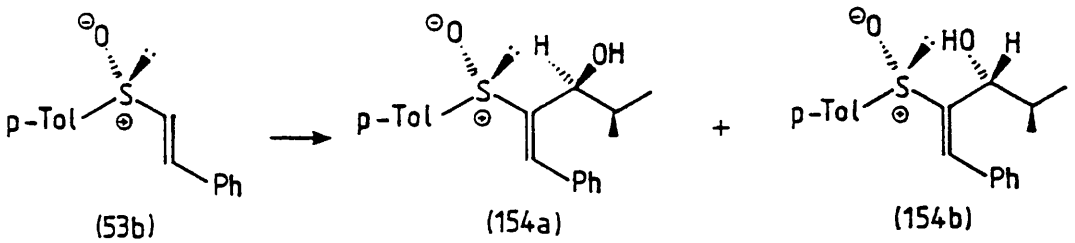
ν_{max} (CH_2Cl_2) 3030w, 2950m, 2920m, 2870w, 1720m, 1595w, 1490m, 1445w, 1395w, 1380w, 1270brm, 1120brw, 1085s, 1045s (S=O), 1015m, 810s;

δ_H (300 MHz; $CDCl_3$) 2.33 (3H, s, CH_3), 2.38 (3H, s, CH_3), 3.16 (1H, dd, J = 13.1, 4.7 Hz), 3.43 (1H, dd, J = 13.1, 10.8 Hz), 4.82 (1H, dd, J = 10.7, 4.7 Hz), 7.05-7.54 (19H, m);

δ_C (75 MHz; $CDCl_3$) 21.34(q), 21.40(q), 39.03(d), 60.99(t), 124.30, 125.64, 127.41, 128.50, 128.62, 128.65, 128.71, 129.04, 129.72, 129.85, 132.99, 134.15, 136.83, 140.08, 140.88, 141.57, 141.63, 147.22.

6. Very intense signal. On comparison with ^{13}C n.m.r. spectra of analogous compounds, it is probable that two peaks are coincidental.
7. Detected as the $(M+H)^+$ species. The observation of these $(M+H)^+$ species is due to an effect which is sometimes observed in the ion source of the spectrometer.

Preparation of (+)-(S)-(E) and (+)-(R)-(E)-4-Methyl-1-phenyl-2-[(S)-p-tolylsulphinyl]-1-penten-3-ol (154a) and (154b)[1] from (53b)



Using the same procedure as for the preparation of (89),[2] (+)-(E)-2-phenyl-1-[(R)-p-tolylsulphinyl]-ethylene (53b) (200 mg, 0.83 mmol) was deprotonated with LDA (1.0 mmol) and quenched with isobutyraldehyde[3] (113 µl, 1.2 mmol). After standard work-up the crude reaction mixture[4] was purified by use of a 'chromatotron' (1:1 ethyl acetate-petroleum ether) to give (+)-(S)-(E) and (+)-(R)-(E)-4-methyl-1-phenyl-2-[(S)-p-tolyl-sulphinyl]-1-penten-3-ol (154a) and (154b) as white solids (114 mg, 44%) m.p. 106-108°C and (42 mg, 16%) m.p. 133-135°C respectively.[5] (Both isomers were recrystallized from isopropyl ether.)

(154a)

$[\alpha]_D$ = +24° (2.1 in $CHCl_3$);

R_f 0.32 (ether);

$C_{19}H_{22}O_2S$ requires C 72.58%, H 7.05%, N 0.00%,

found C 72.68%, H 7.13%, N 0.00%.

ν_{max} (CH_2Cl_2) 3360brm (OH), 3020m, 2960s, 2920m, 2870m, 1595m, 1490m, 1465m, 1445m, 1380m, 1300m, 1205m, 1175m, 1115m, 1080s, 1030brs (S=O), 930m, 910m, 810s, 620m;

δ_H (400 MHz; $CDCl_3$) 0.56 (3H, d, J = 6.7 Hz, CH_3), 0.91 (3H, d, J = 6.5 Hz, CH_3), 2.02 (1H, m, H-4), 2.39 (3H, s, CH_3), 2.95 (1H, d, J = 5.8 Hz, OH), 4.12 (1H, dd, J = 9.3, 5.8 Hz, H-3), 7.20 (1H, s, H-1), 7.25-7.65 (9H, m);

δ_C (100 MHz; $CDCl_3$) 18.98(q), 19.06(q), 21.32(q), 31.52(d), 75.46(d), 126.10(d), 128.32(d), 128.43(d), 129.46(d), 129.96(d), 133.12(d), 134.22(s), 139.94(s), 142.06(s), 147.13(s);

H.p.l.c.; R_t (Partisil PXS 10/25, 7:3 petroleum ether-ethyl acetate, 3 cm^3 min^{-1}) 4.5 mins;

M/Z 314 (M^+), 298(16), 271(100), 255(19), 213(40), 175(16), 157(73), 140(54), 139(66), 131(37), 129(44), 115(43).

(154b)

$[\alpha]_D$ = +35° (2.0 in $CHCl_3$);

R_f 0.37 (ether);

$C_{19}H_{22}O_2S$ requires C 72.58%, H 7.05%, N 0.00%,

found C 72.36%, H 7.18%, N 0.02%.

ν_{max} (CH_2Cl_2) 3380brw (OH), 3020w, 2960m, 2920m, 2870m, 1595w, 1490m, 1465m, 1375w, 1365w, 1080s, 1040brs (S=O), 1015s, 810s;

δ_H (400 MHz; $CDCl_3$) 0.72 (3H, d, J = 6.7 Hz, CH_3), 0.96 (3H, d, J = 6.5 Hz, CH_3), 1.70 (1H, d, J = 6.1 Hz, OH), 2.07 (1H, m, H-4), 2.39 (3H, s, CH_3), 4.41 (1H, dd, J = 9.2, 6.1 Hz, H-3), 7.25 (1H, s, H-1), 7.28-7.66 (9H, m);

δ_C (100 MHz; $CDCl_3$) 18.71(q), 19.10(q), 21.31(q), 32.17(d), 74.53(d), 125.63(d), 128.50(d), 128.55(d), 129.30(d), 129.99(d), 133.29(d), 134.25(s), 141.56(s), 141.78(s), 147.20(s);

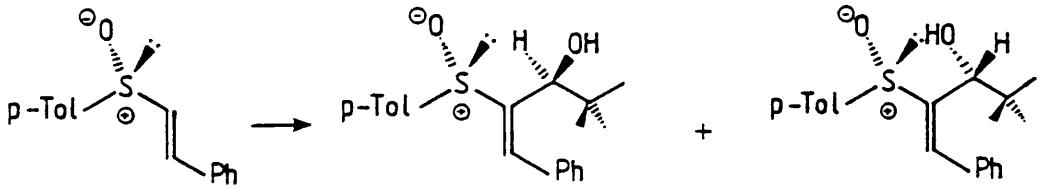
H.p.l.c.; R_t (Partisil PXS 10/25, 7:3 petroleum ether-ethyl acetate, 3 cm^3 min^{-1}) 3.4 mins;

M/Z 314 (M^+), 298(15), 296(21), 271(100), 255(19), 225(36), 213(43), 157(75), 140(55), 139(67), 131(36), 129(44), 115(38).

Notes

1. The assignment of the diastereoisomer shown to that particular set of experimental data is arbitrary.
2. See p.116.
3. Distilled prior to use.
4. The diastereomeric ratio as measured from the crude reaction mixture by h.p.l.c. was (154b):(154a), 1:1.93.
5. (17 mg, 4%) of the dimer (91) (see p.119) were also isolated.

Preparation of (+)-(S)-(E) and (-)-(R)-(E)-4,4-Dimethyl-1-phenyl-2-[(S)-p-tolylsulphinyl]-1-penten-3-ol (94a) and (94b) respectively from (53b)



(53b) (94a) (94b)

Using the same procedure as for the preparation of (89),[1] (+)-(E)-2-phenyl-1-[(R)-p-tolylsulphinyl]-ethylene (53b) (200 mg, 0.83 mmol) was deprotonated with LDA (1.0 mmol) and quenched with trimethylacetaldehyde[2] (220 μl, 2 mmol). After standard work-up the crude reaction mixture[3] was purified by use of a 'chromatotron' (1:1 ethyl acetate-petroleum ether) to give (+)-(S)-(E) and (-)-(R)-(E)-4,4-dimethyl-1-phenyl-2-[(S)-p-tolyl-sulphinyl]-1-penten-3-ol (94a) and (94b) as white solids (130 mg, 48%) m.p. 145-147°C and (31 mg, 11%) m.p. 189-192°C respectively.[4] (Both isomers were recrystallized from isopropyl ether to give white crystals.)

(94a)

$[\alpha]_D$ = +142° (2.0 in $CHCl_3$);

R_f 0.39 (ether);

$C_{20}H_{24}O_2S$ requires C 73.13%, H 7.36%, N 0.00%,

found C 73.10%, H 7.52%, N <0.2%.

ν_{max} (CH_2Cl_2) 3360brm (OH), 3020m, 2950s, 2870m, 1595m, 1490m, 1475s, 1445m, 1395m, 1365m, 1210m, 1180m, 1080s, 1050brs (S=O), 1015s, 810s, 620m;

δ_H (300 MHz; $CDCl_3$) 0.91 (9H, s, $C(CH_3)_3$), 2.39 (3H, s, CH_3), 3.51 (1H, brs, OH), 4.32 (1H, brs, H-3), 7.15 (1H, s, H-1), 7.23-7.63 (9H, m);

δ_C (75 MHz; $CDCl_3$) 21.43(q), 26.99(q), 38.21(s), 79.06(d), 126.43(d), 128.25(d), 128.32(d), 129.70(d), 130.05(d), 132.92(d), 134.96(s),

140.40(s), 142.07(s), 146.39(s);

H.p.l.c.; R_t (Partisil PXS 10/25, 6:1 petroleum ether-ethyl acetate, 3 cm^3 min^{-1}) 10.4 min.;

M/Z 328 (M^+), 272(20), 271(100), 255(31), 225(17), 140(36), 139(36), 135(24), 131(27), 115(20).

(94b)

$[\alpha]_D$ = -52° (2.2 in $CHCl_3$);

R_f 0.44 (ether);

$C_{20}H_{24}O_2S$ requires C 73.13%, H 7.36%, N 0.00%,

found C 72.98%, H 7.38%, N 0.00%.

ν_{max} (CH_2Cl_2) 3360brw (OH), 2950m, 2860m, 1595w, 1490m, 1475m, 1365w, 1175w, 1075s, 1040brs (S=O), 1010s, 810s, 620w;

δ_H (300 MHz; $CDCl_3$) 0.92 (9H, s, $C(CH_3)_3$), 1.57 (1H, brs, OH), 2.39 (3H, s, CH_3), 4.91 (1H, brs, H-3), 7.20-7.79 (10H, m);

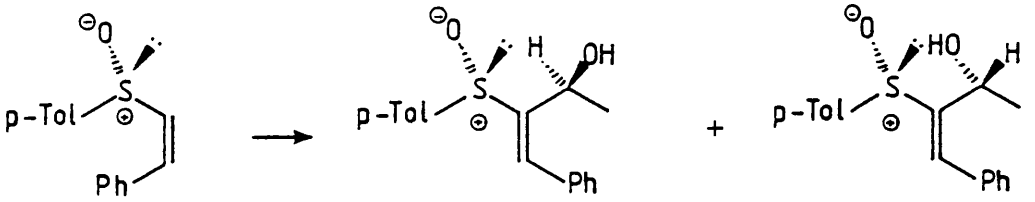
H.p.l.c.; R_t (Partisil PXS 10/25, 6:1 petroleum ether-ethyl acetate, 3 cm^3 min^{-1}) 9.1 min.;

M/Z 328 (M^+), 272(20), 271(100), 255(50), 238(30), 225(42), 210(20), 140(47), 139(41), 135(39), 131(47), 115(47).

Notes

1. See p.116.
2. Distilled prior to use.
3. The diastereomeric ratio as measured from the crude reaction mixture by h.p.l.c. was (94b):(94a), 1:6.04.
4. A negligible amount of the dimer (91) was isolated.

Preparation of (+)-(S)-(E) and (+)-(R)-(E)-4-Phenyl-3-[(S)-p-tolyl-sulphinyl]-3-buten-2-ol (153a) and (153b)[1] from (53a)



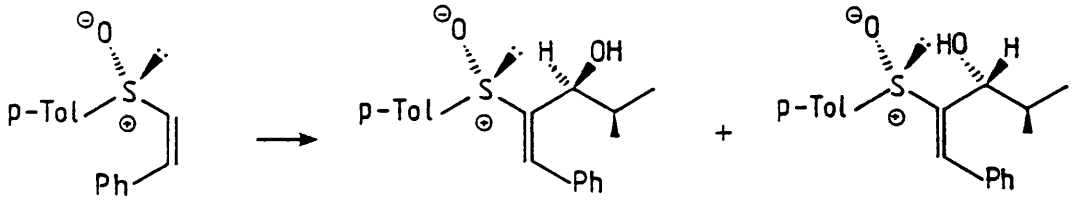
(53a) (153a) (153b)

Using the same procedure as for the preparation of (89),[2] (-)-(Z)-2-phenyl-1-[(R)-p-tolylsulphinyl]-ethylene (53a) (100 mg, 0.42 mmol) was deprotonated with LDA (0.5 mmol) and quenched with acetaldehyde[3] (100 µl, 1.8 mmol). After standard work-up, the crude reaction mixture[4] was purified by use of a 'chromatotron' (1:1 ethyl acetate-petroleum ether) to give (+)-(S)-(E) and (+)-(R)-(E)-4-phenyl-3-[(S)-p-tolylsulphinyl]-3-buten-2-ol (153a) and (153b) as colourless oils (30 mg, 25%) and (21 mg, 18%) respectively.[5] The two diastereoisomers had identical physical and spectral properties as (153a) and (153b) prepared previously from (53b).

Notes

1. See note 1, p.119.
2. See p.116.
3. Fractionally distilled under nitrogen prior to use.
4. The diastereomeric ratio of (153b) to (153a) was consistent with that as measured previously, see p.123.
5. (10 mg, 5%) of the dimer (91) were also isolated.

Preparation of (+)-(S)-(E) and (+)-(R)-(E)-4-Methyl-1-phenyl-2-[(S)-p-tolylsulphinyl]-1-penten-3-ol (154a) and (154b)[1] from (53a)



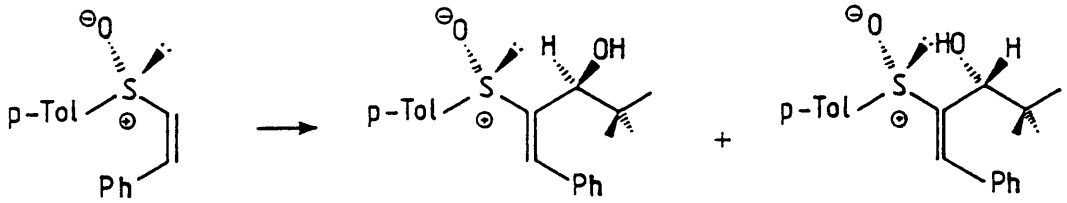
(53a) (154a) (154b)

Using the same procedure as for the preparation of (89),[2] (-)-(Z)-2-phenyl-1-[(R)-p-tolylsulphinyl]-ethylene (53a) (100 mg, 0.42 mmol) was deprotonated with LDA (0.5 mmol) and quenched with isobutyraldehyde[3] (70 µl, 0.74 mmol). After standard work-up the crude reaction mixture[4] was purified by use of a 'chromatotron' (1:1 ethyl acetate-petroleum ether) to give (+)-(S)-(E) and (+)-(R)-(E)-4-methyl-1-phenyl-2-[(S)-p-tolyl-sulphinyl]-1-penten-3-ol (154a) and (154b) as white solids (46 mg, 35%) and (29 mg, 22%) respectively.[5] The two diastereoisomers had identical physical and spectral properties as (154a) and (154b) prepared previously from (53b).

