Novel Enzyme- and Free Radical- Mediated Reactions of Oxirane Derivatives

by

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Abstract.

Novel enzyme- and free radical- mediated reactions of oxirane derivatives.

The thesis describes the use of various hydrolases in the preparation of enantiomerically enriched epoxyesters. Optically enriched n-butyl 4,5-epoxypentanoate was prepared with a 64% enantiomeric excess *via* the porcine pancreatic lipase-catalysed hydrolysis of the racemic ester. The hydrolase-catalysed hydrolysis of two prochiral epoxydiesters; *meso* 2,3-epoxybutan-1,4-diyl dibutanoate and 2,3-epoxy-2-butanoyloxymethylpropan-1-yl butanoate, were performed with several lipases, with the enantiomerically enriched epoxymonoesters being obtained in up to 80% and 65% enantiomeric excesses, respectively. Both isomers of the 4-butanoyloxy-2,3-epoxybutan-1-ol could be obtained *via* the hydrolysis of the diester by varying the lipase used. (2S, 3R)-4-Butanoyloxy-2,3-epoxybutan-1-ol was also isolated in up to 55% enantiomeric excess by the lipase-catalysed transesterification of vinyl butyrate with *meso* 2,3-epoxybutan-1,4-diol.

The directed cleavage of oxiranylcarbinyl radicals was investigated with the aim of developing new methods for performing ring expansions leading to medium ring carbocycles and oxygen containing heterocycles. By directing the oxiranylcarbinyl radical rearrangement *via* C-C cleavage, a route to cyclic enol ethers was achieved. 7- and 8-Membered cyclic enol ethers were prepared in 72% and 66% yields respectively, by treating the thiocarbonylimidazolide derivatives of 2,3-epoxy-3-phenyl-cyclohexan-1-ol and 2,3-epoxy-3-phenyl-cycloheptan-1-ol with tributyltin hydride / A.I.B.N. The 2-methyl substituted enol ether was also prepared using a similar procedure. Also reported is the use of the C-O directed cleavage of the oxiranylcarbinyl radicals leading to 10-membered carbocycles. The key step to this reaction was the stabilisation provided by an ester moiety to the intermediate 10-membered ring radical. This allowed it to be reduced by tributyltin hydride / A.I.B.N. The major products in the reduction of the bicyclic epoxythiocarbonylimidazolides with tributyltin hydride / A.I.B.N. were the expected cyclodecenones and the dihydro-derivatives.

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"*I am the Law, and you'd better believe it Citizen.*"

(Judge Dredd, 1977).

To Mom and Dad,
without whose Love and Support
this work would not have
been possible.

List of abbreviations.

A.I.B.N.	azoisobutyronitrile.
b.p.	boiling point.
C.I.	chemical ionisation.
CT	α-chymotrypsin.
d.e.	diastereomeric excess.
DCM	dichloromethane.
DMD	dimethyldioxirane.
DMF	dimethylformamide.
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone.
DMSO	dimethyl sulfoxide.
E.I.	electron-impact.
e.e.	enantiomeric excess.
G.C.	gas chromatography.
H.M.P.A.	hexamethylphosphoramide.
Hp	$-(CH_2)_6CH_3$.
HPLC	high performance liquid chromatography.
Im	imidazole.
LDA	lithium diisopropylamide.
m.p.	melting point.
m-C.P.B.A.	*meta*-chloroperoxybenzoic acid.
MTPA	(R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid.
MVK	methylvinylketone.
N.M.R.	nuclear magnetic resonance.
n.O.e.	nuclear Overhauser effect.
P.T.S.A.	*para*-toluenesulfonic acid.
p.p.m.	parts per million.
P.L.E.	pig liver esterase.
P.P.L.	porcine pancreatic lipase.
Pr	$-(CH_2)_2CH_3$.
Py	pyridine.
P.C.C.	pyridinium chlorochromate.
SOMO	single occupied molecular orbital.
TBDMS	*tert*-butyldimethylsilyl.
T.B.A.F.	*tetra*-butylammonium fluoride.
THF	tetrahydrofuran.
t.l.c.	thin layer chromatography.

Contents.

Chapter 1. Hydrolases and their use in enantioselective reactions.

1.1. Introduction.

The exploitation of enzymes as practical alternatives to existing non-biological catalysts has expanded rapidly in recent years. With well over 2000 identified enzymes,[1] capable of catalysing most types of organic reactions[2] their potential is seemingly limitless.

The properties of the enzyme, which the organic chemist can use to his advantage, include the following:

(I) Enzymes operate under mild conditions, often at room temperature and neutral pH, thus minimizing problems of substrate isomerisation, racemisation, epimerisation and rearrangement.

(II) Enzymes can be highly efficient catalysts.

(III) Some enzymes are capable of functionalising non-activated,[3] remote positions[4] in organic molecules.

(IV) Enzymes are generally very selective in the type of reactions they catalyse and perhaps most importantly, as chiral macromolecules they are capable of performing stereoselective reactions on both racemic and prochiral substrates.

There are also disadvantages, in particular with the expense of the enzymes, and co-factors which may be required. Also, there may be difficulties with experimental techniques, particularly when dealing with whole cell systems rather than isolated enzymes.[5]

The types of enzymes which this report deals with are classified as hydrolases. These enzymes catalyse the hydrolysis of esters, amides and glycosides *etc.* A large number of hydrolases have been identified,[1] but few have been utilized in organic transformations. Some of the more popular ones include pig liver esterase, porcine pancreatic lipase, α-chymotrypsin and more recently, *Pseudomonas fluorescens* lipase, for its ability to efficiently catalyse transesterification reactions.

1.2. Kinetic hydrolysis of racemic esters.

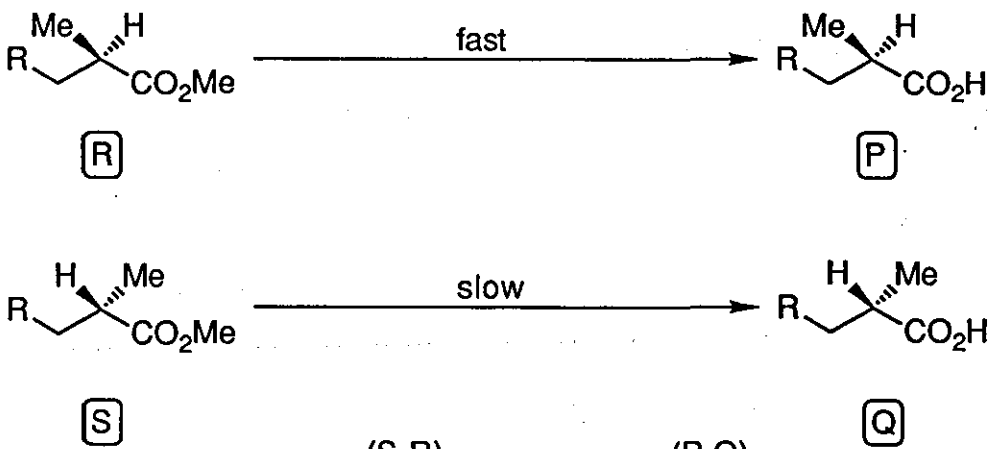
When a hydrolase exhibits absolute enantiomeric selectivity in the hydrolysis of a racemic ester, the transformation will stop at 50% conversion when all of the reactive enantiomer has been removed. In such a resolution, one enantiomer may have an unwanted absolute configuration and may be discarded. As a result, the obvious disadvantage in such a resolution is that the maximum yield of usable material is limited to 50%. However, the unwanted enantiomer

may be converted to the required enantiomer by conventional chemical means, or by racemisation and rehydrolysis with the hydrolase.[6]

A greater problem is encountered when, as is found with the majority of cases, the hydrolase is not entirely enantiomerically selective. In these circumstances both enantiomers are hydrolysed, one at a faster rate than the other.

The enantiomeric specifity of an enzyme towards a substrate is defined by its enantiomer ratio, E.[7] For the simple, irreversible hydrolysis reaction, E is governed by the relative rates of the reacting enantiomers and is independent of time or substrate concentrations.

Scheme 1



$$e.e._S = \frac{(S-R)}{(R+S)} \qquad e.e._P = \frac{(P-Q)}{(P+Q)}$$

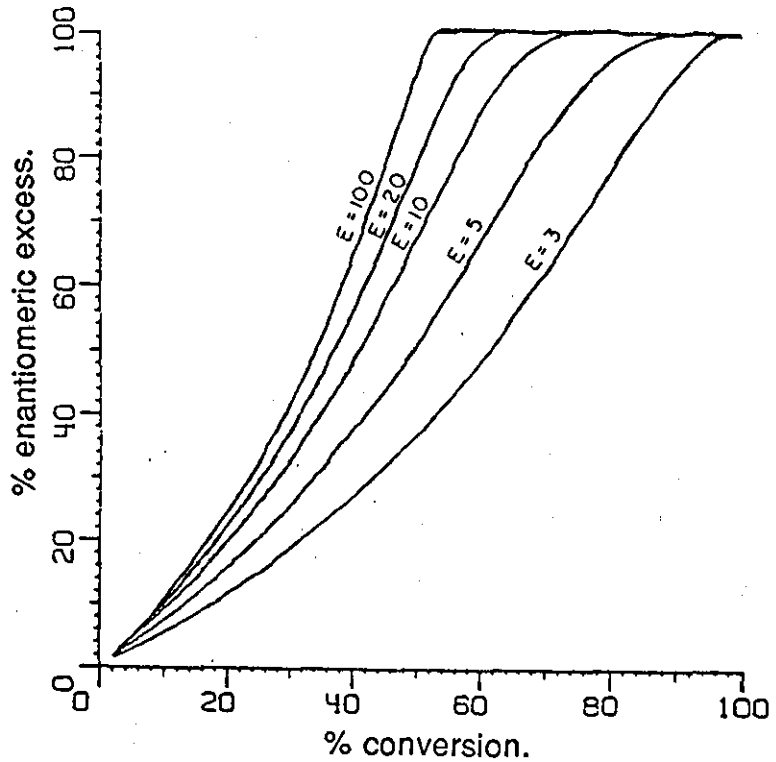
$$\frac{\ln([1-C][1-e.e._S])}{\ln([1-C][1+e.e._S])} = E \qquad -\boxed{1}$$

$$\frac{\ln[1-C(1+e.e._P)]}{\ln[1-C(1-e.e._P)]} = E \qquad -\boxed{2}$$

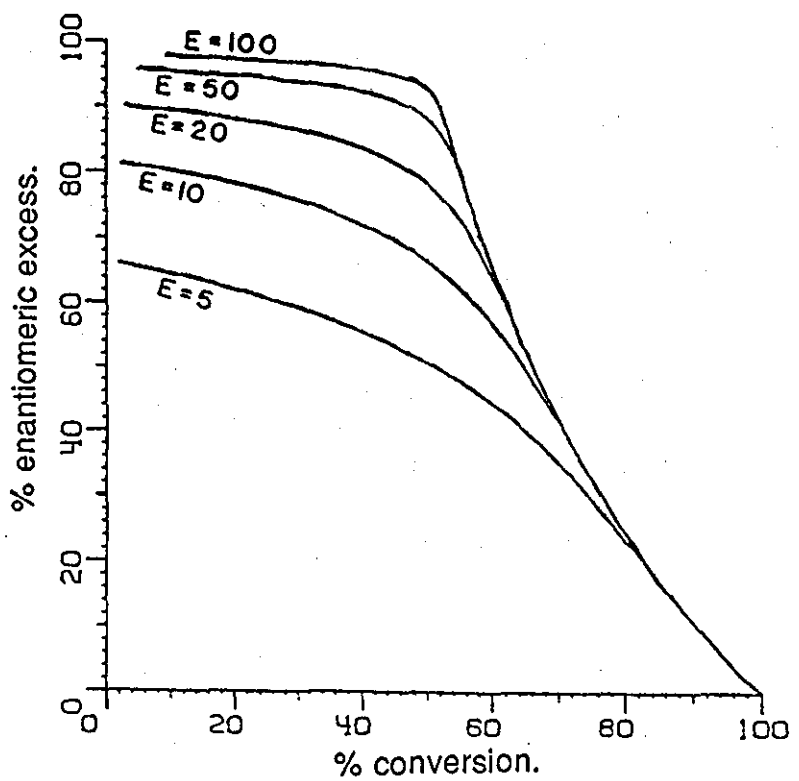
$$\frac{e.e._S}{e.e._S + e.e._P} = C \qquad -\boxed{3}$$

Sih and co-workers[7] have shown that E and the percent conversion (C) relate to the enantiomeric excesses of both resolved substrate and product ($e.e._S$ and $e.e._P$), by equations (1), (2) and (3), as shown in Scheme 1. Hence, in kinetic resolution experiments, if the values of $e.e._S$ and $e.e._P$ are defined, the values of C and E may be calculated accurately from equations (3) and (1), or (2) respectively.

Graph 1. Plot of percent enantiomer excess for remaining substrate fraction *vs.* the percent conversion, for various enantiomer ratios (E).[7]



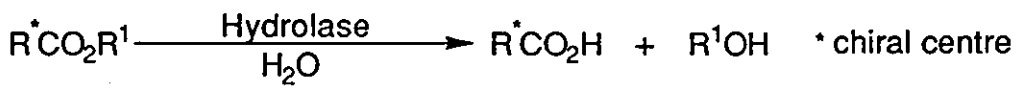
Graph 2. Plot of percent enantiomer excess for product fraction *vs.* the percent conversion, for various enantiomer ratios (E).[7]



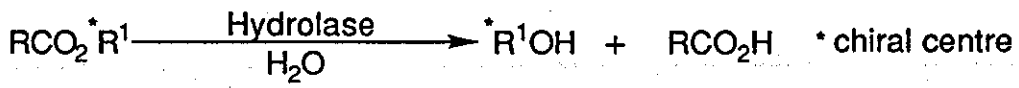
Equations (1) and (2) can be used to provide a graphical representation of how the enantiomeric excesses of both resolved substrate and product varies with the percent conversion, for different E values, Graphs 1 and 2.[7]

It is evident that if a high enantiomeric excess for the product is required, the hydrolysis must be terminated before 50% conversion, irrespective of the E value. The value for the enantiomeric excess of the substrate increases with the extent of conversion and hence high enantiomeric excesses may be obtained with enzymes of low E values by extending the reaction time, but at the expense of the chemical yield.

Hydrolases have been used for two basic kinetic hydrolysis reactions.
(I) Cleavage of racemic esters to afford optically enriched esters and acids.



(II) Removal of acyl groups from racemic acylates, to afford optically enriched acylates and alcohols.



The first example of the second type of hydrolysis, performed on an epoxide- containing compound, was carried out by Ladner and Whitesides[8] in their lipase-catalysed hydrolysis of various gylcidol esters (1), as shown in Scheme 2.

Scheme 2.

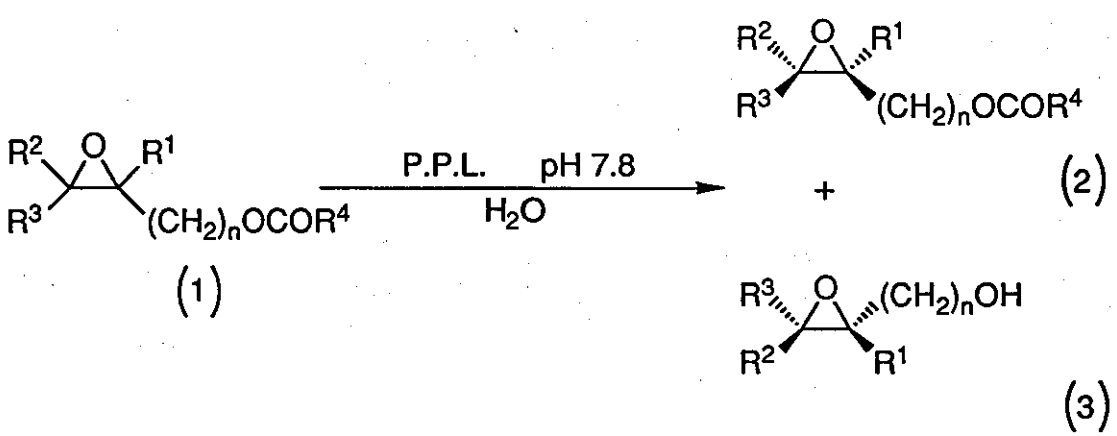


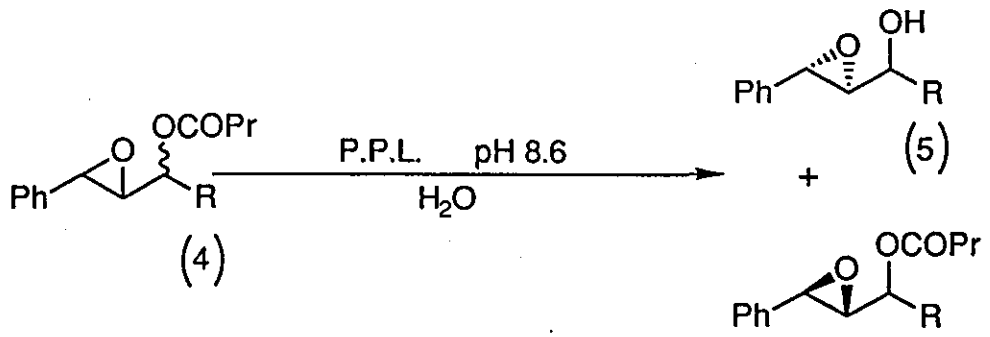
Table 1. Lipase-catalysed hydrolysis of glycidol esters (1).

Nº	Compounds.				n.	% Conv.	E.	% e.e. of acylate.
	R^1	R^2	R^3	R^4				
1	H	H	H	Me	1	60	4	57
2	H	H	H	Et	1	60	11	89
3	H	H	H	nPr	1	60	13	90
4	H	H	H	nBu	1	60	16	92
5	H	C_3H_7	H	nPr	1	60	-	58
6	CH_3	H	H	nPr	1	60	-	52
7	H	CH_3	H	nPr	1	60	-	92
8	H	H	CH_3	nPr	1	60	-	69
9	CH_3	H	CH_3	nPr	1	60	-	72
10	H	H	H	nPr	2	60	-	76
11	H	H	H	nPr	2	75	-	95
12	H	C_2H_5	H	nPr	2	60	-	80
13	H	H	C_2H_5	nPr	2	60	-	69

At 60% conversions, good enantiomeric excesses for the recovered esters (2) were observed. Entries 1-4 of Table 1 demonstrate how altering the acyl moiety can have a dramatic effect on the enantiomeric ratio of the porcine pancreatic lipase. A much improved enantiomeric excess was obtained when the acyl group was a butanoate as opposed to an acetate. Acyl groups longer than pentanoate resulted in practical problems due to foaming and the formation of emulsions. Entry 10 of Table 1 shows how a drop in enantiomeric excess of ~15% was observed when removing the acyl moiety one carbon atom further away from the chiral centre of the epoxide. The authors[8] stated that the alcohols (3), could be prepared in high enantiomeric excesses by terminating the hydrolysis at low percent conversion, but did not quote any values.

In an extension of Whiteside's work, Marples *et al*[9] performed several porcine pancreatic lipase-catalysed hydrolyses on esters of epoxy secondary alcohols (4), as shown in Scheme 3.

Scheme 3.



An excellent enantiomeric excess for the secondary alcohol (5) was obtained for R = Et, at less than 50% conversion (entry 1 of Table 2). When R was a propyl group, both the *threo*-isomer and *erythro*-isomer were hydrolysed, with porcine pancreatic lipase exhibiting a greater enantiomeric selectivity for the *threo*-isomer (entry 3 and entry 4 respectively of Table 2). The authors expressed a particular interest in the hydrolysis of the epoxy diester (4), as a potential intermediate and model for the synthesis of optically active leukotriene antagonists.[10] Although only a relatively low enantiomeric excess was achieved, the conditions employed were non-optimised, with no variation in the enzyme system and / or ester moiety being employed (entry 5 of Table 2).

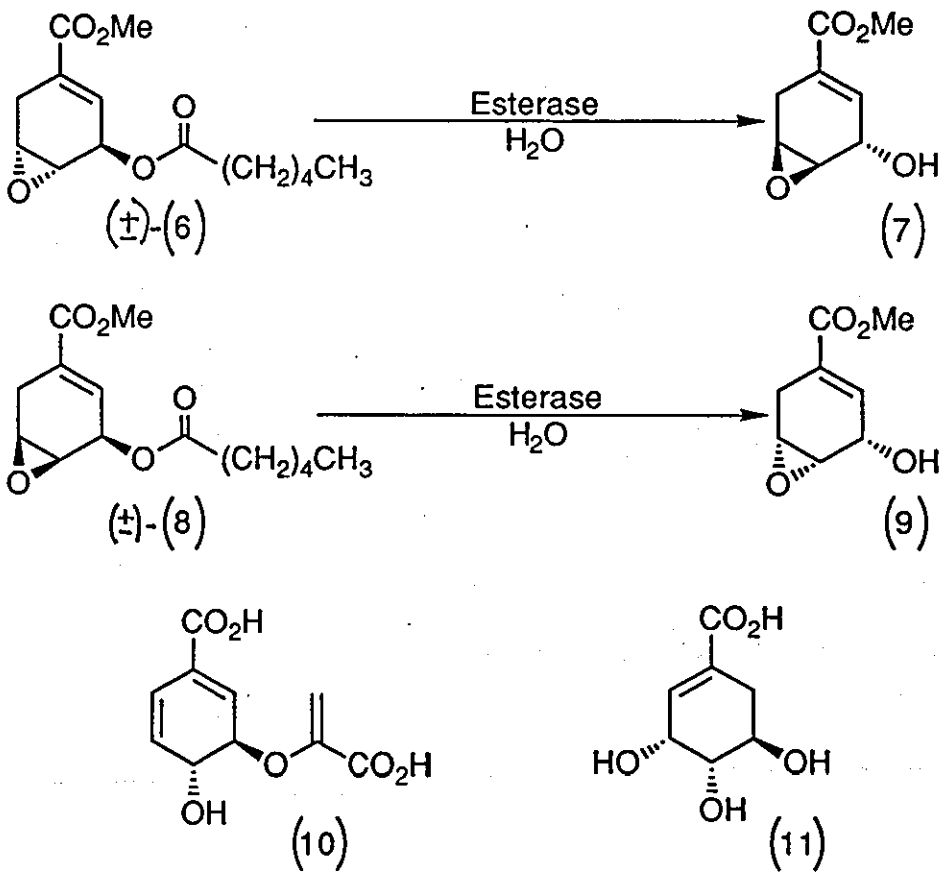
Table 2. Porcine pancreatic lipase-catalysed hydrolysis of (4).

Nº	Compound. R=	% Conv^{n}.	% Yield.[1]	% e.e. of alcohol.
1	Et	49	50	100
2	Et	57	52	85
3	Pr	35	16	100
4	Pr	30	29	60
5	$(CH_2)_2CO_2Et$	48	22	56

[1]calculated on amount of ester consumed.

In a similar fashion, Pawlak and Berchtold[11] carried out the hydrolysis of racemic esters (6) and (8) in an attempt to perform the asymmetric synthesis of (-)-chorismic acid (10) and (-)-shikimic acid (11), as shown in Scheme 4.

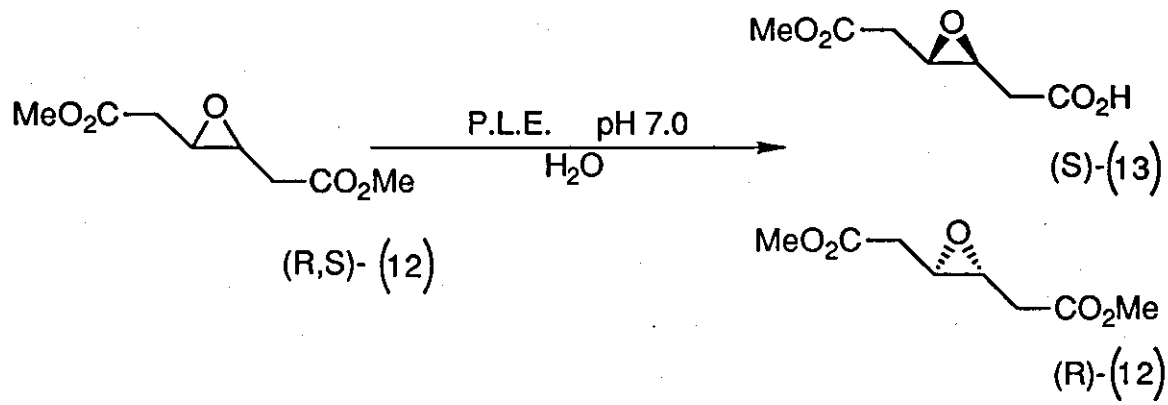
Scheme 4.



Berchtold obtained (+)-(7) with a 80% enantiomeric excess and (+)-(9) with a 93% enantiomeric excess, by hydrolysing with cholesterol esterase isolated from bovine pancreas. When employing porcine pancreatic lipase, an enantiomeric excess of just 48% was obtained for the hydrolysis of (6). No hydrolysis of the methyl carboxylate ester was observed, except when employing pig liver esterase, demonstrating the selectivity of the various hydrolases tried. The total synthesis of (-)-(10) was achieved in several steps from (-)-(7) and (-)-(11) likewise, from (-)-(9).[12]

The majority of the work on the hydrolysis of racemic epoxy carboxylate esters was performed by Mohr and co-workers.[13,14] The first example was of (R,S)-dimethyl 3,4-epoxyhexanedioate[13] (12), as illustrated in Scheme 5.

Scheme 5.



During the hydrolysis, the reaction was seen to almost stop after the consumption of 0.5 equivalents of base, with both the recovered optically enriched diester (R)-(12) and half ester (S)-(13) being isolated in >95% enantiomeric excess. In a later paper Mohr *et al* calculated the enantiomeric ratio to be 21.5.[14]

Although Mohr *et al* were the first to perform the enzymatic hydrolysis of racemic 3,4-epoxybutanoate esters,[14] a more detailed study, with various alkyl 3,4-epoxybutanoate esters (14), was described by Bianchi and co-workers,[15] as shown in Scheme 6 and Table 3.

Enantiomeric excesses in excess of 90% were obtained for recovered (R)-(14) with steapsin, upon the hydrolysis of ester derivatives from n-butanol and n-octanol, when the reaction was taken to 60% conversion. Both enantiomers of (14) could be obtained by varying the enzyme used, with (S)-(14) being recovered with just a 50% enantiomeric excess when employing the hydrolase *Strept. griseus*.

Bianchi *et al* required optically enriched (R)-(14) for the synthesis of (R)-(-)-carnitine chloride (16). In the preparation of this, they found that they required the (R)-epoxy acid (17). They found this difficult to prepare *via* conventional chemical methods and performed a second enzymatic, non-stereoselective hydrolysis with alcalase, entry 5 of Table 3. The preparation of (16) was simply achieved by the treatment of (R)-(17) with trimethylamine and aqueous hydrochloric acid, as illustrated in Scheme 7.

Scheme 6.

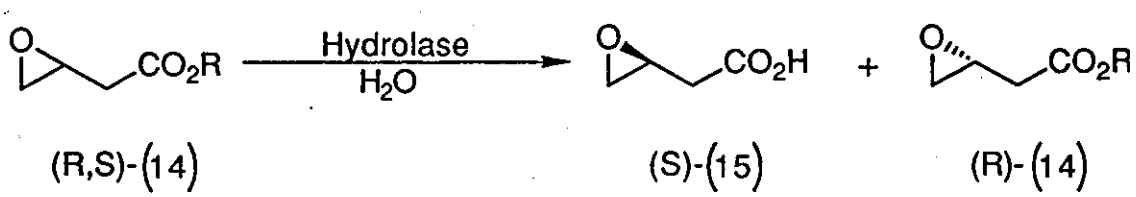
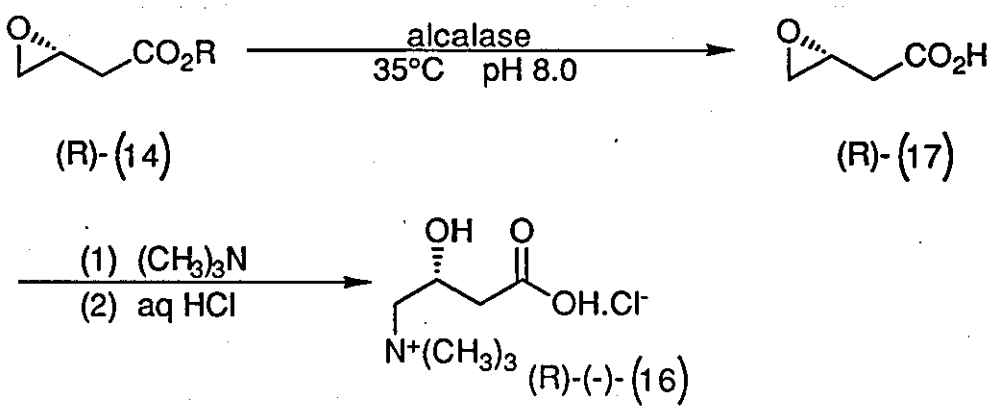


Table 3. Enantioselective hydrolysis of alkyl 3,4-epoxybutanoate esters (14).

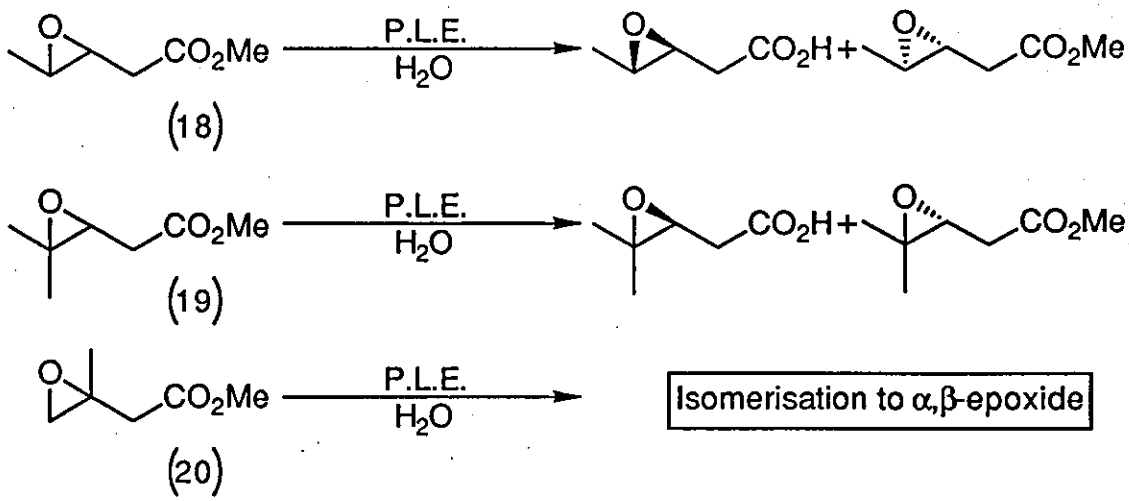
Nº	Compound. R=	Hydrolase.	% Conv^{n}.	% e.e.	Config.
1	i-C_4H_9	steapsin	61	75	R
2	i-C_4H_9	steapsin	70	>95	R
3	i-C_4H_9	P.L.E.	52	62	R
4	i-C_4H_9	*Strept.griseus*	54	50	S
5	i-C_4H_9	alcalase	100	0	-
6	n-C_4H_9	steapsin	60	92	R
7	n-C_8H_{17}	steapsin	60	>95	R

Scheme 7.



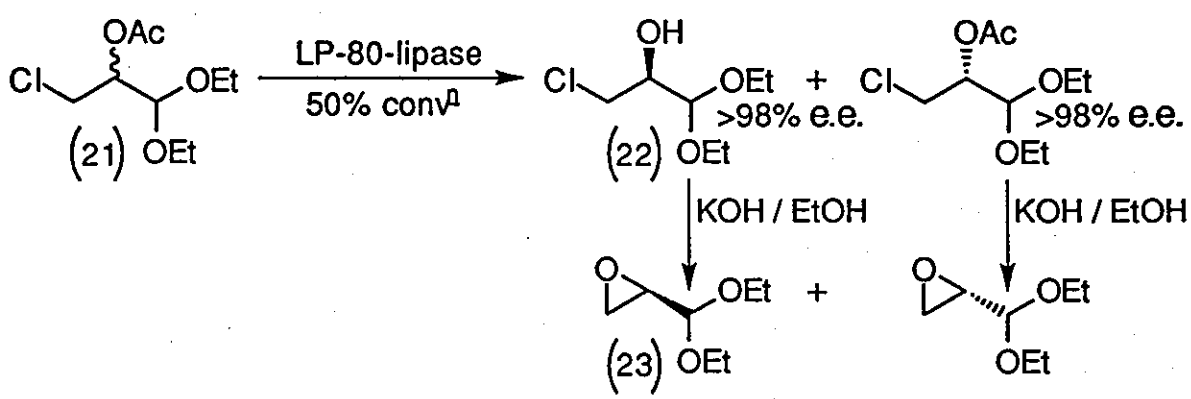
Mohr *et al* also reported the pig liver esterase-catalysed hydrolysis on substituted methyl 3,4-epoxybutanoates[14] (18), (19) and (20), as shown in Scheme 8.

Scheme 8.



Pig liver esterase exhibited an E value of 16 and 17, with substrates (18) and (19) respectively and hence good enantiomeric excesses for both recovered esters and acids could easily be obtained. With substrate (20), the E value could not be calculated as substrate isomerisation to the α,β-epoxide took place. By the use of standard chemical transformations, both of the resolved epoxy esters, (18) and (19), were converted to optically active lactones.

Scheme 9.



A popular, alternative route to the production of optically enriched epoxides, *via* an enzymatic hydrolysis, is one which results in a halohydrin.[16] Scheme 9 shows one of many examples where the hydrolysis of the racemic 2-acetoxy-3-chloropropanal diethyl acetal (21) resulted in an excellent enantiomeric excess of the chlorohydrin[17] (22). This could be easily converted to the optically enriched epoxide (23), *via* a straightforward procedure.

1.3. Hydrolysis of prochiral and *meso* diesters.

As has already been noted, the major drawback to performing the resolution of a racemic substrate is that the maximum yield is restricted to 50%. This problem may be avoided by exploiting the prochiral enantiotopic specificity of the enzymes. For example, when a hydrolase is faced with a prochiral diester, it may either hydrolyse the pro-(S), or pro-(R) ester moiety. If the hydrolase were to exhibit absolute enantiotopic selectivity for the pro-(S) isomer, the half ester with the (R)-stereochemistry could ideally be obtained in 100% yield and optical purity.

1.3.1. Acyclic prochiral diesters.

There are many examples in the literature of the stereoselective hydrolysis of acyclic prochiral diesters. For the purpose of this report, the prochiral epoxide containing substrates are being classed as cyclic, *meso* diesters, and will be covered later in section **1.3.2.** Just one early, and very well studied example of the hydrolysis of an acyclic prochiral diesters, is that of the C-3-substituted glutarate diesters (24), as shown in Scheme 10.

Table 4. Esterase-catalysed hydrolysis of prochiral glutarate diesters (24).

Nº	R^1.	R^2.	R^3.	Hydrolase.	% yield.	% e.e.	Config.
1	OH	H	Me	CT	-	68[1]	R
2	OH	H	Me	P.L.E.	-	22[1]	S
3	OCH_2OMe	H	Me	CT	95	93	R
4	OH	Me	Me	P.L.E.	64	99	S
5	Me	H	Me	P.L.E.	98	100	R
6	NH_2	H	Me	P.L.E.	94	42	R
7	NHCOMe	H	Et	CT	57	>95	R
8	NHCOMe	H	Me	P.L.E.	81	93	R
9	NHOCO-CH_2Ph	H	Me	P.L.E.	93	93	S

Scheme 10.

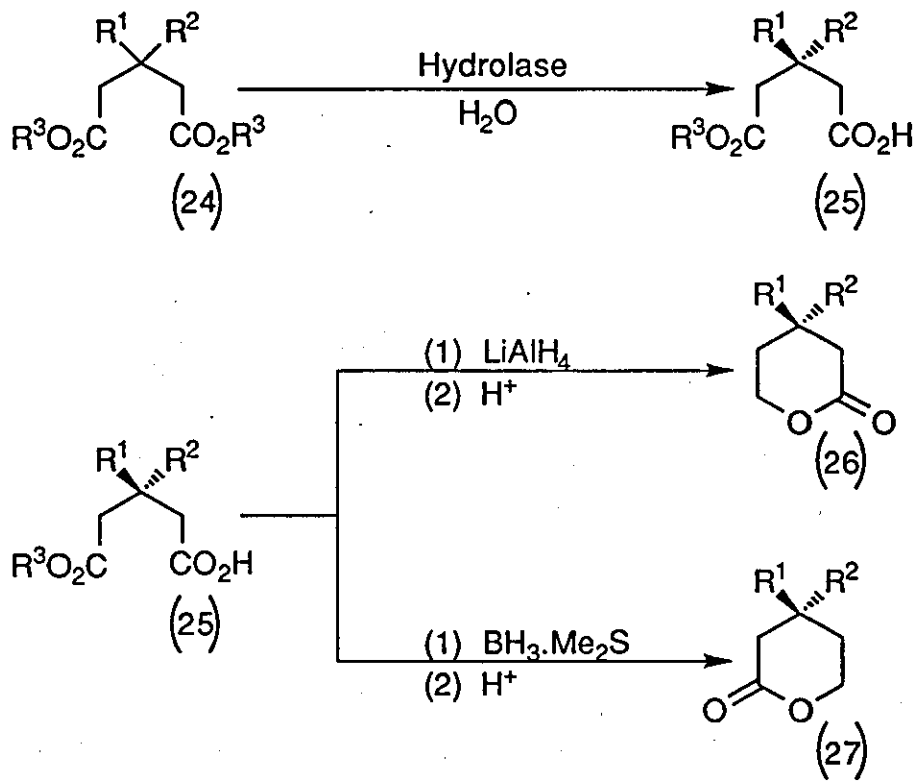


Table 4 shows a small selection of some of the 3-substituted glutarate diesters which have been examined. Initial studies on the hydrolysis of dimethyl β-hydroxyglutarate showed the pig liver esterase and α-chymotrypsin to be highly enantioselective.[18] In calculating the enantiomeric excesses of (25), the authors relied on optical rotation data, which as the specific rotation was relatively low, -1.7°, gave enantiomeric excesses which were fairly inaccurate. Upon re-investigation by Mohr *et al*, the enantiomeric excesses were accurately determined by HPLC analysis of a diastereomeric triester derivative.[13] Entries 1 and 2 of Table 4 show their results, with α-chymotrypsin being more enantiotopically selective than the pig liver esterase.

Roy *et al* demonstrated that converting the alcohol to the methoxymethyl ether prior to hydrolysis resulted in a much improved enantiomeric excess for the (R)-monoester[19] (entry 3 of Table 4). Francis and Jones performed the pig liver esterase-catalysed hydrolysis of various alkyl-, aryl- and cyclohexyl-monosubstituted 3-glutarate diesters, and in all cases isolated the homochiral (R) half ester in good yields.[20] Entry 5 of Table 4 shows just one example. The half ester (25), could be converted into either the (R)-lactone (26), or (S)-lactone (27), by conventional chemical methods, as shown in Scheme 10.

The alternative enzymatic method used in the preparation of such enantiomerically enriched lactones was that which uses the alcohol dehydrogenase-catalysed oxidation of various prochiral 3-substituted pentan-1,5-diols.[21] The hydrolysis route offers an improvement over this method as there is no need for fermentation, and co-enzyme recycling problems are avoided.

Finally, the hydrolysis of various N-substituted dimethyl aminoglutarates have been well studied, due to the fact that the resulting half esters may be converted to optically active β-lactams.[22,23] Hydrolysis of dimethyl β-amino-glutarate,[22] resulted in a relatively poor enantiomeric excess of (25), due in part, to the non-enzymatic hydrolysis of the diester (entry 6 of Table 4). Protection of the amino moiety prior to hydrolysis improved the situation dramatically, with both the (S)- and (R)-isomers being made available in high enantiomeric excesses, by the appropriate choice of protecting groups[24] (entries 7-9 of Table 4).

1.3.2. Cyclic *meso* diesters.

(I) Carboxylate diesters.

In the hydrolysis of the 1,2-cycloalkyl *meso* diesters (28), Sabbioni and Jones[25] observed an interesting reversal in enantiotopic selectivity, from pro-(S) hydrolysis for the cyclopropane and cyclobutane substrates, to pro-(R) hydrolysis for the cyclopentane and cyclohexane substrates (Scheme 11 and Table 5, entries 1-4). It is evident from the low enantiomeric excess obtained in the hydrolysis of the cyclopentane substrate, that this represents the stereoselective reversal structure. Jones *et al* have used this information, along with that obtained in the hydrolysis of many other racemic and prochiral diesters, to develop a simple active site model[26] for pig liver esterase.

Scheme 11.

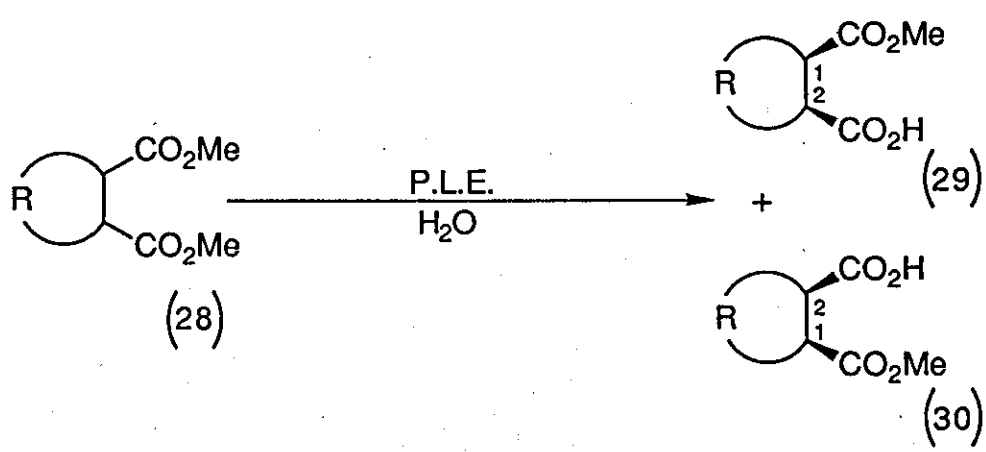
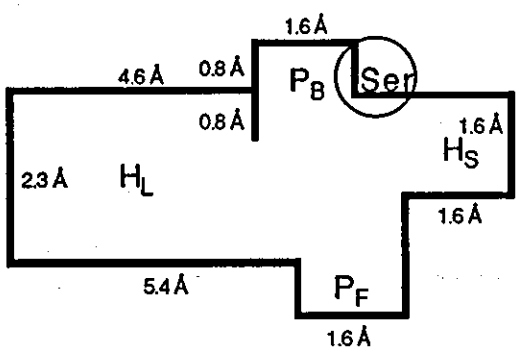


Table 5. Pig liver esterase-catalysed hydrolysis of *meso* diesters (28).

Nº	R	% Yield.	% e.e.	Config.
1	CH_2	88	>97	(1R,2S)
2	$(CH_2)_2$	87	>97	(1R,2S)
3	$(CH_2)_3$	92	17	(1S,2R)
4	$(CH_2)_4$	88	97	(1S,2R)
5	$(CH_2CH{=})_2$	94	95	(1S,2R)
6	O	69	31	(1S,2R)

Figure 1.



Active-site model of P.L.E. Boundaries of model show available space, as limited by amino acid residues of the enzyme. H_L and H_S denote large and small hydrophobic pockets, P_B and P_F denote front and back hydrophilic pockets. Ser; serine, denotes the site where the ester moiety is hydrolysed.

Figure 1 depicts how the cyclo-butane, -pentane and -hexane substrates fit in the active site of pig liver esterase. The relevant guide lines to be followed in the hydrolysis of the various prochiral diesters are:

(I) H_L and H_S are hydrophobic pockets and as such, polar groups such as hydroxy, amino and carbonyl *etc.* are excluded. P_F and P_B are hydrophilic pockets and will allow a variety of alcohol, ether and carbonyl functions.

(II) The most common function of P_F is to bind the second, non-hydrolysed ester.

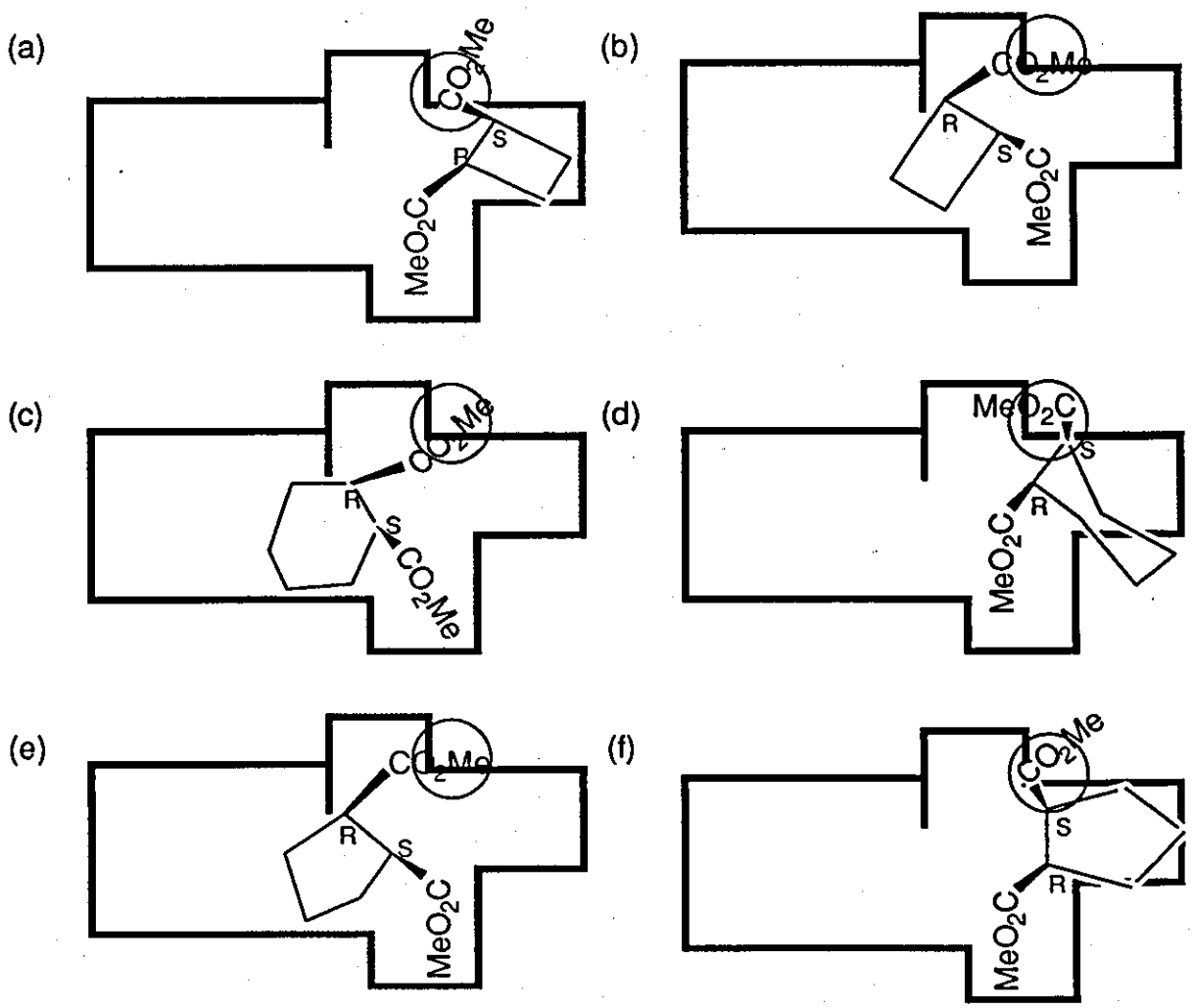
(III) The ester to be hydrolysed must fit, in the correct orientation, within the serine pocket.

(IV) The hydrophobic portions of the substrate, the alkyl rings in this case, will preferentially bind to the H_S pocket, unless they are too large to do so.

Illustrations (a) and (b) of Figure 2, show the potential fits of the cyclobutane substrate. In (a), the cyclobutyl group is found in H_S, where it fits well. In (b), the cyclobutyl group may fit easily into H_L, but the binding rules specify that the hydrophobic groups preferentially fit in H_S. As a result, a high enantiomeric excess was observed for the half ester. The opposite reasoning is true for the

cyclohexane substrate, shown in (c) and (d) of Figure 2. In (d), the cyclohexyl group is too large to fit into H_S and therefore hydrolysis *via* the orientation depicted in illustration (c) predominates, and again a good enantiomeric excess of the half ester was observed. Illustrations (e) and (f) of Figure 2 show the cross-over point, where orientation (e) is only slightly favoured over (f) and hence a poor enantiomeric excess was obtained for the half ester. These rules have been used to predict and account for the P.L.E.-catalysed hydrolysis of various prochiral and racemic esters.

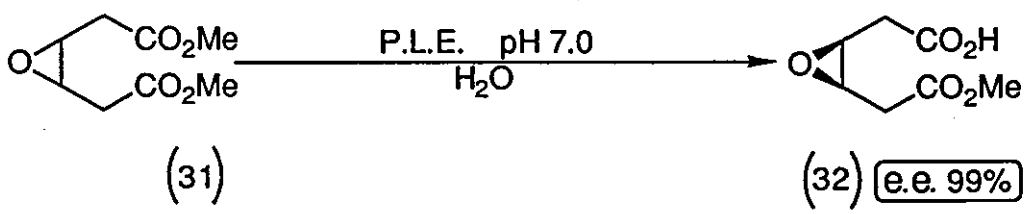
Figure 2.



Entry 6 of Table 5, shows one of the two examples of the enzymatic hydrolysis of a *meso* epoxydiester substrate. As is evident, only a relatively poor enantiomeric excess of 31% was obtained for the half ester.[25] Regardless of the poor enantiomeric excess, this does provide an important route to the preparation of the half ester, a product which is difficult to obtain *via* conventional chemical means. This was emphasised when Häbich *et al* utilised the hydrolysis of this substrate in the preparation of a new carbapenem,[27] although they made no note of any stereoselectivity in the P.L.E.-catalysed hydrolysis.

The second example of the enzyme-catalysed hydrolysis of a *meso* epoxydiester was that described by Mohr *et al* on dimethyl *meso* 3,4-epoxyhexanedioate[13] (31), as shown in Scheme 12.

Scheme 12.

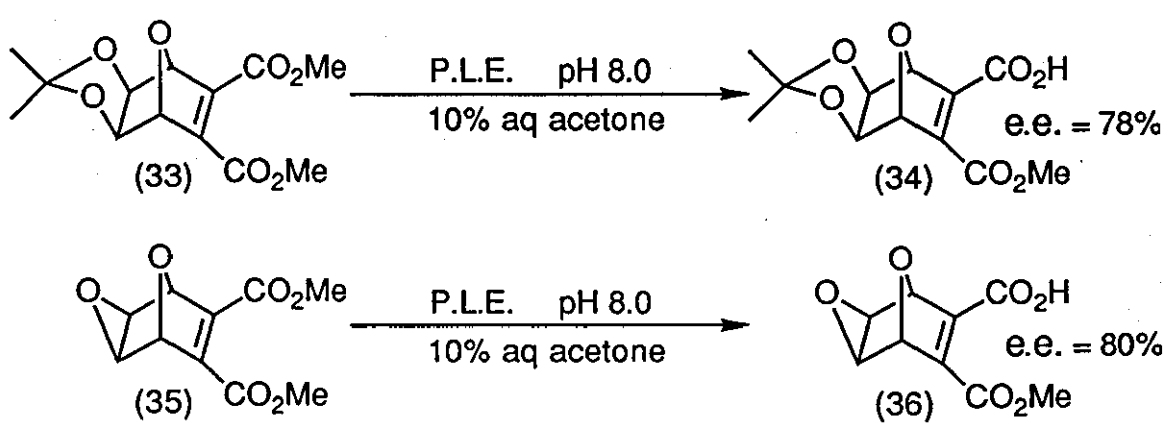


(31) (32) e.e. 99%

Upon the hydrolysis of epoxydiester (31) with pig liver esterase, the half ester (32), was isolated in 90% yield and 99% enantiomeric excess. Mohr *et al* proved the synthetic utility of (32) by converting it to a variety of optically enriched lactones, ethers and β-hydroxy diesters.

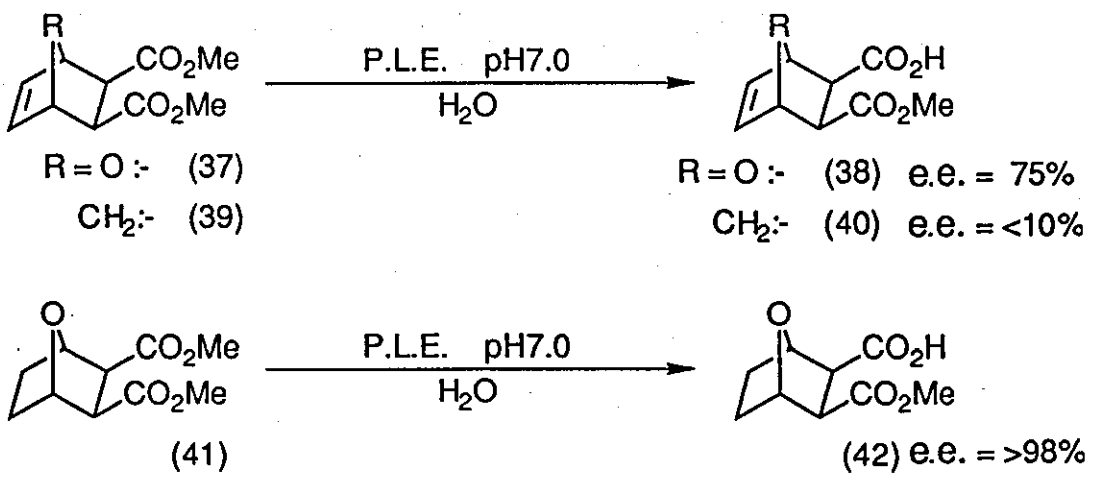
A further interesting group of compounds which are enantioselectively hydrolysed by pig liver esterase, are the *meso* bicyclic and tricyclic diesters shown in Scheme 13.

Scheme 13.



Ohno *et al*[28,29] performed the enzymatic hydrolysis of substrates (33) and (35) with the objective of performing the enantioselective synthesis of methyl L- and D-ribosides, (+)-showdomycin, (-)-6-azapseudouridine and (-)-cordycepin. In both cases the half esters (34) and (36) were isolated in effectively quantitative yields and ~80% enantiomeric excesses. These enantiomeric excesses were improved to >95% by recrystallisation of the half esters. The presence of a double bond for substrate (33) was shown to be essential for an efficient hydrolysis, as in its absence, the saturated substrate was only hydrolysed very slowly, with just a 10% yield of the half ester being isolated after 24 hours.[29] Both (34) and (36) were successfully converted into the aforementioned ribosides.

Scheme 14.



Upon the hydrolysis of bicycles (37) and (39), Bloch and co-workers demonstrated that the oxygen bridge was essential if a reasonable rate of hydrolysis and enantiomeric excess for the half esters (38) and (40) were to be obtained.[30] When the saturated substrate (41) was hydrolysed by the pig liver esterase, an improved enantiomeric excess for the half ester (42) was observed with respect to the saturated bicycle (38). It was also noted that the two ester groups should be in the equatorial position for an efficient hydrolysis to occur. When the analogous diaxial diester of compound (41) was hydrolysed, a 17 fold decrease in the rate of hydrolysis was observed and the half ester was only isolated with a 64% enantiomeric excess (Scheme 14).

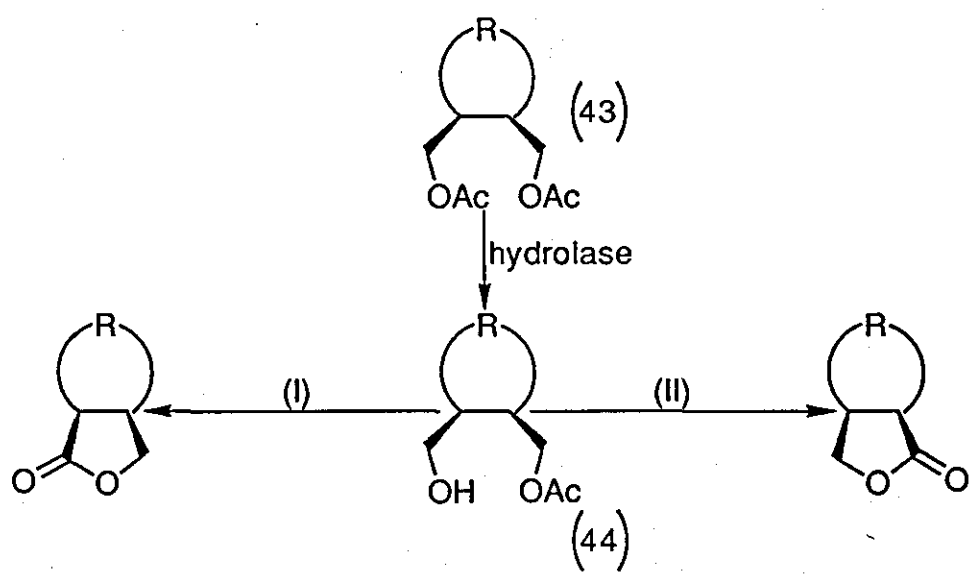
(II) Acylate diesters.

For the acylate diesters of *meso* cyclicdiols, just one example of the enzymatic hydrolysis leading to an optically enriched alcohol will be given.[31,32]

Both Kasel *et al*[31] and Schneider *et al*[32] performed the enzymatic hydrolysis on various acylate *meso* 1,2-cycloalkanediols. Kasel *et al* tended to concentrate on varying the acylate group, where Schneider *et al* made a comparison between the efficiencies of pig liver esterase *verses* porcine pancreatic lipase in the hydrolyses. The results obtained by Schneider *et al* are shown in Scheme 15 and Table 6.

It is clear from Table 6, that both the chemical yields and enantiomeric excesses for the half esters (44), were far superior for porcine pancreatic lipase-catalysed hydrolyses, as compared to those for pig liver esterase. The authors do not quote any absolute configurations, but state that they intended to determine these by the conversion of the half esters to the known lactones, as shown in Scheme 15. These lactones are the same as those prepared by Sabbioni and Jones in their pig liver esterase-catalysed hydrolysis of the *meso* diesters[25] (28). The hydrolysis of (43) was expected to provide a good route to preparing the cyclopentane lactone in good enantiomeric excess, a product not available through the hydrolysis of (28) (entry 4 of Table 6).

Scheme 15.



(I) Oxidation - lactonisation.

(II) Protection - hydrolysis - oxidation - lactonisation.

Table 6. Results of the P.L.E. *vs* P.P.L.-catalysed hydrolysis of (43).

Nº	R	Product.		% Yield.		% e.e.	
		P.L.E.	P.P.L.	P.L.E.	P.P.L.	P.L.E.	P.P.L.
1	$C(CH_3)_2$	(+)-44	(-)-44	69	75	20	40
2	CH_2	(+)-44	(+)-44	54	94	44	72
3	$(CH_2)_2$	44	(-)-44	62	97	0	88
4	$(CH_2)_3$	(+)-44	(-)-44	40	94	8	88
5	$(CH_2)_4$	(-)-44	(-)-44	31	81	4	78
6	$(CH_2CH=)_2$	(+)-44	(-)-44	43	96	40	100

1.4. Enantioselective hydrolase-catalysed esterification and transesterification reactions.

All the hydrolase-catalysed transformations described so far were performed in an aqueous solvent, with maybe a small percentage of an organic co-solvent present to overcome solubility problems. In such a system, the acting nucleophile, water, is in vast excess and therefore an irreversible hydrolysis occurs.[33] It has been shown that many hydrolases sustain their catalytic activity when used in anhydrous organic solvents, or with just a small percentage of water present.[34] In addition to the hydrolysis reaction, hydrolases should be able to catalyse different transformations, where compounds other than water serve as the nucleophile. An alcohol, for example would promote an esterification or transesterification reaction. Many hydrolases, in particular the lipases, also maintain a high degree of stereoselectivity in their reactions,[35] thus providing a new route to optically active acids, alcohols and esters.

The advantages of a lipase-catalysed resolution in an organic medium, compared to those in water are:

(I) There is no need to prepare the ester prior to resolution and hence one step is removed.

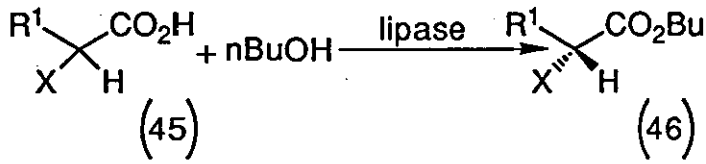
(II) Lipases tend to be more stable in organic solvents than in water.[36]

(III) Some substrates, or products, are unstable in aqueous solutions, *i.e.*, towards racemisation, but are stable in organic solvents.

Examples of such esterification and transesterification reactions, are shown below.

1.4.1. Stereoselective lipase-catalysed esterification.

Scheme 16.



(45) (46)

No	R^1	X	Solvent
1	CH_3	Br	hexane
2	CH_3	Cl	
3	Ph	Cl	1:1hexane: butyl ether
4	Ph	Br	

Kirchner *et al* reported the use of the yeast lipase, *Candida cylindracea*, in the resolution of α-halogenated acids (45), *via* the esterification with n-butanol,[37] as shown in Scheme 16 and Table 7. For entries 1 and 2 of Table 7, anhydrous hexane was employed as the solvent and excellent enantiomeric excesses were obtained for the esters (46), at 40 to 45% conversion. When the reaction was taken to 70% conversion, the resolved acids could be isolated with 95% plus enantiomeric excesses. For entries 3 and 4 of Table 7, a (1:1) hexane : butyl ether solvent was used as the reaction medium, because the acids were insoluble in pure hexane. The enzymatic esterification was also found to be extremely slow unless 0.1% of water was added to the reaction mixture. Excellent enantiomeric excesses were obtained for the esters (46), but at a much lower percent conversion.

Table 7. Results in the *Candida cylindracea* lipase-catalysed esterification of (45) with n-butanol.

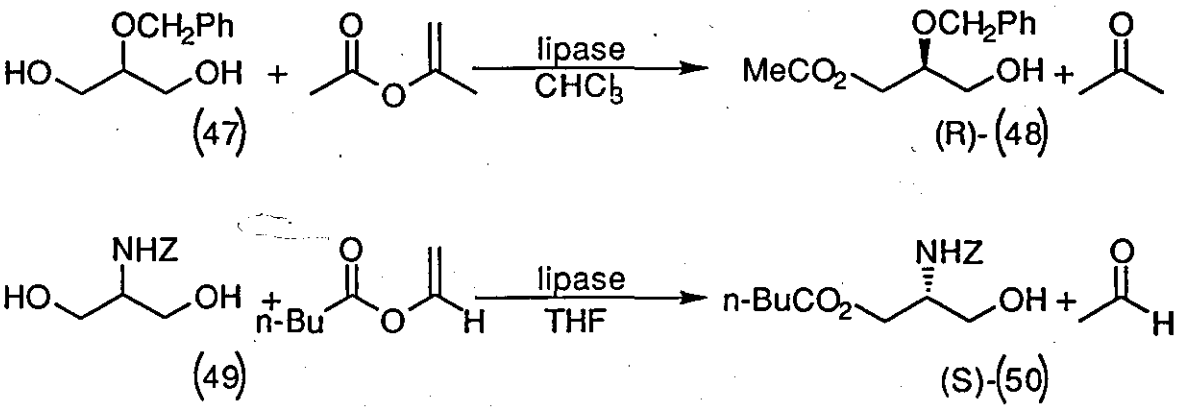
Nº	% Conv^n.	% Yield.	Isomer.	% e.e.
1	45	88	R	96
2	42	87	R	95
3	8	82	R	99
4	20	81	R	99

1.4.2. Enantiotopic lipase-catalysed transesterification.

The major problem with the lipase-catalysed transesterification reaction stems from the reversibility of the transformation, which leads to very slow reactions and often, non-reproducible results.[38] One way of solving this problem

is to make the reaction irreversible. This may be achieved by employing an enol ester as the acyl transfer reagent.[38,39] Upon reacting, the leaving enol group rapidly tautomerises to the carbonyl compound, which does not undergo the reverse reaction. An example where such a process has been used, was by Wong *et al*[40] in their enantioselective acylation of *meso* 1,3-diols (47) and (49).

Scheme 17.



Scheme 17 illustrates the two transesterification reactions they performed. In the first example, a *Pseudomonas* lipase was used and the monoacetate (48), was isolated in 53% yield, with an enantiomeric excess of 96%. The reaction was allowed to continue until all the diol (47) had been consumed. With the 2-*N*-(benzyloxycarbonyl)serinol derivative (49), porcine pancreatic lipase was used to catalyse the transesterification, resulting in the half ester (50) being isolated in 77% yield and >97% enantiomeric excess. Both of these results offer an improvement over that obtained in the lipase-catalysed hydrolysis of the respective diester compounds.

In our work we intended to perform various hydrolase-catalysed transformations on three substrates:-

(I) In an extension to the work of Bianchi *et al*,[15] we performed the lipase-catalysed hydrolysis of n-butyl 4,5-epoxypentanoate. Here the ester moiety was removed one carbon atom further away from the chiral centre.

(II) Both the hydrolase-catalysed hydrolysis and transesterification were performed on the *meso* 2,3 epoxybutan-1,4-diol system.

(III) The lipase-catalysed hydrolysis of the prochiral 2-butanoyloxymethyl-2,3-epoxypropan-1-yl butanoate diester was performed.

In **Chapter 2** the results obtained in these reactions are set out and discussed.

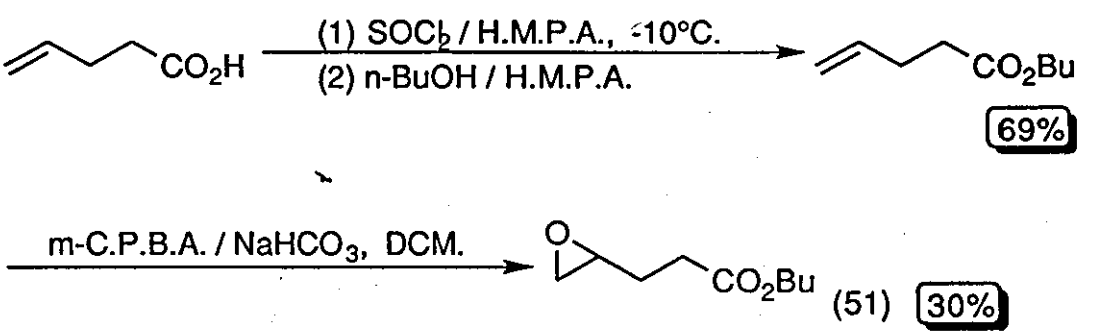
Chapter 2. Enantioselective lipase-catalysed transformations of epoxy esters.

2.1. Lipase-catalysed hydrolysis of racemic n-butyl 4,5-epoxypentanoate.

The lipase-catalysed hydrolysis of n-butyl 4,5-epoxypentanoate was carried out as an extension to the work performed by Bianchi *et al*, as described in Scheme 6 of **Chapter 1.**[15] They obtained an enantiomeric excess of 90% plus, in the lipase-catalysed hydrolysis of racemic n-butyl 3,4-epoxybutanoate. We considered it interesting to see how removing the ester moiety one carbon atom further away from the chiral centre would effect the enantiomeric excess of the resolved substrate.

To this end we prepared the (R,S)-n-butyl 4,5-epoxypentanoate (51), from the commercially available 4-pentenoic acid (Scheme 18). Epoxidation of n-butyl 4-pentenoate proved problematic, the terminal alkene reacting slowly with m-chloroperoxybenzoic acid. The epoxidation was also performed using the method of Heaney,[41] employing urea-hydrogen peroxide. This proved reactive, but the increased acidity of the reaction mixture, even with a large excess of disodium hydrogen phosphate as a buffer, resulted in opening of the epoxide and consequently a reduced yield of epoxide (51) was obtained.

Scheme 18.



The porcine pancreatic lipase-catalysed hydrolysis of n-butyl 4,5-epoxypentanoate was performed using the procedure employed by Bianchi *et al*,[15] with porcine pancreatic lipase being added to a vigorously stirred solution of the substrate, in an aqueous phosphate buffer (0.05 M, pH 7.0), at 20°C. On the addition of the lipase, a drop in pH was anticipated due to the formation of 4,5-epoxypentanoic acid (52). No fall in pH was observed, but it was evident from gas chromatography studies that the hydrolysis was proceeding, as n-butanol was being formed. As the extent of the reaction could not be calculated from the amount of base required to neutralise the acid produced, an alternative correlation was required. Standard solutions, containing varying amounts of n-butanol and

n-butyl 4,5-epoxypentanoate (51) were prepared and analysed by gas chromatography. A calibration curve of percent composition *versus* the percent conversion was plotted, and subsequently used as a reference in the analysis of the reaction mixture. Scheme 19 shows the proposed hydrolysis reaction path, and Table 8 presents the results obtained, at various percent conversions.

Scheme 19.

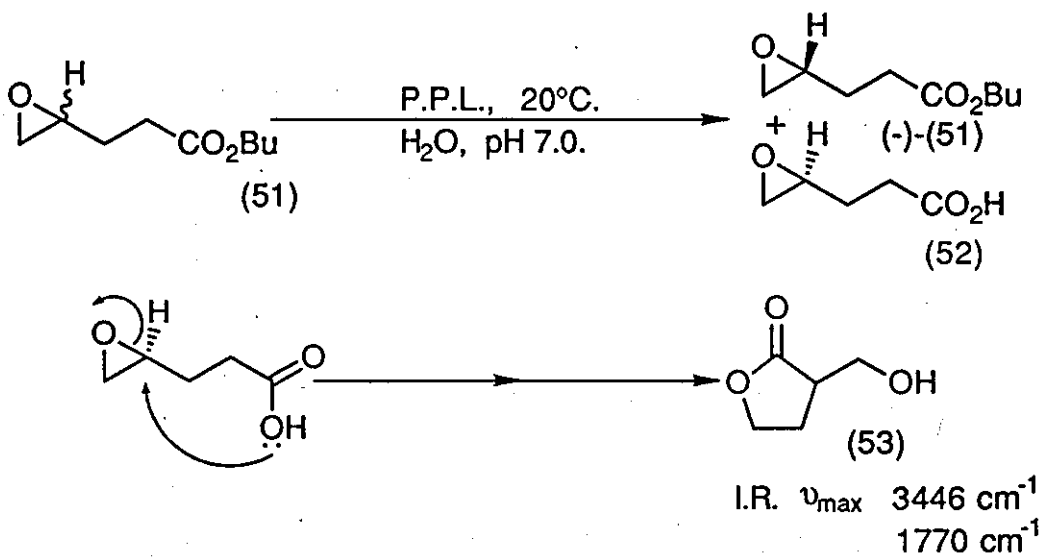


Table 8. Results in the porcine pancreatic lipase-catalysed hydrolysis of racemic n-butyl 4,5-epoxypentanoate.

Nº	% Conversion.	Time / hrs.	% Yield[1].	$[\alpha]_D^{20}$.	% e.e.
1	30	23	78	-6.4	49
2	50	50	78	-7.9	60
3	60	80	77	-8.2	63
4	70	144	66	-8.3	64

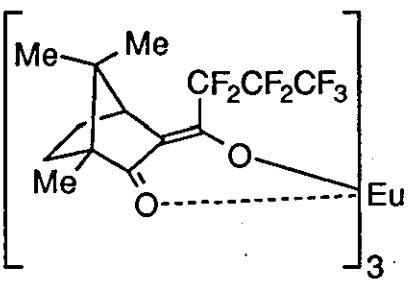
[1]Yield calculation based on % conversion.

It is evident from Table 8, that the course of the hydrolysis proceeded as expected for a kinetic resolution, with the rate of hydrolysis decreasing significantly at 50% conversion, due to the reactive enantiomer being removed.

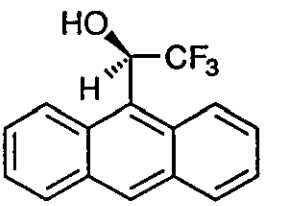
The enantiomeric excess of the resolved substrate could not be calculated directly by either ^1H N.M.R. spectroscopic studies with the chiral shift reagents[42] europium D-3-heptafluorobutyrylcamphorate (68), or (R)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol (69) (Figure 3), or by supercritical fluid

chromatography with a chiral α-cyclodextrin column.[43] Enantiomeric excesses were determined by N.M.R. spectroscopic studies on the diastereomeric Mosher's ester derivative (55), prepared as shown in Scheme 20.

Figure 3. Chiral shift reagents.

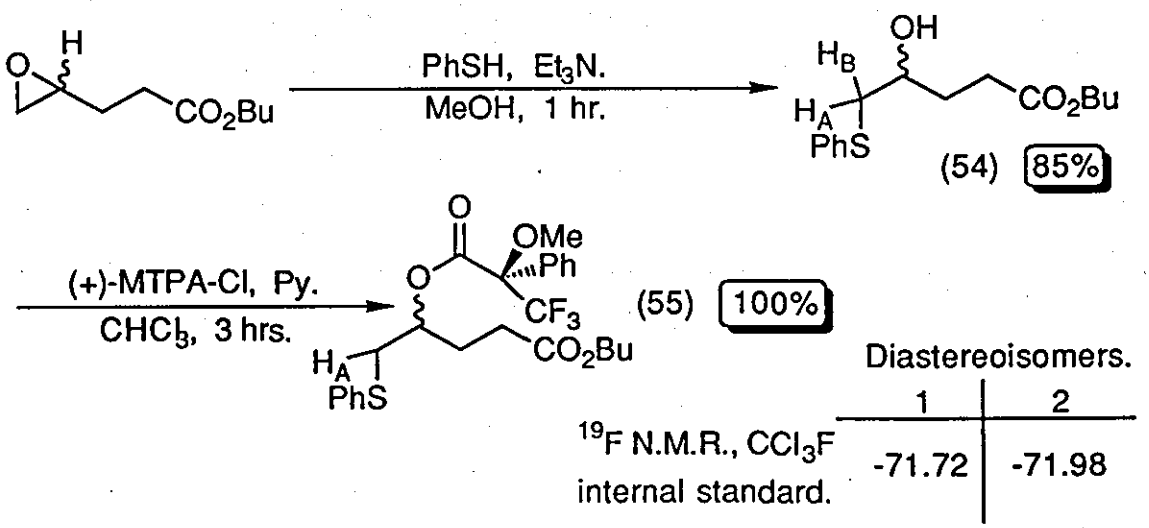


(68)



(69)

Scheme 20.



Diastereoisomers.

	1	2
^{19}F N.M.R., CCl_3F internal standard.	-71.72	-71.98

The ring opening of the epoxide was successfully performed, in good yield, employing the method of Corey *et al*,[44] with an alkaline solution of thiophenol. In the ^1H N.M.R. spectrum of n-butyl 4-hydroxy-5-phenylthiopentanoate (54), no peaks corresponding to the product from ring opening of the epoxide at the 4-position were observed. The protons α to the phenylthio group, H_A and H_B, were clearly visible, at δ 2.88 and 3.11 p.p.m., as the expected double-doublets (J_{AX} = 3.91 Hz, J_{BX} = 8.37 Hz and J_{AB} = 13.73 Hz). Interestingly, the hydroxide proton was seen as a broad doublet, at δ 2.67 p.p.m. (J = 2.83 Hz). When the reaction was performed on optically enriched epoxide (51) (starting from n-butyl 4,5-epoxypentanoate with an $[\alpha]_D^{20}$ of -8.2°), the alcohol (54) obtained had an $[\alpha]_D^{20}$ of 14.2°. Both the racemic and optically enriched alcohol (54) were converted to the Mosher's ester (55), in quantitative yields, using the standard procedure as defined by Mosher *et al*.[45] The enantiomeric excess could

be calculated from either the ^{1}H or ^{19}F N.M.R. spectra. In the ^{1}H N.M.R. spectrum, the enantiomeric excesses were calculated from the integration of the two diastereoisomer peaks associated with either the methoxy group (δ 3.53 and 3.60 p.p.m.) or one of the protons α to the phenylthio group, H_A (δ 2.97 and 3.07 p.p.m.). In the ^{19}F N.M.R. spectrum (with trichlorofluoromethane as the internal standard), the enantiomeric excesses were calculated from the integration of the two diastereoisomer peaks, at δ -71.72 and -71.98 p.p.m. As shown on Table 8, at 60% conversion, an enantiomeric excess of 63% was achieved. This value did not increase to any significant extent by raising the percent conversion to 70%.

As there was no perceptible drop in pH during the hydrolysis, it was considered that as 4,5-epoxypentanoic acid was produced, it was undergoing rapid intramolecular ring opening of the epoxide, at the 4-position, to yield γ-methanol-γ-butyrolactone (53). Scheme 19 shows a plausible mechanism for such a process, involving nucleophilic addition of the acid moiety to the epoxide. After purification of the resolved substrate, the residual oil had an infrared spectrum characteristic of lactone (53) with bands at υ_{max} 3446 cm^{-1} (OH) and υ_{max} 1770 cm^{-1} (C=O). Further attempts to purify this oil, to yield a clean sample of the lactone, proved unsuccessful and hence the by-product was not fully characterised.

When the porcine pancreatic lipase-catalysed hydrolysis of n-butyl 3,4-epoxybutanoate (14) was performed, taking the percent conversion to 63%, an enantiomeric excess of 82% was obtained for epoxybutanoate (R)-(14). Comparing this result to that obtained in the hydrolysis of n-butyl 4,5-epoxypentanoate (51), at 60% conversion, epoxypentanoate (-)-(51) was isolated with a ~20% decrease in enantiomeric excess. This result is perhaps as would be expected, as the chiral centre is being removed one carbon atom further away from the ester moiety. A similar, but less pronounced result was observed by Ladner and Whitesides in their work on the porcine pancreatic lipase-catalysed hydrolysis of various epoxy acylate esters (1),[8] as described in **Chapter 1**, Scheme 2 and Table 1. Entries 3 and 10 on Table 1 show how, on removing the acyl moiety one carbon atom further away from the chiral centre of the epoxide, a drop in enantiomeric excess of ~15% was observed.

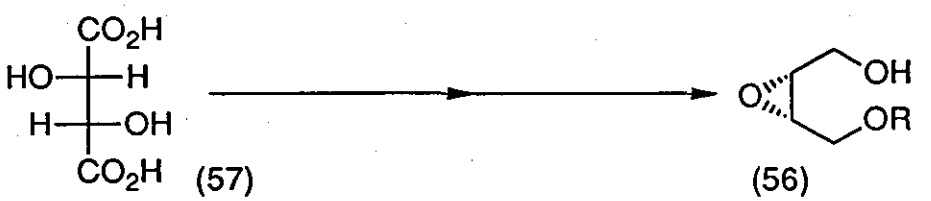
Although the absolute configuration of the epoxypentanoate (-)-(51) was not determined, it can be predicted with a high degree of confidence to have the (R)-configuration, as it was the (S)-enantiomer of (14) which was hydrolysed preferentially by the porcine pancreatic lipase. Although removing the ester moiety one carbon atom further from the epoxide may have decreased the enantiomeric excess by 20%, it is unlikely to have reversed the enantioselectivity of (S)-hydrolysis.

Performing the standard control with the denatured porcine pancreatic lipase and 100 mg of the n-butyl 4,5-epoxypentanoate, resulted in a 98% recovery of the substrate, after 60 hours. The recovered substrate was shown to be pure by ^{1}H, ^{13}C N.M.R. spectra and gas chromatography analysis, and therefore it does not appear that any non-enzymatic hydrolysis occurred.

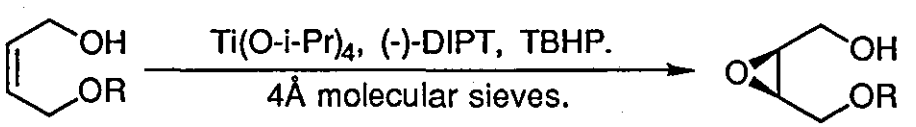
2.2. Lipase-catalysed routes to the preparation of enantiomerically enriched 4-alkanoyloxy-2,3-epoxybutan-1-ol.

Epoxides with the general formula (56) have proved useful as synthetic intermediates. They have been prepared from tartaric acid[46] (57) and more recently, by the asymmetric Sharpless epoxidation of mono-substituted allylic diols (58), R = t-BuMe$_2$Si,[47] t-BuPh$_2$Si[48] or 4-BrC$_6$H$_4$CH$_2$,[49] as shown in Scheme 21.

Scheme 21.



(57) (56)

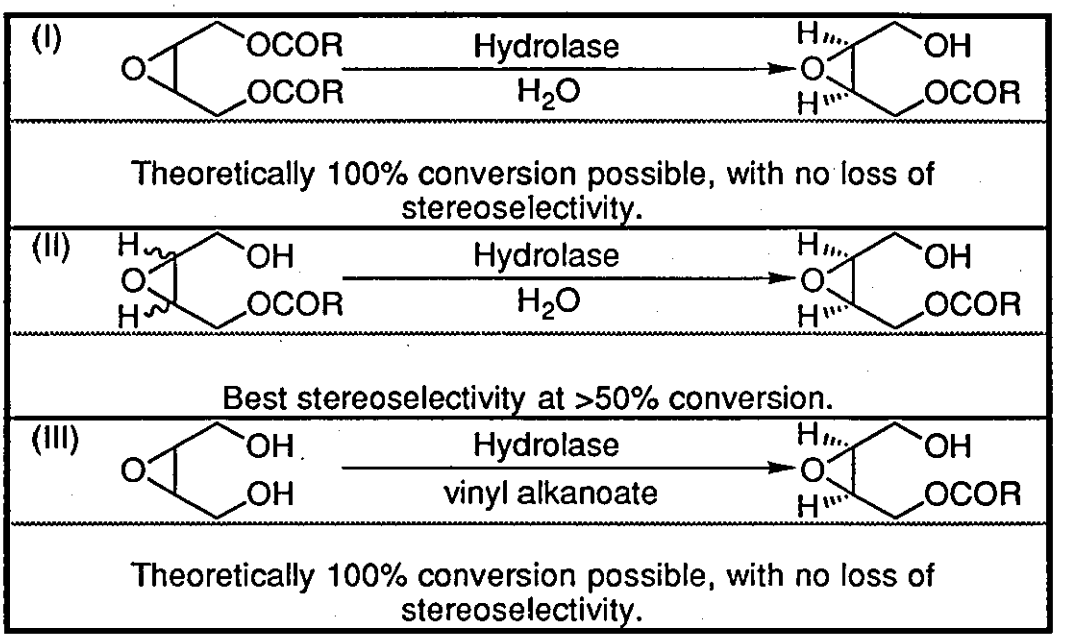


(58) (56) e.e. ≤90%.

The asymmetric Sharpless epoxidation of *trans*-allylic alcohols has been shown to be very efficient and widely applicable.[50] In the asymmetric epoxidation of substrates bearing a *cis* electron-withdrawing substituent at the C-3 position, it is known that the epoxidation proceeds slowly and without complete enantioselectivity.[51]

It was realised that there were several hydrolase mediated routes which would lead to the preparation of epoxides with the general formula (56), where R was an ester moiety. The three routes which we chose to investigate were; (I) the enantioselective hydrolase-catalysed hydrolysis of various *meso* 2,3-epoxybutan-1,4-diyl dialkanoate esters, (II) the enantioselective hydrolase-catalysed hydrolysis of racemic 4-alkanoyloxy-2,3-epoxybutan-1-ol and (III) the enantioselective hydrolase-catalysed transesterification of vinyl alkanoate esters with *meso* 2,3-epoxybutan-1,4-diol (Scheme 22).

Scheme 22.



2.2.1. Enantioselective hydrolase-catalysed hydrolysis of *meso* 2,3-epoxybutan-1,4-diyl dialkanoate esters.

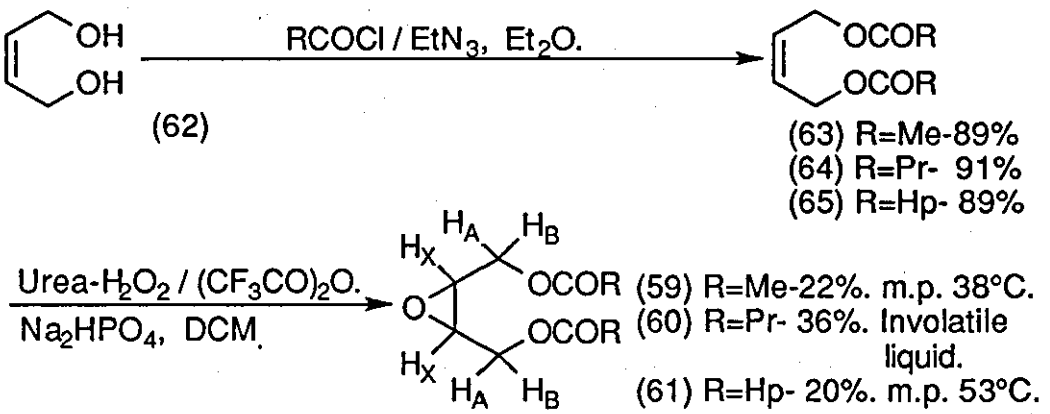
2.2.1-(I). Preparation of *meso* 2,3-epoxybutan-1,4-diyl dialkanoate esters (59), (60) and (61).