Notes

1. See note 1, p.123.
2. See p.116.
3. Distilled prior to use.
4. See note 4, p.125.
5. (13 mg, 7%) of the dimer (91) were also isolated.

Preparation of (+)-(S)-(E) and (-)-(R)-(E)-4,4-Dimethyl-1-phenyl-2-[(S)-p-tolylsulphinyl]-1-penten-3-ol (94a) and (94b) respectively from (53a)



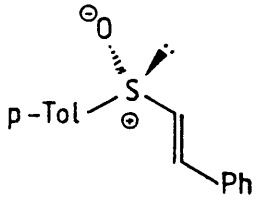
(53a) (94a) (94b)

Using the same procedure as for the preparation of (89),[1] (-)-(Z)-2-phenyl-1-[(R)-p-tolylsulphinyl]-ethylene (53a) (70 mg, 0.29 mmol) was deprotonated with LDA (0.36 mmol) and quenched with trimethylacetaldehyde[2] (80 µl, 0.74 mmol). After standard work-up the crude reaction mixture[3] was purified by use of a 'chromatotron' (1:1 ethyl acetate-petroleum ether) to give a mixture[4] of (+)-(S)-(E) and (-)-(R)-(E)-4,4-dimethyl-1-phenyl-2-[(S)-p-tolylsulphinyl]-1-penten-3-ol (94a) and (94b) as a white solid (70 mg, 74%). The mixture was recrystallized from isopropyl ether to yield the major diastereoisomer (94a) which had identical physical and spectral properties as (94a) prepared previously from (53b).

Notes

1. See p.116.
2. Distilled prior to use.
3. See note 4, p.125.
4. It proved difficult to separate the diastereoisomers. A negligible yield <1% of the dimer (91) was also isolated.

The Deprotonation and Reprotonation of (+)-(E)-2-Phenyl-1-[(R)-p-tolyl-sulphinyl]-ethylene (53b)



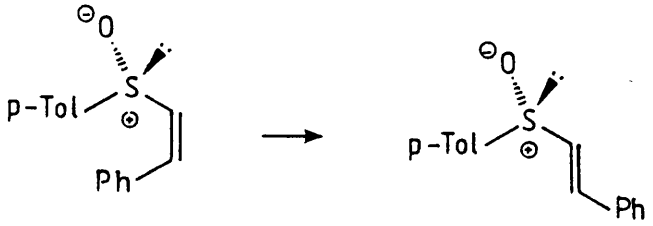
(53b)

Using the same procedure as for the preparation of (89),[1] (+)-(E)-2-phenyl-1-[(R)-p-tolylsulphinyl]-ethylene (53b) (200 mg, 0.83 mmol) was deprotonated with LDA (1.0 mmol) and then quenched with a 1:1 water/THF mixture. The brown colouration of the anionic solution dispersed to leave a yellow precipitate in solution. After 30 min. the reaction mixture was worked-up[1] and purified by recrystallization (petroleum ether) to give (+)-(E)-2-phenyl-1-[(R)-p-tolylsulphinyl]-ethylene (53b) as a white solid (172 mg, 86%) with identical spectral characteristics and optical rotation ($[\alpha]_D$ = +165°) as the original sample.[2]

Notes

1. See p.116.
2. See p.113.

The Isomerization of (-)-(Z)-(53a) to (+)-(E)-2-Phenyl-1-[(R)-p-tolyl-sulphinyl]-ethylene (53b)



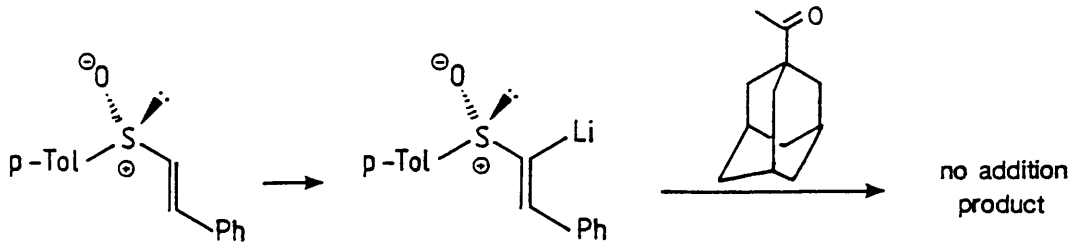
(53a) (53b)

Using the same procedure as for the preparation of (89),[1] (-)-(Z)-2-phenyl-1-[(R)-p-tolylsulphinyl]-ethylene (53a) (100 mg, 0.42 mmol) was deprotonated with LDA (0.5 mmol) and then quenched with a 1:1 water/THF mixture. T.l.c. showed the complete disappearance of the (Z)-starting material and after work-up and recrystallization (petroleum ether), (+)-(E)-2-phenyl-1-[(R)-p-tolylsulphinyl]-ethylene (53b) was obtained as a white solid (74 mg, 74%) m.p. 78-79°C; $[\alpha]_D$ = +162°.

Notes

1. See p.116.

Attempted Reaction of (+)-(E)-1-Lithio-2-phenyl-1-[(R)-p-tolylsulphinyl]-ethylene (53l) and 1-Adamantyl methyl ketone



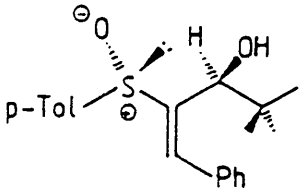
(53b) (53l)

Using the same procedure as for the preparation of (89),[1] (+)-(E)-2-phenyl-1-[(R)-p-tolylsulphinyl]-ethylene (53b) (200 mg, 0.83 mmol) was deprotonated with LDA (1.0 mmol) and 1-adamantyl methyl ketone (162 mg, 0.91 mmol) in THF (2 ml) added. After 2h stirring at -78°C, the reaction mixture was allowed to warm to room temperature and then subjected to work-up. Purification of the crude reaction mixture by use of a 'chromatotron' (1:1 ethyl acetate-petroleum ether) resulted in the recovery of 1-adamantyl ketone (153 mg, 95% recovery), (+)-(E)-2-phenyl-1-[(R)-p-tolylsulphinyl]-ethylene (53b) (34 mg, 17% recovery), the isolation of the dimer (91) (69 mg, 17%), and decomposition products.

Notes

1. See p.116.

Attempted Reduction of (+)-(S)-(E)-4,4-Dimethyl-1-phenyl-2-[(S)-p-tolyl-sulphinyl]-1-penten-3-ol (94a) using Sodium Amalgam[1]



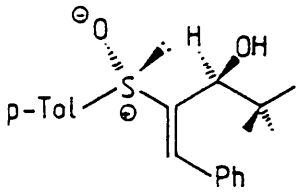
(94a)

(+)-(S)-(E)-4,4-Dimethyl-1-phenyl-2-[(S)-p-tolylsulphinyl]-1-penten-3-ol (94a) (70 mg, 0.21 mmol) in methanol (10 ml) was cooled to -20°C under a nitrogen atmosphere. Anhydrous sodium dihydrogen phosphate (151 mg, 1.1 mmol) and freshly ground 5% sodium amalgam (490 mg, 1.1 mmol) were then added with stirring. T.l.c. after 2h showed mostly starting material and so a further 3 equivalents of sodium dihydrogen phosphate and sodium amalgam were added. After 6h the reaction mixture was quenched with saturated aqueous ammonium chloride solution and the aqueous solution extracted with dichloromethane (3 x 30 ml). The combined extracts were dried ($MgSO_4$) and the solvent removed in vacuo. Purification by 'chromatotron' (1:1 ether-petroleum ether) yielded recovered starting material (30 mg, 43% recovery) and decomposition products.

Notes

1. See Ref. 140.

Attempted Reduction of (+)-(S)-(E)-4,4-Dimethyl-1-phenyl-2-[(S)-p-tolyl-sulphinyl]-1-penten-3-ol (94a) using Activated Zinc[1]



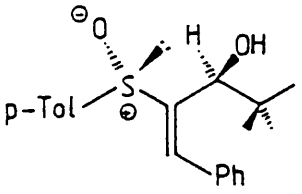
(94a)

Activated zinc (0.57g, 8.7 mmol) was added to a solution of (+)-(S)-(E)-4,4-dimethyl-1-phenyl-2-[(S)-p-tolylsulphinyl]-1-penten-3-ol (94a) (50 mg, 0.15 mmol) in THF (2 ml) under nitrogen. Aqueous saturated ammonium chloride solution (2 ml) was added and the reaction mixture stirred for 24h. T.l.c. after this time showed only the presence of starting material. The reaction mixture was diluted with dichloromethane (10 ml) and the organic layer washed successively with sodium bicarbonate solution (10 ml), water (10 ml) and dried ($MgSO_4$). The solvent was removed in vacuo to give recovered starting material (37 mg, 74% recovery).

Notes

1. See Ref. 109.

Attempted Reduction of (+)-(S)-(E)-4,4-Dimethyl-1-phenyl-2-[(S)-p-tolyl-sulphinyl]-1-penten-3-ol (94a) using Raney Nickel[1]



(94a)

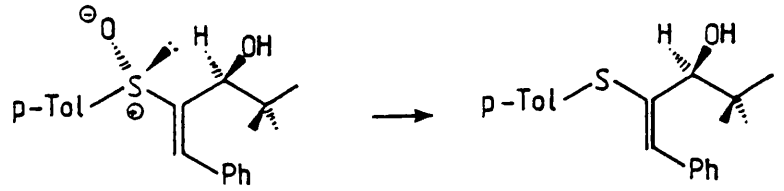
Raney Nickel[2] (720 mg, 6.1 mmol) was placed in a sealed flask under nitrogen. The water was drawn off and the nickel washed with absolute ethanol (2x) which was also removed. Ethanol (3 ml) was then added to the flask, followed by a solution of (+)-(S)-(E)-4,4-dimethyl-1-phenyl-2-[(S)-p-tolylsulphinyl]-1-penten-3-ol (94a) (50 mg, 0.15 mmol) in ethanol (1 ml). T.l.c. of the reaction mixture after 1h at room temperature, showed heavy streaking and several spots. After 20h the t.l.c. showed numerous spots due to decomposition products and the reaction was abandoned.

Notes

1. See Ref. 141.

2. Supplied by Aldrich as a 50% slurry in water.

Reduction of (+)-(S)-(E)-4,4-Dimethyl-1-phenyl-2-[(S)-p-tolylsulphinyl]-1-penten-3-ol (94a) to (S)-(E)-4,4-Dimethyl-1-phenyl-2-(p-tolylthio)-1-penten-3-ol (98) using Aluminium Amalgam[1]



(94a) (98)

(+)-(S)-(E)-4,4-Dimethyl-1-phenyl-2-[(S)-p-tolylsulphinyl]-1-penten-3-ol (94a) (70 mg, 0.21 mmol) was dissolved in a 9:1 THF/H_2O mixture (4 ml) and stirred under nitrogen at 0°C. Aluminium amalgam[2] (75 mg, 2.8 mmol)[3] was added and the reaction monitored by t.l.c.[4] After 6h the reaction mixture was quenched with water, the aqueous solution extracted with dichloromethane (2 x 30 ml), the extracts combined and dried ($MgSO_4$). The solvent was removed in vacuo and after purification by a 'chromatotron' (4:1 petroleum ether-ether), (S)-(E)-4,4-dimethyl-1-phenyl-2-(p-tolylthio)-1-penten-3-ol (98) was obtained as a white solid (54 mg, 82%).

R_f 0.68 (ether);

ν_{max} (CH_2Cl_2) 3520brw (OH), 3020m, 2950s, 2860s, 1600m, 1490s, 1475s, 1390s, 1365s, 1230m, 1210m, 1180m, 1070s, 1035s, 1015s, 920m, 810s;

δ_H (300 MHz; $CDCl_3$) 0.93 (9H, s, $C(CH_3)_3$), 2.34 (3H, s, CH_3), 2.57 (1H, brd, OH), 4.78 (1H, brd, H-3), 6.57 (1H, s, H-1), 7.15-7.50 (9H, m);

δ_C (75 MHz; $CDCl_3$) 21.09(q), 26.70(q), 36.72(s), 76.45(s), 126.86(d), 128.26(d), 128.34(d), 130.10(d), 131.84(s), 132.64(d), 134.17(d), 137.42(s), 137.70(s), 142.36(s).

Notes

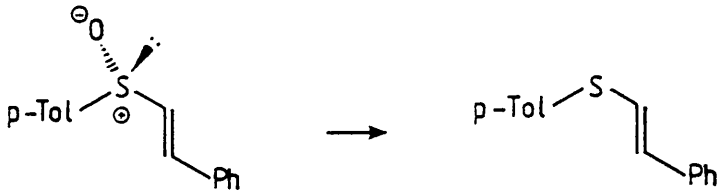
1. See Ref. 85.

2. See Ref. 142.

3. Based on the weight of aluminium used.

4. Further amounts of aluminium amalgam can be added if necessary.

Reduction of (+)-(E)-2-Phenyl-1-[(R)-p-tolylsulphinyl]-ethylene (53b) to (E)-2-phenyl-1-[p-tolylthio)-ethylene (99) using Aluminium Amalgam



(53b) (99)

Using the same procedure as for the reduction of (94a)[1] (+)-(E)-2-phenyl-1-[(R)-p-tolylsulphinyl]-ethylene (53b) (108 mg, 0.45 mmol) was reduced by aluminium amalgam (120 mg, 4.4 mmol) in 4h. After work-up and removal of solvent in vacuo, the crude white solid was purified by 'chromatotron' (petroleum ether) to give (E)-2-phenyl-1-(p-tolylthio)-ethylene (99) as a white solid (85 mg, 84%).

R_f 0.77 (1:1 ether-petroleum ether);

ν_{max} (CH_2Cl_2) 3040m, 3020m, 2980s, 2920m, 1590m, 1485m, 1090m, 1010m, 940s, 805s;

δ_H (300 MHz; $CDCl_3$) 2.33 (3H, s, CH_3), 6.63 (1H, d, J_{trans} = 15.5 Hz, C<u>H</u>=CH), 6.84 (1H, d, J_{trans} = 15.5 Hz, CH=C<u>H</u>), 7.11-7.53 (9H, m);

δ_C (75 MHz; $CDCl_3$) 21.05(q), 124.42(d), 125.86(d), 127.30(d), 128.58(d), 129.90(d), 130.45(d), 130.56(d), 131.12(s), 136.62(s), 137.18(s);

Low resolution ammonia chemical ionization mass spectrum;[2]

244(68) $(M+NH_4)^+$, 227(100 $(M+H)^+$, 226(38).

Notes

1. See p.135.
2. Under the same conditions (53b) showed 260(48) $(M+NH_4)^+$, 243(100) $(M+H)^+$, 227(21).

Preparation of tert-Butylsulphinyl chloride[1] (101)

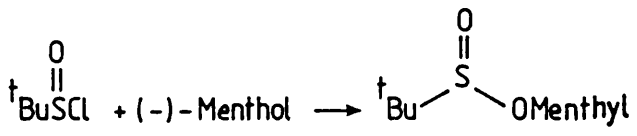
tert-Butyl mercaptan (6.36g, 71 mmol) was dissolved in dichloromethane (30 ml) and cooled to -40°C under nitrogen. A pre-cooled (-78°C) suspension of m-chloroperbenzoic acid (30.2g, 175 mmol) in dichloromethane (300 ml) was added in 30 ml portions every $^1_2$ h with vigorous stirring. Once the addition was complete, the resulting white suspension was stirred overnight at -30°C. After cooling back to -78°C, the suspension was rapidly filtered and then the filtrate refiltered to remove all traces of m-chloroperbenzoic acid. The solvent was removed in vacuo and after drying in an evacuated desiccator (containing P_2O_5), tert-butylsulphinic acid remained as a white solid (4.3g, 50%), [^{1}H n.m.r. showed δ1.2 (9H, s, $C(CH_3)_3$) and δ10.6 (1H, s, COOH)].