The ideal hydrolase-catalysed route to the preparation of enantiomerically enriched 4-alkanoyloxy-2,3-epoxybutan-1-ol was considered to be *via* the enantioselective hydrolysis of *meso* 2,3-epoxybutan-1,4-diyl dialkanoate esters, as shown in Scheme 22-(I). As *meso* diesters are prochiral compounds, the hydrolysis could be taken to 100% conversion with no detrimental effect to the enantiomeric excess of the obtained 4-alkanoyloxy-2,3-epoxybutan-1-ol esters.

The *meso* 2,3-epoxybutan-1,4-diyl dialkanoate esters chosen to investigate were the diacetate (59), dibutanoate (60) and dioctanoate (61). These were chosen as a consequence of the results obtained by Ladner and Whitesides, in their lipase-catalysed hydrolysis of the glycidol esters (1),[8] where an improvement in the enantiomeric excesses for the resolved substrates was observed with longer acyl groups. Scheme 23 shows how the epoxydiesters (59), (60) and (61) were initially prepared from commercially available *cis*-2-buten-1,4-diol (62). The *cis*-2-buten-1,4-diol was determined by gas chromatography analysis of the bis(trimethylsilyloxy) derivative to be 95% pure, with the remaining 5% being the *trans*-isomer. This level of impurity was considered to be too high, as the formed *trans*-2,3-epoxybutan-1,4-diyl dialkanoate esters could also act as

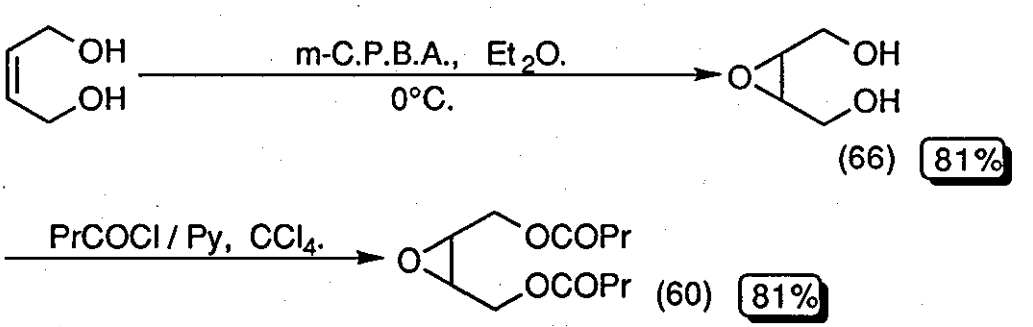
substrates for the hydrolases, leading to possible inaccuracies in the results, particularly with respect to the optical rotation data. The purity was improved to ≥99% by fractional distillation of the *cis*-2-buten-1,4-diol (62) using a spinning-band column. In all cases, esterifications of the diols proceeded smoothly to yield the diesters (63), (64) and (65) in good yields. Attempted epoxidations of these substrates with m-chloroperoxybenzoic acid all proved extremely slow, and so the epoxidations were accomplished with urea-hydrogen peroxide,[41] though in low yields of 20-36%.

Scheme 23.



A much improved method for forming the *meso* epoxydiesters was that shown in Scheme 24. Here the method of Schloss and Hartman[52] for the epoxidation of the *cis*-2-buten-1,4-diol (62) was employed, which yielded *meso* epoxydiol (66) as a colourless crystalline solid in 81% yield. The added advantage of preparing the substrates *via* this method was that any of the *trans* product could be easily be removed by recrystallisation of *meso* epoxydiol (66). Esterification of *meso* epoxydiol (66) with butanoyl chloride in pyridine and anhydrous carbon tetrachloride, afforded *meso* epoxydiester (60) in good yield.

Scheme 24.

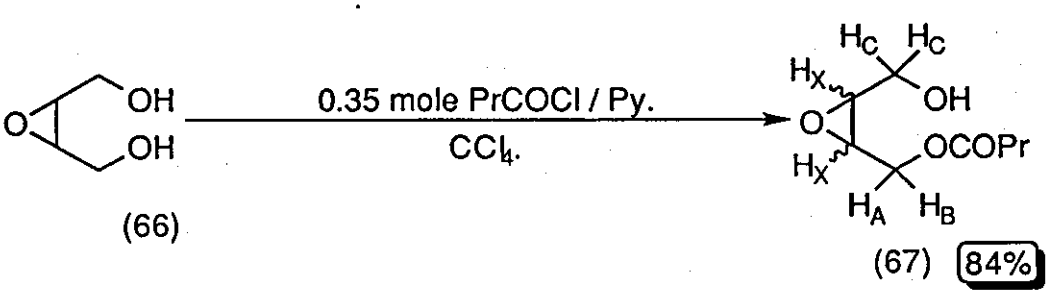


The prochirality of the *meso* epoxydiesters was clearly confirmed in their ^{1}H N.M.R. spectra. For *meso* 2,3-epoxybutan-1,4-diyl dibutanoate (60), the protons β to the epoxide ring, H_A and H_B, were observed as two clearly distinguishable double-doublets, at δ 4.11 and 4.35 p.p.m. (J_{AX} = 3.86, J_{BX} = 6.58 Hz and J_{AB} = 12.34 Hz). The protons α to the epoxide ring, H_X, at δ 3.28 p.p.m., were seen as a distorted quintet ($J_{apparent}$ = 3.90 Hz). Similar coupling patterns were observed for epoxydiesters (59) and (61).

2.2.1-(II). Preparation of racemic 4-butanoyloxy-2,3-epoxybutan-1-ol (67).

As an aid to enantiomeric excess calculations, a sample of racemic 4-butanoyloxy-2,3-epoxybutan-1-ol (67) was prepared. This was achieved in good yield by the partial esterification of *meso* epoxydiol (66), as shown in Scheme 25. In the ^{1}H N.M.R. spectrum of (67), the two protons α to the acyl moiety, H_A and H_B, were clearly visible as two double-doublets, at δ 4.15 and 4.34 p.p.m. (J_{AX} = 5.17 Hz, J_{BX} = 5.65 Hz and J_{AB} = 12.20 Hz). The signal associated with the two protons α to the hydroxy group, H_C, appeared as a doublet, at 3.82 p.p.m. (J_{CX} = 4.93 Hz). The protons α to the epoxide ring, H_X, at δ 3.24 p.p.m., were observed as a distorted sextet ($J_{apparent}$ = 4.83 Hz).

Scheme 25.



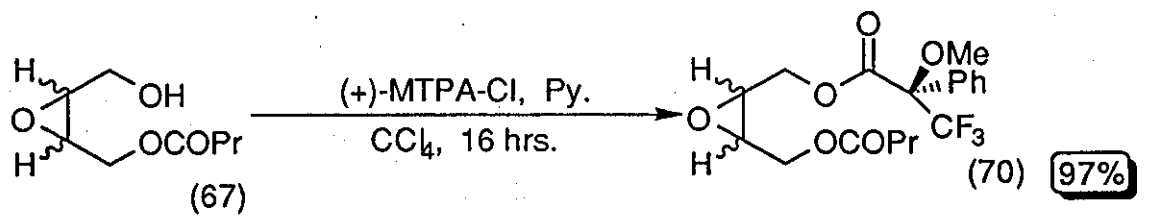
(66) (67) 84%

^{1}H N.M.R. spectroscopic studies on racemic epoxymonoester (67), with the chiral shift reagent europium D-3-heptafluorobutyrylcamphorate (68), gave an appreciable splitting of the signal associated with the α-methylene of the ester moiety, with the triplets of the two enantiomeric compounds being separated by the chiral shift reagent, but not sufficiently so that the signal could be accurately integrated. A similar situation was observed with the shift reagent, (R)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol (69) (Figure 3).

As the enantiomeric excess could not be calculated directly, the diastereomeric Mosher's ester derivative (70) was prepared using the standard procedure as defined by Mosher *et al*[45] (Scheme 26). From the ^{1}H N.M.R. spectrum of the Mosher's ester (70), the signals associated with the two

diastereoisomers can be distinguished. For example, two singlets at δ 3.57 and 3.58 p.p.m. and overlapping triplets at δ 2.32 and 2.33 p.p.m., due to the O-methoxy group and α-methylene of the ester moiety respectively are evident, but their integrations were not feasible. The diastereomeric excess of Mosher's ester (70) and hence the enantiomeric excess of the epoxymonoester (67), was calculated by integration of the two diastereomeric peaks at δ -72.155 and -72.208 p.p.m., in the ^{19}F N.M.R. spectrum (with trichlorofluoromethane as the internal standard).

Scheme 26.



Diastereoisomers.

	1	2
^{19}F N.M.R., CCl_3F internal standard.	-72.155	-72.208

2.2.1-(III). Hydrolase-catalysed hydrolysis of *meso* 2,3-epoxybutan-1,4-diyl dibutanoate (60).

All the hydrolyses described in Tables 9, 10 and 11 were performed with 150-250 mg of the *meso* 2,3-epoxybutan-1,4-diyl dibutanoate (60), in an 0.05 M aqueous phosphate buffer (pH 7.0, 15 cm^3) and with 5-15 mg of the respective hydrolase. The hydrolyses were carried out by adding the hydrolase to a vigorously stirred solution of the epoxydiester. The pH of the solution was maintained at 7.0 by the addition of 1.0 M sodium hydroxide solution, from a Metrohm 665 Dosimat in conjunction with a Metrohm 691 pH meter. The percent conversion of the reaction was calculated from the volume of sodium hydroxide solution required to neutralise the liberated butyric acid, assuming that the hydrolysis of only a single ester group was occurring. The reaction was terminated by rapid extraction with diethyl ether (5 x 10 cm^3), with epoxymonoester (67) being isolated after purification by flash chromatography, or preparative t.l.c. The enantiomeric excesses were initially determined *via* preparation of the Mosher's ester (70). After several results were obtained (entries 1, 6 and 12 from Table 9 and entries 1 and 3 from Table 10), a graph, Graph 3, of $[\alpha]_D^{20}$ *vs* enantiomeric excess was constructed, and a straight line, passing through the origin, was

obtained. Subsequent enantiomeric excesses were determined from this graph. Scheme 27 illustrates a typical hydrolysis reaction with porcine pancreatic lipase.

Scheme 27.

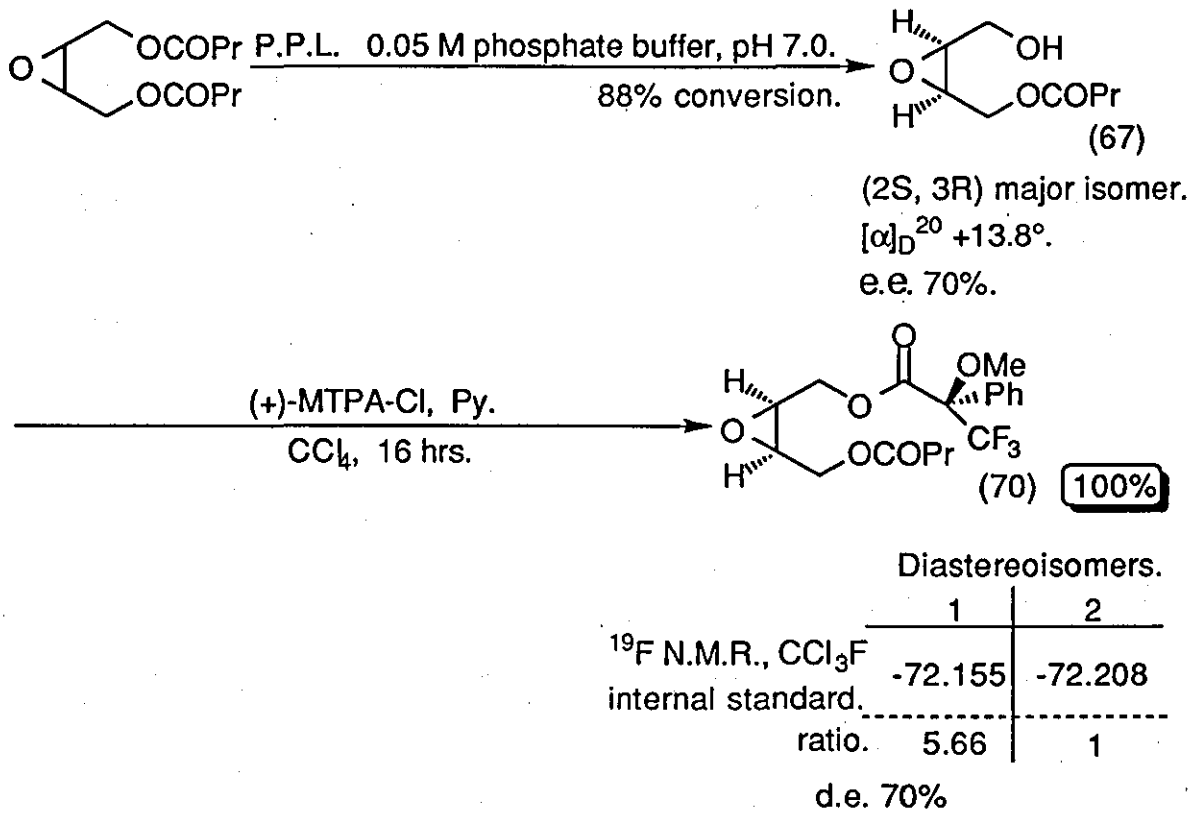


Table 9 lists the lipases which demonstrated an enantiotopic selectivity towards the hydrolysis of the pro-(S) ester of *meso* 2,3-epoxybutan-1,4-diyl dibutanoate, with the (2S, 3R)-4-butanoyloxy-2,3-epoxybutan-1-ol isomer being isolated in an enantiomerically enriched form. The absolute configuration was calculated by comparison to a compound prepared *via* the Sharpless epoxidation. This work is described in section **2.2.1-(V)**.

Graph 3. Graph of % enantiomeric excess [calculated from the Mosher's esters (70)] *vs* optical rotation for enantiomerically enriched epoxymonoester (67).

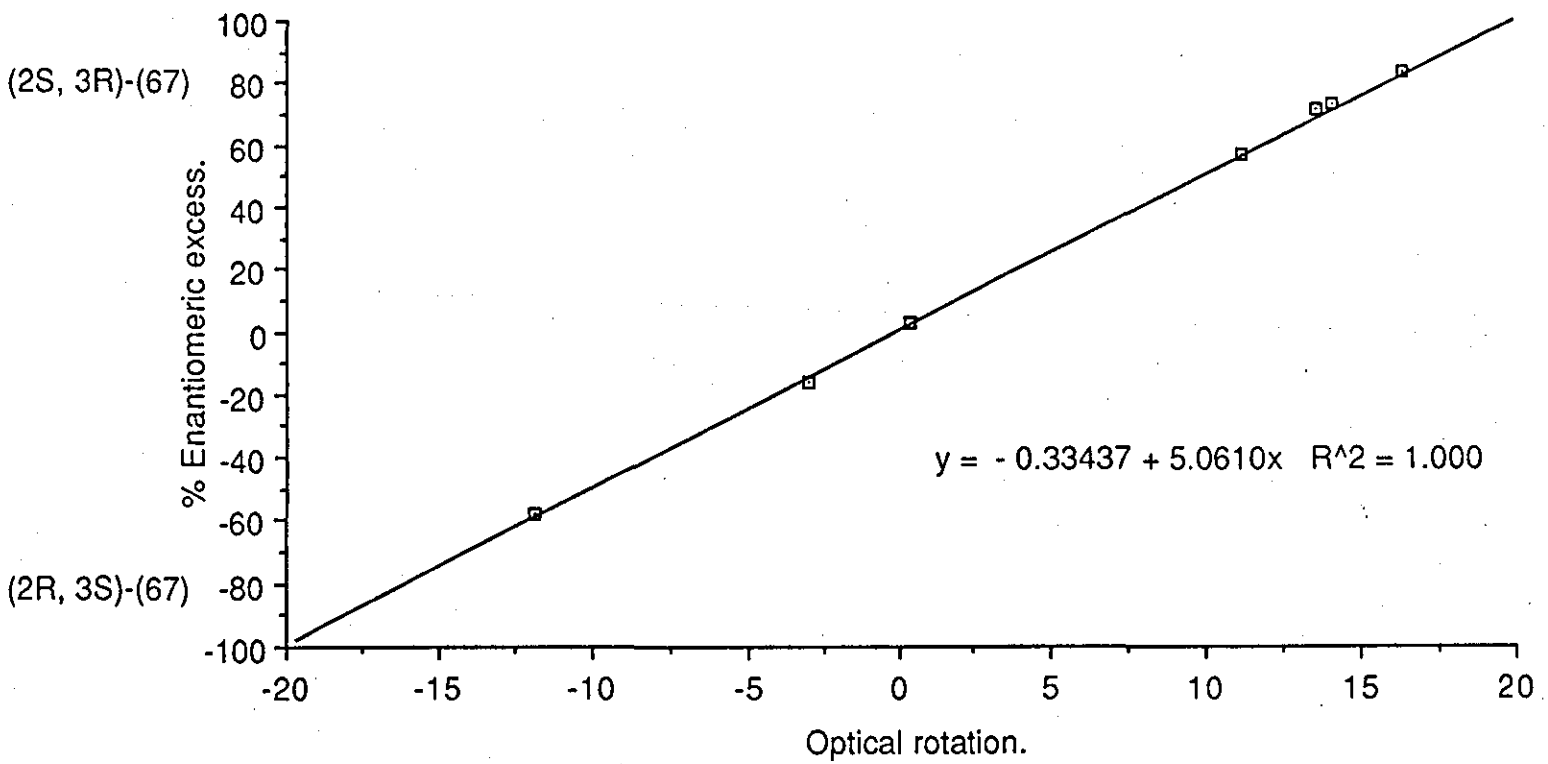


Table 9. Results of the lipase-catalysed hydrolysis of epoxydiester (60), leading to (2S, 3R)-4-butanoyloxy-2,3-epoxybutan-1-ol (67).

Nº	Hydrolase.	Conv^{n} %.[1]	Time hrs.	Temp °C.	Yield %.[2]	$[\alpha]_D^{20}$	e.e. %.
1	porcine pancreatic l.	88	1.6	20	62	+13.8	70
2	porcine pancreatic l.	78	2.0	4	61	+13.5	69
3	porcine pancreatic l.	94	1.0	35	65	+7.8	40
4	*Pseudomonas fluorescens* l.	100	0.2	20	83	+3.3	16
5	*Rhizopus niveus* l.	66	13.0	20	71	+10.7	54
6	*Rhizopus delemar* l.	79	6.0	20	86	+10.8	54
7	porcine pancreatic l.[3]	100	0.75	22	41	+2.1	11
8	*Geotrichum candidum* l.[3]	76	5.0	20	65	+1.3	7
9	*Mucor* l.[3]	80	2.0	20	73	+11.0	56
10	*Humicola laruginosa* l.[3]	73	2.5	20	49	+4.8	24
11	*Aspergillus* l [LIP F9].[3]	43	24	20	56	+1.8	9
12	*Rhizopus delemar* l.[3]	85	4.7	24	85	+13.3	68
13	*Rhizopus* l [LIP F1].[3]	82	4.5	20	59	+14.7	75
14	*Rhizopus* l [LIP F3].[3]	78	1.5	18	59	+15.8	77
15	*Rhizopus* l [LIP F4].[3]	88	6.0	19	75	+11.9	61

[1]The percent conversion was calculated from the volume of sodium hydroxide added, assuming that the hydrolysis of only a single ester group was occurring.

[2]The yield of the epoxymonoester (67) was calculated taking into account the amount of diester consumed.

[3]Lipase was immobilised.

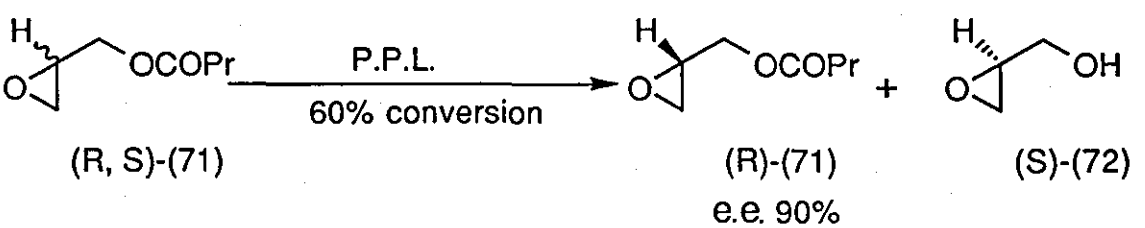
As is evident from Table 9, the best enantiomeric excess of 77%, for (2S, 3R)-4-butanoyloxy-2,3-epoxybutan-1-ol, was obtained with the immobilised *Rhizopus* lipase [LIP F3], entry 14 of Table 9. All *Rhizopus* lipases, entries 4, 5 and 12-15 of Table 9, afforded (2S, 3R)-epoxymonoester (67) in >50% enantiomeric excess and in yields varying from 59-86%. Porcine pancreatic lipase also demonstrated a relatively high enantiotopic selectivity towards the hydrolysis of the pro-(S) ester, with an enantiomeric excess of 70% being obtained at 88%

conversion, entry 1 of Table 9. This result is perhaps a little disappointing when compared to the results obtained by Ladner and Whitesides in their porcine pancreatic lipase-catalysed hydrolysis of the glycidol ester, racemic 1-butanoyloxy-2,3-epoxypropane (71)[8] (Scheme 28). The enantioselectivity of porcine pancreatic lipase towards epoxyester (71) was consistent with the results obtained in the hydrolysis of epoxydiester (60), with the (S)-enantiomer of epoxyester (71) and the pro-(S) ester of epoxydiester (60) being preferentially hydrolysed. A direct comparison of the enantiomeric excess obtained for (R)-epoxyester (71), and (2S, 3R)-epoxymonoester (67) is perhaps not strictly relevant, for two reasons.

(I) In Ladner and Whitesides work they were dealing with a kinetic resolution, whereas with the hydrolysis of the *meso* 2,3-epoxybutan-1,4-diyl dibutanoate, a different enantiomerically enriched product (2S, 3R)-epoxymonoester (67), was isolated. A better comparison would have been between the enantiomeric excesses obtained for the (S)-epoxyalcohol (72) and (2S, 3R)-epoxymonoester (67). Unfortunately Ladner and Whitesides did not quote any enantiomeric excesses for (S)-epoxyalcohol (72), but rather said that it could be obtained in high enantiomeric excess by carrying out the hydrolysis with a low conversion.

(II) As Ladner and Whitesides hydrolysis was a kinetic resolution, an improved enantiomeric excess for (R)-epoxyester (71) was obtained by increasing the extent of conversion to 60%. This method of improving the enantiomeric excess is not possible with a *meso* compound, assuming that only one of the ester moieties is being hydrolysed by the lipase. A direct comparison between the results would be possible if Ladner and Whitesides had quoted an enantiomeric excess for (R)-epoxyester (71), or (S)-epoxyalcohol (72) at 50% conversion.

Scheme 28.



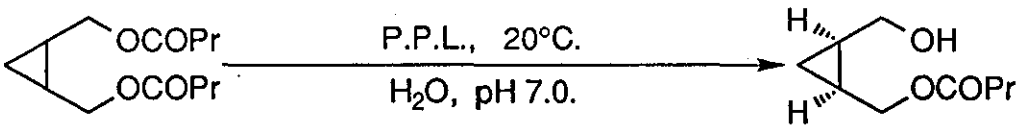
(R, S)-(71) (R)-(71) e.e. 90% (S)-(72)

The result for the porcine pancreatic lipase-catalysed hydrolysis of epoxydiester (60) may be compared to that obtained by Kasel *et al* in the hydrolysis of the analogous *meso* 1,2-dibutanoyloxycylopropanedimethanol (73)[31] (Scheme 29). In both cases, porcine pancreatic lipase exhibited an enantioselecivity towards the hydrolysis of the pro-(S) ester. The enantiomeric excesses for (2S, 3R)-(67) were somewhat disappointing compared to those

obtained for (1R, 2S)-(74), but some change in enantiotopic selectivity is to be expected as the active site of the porcine pancreatic lipase is unlikely to recognise the epoxide in the same way as the cyclopropane ring. The drop in enantiotopic selectivity was not as dramatic as that observed by Sabbioni and Jones in their pig liver esterase-catalysed hydrolysis of the analogous *meso* dicarboxylate esters (75) and (77),[25] as shown in Scheme 29. As well as a drop in enantiomeric excess of ~70% for (76) compared to (78), Sabbioni and Jones noted a complete reversal in enantiotopic selectivity, with the pig liver esterase preferentially hydrolysing the pro-(R) ester of (75) and the pro-(S) ester of (77).

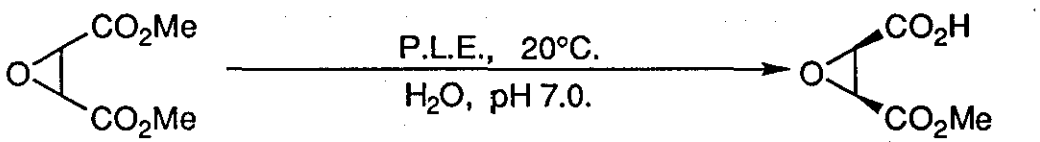
Scheme 29.

Kasel *et al.*

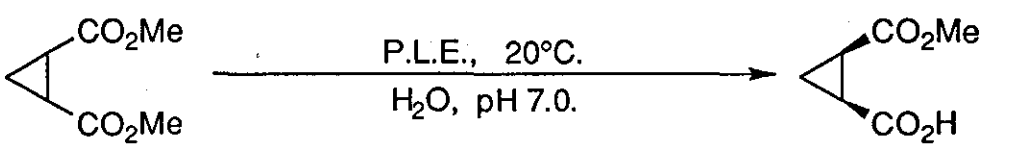


(73) (1R, 2S)-(74)
yield 84%.
e.e. 94%.

Sabbioni and Jones.



(75) (1S, 2R)-(76)
e.e. 31%.



(77) (1R, 2S)-(78)
e.e. >97%.

As the stereoselectivity of the lipase-catalysed hydrolysis of various racemic systems has been shown to improve at lower temperatures,[53] the hydrolysis of epoxydiester (60), with porcine pancreatic lipase, was performed at 4°C and 35°C, entries 2 and 3 of Table 9. As expected, at 35°C the rate of hydrolysis was seen to increase, with a corresponding drop in enantiomeric excess of 30%, compared to that obtained at 20°C. When the hydrolysis was carried out at 4°C, the rate of hydrolysis was noted to decrease, as anticipated, but

the enantiomeric excess for the recovered (2S, 3R)-epoxymonoester (67) remained the same as that at 20°C. As no improvement was obtained, the hydrolyses were performed at 20°C, as the rate of hydrolysis was faster.

With the notable exceptions of *Pseudomonas fluorescens* lipase, entry 4 and *Rhizopus delemar* lipases, entries 6 and 12 of Table 9, the rate of hydrolysis for the other lipases leading to (2S, 3R)-epoxymonoester (67), did not decrease dramatically approaching 100% conversion, as would be expected. Coupling this observation with the relatively low yields of epoxymonoester (67), and t.l.c. evidence that a significant quantity of the epoxydiester (60) remained approaching 100% hydrolysis, it suggests that the epoxymonoester (67) was also acting as a substrate to the lipases. The significance of this observation is expanded in section **2.2.2**, where examples of the hydrolysis of racemic epoxymonoester (67) are detailed, along with additional examples of the hydrolysis of *meso* epoxydiester (60) with porcine pancreatic lipase, at lower conversion.

Table 10. Results of the lipase-catalysed hydrolysis of (60), leading to (2R, 3S)-4-butanoyloxy-2,3-epoxybutan-1-ol (67).

Nº	Hydrolase.	Conv¤ %.[1]	Time hrs.	Temp °C.	Yield %.[2]	$[\alpha]_D^{20}$	e.e. %.
1	*Candida cylindracea* l.	100	1.6	24	68	-3.3	19
2	*Penicillium* l. [LIP F11].[3]	82	5.0	17	47	-9.9	50
3	*Penicillium* l. [LIP F12].[3]	70	7.25	20	74	-12.2	61

Prefixes as for Table 9.

Table 10 demonstrates the versatility of the lipase-catalysed hydrolysis of *meso* 2,3-epoxybutan-1,4-diyl dibutanoate (60), with the lipases listed showing an affinity towards the hydrolysis of the pro-(R) ester. The enantiotopic selectivity of these lipases were not as good as that demonstrated by porcine pancreatic lipase, with the immobilised *Penicillium* lipase [LIP F12] giving the best enantiomeric excess of 61% for (2R, 3S)-4-butanoyloxy-2,3-epoxybutan-1-ol (67). The results are never the less important as it showsthat both enantiomers of epoxymonoester (67) may be accessed directly from epoxydiester (60).

Table 11. Results of the hydrolase-catalysed hydrolysis of epoxydiester (60), leading to racemic 4-butanoyloxy-2,3-epoxybutan-1-ol (67).

Nº	Hydrolase.	Conv[n] %.[1]	Time hrs.	Temp °C.	Yield %.[2]	$[\alpha]_D^{20}$	e.e. %.
1	pig liver esterase	100	0.75	24	45	0	0
2	*Pseudomonas fluorescens* l.[3]	85	1.25	20	80	0	0
3	*Candida* l. [LIP F6].[3]	78	0.7	20	71	0	0
4	*Aspergillus usamii* l.[3]	0	24	20	—	—	—

Prefixes as for Table 9.

Table 11 lists the hydrolases which either hydrolysed the *meso* epoxydiester (60) non-stereoselectively, entries 1-3, or, as was the case with the immobilised *Aspergillus usamii* lipase, entry 4, did not hydrolyse the substrate at all. It is noteworthy that the pig liver esterase, entry 1, was an efficient catalyst for the hydrolysis, but was totally non-selective. Schneider *et al*[62] noted a similar low selectivity for the pig liver esterase-catalysed *versus* the porcine pancreatic lipase-catalysed hydrolysis of *meso* diesters (43), as detailed in Table 6 of **Chapter 1.**

2.2.1-(IV). Lipase-catalysed hydrolysis of *meso* 2,3-epoxybutan-1,4-diyl dibutanoate (60), in mixed solvent systems.

As many lipases are known to retain their catalytic activity in the presence of organic solvents,[34,35] it was considered interesting to see what effect changing the solvent in the hydrolysis of epoxydiester (60) would have on both the rate, and enantiotopic selectivity of the reaction. To this end, three solvent systems were chosen to investigate; (I) 1:1 aq. phosphate buffer : hexane, (II) 9:1 aq. phosphate buffer : *tert*-butanol and (III) 9:1 aq. phosphate buffer : dimethylsulfoxide. Table 12 lists the results obtained in the hydrolysis with porcine pancreatic lipase and immobilised *Rhizopus* lipase [LIP F1]. With entries 2 and 4, the 1:1 aq. phosphate buffer : hexane system and 9:1 aq. phosphate buffer : dimethylsulfoxide solvent system, the rate of hydrolysis was seen to double, with only a very slight drop in the enantiotopic selectivity. A different situation was observed with entry 3; the 9:1 aq. phosphate buffer : *tert*-butanol solvent system. Here both the rate of hydrolysis and enantiotopic selectivity were seen to drop significantly. As no improvement in the enantiotopic selectivity was observed, no advantage was seen to using the mixed solvent system as the rate of hydrolysis was fast enough in the purely aqueous system.

Table 12. Solvent effects in the lipase-catalysed hydrolysis of *meso* 2,3-epoxybutan-1,4-diyl dibutanoate (60).

Nº	Solvent system.	Relative rate.	% e.e.[1]	% e.e.[2]
1	phosphate buffer	10	70	75
2	1:1 buffer : hexane	22	68	—
3	9:1 buffer : t-BuOH	4.7	—	63
4	9:1 buffer : DMSO	18	—	73

[1]For porcine pancreatic lipase.

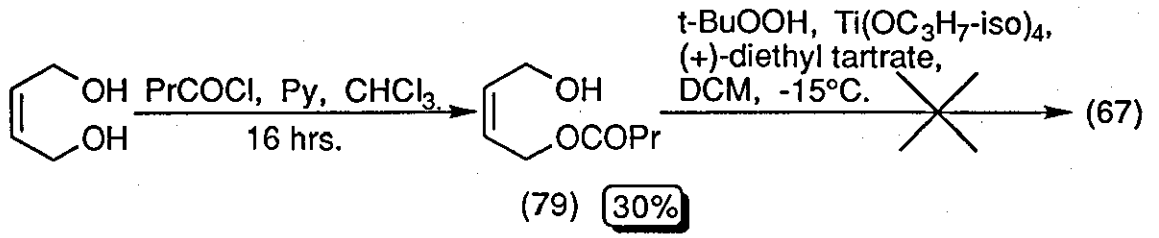
[2]For *Rhizopus* lipase [LIP F1].

Four control hydrolyses were performed using the following denatured lipases; porcine pancreatic lipase, *Rhizopus* lipase [LIP F1], *Penicillium* lipase [LIP F12] and *Rhizopus delemar* lipase. In all cases, after a stir time of 4 hours, no drop in the pH was observed and the *meso* 2,3-epoxybutan-1,4-diyl dibutanoate was recovered pure by ^{1}H and ^{13}C N.M.R. spectroscopic analysis.

2.2.1-(V). Absolute configuration determination of enantiomerically enriched 4-butanoyloxy-2,3-epoxybutan-1-ol (67), utilising the Sharpless epoxidation.

The absolute configuration of the enantiomerically enriched 4-butanoyloxy-2,3-epoxybutan-1-ol (67) was determined using the Sharpless epoxidation of an allylic alcohol. As the absolute configuration of the epoxide produced in the Sharpless epoxidation may be predicted,[54] it was initially considered that performing the Sharpless oxidation on mono-allylic ester (79) would provide the common compound epoxymonoester (67). Comparison of the $[\alpha]_D^{20}$ for this compound with that obtained for epoxymonoester (67) in the lipase-catalysed hydrolysis of epoxydiester (60) would indicate the absolute configuration. Unfortunately, several attempts at performing the Sharpless oxidation with (+)-diethyl tartrate on mono-allylic ester (79) all failed, and only unreacted starting material was recovered, as shown in Scheme 30.

Scheme 30.

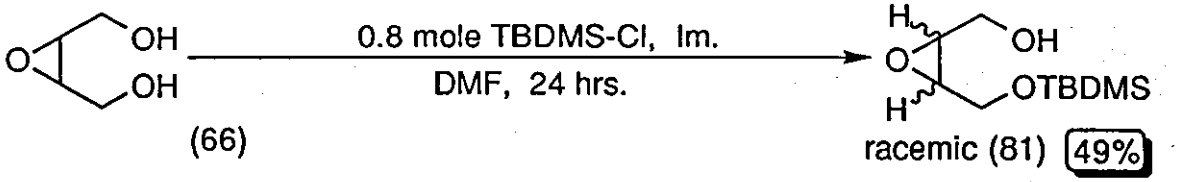


(79) 30%

Instead of forming epoxymonoester (67) directly by the Sharpless oxidation, the common compound 4-(tert-butyldimethylsilyloxy)-1-butanoyloxy-2,3-epoxybutane (83) was prepared (Scheme 31).

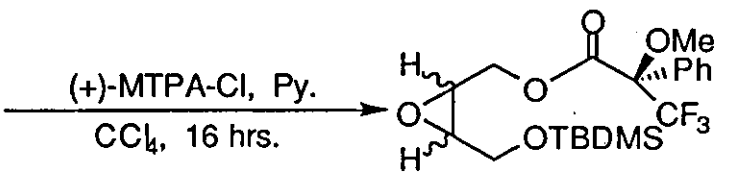
A racemic sample of epoxymonoether (81) was initially prepared to check whether the enantiomeric excess of an enantiomerically enriched sample could be determined. Treatment of 2,3-epoxybutan-1,4-diol (66) with 0.8 equivalents of *tert*-butyldimethylsilyl chloride, in the presence of imidazole in anhydrous DMF, afforded epoxymonoether (81) in moderate yield. Preparation of the Mosher's ester, under standard conditions,[45] afforded Mosher's ester (82) in quantitative yield. Although there was no visible differentiation between the two diastereoisomers in the ^{1}H N.M.R. spectrum of Mosher's ester (82), two well separated signals were clearly seen in the ^{19}F N.M.R. spectrum (Scheme 31). The Sharpless epoxidation of the mono-protected *cis*-diol (80), performed under standard conditions,[55] proceeded very slowly and afforded (2S, 3R)-epoxymonoether (81) with a 53% enantiomeric excess, as determined from its Mosher's ester (82). (2S, 3R)-4-(*tert*-Butyldimethylsilyloxy)-1-butanoyloxy-2,3-epoxybutane (-)-(83) was simply prepared by esterification of (2S, 3R)-epoxymonoether (81) with butanoyl chloride. It was found to have a negative optical rotation of -10.3°. When the equivalent compound was prepared from a sample of epoxymonoester (67), with a positive $[\alpha]_D^{20}$ and an enantiomeric excess of 50%, the resulting compound (+)-(83), was found to have a positive optical rotation of +7.6°. As the two samples of 4-(*tert*-Butyldimethylsilyloxy)-1-butanoyloxy-2,3-epoxybutane (83) had rotations of different signs, it shows that the sample of epoxymonoester (67) had the (2S, 3R)-absolute configuration. One discrepancy in this result was that the optical rotation for (+)-(83) was low compared to (-)-(83). This result suggests that some racemisation of epoxymonoester (67) or epoxymonoether (81) occurs during the preparation of (83).

Scheme 31.



(66)

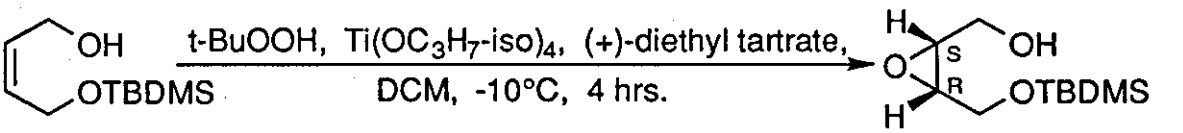
racemic (81) 49%



(82) 100%

Diastereoisomers.

	1	2
^{19}F N.M.R., CCl_3F internal standard.	-72.176	-72.253
ratio	1	1

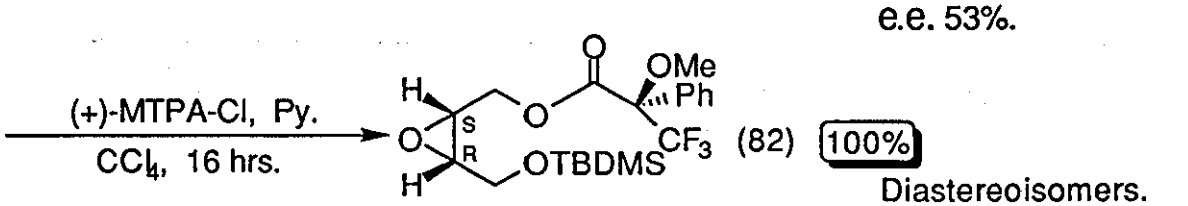


(80)

(2S,3R)-(81) 49%

$[\alpha]_D^{20}$ -12.1°.

e.e. 53%.

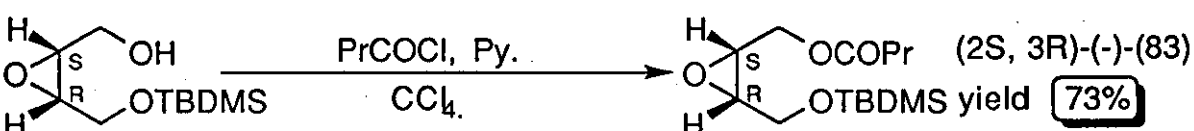


(82) 100%

Diastereoisomers.

	1	2
^{19}F N.M.R., CCl_3F internal standard.	-72.176	-72.253
ratio	3.26	1

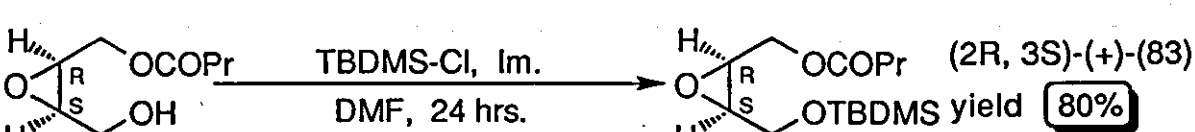
d.e. 53%.



(81)

(2S, 3R)-(-)-(83) yield 73%

$[\alpha]_D^{20}$ -10.3°



(67) $[\alpha]_D^{20}$ +9.9°

(2R, 3S)-(+)-(83) yield 80%

$[\alpha]_D^{20}$ +7.6°

2.2.1-(VI). Lipase-catalysed hydrolysis of *meso* 2,3-epoxybutan-1,4-diyl diacetate (59) and *meso* 2,3-epoxybutan-1,4-diyl dioctanoate (61).

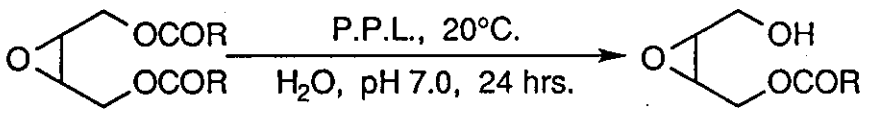
The porcine pancreatic lipase-catalysed hydrolysis of *meso* 2,3-epoxybutan-1,4-diyl diacetate (59) and *meso* 2,3-epoxybutan-1,4-diyl dioctanoate (61), were observed to be extremely slow. For epoxydiacetate (59), after 24 hours a conversion of 52% was achieved, with just a 4% hydrolysis being reached for epoxydioctanoate (61) in the same time period. After the usual aqueous work up for the reactions, the hydrolysis of epoxydiacetate (59) yielded just 3% of the epoxymonoacetate (84), whereas the hydrolysis of epoxydioctanoate (61) yielded no products, other than starting material (Scheme 32). These apparent anomalous results were attributed to the fact that both the *meso* epoxy-diacetate and -dioctanoate esters were crystalline solids at room temperature, whereas the *meso* epoxydibutanoate ester (60) was a mobile liquid. In the hydrolysis of *meso* epoxydibutanoate ester (60), an emulsion was formed between the substrate and aqueous buffer, with the lipase being active at the water-organic interface. As the other two substrates were solids, and poorly soluble in the aqueous system, it was considered that this water-organic interface was less likely to be formed, thus explaining the slower rate of hydrolysis. The poor yield of epoxymonoacetate (84), and lack of yield of epoxymonooctanoate (85), must be due to the epoxymonoesters being better substrates for the lipase, than their parent epoxydiesters. This could again stem from a solubility problem, with epoxymonoacetate (84) and epoxymonooctanoate (85) being more lipophilic than the epoxydiacetate (59) and epoxydioctanoate (61), and thus they form the water-organic interface more readily .

In an attempt to resolve this problem, the hydrolyses were performed in a biphasic, aq. buffer : hexane solvent system. As previously described, the hydrolysis of epoxydibutanoate (60) in this solvent system resulted in an increase in the rate of hydrolysis, with little change in the enantiotopic selectivity. As diesters (59) and (61) were soluble in hexane, the water-organic interface should be formed better, leading to faster rates of hydrolysis and improved yields of the epoxymonoesters (84) and (85). Scheme 32 shows the results of the hydrolyses of diesters (59) and (61) in the biphasic solvent system. As is evident, the rate of hydrolyses were seen to increase dramatically, especially with the epoxydioctanoate ester (61). Unfortunately, a significant increase in yield for the epoxymonoesters (84) and (85) was not observed. As Ladner and Whitesides[8] found that the best enantiomeric excesses were achieved with the butanoate ester, in the hydrolysis of the glycidol esters (1), it was considered that further time consuming investigations into the hydrolysis of diesters (59) and (61), would not

lead to any improvements in the results obtained in the lipase-catalysed hydrolysis of the epoxydibutanoate (60).

Scheme 32.

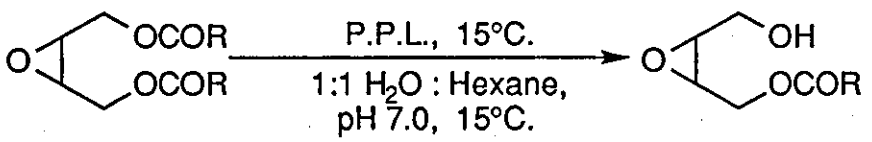
Porcine pancreatic lipase-catalysed hydrolysis in an aqueous solvent.



R = Me (59).
= Hp (61).

R = Me (84).
52% Conv^{n}, 3% yield.
R = Hp (85).
5% Conv^{n}, 0% yield.

Porcine pancreatic lipase-catalysed hydrolysis in a biphasic aqueous:hexane solvent system.



R = Me (59).
= Hp (61).

R = Me (84).
5.0 hrs.
86% Conv^{n}, 15% yield.

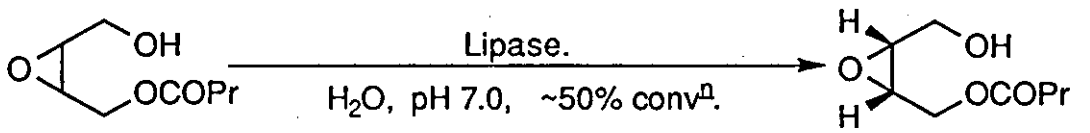
R = Hp (85).
1.5 hrs.
82% Conv^{n}, 4% yield.

2.2.2. Enantioselective lipase-catalysed hydrolysis of racemic 4-butanoyloxy-2,3-epoxybutan-1-ol (67).

The lipase-catalysed hydrolysis of racemic 4-butanoyloxy-2,3-epoxybutan-1-ol (67) was investigated for two reasons;
(I) to see if the resolved epoxymonoester (67) could be obtained with a high enantiomeric excess, and, perhaps more importantly,
(II) to determine which enantiomer of epoxymonoester (67) is hydrolysed preferentially, as this could have a marked effect on the enantiomeric excess of epoxymonoester (67) obtained in the hydrolysis of *meso* 2,3-epoxybutan-1,4-diyl dibutanoate (60), as described in section **2.2.1**.

Racemic-epoxymonoester (67) was prepared as previously describe in Scheme 25. The hydrolyses were performed in a similar fashion to that of the *meso* epoxydiesters (Scheme 33). As this was an example of a kinetic resolution, the conversions were taken to 50% plus, as this should give the best enantiomeric excess for the resolved substrate. The results are listed in Table 13.

Scheme 33.



racemic-(67). (2R, 3S)-(67).

Table 13. Results of the lipase-catalysed hydrolysis of racemic 4-butanoyloxy-2,3-epoxybutan-1-ol (67).

Nº	Lipase.	Conv^n %.[1]	Time hrs.	Temp °C.	Yield %.[2]	$[\alpha]_D^{20}$	e.e. %.
1	porcine pancreatic lipase.	55	10.5	20	79.[4]	-10.9	55
2	*Rhizopus* l. [LIP F3].[3]	57	13.5	20	80	-9.5	48
3	*Penicillium* l. [LIP F11].[3]	49	28	20	57	-1.9	10

[1]The percent conversion was calculated from the volume of sodium hydroxide added.

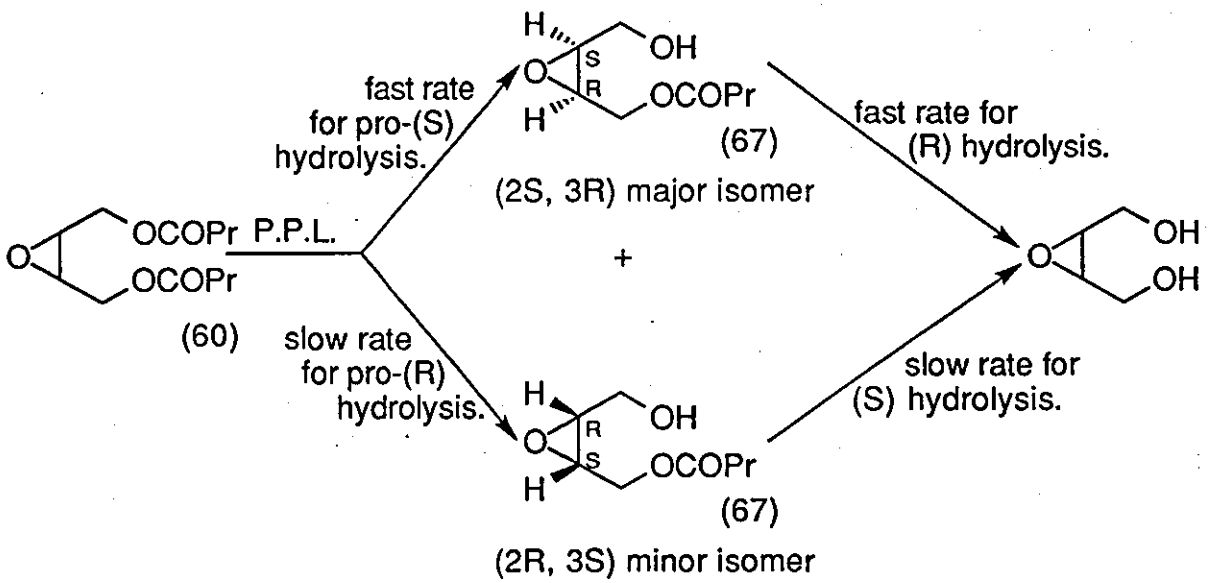
[2]The yield of the resolved ester was calculated taking into account the percent conversion.

[3]Enzyme was immobilised.

[4]Also isolated from the reaction was 4 mg of *meso* 2,3-epoxybutan-1,4-diyl dibutanoate (60).

All three lipase tested demonstrated a relatively low enantioselectivity towards the hydrolysis of the racemic-epoxymonoester (67). The porcine pancreatic lipase and immobilised *Rhizopus* lipase [LIP F3] showed a similar affinity, both yielding (2R, 3S)-epoxymonoester (67) in 50-55% enantiomeric excess. Interestingly, it was the (R)-enantiomer of (67) which both of these lipases hydrolysed preferentially, a result which would not be expected for the porcine pancreatic lipase, as it usually shows an affinity towards the hydrolysis of the (S)-, or pro-(S)-ester, with these types of compounds. This result proved to be detrimental in the *Rhizopus* lipase- and porcine pancreatic lipase-catalysed hydrolysis of epoxydiester (60), with the *meso* epoxydiester being hydrolysed to give (2S, 3R)-epoxymonoester (67), where it was the (2S, 3R)-isomer of epoxymonoester (67) which was preferentially removed in the hydrolysis of (67). Fortunately, the rate of hydrolysis of the epoxymonoester (67) was a factor of ~7 slower than the hydrolysis of the epoxydiester (60), for both the *Rhizopus* and porcine pancreatic lipase. These results are summarised in Scheme 34.

Scheme 34.



Extending the conversion will reduce the enantiomeric excess for (2S, 3R)-epoxymonoester (67), as the competing lipase-catalysed hydrolysis of epoxymonoester (67) hydrolyses the (2S, 3R)-isomer faster than the (2R, 3S)-isomer.

With the aim to determining how much this competing hydrolysis effects the enantiomeric excess of (2S, 3R)-(67), obtained in the porcine pancreatic lipase-catalysed hydrolysis of epoxydiester (60), two hydrolyses of epoxydiester (60) were performed at lower conversions. Table 14 gives the results of these hydrolyses, along with the comparative hydrolysis, taken to 88% conversion. As is evident, the anticipated improvement in enantiomeric excess, was seen when reducing the conversion from 88% to 30%. The obvious disadvantage to carrying out the hydrolysis to a low conversion is that the maximum yield of product is reduced.

Table 14. The effect of reducing the percent hydrolysis of epoxydiester (60), on the enantiomeric excess obtained for (2S, 3R)-epoxymonoester (67).

Nº	Lipase.	Conv. %.[1]	Time hrs.	Temp °C.	Yield %.[2]	$[\alpha]_D^{20}$	e.e. %.
1	porcine pancreatic l.	88	1.6	20	62	+13.8	70
2	porcine pancreatic l.	51	0.5	20	62	+15.8	77
3	porcine pancreatic l.	31	0.3	20	64	+16.0	80

Prefixes as for Table 9.

As is evident from entry 3 of Table 13, the *Penicillium* lipase [LIP F11] demonstrates the same enantioselectivity for the hydrolysis of both epoxydiester (60) and epoxymonoester (67), with the pro-(R)-ester of (60), and the (R)-ester of (67) being hydrolysed preferentially. This observation is unlikely to have a dramatic effect on the result of the hydrolysis of epoxydiester (60), as the enantioselectivity in the hydrolysis of epoxymonoester (67) was very poor.

One further interesting observation was that in the porcine pancreatic lipase-catalysed hydrolysis of racemic-epoxymonoester (67), a small amount of *meso* 2,3-epoxybutan-1,4-diyl dibutanoate (60) was isolated in the reaction mixture. There are two explanationswhich account for the formation of this product; (I) there was a lipase-catalysed esterification of epoxymonoester (67) with butyric acid, or (II) there was an intermolecular lipase-catalysed transesterification reaction occurring between two molecules of epoxymonoester (67). Both processes are possible, but in the dilute aqueous media, neither are thermodynamically favourable. Also of some note was that none of the epoxydiester (60) was isolated in the hydrolysis of racemic-(67) with the *Rhizopus* lipase [LIP F3] or *Penicillium* lipase [LIP F11]. This suggests that the porcine pancreatic lipase catalyses the esterification, and / or transesterification of epoxymonoester (67) was more efficiently than either of the other two lipases. Further transesterification reactions of this system are discussed in section **2.2.3.**

2.2.3. Enantioselective lipase-catalysed transesterification of vinyl butyrate with *meso* 2,3-epoxybutan-1,4-diol (66).

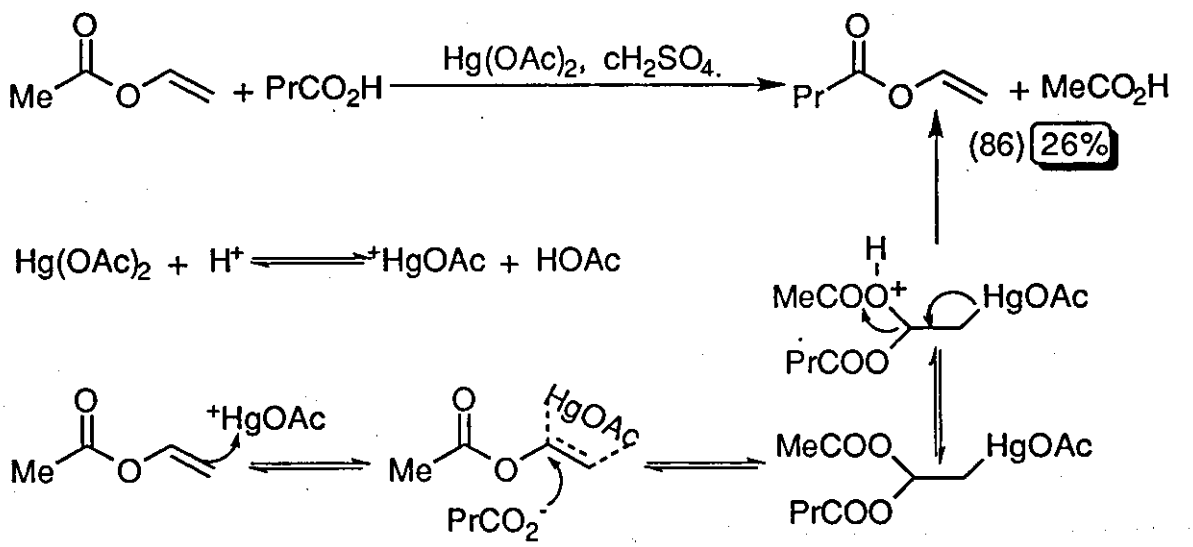
In attempting to prepare a sample of enantiomerically enriched epoxymonoester (67), *via* a lipase-catalysed transesterification reaction with the *meso* epoxybutan-1,4-diol (66), the advantages which applied to the lipase-catalysed hydrolysis of *meso* epoxydiester (60) are again relevant, with it being possible to take the conversion to 100%, with no loss in enantiotopic selectivity.

As already detailed in **Chapter 1**, the major draw back in the lipase-catalysed transesterification reactions arise from the reversible nature of the reaction, which results in slow reactions and often non-reproducible results.[38] This problem may be avoided by employing a vinyl ester as the acyl transfer reagent,[38,39] as the enol by-product rapidly tautomerises to acetaldehyde, which is unable to engage in the reverse reaction.

We chose to use vinyl butyrate (86), as the acyl transfer reagent as the resulting epoxymonoester would be the butanoate ester (67), and hence the enantiomeric excesses could be calculated directly from Graph 3. Vinyl butyrate (86) was prepared from vinyl acetate, employing the method of Mondal *et al*[56] (Scheme 35). Only a relatively poor yield of vinyl butyrate (86) was obtained, but

as the reaction was performed on a large scale, this was not considered to be a problem. The ^1H N.M.R. spectrum of vinyl butyrate (86) clearly showed the presence of the vinyl ether group, with a pair of double-doublets at δ 4.6 and 4.9 p.p.m. (J_{gem} = 1.7 Hz, J_{trans} = 6.4 Hz and J_{cis} = 15.5 Hz). The proton α to the oxygen was shifted significantly downfield, to δ 7.30 p.p.m. and appeared as a double-doublet.

Scheme 35.



Scheme 36 shows the basic course of the lipase-catalysed transesterification reaction.

Scheme 36.

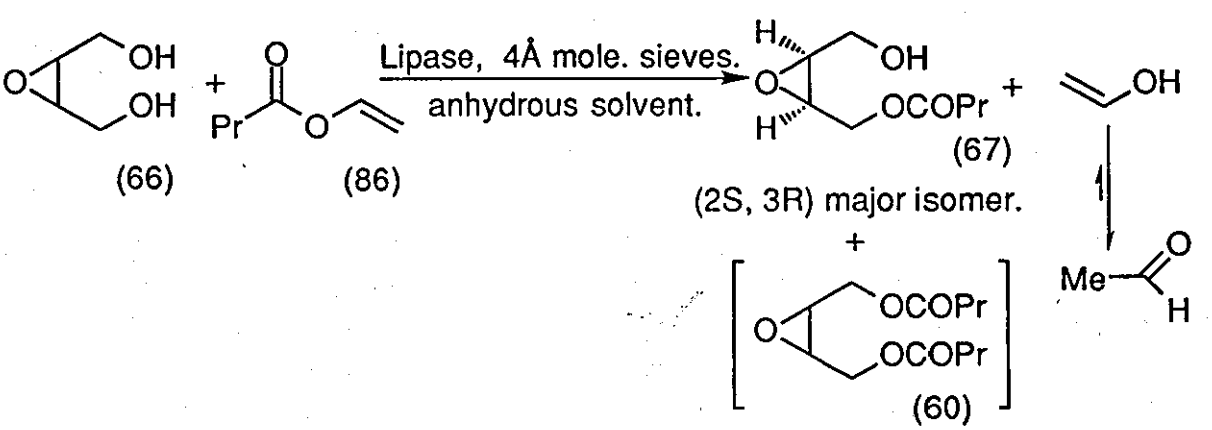


Table 15. Results of the lipase-catalysed transesterification of vinyl butyrate with *meso* 2,3-epoxybutan-1,4-diol (66).

Nº	Lipase.	lipase mg.	Vinyl butyrate / equiv's	Time hrs.	Yield %.	$[\alpha]_D^{20}$	e.e. %.
1	porcine pancreatic lipase.	500	1	22.[1]	22	+2.4	12
2	porcine pancreatic lipase.	500	1	16.[2]	30	+3.3	16
3	porcine pancreatic lipase.	30	1	96.[2]	18	+6.1	30
4	porcine pancreatic lipase.	30	2	60.[2]	30	+2.5	13
5	porcine pancreatic lipase.	40	5	9.[2]	13	+9.1	46
6	porcine pancreatic lipase.	38	5	5.5.[2]	5	+9.6	48
7	*Penicillium* l. [LIP F11].[3]	30	1	96.[2]	0	—	—
8	*Candida cylindracea* lipase.	30	1	69.[2]	0	—	—
9	*Rhizopus* l. [LIP F3].[3]	30	1	69.[2]	0	—	—
10	*Pseudomonas fluorescens* l.[3]	40	4	3.5.[2]	22	+5.0	25
11	*Pseudomonas fluorescens* l.	27	5	1.3.[2]	6	+10	54
12	Denatured lipase.[4]	50	5	20.[2]	0	—	—

[1]Reaction performed in refluxing THF.

[2]Reaction performed in THF at 20°C.

[3]Lipase was immobilised.

[4]Porcine pancreatic lipase and *Pseudomonas fluorescens* lipase were denatured, by boiling in water for 3 minutes, and then dried under high vacuum for 6 hours.

The initial transesterification was performed employing the conditions of Degueil-Castaing *et al*,[38] with the vinyl butyrate and *meso* epoxybutan-1,4-diol (66) being heated at reflux, in THF, with powdered 4Å molecular sieves (~300 mg) present to absorb any water entering the reaction mixture. Porcine pancreatic lipase (500 mg) was then added and the solution heated for 22 hours, entry 1 on Table 15. As this resulted in a poor enantiomeric excess, of 12% for the (2S, 3R)-enantiomer of (67), the reaction was repeated with the alterations listed in Table 15, entries 2-6. Decreasing the temperature to 20°C resulted in an increase in the enantiomeric excess of (2S, 3R)-epoxymonoester (67), as did decreasing the amount of lipase used. The best condition, in terms of the enantiomeric excess

obtained, was with a short reaction time, and using an excess of vinyl butyrate, as illustrated in entry 6 of Table 15. In this case the reaction was terminated, by removal of the lipase by filtration, upon the first appearance of the epoxydiester (60), by t.l.c. analysis. As a consequence of this short reaction time, the chemical yields are correspondingly low.

As this transesterification reaction is effectively the reverse of the porcine pancreatic lipase-catalysed hydrolysis of the epoxymonoester (67), and also of the epoxydiester (60), as the epoxydiester was formed, it was not surprising that in this transesterification;

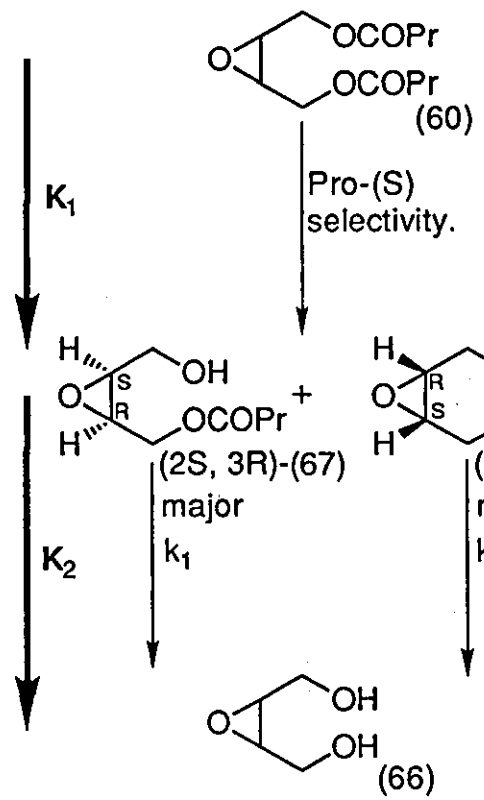
(I) it was the (2S, 3R)-enantiomer of epoxymonoester (67) which was preferentially formed, and

(II) that the enantiomeric excess of epoxymonoester (67) was observed to decrease as the reaction proceeded with the appearance of epoxydiester (60) being evident early on in the reaction .

As already stated, these lipase-catalysed reaction are reversible, with the transesterification of the epoxydiol (66) being the reverse of the hydrolysis of the epoxymonoester (67). The porcine pancreatic lipase has demonstrated that it hydrolyses the epoxymonoester (67) with a (R)-stereoselectivity, leaving behind the (2R, 3S)-enantiomer of (67). It would be expected for the transesterification of the epoxybutandiol (66), with porcine pancreatic lipase, to occur with a pro-(R) enantiotopic selectivity, with the formed epoxymonoester (67) having the (2S, 3R)-absolute configuration. This was observed experimentally. Unfortunately, as the hydrolysis of epoxymonoester (67) preferentially removed the (2S, 3R)-isomer, effectively reducing the enantiomeric excess obtained in the hydrolysis of epoxydiester (60), the same would be expected for the transesterification of (67), with porcine pancreatic lipase transesterifying the epoxymonoester (67) with (S)-stereoselectivity. This would remove the (2S, 3R)-enantiomer preferentially, and thus reduce the enantiomeric excess of (2S, 3R)-(67) obtained in the transesterification. With the hydrolysis of epoxydiester (60), a reasonable yield and enantiomeric excess for (67) was obtained as epoxymonoester (67) was a poor substrate compared to epoxydiester (60), being hydrolysed considerably slower. As (60) appears in the reaction mixture of the transesterification at an early stage, and such poor yields were obtained for epoxymonoester (67), this suggests that the transesterification of the epoxymonoester (67) occurs at a comparable rate to that of the epoxydiol (66). This is as would be expected, considering the data obtained in the hydrolysis of both epoxydiester (60) and epoxymonoester (67) An outline of this discussion is summarised in Scheme 37.

Scheme 37.

Porcine pancreatic lipase-catalysed hydrolysis of epoxydiester (60).

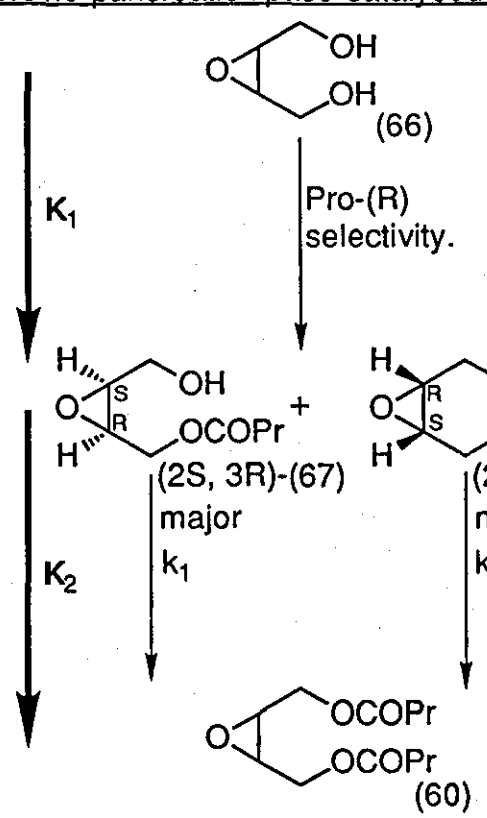


Porcine pancreatic lipase hydrolysed epoxydiester (60) with pro-(S) selectivity and therefore the (2S, 3R)-isomer of epoxymonoester (67) was preferentially formed.

As $k_1 > k_2$, the enantiomeric excess of (2S, 3R)-(67) was seen to diminish as the reaction time increased.

As $\mathbf{K_1} > \mathbf{K_2}$, a reasonable enantiomeric excess and yield of (2S, 3R)-(67) was obtained in the hydrolysis of epoxydiester (60).

Porcine pancreatic lipase-catalysed transesterification with epoxydiol (66).



The porcine pancreatic lipase transesterification of epoxydiol (66), with vinyl butyrate, went with pro-(R) selectivity and therefore the (2S, 3R)-isomer of epoxymonoester (67) was preferentially formed.

It is probable that $k_1 > k_2$, because the enantiomeric excess of (2S, 3R)-(67) was seen to diminish as the reaction time increased.

As it is also probable that $\mathbf{K_2} > \mathbf{K_1}$, the reaction would have to be terminated very early to obtain a reasonable enantiomeric excess of (67) in the transesterification .

Entries 10 and 11 of Table 15 show the only other lipase, of those tested, which successfully catalysed this transesterification reaction. *Pseudomonas fluorescens* lipase proved to be reasonably enantiotopically selective, at a low percent conversion, showing the same pro-(R) stereoselectivity as porcine pancreatic lipase. The appearance of epoxydiester (60) was noted early on in the reaction and hence only a poor yield of epoxymonoester (67) was isolated.

All examples of the lipase-catalysed transesterification discussed so far were carried out in anhydrous THF. Table 16 shows other solvents which the reaction was performed in, in an attempt to improve the enantiomeric excess and yield of (2S, 3R)-(67). An extremely slow reaction was observed in hexane, probably due to the low solubility of the epoxydiol (66), with only a low yield of racemic-(67) being isolated after 7 days. With DMSO as the solvent no reaction was observed, even after 7 days. *tert*-Butanol proved to be a reasonable solvent, giving a comparable yield to that obtained in THF, but the enantiomeric excess for the isolate (67) was only half that obtained in THF.

Table 16. Results of the lipase-catalysed transesterification in varying anhydrous organic solvents.

Nº	Lipase.	Solvent.	Time hrs.	Yield %.	$[\alpha]_D^{20}$	e.e. %.
1	porcine pancreatic lipase.	THF	16	30	+3.3	16
2	porcine pancreatic lipase.	Hexane	168	6	0	0
3	porcine pancreatic lipase.	DMSO	168	0	—	—
4	porcine pancreatic lipase.	t-BuOH	40	31	+1.7	8

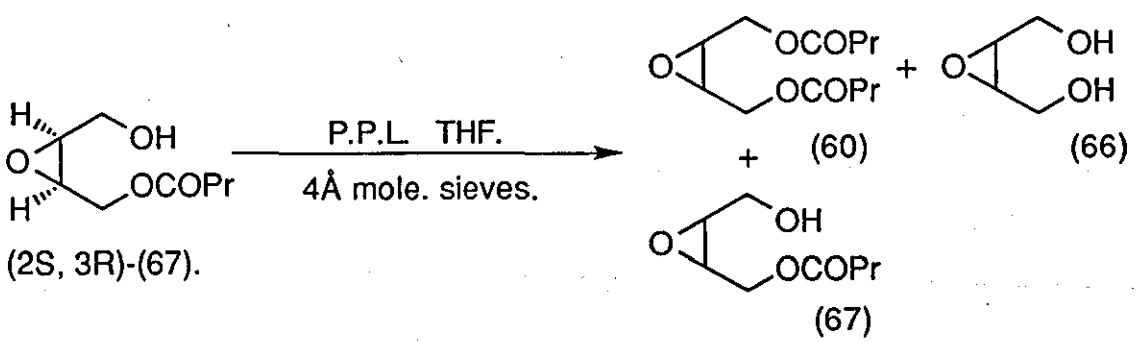
All transesterifications performed with 500 mg of lipase and 1 equivalent of vinyl butyrate at 20°C.

As already mentioned in section **2.2.2**, in the porcine pancreatic lipase-catalysed hydrolysis of racemic-(67), a small quantity of the epoxydiester (60) was isolated. This was thought to be formed by one of two possible methods;
(I) *via* a lipase-catalysed esterification of epoxymonoester (67) with butyric acid, or
(II) *via* an intermolecular lipase-catalysed transesterification reaction between two molecules of epoxymonoester (67). It was considered that if the latter transesterification were occurring in an aqueous media, it would also do so in the organic solvent media. As this process might also racemise the formed

(2S, 3R)-(67), the control reactions, shown in Scheme 38 and Table 17, were performed.

As is clearly evident from the results, racemisation of (2S, 3R)-(67) does occur upon stirring with porcine pancreatic lipase in anhydrous THF. Both the epoxydiol (66) and epoxydiester (60) were also present at the end of the reaction, with ~50% of the epoxymonoester (67) being recovered. As there was no butyric acid, or water in the reaction mixture, the products must have been formed by an intermolecular transesterification reaction, catalysed by the lipase (no reaction noted when using denatured lipase). It is also possible that this racemisation could have occurred *via* an intramolecular transesterification, but this would have required forming the thermodynamically less plausible 7-membered ring transition state.

Scheme 38.



(2S, 3R)-(67).

Table 17. Racemisation of (2S, 3R)-(67) by porcine pancreatic lipase.

% e.e. of starting (67)[1].	Lipase / mg.	Reaction time / hrs.	Recovered (67) / %.	% e.e. of Recovered (67).
67	500	23	47	6
71	50	44	53	36
71	50[2]	44	98	71

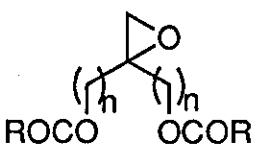
[1](2S, 3R)-Isomer of epoxymonoester (67) employed as starting material.
[2]Lipase denatured.

The work on the hydrolases-catalysed hydrolysis of the *meso* epoxydiesters (59) and (60) was reported by two other groups [57,58] at around the same time as we published our results.[59] The results they obtained were in reasonable agreement with ours.

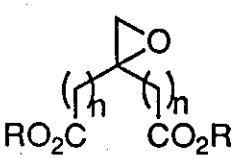
2.3. Lipase-catalysed hydrolysis of the 2-butanoyloxymethyl-2,3-epoxypropan-1-yl butanoate (89).

A review of the literature to date showed no examples of the hydrolase-catalysed hydrolysis of prochiral epoxydiesters, with the general formula (87) or (88), as depicted in Figure 4. Epoxydiesters (87) are the prochiral homologues of the epoxyesters studied by Ladner and Whitesides. Also if n were equal to 1, a comparison could be drawn with the hydrolysis of epoxydiester (60), as described in section **2.2.** Epoxydiesters (88) are the prochiral homologues to those studied by Mori *et al*[14] and Bianchi *et al*,[15] and, when n=2, with the n-butyl 4,5-epoxypentanoate (51), as detailed in section **2.1.**

Figure 4.



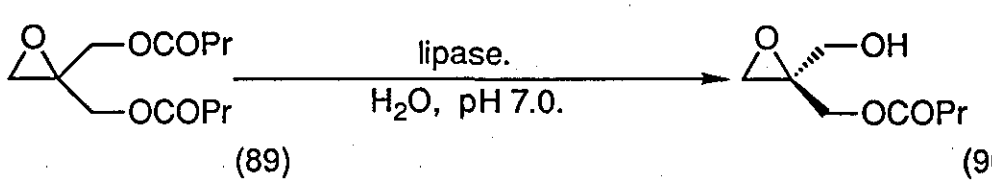
n= 1 or 2. (87)



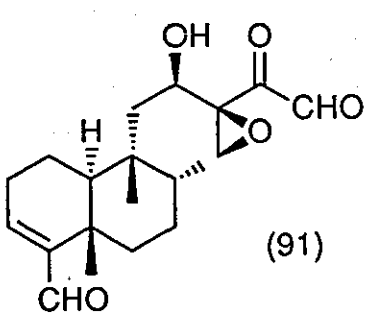
n= 0, 1 or 2. (88)

The substrate chosen to investigate was 2-butanoyloxymethyl-2,3-epoxypropan-1-yl butanoate (89). Hydrolysis of this would afford the epoxymonoester (90), a compound structurally similar to the side chain found in clerocidin (91) and it co-metabolites[60] (Scheme 39).

Scheme 39.



(89) (90)

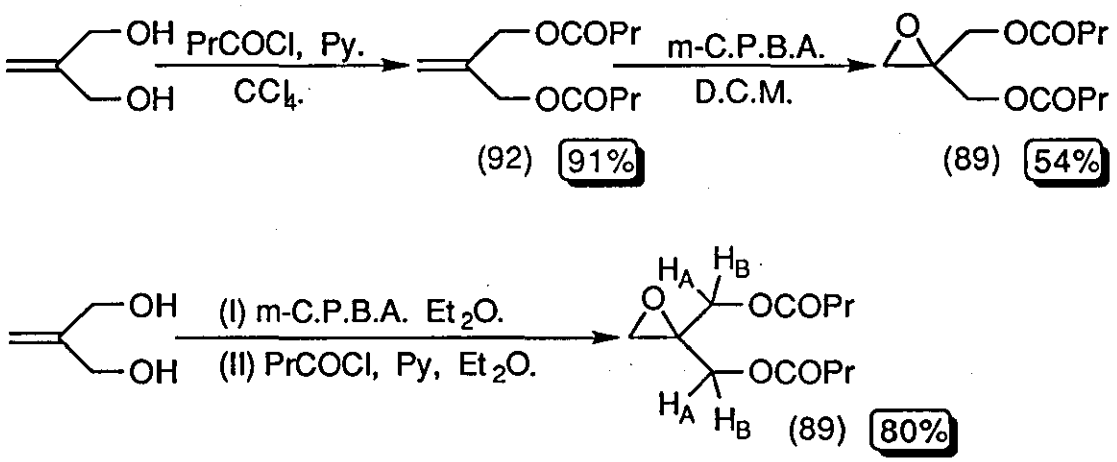


(91)

2.3.1. Preparation of 2-butanoyloxymethyl-2,3-epoxypropan-1-yl butanoate (89).

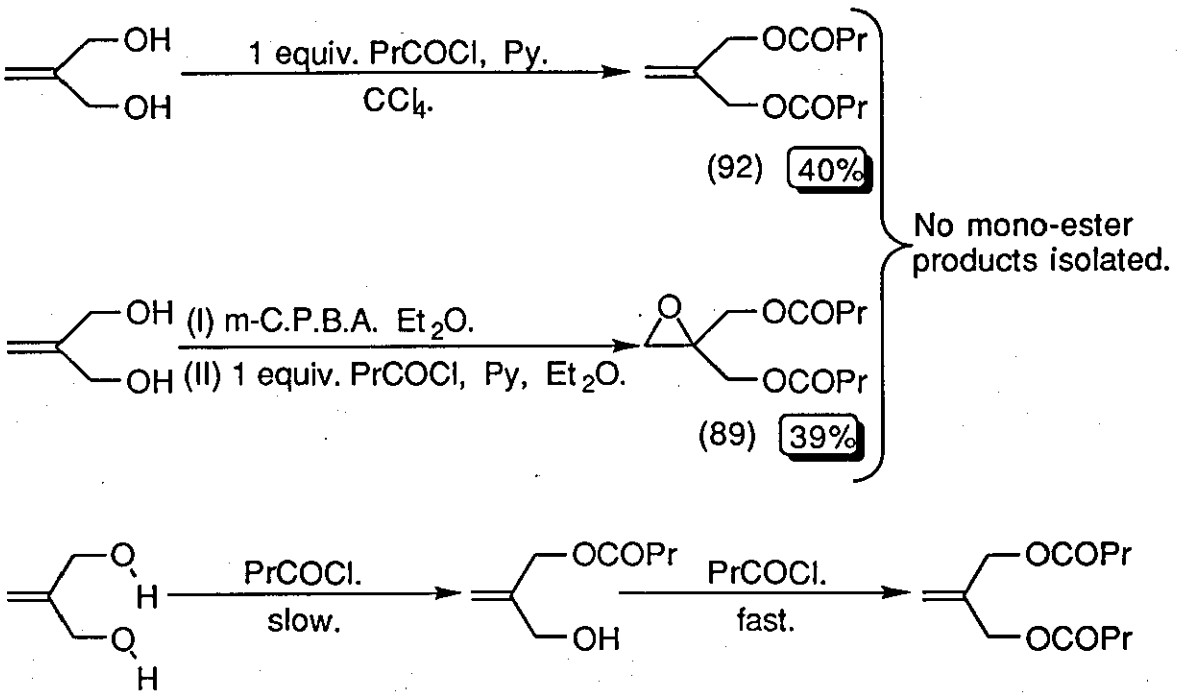
2-Butanoyloxymethyl-2,3-epoxypropan-1-yl butanoate (89) was prepared *via* two methods. (I) Esterification of 2-methylenepropan-1,3-diol, affording 2-methylenepropan-1,3-diyl dibutanoate (92), which was epoxidised with m-chloroperoxybenzoic acid, giving epoxydiester (89) in 50% overall yield. (II) m-Chloroperoxybenzoic acid epoxidation of 2-methylenepropan-1,3-diol, followed by esterification of the epoxydiol, afforded epoxydiester (89) in 80% yield (Scheme 40). In the ^1H N.M.R. spectrum of epoxydiester (89) the protons β to the epoxide, H_A and H_B, appeared as two doublets at δ 4.14 and 4.28 p.p.m. (J_{gem} = 12.14 Hz).

Scheme 40.



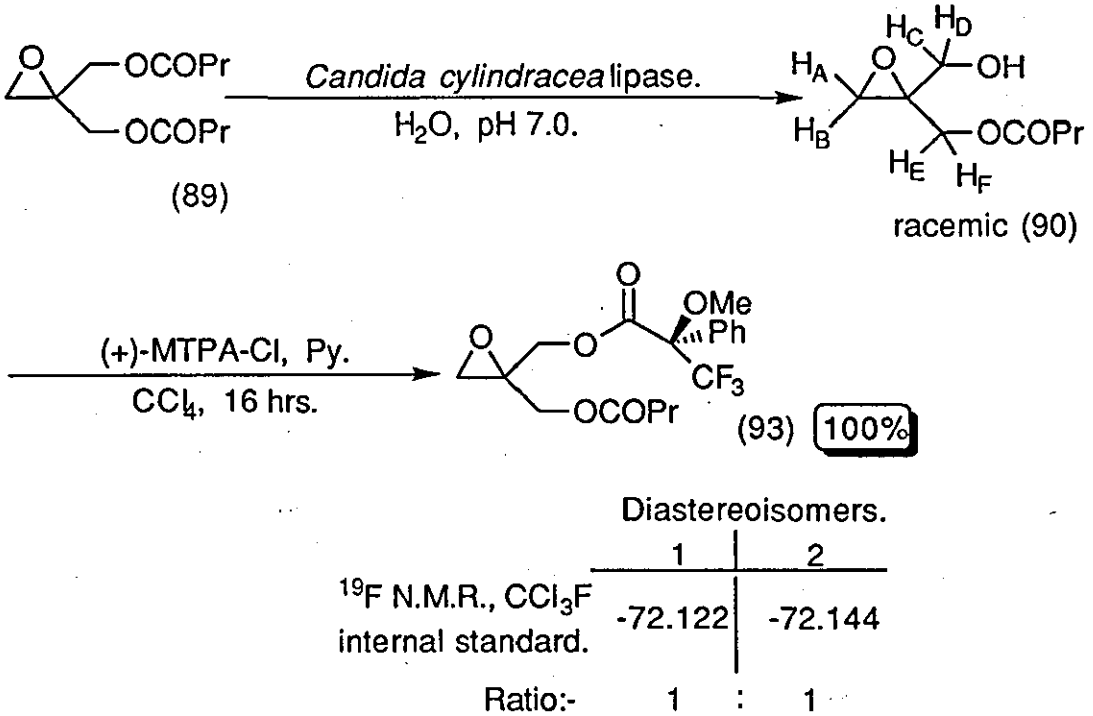
In order to aid the enantiomeric excess determinations of the enantiomerically enriched epoxymonoesters (90), obtained in the lipase-catalysed hydrolysis of epoxydiester (89), the preparation of racemic epoxymonoester (90) was attempted (Scheme 41). When the partial esterification of both 2-methylenepropan-1,3-diol, and the epoxydiol, were attempted, only the diester products (92) and (89) were isolated. A possible explanation for this is that the alcohol groups in the diol compounds are less susceptible to esterification due to intramolecular hydrogen bonding making them weaker nucleophiles (Scheme 41). Once the monoester is formed, these hydrogen bonds can no longer occur, and hence the alcohol is more reactive and diesterification occurs, resulting in diesters (92) and (89).

Scheme 41.



A sample of racemic epoxymonoester (90) was obtained by the non-stereoselective *Candida cylindracea* lipase-catalysed hydrolysis of the epoxydiester (89) (Scheme 42). In the ^1H N.M.R. spectrum of (89), three geminal coupling systems were clearly visible, at δ 2.82 and 2.94 p.p.m. (J_{gem} = 4.65 Hz), due to protons H_A and H_B, at δ 3.73 and 3.82 p.p.m. (J_{gem} = 12.44 Hz), due to protons H_C and H_D and at δ 4.15 and 4.35 p.p.m. (J_{gem} = 12.29 Hz), due to protons H_E and H_F. When ^1H N.M.R. spectroscopic studies were performed on epoxymonoester (90), with the chiral shift reagent europium D-3-heptafluorobutyrylcamphorate (68), both the triplet, and the sextet, associated with the methylenes of the ester moiety were seen to split into two signals, the integration of which provided the enantiomeric excess of epoxymonoester (90). The Mosher's ester (93) was prepared following the procedure of Mosher *et al.*[45] Integration of the signals in the ^1H N.M.R. spectrum of Mosher's ester (93) did not provide any insight into the enantiomeric excess determination. The diastereomeric excess of Mosher's ester (93) and hence the enantiomeric excess of the epoxymonoester (90) was calculated by integration of the two diastereomeric peaks at δ -72.122 and -72.144 p.p.m., in the ^{19}F N.M.R. spectrum (with trichlorofluoromethane as the internal standard).