To the tert-butylsulphinic acid (4g, 32.8 mmol), prepared above, was added thionyl chloride[2] (15 ml, 206 mmol) under nitrogen at -40°C with stirring. After the addition was complete, the mixture was allowed to warm to room temperature and stirred for a further 2h at this temperature. The excess thionyl chloride was removed in vacuo to leave the crude tert-butylsulphinyl chloride (101) as a yellow oil (4.3g, 93%).

Notes

1. Known compound and literature procedure, see Ref. 72.
2. Freshly distilled from linseed oil.

Preparation of Menthyl tert-butylsulphinate[1]



(101)

A solution of tert-butylsulphinyl chloride (101) (4g, 28.5 mmol) in dry ether (50 ml) was added dropwise to a stirred solution of (-)-menthol (4.5g, 29 mmol) in dry pyridine (15 ml) at -78°C. After 3h at this temperature, the reaction mixture was stirred in an ice bath overnight. A solution of 5% sodium hydrogen carbonate (50 ml) was added and the aqueous solution extracted with ether (75 ml); the ether extract was washed successively with 5% cold hydrochloric acid (100 ml), 5% sodium hydrogen carbonate solution (100 ml), brine (100 ml) and dried (K_2CO_3). The solvent was removed in vacuo and after flash chromatography (4:1 petroleum ether-ether), menthyl tert-butylsulphinate was obtained as a colourless oil (4.48g, 57%) and a (1.6:1)[2] mixture of diastereoisomers.

R_f 0.35 (4:1 petroleum ether-ether);

δ_H (300 MHz; $CDCl_3$) 0.76-0.94 (10H, m), 1.18 and 1.19 (9H, s, $C(CH_3)_3$), 1.24-2.30 (8H, m), 3.93-4.00 (1H, m);

δ_C (75 MHz; $CDCl_3$) 15.3, 15.6, 20.7, 20.9, 21.8,[3] 21.9, 22.0, 22.8, 23.2, 25.1, 25.4, 31.4, 31.7, 33.9, 34.0, 41.9, 43.3, 48.0, 48.4, 56.6, 57.4, 79.2, 81.8;

G.l.c.; R_t (3% OV17, 225°C) 9.25 and 9.43 min.

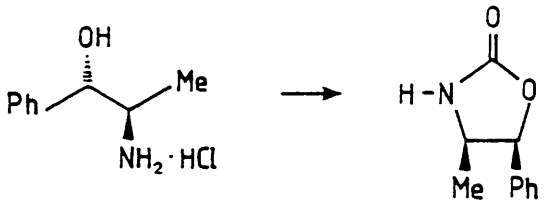
Notes

1. See Ref. 72 and p.60.

2. Ratio as measured by g.l.c.

3. Signal common to both diastereoisomers (methyl carbons of tert-butyl groups).

Preparation of (+)-(4R,5S)-4-Methyl-5-phenyl-2-oxazolidinone (102)[1]



(103) (102)

(+)-(1S,2R)-Norephedrine hydrochloride (103) (9g, 48 mmol) was dissolved in 2M hydrochloric acid (50 ml) and the acidic solution rendered basic by the slow addition of 2M potassium hydroxide solution. The aqueous solution was extracted with chloroform (2 x 50 ml) and the combined extracts dried ($MgSO_4$). After removal of the solvent in vacuo, the ephedrine free base was left as a viscous yellow liquid. To the flask containing the ephedrine free base was added anhydrous potassium carbonate (6.8g, 49 mmol) and diethyl carbonate (25 ml, 207 mmol), the flask fitted with a Vigreux column (10 cm) and set up for distillation. The flask was lowered into a preheated oil bath at ~145°C; within a few minutes ethanol began to distil, and the reaction mixture was stirred for 2½ h at this temperature, whilst the distillation continued. After cooling to room temperature, the distillation residue was diluted with dichloromethane (75 ml), washed with water (100 ml) and dried ($MgSO_4$). The solvent was removed in vacuo to give a solid which after recrystallization (2:1 ethyl acetate-petroleum ether) gave (+)-(4R,5S)-4-methyl-5-phenyl-2-oxazolidinone (102) as white crystals (5.3g, 62%) m.p. 120-121°C (lit.[110] 121-122°C).

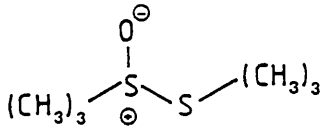
$[\alpha]_D$ = +174° (2.0 in $CHCl_3$), (lit.[110] +177.2°C);

δ_H (90 MHz; $CDCl_3$) 0.8 (3H, d, J *ca.* 6 Hz, CH_3), 4.2 (1H, m, H-4), 5.65 (1H, d, J *ca.* 7 Hz, H-5), 6.15 (1H, brs, NH), 7.15-7.4 (5H, m, C_6H_5).

Notes

1. Known compound, see Ref. 110 and adapted procedure.

Preparation of 2-Methyl-2-[{(2-methylpropyl)sulphinyl}thio]-propane[1] (104)



(104)

To a stirred solution of di-tert-butyl disulphide (105) (9.09g, 52 mmol) in glacial acetic acid (50 ml) was added hydrogen peroxide[2] (7.7 ml, 68 mmol) in glacial acetic acid (50 ml), at room temperature. After stirring overnight, the solvent was removed in vacuo to leave a colourless liquid which after distillation (85°C at 0.5 mmHg) (lit.[143] b.p. 55°C at 0.05 mmHg) gave 2-methyl-2-[{(2-methylpropyl)sulphinyl}thio]-propane (104) as a colourless liquid (7.2g, 71%).

ν_{max} (neat) 2910s, 1430s, 1340s, 1140s, 1060s (S=O), 890m, 710s;

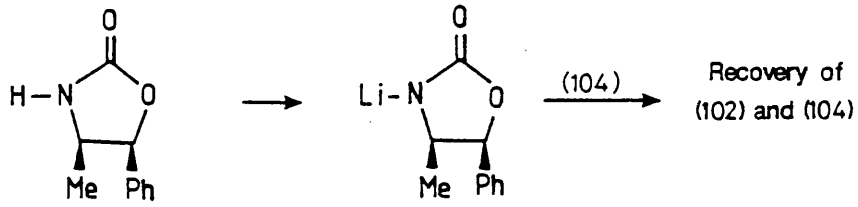
δ_H (90 MHz; $CDCl_3$) 1.4 (9H, s, $C(CH_3)_3$), 1.6 (9H, s, $C(CH_3)_3$).

Notes

1. Known compound, see Ref. 143. For procedure, see Ref. 111.

2. 100 vol. (30%) hydrogen peroxide.

Attempted Reaction of N-Lithiated (+)-(4R,5S)-4-methyl-5-phenyl-2-oxazolidinone and 2-Methyl-2-[{(2-methylpropyl)sulphinyl}thio]-propane (104)



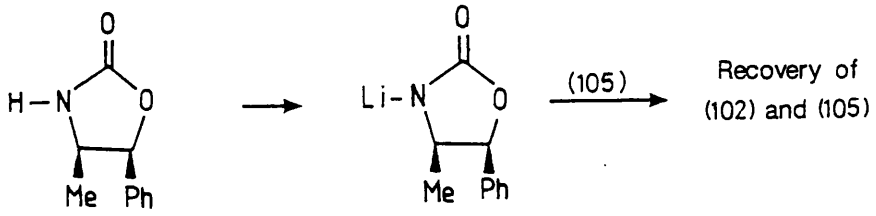
(102)

n-Butyllithium[1] (516 μl, 1.24 mmol) was added dropwise to a solution of (+)-(4R,5S)-4-methyl-5-phenyl-2-oxazolidinone (102) (200 mg, 1.13 mmol) in THF (2^1_2 ml) at -78°C, under nitrogen. After stirring for 10 min at this temperature, a solution of 2-methyl-2-[{(2-methylpropyl)-sulphinyl}thio]-propane (104) (240 mg, 1.24 mmol) in THF (2 ml) was added. Left stirring for 1h at -78°C, the solution was then allowed to warm slowly to room temperature and left for a further 1h. The solution was quenched with aqueous saturated ammonium chloride solution and the aqueous solution extracted with dichloromethane (2 x 20 ml). The combined dichloromethane extracts were dried ($MgSO_4$) and removal of the solvent in vacuo gave a yellow oil which t.l.c. and ^1H n.m.r. showed to be starting materials (102) and (104).

Notes

1. n-Butyllithium was 2.4M by titration.

Attempted Reaction of N-Lithiated (+)-(4R,5S)-4-Methyl-5-phenyl-2-oxazolidinone and Di-tert-butyl disulphide (105)



(102)

Using the same procedure as p.144, (+)-(4R,5S)-4-methyl-5-phenyl-2-oxazolidinone (102) (200 mg, 1.13 mmol) was deprotonated and di-tert-butyl disulphide (105) (220 mg, 1.24 mmol) added in THF (2 ml). After work-up and removal of solvent in vacuo, a yellow oil remained which t.l.c. and ^1H n.m.r. showed to be the starting materials (102) and (105).

Preparation of 2-tert-Butyl-1-chlorodisulphane (109)[1]

$t\text{-Bu-}S_2\text{-Cl}$

(109)

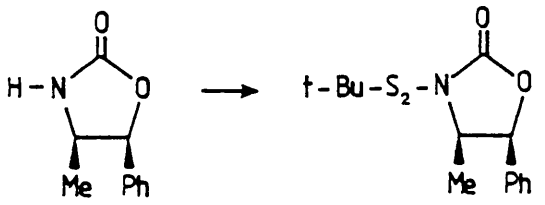
Chlorine gas (5g, 70 mmol) in dry carbon tetrachloride[2] (70 ml) was added dropwise to a solution of di-tert-butyl disulphide (12.7g, 71 mmol) in dry carbon tetrachloride (70 ml) at -40°C under a nitrogen atmosphere. After the addition was complete (1h), the reaction mixture was stirred for a further 1h. The solvent was removed *in vacuo* to leave a foul smelling, yellow oil. Kugelröhr distillation (200°C at 15 mmHg) gave 2-tert-butyl-1-chlorodisulphane (109) as an oil (10.9g, 49%).

δ_H (90 MHz; $CDCl_3$) 1.45(s) (cf. δ1.30(s) for the disulphide starting material).

Notes

1. See Ref. 114.
2. See Ref. 144.

Preparation of (-)-(4R,5S)-3-(2-tert-Butyldithio)-4-methyl-5-phenyl-2-oxazolidinone (110)



(102) (110)

A mixture of (+)-(4R,5S)-4-methyl-5-phenyl-2-oxazolidinone (102) (2g, 11.3 mmol) and triethylamine (6.2 ml, 44.6 mmol) in THF (25 ml) was added dropwise to a solution of 2-tert-butyl-1-chlorodisulphane (109) (2.5g, 16 mmol) in THF (25 ml) under nitrogen at 0°C. After 2h at this temperature, the reaction mixture was allowed to warm to room temperature and stirred for a further 30 min. After quenching with water, the aqueous solution was extracted with dichloromethane (2 x 50 ml) and the combined extracts dried ($MgSO_4$). Removal of the solvent <u>in vacuo</u> gave the crude product which after flash chromatography (4:1 petroleum ether-ethyl acetate) and recrystallization[1] (6:1 petroleum ether-ethyl acetate) gave <u>(-)-(4R,5S)-3-(2-tert-butyldithio)-4-methyl-5-phenyl-2-oxazolidinone (110)</u> as a white solid (2.1g, 62%) m.p. 109-111°C.

α_D = -172° (2.0 in $CHCl_3$);

R_f 0.38 (4:1 petroleum ether-ethyl acetate);

$C_{14}H_{19}O_2NS$ requires C 56.54%, H 6.44%, N 4.71%,

found C 56.41%, H 6.39%, N 4.72%.

ν_{max} (CH_2Cl_2) 2960w, 1760s (C=0), 1450w, 1365m, 1340m, 1200brm, 1145m, 1050w, 970w, 910w;

δ_H (300 MHz; $CDCl_3$) 0.90 (3H, d, J = 6.6 Hz, CH_3), 1.45 (9H, s, $C(CH_3)_3$), 4.30 (1H, dq, J = 8.1, 6.6 Hz, H-4), 5.58 (1H, d, J = 8.2 Hz, H-5), 7.21-7.40 (5H, m, C_6H_5);

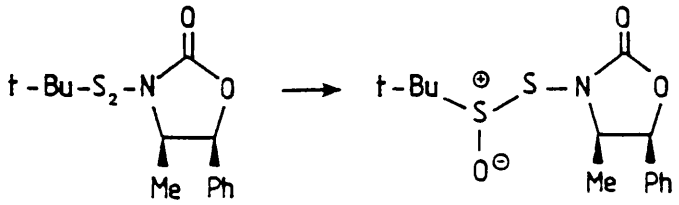
δ_C (75 MHz; $CDCl_3$) 15.20(q), 30.26(q), 48.82(s), 57.37(d), 79.25(d), 126.03(d), 128.47(d), 128.66(d), 134.65(s), 157.67(s);

M/Z 297 (M^+), 241(75), 177(100), 176(16), 133(19), 132(42), 118(44), 117(38), 107(39), 105(36).

Notes

1. Subsequently recrystallized from petroleum ether only.

Oxidation of (-)-(4R,5S)-3-(2-tert-Butyldithio)-4-methyl-5-phenyl-2-oxazolidinone (110)



(110) (111)

m-Chloroperbenzoic acid (1.48g, 6.9 mmol) in chloroform (25 ml) was added dropwise over 20 min to a solution of (-)-(4R,5S)-3-(2-tert-butyldithio)-4-methyl-5-phenyl-2-oxazolidinone (110) (1.12g, 3.8 mmol) in chloroform (20 ml) at 0°C. After stirring for 45 min at this temperature, aqueous saturated sodium hydrogen carbonate solution was added. The chloroform layer was removed and the aqueous layer re-extracted with chloroform (30 ml), the combined extracts were washed with water (50 ml) and dried ($MgSO_4$). Removal of the solvent in vacuo afforded a solid which after purification by flash chromatography (3:2 petroleum ether-ethyl acetate) and recrystallization (1:1 petroleum ether-ethyl acetate) gave (4R,5S)-3-[(tert-butylsulphinyl)thio]-4-methyl-5-phenyl-2-oxazolidinone as a white solid consisting of a (1:1) mixture of diastereoisomers of (111) (0.84g, 71%) m.p. 96.5-100.5°C.

R_f 0.36[2] (7:3 petroleum ether-ethyl acetate);

$C_{14}H_{19}NO_3S_2$ requires C 56.65%, H 6.11%, N 4.47%,

found C 56.68%, H 6.08%, N 4.47%.

ν_{max} (CH_2Cl_2) 2960w, 1765brs (C=O), 1450w, 1365m, 1340s, 1185s, 1145m, 1115m, 1075s (S=O), 1010w, 970w;

δ_H (300 MHz; $CDCl_3$) 0.92 (3H, d, J = 6.6 Hz, CH_3), 1.04 (3H, d, J = 6.7 Hz, CH_3), 1.47 (9H, s, $C(CH_3)_3$), 1.48 (9H, s, $C(CH_3)_3$), 4.23 (1H, dq, J = 7.8, 6.7 Hz, H-4), 4.50 (1H, dq, J = 8.0, 6.6 Hz, H-4), 5.76 (1H, d,

J = 7.8 Hz, H-5), 5.78 (1H, d, J = 7.9 Hz, H-5), 7.24-7.44 (10H, m, C_6H_5);[3]

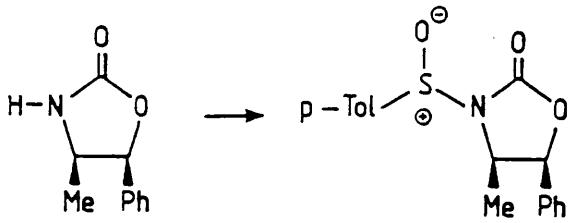
δ_C (75 MHz; $CDCl_3$) 15.13(q), 16.10(q), 24.03(q), 24.10(q), 60.85(d), 60.94(d), 79.59(d),[3] 125.93(d),[3] 125.97(d),[3] 128.63(d),[3] 128.86(d),[3] 134.15(s),[3] 157.20(s);[3]

M/Z 177(21), 107(100), 105(19).