Scheme 42.



	Diastereoisomers.	
	1	2
^{19}F N.M.R., CCl_3F internal standard.	-72.122	-72.144
Ratio:-	1	1

2.3.2. Lipase-catalysed hydrolysis of 2-butanoyloxymethyl-2,3-epoxypropan-1-yl butanoate (89).

The lipase-catalysed hydrolysis of 2-butanoyloxymethyl-2,3-epoxypropan-1-yl butanoate (89) was performed in the same manner as that of the *meso* 2,3-epoxybutan-1,4-diyl dibutanoate (60). The percent conversions were calculated from the volume of sodium hydroxide required to neutralise the liberated butyric acid. The yields of 2-butanoyloxymethyl-2,3-epoxypropan-1-ol (90) were calculated taking into account the percent conversion of the hydrolysis. The enantiomeric excesses were either calculated from the ^{19}F N.M.R. spectra of the Mosher's ester (93), or *via* ^{1}H N.M.R. spectroscopic studies with the europium D-3-heptafluorobutyrylcamphorate (68) chiral shift reagent.

As can be seen from Table 18, with the lipases examined, only one enantiomer of epoxymonoester (90) was obtained in an enantiomerically enriched form. The best enantiomeric excess for (-)-(90), of 49%, was obtained with the *Pseudomonas fluorescens* lipase-catalysed hydrolysis of epoxydiester (89), entry 7 of Table 18. The non-immobilised *Rhizopus delemar* lipase gave a similar result, affording (-)-(90) with an enantiomeric excess of 48%, entry 4 of Table 18.

Although the absolute configuration of (-)-(90) was not determined, it is reasonable to assume that porcine pancreatic lipase will hydrolyse the pro-(S) ester preferentially, based on the results obtained by Ladner and Whitesides,[8] and

the results obtained in section **2.2.1-(I)**. The enantiomerically enriched epoxymonoester (90) would therefore be expected to have the (2S)-2-butanoyloxymethyl-2,3-epoxypropan-1-ol absolute configuration. It is interesting to note that the *Penicillium* lipase [LIP F11] afforded the epoxymonoester (90) as a racemic mixture. When the *meso* 2,3-epoxybutan-1,4-diyl dibutanoate (60) was hydrolysed with this lipase, the epoxymonoester (67) isolated had the opposite absolute configuration to that obtained in the porcine pancreatic lipase-catalysed hydrolysis of epoxydiester (60). It would therefore have perhaps been expected for the *Penicillium* lipase [LIP F11] to have shown a pro-(R) selectivity in the hydrolysis of the epoxydiester (89).

Table 18. Results of the lipase-catalysed hydrolysis of 2-butanoyloxymethyl-2,3-epoxypropan-1-yl butanoate (89).

Nº	Hydrolase.	Conv[n] %.[1]	Time hrs.	Temp °C.	Yield %.[2]	$[\alpha]_D^{20}$	e.e. %.
1	*Candida cylindracea* l.	98	2.0	20	60	0	0
2	porcine pancreatic l.	97	0.5	20	77	-2.8	37
3	*Rhizopus* l [LIP F3].[3]	95	0.7	20	60	0	0
4	*Rhizopus delemar* l.	97	0.7	20	76	-3.6	48
5	*Rhizopus delemar* l.[3]	98	1.0	20	63	-2.1	28
6	*Penicillium* lipase [LIP F11].[3]	71	5.5	20	52	0	0
7	*Pseudomonas fluorescens* l.	97	0.25	20	70	-3.7	49

[1]The percent conversion was calculated from the volume of sodium hydroxide added, assuming that the hydrolysis of only a single ester group was occurring.

[2]The yield of the mono-ester was calculated based on the diester consumed.

[3]Lipase was immobilised.

There are several plausible explanations for the low enantiomeric excesses obtained for the epoxymonoester (90):

(I) The lipase tested have a low enantiotopic selectivity towards the hydrolysis of the pro-(S) ester moiety.

(II) A lipase-catalysed intermolecular, or intramolecular transesterification reaction was occurring, which was racemising the formed (-)-(90). The intermolecular transesterification process was shown to occur in the porcine pancreatic lipase-

catalysed hydrolysis of epoxydiester (60), and as this system is more likely to undergo a 1,3-acyl transfer, the possibility of the intramolecular transesterification is plausible.

(III) The epoxymonoester (90) is being hydrolysed with the opposite enantioselectivity to the hydrolysis of the epoxydiester (89), and thus the enantiomerically enriched product is being removed in a similar fashion as was observed for epoxymonoester (67), as described in section **2.2.2.** As the epoxymonoester (90) could not be obtained easily, the hydrolysis of epoxymonoester (90) was not explored and therefore racemisation *via* this method can only be tentative suggested.

The results of the hydrolyses described in section **2.2.** have recently been published.[59]

Chapter 3. Experimental.

3.1. General Information.

Solvents and reagents: All solvents were distilled before use. Dry solvents and reagents were obtained as follows: Chloroform, dichloromethane, carbon tetrachloride, ethyl acetate and cyclohexane; distilled over phosphorus pentoxide. Dimethylsulfoxide and dimethylformamide; stirred with barium oxide for 18 hours, filtered, then distilled under reduced pressure and stored over 4 Å molecular sieves. Ethanol, methanol and butanol; distilled over magnesium. Diethyl ether and tetrahydrofuran; distilled over sodium / benzophenoneketyl. Hexane, pentane and light petroleum (b.p. 40-60°C); distilled over calcium chloride. Pyridine and triethylamine; distilled and stored over potassium hydroxide. Thionyl chloride; distilled over quinoline. Toluene and benzene; distilled over sodium hydride. Starting materials were obtained predominantly from Aldrich Chemical Co. Ltd. or from Lancaster Synthesis Ltd., and recrystallised or distilled, if appropriate. The hydrolases were obtained from either Sigma Chemical Co. Ltd., Fluka Chemika-BioChemika or Enzymatix.

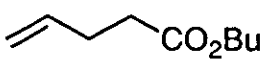
Chromatographic Procedures: Analytical thin layer chromatography was carried out using aluminium backed plates, coated with Merck Kieselgel 60 GF_{254}. Flash chromatography was carried out using Merck Kieselgel 60 H silica or Sorbsil C 60 Silica gel. Alumina chromatography was carried out using aluminum oxide, activated, basic, Brockmann 3, ~150 mesh, 58 Å.
Gas chromatography analysis were performed on a Carlo Erba 6000 G.C., using a 25 m B.P. 1 column and a flame ionization detector, with nitrogen as the mobile phase.

Spectroscopic techniques: Infrared spectra were obtained using a Pye Unicam PU9516 spectrometer and a Nicolet 205 FT-IR spectrometer. Ultraviolet spectra were obtained using a Shimadzu UV-10 instrument. 400 MHz N.M.R. and n.O.e. difference spectra were provided by the SERC High Field N.M.R. Service at the University of Warwick. δ-Chloroform was used as the N.M.R. solvent, with tetramethylsilane as internal standard. 250 MHz N.M.R. spectra were obtained using a Brucker AC250 spectrometer. 60 MHz N.M.R. spectra were obtained using a Varian EM360A spectrometer. Mass spectra were obtained on a Kratos MS80 instrument, or on a VG Analytical ZAB-E instrument, courtesy of the SERC Mass Spectrometry Service at University College, Swansea.

Other data and instrumentation: Elemental analysis were obtained courtesy of MEDAC Ltd, Brunel University. Optical rotation data were obtained using an Automatic Polarimeter AA-10. Melting points were determined with Kofler hot stage and digital melting point apparatus. Temperatures quoted for Kugelrorh distillations were those of the heating bath.

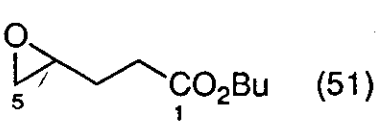
3.2. Experimental for **Chapter 2.**

Preparation of *n-butyl 4-pentenoate.*



To a stirred solution of 4-pentenoic acid (10.0 g, 100 mmol) in anhydrous hexamethylphosphoramide (25 cm^3) at -10°C, a solution of thionyl chloride (8.0 cm^3, 60 mmol) was added drop-wise, keeping the temperature below -5°C. After stirring at -10°C for 3 hours, n-butanol (8.8 cm^3, 95 mmol) in anhydrous hexamethylphosphoramide (10 cm^3) was added drop-wise. The resulting solution was stirred at room temperature for 16 hours, diluted with diethyl ether (80 cm^3) and washed with a saturated sodium hydrogen carbonate solution (x 3) and a saturated sodium chloride solution. After drying (sodium sulfate) the solvent was evaporated to give a yellow liquid. Purification by distillation afforded n-butyl 4-pentenoate as a clear and colourless liquid (10.7 g, 69%); b.p. (20 mmHg) 85°C;
υ_{max}/cm^{-1} (neat) 1734 (ester C=O);
δ_H (60 MHz $CDCl_3$) 0.90 (3H, t, J = 7.00 Hz, O-$CH_2CH_2CH_2C\underline{H}_3$), 1.10-1.80 (4H, m, O-$CH_2C\underline{H}_2C\underline{H}_2CH_3$), 2.30 (4H, m, 2- and 3-CH_2), 4.10 (2H, t, J = 7.10 Hz, O-$C\underline{H}_2CH_2CH_2CH_3$), 5.00 (2H, m, 5-$CH_2$) and 5.90 (1H, m, 4-CH).

Preparation of *n-butyl 4,5-epoxypentanoate* (51).



(51)

To a cooled (ice-bath) and stirred solution of n-butyl 4-pentenoate (6.0 g, 38 mmol) and sodium hydrogen carbonate (4.2 g, 50 mmol) in anhydrous dichloromethane (250 cm^3), m-chloroperoxybenzoic acid (17.2 g, 50 mmol) was added in one portion. After stirring at room temperature for 4 days, the solution was washed with a saturated sodium hydrogen carbonate solution (x 4), water, a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a yellow liquid. Purification by flash chromatography (1:3 diethyl ether : light petroleum (b.p. 40-60°C)) yielded (51) as clear liquid (2.0 g, 30%);

υ_{max}/cm^{-1} (neat) 1734 (ester C=O);
δ_H (250 MHz $CDCl_3$) 0.93 (3H, t, J = 7.30 Hz, O-$CH_2CH_2CH_2C\underline{H_3}$), 1.38 (2H, sextet, J = 7.81 Hz, O-$CH_2CH_2C\underline{H_2}CH_3$), 1.61 (2H, q, J = 7.61 Hz, O-$CH_2C\underline{H_2}CH_2CH_3$), 1.79 (1H, m, 3-$CH_\alpha$), 1.95 (1H, m, 3-$CH_\beta$), 2.46 (2H, t, J = 7.30 Hz, 2-CH_2), 2.50 (1H, dd, J_{trans} = 2.63 and J_{gem} = 4.92 Hz, 5-CH_{trans}), 2.77 (1H, t, J = 4.92 Hz, 5-CH_{cis}), 2.98 (1H, m, 4-CH) and 4.09 (2H, t, J = 7.38 Hz, O-$C\underline{H_2}CH_2CH_2CH_3$);
δ_C (62.9 MHz, $CDCl_3$) 13.71 (CH_3), 19.15 (CH_2), 27.69 (CH_2), 30.46 (CH_2), 30.66 (CH_2), 47.07 (5-CH_2), 51.27 (4-CH), 64.49 (CH_2) and 172.94 (CO_2);
m/z (C.I., ammonia) 173.1178 (MH^+, 100%, $C_9H_{17}O_3$ requires 173.1178) and 190 (2, MNH_4^+).

Enzymatic hydrolysis of *n-butyl 4,5-epoxypentanoate.*

Before performing the hydrolysis, a gas chromatography analysis (Carlo Erba 6000 G.C. with a flame ionization detector, 120-170°C at 5°C / min) of various standard n-butanol (retention time 3.0 minutes) : n-butyl 4,5-epoxypentanoate (retention time 9.5 minutes) mixtures (10%, 20% *etc.*) were carried out, and a graph of percentage composition calculated. The percent conversion of reaction was calculated from this graph.

To a rapidly stirred solution of n-butyl 4,5-epoxypentanoate (533 mg, 3.1 mmol) in aqueous phosphate buffer (0.05 M, pH 7.0, 20 cm^3) at 20°C, porcine pancreatic lipase (15 mg) was added in one portion. The mixture was stirred at 20°C for 70 hours (60% conversion), with a 20 µl sample being removed intermittently to calculate the percent conversion. The solution was then saturated with sodium chloride, extracted with diethyl ether (3 x 30 cm^3), dried (magnesium sulfate) and evaporated to dryness giving a colourless liquid. Purification by flash chromatography (1:3 diethyl ether : light petroleum (b.p. 40-60°C)) yielded optically enriched (51) as a clear liquid (205 mg, 77%);
$[\alpha]_D^{20}$ -8.2°; 63% e.e. (by integration of ^1H and ^{19}F N.M.R. spectra of (55)). All spectroscopic data as for previously prepared (51).

Hydrolysis of n-butyl 4,5-epoxypentanoate (500 mg, 2.9 mmol) repeated with a 23 hour stir-time (30% conversion). Purification by flash chromatography (1:3 diethyl ether : light petroleum (b.p. 40-60°C)) yielded optically enriched (51) as a clear liquid (195 mg, 78%);
$[\alpha]_D^{20}$ -6.4°; 49% e.e. All spectroscopic data as for previously prepared (51).

Hydrolysis of n-butyl 4,5-epoxypentanoate (511 mg, 2.7 mmol) repeated with a 50 hour stir-time (50% conversion). Purification by flash chromatography (1:3 diethyl ether : light petroleum (b.p. 40-60°C)) yielded optically enriched (51) as a clear liquid (199 mg, 78%);
$[\alpha]_D^{20}$ -7.9°; 60% e.e. All spectroscopic data as for previously prepared (51).

Hydrolysis of n-butyl 4,5-epoxypentanoate (521 mg, 2.9 mmol) repeated with a 144 hour stir-time (70% conversion). Purification by flash chromatography (1:3 diethyl ether : light petroleum (b.p. 40-60°C)) yielded optically enriched (51) as a clear liquid (172 mg, 66%);
$[\alpha]_D^{20}$ -8.3°; 64% e.e. All spectroscopic data as for previously prepared (51).

Controls for the enzymatic hydrolysis of *n-butyl 4,5-epoxypentanoate*

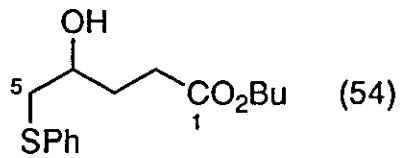
(I) Hydrolysis with denatured porcine pancreatic lipase.

A sample of porcine pancreatic lipase (50 mg) was added to a stirred and refluxing aqueous phosphate buffer (0.05 M, pH 7.0, 20 cm^3). After 3 minutes the solution was cooled to 20°C and racemic n-butyl 4,5-epoxypentanoate (100 mg, 0.58 mmol) added. After 60 hours the solution was extracted with diethyl ether (3 x 20 cm^3), washed with a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a clear liquid (98 mg). All spectroscopic data for the crude product were the same as for previously prepared (51).

(II) Analysis of extract from porcine pancreatic lipase.

An aqueous phosphate buffer (0.05 M, pH 7.0, 20 cm^3) containing porcine pancreatic lipase (50 mg) was extracted with diethyl ether (3 x 20 cm^3), washed with a saturated sodium chloride solution, dried (magnesium sulfate) and concentrated to ~1 cm^3. G.C. analysis (Carlo Erba 6000 G.C. with a flame ionization detector, 120-170°C at 5°C / min) of this solution did not show any peak with a retention time of 9.5 minutes, corresponding to authentic n-butyl 4,5-epoxypentanoate.

Preparation of racemic *n-butyl 4-hydroxy-5-phenylthiopentanoate* (54).



(54)

To a stirred solution of racemic n-butyl 4,5-epoxypentanoate (100 mg, 0.59 mmol) and triethylamine (0.32 cm^3, 2.35 mmol) in anhydrous methanol (5 cm^3), thiophenol (0.18 cm^3, 1.76 mmol) was added in one portion. After stirring for 1 hour, the solution was diluted with diethyl ether (20 cm^3), washed with hydrochloric acid (2 M) (x 2), a saturated sodium hydrogen carbonate solution (x 2), a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a clear liquid. Purification by flash chromatography (2:1 light petroleum (b.p. 40-60°C) : diethyl ether) afforded (54) as a clear and colourless liquid (140 mg, 85%);

υ_{max}/cm^{-1} (neat) 3450 (OH), 1731 (ester C=O) and 1584 (C=C);

δ_H (250 MHz $CDCl_3$) 0.92 (3H, t, J = 7.29 Hz, $OCH_2CH_2CH_2C\underline{H_3}$), 1.35 (2H, sextet, J = 7.32 Hz, $OCH_2CH_2C\underline{H_2}CH_3$), 1.58 (2H, m, $OCH_2C\underline{H_2}CH_2CH_3$), 1.83 (2H, m, 3-$CH_2$), 2.46 (2H, dt, J = 3.26 Hz and 7.22 Hz, 2-CH_2), 2.67 (1H, br d (D_2O exchange), J = 2.83 Hz, OH), 2.88 (1H, dd, J_{AX} = 8.37 and J_{AB} = 13.73 Hz, 5-CH_A), 3.11 (1H, dd, J_{BX} = 3.91 and J_{AB} 13.73 Hz, 5-CH_B), 3.70 (1H, m, 4-CH), 4.06 (2H, t, J = 6.61 Hz, $OC\underline{H_2}CH_2CH_2CH_3$) and 7.30 (5H, m, -$C_6H_5$);

δ_C (62.9 MHz, $CDCl_3$) 13.72 (CH_3), 19.12 (CH_2), 30.62 (CH_2), 30.69 (CH_2), 30.93 (CH_2), 41.90 (5-CH_2), 64.49 (O-CH_2), 68.79 (4-CH), 126.63 (Ar-CH), 129.10 (Ar-CH), 129.96 (Ar-CH), 135.15 (Ar-C) and 173.88 (CO_2);

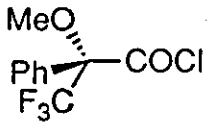
m/z (E.I.) 282.1300 (M^+, 10%, $C_{15}H_{22}O_3S$ requires 282.1290) and 264 (100, M^+ minus H_2O).

Preparation of optically enriched *n-butyl 4-hydroxy-5-phenylthiopentanoate* (54).

Prepared as above using n-butyl 4,5-epoxypentanoate with an $[\alpha]_D^{20}$ of -8.2°. After purification by flash chromatography, (54) was isolated as a clear liquid (80%);

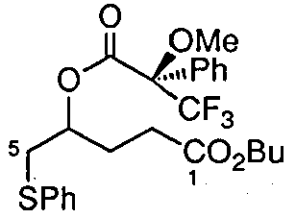
$[\alpha]_D^{20}$ +14.2°. All spectroscopic data as for previously prepared (54).

Preparation of *(R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride.*



A stirred solution of (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (650 mg, 2.7 mmol) and sodium chloride (15 mg) in thionyl chloride (6.0 cm^3) was heated at reflux for 60 hours. Excess thionyl chloride was removed *in vacuo.* Kugelrohr distillation afforded (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride as a clear liquid, b.p. (2.5 mmHg) 80°C;
υ_{max}/cm^{-1} (neat) 1788 (C=O), 1496, 1451 (C=C) and 709 (mono sub-Ar).

Preparation of racemic *n-butyl 4-([(R)-(+)-α-methoxy-α-(trifluoromethyl)phenyl]-acetoxy)-5-phenylthiopentanoate* (55).



(55)

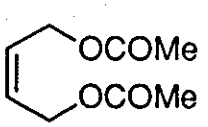
To a stirred solution of racemic n-butyl 4-hydroxy-5-phenylthiopentanoate (31 mg, 0.11 mmol) and anhydrous pyridine (10 drops) in anhydrous chloroform (1 cm^3), (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (33 mg, 0.13 mmol) was added in one portion. After stirring at room temperature for 3 hours, the solution was diluted with diethyl ether (20 cm^3), washed with a saturated sodium hydrogen carbonate solution (x 3), hydrochloric acid (2 M) (x 4), a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a viscous oil. Purification by flash chromatography (2:1 light petroleum (b.p. 40-60°C) : diethyl ether) afforded (55) as a clear and colourless liquid (54 mg, 98%);
υ_{max}/cm^{-1} (neat) 1743 (Mosher's ester C=O), 1735 (ester C=O), 1584 and 1482 (C=C);
δ_H (250 MHz $CDCl_3$) 0.89 (3H, t, J = 7.31 Hz, $OCH_2CH_2CH_2C\underline{H}_3$), 1.33 (2H, sextet, J = 7.48 Hz, $OCH_2CH_2C\underline{H}_2CH_3$), 1.58 (2H, m, $OCH_2C\underline{H}_2CH_2CH_3$), 1.90-2.40 (4H, m, 2- and 3-CH_2), 2.97 (0.5H, dd, J_{AX} = 6.73 and J_{AB} = 13.98 Hz, 5-CH_A R or S), 3.07 (0.5H, dd, J_{AX} = 6.00 and J_{AB} = 13.93 Hz, 5-CH_A S or R), 3.22 (1H, 2 x dd, J_{BX} = 6.10, J_{AB} = 13.93, J_{BX} = 6.62 and J_{AB} = 13.87 Hz, 5-CH_B S and R), 3.53 (1.5H, q, J = 1.26 Hz, -OMe R or S), 3.60 (1.5H, q, J = 1.26 Hz, -OMe R or S),

4.05 (2H, m, $OC\underline{H}_2CH_2CH_2CH_3$), 5.21 (1H, m, 4-CH) and 7.19-7.55 (10H, m, 2 x $-C_6H_5$);
δ_C (62.9 MHz, $CDCl_3$) 13.55 (CH_3), 18.96 (CH_2), 27.97 and 28.05 (CH_2), 29.28 and 29.62 (CH_2), 30.44 (CH_2), 36.89 and 37.39 (5-CH_2), 55.50 and 55.74 (OMe), 64.53 and 64.62 (O-CH_2), 74.26 and 74.42 (4-CH), 126.77 and 126.90 (Ar-CH), 127.26 and 127.54 (Ar-CH), 128.47 (Ar-CH), 129.18 and 129.21 (Ar-CH), 129.69 and 129.72 (Ar-CH), 129.85 and 130.07 (Ar-CH),131.72 and 131.98 (Ar-C), 134.90 (Ar-C), 166.23 (O_2C-Mosher) and 173.88 (CO_2Bu);
δ_F (340 MHz, CCl_3F) -71.723 (CF_3 R or S) and -71.979 (CF_3 S or R);
m/z (E.I.) 498.1687 (M^+, 1%, $C_{25}H_{29}O_5SF_3$ requires 498.1688) and 264 (30, M^+ minus $CO_2C[CF_3OMePh]$).

Preparation of optically enriched *n-butyl 4-([(R)-(+)-α-methoxy-α-(trifluoromethyl)-phenyl]-acetoxy)-5-phenylthiopentanoate* (55).

Prepared as above using n-butyl 4-hydroxy-5-phenylthiopentanoate with an $[\alpha]_D^{20}$ of +14.2°. After purification by flash chromatography (55) was isolated as a clear liquid (100%);
$[\alpha]_D^{20}$ +32.3°;
63% d.e. by integration of ^1H N.M.R. (CH_3O) peaks; ratio of δ 3.53 : δ 3.60 was 5.63 : 1 and by integration of ^{19}F N.M.R. (CF_3) peaks; ratio of δ -71.723 : δ -71.979 was 1 : 5.6. All spectroscopic data as for previously prepared (55).

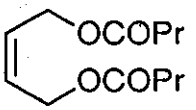
Preparation of *cis-2-buten-1,4-diyl diacetate* (63).



(63)

To a stirred and cooled (ice-bath) solution of *cis*-2-buten-1,4-diol (20 g, 230 mmol) and triethylamine (73 cm^3, 500 mmol) in anhydrous diethyl ether (250 cm^3), acetyl chloride (35.5 cm^3, 500 mmol) was added drop-wise. After stirring at room temperature for 16 hours, the solution was washed with a saturated sodium hydrogen carbonate solution (x 3), hydrochloric acid (2 M) (x 4), a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a yellow liquid. Purification by vacuum distillation afforded (63) as a clear and colourless liquid (35 g, 89%); b.p. (20 mmHg) 118-119°C;
υ_{max}/cm^{-1} (neat) 1738 (ester C=O), and 1442 (C=C);
δ_H (60 MHz $CDCl_3$) 2.10 (6H, s, 2 x CH_3), 4.70 (4H, m, 1- and 4-CH_2) and 5.70 (2H, m, 2- and 3-CH).

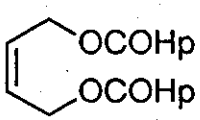
Preparation of *cis-2-buten-1,4-diyl dibutanoate* (64).



(64)

cis-2-Buten-1,4-diol was treated with butanoyl chloride as above. Purification by vacuum distillation afforded (64) as a clear and colourless liquid (91%); b.p. (0.5 mmHg) 90-92°C;
υ_{max}/cm^{-1} (neat) 1736 (ester C=O), and 1459 (C=C);
δ_H (60 MHz $CDCl_3$) 0.90 (6H, t, J = 7.31 Hz, 2 x $O_2CCH_2CH_2C\underline{H_3}$), 1.60 (4H, sextet, J = 7.40 Hz, $O_2CCH_2C\underline{H_2}CH_3$), 2.30 (4H, t, J = 7.40 Hz, 2 x $O_2CC\underline{H_2}CH_2CH_3$), 4.70 (4H, m, 1- and 4-CH_2) and 5.70 (2H, m, 2- and 3-CH).

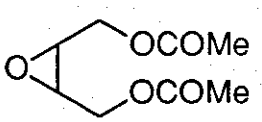
Preparation of *cis-2-buten-1,4-diyl dioctanoate* (65)



(65)

cis-2-Buten-1,4-diol was treated with octanoyl chloride as above. *cis*-2-Buten-1,4-diyl dioctanoate (65) was isolated as an orange liquid (89%);
υ_{max}/cm^{-1} (neat) 1737 (ester C=O) and 1442 (C=C);
δ_H (60 MHz $CDCl_3$) 0.90 (6H, t, J = 7.40 Hz, 2 x $O_2CCH_2[CH_2]_5C\underline{H_3}$), 1.00-1.70 (20H, m, 2 x $O_2CCH_2[C\underline{H_2}]_5CH_3$), 2.30 (4H, t, J = 7.40 Hz, 2 x $O_2CC\underline{H_2}[CH_2]_5CH_3$), 4.70 (4H, m, 1- and 4-CH_2) and 5.70 (2H, m, 2- and 3-CH).

Preparation of *meso 2,3-epoxybutan-1,4-diyl diacetate* (59).

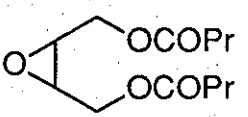


(59)

To a rapidly stirred and cooled (ice-bath) solution of *cis*-2-buten-1,4-diyl diacetate (3.65 g, 16 mmol), urea hydrogenperoxide (15 g, 160 mmol) and disodium hydrogen phosphate (22.6 g, 160 mmol) in anhydrous dichloromethane (120 cm^3), trifluoroacetic anhydride (6 cm^3, 40 mmol) was added over 30 minutes. The resulting mixture was stirred at 0°C for 1.5 hours, heated at reflux for an hour and then stirred at room temperature for 14 hours. After this time the solution was washed with a saturated sodium hydrogen carbonate solution (x 4), a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a yellow liquid. Purification by flash chromatography (1:3 diethyl ether :

light petroleum (b.p. 40-60°C)), followed by recrystallisation from 1:1 ethyl acetate : light petroleum (b.p. 40-60°C) gave (59) as clear crystals (22%); m.p. 38°C [lit.[58] m.p. 38-39°C];
υ_{max}/cm^{-1} (KBr disc) 1739 (ester C=O);
δ_H (250 MHz $CDCl_3$) 2.11 (6H, s, 2 x CH_3), 3.29 (2H, quintet, J = 4.25 Hz, 2- and 3-CH), 4.11 (2H, dd, J_{AX} = 6.60 and J_{AB} = 12.34 Hz, 1- and 4-CH_A) and 4.35 (2H, dd, J_{BX} = 3.71 and J_{AB} = 12.30 Hz, 1 and 4-CH_B);
δ_C (62.9 MHz, $CDCl_3$) 20.72 (2 x CH_3), 53.32 (2- and 3-CH), 62.21 (1- and 4-CH_2) and 170.63 (2 x CO_2);
m/z (F.A.B.) 189 (46%, MH^+), 231 (60, M plus $COMe^+$) and 43 (100, $COMe^+$).

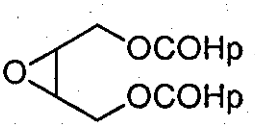
Preparation of *meso 2,3-epoxybutan-1,4-diyl dibutanoate* (60).



(60)

Meso 2,3-epoxybutan-1,4-diyl dibutanoate (60) was prepared from (64), using the same conditions as were employed in the preparation of (59). Purification by flash chromatography (3:1 light petroleum (b.p. 40-60°C) : diethyl ether) afforded (60) as a clear and colourless liquid (36%);
υ_{max}/cm^{-1} (neat) 1738 (ester C=O);
δ_H (250 MHz $CDCl_3$) 0.96 (6H, t, J = 7.41 Hz, 2 x $O_2CCH_2CH_2C\underline{H}_3$), 1.67 (4H, sextet, J = 7.41 Hz, 2 x $O_2CCH_2C\underline{H}_2CH_3$), 2.34 (4H, t, J = 7.40 Hz, 2 x $O_2C\underline{C}H_2CH_2CH_3$), 3.28 (2H, quintet, J = 3.90 Hz, 2- and 3-CH), 4.11 (2H, dd, J_{AX} = 6.58 and J_{AB} = 12.34 Hz, 1- and 4-CH_A) and 4.35 (2H, dd, J_{BX} = 3.86 and J_{AB} = 12.36 Hz, 1- and 4-CH_B);
δ_C (62.9 MHz, $CDCl_3$) 13.65 (2 x CH_3), 18.36 (2 x CH_2), 35.89 (2 x CH_2), 53.40 (2- and 3-CH), 62.03 (1- and 4-CH_2) and 173.27 (2 x CO_2);
m/z (F.A.B.) 245 (60%, MH^+), 315 (5, M plus ^+COPr) and 71 (100, ^+COPr).

Preparation of *meso 2,3-epoxybutan-1,4-diyl dioctanoate* (61).

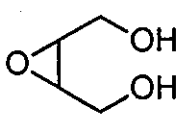


(61)

Meso 2,3-epoxybutan-1,4-diyl dioctanoate (61) was prepared from (65), using the same conditions as were employed in the preparation of (59). Purification by recrystallisation from 1:5 diethyl ether : light petroleum (b.p. 40-60°C) afforded (61) as colourless crystals (20%); m.p. 52.5°C;
υ_{max}/cm^{-1} (KBr disc) 1736 (ester C=O);

δ_H (250 MHz $CDCl_3$) 0.88 (6H, t, J = 7.40 Hz, 2 x $O_2CCH_2CH_2[CH_2]_4C\underline{H}_3$), 1.28 (16H, m, 2 x $O_2CCH_2CH_2[C\underline{H}_2]_4CH_3$), 1.63 (4H, quintet, J = 7.26 Hz, 2 x $O_2CCH_2C\underline{H}_2[CH_2]_4CH_3$), 2.36 (4H, t, J = 7.49 Hz, 2 x $O_2CC\underline{H}_2CH_2[CH_2]_4CH_3$), 3.28 (2H, quintet, J = 4.21 Hz, 2- and 3-CH), 4.11 (2H, dd, J_{AX} = 6.57 and J_{AB} = 12.32 Hz, 1- and 4-CH_A) and 4.34 (2H, dd, J_{BX} = 3.66 and J_{AB} = 12.27 Hz, 1- and 4-CH_B);
δ_C (62.9 MHz, $CDCl_3$) 14.07 (2 x CH_3), 22.61 (2 x CH_2), 24.88 (2 x CH_2), 28.92 (2 x CH_2), 29.09 (2 x CH_2), 31.66(2 x CH_2), 34.06 (2 x CH_2), 53.41 (2- and 3-CH), 62.04 (1- and 4-CH_2) and 173.47 (2 x CO_2);
m/z (F.A.B.) 357 (45%, MH^+), 483 (10, M plus $COC_7H_{15}^+$) and 127 (100, $COC_7H_{15}^+$).

Preparation of *meso 2,3-epoxybutan-1,4-diol* (66).



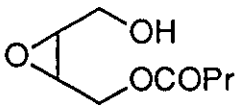
(66)

To a stirred and cooled (ice-bath) solution of *cis*-2-buten-1,4-diol (5.0 g, 57 mmol) in anhydrous diethyl ether (50 cm^3), m-chloroperoxybenzoic acid (11.7 g, 68 mmol) was added in one portion. After stirring at room temperature for 2 hours the mixture was cooled to -5°C and the solid filtered and washed with cold diethyl ether (30 cm^3). *Meso* 2,3-epoxybutan-1,4-diol (66) was isolated as clear crystals (4.8 g, 81%) after recrystallisation from 1:3 diethyl ether : light petroleum (b.p. 40-60°C); m.p. 52-53°C [lit.[52] m.p. 50-52°C];
υ_{max}/cm^{-1} (KBr disc) 3386 (OH);
δ_H (250 MHz $CDCl_3$) 2.97 (2H, t, J = 4.83 Hz, 2- and 3-CH), 3.48 (4H, m, 1- and 4-CH_2) and 4.29 (2H, br s, 2 x OH);
δ_C (62.9 MHz, $CDCl_3$) 56.54 (2- and 3-CH) and 59.82 (1- and 4-CH_2).

Alternative preparation of *meso 2,3-epoxybutan-1,4-diyl dibutanoate* (60).

To a stirred solution of *meso* 2,3-epoxy-1,4-diol (1 g, 9.6 mmol) and pyridine (4.0 cm^3) in anhydrous carbon tetrachloride (20 cm^3), butanoyl chloride (2.3 cm^3, 22 mmol) was added drop-wise. After stirring at room temperature for 16 hours the solution was washed with a saturated sodium hydrogen carbonate solution (x 3), hydrochloric acid (2 M) (x 4), a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a clear orange liquid. Kugelrohr distillation afforded (60) as a clear liquid (1.9 g, 81%); b.p. (0.05 mmHg) 155°C. All spectroscopic data as for previously prepared (60).

Preparation of *4-butanoyloxy-2,3-epoxybutan-1-ol* (67).



(67)

To a stirred solution of *meso* 2,3-epoxy-1,4-diol (1.5 g, 14.4 mmol) and pyridine (5 cm^3) in anhydrous chloroform (30 cm^3), butanoyl chloride (1.6 cm^3, 14.4 mmol) was added drop-wise. After stirring at room temperature for 16 hours the solution was washed with a saturated sodium hydrogen carbonate solution (x 3), hydrochloric acid (2 M) (x 4), a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a clear liquid. Purification by flash chromatography (3:1 light petroleum (b.p. 40-60°C) : diethyl ether) afforded (67) as a clear and colourless liquid (1.4 g, 56%);
υ_{max}/cm^{-1} (neat) 3424 (OH) and 1734 (ester C=O);
δ_H (250 MHz $CDCl_3$) 0.96 (3H, t, J = 7.36 Hz, $O_2CCH_2CH_2C\underline{H}_3$), 1.67 (2H, sextet, J = 7.44 Hz, $O_2CCH_2C\underline{H}_2CH_3$), 2.36 (2H, t, J = 7.36 Hz, $O_2CC\underline{H}_2CH_2CH_3$), 2.59 (1H, br s, OH), 3.24 (2H, sextet, J = 4.83 Hz, 2- and 3-CH), 3.82 (2H, d, J = 4.93 Hz, 1-CH_2), 4.15 (1H, dd, J_{AX} = 5.65 and J_{AB} = 12.13 Hz, 4-CH_A) and 4.34 (1H, dd, J_{BX} = 5.17 and J_{AB} = 12.26 Hz, 4-CH_B);
δ_C (62.9 MHz, $CDCl_3$) 13.56 (CH_3), 18.27 (CH_2), 35.86 (CH_2), 53.89 (2-CH), 56.35 (3-CH), 60.12 (1-CH_2), 62.03 (4-CH_2) and 173.71 (CO_2);
m/z (F.A.B.) 175 (MH^+, 100%), 245 (10, M plus +COPr) and 71 (80, +COPr).

Enzymatic hydrolysis of *meso 2,3-epoxybutan-1,4-diyl dibutanoate.*

9-(1) Porcine pancreatic lipase, 88% conversion.

To a vigorously stirred solution of *meso* 2,3-epoxybutan-1,4-diyl dibutanoate (170 mg, 0.7 mmol) in an aqueous phosphate buffer (0.05 M, pH 7.0, 15 cm^3) at 20°C, porcine pancreatic lipase (15 mg) was added. The pH of the solution was maintained at 7.0 by the addition of sodium hydroxide solution (1M) from a Metrohm 665 Dosimat, in conjunction with a Metrohm 691 pH meter. After 1.6 hours, 0.616 cm^3 of sodium hydroxide solution had been added (88% conversion) and the solution was quickly extracted with diethyl ether (5 x 10 cm^3). The extracts were washed with a saturated sodium hydrogen carbonate solution (x 3), a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a clear liquid. Purification by flash chromatography (3:1 light petroleum (b.p. 40-60°C) : ethyl acetate) afforded optically enriched (2S, 3R)-4-butanoyloxy-2,3-epoxybutan-1-ol as a clear liquid (66 mg, 62%);

$[\alpha]_D^{20}$ +13.8°; 70% e.e. [by integration of ^{19}F N.M.R. spectrum of (70)]. All spectroscopic data as for previously prepared (67).

9-(2) Porcine pancreatic lipase, at 4°C.

The general hydrolysis procedure, as described above, was followed with the following parameters; enzyme:- porcine pancreatic lipase; temperature 4°C; reaction time 2.0 hours; percentage conversion 69%; chemical yield 61%; $[\alpha]_D^{20}$ +13.5°; e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 69% (2S, 3R major isomer). All spectroscopic data as for previously prepared (67).

9-(3) Porcine pancreatic lipase, at 35°C.

The general hydrolysis procedure, as described above, was followed with the following parameters; enzyme:- porcine pancreatic lipase; temperature 35°C; reaction time 1.0 hours; percentage conversion 94%; chemical yield 65%; $[\alpha]_D^{20}$ +7.8°; e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 40% (2S, 3R major isomer). All spectroscopic data as for previously prepared (67).

9-(4) *Pseudomonas fluorescens* lipase.

The general hydrolysis procedure, as described above, was followed with the following parameters; enzyme:- *Pseudomonas fluorescens* lipase; temperature 20°C; reaction time 0.2 hours; percentage conversion 100%; chemical yield 83%; $[\alpha]_D^{20}$ +3.3°; e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 16% (2S, 3R major isomer). All spectroscopic data as for previously prepared (67).

9-(5) *Rhizopus niveus* lipase.

The general hydrolysis procedure, as described above, was followed with the following parameters; enzyme:- *Rhizopus niveus* lipase; temperature 20°C; reaction time 13.0 hours; percentage conversion 66%; chemical yield 71%; $[\alpha]_D^{20}$ +10.7°; e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 54% (2S, 3R major isomer). All spectroscopic data as for previously prepared (67).

9-(6) *Rhizopus delemar* lipase.

The general hydrolysis procedure, as described above, was followed with the following parameters; enzyme:- *Rhizopus delemar* lipase; temperature 20°C; reaction time 6.0 hours; percentage conversion 79%; chemical yield 86%; $[\alpha]_D^{20}$ +10.8°; e.e. [by integration of ^{19}F N.M.R. spectrum of (70)] 54% (2S, 3R major isomer). All spectroscopic data as for previously prepared (67).

9-(7) Immobilized porcine pancreatic lipase.

The general hydrolysis procedure, as described above, was followed with the following parameters; enzyme:- immobilized porcine pancreatic lipase; temperature 22°C; reaction time 0.75 hours; percentage conversion 100%; chemical yield 83%; $[\alpha]_D^{20}$ +2.1°; e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 11% (2S, 3R major isomer). All spectroscopic data as for previously prepared (67).

9-(8) Immobilized *Geotrichum candidum* lipase.

The general hydrolysis procedure, as described above, was followed with the following parameters; enzyme:- immobilized *Geotrichum candidum* lipase; temperature 20°C; reaction time 5.0 hours; percentage conversion 76%; chemical yield 65%; $[\alpha]_D^{20}$ +1.3°; e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 7% (2S, 3R major isomer). All spectroscopic data as for previously prepared (67).

9-(9) Immobilized *Mucor* lipase (LIP F8).

The general hydrolysis procedure, as described above, was followed with the following parameters; enzyme:- immobilized *Mucor* lipase (LIP F8); temperature 20°C; reaction time 2.0 hours; percentage conversion 80%; chemical yield 73%; $[\alpha]_D^{20}$ +11.0°; e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 56% (2S, 3R major isomer). All spectroscopic data as for previously prepared (67).

9-(10) Immobilized *Humicola laruginosa* lipase.

The general hydrolysis procedure, as described above, was followed with the following parameters; enzyme:- immobilized *Humicola laruginosa* lipase; temperature 20°C; reaction time 2.5 hours; percentage conversion 73%; chemical yield 49%; $[\alpha]_D^{20}$ +4.8°; e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 24% (2S, 3R major isomer). All spectroscopic data as for previously prepared (67).

9-(11) Immobilized *Aspergillus* lipase (LIP F9).

The general hydrolysis procedure, as described above, was followed with the following parameters; enzyme:- immobilized *Aspergillus* lipase (LIP F9); temperature 20°C; reaction time 24 hours; percentage conversion 43%; chemical yield 56%; $[\alpha]_D^{20}$ +1.8°; e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 9% (2S, 3R major isomer). All spectroscopic data as for previously prepared (67).

9-(12) Immobilized *Rhizopus delemar* lipase.

The general hydrolysis procedure, as described above, was followed with the following parameters; enzyme:- immobilized *Rhizopus delemar* lipase; temperature 24°C; reaction time 4.7 hours; percentage conversion 85%; chemical yield 85%; $[\alpha]_D^{20}$ +13.3°; e.e. [by integration of ^{19}F N.M.R. spectrum of (70)] 68% (2S, 3R major isomer). All spectroscopic data as for previously prepared (67).

9-(13) Immobilized *Rhizopus* lipase (LIP F1).

The general hydrolysis procedure, as described above, was followed with the following parameters; enzyme:- immobilized *Rhizopus* lipase (LIP F1); temperature 20°C; reaction time 4.5 hours; percentage conversion 82%; chemical yield 59%; $[\alpha]_D^{20}$ +14.7°; e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 75% (2S, 3R major isomer). All spectroscopic data as for previously prepared (67).

9-(14) Immobilized *Rhizopus* lipase (LIP F3).

The general hydrolysis procedure, as described above, was followed with the following parameters; enzyme:- immobilized *Rhizopus* lipase (LIP F3); temperature 18°C; reaction time 1.5 hours; percentage conversion 78%; chemical yield 59%; $[\alpha]_D^{20}$ +15.8°; e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 77% (2S, 3R major isomer). All spectroscopic data as for previously prepared (67).

9-(15) Immobilized *Rhizopus* lipase (LIP F4).

The general hydrolysis procedure, as described above, was followed with the following parameters; enzyme:- immobilized *Rhizopus* lipase (LIP F4); temperature 19°C; reaction time 6.0 hours; percentage conversion 88%; chemical yield 75%; $[\alpha]_D^{20}$ +11.9°; e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 61% (2S, 3R major isomer). All spectroscopic data as for previously prepared (67).

10-(1) *Candida cylindracea* lipase.

The general hydrolysis procedure, as described above, was followed with the following parameters; enzyme:- *Candida cylindracea* lipase; temperature 24°C; reaction time 1.6 hours; percentage conversion 100%; chemical yield 68%; $[\alpha]_D^{20}$ -3.3°; e.e. [by integration of ^{19}F N.M.R. spectrum of (70)] 19% (2R, 3S major isomer). All spectroscopic data as for previously prepared (67).

10-(2) Immobilized *Penicillium* lipase (LIP F11).

The general hydrolysis procedure, as described above, was followed with the following parameters; enzyme:- immobilized *Penicillium* lipase (LIP F11); temperature 17°C; reaction time 5.0 hours; percentage conversion 82%; chemical yield 47%; $[\alpha]_D^{20}$ -9.9°; e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 50% (2R, 3S major isomer). All spectroscopic data as for previously prepared (67).

10-(3) Immobilized *Penicillium* lipase (LIP F12).

The general hydrolysis procedure, as described above, was followed with the following parameters; enzyme:- immobilized *Penicillium* lipase (LIP F12); temperature 20°C; reaction time 7.25 hours; percentage conversion 70%; chemical yield 74%; $[\alpha]_D^{20}$ -12.2°; e.e. [by integration of ^{19}F N.M.R. spectrum of (70)] 61% (2R, 3S major isomer). All spectroscopic data as for previously prepared (67).

11-(1) Pig liver esterase.

The general hydrolysis procedure, as described above, was followed with the following parameters; enzyme:- pig liver esterase; temperature 24°C; reaction time 0.75 hours; percentage conversion 100%; chemical yield 45%; $[\alpha]_D^{20}$ 0°; e.e. 0%. All spectroscopic data as for previously prepared (67).

11-(2) Immobilized *Pseudomonas fluorescens* lipase.

The general hydrolysis procedure, as described above, was followed with the following parameters; enzyme:- immobilized *Pseudomonas fluorescens* lipase; temperature 20°C; reaction time 1.25 hours; percentage conversion 85%; chemical yield 80%; $[\alpha]_D^{20}$ 0°; e.e. 0%. All spectroscopic data as for previously prepared (67).

11-(3) Immobilized *Candida* lipase (LIP F6).

The general hydrolysis procedure, as described above, was followed with the following parameters; enzyme:- immobilized *Candida* lipase (LIP F6); temperature 20°C; reaction time 0.7 hours; percentage conversion 78%; chemical yield 71%; $[\alpha]_D^{20}$ 0°; e.e. 0%. All spectroscopic data as for previously prepared (67).

11-(4) Immobilized *Aspergillus usamii* lipase.

The general hydrolysis procedure, as described above, was followed with the following parameters; enzyme:- immobilized *Aspergillus usamii* lipase; temperature 20°C; reaction time 24 hours; percentage conversion 0%. No hydrolysis occurred and starting material recovered in 92% yield.

14-(2) Porcine pancreatic lipase, 51% conversion.

The general hydrolysis procedure, as described above, was followed with the following parameters; enzyme:- porcine pancreatic lipase; temperature 20°C; reaction time 0.5 hours; percentage conversion 51%; chemical yield 62%; $[\alpha]_D^{20}$ +15.8°; e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 77% (2S, 3R major isomer). All spectroscopic data as for previously prepared (67).

14-(3) Porcine pancreatic lipase, 31% conversion.

The general hydrolysis procedure, as described above, was followed with the following parameters; enzyme:- porcine pancreatic lipase; temperature 20°C; reaction time 0.3 hours; percentage conversion 31%; chemical yield 64%; $[\alpha]_D^{20}$ +16.0°; e.e. [by integration of ^{19}F N.M.R. spectrum of (70)] 80% (2S, 3R major isomer). All spectroscopic data as for previously prepared (67).

Controls for enzymatic hydrolysis of *meso* 2,3-epoxybutan-1,4-diyl dibutanoate.

(I) Hydrolysis with denatured lipase.

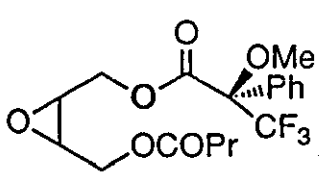
A sample of porcine pancreatic lipase (30 mg) was added to a stirred and refluxing aqueous phosphate buffer (0.05 M, pH 7.0, 15 cm^3). After 3 minutes the solution was cooled to 20°C and *meso* 2,3-epoxybutan-1,4-diyl dibutanoate (50 mg, 0.2 mmol) added. The pH of the solution was monitored for 5 hours, during which no decrease in pH was observed. The t.l.c. (1:1 diethyl ether : light petroleum (b.p. 40-60°C)) of the solution was taken after this time and showed only the presence of *meso* 2,3-epoxybutan-1,4-diyl dibutanoate (R_f. 0.7).

The above procedure was repeated with the following lipases:- *Rhizopus delemar* lipase, immobilized *Rhizopus delemar* lipase, *Candida cylindracea* lipase, *Penicillium* lipase (LIP F11) and *Pseudomonas fluorescens* lipase. In all cases no decrease in pH was observed and no other products were observed by t.l.c. analysis.

(II) Analysis of extract from lipase.

An aqueous phosphate buffer (0.05 M, pH 7.0, 20 cm^3), containing porcine pancreatic lipase (50 mg) was extracted with diethyl ether (3 x 20 cm^3), washed with a saturated sodium chloride solution, dried (magnesium sulfate) and concentrated to ~1 cm^3. T.l.c. (1:1 diethyl ether : light petroleum (b.p. 40-60°C)) analysis of this solution did not show the presence any *meso* 2,3-epoxybutan-1,4-diyl dibutanoate (R_f. 0.7) or 4-butanoyloxy-2,3-epoxybutan-1-ol (R_f. 0.3).

Preparation of racemic *4-butanoyloxy-2,3-epoxy-1-([(R)-(+)-α-methoxy-α-(trifluoromethyl)phenyl]acetoxy)-butane* (70).



(70)

To a stirred solution of racemic 4-butanoyloxy-2,3-epoxybutan-1-ol (24 mg, 0.14 mmol) and anhydrous pyridine (6 drops) in anhydrous carbon tetrachloride (1 cm^3), (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (50 mg, 0.18 mmol) was added in one portion. After stirring at room temperature for 16 hours, the solution was diluted with diethyl ether (20 cm^3), washed with a saturated sodium hydrogen carbonate solution (x 3), hydrochloric acid (2 M) (x 4),

a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness affording (70) as a viscous oil (52 mg, 97%);
υ_{max}/cm^{-1} (neat) 1748 (Mosher's ester C=O) and 1739 (ester C=O);
δ_H (250 MHz $CDCl_3$) 0.95 (3H, t, J = 7.37 Hz, $O_2CCH_2CH_2C\underline{H_3}$), 1.65 (2H, sextet, J = 7.37 Hz, $O_2CCH_2C\underline{H_2}CH_3$), 2.32 and 2.33 (2H, 2 x t, J = 7.38 Hz, R and S $O_2CC\underline{H_2}CH_2CH_3$), 3.36 (2H, m, 2- and 3-CH), 3.57 and 3.58 (3H, 2 x s, R and S - OMe), 4.13 (1H, dd, J_{AX} = 6.27 and J_{AB} = 12.32 Hz, 4-CH_A), 4.25-4.54 (3H, m, 4-CH_B and 1-CH_2) and 7.42 (5H, m, C_6H_5);
δ_F (340 MHz, CCl_3F) -72.155 (CF_3 R or S) and -72.208 (CF_3 S or R).

Preparation of optically enriched *(2S, 3R)-4-butanoyloxy-2,3-epoxy-1-([(R)-(+)-α-methoxy-α-(trifluoromethyl)phenyl]acetoxy)-butane (70).*

Prepared as above using 4-butanoyloxy-2,3-epoxybutan-1-ol with an $[\alpha]_D^{20}$ of +16.0°. (2S, 3R)-4-Butanoyloxy-2,3-epoxy-1-([(R)-(+)-α-methoxy-α-(trifluoromethyl)phenyl]acetoxy)-butane (70) was isolated as a clear liquid (100%); 80% d.e. by integration of ^{19}F N.M.R. (CF_3) peaks; ratio of δ -72.155 : δ -72.208 was 9 : 1. All other spectroscopic data as for previously prepared (70).

Prepared as above using 4-butanoyloxy-2,3-epoxybutan-1-ol with an $[\alpha]_D^{20}$ of +13.8°. (2S, 3R)-4-Butanoyloxy-2,3-epoxy-1-([(R)-(+)-α-methoxy-α-(trifluoromethyl)phenyl]acetoxy)-butane (70) was isolated as a clear liquid (96%); 70% d.e. by integration of ^{19}F N.M.R. (CF_3) peaks; ratio of δ -72.155 : δ -72.208 was 5.66 : 1. All other spectroscopic data as for previously prepared (70).

Prepared as above using 4-butanoyloxy-2,3-epoxybutan-1-ol with an $[\alpha]_D^{20}$ of +13.3°. (2S, 3R)-4-Butanoyloxy-2,3-epoxy-1-([(R)-(+)-α-methoxy-α-(trifluoromethyl)phenyl]acetoxy)-butane (70) was isolated as a clear liquid (100%); 68% d.e. by integration of ^{19}F N.M.R. (CF_3) peaks; ratio of δ -72.155 : δ -72.208 was 5.28 : 1. All other spectroscopic data as for previously prepared (70).

Prepared as above using 4-butanoyloxy-2,3-epoxybutan-1-ol with an $[\alpha]_D^{20}$ of +10.8°. (2S, 3R)-4-Butanoyloxy-2,3-epoxy-1-([(R)-(+)-α-methoxy-α-(trifluoromethyl)phenyl]acetoxy)-butane (70) was isolated as a clear liquid (100%); 54% d.e. by integration of ^{19}F N.M.R. (CF_3) peaks; ratio of δ -72.155 : δ -72.208 was 3.35 : 1. All other spectroscopic data as for previously prepared (70).

Preparation of optically enriched *(2R, 3S)-4-butanoyloxy-2,3-epoxy-1-([(R)-(+)-α-methoxy-α-(trifluoromethyl)phenyl]acetoxy)-butane* (70).

Prepared as above using 4-butanoyloxy-2,3-epoxybutan-1-ol with an $[\alpha]_D^{20}$ of -3.3°. (2R, 3S)-4-Butanoyloxy-2,3-epoxy-1-([(R)-(+)-α-methoxy-α-(trifluoromethyl)phenyl]acetoxy)-butane (70) was isolated as a clear liquid (92%); 19% d.e. by integration of ^{19}F N.M.R. (CF_3) peaks; ratio of δ -72.155 : δ -72.208 was 1 : 1.47. All other spectroscopic data as for previously prepared (70).

Prepared as above using 4-butanoyloxy-2,3-epoxybutan-1-ol with an $[\alpha]_D^{20}$ of -12.2°. (2R, 3S)-4-Butanoyloxy-2,3-epoxy-1-([(R)-(+)-α-methoxy-α-(trifluoromethyl)phenyl]acetoxy)-butane (70) was isolated as a clear liquid (98%); 61% d.e. by integration of ^{19}F N.M.R. (CF_3) peaks; ratio of δ -72.155 : δ -72.208 was 1 : 4.17. All other spectroscopic data as for previously prepared (70).

Enzymatic hydrolysis of *meso 2,3-epoxybutan-1,4-diyl dibutanoate* in mixed solvent systems.

(1) 2:1 Aqueous phosphate buffer : hexane.

The general hydrolysis procedure, as described previously, was followed with the following parameters; solvent:- aqueous phosphate buffer (0.05 M, pH 7.0, 10 cm^3) : hexane (5 cm^3); enzyme:- porcine pancreatic lipase; temperature 15°C; reaction time 0.75 hours; percentage conversion 77%; chemical yield 53%; $[\alpha]_D^{20}$ +13.3°; e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 68% (2S, 3R major isomer). All spectroscopic data as for previously prepared (67).

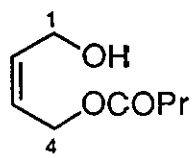
(2) 9:1 Aqueous phosphate buffer : *tert*-butanol.

The general hydrolysis procedure, as described previously, was followed with the following parameters; solvent:- aqueous phosphate buffer (0.05 M, pH 7.0, 13 cm^3) : *tert*-butanol (1.4 cm^3); enzyme:- immobilized *Rhizopus* lipase (LIP F1); temperature 20°C; reaction time 9.5 hours; percentage conversion 100%; chemical yield 49%; $[\alpha]_D^{20}$ +12.3°; e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 63% (2S, 3R major isomer). All data as for previously prepared (67).

(3) 9:1 Aqueous phosphate buffer : dimethylsulfoxide.

The general hydrolysis procedure, as described previously, was followed with the following parameters; solvent:- aqueous phosphate buffer (0.05 M, pH 7.0, 18 cm^3) : dimethylsulfoxide (2.0 cm^3); enzyme:- immobilized *Rhizopus* lipase (LIP F1); temperature 20°C; reaction time 2.5 hours; percentage conversion 91%; chemical yield 59%; $[\alpha]_D^{20}$ +14.3°; e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 72% (2S, 3R major isomer). All data as for previously prepared (67).

Preparation of *cis-4-butanoyloxy-2-buten-1-ol* (79).



(79)

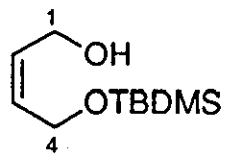
To a stirred solution of *cis*-2-buten-1,4-diol (3.0 g, 34 mmol) and anhydrous pyridine (5 cm^3) in anhydrous chloroform (50 cm^3) butanoyl chloride (3.5 cm^3, 33.5 mmol) was added drop-wise. After stirring at room temperature for 16 hours, the solution was washed with a saturated sodium hydrogen carbonate solution (x 3), hydrochloric acid (2 M) (x 3), a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a yellow liquid. Purification by flash chromatography (1:2 ethyl acetate : light petroleum (b.p. 40-60°C)), followed by Kugelrohr distillation afforded (79) as a clear and colourless liquid (1.55 g, 30%); b.p. (0.05 mmHg) 100°C;
υ_{max}/cm^{-1} (neat) 3343 (OH), 1738 (ester C=O) and 1458 (C=C);
δ_H (60 MHz $CDCl_3$) 0.90 (3H, t, J = 7.30 Hz, $O_2CCH_2CH_2C\underline{H_3}$), 1.60 (2H, sextet, J = 7.40 Hz, $O_2CCH_2C\underline{H_2}CH_3$), 2.30 (2H, t, J = 7.40 Hz, $O_2CC\underline{H_2}CH_2CH_3$), 3.20 (1H, br s, OH), 4.20 (2H, d, J = 5.50 Hz, 1-CH_2), 4.70 (2H, d, J = 5.5 Hz, 4-CH_2) and 5.70 (2H, m, 2- and 3-CH);
m/z (E.I.) 71 (+COPr, 100%).

Attempted Sharpless asymmetric epoxidation of *cis-4-butanoyloxy-2-buten-1-ol.*

A vigorously stirred solution of diethyl-(L)-tartrate (146 mg, 0.7 mmol), titanium(IV) isopropoxide (133 mg, 0.47 mmol), powdered 4Å molecular sieves (0.4 g) and anhydrous *tert*-butylhydroperoxide (4.98 M, 2.9 cm^3, 14.2 mmol) in anhydrous dichloromethane (10 cm^3) was cooled to -30°C. After 10 minutes at this temperature *cis*-4-butanoyloxy-2-buten-1-ol (1.5 g, 9.5 mmol) in anhydrous dichloromethane (1 cm^3) was added drop-wise over 15 minutes. The resulting solution was stirred at -15°C for 4 hours and then washed with hydrochloric acid

(2 M) (x 3), a saturated sodium hydrogen carbonate solution, a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a light yellow liquid. The ^1H .N.M.R spectrum of this crude product showed only the presence of *cis*-4-butanoyloxy-2-buten-1-ol, and none of the epoxidised product.

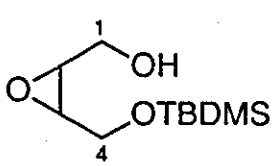
Preparation of *cis-4-(tert-butyldimethylsilyloxy)-2-buten-1-ol* (80).



(80)

To a stirred solution of *cis*-2-buten-1,4-diol (10.0 g, 113 mmol) and imidazole (1.35 g, 19.9 mmol) in anhydrous *N,N*-dimethylformamide (40 cm^3), *tert*-butlydimethylsilyl chloride (5.7 g, 37.6 mmol) in anhydrous *N,N*-dimethylformamide (10 cm^3) was added in one portion. After stirring at room temperature for 48 hours, the solution was diluted with diethyl ether (200 cm^3), washed with water (x 3), a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a clear liquid. Purification by dry flash chromatography (1:3 ethyl acetate : light petroleum (b.p. 40-60°C)), followed by Kugelrohr distillation, afforded (80) as a clear and colourless liquid (2.77 g, 83%);
b.p. (0.4 mmHg) 90°C;
υ_{max}/cm^{-1} (neat) 3343 (OH) and 1472 (C=C);
δ_H (250 MHz $CDCl_3$) 0.07 (6H, s, Si-Me_2), 0.91 (9H, s, t-Bu), 1.88 (1H, br s, OH), 4.21 (4H, m, 1- and 4-CH_2) and 5.77 (2H, m, 2- and 3-CH);
δ_C (62.9 MHz, $CDCl_3$) -3.61 ($SiMe_2$), 18.33 (C), 25.89 (3 x Me), 58.83 (CH_2), 59.65 (CH_2), 130.03 (CH) and 131.17 (CH).

Preparation of racemic *4-(tert-butyldimethylsilyloxy)-2,3-epoxybutan-1-ol* (81).



(81)

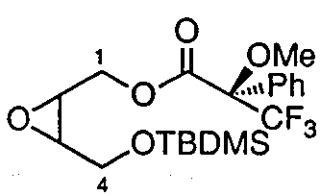
4-(*tert*-Butyldimethylsilyloxy)-2,3-epoxybutan-1-ol (81) was prepared from *meso* 2,3-epoxybutan-1,4-diol (66), using the same conditions employed in the preparation of (80). Purification by flash chromatography (1:6 ethyl acetate : light petroleum (b.p. 40-60°C)) afforded (81) as a clear colourless liquid (400 mg, 49%);
υ_{max}/cm^{-1} (neat) 3428 (OH);

δ_H (250 MHz $CDCl_3$) 0.11 (3H, s, Si-Me), 0.12 (3H, s, Si-Me), 0.91 (9H, s, t-Bu), 2.00 (1H, br s, OH), 3.23 (2H, m, 2- and 3-CH), 3.74 (3H, m, 1-CH_2 and 4-CH_A) and 3.92 (1H, dd, J_{BX} = 5.56 and J_{AB} = 11.60 Hz, 4-CH_B);
δ_C (62.9 MHz, $CDCl_3$) -5.44 (SiMe), -5.28 (SiMe), 18.27 (C), 25.83 (3 x Me), 56.05 (CH), 56.37 (CH), 60.84 (CH_2) and 61.61 (CH_2).

Preparation of *(2S, 3R)-4-(tert-butyldimethylsilyloxy)-2,3-epoxybutan-1-ol* (81)

A vigorously stirred solution of diethyl-(L)-tartrate (146 mg, 0.7 mmol), titanium(IV) isopropoxide (133 mg, 0.47 mmol), powdered 4Å molecular sieves (0.4 g) and anhydrous *tert*-butylhydroperoxide (4.98 M, 3.0 cm^3, 15 mmol) in anhydrous dichloromethane (10 cm^3) was cooled to -20°C. After 10 minutes at this temperature the *cis*-4-(*tert*-butyldimethylsilyloxy)-2-buten-1-ol (1.92 g, 9.5 mmol) was added drop-wise. The resulting solution was stirred at -10°C for 3.0 hours and then at 0°C for 0.7 hours. The resulting solution was washed with sodium hydroxide solution (1 M), hydrochloric acid (2 M) (x 3), a saturated sodium hydrogen carbonate solution, a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a clear and colourless liquid. Purification by flash chromatography (1:2 diethyl ether : light petroleum (b.p. 40-60°C)), followed by Kugelrohr distillation afforded optically enriched (2S, 3R)-4-(*tert*-butyldimethylsilyloxy)-2,3-epoxybutan-1-ol (81) as a clear and colourless liquid (600 mg, 34%); b.p. (0.04 mmHg) 70°C;
$[\alpha]_D^{20}$ -12.1°; e.e. [by integration of ^{19}F N.M.R spectrum of (82)] 53%. All spectroscopic data as for previously prepared (81).

Preparation of racemic *4-(tert-butyldimethylsilyloxy)-2,3-epoxy-1-[[(R)-(+)-α-methoxy-α-(trifluoromethyl)phenyl]acetoxy)-butane* (82).



(82)

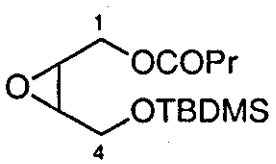
To a stirred solution of racemic 4-(*tert*-butyldimethylsilyloxy)-2,3-epoxy-butan-1-ol (23 mg, 0.11 mmol) and anhydrous pyridine (10 drops) in anhydrous carbon tetrachloride (1 cm^3), (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (40 mg, 0.16 mmol) was added in one portion. After stirring at room temperature for 16 hours the solution was diluted with chloroform (40 cm^3), washed with a saturated sodium carbonate solution, hydrochloric acid (2 M) (x 2), a saturated sodium hydrogen carbonate solution (x 4), a saturated sodium

chloride solution, dried (magnesium sulfate) and evaporated to dryness giving (82) as a viscous oil (46 mg, 100%);
υ_{max}/cm^{-1} (neat) 1747 (Mosher's ester C=O);
δ_H (250 MHz $CDCl_3$) 0.08 (3H, s, Si-Me), 0.09 (3H, s, Si-Me), 0.90 (9H, s, t-Bu), 3.23 (2H, m, 2- and 3-CH), 3.57 (3H, m, OMe), 3.81 (2H, m, 4-CH_2), 4.28 (2H, m, 1-CH_2) and 7.47 (5H, m, C_6H_5);
δ_F (340 MHz, CCl_3F) -72.176 (CF_3 R or S) and -72.253 (CF_3 S or R).

Preparation of optically enriched *(2S, 3R)-4-(tert-butyldimethylsilyloxy)-2,3-epoxy-1-([(R)-(+)-α-methoxy-α-(trifluoromethyl)phenyl]acetoxy)-butane* (82).

Prepared as above, using (2S, 3R)-4-(*tert*-butyldimethylsilyloxy)-2,3-epoxybutan-1-ol with an $[\alpha]_D^{20}$ of -12.1°. (2S, 3R)-4-(*tert*-Butyldimethylsilyloxy)-2,3-epoxy-1-([(R)-(+)-α-methoxy-α-(trifluoromethyl)phenyl]acetoxy)-butane (82) was isolated as a clear oil (100%);
53% d.e. by integration of ^{19}F N.M.R (CF_3) peaks; ratio of δ -72.176 : -72.253 was 3.26 : 1. All other spectroscopic data as for previously prepared (82).

Preparation of optically enriched *(2S, 3R)-4-(tert-butyldimethylsilyloxy)-1-butanoyloxy-2,3-epoxybutane* (83).



(83)

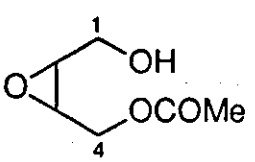
To a stirred solution of optically enriched (2S, 3R)-4-(*tert*-butyldimethylsilyloxy)-2,3-epoxy-butan-1-ol ($[\alpha]_D^{20}$ -12.1°, e.e. 53%, 215 mg, 1 mmol) and pyridine (15 drops) in anhydrous carbon tetrachloride (5 cm^3), butanoyl chloride (160 mg, 1.5 mmol) was added. After stirring at room temperature for 16 hours, the solution was diluted with dichloromethane (20 cm^3) and washed with a saturated sodium hydrogen carbonate solution (x 3), hydrochloric acid (2 M) (x 4), a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a yellow liquid. Purification by flash chromatography (2:1 light petroleum (b.p. 40-60°C) : diethyl ether) afforded (2S, 3R)-(83) as a clear and colourless liquid (207 mg, 73%);
$[\alpha]_D^{20}$ of -10.3°;
υ_{max}/cm^{-1} (neat) 1740 (ester C=O);
δ_H (250 MHz $CDCl_3$) 0.08 (3H, s, SiMe), 0.09 (3H, s, SiMe), 0.91 (9H, s, t-Bu), 0.96 (3H, t, J = 7.32 Hz, $O_2CCH_2CH_2C\underline{H_3}$), 1.67 (2H, sextet, J = 7.37 Hz, $O_2CCH_2C\underline{H_2}CH_3$), 2.33 (2H, t, J = 7.37 Hz, $O_2CC\underline{H_2}CH_2CH_3$), 3.22 (2H, m, 2- and

3-CH), 3.80 (2H, m, 4-CH_2), 4.07 (1H, dd, J_{AX} = 7.01 and J_{AB} = 12.28 Hz, 1-CH_A) and 4.35 (1H, dd, J_{BX} = 3.68 and J_{AB} = 12.28 Hz, 1-CH_B).

Preparation of optically enriched *(2R, 3S)-4-(tert-butyldimethylsilyloxy)-1-butanoyloxy-2,3-epoxybutane* (83).

To a stirred solution of optically enriched (2S, 3R)-4-butanoyloxy-2,3-epoxybutan-1-ol ($[\alpha]_D^{20}$ +9.9°, e.e. 50%, 120 mg, 0.7 mmol) and imidazole (80 mg, 1.2 mmol) in anhydrous *N,N*-dimethylformamide (5 cm^3), *tert*-butlydimethylsilyl chloride (156 mg, 1.0 mmol) in anhydrous *N,N*-dimethylformamide (1 cm^3) was added in one portion. After stirring at room temperature for 20 hours, the solution was diluted with diethyl ether (30 cm^3), washed with a saturated sodium chloride solution (x 3), dried (magnesium sulfate) and evaporated to dryness giving a clear liquid. Purification by flash chromatography (1:3 ethyl acetate : light petroleum (b.p. 40-60°C)) afforded (2R, 3S)-(83) as a clear liquid (160 mg, 80%);
$[\alpha]_D^{20}$ +7.6°. All spectroscopic data as for previously prepared (83).

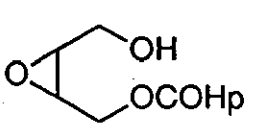
Enzymatic hydrolysis of *meso 2,3-epoxybutan-1,4-diyl diacetate.*



(84)

The general hydrolysis procedure, as described for (60), was followed with *meso* 2,3-epoxybutan-1,4-diyl diacetate (59) as the substrate. The other parameters followed were; enzyme:- porcine pancreatic lipase; temperature 20°C; reaction time 24 hours; percentage conversion 52%. After purification by flash chromatography (3:1 light petroleum (b.p. 40-60°C) : ethyl acetate) the 4-acetoxy-2,3-epoxybutan-1-ol (84) was isolated as a clear liquid (3%);
υ_{max}/cm^{-1} (neat) 3484 (OH) and 1734 (ester C=O);
δ_H (60 MHz $CDCl_3$) 2.10 (3H, s, Me), 3.10 (1H, br s (D_2O exchange), OH), 3.30 (2H, m, 2- and 3-CH), 3.80 (2H, m, 1-CH_2) and 4.20 (2H, m, 4-CH_2).

Enzymatic hydrolysis of *meso 2,3-epoxybutan-1,4-diyl dioctanoate.*



(88)

The general hydrolysis procedure, as described for (60), was followed with *meso* 2,3-epoxybutan-1,4-diyl dioctanoate (61) as the substrate and porcine

pancreatic lipase as the hydrolase. After 24 hours at 20°C, only 5% hydrolysis had been achieved and the reaction was worked up, as with the hydrolysis of (60). Only *meso* 2,3-epoxybutan-1,4-diyl dioctanoate (61) was obtained. No 2,3-epoxy-4-octanoyloxy-butan-1-ol (85) was isolated.

Enzymatic hydrolysis of *meso 2,3-epoxybutan-1,4-diyl diacetate* in an 1:1 aqueous phosphate buffer : hexane mixed solvent system.

The general hydrolysis procedure, as described for (60), was performed on (59), with the following parameters; solvent:- aqueous phosphate buffer (0.05 M, pH 7.0, 10 cm^3) : hexane (10 cm^3); enzyme porcine pancreatic lipase; temperature 15°C; reaction time 5.0 hours; percentage conversion 86%; chemical yield 15%. All spectroscopic data as for previously prepared (84).

Enzymatic hydrolysis of *meso 2,3-epoxybutan-1,4-diyl dioctanoate* in an 1:1 aqueous phosphate buffer : hexane mixed solvent system.

The general hydrolysis procedure, as described for (60), was performed on (59), with the following parameters; solvent:- aqueous phosphate buffer (0.05 M, pH 7.0, 10 cm^3) : hexane (10 cm^3); enzyme porcine pancreatic lipase; temperature 15°C; reaction time 1.5 hours; percentage conversion 82%; chemical yield 4%;
υ_{max}/cm^{-1} (neat) 3454 (OH) and 1736 (ester C=O);
δ_H (250 MHz $CDCl_3$) 0.88 (3H, t, J = 7.39 Hz, $O_2CCH_2CH_2[CH_2]_4C\underline{H}_3$), 1.28 (8H, m, $O_2CCH_2CH_2[C\underline{H}_2]_4CH_3$), 1.63 (2H, m, $O_2CCH_2C\underline{H}_2[CH_2]_4CH_3$), 2.36 (2H, t, J = 7.49 Hz, $O_2CC\underline{H}_2CH_2[CH_2]_4CH_3$), 3.01 (1H, br s ($D_2O$ exchange), OH), 3.34 (2H, m, 2- and 3-CH), 3.82 (2H, dd, J = 2.15 and 5.53 Hz, 1-CH_2), 4.18 (1H, dd, J_{AX} = 5.59 and J_{AB} = 12.25 Hz, 4-CH_A) and 4.33 (1H, dd, J_{BX} = 5.42 and J_{AB} = 12.25 Hz, 4-CH_B).

Enzymatic hydrolysis of racemic *4-butanoyloxy-2,3-epoxybutan-1-ol.*

13-(1) Porcine pancreatic lipase.

To a vigorously stirred solution of racemic 4-butanoyloxy-2,3-epoxybutan-1-ol (179 mg, 1.03 mmol) in an aqueous phosphate buffer (0.05 M, pH 7.0, 10 cm^3) at 20°C, porcine pancreatic lipase (15 mg) was added. The pH of the solution was maintained at 7.0 by the addition of sodium hydroxide solution (1M) from a Metrohm 665 Dosimat in conjunction with a Metrohm 691 pH meter. After 10.5 hours, 0.566 cm^3 of sodium hydroxide solution (55% conversion) had

been added and the solution was extracted with diethyl ether (5 x 10 cm^3). The extracts were washed with a saturated sodium hydrogen carbonate solution (x 3), a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a clear liquid. Purification by flash chromatography (3:1 light petroleum (b.p. 40-60°C) : ethyl acetate) afforded two products;
(I) optically enriched (2R, 3S)-4-butanoyloxy-2,3-epoxybutan-1-ol as a clear liquid (64 mg, 79%);
$[\alpha]_D^{20}$ -10.9°; e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 55%. All spectroscopic data as for previously prepared (67) and
(II) *meso* 2,3-epoxybutan-1,4-diyl dibutanoate (4 mg). All spectroscopic data as for previously prepared (60).

13-(2) Immobilised *Rhizopus* lipase (LIP F3).

The general hydrolysis procedure, as described above, was followed, with optically enriched (2R, 3S)-4-butanoyloxy-2,3-epoxybutan-1-ol (67) being isolated. The following parameters were utilised; enzyme:- immobilised *Rhizopus* lipase (LIP F3); temperature 20°C; reaction time 13.5 hours; percentage conversion 57%; chemical yield 80%; $[\alpha]_D^{20}$ -9.5°; e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 48%. All spectroscopic data as for previously prepared (67).

13-(3) Immobilised *Penicillium* lipase (LIP F11).

The general hydrolysis procedure, as described above, was followed, with optically enriched (2R, 3S)-4-butanoyloxy-2,3-epoxybutan-1-ol being isolated. The following parameters were utilised; enzyme:- immobilised *Penicillium* lipase (LIP F11); temperature 20°C; reaction time 28 hours; percentage conversion 49%; chemical yield 57%; $[\alpha]_D^{20}$ -1.9°; e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 9.6%. All spectroscopic data as for previously prepared (67).

Preparation of *vinyl butyrate* (86).

(86)

To a stirred solution of vinyl acetate (206 g, 2.4 mol), butyric acid (37 cm^3, 400 mmol) and mercury(II) acetate (1.6 g), sulfuric acid (100%, 0.2 cm^3) was added. The resulting solution was heated at reflux for 3 hours, after which sodium acetate (1 g) and sodium hydrogen carbonate (5 g) were added and the solution distiled *in vacuo* (~40 mmHg). The fraction at 40-44°C was collected (21 g), dissolved in diethyl ether (50 cm^3) and washed with a saturated sodium hydrogen

carbonate solution (x 4), a saturated sodium chloride solution, dried (magnesium sulfate) and carefully evaporated *in vacuo* affording (86) as a clear liquid (16 g, 26%);
υ_{max}/cm^{-1} (neat) 1758 (ester C=O) and 1644 (C=C, enol ether);
δ_H (60 MHz $CDCl_3$) 0.90 (3H, t, J = 7.20 Hz, $O_2CCH_2CH_2C\underline{H_3}$), 1.60 (2H, sextet, J = 7.50 Hz, $O_2CCH_2C\underline{H_2}CH_3$), 2.30 (2H, t, J = 7.30 Hz, $O_2CC\underline{H_2}CH_2CH_3$), 4.60 (1H, dd, J_{gem} = 1.7 and J_{cis} = 6.4 Hz, 2-CH_{cis}), 4.90 (1H, dd, J_{gem} = 1.7 and J_{trans} = 15.5 Hz, 2-CH_{trans}) and 7.30 (1H, dd, J_{cis} = 6.4 and J_{trans} = 15.5 Hz, 1-CH).

Enzymatic transesterification of *vinyl butyrate* with *meso 2,3-epoxybutan-1,4-diol.*

15-(1) Porcine pancreatic lipase at 65°C.

To a stirred solution of *meso* 2,3-epoxybutan-1,4-diol (500 mg, 4.8 mmol), vinyl butyrate (550 mg, 4.8 mmol) and powdered 4Å molecular sieves (500 mg) in anhydrous tetrahydrofuran (20 cm^3), porcine pancreatic lipase (500 mg) was added and the solution heated at gentle reflux. After 22 hours the solution was cooled to room temperature, filtered through celite, the filtrate diluted with diethyl ether and washed with a saturated sodium hydrogen carbonate solution (x 2), water and a saturated sodium chloride solution. After drying (magnesium sulfate) the solvent was evaporate to give a yellow liquid. All material purified by flash chromatography (1:1.5 ethyl acetate : light petroleum (b.p. 40-60°C)) to afford two products;
(I) *meso* 2,3-epoxybutan-1,4-diyl dibutanoate (104 mg), all spectroscopic data as for previously prepared (60) and
(II) optically enriched (2S, 3R)-4-butanoyloxy-2,3-epoxybutan-1-ol (185 mg, 22%); $[\alpha]_D^{20}$ +2.4°; e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 12%. All spectroscopic data as for previously prepared (67).

15-(2) Porcine pancreatic lipase at 20°C.

The general transesterification procedure, as described above, was followed with the following parameters; enzyme (quantity):- porcine pancreatic lipase (500 mg); solvent anhydrous tetrahydrofuran; temperature 20°C; reaction time 16 hours; number of vinyl butyrate equivalents 1; for optically enriched (2S, 3R)-4-butanoyloxy-2,3-epoxybutan-1-ol; chemical yield 30%; $[\alpha]_D^{20}$ +3.3°; e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 16%. All spectroscopic data as for previously prepared (67).

15-(3) Porcine pancreatic lipase.

The general transesterification procedure, as described above, was followed with the following parameters; enzyme (quantity):- porcine pancreatic lipase (30 mg); solvent anhydrous tetrahydrofuran; temperature 20°C; reaction time 96 hours; number of vinyl butyrate equivalents 1; for optically enriched (2S, 3R)-4-butanoyloxy-2,3-epoxybutan-1-ol; chemical yield 18%; $[\alpha]_D^{20}$ +6.1°; e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 30%. All spectroscopic data as for previously prepared (67).

15-(4) Porcine pancreatic lipase, 2 equivalents of *vinyl butyrate.*

The general transesterification procedure, as described above, was followed with the following parameters; enzyme (quantity):- porcine pancreatic lipase (30 mg); solvent anhydrous tetrahydrofuran; temperature 20°C; reaction time 60 hours; number of vinyl butyrate equivalents 2; for optically enriched (2S, 3R)-4-butanoyloxy-2,3-epoxybutan-1-ol; chemical yield 30%; $[\alpha]_D^{20}$ +2.5°; e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 13%. All spectroscopic data as for previously prepared (67).

15-(5) Porcine pancreatic lipase, 5 equivalents of *vinyl butyrate.*

The general transesterification procedure, as described above, was followed with the following parameters; enzyme (quantity):- porcine pancreatic lipase (40 mg); solvent anhydrous tetrahydrofuran; temperature 20°C; reaction time 9 hours; number of vinyl butyrate equivalents 5; for optically enriched (2S, 3R)-4-butanoyloxy-2,3-epoxybutan-1-ol; chemical yield 13%; $[\alpha]_D^{20}$ +9.1°; e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 46%. All spectroscopic data as for previously prepared (67).

15-(6) Porcine pancreatic lipase, 5 equivalents of *vinyl butyrate.*

The general transesterification procedure, as described above, was followed with the following parameters; enzyme (quantity):- porcine pancreatic lipase (38 mg); solvent anhydrous tetrahydrofuran; temperature 20°C; reaction time 5.5 hours; number of vinyl butyrate equivalents 5; for optically enriched (2S, 3R)-4-butanoyloxy-2,3-epoxybutan-1-ol; chemical yield 5%; $[\alpha]_D^{20}$ +9.6°; e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 48%. All spectroscopic data as for previously prepared (67).

15-(7) Immobilized *Penicillium* lipase (LIP F11).

The general transesterification procedure, as described above, was followed with the following parameters; enzyme (quantity):- immobilized *Penicillium* lipase (LIP F11) (30 mg); solvent anhydrous tetrahydrofuran; temperature 20°C; reaction time 96 hours; number of vinyl butyrate equivalents 1; no transesterification transpired.

15-(8) *Candida cylindracea* lipase.

The general transesterification procedure, as described above, was followed with the following parameters; enzyme (quantity):- *Candida cylindracea* lipase (30 mg); solvent anhydrous tetrahydrofuran; temperature 20°C; reaction time 69 hours; number of vinyl butyrate equivalents 1; no transesterification transpired.

15-(9) Immobilized *Rhizopus* lipase (LIP F3).

The general transesterification procedure, as described above, was followed with the following parameters; enzyme (quantity):- immobilized *Rhizopus* lipase (LIP F3) (30 mg); solvent anhydrous tetrahydrofuran; temperature 20°C; reaction time 69 hours; number of vinyl butyrate equivalents 1; no transesterification transpired.

15-(10) Immobilized *Pseudomonas fluorescens* lipase.

The general transesterification procedure, as described above, was followed with the following parameters; enzyme (quantity):- immobilized *Pseudomonas fluorescens* lipase (40 mg); solvent anhydrous tetrahydrofuran; temperature 20°C; reaction time 3.5 hours; number of vinyl butyrate equivalents 4; for optically enriched (2S, 3R)-4-butanoyloxy-2,3-epoxybutan-1-ol; chemical yield 22%; $[\alpha]_D^{20}$ +5.0°; e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 25%. All spectroscopic data as for previously prepared (67).

15-(11) *Pseudomonas fluorescens* lipase.

The general transesterification procedure, as described above, was followed with the following parameters; enzyme (quantity):- *Pseudomonas fluorescens* lipase (27 mg); solvent anhydrous tetrahydrofuran; temperature 20°C; reaction time 1.3 hours; number of vinyl butyrate equivalents 5; for optically

enriched (2S, 3R)-4-butanoyloxy-2,3-epoxybutan-1-ol; chemical yield 6%; $[\alpha]_D^{20}$ +10°; e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 54%. All spectroscopic data as for previously prepared (67).

16-(2) Porcine pancreatic lipase in hexane.

The general transesterification procedure, as described above, was followed with the following parameters; enzyme (quantity):- porcine pancreatic lipase (500 mg); solvent anhydrous hexane; temperature 20°C; reaction time 168 hours; number of vinyl butyrate equivalents 1; for 4-butanoyloxy-2,3-epoxybutan-1-ol; chemical yield 6%; $[\alpha]_D^{20}$ 0°; e.e. 0%. All spectroscopic data as for previously prepared (67).

16-(3) Porcine pancreatic lipase in dimethylsulfoxide.