Notes

1. Obtained from Aldrich, 80-85% pure.
2. Pair of diastereoisomers appear as 1 spot by t.l.c.
3. Signals common to both diastereoisomers.

Preparation of (-)-(4R,5S)-4-methyl-5-phenyl-3-(p-tolylsulphinyl)-2-oxazolidinone (112)



(102) (112)

n-Butyllithium[1] (11 ml, 17.5 mmol) was added dropwise under nitrogen to a solution of (+)-(4R,5S)-4-methyl-5-phenyl-2-oxazolidinone (102) (3g, 17 mmol) in THF (75 ml) at -78°C. After stirring for 15 min at this temperature, p-tolylsulphinyl chloride[2] (3.26g, 18.7 mmol) in THF (75 ml) was added dropwise. Once the addition was complete, the reaction mixture was stirred for a further 2h at -78°C and quenched with water. The aqueous solution was extracted with dichloromethane (3 x 100 ml), the combined extracts were dried ($MgSO_4$) and the solvent removed in vacuo. After purification by flash chromatography (7:3 petroleum ether-ethyl acetate), (-)-(4R,5S)-4-methyl-5-phenyl-3-(p-tolylsulphinyl)-2-oxazolidinone (112) was obtained as a white solid, a (4:1) mixture of diastereoisomers as measured by 90 MHz, ^1H n.m.r. After recrystallization (x 2) (2:1 ethyl acetate-petroleum ether), the major isomer was obtained pure as a white solid (1.22g, 23%) m.p. 105-106°C.

$[\alpha]_D$ = -220° (1.7 in $CHCl_3$);

R_f 0.31 (7:3 petroleum ether-ethyl acetate);

$C_{17}H_{17}NO_3S$ requires C 64.74%, H 5.43%, N 4.44%,

found C 64.51%, H 5.39%, N 4.42%.

ν_{max} (CH_2Cl_2) 1760s (C=0), 1325m, 1190s, 1140m, 1115s, 1105m, 1070m, 1010m, 810m;

δ_H (300 MHz; $CDCl_3$) 0.90 (3H, d, J = 6.7 Hz, CH_3), 2.47 (3H, s, CH_3),

3.83 (1H, quin, J *ca.* 6.8 Hz, H-4), 5.49 (1H, d, J = 7.4 Hz, H-5), 7.17-7.68 (9H, m);

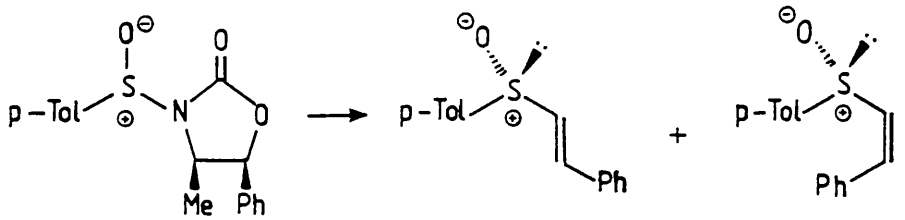
δ_C (75 MHz; $CDCl_3$) 17.28(q), 21.51(q), 56.01(d), 80.25(d), 125.03(d), 125.82(d), 128.56(d), 128.82(d), 130.40(d), 133.02(s), 137.53(s), 143.00(s), 155.74(s);

M/Z 315 (M^+), 177(12), 140(12), 139(50), 118(15), 108(12), 107(100).

Notes

1. n-Butyllithium was 1.6M by titration.
2. See p.110.

Preparation of (+)-(E) and (-)-(Z)-2-Phenyl-1-[(R)-p-tolylsulphinyl]-ethylene (53b) and (53a) from (-)-(4R,5S)-4-Methyl-5-phenyl-3-(p-tolyl-sulphinyl)-2-oxazolidinone (112)



Styryl magnesium bromide[1] (2.2 mmol) in THF (5 ml) was added dropwise to a solution of (-)-(4R,5S)-4-methyl-5-phenyl-3-(p-tolylsulphinyl)-2-oxazolidinone (112) (500 mg, 1.6 mmol) in THF (8 ml) at -78°C under nitrogen. After 2h at this temperature, the reaction mixture was quenched with saturated aqueous ammonium chloride solution, the aqueous solution was extracted with chloroform (3 x 25 ml), the combined extracts were washed successively with water (50 ml), brine (50 ml) and dried ($MgSO_4$). The solvent was removed in vacuo and after purification by flash chromatography (4:1 ether-petroleum ether), (+)-(E) and (-)-(Z)-2-phenyl-1-[(R)-p-tolylsulphinyl]-ethylene (53b) and (53a) were obtained as a white solid (254 mg, 66%) and a yellow oil (77 mg, 20%) respectively. A sample of the (E)-isomer was recrystallized[2] (petroleum ether) to constant rotation ($[\alpha]_D$ = +160° (2.0 in $CHCl_3$)) showing it to have the same configuration at S as the isomer prepared previously.[3] [All spectral properties of the two isomers were identical with those of the isomers prepared previously.[3]]

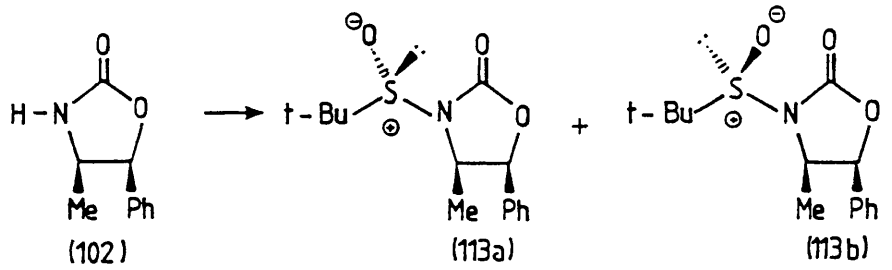
Notes

1. See p.113.
2. Frequently the (E) and (Z)-isomers became contaminated with the free oxazolidinone (102). To remove the oxazolidinone, the 'crude'

columned isomer was dissolved in hot, excess isopropyl ether and allowed to cool. The oxazolidinone crystallized out and could be removed by filtration. The filtrate was concentrated and recrystallized as before from petroleum ether.

3. See p.113.

Preparation of (4R,5S)-3-[(S)-tert-Butylsulphinyl] and (4R,5S)-3-[(R)-tert-butylsulphinyl]-4-methyl-5-phenyl-2-oxazolidinone (113a) and (113b)



n-Butyllithium[1] (9.7 ml, 15.5 mmol) was added dropwise to a solution of (+)-(4R,5S)-4-methyl-5-phenyl-2-oxazolidinone (102) (2.6g, 14.7 mmol) in THF (50 ml) under nitrogen at -78°C. After stirring for 15 min at this temperature, a solution of tert-butylsulphinyl chloride[2] (2.3g, 16.4 mmol) in THF (50 ml) was added dropwise. Once the addition was complete, the reaction mixture was stirred for a further 2h at -78°C and quenched with water. The aqueous solution was extracted with dichloromethane (3 x 100 ml), the combined extracts were dried ($MgSO_4$), the solvent was removed in vacuo and after flash chromatography[3] (3:2 petroleum ether-ethyl acetate) and recrystallization (4:1 petroleum ether-ethyl acetate) (both isomers), (4R,5S)-3-[(S)-tert-butylsulphinyl] and (4R,5S)-3-[(R)-tert-butylsulphinyl]-4-methyl-5-phenyl-2-oxazolidinone (113a) and (113b) were obtained as white solids, the major isomer (1.70g, 41%) m.p. 82-84°C and the minor isomer (0.98g, 24%) m.p. 98-99°C.

Major isomer

R_f 0.48 (1:1 ethyl acetate-petroleum ether);

$C_{14}H_{19}NO_3S$ requires C 59.76%, H 6.81%, N 4.98%,

found C 59.79%, H 6.78%, N 5.01%.

ν_{max} (CH_2Cl_2) 2960w, 1755s (C=0), 1450m, 1365m, 1330s, 1190s, 1125s, 1115s, 1095s, 1060m, 1045m, 1010m;

δ_H (300 MHz; $CDCl_3$) 0.95 (3H, d, J = 6.7 Hz, CH_3), 1.32 (9H, s,

$C(CH_3)_3$), 4.50 (1H, dq, J = 7.8, 6.7 Hz, H-4), 5.68 (1H, d, J = 7.8 Hz, H-5), 7.25-7.44 (5H, m, C_6H_5);

δ_C (75 MHz; $CDCl_3$) 17.73(q), 22.67(q), 51.63(d), 59.10(s), 82.07(d), 126.06(d), 128.63(d), 128.83(d), 134.31(s), 157.80(s);

M/Z 177(13), 107(100), 105(26).

Minor isomer

R_f 0.40 (1:1 ethyl acetate-petroleum ether);

$C_{14}H_{19}NO_3S$ requires C 59.76%, H 6.81%, N 4.98%,

found C 59.68%, H 6.81%, N 4.965%.

ν_{max} (CH_2Cl_2) 2960w, 1760s (C=0), 1450w, 1365m, 1330m, 1210w, 1185m, 1135m, 1095s, 1065w, 1010w, 965w;

δ_H (300 MHz; $CDCl_3$) 1.01 (3H, d, J = 6.5 Hz, CH_3), 1.37 (9H, s, $C(CH_3)_3$), 4.54 (1H, quin, J = 6.6 Hz, H-4), 5.70 (1H, d, J = 6.7 Hz, H-5), 7.29-7.43 (5H, m, C_6H_5);

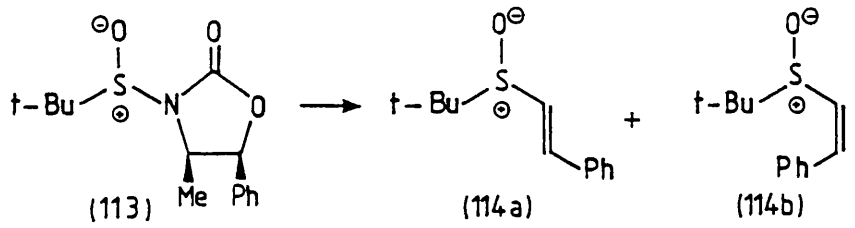
δ_C (75 MHz; $CDCl_3$) 16.12(q), 22.55(q), 57.06(d), 66.30(s), 80.41(d), 125.63(d), 128.43(d), 128.56(d), 132.86(s), 155.27(s);

M/Z 225(58), 177(57), 118(100), 117(15), 107(26), 105(11).

Notes

1. n-Butyllithium was 1.6M by titration.
2. See p.138.
3. Crude ^1H n.m.r. showed an approximate (2:1) mixture of diastereo-isomers.

Preparation of (E) and (Z)-1-(tert-Butylsulphinyl)-2-phenylethylene (114a) and (114b)



(113) (114a) (114b)

Styryl magnesium bromide[1] (4.0 mmol) in THF (8 ml) was added dropwise to a solution of (4R,5S)-3-(t-butylsulphinyl)-4-methyl-5-phenyl-2-oxazolidinone[2] (113) (700 mg, 2.5 mmol) in THF (10 ml) at -78°C under nitrogen. After 2h at this temperature, the reaction mixture was quenched with saturated aqueous ammonium chloride solution. The aqueous solution was extracted with chloroform (3 x 25 ml), the combined extracts were washed successively with water (50 ml), brine (50 ml) and dried ($MgSO_4$). The solvent was removed in vacuo and after purification by use of a 'chromatotron' (3:2 petroleum ether-ethyl acetate) and recrystallization (petroleum ether) [only (114a)], (E)-1-(tert-butylsulphinyl)-2-phenylethylene (114a) was obtained as a white solid (316 mg, 61%) m.p. 89-91°C and (Z)-1- (tert-butylsulphinyl)-2-phenylethylene (114b) as a yellow oil (39 mg, 8%).

(114a)

R_f 0.35 (ether);

$C_{12}H_{16}OS$ requires C 69.19%, H 7.74%, N 0.00%,

found C 69.53%, H 7.70%, N 0.05%.

ν_{max} (CH_2Cl_2) 2960m, 1605w, 1490m, 1470m, 1455m, 1440m, 1360m, 1170m, 1045brs (S=O), 965s, 855m.

δ_H (300 MHz; $CDCl_3$) 1.28 (9H, s, $C(CH_3)_3$), 6.80 (1H, d, J_{trans} = 15.5 Hz, C<u>H</u>=CH), 7.22 (1H, d, J_{trans} = 15.5 Hz, CH=C<u>H</u>), 7.31-7.48 (5H, m,

C_6H_5);

δ_C (75 MHz; $CDCl_3$) 22.98(q), 55.53(s), 126.64(d), 127.44(d), 128.70(d), 128.80(d), 129.39(d), 134.03(s), 138.03(d);

M/Z 208 (M^+), 153(11), 152(100), 136(28), 135(36), 134(14), 104(28).

(114b)

R_f 0.18 (ether);

ν_{max} (CH_2Cl_2) 2960m, 1600w, 1490m, 1455m, 1440m, 1360m, 1170m, 1025brs (S=O), 905m;

δ_H (90 MHz; $CDCl_3$) 1.3 (9H, s, $C(CH_3)_3$), 6.2 (1H, d, J_{cis} *ca.* 12 Hz, H-1), 7.0-7.55 (6H, m);

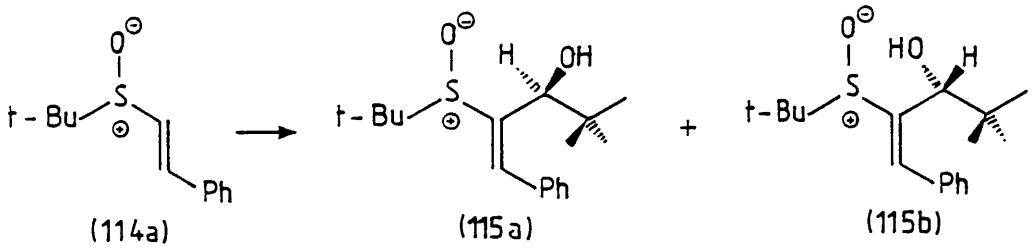
$C_{12}H_{16}OS$ requires 208.0922

found 208.0926.[3]

Notes

1. See p.113.
2. The major isomer of (113a) and (113b).
3. Detected as the $(M+H)^+$ ion.

Preparation of (S)-(E) and (R)-(E)-2-(tert-Butylsulphinyl)-4,4-dimethyl-1-phenyl-1-penten-3-ol (115a) and (115b)



Using the same procedure as for the preparation of (89),[1] (E)-1-(tert-butylsulphinyl)-2-phenylethylene (114a) (100 mg, 0.48 mmol) in THF (2½ ml) was deprotonated with LDA (0.58 mmol) and quenched with trimethylacetaldehyde[2] (68 μl, 0.62 mmol). After work-up, the crude reaction mixture[3] was purified by use of a 'chromatotron' (1:1 ether-petroleum ether) to give the major isomer of (E)-2-(tert-butylsulphinyl)-4,4-dimethyl-1-phenyl-1-penten-3-ol (115) as a white solid (68 mg, 48%) m.p. 172-174°C (recrystallized from ethyl acetate) and the minor isomer also as a white solid[4] (10 mg, 7%).

Major isomer

R_f 0.50 (ether);

$C_{17}H_{26}O_2S$ requires C 69.34%, H 8.90%, N 0.00%,

found C 69.31%, H 8.84%, N 0.03%.