The general transesterification procedure, as described above, was followed with the following parameters; enzyme (quantity):- porcine pancreatic lipase (500 mg); solvent anhydrous dimethylsulfoxide; temperature 20°C; reaction time 168 hours; number of vinyl butyrate equivalents 1; no transesterification transpired.

16-(4) Porcine pancreatic lipase in *tert*-butanol.

The general transesterification procedure, as described above, was followed with the following parameters; enzyme (quantity):- porcine pancreatic lipase (500 mg); solvent anhydrous *tert*-butanol; temperature 20°C; reaction time 40 hours; number of vinyl butyrate equivalents 1; for optically enriched (2S, 3R)-4-butanoyloxy-2,3-epoxybutan-1-ol; chemical yield 31%; $[\alpha]_D^{20}$ +1.7°; e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 8%. All spectroscopic data as for previously prepared (67).

Controls for enzymatic transesterifications.

(1) Transesterification with denatured lipases.

A sample of porcine pancreatic lipase (50 mg) was heated at reflux in water (1 cm^3) for 3 minutes and the water then removed under reduced pressure. The resulting denatured lipase was dried *in vacuo* (0.5 mmHg) for 24 hours, and then used in the reaction as described for the previous transesterifications. After 20 hours, only *meso* 2,3-epoxybutan-1,4-diol was detected in the reaction mixture.

The above was repeated using *Pseudomonas fluorescens* lipase; no transesterification transpired.

Racemisation of optically enriched *(2S, 3R)-4-butanoyloxy-2,3-epoxybutan-1-ol* with porcine pancreatic lipase.

17-(1) Using 500 mg of porcine pancreatic lipase.

To a stirred solution of optically enriched (2S, 3R)-4-butanoyloxy-2,3-epoxybutan-1-ol ($[\alpha]_D^{20}$ +13.3°, e.e. 68%, 90 mg, 0.51 mmol) and powdered 4Å molecular sieves (500 mg) in anhydrous tetrahydrofuran (20 cm^3), porcine pancreatic lipase (500 mg) was added. After 23 hours the solution was filtered through celite, the filtrate diluted with diethyl ether and washed with a saturated sodium hydrogen carbonate solution (x 2), water and a saturated sodium chloride solution. After drying (magnesium sulfate), the solvent was evaporated to give a clear liquid. All material was purified by flash chromatography (1:1.5 ethyl acetate : light petroleum (b.p. 40-60°C)) to afford two products;
(I) *meso* 2,3-epoxybutan-1,4-diyl dibutanoate (29 mg); all spectroscopic data as for previously prepared (60) and
(II) optically enriched (2S, 3R)-4-butanoyloxy-2,3-epoxybutan-1-ol (42 mg, 47% recovered);
$[\alpha]_D^{20}$ +1.2°, e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 6%. All spectroscopic data as for previously prepared (67).

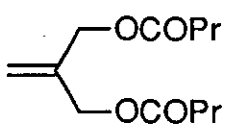
17-(2) Using 50 mg of porcine pancreatic lipase.

The above was repeated using porcine pancreatic lipase (50 mg) and optically enriched (2S, 3R)-4-butanoyloxy-2,3-epoxybutan-1-ol ($[\alpha]_D^{20}$ +14.2°, e.e. 71%, 98 mg, 0.56 mmol). With the exception of the reaction time, 44 hours this time, the reaction conditions were the same as before. Two products were isolated after chromatography;
(I) *meso* 2,3-epoxybutan-1,4-diyl dibutanoate (28 mg), all spectroscopic data as for previously prepared (60) and
(II) optically enriched (2S, 3R)-4-butanoyloxy-2,3-epoxybutan-1-ol (52 mg, 53% recovered);
$[\alpha]_D^{20}$ +7.2°, e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 36%. All spectroscopic data as for previously prepared (67).

17-(3) Using 50 mg of denatured porcine pancreatic lipase.

The above was repeated using denatured porcine pancreatic lipase (denatured and dried as before, 50 mg) and optically enriched (2S, 3R)-4-butanoyloxy-2,3-epoxybutan-1-ol ($[\alpha]_D^{20}$ +14.2°, e.e. 71%, 108 mg, 0.60 mmol). With the exception of the reaction time, 44 hours this time, the reaction conditions were the same as before. Only optically enriched (2S, 3R)-4-butanoyloxy-2,3-epoxybutan-1-ol was recovered after chromatography (99 mg, 98% recovered); $[\alpha]_D^{20}$ +14.2°, e.e. (calculated from $[\alpha]_D^{20}$ *vs* e.e. graph) 71%. All spectroscopic data as for previously prepared (67).

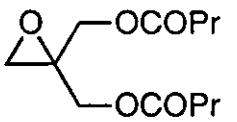
Preparation of *2-methylenepropan-1,3-diyl dibutanoate* (92).



(92)

To a stirred solution of 2-methylenepropan-1,3-diol (500 mg, 5.7 mmol) and pyridine (2.5 cm^3) in anhydrous carbon tetrachloride (30 cm^3), butanoyl chloride (1.5 cm^3, 14.2 mmol) was added drop-wise. After stirring at room temperature for 16 hours, the solution was washed with a saturated sodium hydrogen carbonate solution (x 3), hydrochloric acid (2 M) (x 4), a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a yellow liquid. Purification by Kugelrohr distillation afforded (92) as clear and colourless liquid (820 mg, 91%); b.p. (0.05 mmHg) 85°C;
υ_{max}/cm^{-1} (neat) 1738 (ester C=O) and 1458 (C=C);
δ_H (250 MHz $CDCl_3$) 0.96 (6H, t, J = 7.38 Hz, 2 x $O_2CCH_2CH_2C\underline{H}_3$), 1.66 (4H, sextet, J = 7.44 Hz, 2 x $O_2CCH_2C\underline{H}_2CH_3$), 2.31 (4H, t, J = 7.37 Hz, 2 x $O_2CC\underline{H}_2CH_2CH_3$), 4.61 (4H, s, 1- and 3-CH_2) and 5.27 (2H, s, C=CH_2);
δ_C (62.9 MHz, $CDCl_3$) 13.68 (2 x CH_3), 18.45 (2 x CH_2), 36.11 (2 x CH_2), 64.30 (1 and 3-CH_2), 116.39 (CH_2), 139.02 (2-C) and 173.16 (2 x CO_2);
m/z (E.I.) 228 (M^+, 1%), 157 (5, M^+ minus COPr), 141 (10, M^+ minus OCOPr) and 71 (100, $^+$COPr).

Preparation of *2-butanoyloxymethyl-2,3-epoxypropan-1-yl butanoate* (89).



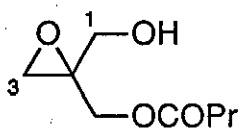
(89)

To a stirred solution of 2-methylenepropan-1,3-diyl dibutanoate (730 mg, 4.6 mmol) in anhydrous dichloromethane (30 cm^3), m-chloroperoxybenzoic acid (1.3 g, 6.6 mmol) was added in one portion. After stirring at room temperature for 16 hours, the solution was washed with a saturated sodium hydrogen carbonate solution (x 4), water, a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a viscous yellow liquid. Purification by flash chromatography (4:1 light petroleum (b.p. 40-60°C) : diethyl ether) afforded (89) as a clear liquid (400 mg, 54%); b.p. (0.3 mmHg) 90°C;
found: C, 58.42; H, 8.23%; $C_{12}H_{20}O_5$ requires C, 59.00; H, 8.25%;
υ_{max}/cm^{-1} (neat) 1738 (ester C=O);
δ_H (250 MHz $CDCl_3$) 0.95 (6H, t, J = 7.44 Hz, 2 x $O_2CCH_2CH_2C\underline{H}_3$), 1.66 (4H, sextet, J = 7.27 Hz, 2 x $O_2CCH_2C\underline{H}_2CH_3$), 2.41 (4H, t, J = 7.31 Hz, 2 x $O_2CC\underline{H}_2CH_2CH_3$), 2.84 (2H, s, 3-$CH_2$), 4.14 (2H, d, J_{gem} = 12.14 Hz, 2 x O-CH_A) and 4.28 (2H, d, J_{gem} = 12.14 Hz, 2 x O-CH_B);
δ_C (62.9 MHz, $CDCl_3$) 13.65 (2 x CH_3), 18.38 (2 x CH_2), 35.92 (2 x CH_2), 49.71 (3-CH_2), 55.45 (2-C), 63.51 (2 x CH_2) and 173.05 (2 x CO_2);
m/z (E.I.) 244 (M^+, <1%) and 71 (100, $^+$COPr).

Alternative preparation of *2-butanoyloxymethyl-2,3-epoxypropan-1-yl butanoate* (89).

To a stirred solution of 2-methylenepropan-1,3-diol (550 mg, 6.25 mmol) in anhydrous diethyl ether (30 cm^3), m-chloroperoxybenzoic acid (2.0 g, 10 mmol) was added in one portion. After stirring at room temperature for 15 hours, pyridine (3 cm^3) and butanoyl chloride (1.8 cm^3, 12.5 mmol) were added and the solution stirred at room temperature for 24 hours. The solution was then washed with a saturated sodium hydrogen carbonate solution (x 3), hydrochloric acid (2 M) (x 4), a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a yellow liquid. Purification by Kugelrohr distillation afforded (89) as a clear and colourless liquid (1.2 g, 80%); b.p. (0.1 mmHg) 85°C. All spectroscopic data as for previously prepared (89).

Attempted preparation of racemic *2-butanoyloxymethyl-2,3-epoxy-propan-1-ol* (90).



(90)

(I) Partial esterification of *2-methylenepropan-1,3-diol.*

Prepared as for (92), using one equivalent of butanoyl chloride. Purification by flash chromatography (2:1 light petroleum (b.p. 40-60°C) : diethyl ether) afforded (92) as a clear and colourless liquid (510 mg, 40%). All spectroscopic data as for previously prepared (92). No 2-butanoyloxymethyl-2-propen-1-ol was observed in the reaction mixture.

(II) Partial esterification of *2,3-epoxy-2-(hydroxymethyl)-propan-1-ol.*

To a stirred solution of 2-methylenepropan-1,3-diol (440 mg, 5.0 mmol) in anhydrous diethyl ether (20 cm^3), m-chloroperoxybenzoic acid (1.4 g, 7.5 mmol) was added in one portion. After stirring at room temperature for 16 hours, pyridine (4 cm^3) and butanoyl chloride (0.5 cm^3, 5.0 mmol) were added and the solution stirred at room temperature for 16 hours. The solution was then washed with a saturated sodium hydrogen carbonate solution (x 3), hydrochloric acid (2 M) (x 4), a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a clear liquid. Purification by flash chromatography (3:1 light petroleum (b.p. 40-60°C) : diethyl ether) afforded (89) as a clear and colourless liquid (470 mg, 39%). All spectroscopic data as for previously prepared (89). No 2-butanoyloxymethyl-2,3-epoxypropan-1-ol was observed in the reaction mixture.

Enzymatic hydrolysis of *2-butanoyloxymethyl-2,3-epoxypropan-1-yl butanoate.*

18-(1) *Candida cylindracea* lipase.

To a vigorously stirred solution of 2-butanoyloxymethyl-2,3-epoxy-propan-1-yl butanoate (178 mg, 0.73 mmol) in an aqueous phosphate buffer (0.05 M, pH 7.0, 15 cm^3) at 20°C, *Candida cylindracea* lipase (25 mg) was added. The pH of the solution was maintained at 7.0 by the addition of sodium hydroxide solution (1 M) from a Metrohm 665 Dosimat, in conjunction with a Metrohm 691 pH meter. After 2.0 hours, 0.74 cm^3 of sodium hydroxide solution had been added (98% conversion) and the solution was quickly extracted with diethyl ether

(5 x 10 cm^3). The extracts were washed with a saturated sodium hydrogen carbonate solution (x 3), a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a clear liquid. Purification by flash chromatography (1:1 light petroleum (b.p. 40-60°C) : ethyl acetate) afforded 2-butanoyloxymethyl-2,3-epoxy-propan-1-ol (90) as a clear liquid (76 mg, 60%);
$[\alpha]_D^{20}$ 0°;
found: C, 54.39; H, 8.37%; $C_8H_{14}O_4$ requires C, 55.16; H, 8.10%;
υ_{max}/cm^{-1} (neat) 3480 (OH) and 1738 (ester C=O);
δ_H (250 MHz $CDCl_3$) 0.96 (3H, t, J = 7.33 Hz, $O_2CCH_2CH_2C\underline{H_3}$), 1.65 (2H, sextet (splitting into two equal intensity sextets on treatment with 0.7 equivalents of Eu[hfc]$_3$, indicating a racemic mixture), J = 7.45 Hz, $O_2CCH_2C\underline{H_2}CH_3$), 1.88 (1H, br s, OH), 2.34 (2H, t (splitting into two equal intensity triplets on treatment with 0.7 equivalents of Eu[hfc]$_3$, indicating a racemic mixture), J = 7.30 Hz, $O_2CC\underline{H_2}CH_2CH_3$), 2.82 (1H, d, J_{gem} = 4.65 Hz, 3-CH_A), 2.94 (1H, d, J_{gem} = 4.65 Hz, 3-CH_B), 3.73 (1H, d, J_{gem} = 12.44 Hz, 1-CH_A), 3.82 (1H, d, J_{gem} = 12.44 Hz, 1-CH_B), 4.15 (1H, d, J_{gem} = 12.29 Hz, O-CH_A) and 4.35 (1H, d, J_{gem} = 12.29 Hz, O-CH_B);
δ_C (62.9 MHz, $CDCl_3$) 13.65 (CH_3), 18.38 (CH_2), 35.91 (CH_2), 49.18 (3-CH_2), 57.73 (2-C), 61.51 (1-CH_2), 63.89 (O-CH_2) and 173.10 (CO_2);
m/z (E.I.) 143 (M^+ minus CH_2OH) and 71 (100, $^+$COPr).

18-(2) Porcine pancreatic lipase.

The general hydrolysis procedure, as described above, was followed with the following parameters; enzyme:- porcine pancreatic lipase; temperature 20°C; reaction time 0.5 hours; percentage conversion 97%; chemical yield 77%; $[\alpha]_D^{20}$ -2.8°; e.e. [by integration of ^{19}F N.M.R spectrum of (93), and ^1H N.M.R studies with Eu[hfc]$_3$ chiral shift reagent on (90)] 37%. All spectroscopic data as for previously prepared (90).

18-(3) Immobilized *Rhizopus* lipase (LIP F3).

The general hydrolysis procedure, as described above, was followed with the following parameters; enzyme:- immobilized *Rhizopus* lipase (LIP F3); temperature 20°C; reaction time 0.7 hours; percentage conversion 95%; chemical yield 60%; $[\alpha]_D^{20}$ 0°; e.e. 0%. All spectroscopic data as for previously prepared (90).

18-(4) *Rhizopus delemar* lipase.

The general hydrolysis procedure as described above was followed with the following parameters; enzyme:- *Rhizopus delemar* lipase, temperature 20°C, reaction time 0.75 hours, percentage conversion 97%, chemical yield 76%, $[\alpha]_D^{20}$ -3.6°, e.e. [^{1}H N.M.R studies with Eu[hfc]$_3$ chiral shift reagent on (90)] 48%. All spectroscopic data as for previously prepared (90).

18-(5) Immobilized *Rhizopus delemar* lipase.

The general hydrolysis procedure, as described above, was followed with the following parameters; enzyme:- immobilized *Rhizopus delemar* lipase; temperature 20°C; reaction time 1.0 hours; percentage conversion 98%; chemical yield 63%; $[\alpha]_D^{20}$ -2.1°; e.e. [^{1}H N.M.R studies with Eu[hfc]$_3$ chiral shift reagent on (90)] 28%. All spectroscopic data as for previously prepared (90).

18-(6) Immobilized *Penicillium* lipase (LIP F11).

The general hydrolysis procedure, as described above, was followed with the following parameters; enzyme:- immobilized *Penicillium* lipase (LIP F11); temperature 20°C; reaction time 5.5 hours; percentage conversion 71%; chemical yield 52%; $[\alpha]_D^{20}$ 0°; e.e. 0%. All spectroscopic data as for previously prepared (90).

18-(7) *Pseudomonas fluorescens* lipase.

The general hydrolysis procedure, as described above, was followed with the following parameters; enzyme:- *Pseudomonas fluorescens* lipase; temperature 20°C; reaction time 0.25 hours; percentage conversion 97%; chemical yield 70%; $[\alpha]_D^{20}$ -3.7°; e.e. [^{1}H N.M.R studies with Eu[hfc]$_3$ chiral shift reagent on (90)] 49%. All spectroscopic data as for previously prepared (90).

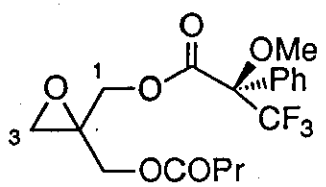
Control for enzymatic hydrolysis of *2-butanoyloxymethyl-2,3-epoxy-propan-1-yl butanoate.*

Hydrolysis with denatured *Pseudomonas fluorescens* lipase.

A sample of *Pseudomonas fluorescens* lipase (30 mg) was added to a stirred and refluxing aqueous phosphate buffer (0.05 M, pH 7.0, 15 cm^3). After 3 minutes the solution was cooled to 20°C and 2-butanoyloxymethyl-2,3-epoxy-

propan-1-yl butanoate (100 mg, 0.4 mmol) added. The pH of the solution was monitored for 9 hours and no decrease in pH was observed. The t.l.c. (1:1 ethyl acetate : light petroleum (b.p. 40-60°C)) of the solution after this time showed only the presence of the 2-butanoyloxymethyl-2,3-epoxy-propan-1-yl butanoate (R_f. 0.85).

Preparation of racemic *2-butanoyloxymethyl-2,3-epoxy-1-[[(R)-(+)-α-methoxy-α-(trifluoromethyl)phenyl]acetoxy)propane* (93).



(93)

To a stirred solution of racemic 2-butanoyloxymethyl-2,3-epoxypropan-1-ol (24 mg, 0.14 mmol) and anhydrous pyridine (10 drops) in anhydrous carbon tetrachloride (1 cm^3), (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (54 mg, 0.19 mmol) was added in one portion. After stirring at room temperature for 16 hours, the solution was diluted with chloroform (30 cm^3), washed with a saturated sodium hydrogen carbonate solution (x 3), hydrochloric acid (2 M) (x 4), a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving (93) as a clear oil (54 mg, 100%);
υ_{max}/cm^{-1} (neat) 1750 (Mosher's ester C=O) and 1738 (ester C=O);
δ_H (250 MHz $CDCl_3$) 0.96 (3H, t, J = 7.30 Hz, $O_2CCH_2CH_2C\underline{H_3}$), 1.64 (2H, two overlapping sextets, J = 7.40 Hz, $O_2CCH_2C\underline{H_2}CH_3$), 2.34 (2H, two overlapping t, J = 7.30 Hz, $O_2CC\underline{H_2}CH_2CH_3$), 2.81 (1H, d, J_{AB} = 4.46 Hz, 3-CH_A), 2.86 (1H, d, J_{AB} = 4.46 Hz, 3-CH_B), 3.54 (3H, q, J = 1.10 Hz, OMe), 4.15 (2H, m, CH_2-OCOPr), 4.58 (2H, m, 1-CH_2) and 7.35 (5H, m, C_6H_5);
δ_F (340 MHz, CCl_3F) -72.122 (CF_3 R or S) and -72.144 (CF_3 S or R).

Preparation of optically enriched *2-butanoyloxymethyl-2,3-epoxy-1-[[(R)-(+)-α-methoxy-α-(trifluoromethyl)phenyl]acetoxy)-propane* (93).

Preparation as for previously prepared (93), using 2-butanoyloxymethyl-2,3-epoxy-propan-1-ol with an $[\alpha]_D^{20}$ of -2.8°. 2-Butanoyloxymethyl-2,3-epoxy-1-([(R)-(+)-α-methoxy-α-(trifluoromethyl)phenyl]-acetoxy)-propane (93) was isolated as a clear oil (100%);
37% d.e. by integration of ^{19}F N.M.R (CF_3) peaks; ratio of δ -72.122 : -72.144 was 2.15 : 1. All other spectroscopic data as for (93).

Chapter 4. Rearrangements of cyclopropylcarbinyl and oxiranylcarbinyl radicals.

4.1. Introduction.

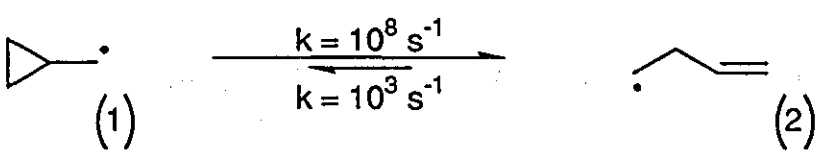
Since their first discovery by Gomberg[61,62] in 1900, free radical reactions have not been seen by many organic chemists as being synthetically useful in the production of fine chemicals, due to their apparent lack of selectivity. The past 20 years have, however, witnessed a marked increase in the understanding of radical reactions, and consequently the use of the, 'controlled and disciplined free radical' is now routinely considered in retrosynthetic strategies.

The main advantage of radicals which makes them attractive to the modern synthetic chemist is their apparent neutrality. As a result, solvation effects[63] are minimal and the small radical is capable of carrying out transformations in highly hindered, polar environments.

4.2. Rearrangement of the cyclopropylcarbinyl radical.

The ring opening of the cyclopropylcarbinyl radical has been one of the most studied radical rearrangements to date, with the rates of both the opening and closure being accurately determined,[64] (Scheme 1).

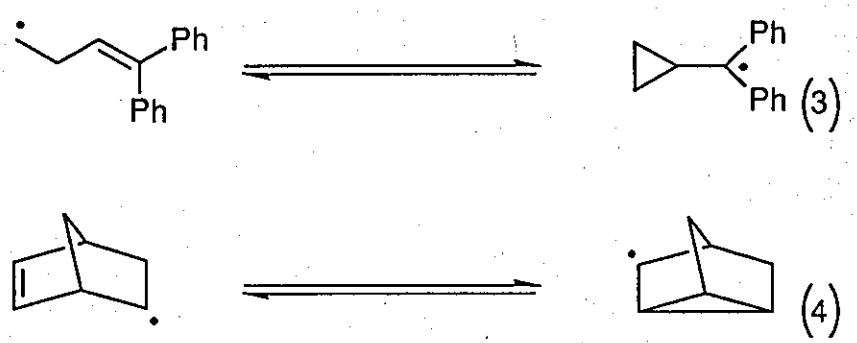
Scheme 1.



As the rate of this rearrangement is known, it has been used by Ingold and others to act as a radical clock.[64] A cyclopropyl ring is substituted into a system, so that a cyclopropylcarbinyl radical is formed at the site of interest and analysis of the formed products will allow predictions to be made about how rapidly the radical undergoes the reaction being studied.

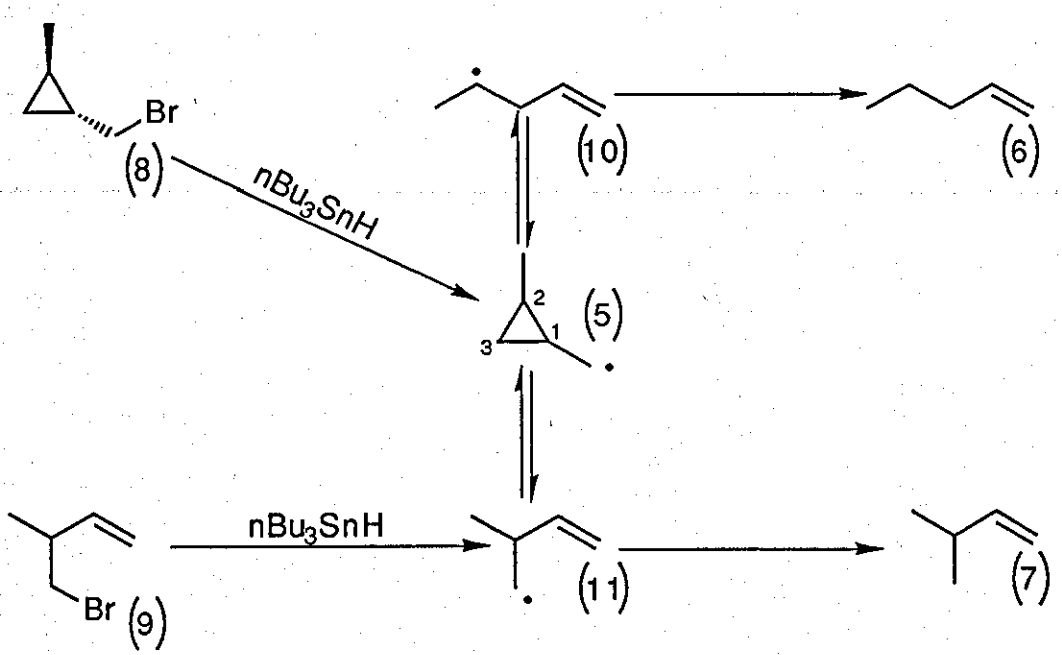
There are cases where the usually more stable acyclic radical (2) cyclises at such a rate as to afford the cyclopropylcarbinyl radical (1), but only when there are additional stabilising substituents,[65] as is the case with (3), or where there is a large degree of ring strain already present in the system,[66] which is the case with (4) (Scheme 2).

Scheme 2.



When dealing with substituted cyclopropylcarbinyl radicals, the rearrangement is complicated by the availability of two β-bonds for scission. In the rearrangement of the trans-2-methylcyclopropylcarbinyl radical[67] (5), two products pent-1-ene (6) and 3-methylbut-1-ene (7) are isolated, as shown in Scheme 3.

Scheme 3.



Tributyltin hydride reduction of either the 2-methylcyclopropyl-1-methylbromide (8), or the homoallylic bromide (9) under thermodynamic conditions, when the concentration of the tributyltin hydride is kept low, favours formation of pent-1-ene (6) (entries 2 and 4 of Table 1). This would be expected since the rearrangement proceeds *via* the more stable secondary radical (10) prior to reduction. On carrying out the reduction under kinetically controlled conditions, with a high concentration of reductant, it is the 3-methylbut-1-ene (7) which predominates (entries 1 and 3 of Table 1).

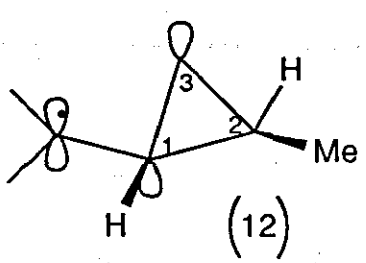
Table 1. Results of the tributyltin hydride reduction of (8) and (9).

Nº	substrate.	nBu_3SnH concentration.	% yield.	Product ratio (6) : (7).
1	(8)	neat	85	34:66
2	(8)	dilute	85	92:8
3	(9)	neat	85	10:90
4	(9)	dilute	85	86:14

This result suggests that scission of the 1,3-bond, leading to the less stable primary radical (11), occurs more rapidly than scission of the 1,2-bond. This observation is best explained assuming the cleavage is under stereoelectronic control.

4.2.1. Stereoelectronic effects in cyclopropylcarbinyl radical rearrangements.

Figure 1.

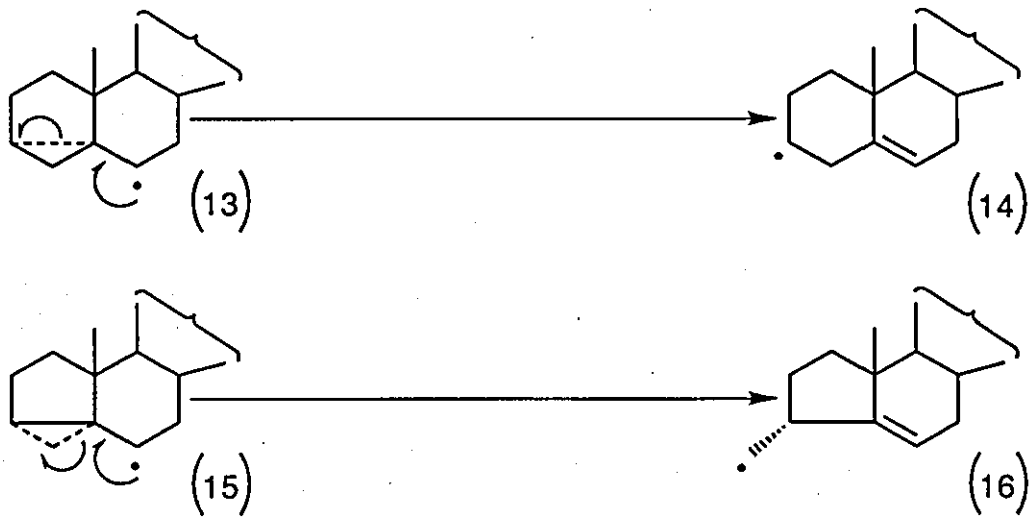


(12)

The supposition that the ring opening of the cyclopropylcarbinyl ring is under stereoelectronic control results from the interaction of the semi-occupied p-orbital of the radical centre, with the 1,3-σ^* orbital being most favoured in conformation (12), as illustrated in Figure 1. Hence, scission of the 1,3-bond leading to the primary radical will occur more rapidly than that of the 1,2-bond.

The stereoelectronic effect was also clearly observed in the regiospecific ring opening of the two isomeric steroidal, cyclopropylcarbinyl radicals[68,69] (13) and (15), as shown in Scheme 4.

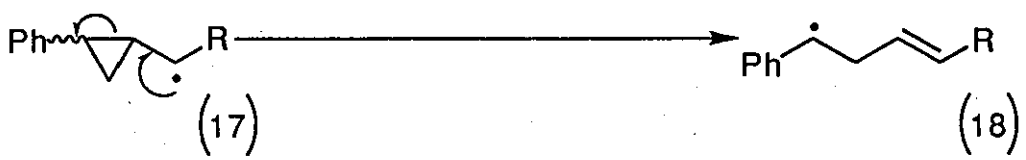
Scheme 4.



Under kinetically controlled conditions, cyclopropylcarbinyl radical (13) opened to yield the more stable secondary radical (14), whereas cyclopropylcarbinyl radical (15) rearranged to give, exclusively, the less stabilised primary radical (16). These results were conveniently explained as the bond which is nearest to the eclipsed conformation with respect to the semi-occupied p-orbital of the radical centre was the one preferentially cleaved.

The presence of a radical stabilising group, such as a phenyl group, at the two position of a cyclopropylcarbinyl radical had a marked effect on its rearrangement,[70] *e.g.* radical (17) in Scheme 5. Here, regardless of whether it was in the *cis* or *trans* relationship, only the secondary radical (18) was formed, due presumably, to benzylic radical stabilisation.

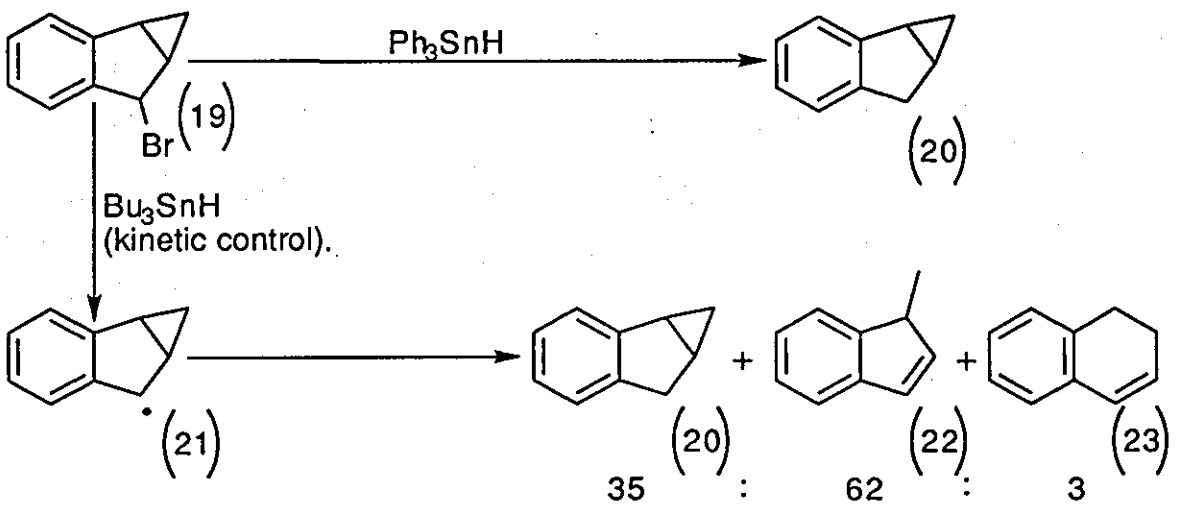
Scheme 5.



When a similar reduction was performed on the more rigidly constrained bicyclic system (19), where the benzylic radical stabilising group was still present, a different result was obtained,[71,72] as shown in Scheme 6. The major product (22) was that derived from the reduction of the higher energy cycloalkyl methyl radical.[73,74] The bicycle (23), resulting from the reduction of the benzylic stabilised secondary radical, was only isolated in a very low yield. This result was not dependent on the stereochemistry of the cyclopropyl ring. Reduction of

bicycle (19) with triphenyltin hydride,[72] a faster hydride radical donor than tributyltin hydride, capable of reducing the stabilised secondary radical (21) prior to rearrangement, afforded norcane (20).

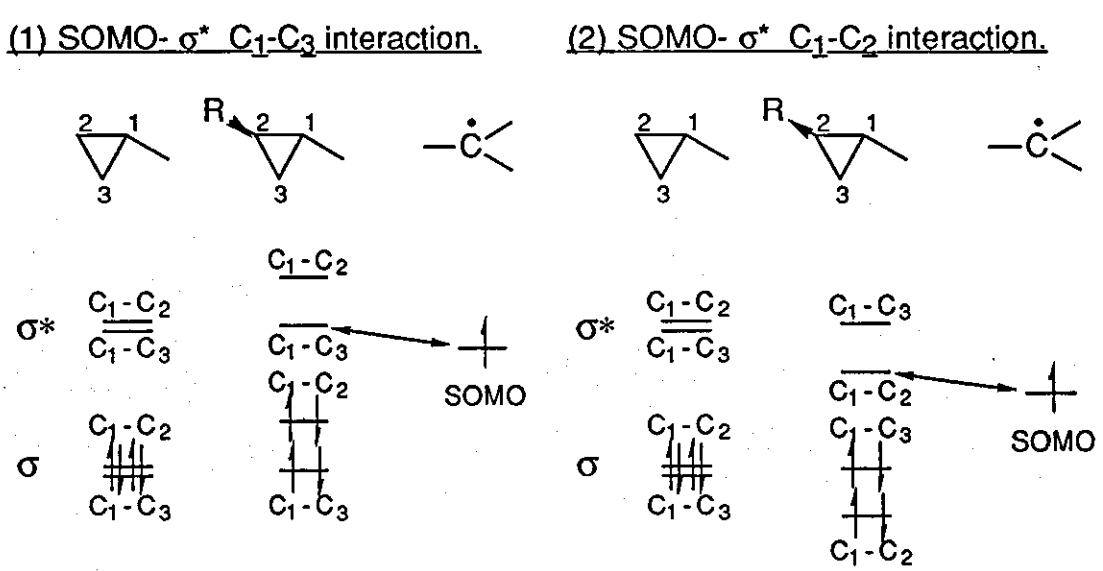
Scheme 6.



4.2.2. Frontier orbital interactions in cyclopropylcarbinyl radical rearrangements.

An alternative explanation for the observation that the primary radical is preferentially formed in the kinetically controlled rearrangement of the *trans*-2-alkylcyclopropylcarbinyl radical comes from an examination of the frontier orbital interactions,[75] as shown in Figure 2.

Figure 2.

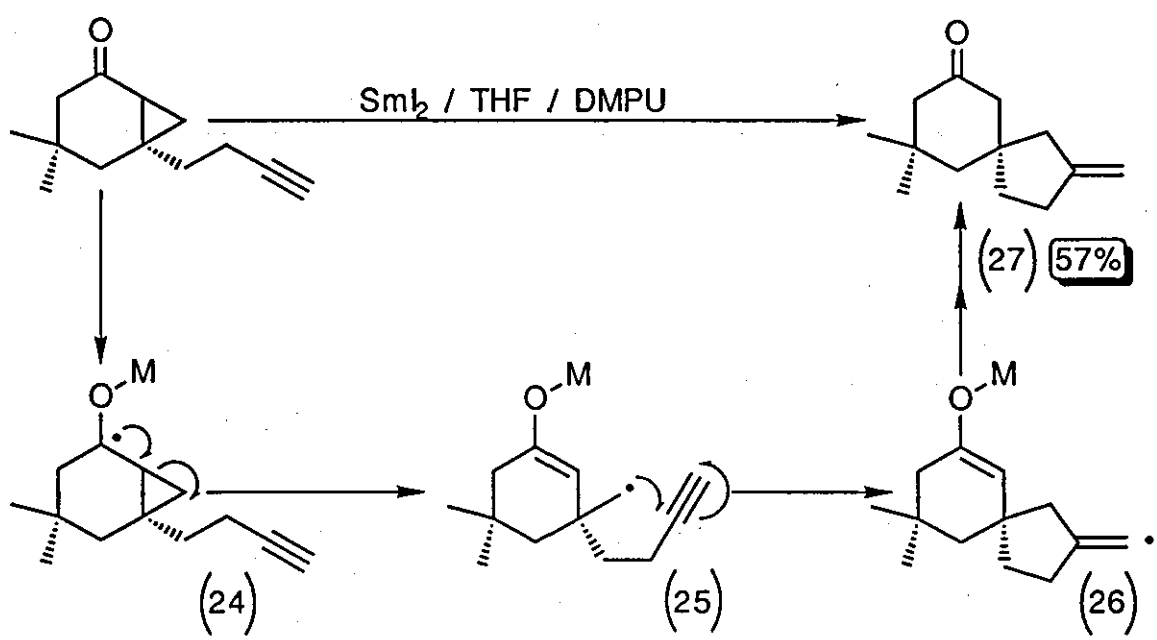


If R were an electron releasing group, the energy levels of the σ and σ* orbitals of the C_1-C_2 bond would be increased relative to the C_1-C_3 bond. Consequently, the interaction of the 2p SOMO of the radical centre would preferentially be with the C_1-C_3 σ* orbital, leading to the primary radical (Figure 2-[1]).

By substituting R with an electron withdrawing group, a reversal of this effect is achieved and the 2p SOMO of the radical centre interacts preferentially with the C_1-C_2 σ* orbital, leading to the secondary radical. This prediction has been borne out experimentally by substituting the alkyl group with an electron withdrawing trifluoromethyl group (Figure 2-[2]).

Rearrangement of the cyclopropylcarbinyl radical has been exploited in various tandem cyclisation processes.[76] A recent example of such a tandem reaction was that of the samarium(II) iodide promoted rearrangement,[77] and subsequent cyclisation of substituted cyclopropyl ketones, as shown in Scheme 7.

Scheme 7.

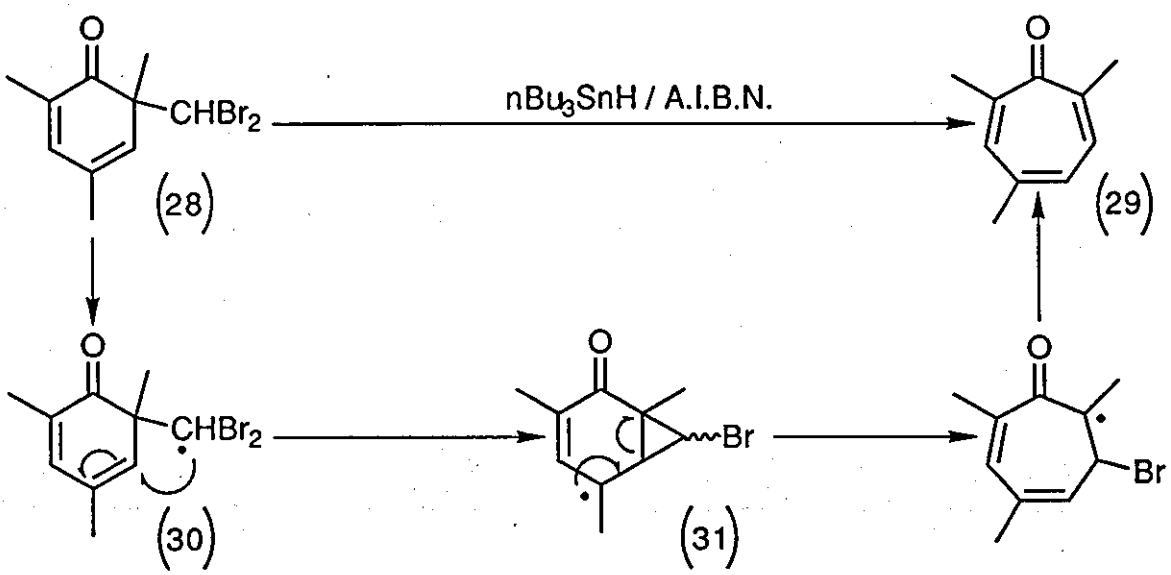


In the reduction, the samarium(II) iodide acts as an efficient single electron donor, affording the cyclopropyl(oxy)carbinyl radical (24). Rearrangement of (24) afforded the primary radical, samarium enolate (25), which underwent a 5-exo addition to the terminal alkyne, resulting in the fused spirocycle (27), after reduction and hydrolysis of vinyl radical (26).

There are several examples where cyclopropylcarbinyl radicals, or the analogous cyclopropylalkoxy radicals, form the key intermediate in ring expansion and contraction reactions.[78,79,80]

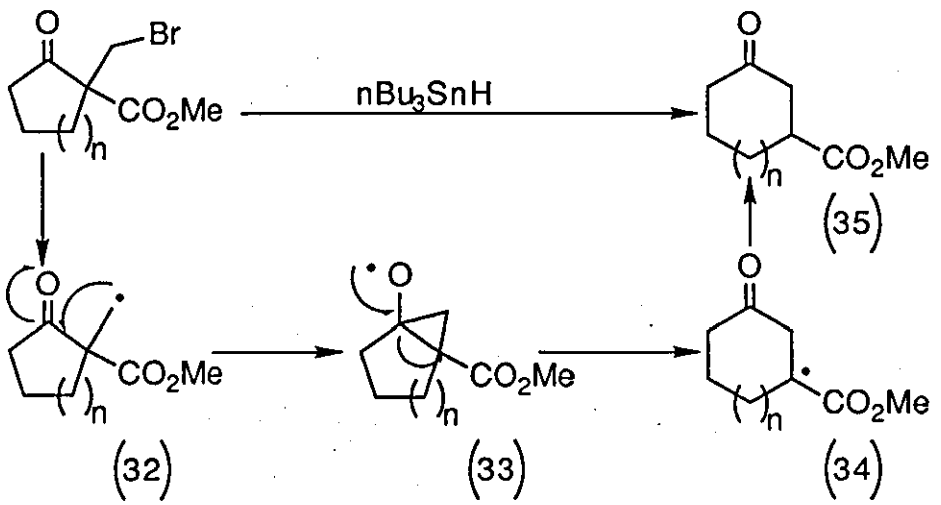
Scheme 8 demonstrates how the dibromo derivative[78] (28) was cleanly converted to the tropone (29) by treatment with tributyltin hydride / A.I.B.N. The formation and rearrangement of the cyclopropylcarbinyl radical (31) was the key step in the reaction path, with the formation of the aromatic tropone nucleus being the driving force for the β-scission of the cyclopropyl ring.