δ_H (300 MHz; $CDCl_3$) 0.86 (9H, s, $C(CH_3)_3$), 1.36 (9H, s, $C(CH_3)_3$), 3.83 (1H, brs, OH), 4.47 (1H, brd, J = 7.3 Hz, H-3), 7.00 (1H, s, H-1), 7.26-7.58 (5H, m, C_6H_5);

δ_C (75 MHz; $CDCl_3$) 23.90(q), 26.81(q), 39.74(s), 59.38(s), 81.20(d), 128.29(d), 128.47(d), 129.77(d), 133.50(d), 135.47(s), 141.07(s);

H.p.l.c.; R_t (Partisil PXS 10/25, ether, 2 cm^3 min^{-1}) 3.3 min;

M/Z 202(82), 187(70), 172(85), 162(79), 157(45), 116(95), 115(100).

Minor isomer

R_f 0.34 (ether);

δ_H (300 MHz; $CDCl_3$) 0.89 (9H, s, $C(CH_3)_3$), 1.32 (9H, s, $C(CH_3)_3$), 4.80 (1H, s, H-3), 7.30-7.45 (6H, m);

H.p.l.c.; R_t (Partisil PXS 10/25, ether, 2 cm^3 min^{-1}) 5.1 min;

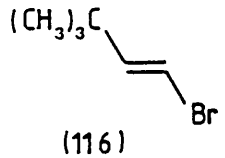
$C_{17}H_{26}O_2S$ requires 294.1653

found 294.1662.[5]

Notes

1. See p.116.
2. Distilled prior to use.
3. The diastereomeric ratio, as measured from the crude reaction mixture by h.p.l.c., was 1:4.6.
4. The minor isomer was contaminated with starting material which could be removed by recrystallizing the sample obtained from the chromatotron using ethyl acetate - the starting material (114a) remained in solution.
5. Detected as the $(M+H)^+$ species.

Preparation of (E)-1-Bromo-3,3-dimethyl-1-butene (116)[1]



(116)

Diisobutylaluminium hydride (DIBAL-H)[2] (61 ml, 61 mmol) was added to a solution of 3,3-dimethyl-but-1-yne (5g, 61 mmol) in n-heptane[3] at 0°C. After the addition, the reaction mixture was warmed to 50°C and stirred for 2h followed by removal of the solvent by use of a vacuum pump. The white residue was redissolved in THF (30 ml) and a solution of bromine (3.2 ml, 61 mmol) in dichloromethane (25 ml) was added at -50°C.

After allowing the reaction mixture to warm to room temperature, sulphuric acid (20% aqueous solution) was added dropwise whilst keeping the reaction mixture cold. Once the evolution of gas had stopped, the mixture was poured into an ice/20% sulphuric acid mixture and the vinyl bromide extracted with dichloromethane (2 x 50 ml). The combined extracts were washed successively with sodium thiosulphate solution (100 ml), sodium hydrogen carbonate solution (100 ml) and dried ($MgSO_4$). The solvent was removed in vacuo and after Kugelrohr distillation, (E)-1-bromo-3,3-dimethyl-1-butene (116) was obtained as a colourless liquid (4.4g, 44%) b.p. 134-136°C (lit.[145] 48°C at 50 mmHg).

$C_6H_{11}Br$ requires C 44.20%, H 6.80%, N 0.00%,

found C 44.57%, H 6.87%, N 0.06%.

ν_{max} (CH_2Cl_2) 2940s, 2890s, 2860s, 1610m, 1460s, 1360s, 1225m, 1195w, 1165m, 1110m, 1020m, 945s, 905m;

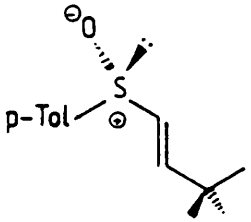
δ_H (90 MHz; $CDCl_3$) 1.05 (9H, s, $C(CH_3)_3$), 5.9 (1H, d, J_{trans} *ca.* 15 Hz, C<u>H</u>=CH), 6.2 (1H, d, J_{trans} *ca.* 15 Hz, CH=C<u>H</u>);

M/Z 164, 162 (M^+), 149(14), 147(16), 121(10), 119(11).

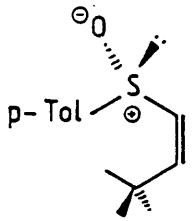
Notes

1. Known compound see Ref. 145. Literature procedure see Ref. 116.
2. Obtained from Aldrich as a 1.0M solution in heptane.
3. n-Heptane was purified by shaking with small portions of conc. sulphuric acid and then washed with water, aqueous 10% sodium carbonate solution and water (x 2), dried and distilled from sodium wire.

Preparation of (E) and (Z)-3,3-Dimethyl-1-[(R)-p-tolylsulphinyl]-1-butene (118a) and (118b)



(118a)



(118b)

Magnesium turnings (0.33g, 13.5 mmol) and a crystal of iodine were covered by the minimum of THF (2 ml) under nitrogen. 1-Bromo-3,3-dimethyl-1-butene (116) (2g, 12.03 mmol) was added dropwise and once the reaction had started,[1] a further volume of THF (6 ml) was added slowly so as to maintain the reflux. The reaction mixture was refluxed for several hours until the majority of the turnings had been consumed. A further volume of THF (10 ml)[2] was added and the mixture allowed to cool to room temperature. The Grignard reagent was added dropwise to (-)-menthyl (-)-(S)-p-toluenesulphinate (3.62g, 12.3 mmol) in benzene (20 ml) at room temperature and after 2h the reaction mixture was quenched with saturated aqueous ammonium chloride solution. The aqueous solution was extracted with chloroform (3 x 40 ml), the combined extracts washed successively with water (100 ml), brine (100 ml) and dried ($MgSO_4$). The solvent was removed in vacuo and after purification by flash chromatography (ether), (E) and (Z)-3,3-dimethyl-1-[(R)-p-tolylsulphinyl]-1-butene (118a) and (118b) were obtained as a white solid (457 mg, 17%) and a yellow oil (408 mg, 15%) respectively.

(118a)

R_f 0.46 (ether);

ν_{max} (CH_2Cl_2) 2950s, 2860m, 1590w, 1490m, 1460m, 1390w, 1360m, 1080s, 1040s (S=O), 1010s, 965s, 910m, 805s;

δ_H (300 MHz; $CDCl_3$) 1.08 (9H, s, $C(CH_3)_3$), 2.40 (3H, s, CH_3), 6.11 (1H, d, J_{trans} = 15.4 Hz, C<u>H</u>=CH), 6.59 (1H, d, J_{trans} = 15.4 Hz, CH=C<u>H</u>), 7.30 (2H, m, aromatic), 7.49 (2H, m, aromatic);

δ_C (75 MHz; $CDCl_3$) 21.36(q), 28.74(q), 34.14(s), 124.58(d), 129.93(d), 131.09(d), 141.15(s), 141.21(s), 150.53(d);

$C_{13}H_{18}OS$ requires 222.1078

found 222.1059.

(118b)

R_f 0.31 (ether);

ν_{max} (CH_2Cl_2) 2960s, 2860m, 1595w, 1490m, 1470m, 1360m, 1205m, 1080s, 1030s (S=O), 1010s, 810m, 790m;

δ_H (300 MHz; $CDCl_3$) 1.31 (9H, s, $C(CH_3)_3$), 2.39 (3H, s, CH_3), 6.02 (1H, d, J_{cis} = 10.9 Hz, C<u>H</u>=CH), 6.11 (1H, d, J_{cis} = 10.9 Hz, CH=C<u>H</u>), 7.30 (2H, m, aromatic), 7.53 (2H, m, aromatic);

δ_C (75 MHz; $CDCl_3$) 21.31(q), 31.33(q), 35.35(s), 124.26(d), 129.92(d), 134.51(d), 141.01(s), 141.73(s), 150.07(d);

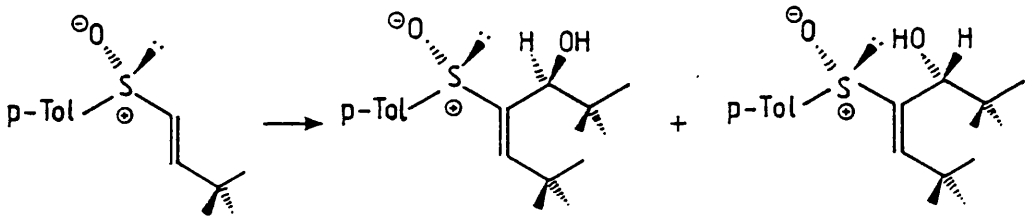
$C_{13}H_{18}OS$ requires 222.1078

found 222.1074.

<u>Notes</u>

1. The use of dibromoethane was employed if the reaction initiation was slow.
2. Further volume added to prevent the Grignard reagent crystallizing out on cooling.

Preparation of (S)-(E) and (R)-(E)-2,2,6,6-Tetramethyl-4-[(S)-p-tolyl-sulphinyl]-4-hepten-3-ol (119a) and (119b)



(118a) (119a) (119b)

Using the same procedure as for the preparation of (89),[1] (E)-3,3-dimethyl-1-[(R)-p-tolylsulphinyl]-1-butene (118a) (100 mg, 0.45 mmol) was deprotonated with LDA (0.54 mmol) and stirred at -78°C for 1h. Quenching with trimethylacetaldehyde[2] (60 μl, 0.54 mmol) followed by standard work-up gave the solid crude reaction mixture.[3] This was dissolved in the minimum amount of hot ethyl acetate and allowed to cool to give white crystals (62 mg, 45%) m.p. 212-214°C of the less polar diastereoisomer of (E)-2,2,6,6-tetramethyl-4-[(S)-p-tolylsulphinyl]-4-hepten-3-ol (119). The filtrate was concentrated and purified by use of a 'chromatotron' (1:1 ethyl acetate-petroleum ether) to give white crystals (51 mg, 37%) of the other (more polar) diastereoisomer of (119).

Diastereoisomer 1 [the less polar diastereoisomer of (119)]

$[\alpha]_D$ = +179.6° (1.4 in $CHCl_3$);

R_f 0.49 (ether);

$C_{18}H_{28}O_2S$ requires C 70.09%, H 9.15%, N 0.00%,

found C 69.81%, H 8.97%, N 0.05%.

δ_H (300 MHz; $CDCl_3$) 1.09 (9H, s, $C(CH_3)_3$), 1.12 (9H, s, $C(CH_3)_3$), 2.36 (3H, s, CH_3), 4.88 (1H, s, H-3), 6.82 (1H, s, H-5), 7.23 (2H, m, aromatic), 7.56 (2H, m, aromatic);

δ_C (75 MHz; $CDCl_3$) 21.41(q), 27.49(q), 30.83(q), 34.68(s), 36.21(s), 75.28(d), 125.77(d), 129.72(d), 141.37(s), 141.91(d), 143.02(s),

144.36(s);

H.p.l.c.; R_t (Partisil PXS 10/25, ether, 5 cm^3 min^{-1}) 1.26 min;

M/Z 308 (M^+), 251(37), 235(21), 169(32), 151(51), 140(100), 139(47), 124(49), 111(71), 109(40).

Diastereoisomer 2 [the more polar diastereoisomer of (119)]

R_f 0.24 (ether);

ν_{max} (CH_2Cl_2) 3340brm (OH), 2950s, 2860s, 1590w, 1470m, 1390m, 1360m, 1195m, 1175m, 1075s, 1045s, 1010s, 805s;

δ_H (300 MHz; $CDCl_3$) 1.10 (9H, s, $C(CH_3)_3$), 1.12 (9H, s, $C(CH_3)_3$), 2.41 (3H, s, CH_3), 4.88 (1H, s, H-3), 5.64 (1H, d, J = 0.6 Hz, H-5), 7.31 (2H, m, aromatic), 7.55 (2H, m, aromatic);

δ_C (75 MHz; $CDCl_3$) 21.43(q), 27.72(q), 30.66(q), 34.88(s), 36.29(s), 77.84(d), 126.41(d), 129.77(d), 141.02(s), 141.61(s), 145.32(s), 146.93(d);

H.p.l.c.; R_t (Partisil PXS 10/25, ether, 5 cm^3 min^{-1}) 4.11 min;

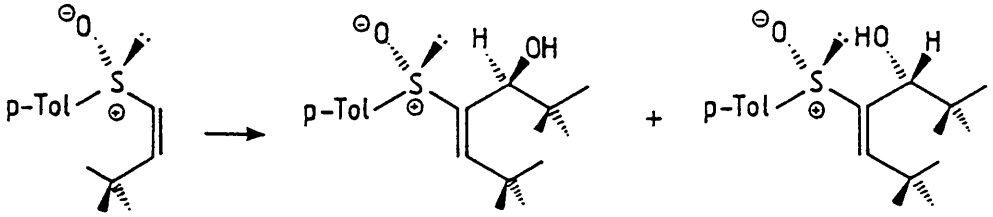
$C_{18}H_{28}O_2S$ requires 308.1810

found 308.1797.[4]

Notes

1. See p.116.
2. Distilled prior to use.
3. The diastereomeric ratio, as measured from the crude reaction mixture by h.p.l.c., was 1:1.2 (less polar dias:more polar dias).
4. Detected as $(M+H)^+$ under ammonia chemical ionization conditions.

Preparation of (S)-(E) and (R)-(E)-2,2,6,6-Tetramethyl-4-[(S)-p-tolyl-sulphinyl]-4-hepten-3-ol (119a) and (119b) from (118b)



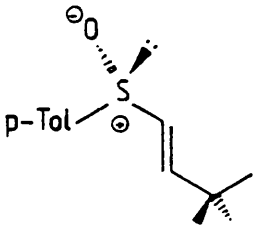
(118b) (119a) (119b)

Using the same procedure as for the preparation of (119a) and (119b) from (118a),[1] (Z)-3,3-dimethyl-1-[(R)-p-tolylsulphinyl]-1-butene (118b) (100 mg, 0.45 mmol) was deprotonated with LDA (0.63 mmol) and quenched with trimethylacetaldehyde[2] (195 μl, 1.8 mmol). After standard work-up, a crude white solid remained. This was dissolved in the minimum of hot ethyl acetate and allowed to cool to yield white crystals (38 mg, 27%)[3] of the less polar diastereoisomer of (119). The filtrate was concentrated and purified by use of a 'chromatotron' (2% methanol in chloroform) to give the other (more polar) diastereoisomer of (119) as a white solid (62 mg, 45%). The diastereomeric ratio was the same as measured previously for the preparation of (119a) and (119b) from (118a)[4] with each isomer having identical spectral properties to (119a) and (119b) prepared from (118a).[4]

Notes

1. See p.165.
2. Distilled prior to use.
3. Yield after 2 recrystallizations.
4. See p.165.

The Deprotonation and Reprotonation of (E)-3,3-Dimethyl-1-[(R)-p-tolyl-sulphinyl]-1-butene (118a)



(118a)

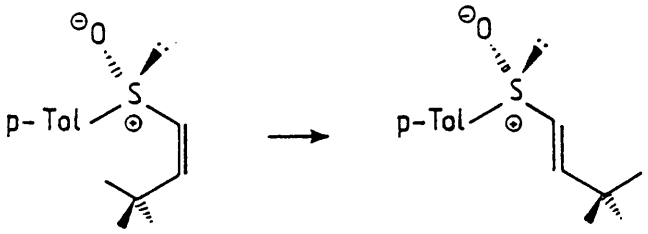
Using the same procedure as for the isomerization of (53a),[1] (E)-3,3-dimethyl-1-[(R)-p-tolylsulphinyl]-1-butene (118a) (100 mg, 0.45 mmol) was deprotonated with LDA (0.63 mmol). After quenching and work-up, followed by purification by 'chromatotron' (ether), (E)-3,3-dimethyl-1-[(R)-p-tolylsulphinyl]-1-butene (118a) was recovered as a white solid (82 mg, 82% recovery) with the spectral characteristics of the original sample.[2]

Notes

1. See p.130.

2. See p.163.

The Isomerization of (Z)-3,3-Dimethyl-1-[(R)-p-tolylsulphinyl]-1-butene (118b)



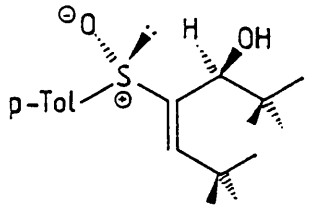
(118b) (118a)

Using the same procedure as for the deprotonation of (53a),[1] (Z)-3,3-dimethyl-1-[(R)-p-tolylsulphinyl]-1-butene (118b) (100 mg, 0.45 mmol) was deprotonated with LDA (0.63 mmol) and after 1h quenched with a 1:1 water/THF mixture. T.l.c. showed the complete disappearance of the (Z)-starting material and after work-up and purification by 'chromatotron' (ether), (E)-3,3-dimethyl-1-[(R)-p-tolylsulphinyl]-1-butene (118a) was obtained as a white solid[2] (70 mg, 70%).

Notes

1. See p.130.
2. All spectra data consistent with that of the original sample, see p.163.

Attempted Reduction of (S)-(E)-2,2,6,6-Tetramethyl-4-[(S)-p-tolyl-sulphinyl]-4-hepten-3-ol (119a)[1] (the less polar diastereoisomer) using Aluminium Amalgam



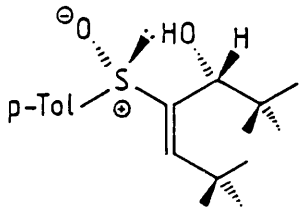
(119a)

Using the same procedure as for the reduction of (94a),[2] (S)-(E)-2,2,6,6-tetramethyl-4-[(S)-p-tolylsulphinyl]-4-hepten-3-ol (119a) (62 mg, 0.20 mmol) was dissolved in a THF/H_2O (9:1) mixture (7½ ml) under nitrogen at 0°C. Aluminium amalgam (110 mg, 4.0 mmol) was added and the reaction monitored by t.l.c. After 20h, t.l.c. indicated no product formation, only a spot indicative of the starting material. After standard work-up (119a) was recovered in 100% yield.

Notes

1. For convenience, we have arbitrarily assigned this diastereoisomer as the less polar of the two.
2. See p.135.

Attempted Reduction of (R)-(E)-2,2,6,6-Tetramethyl-4-[(S)-p-tolyl-sulphinyl]-4-hepten-3-ol (119b)[1] (the more polar diastereoisomer) using Aluminium Amalgam



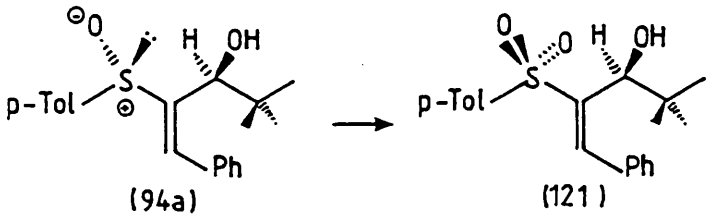
(119b)

Using the same procedure as for the reduction of (94a),[2] (R)-(E)-2,2,6,6-tetramethyl-4-[(S)-p-tolylsulphinyl]-4-hepten-3-ol (119b) (96 mg, 0.31 mmol) was dissolved in a THF/H_2O (9:1) mixture (10 ml) under nitrogen at 0°C. Aluminium amalgam (167 mg, 6.2 mmol) was added and the reaction monitored by t.l.c. After 22h, t.l.c. showed no product formation, only a spot indicative of the starting material. After standard work-up the starting material was recovered in 100% yield.

Notes

1. Again for convenience, we have arbitrarily assigned this diastereoisomer as the more polar of the two.
2. See p.135.

Oxidation of (+)-(S)-(E)-4,4-Dimethyl-1-phenyl-2-[(S)-p-tolylsulphinyl]-1-penten-3-ol (94a) using m-Chloroperbenzoic acid[1]



A solution of (+)-(S)-(E)-4,4-dimethyl-1-phenyl-2-[(S)-p-tolylsulphinyl]-1-penten-3-ol (94a) (65 mg, 0.2 mmol) in dichloromethane (4½ ml) was cooled to -78°C and m-chloroperbenzoic acid (41 mg, 0.24 mmol) added with stirring. The reaction was left for several hours at -78°C and then left to warm up slowly overnight. T.l.c. showed the complete disappearance of starting material. A further volume of dichloromethane (10 ml) was added, the solution washed with saturated aqueous sodium hydrogen carbonate solution (15 ml), brine (15 ml) and dried ($MgSO_4$). Removal of the solvent in vacuo followed by recrystallization (petroleum ether 6080°C) gave (+)-(S)-(E)-4,4-dimethyl-1-phenyl-2-[p-tolylsulphonyl]-1-penten-3-ol (121) as a white solid (44 mg, 64%) m.p. 119- 120°C.

$[\alpha]_D$ = +159.4° (1.65 in $CHCl_3$);

R_f 0.6 (ether);

$C_{20}H_{24}O_3S$ requires C 69.74%, H 7.02%, N 0.00%,

found C 69.75%, H 7.09%, N 0.00%.

ν_{max} (CH_2Cl_2) 3510w (OH), 2950m, 1590w, 1290m, 1270m, 1130 (O=S=O), 1080s, 1040s, 1010s, 800s;

δ_H (300 MHz; $CDCl_3$) 0.89 (9H, s, $(CH_3)_3$), 2.42 (3H, s, CH_3), 3.74 (1H, brs, OH), 4.85 (1H, s, H-3), 7.26-7.89 (10H, m);

δ_C (75 MHz; $CDCl_3$) 21.57(q), 26.97(q), 37.88(s), 77.25(d), 127.78(d), 128.68(d), 128.96(d), 129.77(d), 134.15(s), 139.09(s), 143.36(d),

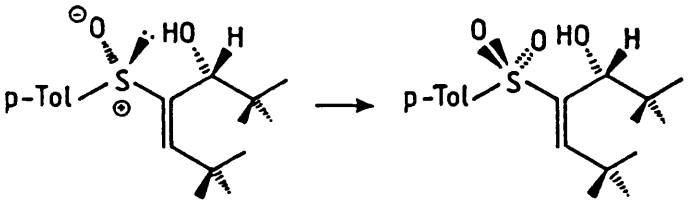
144.19(s), 144.99(s);

M/Z 344 (M^+), 289(22), 288(84), 287(58), 213(17), 195(19), 158(16), 157(54), 156(44), 149(50), 141(24), 140(100), 139(68), 132(39), 131(80), 115(28), 111(25), 103(73).

Notes

1. See Refs. 146 and 147.

Oxidation of (S)-(E)-2,2,6,6-Tetramethyl-4-[(S)-p-tolylsulphinyl]-4-hepten-3-ol (119a)[1] using m-Chloroperbenzoic acid



(119a) (122a)

Using the same procedure as for the oxidation of (94a),[2] (S)-(E)-2,2,6,6-tetramethyl-4-[(S)-p-tolylsulphinyl]-4-hepten-3-ol (119a) (65 mg, 0.21 mmol) was dissolved in dichloromethane (8 ml) and cooled to -15°C. m-Chloroperbenzoic acid (46 mg, 0.27 mmol) was added and the reaction stirred overnight. After standard work-up a crude white solid remained which, after recrystallization (petroleum ether 60-80°) gave (-)-(S)-(E)-2,2,6,6-tetramethyl-4-[p-tolylsulphonyl]-4-hepten-3-ol (122a) as a white solid (31 mg, 46%) m.p. 126-128°C.

$[\alpha]_D$ = -20.8° (2.0 in $CHCl_3$);

R_f 0.63 (ether);

$C_{18}H_{26}O_3S$ requires C 66.63%, H 8.70%, N 0.00%,

found C 66.20%, H 8.50%, N 0.10%.

ν_{max} (CH_2Cl_2) 3510m (OH), 2950s, 1590w, 1360m, 1280m, 1250m, 1125 (O=S=O), 1080s, 1040m, 1015m, 810m;

δ_H (300 MHz; $CDCl_3$) 1.096 (9H, s, $C(CH_3)_3$), 1.101 (9H, s, $C(CH_3)_3$), 2.44 (3H, s, CH_3), 4.14 (1H, brs, OH), 4.87 (1H, s, H-3), 6.17 (1H, s, H-5), 7.32 (2H, m, aromatic), 7.78 (2H, m, aromatic);

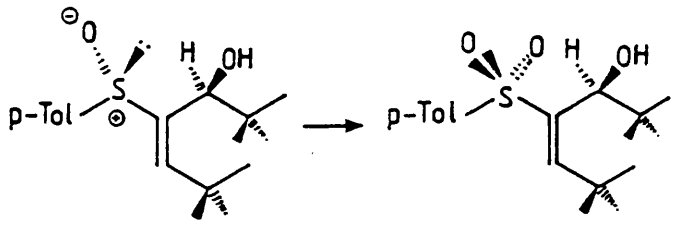
δ_C (75 MHz; $CDCl_3$) 21.58(q), 27.63(q), 30.39(q), 35.24(s), 36.14(s), 76.57(d), 127.65(d), 129.51(d), 139.30(s), 141.98(s), 143.95(s), 154.77(d);

M/Z 268(33), 267(57), 157(100), 140(69), 139(61), 111(69).

Notes

1. Again, the assignment of the diastereoisomer is arbitrary. See note 1, p.170.
2. See p.172.

Oxidation of (R)-(E)-2,2,6,6-Tetramethyl-4-[(S)-p-tolylsulphinyl]-4-hepten-3-ol (119b)[1] using m-Chloroperbenzoic acid



(119b) (122b)

Using the same procedure as for the oxidation of (94a),[2] (R)-(E)-2,2,6,6-tetramethyl-4-[(S)-p-tolylsulphinyl]-4-hepten-3-ol (119b) (165 mg, 0.54 mmol) was dissolved in dichloromethane (12 ml) and cooled to -78°C. m-Chloroperbenzoic acid (115 mg, 0.67 mmol) was added and the reaction stirred overnight. After standard work-up a crude white solid remained which, after recrystallization (petroleum ether 60-80°), gave (+)-(R)-(E)-2,2,6,6-tetramethyl-4-[p-tolylsulphonyl]-4-hepten-3-ol (122b) as a white solid (106 mg, 61%) m.p. 125-127°C.

$[\alpha]_D$ = +21.3° (2.1 in $CHCl_3$);

R_f 0.71 (ether);

$C_{18}H_{28}O_3S$ requires C 66.63%, H 8.70%, N 0.00%,

found C 66.50%, H 8.69%, N 0.00%.

ν_{max} (CH_2Cl_2) 3510m (OH), 2950s, 1590w, 1390m, 1360m, 1280m, 1250s, 1185m, 1125s (O=S=O), 1080s, 1040s, 1015s, 810m;

δ_H (300 MHz; $CDCl_3$) 1.10 (18H, s, 2 x $C(CH_3)_3$), 2.43 (3H, s, CH_3), 4.12 (1H, d, J = 11.4 Hz, OH), 4.86 (1H, d, J = 11.4 Hz, H-3), 6.18 (1H, s, H-5), 7.31 (2H, m, aromatic), 7.77 (2H, m, aromatic);

δ_C (75 MHz; $CDCl_3$) 21.56(q), 27.61(q), 30.38(q), 35.21(s), 36.11(s), 76.52(d), 127.61(d), 129.49(d), 139.28(s), 141.98(s), 143.93(s), 154.72(d);

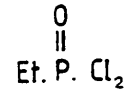
M/Z 268(48), 267(78), 194(26), 157(100), 141(22), 140(95), 139(89),

135(36), 127(29), 124(32), 123(34), 111(96).

Notes

1. Again, the assignment of the diastereoisomer is arbitrary. See note 1, p.170.
2. See p.172.

Preparation of Ethylphosphonic dichloride (147)[1]



(147)

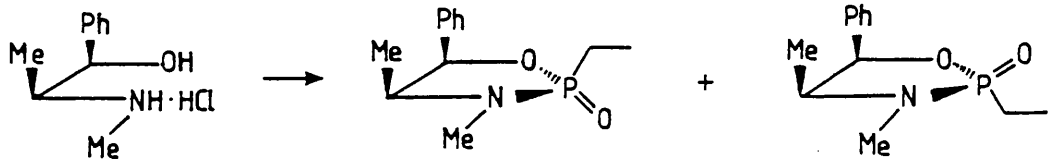
Phosphorus pentachloride (64g, 306 mmol) was added portionwise to diethyl ethanephosphonate (24.9g, 150 mmol) under nitrogen at room temperature. Once the addition was complete, the reaction mixture was refluxed for 4h,[2] after which time it was distilled at atmospheric pressure using a Vigreux column to remove the more volatile impurities (ethyl chloride and phosphorus oxychloride). It was redistilled to give ethylphosphonic dichloride (147) as a colourless liquid (17.6g, 84%) b.p. 72-76°C at 20 mmHg (lit.[148] 60-61°C at 10 mmHg).

δ_P (24 MHz; neat) 53.6(s) (lit.[148] 53).

Notes

1. Known compound see Ref. 148 and 149.
2. At this stage a sample of the crude reaction mixture can be removed and the composition determined by ^{31}P n.m.r. The presence of starting material or monohalogenated product can be removed by continuing the reflux.

Preparation of (2S,4S,5R) and (2R,4S,5R)-2-Ethyl-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one[1] (145a) and (145b) respectively



(146) (145a) (145b)

To a solution of ethylphosphonic dichloride (146) (15g, 102 mmol) and triethylamine (70 ml, 510 mmol) in dry benzene (350 ml) was added (-)-ephedrine hydrochloride (146) (20.6g, 102 mmol) in one portion at 0°C. After allowing to warm to room temperature, the reaction mixture was stirred under nitrogen for 48h. The white solid (triethylamine hydrochloride) was removed by filtration, washed with benzene (2 x 50 ml) and the solvent removed in vacuo to leave a crude yellow product. Flash chromatography (2:2:1 benzene-acetone-ether) and recrystallization (petroleum ether 60-80°C, both isomers)[2] gave (2S,4S,5R) and (2R,4S,5R)-2-ethyl-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (145a) and (145b) as white crystalline solids (7.8g, 32%) m.p. 62-66°C and (6.9g, 28%) m.p. 69-71°C respectively.

(145a)

R_f 0.31 (acetone);

$C_{12}H_{18}NO_2P$ requires C 60.24%, H 7.58%, N 5.85%,

found C 59.77%, H 7.52%, N 5.63%.

ν_{max} (CH_2Cl_2) 3030m, 2970m, 2940m, 2910m, 1495w, 1450m, 1380m, 1325s, 1225s, 1210s, 1185s, 1110m, 1080m, 1060s, 1030m, 1005m, 975s, 955s, 880s, 850s, 810m;

δ_H (300 MHz; $CDCl_3$) 0.69 (3H, d, J = 6.6 Hz, 4-CH_3), 1.28 (3H, dt, J_p = 20.1, J = 7.6 Hz, 2'-CH_3), 1.98 (2H, m, CH_2), 2.80 (3H, d, J_p = 9 Hz, 3-CH_3), 3.67 (1H, m, H-4), 5.75 (1H, d, J = 6.1 Hz, H-5), 7.25-7.41 (5H,

m, C_6H_5);

δ_C (75 MHz; $CDCl_3$) 7.26, 7.35(2 x q),[3] 14.00(q), 19.95, 21.65 (2 x t),[3] 29.47, 29.55(2 x q),[3] 60.41, 60.52(2 x d),[3] 79.40(d), 125.15(d), 127.56(d), 127.92(d), 135.71, 135.83(2 x s)[3];

δ_P (24 MHz; $CDCl_3$) 45.58(s);

M/Z 239 (M^+,21), 224(14), 133(40), 104(100).

(145b)

R_f 0.44 (acetone);

$C_{12}H_{18}NO_2P$ requires C 60.24%, H 7.58%, N 5.85%,

found C 59.99%, H 7.61%, N 5.73%.

ν_{max} (CH_2Cl_2) 3030w, 2970m, 2940m, 2910m, 1450m, 1380m, 1320m, 1225s, 1210s, 1175s, 1080m, 1060s, 1005m, 975s, 950m, 880s, 850s;

δ_H (300 MHz; $CDCl_3$) 0.82 (3H, d, J = 6.5 Hz, 4-CH_3), 1.22 (3H, dt, J_P = 20.0, J = 7.6 Hz, 2'-CH_3), 1.99 (2H, m, CH_2), 2.70 (3H, d, J_P = 9.8 Hz, 3-CH_3), 3.64 (1H, m, H-4), 5.44 (1H, dd, J = 6.2, 4.1 Hz, H-5), 7.27-7.41 (5H, m, C_6H_5);

δ_C (75 MHz; $CDCl_3$) 6.93, 7.02(2 x q),[3] 13.87(q), 18.81, 20.48 (2 x t),[3] 28.23, 28.31(2 x q),[3] 58.56, 58.68(2 x d),[3] 82.04, 82.06 (2 x d),[3] 125.81(d), 127.75(d), 127.99(d), 136.06, 136.13(2 x s)[3];

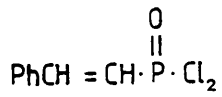
δ_P (24 MHz; $CDCl_3$) 47.70(s);

M/Z 239 (M^+,18), 224(12), 133(38), 104(100).

Notes

1. Prepared previously by M. R. Selim. See Ph.D. Thesis "Studies on Asymmetric Induction", July 1987, Leicester University.
2. Subsequently, after the initial recrystallization, (145a) was recrystallized with difficulty from petroleum ether.
3. Due to phosphorus coupling.

Preparation of Styrylphosphonic dichloride (149)[1]



(149)

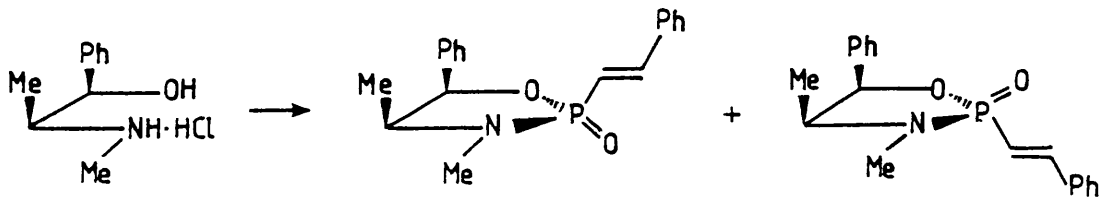
Styrene (13g, 0.13 mol) in dry benzene (25 ml) was added dropwise over, 15 min, to phosphorus pentachloride (52g, 0.25 mol) in dry benzene (175 ml) under nitrogen at 0°C. After the addition, the reaction mixture (containing a dense white solid) was stirred for 30 min. Sulphur dioxide was bubbled through the stirred reaction mixture with occasional cooling until the white precipitate had dissolved and the solvent was removed in vacuo. Distillation using a Vigreux column gave styrylphosphonic dichloride (149) as a colourless liquid (23.4g, 85%) b.p. 114-117°C at 0.2 mmHg (lit.[132] 89-94%, 107-110°C at 0.2 mmHg) which on cooling and standing solidified to a crystalline solid.

δ_P (24 MHz; $CDCl_3$) 33.3(s);

Notes

1. Known compound and literature procedure see Ref. 132.

Preparation of (2S,4S,5R) and (2R,4S,5R)-3,4-Dimethyl-5-phenyl-2-[(E)-2-phenylvinyl]-1,3,2-oxazaphospholidin-2-one (148a) and (148b)[1] respectively



(146) (148a) (148b)

To a solution of styrylphosphonic dichloride (149) (5.25g, 23.8 mmol) and triethylamine (17 ml, 119 mmol) in dry benzene (60 ml) was added (-)-ephedrine hydrochloride (146) (4.8g, 23.8 mmol) under nitrogen at 0°C. After 1h at this temperature, the reaction mixture was allowed to reach room temperature and stirred for a further 48h. The white solid was removed by filtration and washed with benzene (2 x 25 ml). Removal of the solvent in vacuo left a crude 1:1 mixture of products which after purification by flash chromatography (2:1:1, benzene-acetone-ether) and recrystallization [(148a) isopropyl ether, (148b) ethyl acetate] gave (2S,4S,5R) and (2R,4S,5R)-3,4-dimethyl-5-phenyl-2-[(E)-2-phenylvinyl]-1,3,2-oxazaphospholidin-2-one (148a) and (148b) as white crystalline solids, (2.89g, 41%) (lit.[133] 41%) m.p. 138-139°C and (2.78g, 39%) (lit.[133] 40%) m.p. 149-151°C (lit.[133] 144.5-146°C) respectively.

(148a)

R_f 0.22 (2:1:1 benzene-ether-acetone);

$C_{18}H_{20}NO_2P$ requires C 69.00%, H 6.43%, N 4.47%,

found C 68.67%, H 6.52%, N 4.26%.

ν_{max} (CH_2Cl_2) 3020w, 2960m, 2910m, 1610m, 1490w, 1445m, 1325m, 1230s, 1210s, 1180s, 1080w, 1055s, 975s, 950s, 880s, 855s, 825m;

δ_H (300 MHz; $CDCl_3$) 0.79 (3H, d, J = 6.6 Hz, 4-CH_3), 2.77 (3H, dt, J_p

= 9.4 Hz, 3-CH_3), 3.77 (1H, m, H-4), 5.81 (1H, d, J = 5.8 Hz, H-5), 6.18 (1H, dd, J_p = 19.7, J_{trans} = 17.1 Hz, C<u>H</u>=CH), 7.28-7.57 (10H, m), 7.69 (1H, dd, J_p = 22.8, J_{trans} = 17.1 Hz, CH=C<u>H</u>);

δ_C (75 MHz; $CDCl_3$) 14.18(q), 29.04, 29.14(2 x q),[2] 60.41, 60.53 (2 x d),[2] 80.37(d), 114.81, 117.14(2 x d),[2] 125.68(d), 127.74(d), 128.05(d), 128.38(d), 128.80(d), 130.14(d), 134.91, 135.21(2 x s),[2] 136.11, 136.23(2 x s),[2] 150.35, 150.43(2 x d)[2];

δ_P (24 MHz; $CDCl_3$) 30.25(s) (lit.[133] 27.18(s));

M/Z 313 (M^+,19), 298(11), 207(19), 194(20), 193(100), 160(11), 149(16), 104(28).

(148b)

R_f 0.39 (2:1:1 benzene-ether-acetone);

$C_{18}H_{20}NO_2P$ requires C 69.00%, H 6.43%, N 4.47%,

found C 68.80%, H 6.54%, N 4.25%.

ν_{max} (CH_2Cl_2) 3020w, 2960w, 2900w, 1605m, 1590w, 1445w, 1320m, 1235m, 1205s, 1175m, 1080m, 1060m, 985s, 975s, 950m, 885s, 855s, 815m;

δ_H (300 MHz; $CDCl_3$) 0.87 (3H, d, J = 6.5 Hz, 4-CH_3), 2.68 (3H, dt, J_p = 19.7 Hz, 3-CH_3), 3.68 (1H, dq, J = 20.8, 6.4 Hz, H-4), 5.54 (1H, dd, J = 6.0, 4.5 Hz, H-5), 6.33 (1H, dd, J_p = 19.3, J_{trans} = 17.2 Hz, CH=C<u>H</u>), 7.27-7.52 (10H, m), 7.57 (1H, dd, J_p = 22.5, J_{trans} = 17.2 Hz, C<u>H</u>=CH);

δ_C (75 MHz; $CDCl_3$) 14.35, 14.38(2 x q),[2] 28.43, 28.51(2 x q),[2] 58.73, 58.86(2 x d),[2] 81.84(d), 113.98, 116.28(2 x d),[2] 126.17(d), 127.68(d), 128.10(d), 128.30(d), 128.77(d), 130.04(d), 134.88, 135.17(2 x s),[2] 136.19, 136.27(2 x s),[2] 148.95, 149.02(2 x d)[2];

δ_P (24 MHz; $CDCl_3$) 32.67(s) (lit.[133] 29.72(s));

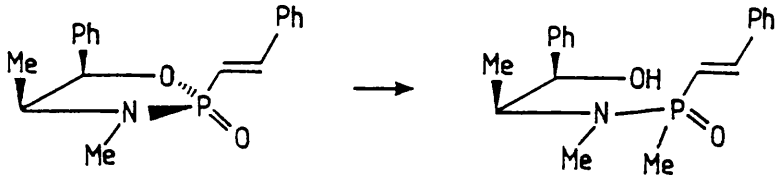
M/Z 313 (M^+,27), 298(13), 207(21), 194(21), 193(100), 160(10), 149(14), 115(15), 104(29).

Notes

1. Known compounds see Ref. 133. Data reported m.p. [(148b) only], δ_H, δ_P values and analyses (no figures).

2. Due to phosphorus coupling.

Reaction of (2S,4S,5R)-3,4-Dimethyl-5-phenyl-2-[(E)-2-phenylvinyl]-1,3,2-oxazaphospholidin-2-one (148a) and Methyllithium to give the Ring Opened Product (150)



(148a) (150)

Methyllithium (236 μl, 0.35 mmol) was added dropwise to (2S,4S,5R)-3,4-dimethyl-5-phenyl-2-[(E)-2-phenylvinyl]-1,3,2-oxazaphospholidin-2-one (148a) (100 mg, 0.32 mmol) in THF (3 ml) at -78°C under nitrogen. After stirring for 2h, the reaction mixture was quenched with water and the aqueous solution extracted with dichloromethane (3 x 15 ml). The combined extracts were dried ($MgSO_4$) and the solvent removed in vacuo to leave a solid which after recrystallization (toluene) gave (150) as a white solid (80 mg, 76%).

R_f 0.15 (2:1:1 benzene-ether-acetone);

ν_{max} (CH_2Cl_2) 3270brm (OH), 3020m, 2960m, 1615m, 1490w, 1445m, 1295m, 1175brs, 1000brm, 940m, 900z;

δ_H (300 MHz; $CDCl_3$) 1.29 (3H, d, J = 6.8 Hz, CH_3), 1.36 (3H, d, J_p = 13.6 Hz, CH_3), 2.52 (3H, d, J_p = 10.8 Hz, CH_3), 3.66 (1H, septet, J *ca.* 6.4 Hz), 4.22 (1H, brs, OH), 4.70 (1H, d, J = 5.9 Hz), 5.80 (1H, dd, J_p = 19.6, J_{trans} = 17.5 Hz, CH=CH), 7.16-7.39 (11H, m);

δ_p (24 MHz; $CDCl_3$) 36.71(s);

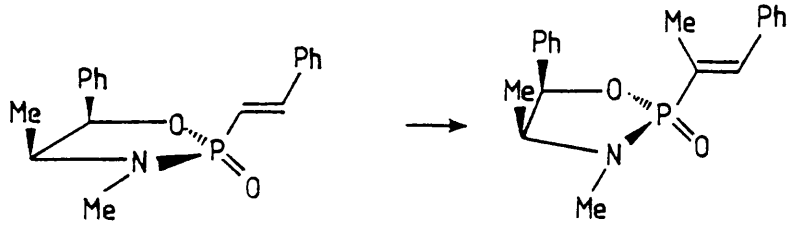
$C_{19}H_{24}NO_2P$ requires 329.1545,

found 329.1553.[1]

Notes

1. Detected as the $(M+H)^+$ ion by ammonia chemical ionization conditions.

Preparation of (2S,4S,5R)-3,4-Dimethyl-5-phenyl-2-[(E)-1-methyl-2-phenylvinyl]-1,3,2-oxazaphospholidin-2-one (151)



(148a) (151)

A solution of (2S,4S,5R)-3,4-dimethyl-5-phenyl-2-[(E)-2-phenylvinyl]-1,3,2-oxazaphospholidin-2-one (148a) (100 mg, 0.32 mmol) in THF (3 ml) was added dropwise to a solution of LDA (0.35 mmol) under nitrogen at -78°C. After 15 min, the orange anionic solution was quenched with methyl iodide (100 μl, 1.6 mmol) in THF (1 ml), stirred for 2h, and then quenched with water. The aqueous solution was extracted with dichloromethane (3 x 20 ml) and the extracts combined and dried ($MgSO_4$). Removal of the solvent in vacuo gave the crude (2S,4S,5R)-3,4-dimethyl-5-phenyl-2-[(E)-1-methyl-2-phenylvinyl]-1,3,2-oxazaphospholidin-2-one (151) as an oil (80 mg, 77%).[1]

R_f 0.21 (2:1:1 benzene-ether-acetone);

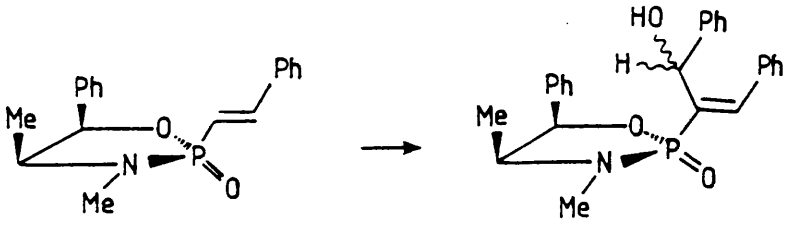
δ_H (90 MHz; $CDCl_3$) 0.75 (3H, d, J *ca.* 7 Hz, 4-CH_3), 2.1 (3H, dd, J_p *ca.* 15 Hz and further small allylic coupling, 1'-CH_3), 2.75 (3H, d, J_p *ca.* 9 Hz, 3-CH_3), 3.7 (1H, m, H-4), 5.85 (1H, d, J *ca.* 7 Hz, H-5), 7.05-7.45 (10H, m), 7.6 (1H, brd, J *ca.* 24 Hz, H-2');

δ_P (24 MHz; $CDCl_3$) 35.09(s).

Notes

1. The crude product was cleanly one peak by ^{31}P n.m.r. and reasonably clean by ^{1}H n.m.r. It proved difficult to purify by chromatographic methods and would not distil.

Deprotonation of (2S,4S,5R)-3,4-Dimethyl-5-phenyl-2-[(E)-2-phenylvinyl]-1,3,2-oxazaphospholidin-2-one (148a) and Reaction with Benzaldehyde



(148a) (152a) and (152b)

Using the same procedure as for the preparation of (151),[1] (2S,4S,-5R)-3,4-dimethyl-5-phenyl-2-[(E)-2-phenylvinyl] 1,3,2 oxazaphospholidin-2-one (148a) (100 mg, 0.32 mmol) was deprotonated with LDA (0.35 mmol) and quenched with benzaldehyde (40 μl, 0.38 mmol). After work-up, the ^{31}P n.m.r. of the crude product showed 5 peaks; δ_P (30.25 (starting material), 33.07, 35.29, 36.71, 37.71) in a ratio (1:2.97:1.01:1.88:2.51) respectively. The crude material was 'purified' by flash chromatography (2:1:1, benzene-ether-acetone) to give 3 major fractions, all of which showed traces of decomposition whilst on the silica gel flash column.

Fraction 1

Decomposition material (25 mg);

δ_P (24 MHz; $CDCl_3$) 35.29(s), 36.71(s).

Fraction 2 (152a)

(18 mg, 13%);

δ_H[2] (90 MHz; $CDCl_3$) 0.75 (3H, d, J *ca.* 7 Hz, 4-CH_3), 1.95 (3H, d, J_P *ca.* 9 Hz, 3-CH_3), 3.4-3.85 (1H, m, H-4), 5.25 (1H, t, J is unmeasurable), 5.75 (1H, d, J *ca.* 6 Hz, H-5), 6.2 (1H, brd, J *ca.* 9 Hz), 7.15-7.45 (15H, m), 7.6 (1H, d, J *ca.* 24 Hz, H-2');

δ_P (24 MHz; $CDCl_3$) 33.07(s).

Fraction 3 (152b)

(27 mg, 20%);

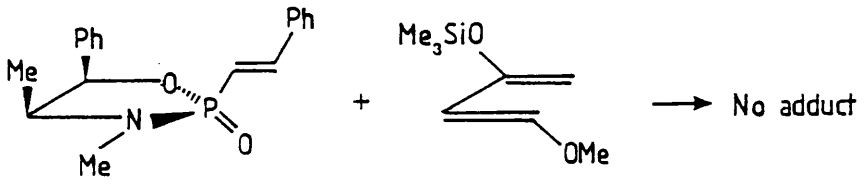
δ_H[2] (90 MHz; $CDCl_3$) 0.80 (3H, d, J *ca.* 7 Hz, 4-CH_3), 2.85 (3H, d, J_p *ca.* 9 Hz, 3-CH_3), 3.55-3.95 (1H, m, H-4), 5.25 (1H, t, J is unmeasurable), 5.7 (1H, d, J *ca.* 6 Hz, H-5), 6.2 (1H, brd, J *ca.* 9 Hz), 6.95-7.6 (16H, m);

δ_p (24 MHz; $CDCl_3$) 37.71(s).

Notes

1. See p.186.
2. The ^1H n.m.r. data is of a partially decomposed product and hence values quoted are only an approximation.

Attempted Diels-Alder reaction of (2S,4S,5R)-3,4-Dimethyl-5-phenyl-2-[(E)-2-phenylvinyl]-1,3,2-oxazaphospholidin-2-one (148a) and 1-Methoxy-3-(trimethylsilyloxy)-1,3-butadiene (Danishefsky's diene)[1]



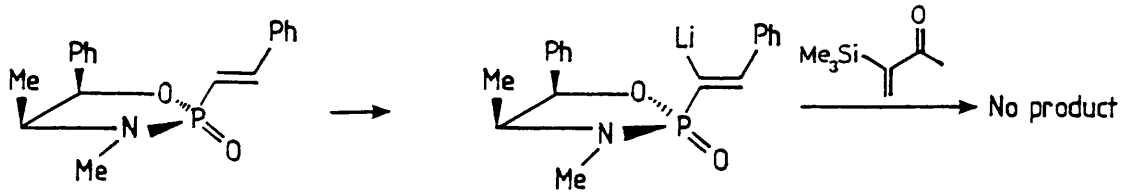
(148a)

1-Methoxy-3-(trimethylsilyloxy)-1,3-butadiene (70 μl, 0.32 mmol) was added to a stirred solution of (2S,4S,5R)-3,4-dimethyl-5-phenyl-2-[(E)-2-phenylvinyl]-1,3,2-oxazaphospholidin-2-one (148a) (100 mg, 0.32 mmol) in toluene (2 ml) in a reactivial under nitrogen. The reactants were heated to 150°C[2] and over a period of 6 days further volumes of the diene added as the reaction was followed by t.l.c. This, however, showed only starting material and streaking due to decomposition products.

Notes

1. See Ref. 134.
2. The reaction was repeated using a Lewis acid, $BF_3.OEt_2$ in dichloromethane at -78°C. T.l.c. showed only starting material.

Attempted Reaction of Lithiated (2S,4S,5R)-3,4-Dimethyl-5-phenyl-2-[(E)-2-phenylvinyl]-1,3,2-oxazaphospholidin-2-one and 3-Trimethylsilyl-3-buten-2-one[1]



(148a)

Using the same procedure as for the preparation of (151),[2] (2S,4S,5R)-3,4 dimethyl-5-phenyl-2-[(E) 2 phenylvinyl] 1,3,2-oxazaphospholidin-2-one (148a) (100 mg, 0.32 mmol) was deprotonated with LDA (0.35 mmol) and 3-trimethylsilyl-3-buten-2-one (55 mg, 0.38 mmol) in THF (½ ml) added under nitrogen at -78°C. After 1h the reaction mixture was allowed to warm to room temperature. T.l.c., however, showed only starting material and decomposition products.

Notes

1. Prepared by Dr. R. V. Bonnert who kindly left this compound after completing his work, see Ref. 150.
2. See p.186.

APPENDIX

APPENDIX

X-RAY CRYSTAL STRUCTURE DATA FOR (94a)

Crystal Data $C_{20}H_{24}O_2S$, M = 328.47, Orthorhombic, Space Group $P2_12_12_1$, $\underline{a}$ = 11.026(30), $\underline{b}$ = 9.9198(10), $\underline{c}$ = 18.065(13) Å, $\underline{U}$ = 1832.1 Å^3, Z = 4, $\underline{\mu}$ = 1.45 cm^{-1}, $\underline{\lambda}(M_0\text{-}K_\alpha)$ = 0.7107 Å, F(000) = 704.0, d_x = 1.191g cm^{-3}.

The unit cell parameters were determined from an oscillation photograph for the rotation axis $\underline{a}$ and from the optimized counter angles for $\underline{b}$ and $\underline{c}$. The intensities of 1699 unique reflections with $2\theta < 52^o$ and (+h ± k + l) were measured on a Stoe STADI-2 Weissenberg diffractometer, with graphite monochromated $M_0\text{-}K_\alpha$ radiation using an omega-scan technique. The data were corrected for Lorentz and polarization effects to yield 1180 reflections with $\underline{I} \geq 3\underline{\sigma}(I)$.

The structure was solved using the TREF option of SHELXS 84.* All subsequent calculations were carried out using the computer program SHELX.** Most hydrogen atoms were included in calculated positions (C-H = 1.08 Å) with group thermal parameters. The hydrogen atoms of the tolyl methyl group appeared disordered and were thus omitted. The hydrogen atom of the hydroxyl group was located and, therefore, refined as a normal atom. All non-hydrogen atoms were refined as anisotropic.

Final cycles of refinement employed a weighting parameter g(·00051) $\{w=1/[\sigma^2(F) + g(F)^2]\}$ and gave the final residual indices $R\{=\Sigma||F_o|-|F_c||/\Sigma|F_o|\}$ 0.060 and $R_w\{=[\Sigma_w(|F_o|-|F_c|)^2/\Sigma_w|F_o|^2]^{1/2}\}$ 0.065. The final difference Fourier map was featureless and an analysis of the weighing scheme over $|F_o|$ and sin θ/λ was satisfactory.

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* G. M. Sheldrick SHELXS 84. Private communication.

** G. M. Sheldrick SHELX 76. Program for crystal structure determination. University of Cambridge, 1976.

The geometry of the molecule is shown in Fig. 7. Selected bond distances and angles are in Tables 5 and 6. Final atomic positional and thermal parameters and lists of $|F_o|$ and $|F_c|$ values have been deposited as supplementary material with the editor from whom copies are available on request.

Acknowledgements - Leicester University Computer Laboratory who provided support and facilities for X-ray single crystal work and G. M. Sheldrick for the use of SHELXS.

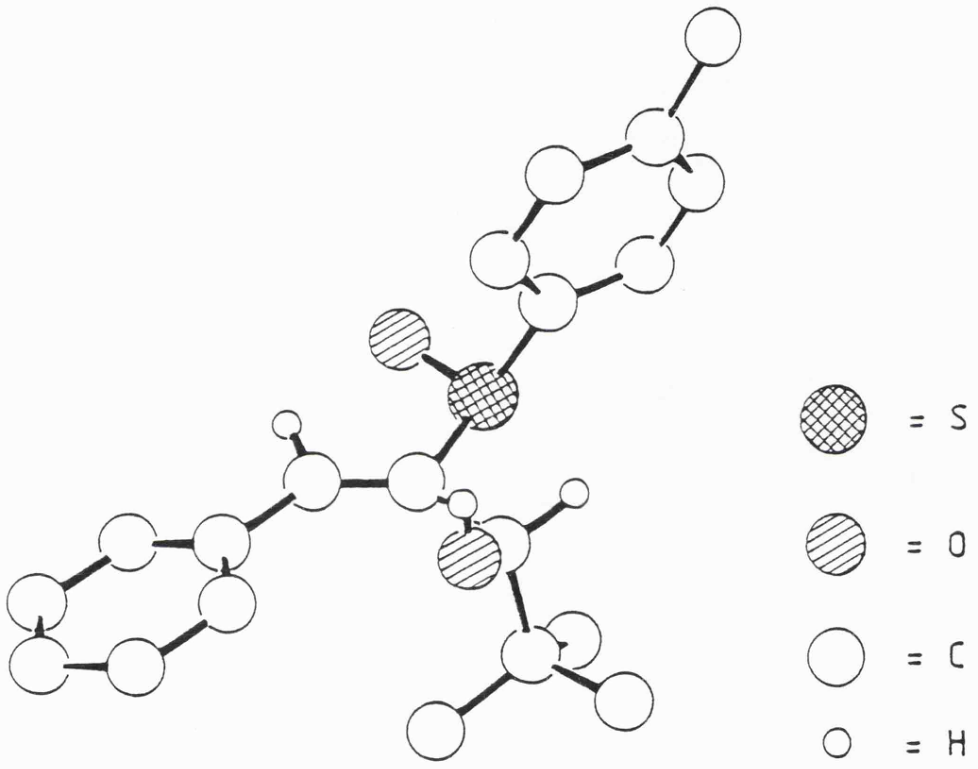

Fig. 7

X-ray Crystal Structure of (+)-(S)-(E)-4,4-Dimethyl-2-[(S)-p-tolylsulphinyl]-1-penten-3-ol (94a).

TABLE 5

Bond Distances (Å) for (94a) $C_{20}H_{25}O_2S$

O(1)-S(1)	1.498(5)	C(2)-S(1)	1.816(6)
C(14)-S(1)	1.775(4)	H(2)-O(2)	0.78(13)
C(3)-O(2)	1.440(8)	H(1)-C(1)	1.080(0)
C(2)-C(1)	1.340(10)	C(8)-C(1)	1.477(9)
C(3)-C(2)	1.518(10)	H(3)-C(3)	1.080(0)
C(4)-C(3)	1.560(9)	C(5)-C(4)	1.536(10)
C(6)-C(4)	1.524(11)	C(7)-C(4)	1.542(11)
H(51)-C(5)	1.080(0)	H(52)-C(5)	1.080(0)
H(53)-C(5)	1.080(0)	H(61)-C(6)	1.080(0)
H(62)-C(6)	1.080(0)	H(63)-C(6)	1.080(0)
H(71)-C(7)	1.080(0)	H(72)-C(7)	1.080(0)
H(73)-C(7)	1.080(0)	C(9)-C(8)	1.395(0)
C(13)-C(8)	1.395(0)	C(10)-C(9)	1.395(0)
H(9)-C(9)	1.080(0)	C(11)-C(10)	1.395(0)
H(10)-C(10)	1.080(0)	C(12)-C(11)	1.395(0)
H(11)-C(11)	1.080(0)	C(13)-C(12)	1.395(0)
H(12)-C(12)	1.080(0)	H(13)-C(13)	1.080(0)
C(15)-C(14)	1.395(0)	C(19)-C(14)	1.395(0)
C(16)-C(15)	1.395(0)	H(15)-C(15)	1.080(0)
C(17)-C(16)	1.395(0)	H(16)-C(16)	1.080(0)
C(18)-C(17)	1.395(0)	C(20)-C(17)	1.546(11)
C(19)-C(18)	1.395(0)	H(18)-C(18)	1.080(0)
H(19)-C(19)	1.080(0)		

TABLE 6

Bond Angles (°) for (94a) $C_{20}H_{25}O_2S$

C(2)-S(1)-O(1)	107.7(3)	C(14)-S(1)-O(1)	106.9(3)
C(14)-S(1)-C(2)	100.6(3)	C(3)-O(2)-H(2)	116(9)
C(2)-C(1)-H(1)	112.0(4)	C(8)-C(1)-H(1)	112.0(3)
C(8)-C(1)-C(2)	136.0(6)	C(1)-C(2)-S(1)	113.9(5)
C(3)-C(2)-S(1)	111.0(5)	C(3)-C(2)-C(1)	134.9(6)
C(2)-C(3)-O(2)	112.2(6)	H(3)-C(3)-O(2)	111.7(4)
H(3)-C(3)-C(2)	101.8(4)	C(4)-C(3)-O(2)	107.5(5)
C(4)-C(3)-C(2)	116.3(6)	C(4)-C(3)-H(3)	107.2(4)
C(5)-C(4)-C(3)	106.8(6)	C(6)-C(4)-C(3)	112.5(6)
C(6)-C(4)-C(5)	110.0(6)	C(7)-C(4)-C(3)	109.5(6)
C(7)-C(4)-C(5)	109.3(7)	C(7)-C(4)-C(6)	108.7(7)
H(51)-C(5)-C(4)	109.5(4)	H(52)-C(5)-C(4)	109.5(5)
H(52)-C(5)-H(51)	109.5(0)	H(53)-C(5)-C(4)	109.5(4)
H(53)-C(5)-H(51)	109.5(0)	H(53)-C(5)-H(52)	109.5(0)
H(61)-C(6)-C(4)	109.5(4)	H(62)-C(6)-C(4)	109.5(4)
H(62)-C(6)-H(61)	109.5(0)	H(63)-C(6)-C(4)	109.5(4)
H(63)-C(6)-H(61)	109.5(0)	H(63)-C(6)-H(62)	109.5(0)
H(71)-C(7)-C(4)	109.5(5)	H(72)-C(7)-C(4)	109.5(5)
H(72)-C(7)-H(71)	109.5(0)	H(73)-C(7)-C(4)	109.5(4)
H(73)-C(7)-H(71)	109.5(0)	H(73)-C(7)-H(72)	109.5(0)
C(9)-C(8)-C(1)	124.4(3)	C(13)-C(8)-C(1)	115.6(3)
C(13)-C(8)-C(9)	120.0(0)	C(10)-C(9)-C(8)	120.0(0)
H(9)-C(9)-C(8)	120.0(0)	H(9)-C(9)-C(10)	120.0(0)
C(11)-C(10)-C(9)	120.0(0)	H(10)-C(10)-C(9)	120.0(0)
H(10)-C(10)-C(11)	120.0(0)	C(12)-C(11)-C(10)	120.0(0)
H(11)-C(11)-C(10)	120.0(0)	H(11)-C(11)-C(12)	120.0(0)
C(13)-C(12)-C(11)	120.0(0)	H(12)-C(12)-C(11)	120.0(0)
H(12)-C(12)-C(13)	120.0(0)	C(12)-C(13)-C(8)	120.0(0)
H(13)-C(13)-C(8)	120.0(0)	H(13)-C(13)-C(12)	120.0(0)
C(15)-C(14)-S(1)	123.5(2)	C(19)-C(14)-S(1)	116.3(2)
C(19)-C(14)-C(15)	120.0(0)	C(16)-C(15)-C(14)	120.0(0)
H(15)-C(15)-C(14)	120.0(0)	H(15)-C(15)-C(16)	120.0(0)
C(17)-C(16)-C(15)	120.0(0)	H(16)-C(16)-C(15)	120.0(0)
H(16)-C(16)-C(17)	120.0(0)	C(18)-C(17)-C(16)	120.0(0)
C(20)-C(17)-C(16)	119.4(5)	C(20)-C(17)-C(18)	120.6(5)
C(19)-C(18)-C(17)	120.0(0)	H(18)-C(18)-C(17)	120.0(0)
H(18)-C(18)-C(19)	120.0(0)	C(18)-C(19)-C(14)	120.0(0)
H(19)-C(19)-C(14)	120.0(0)	H(19)-C(19)-C(18)	120.0(0)

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