Scheme 8.



In the one carbon ring expansions[79,80] involving a cyclopropylalkoxy radical as the key intermediate, the initial step was the addition of the methyl radical (32) to the adjacent carbonyl (Scheme 9). Similar addition of radical centres to carbonyl compounds have been fairly well documented in recent literature.[81] The formed alkoxy radical (33) then underwent β-scission of the cyclopropyl ring which afforded the carboxylate stabilised, tertiary radical (34). The various ring expanded γ-keto esters (35) were isolated in good yields after the reduction of (34).

Scheme 9.



n	% yield
1-	75
2-	73
3-	71
7-	79
9-	not given
10-	not given

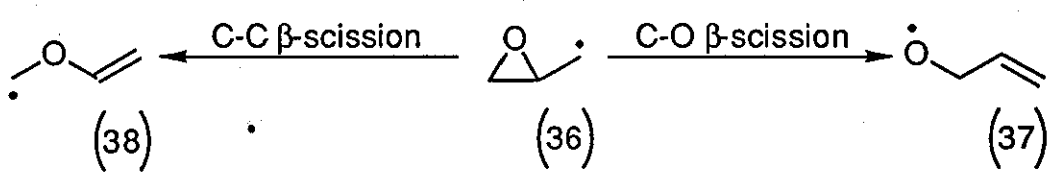
4.3. Ring opening of oxiranylcarbinyl radicals.

Rearrangement of the oxiranylcarbinyl radical (36) is similar to that of the cyclopropylcarbinyl radical in-so-far as the cleavage is an extremely rapid process. It is evident though that two different β-scissions are possible, as shown in Scheme 10.

(I) C-O β-scission leading to the allylic alkoxy radical (37).

(II) C-C bond cleavage, resulting in the enol ether carbon radical (38).

Scheme 10.



4.3.1. Stereoelectronic and electronic effects.

If the ring opening of the oxiranylcarbinyl radical was under stereoelectronic control, the stereochemistry of the epoxide should determine whether the C-O or C-C bond were co-planar with the semi-occupied p-orbital of the radical centre, and consequently which bond was to cleave (Figure 3).

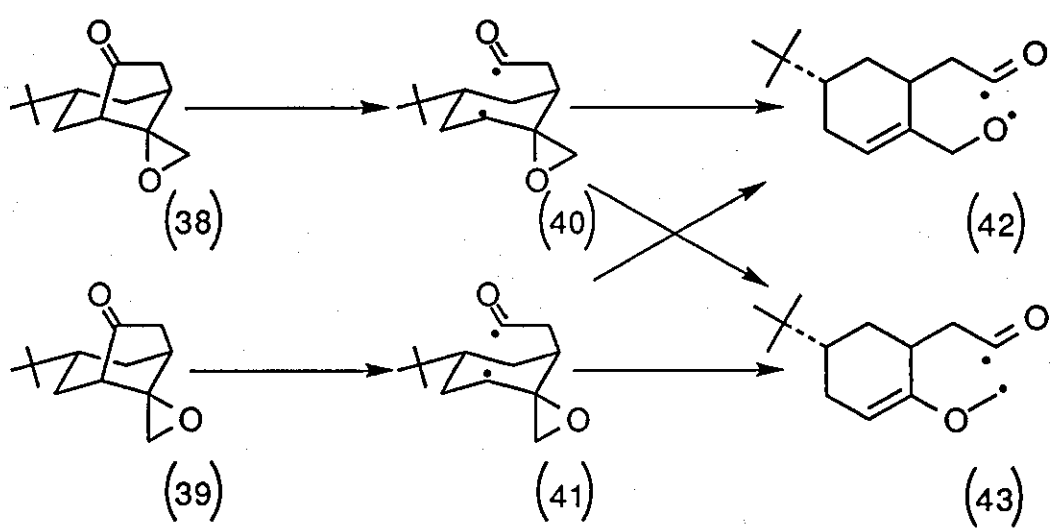
Figure 3.

predict C-O
β-scission.

predict C-C
β-scission.

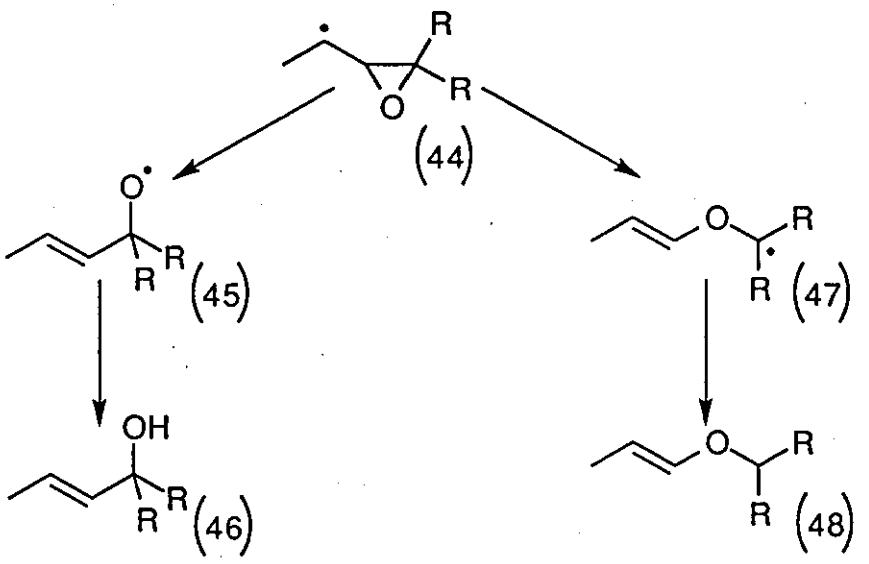
In an attempt to determine whether the opening of the oxiranylcarbinyl radical was under stereoelectronic control, the two spiroepoxyketones (38) and (39) were prepared,[82] as shown in Scheme 11. On photolysis these would be expected to produce the oxiranylcarbinyl radicals (40) and (41). If these radicals were to rearrange under stereoelectronic control,[70] biradical (42) would be expected from (40) and biradical (43) from (41). Only products derived from biradical (42) were isolated in both cases, suggesting that stereoelectronic effects are unimportant in the β-scission of oxiranylcarbinyl radicals.

Scheme 11.



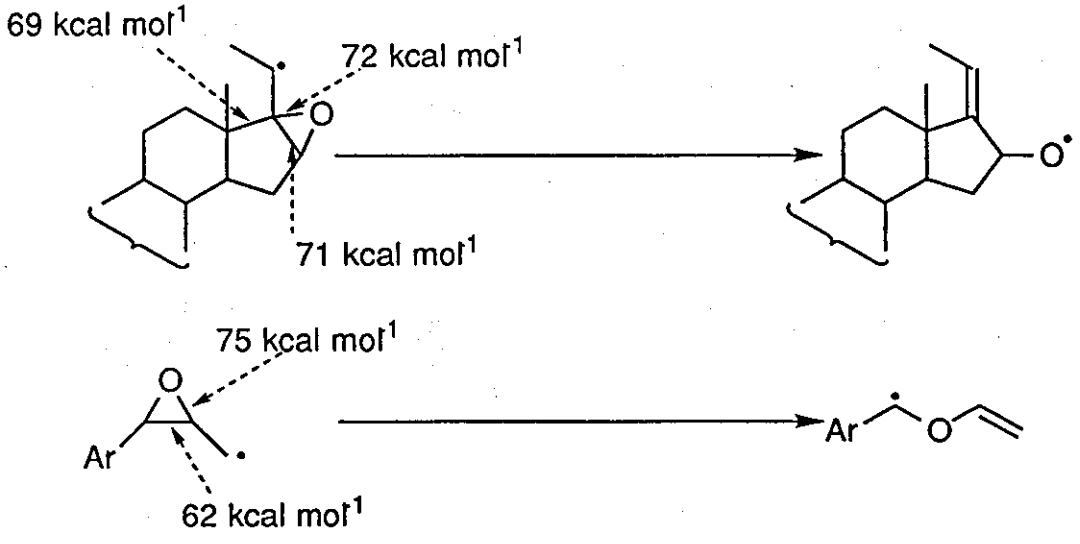
A more important factor which determined the rearrangement of the oxiranylcarbinyl radical was the nature of the substituent on the epoxide ring[83] (44), as shown in Scheme 12. By far the most common rearrangement was that by C-O bond cleavage, which occurred when R was an alkyl group or a proton. Reduction of the alkoxy radical (45) afforded the allylic alcohol (46). The alternative cleavage, which tended to predominate when R was either aryl or vinyl, was C-C β-scission.[84] This gave the enol ether (48), after reduction of the low energy, stabilised carbon centred radical (47).

Scheme 12.



It was calculated by Jorgensen *et al*[85] that C-C bond cleavage tended to predominate when the C-C bond in an epoxide ring had a bond dissociation energy of ≤ 65 kcal mol^{-1}, as shown in Scheme 13.

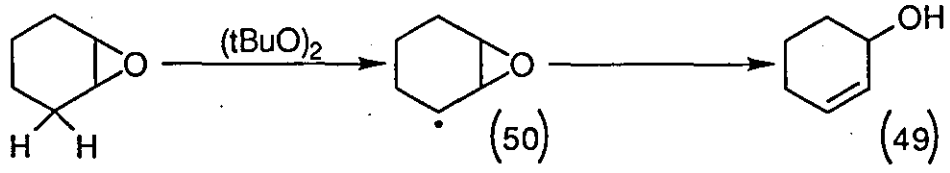
Scheme 13.



4.3.2. Oxiranylcarbinyl radical rearrangements *via* C-O β-scission.

An early example of the oxiranylcarbinyl radical rearrangement, *via* C-O β-scission, was that described by Sabatino *et al*[86] in their work on β-hydrogen atom abstraction from epoxide systems, as illustrated in Scheme 14.

Scheme 14.

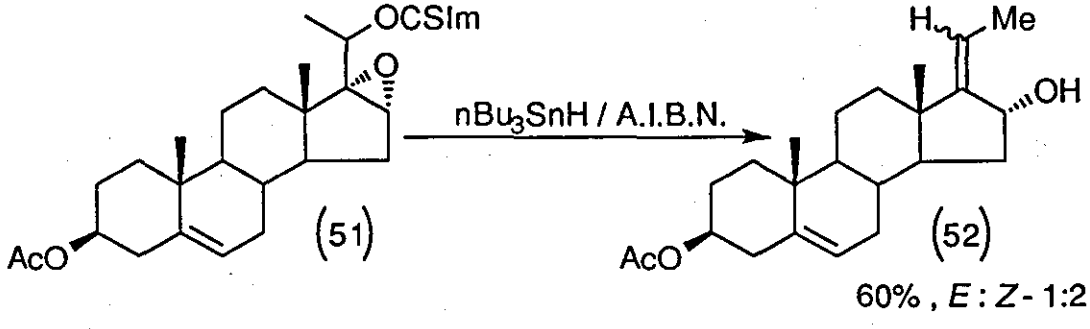


During their reactions they observed one of the products to be the allylic alcohol (49), formed by C-O β-scission of (50).

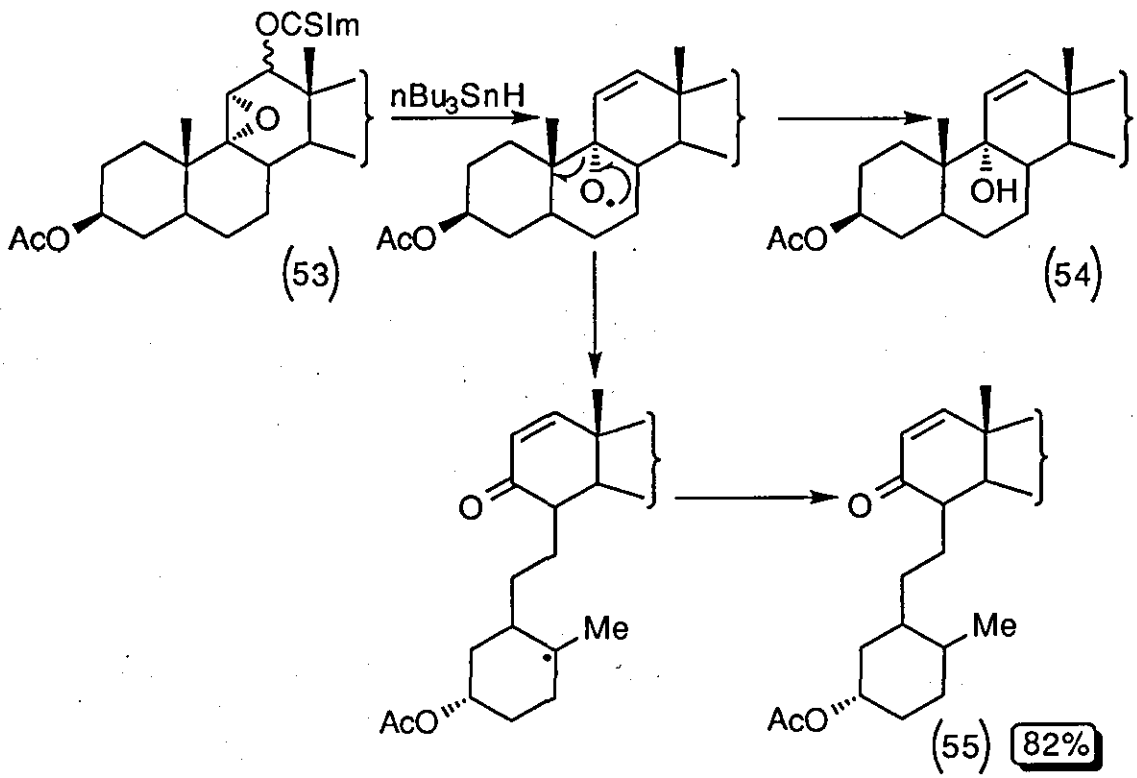
In 1981 Barton *et al*[87] performed the tributyltin hydride reduction of various α,β-epoxy-O-thiocarbonylimidazolide derivatives with an aim to providing an alternative to the Wharton rearrangement.[88]

Scheme 15 shows how the tributyltin hydride reduction of epoxypregnenolone derivative (51) using inverse addition conditions, gave (52) cleanly as a 2:1 mixture of the *Z*- and *E*- isomers. This offered an improvement over the Wharton rearrangement of the corresponding ketone, which led to unwanted pyrazoline formation.[89]

Scheme 15.



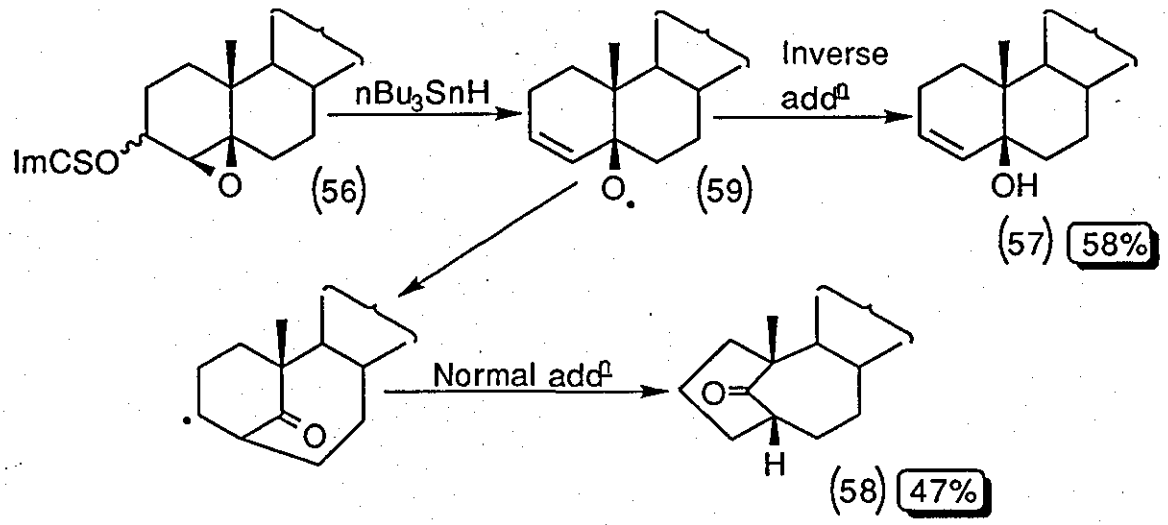
Scheme 16.



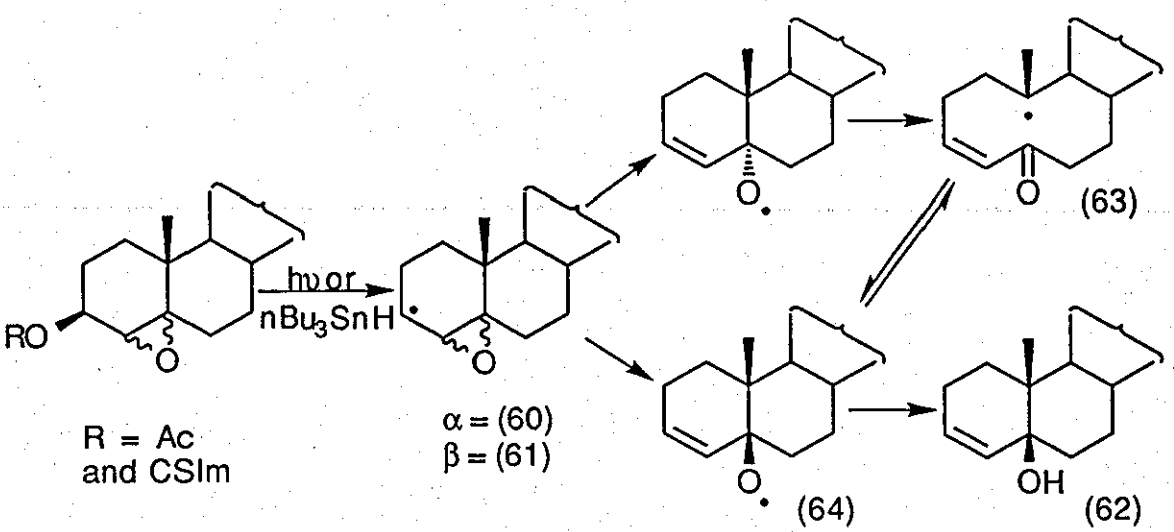
In the same paper, Barton described how an alkoxy radical may rearrange under appropriate conditions. The tributyltin hydride reduction of the α,β-epoxy-O-thiocarbonylimidazolide (53), did not afford the expected tertiary allylic alcohol (54), but rather the enone (55), *via* β-scission of the ring junction C-C bond. When the reduction was performed under inverse addition condition, the major product was the fully saturated ketone, resulting from the tributyltin hydride reduction of the enone carbon-carbon double bond[90] (Scheme 16).

A further novel fragmentation reaction[87] which exemplifies the importance of the mode of addition of the reductant, was that of the cholestanol derivative (56), as shown in Scheme 17. Inverse addition of tributyltin hydride led to isolation of the expected tertiary, allylic alcohol (57). When the reduction was performed under normal addition conditions, the major product was the bridged ketone (58), formed by β-scission of the alkoxy radical (59), followed by recombination with the olefin.

Scheme 17.



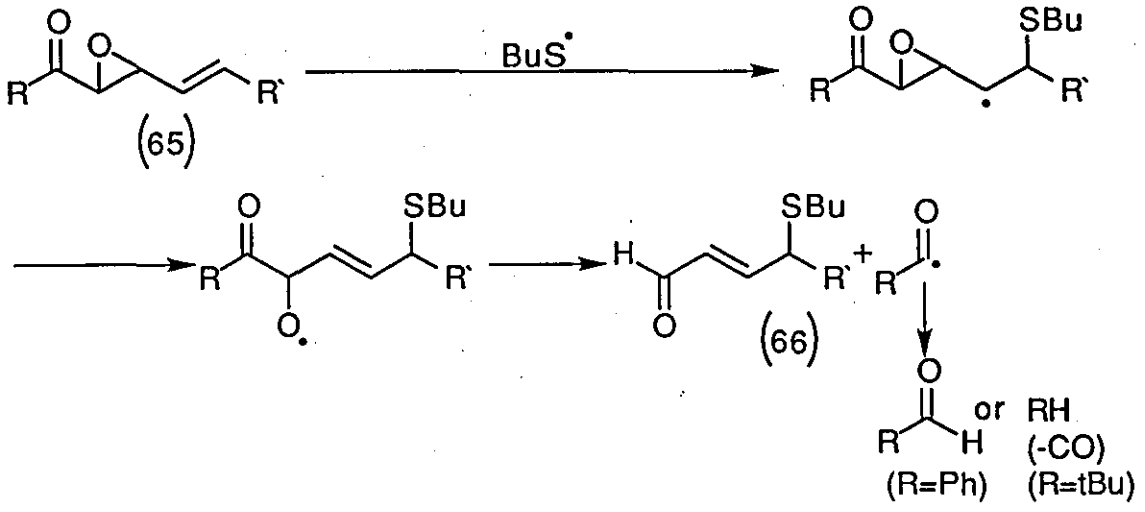
Scheme 18.



It was demonstrated by Marples *et al*[91] that rearrangement of both the α- and β-oxiranylcarbinyl radicals (60) and (61) led to the single β-alcohol product (62) (Scheme 18). Formation of this single isomer from both compounds suggested the presence of the discrete radical (63), which cyclised highly selectively and gave the 5β-alkoxy radical (64). This demonstrates the reversibility of the β-scission process, involving the addition of an alkyl radical to a ketone.

An acyclic example involving β-scission of the formed alkoxy radical was observed by Murphy *et al*,[92] when the epoxide (65) was substituted with a carbonyl group, as shown in Scheme 19. The α,β-unsaturated aldehydes (66) were only isolated in modest yields, 19-28%, due possibly to C-C bond cleavage occurring and the resulting enol ether being lost during the work up. This process is described in greater detail in section **4.3.3.**

Scheme 19.

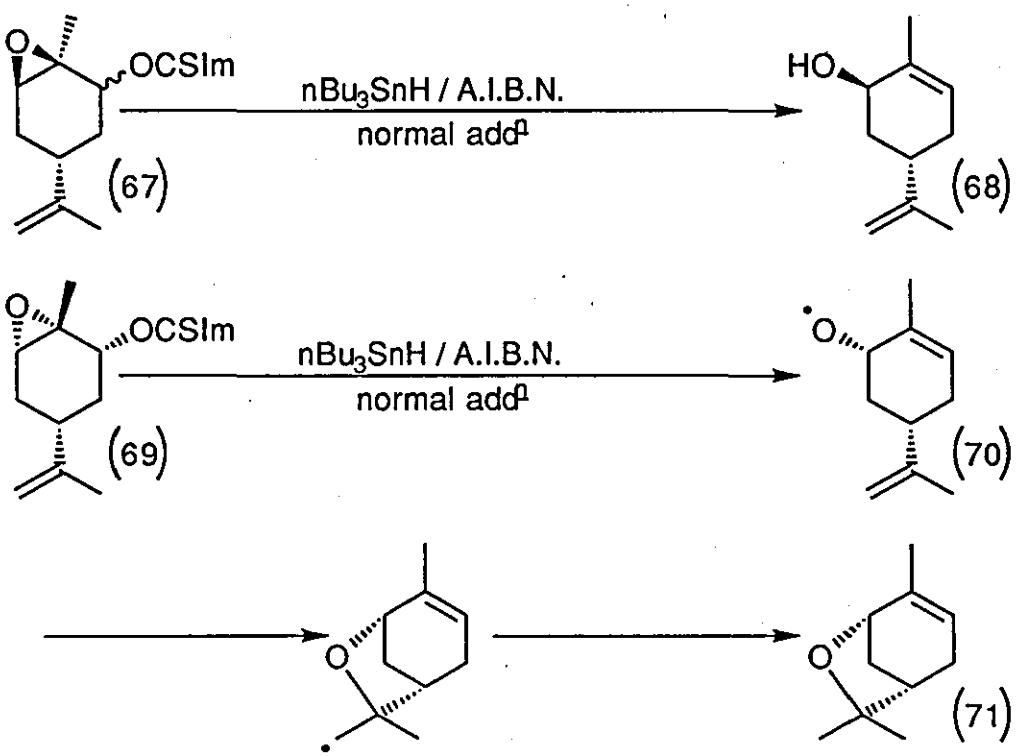


In an appropriate system, the formed alkoxy radical may be presented with the option of intramolecular cyclisation as well as reduction, or a β-scission process.

An early example of this was observed by Barton *et al*[87] in the reduction of the two epoxythiocarbonylimidazolide isomers (67) and (69), as shown in Scheme 20.

When isomer (67) was reduced with tributyltin hydride / A.I.B.N., using normal addition conditions, only the expected (+)-*trans*-carveol (68) was isolated in 65% yield. On reducing isomer (69) under the same conditions, pinol (71) was formed, with (-)-*cis*-carveol only being isolated in reasonable yield (47%) when the reduction was carried out using inverse addition conditions with a large excess of tributyltin hydride. The formation of pinol (71) showed that the intramolecular cyclisation of the alkoxy radical (70) onto the isopropenyl double bond was an efficient competing reaction.

Scheme 20.

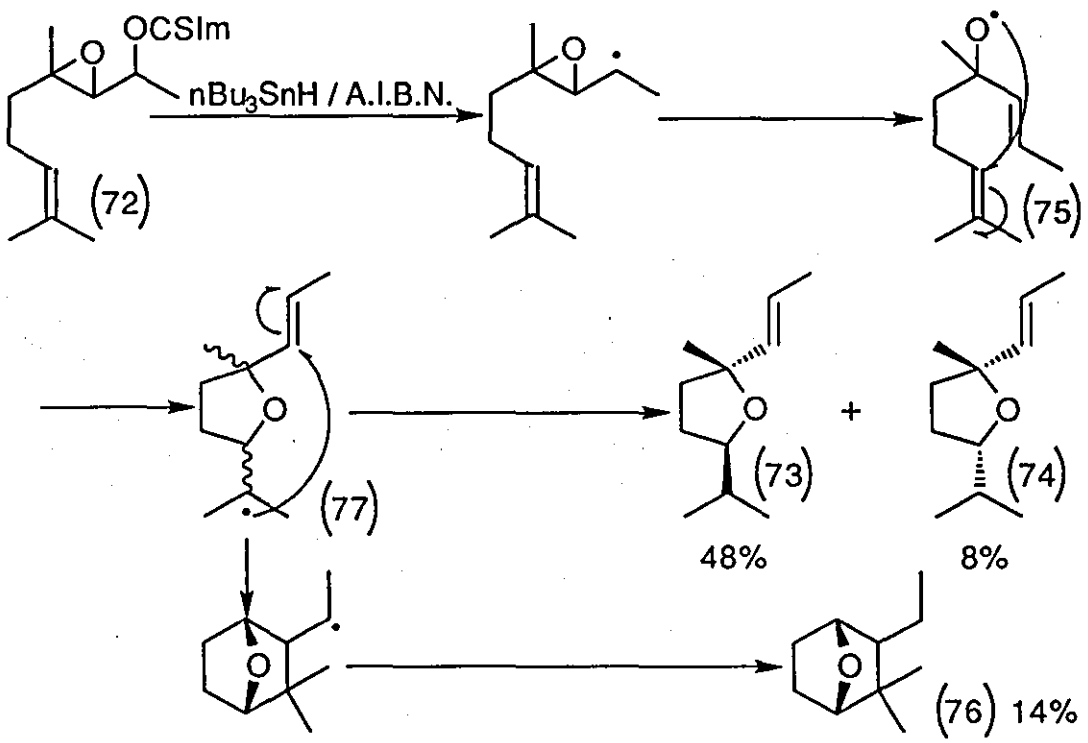


After this initial reaction in forming the strained pinol system, various other intramolecular cyclisation reactions involving alkoxy radicals were performed.

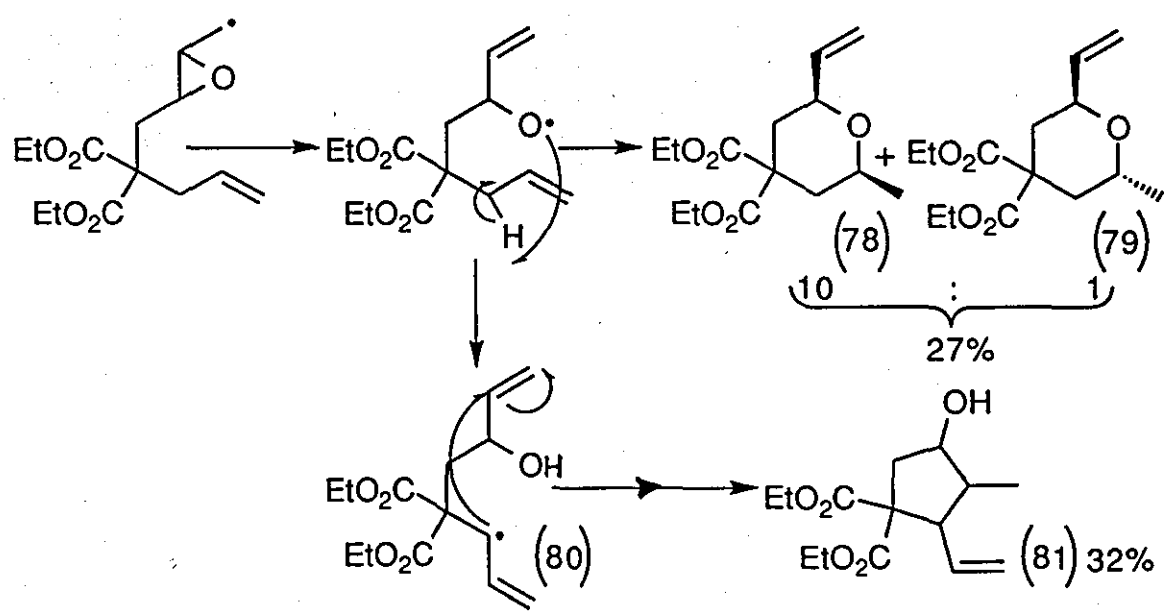
In attempting to form 2,2,5-trisubstituted tetrahydrofurans, epoxythiocarbonylimidazolide derivative (72) was treated with tributyltin hydride / A.I.B.N. using normal addition conditions,[93] as shown in Scheme 21. The two tetrahydrofuran diastereoisomers (73) and (74), were formed in a 5:1 ratio *via* the 5-exo addition of alkoxy radical (75) onto the olefin. The third isolated product, the bicyclic ether (76), was formed by the 5-exo cyclisation of the *cis*-isomer of the tertiary radical (77) onto the olefin.

When a similar reduction was performed for the preparation of the 2,6-disubstituted tetrahydropyranyl ethers (78) and (79), a higher degree of diastereoselectivity was observed,[94] as shown in Scheme 22. Again, a third product was isolated, this time from the intramolecular hydrogen abstraction,[95] which led to the allylic stabilised radical (80). 5-Exo cyclisation of this onto the olefin resulted in (81).

Scheme 21.



Scheme 22.

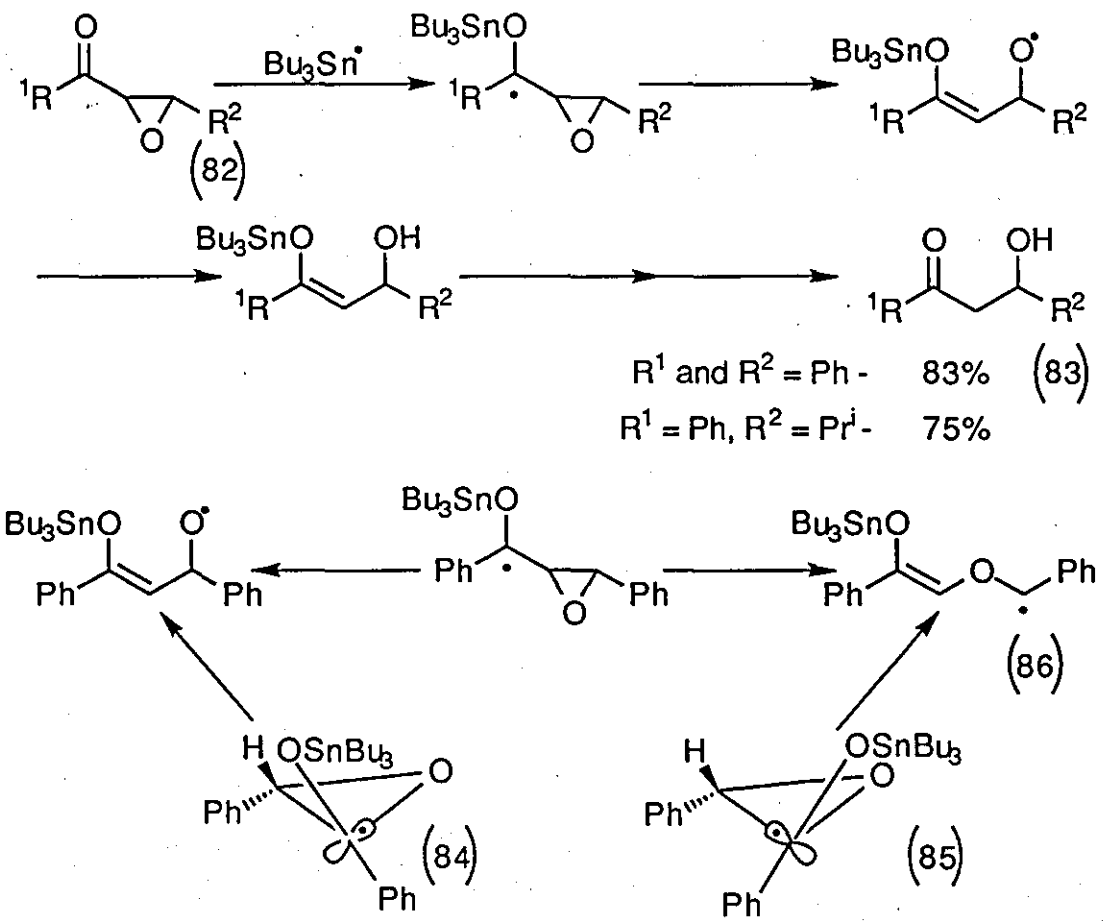


A selection of alternative and convenient routes to the oxiranylcarbinyl radicals are those which start from α,β-epoxyketones. The following are three methods of reducing the α,β-epoxyketone, all of which result in C-O β-scission of the resulting oxiranylcarbinyl radicals.

4.3.2 (I). Reduction with tributyltin hydride.

Hasegawa *et al*[96] performed the tributyltin hydride / A.I.B.N. reduction of various aryl- and alkyl-substituted α,β-epoxyketones (82) and observed that in all cases, only the products (83), resulting from C-O bond cleavage, were isolated. The reduction path for these tributyltin hydride reductions are outlined in Scheme 23.

Scheme 23.



It would have been expected that the enol ether product would be formed from the aryl derivatives, due to the radical stabilisation of the carbon centre radical. Hasegawa *et al* explained this apparent anomaly in terms of stereoelectronic effects. For maximum overlap of the semi-occupied p-orbitals of the radical centre, with the relevant σ-orbital bonds, either conformer (84) or conformer (85) must be obtained. Conformer (85), leading to the enol ether carbon centred radical (86), was assigned as the higher energy conformer due to the increase in electron pair-electron pair repulsions between the two oxygen lone

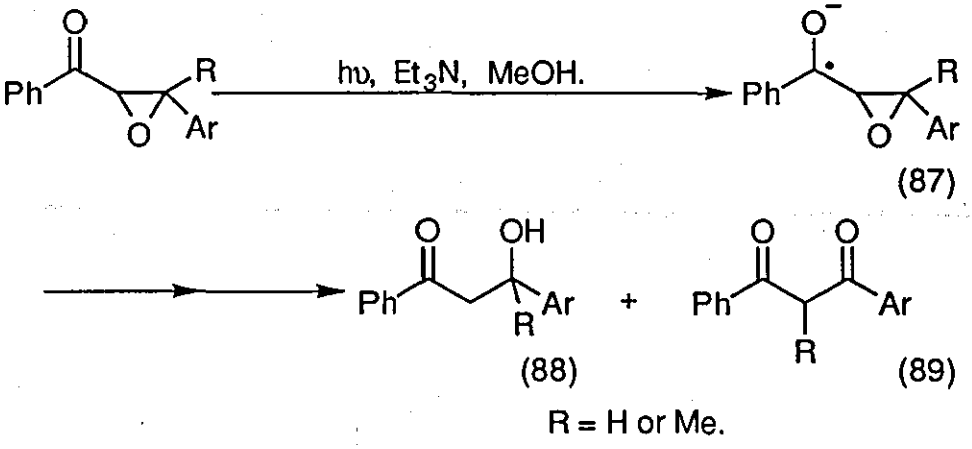
pairs. This method does provide a useful route through to the aldols (83), starting with the appropriate α,β-epoxyketones (82).

4.3.2 (II). Photochemical reduction.

The photochemistry of α,β-epoxyketones has been well studied.[97] The α,β-epoxyketone systems are known to rearrange *via* a variety of different methods, depending on the substitution and nature of the reactive excited states.

Of particular interest was the photoinduced reduction of α,β-epoxyketones in the presence of amines, as described by Hasegawa *et al.*[98] Here, irradiation in the presence of the electron donating amine affords the oxiranylcarbinyl radical anion (87), as shown in Scheme 24. Rearrangement of this affords either the reduced hydroxy ketone (88) or the β-diketone (89).

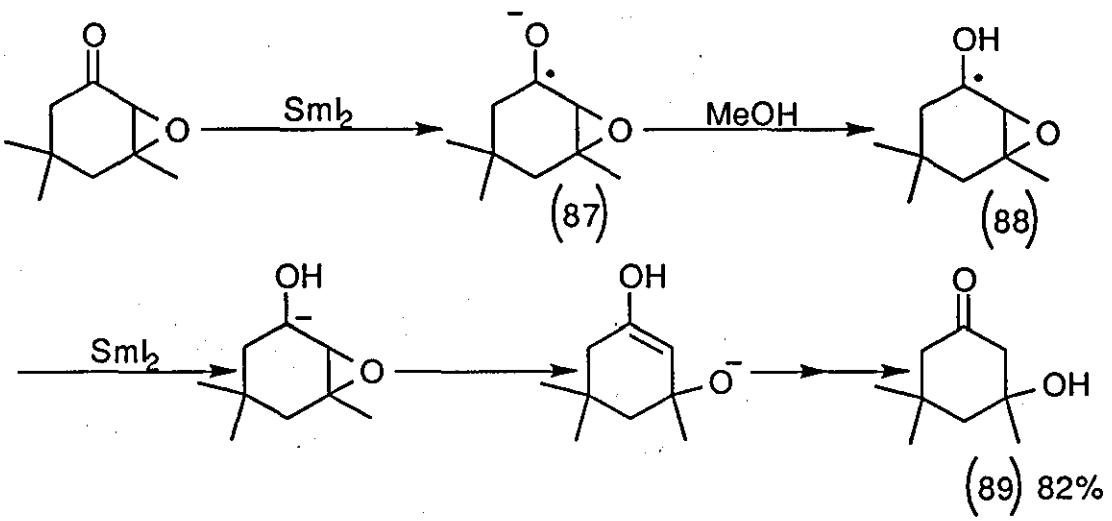
Scheme 24.



4.3.2 (III). Reduction with samarium(II) iodide.

In contrast to the previously described samarium(II) iodide reduction of the cyclopropylketones,[77] Molander *et al* performed the reduction of the α,β-epoxyketones in a protic solvent.[99] Their proposed reaction path is shown in Scheme 25.

Scheme 25.

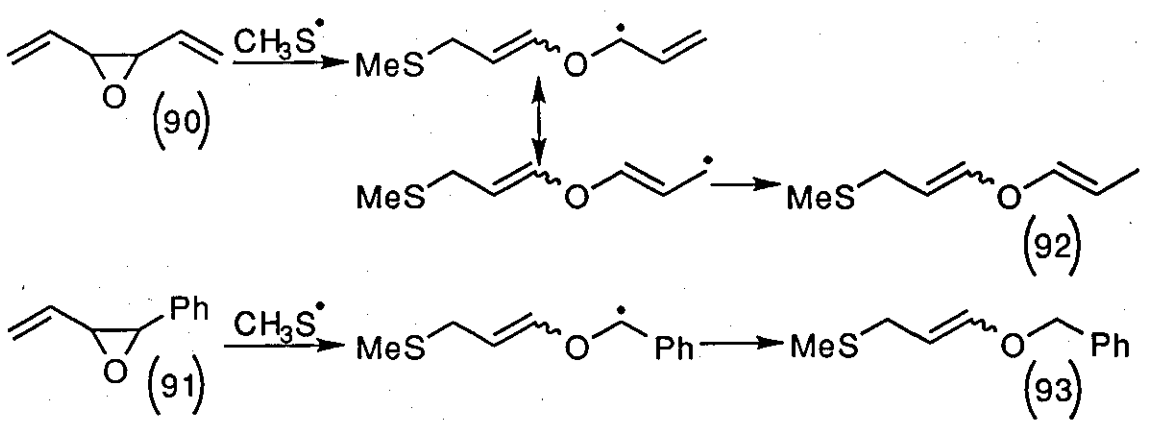


Molander suggested that once the oxiranylcarbinyl radical (88) was formed, it was further reduced by the samarium(II) iodide before rearranging, and accordingly, anionic ring cleavage of the epoxide was responsible for the aldol product (89).

4.3.3. Oxiranylcarbinyl radical rearrangements *via* C-C β-scission.

β-Scission of the C-C bond of the oxiranylcarbinyl radical was first observed by Stogryn *et al*[83] in their study of the reactions of methylthiyl radicals, with either 2,3-divinyloxirane (90), or 2-phenyl-3-vinyloxirane (91), (Scheme 26).

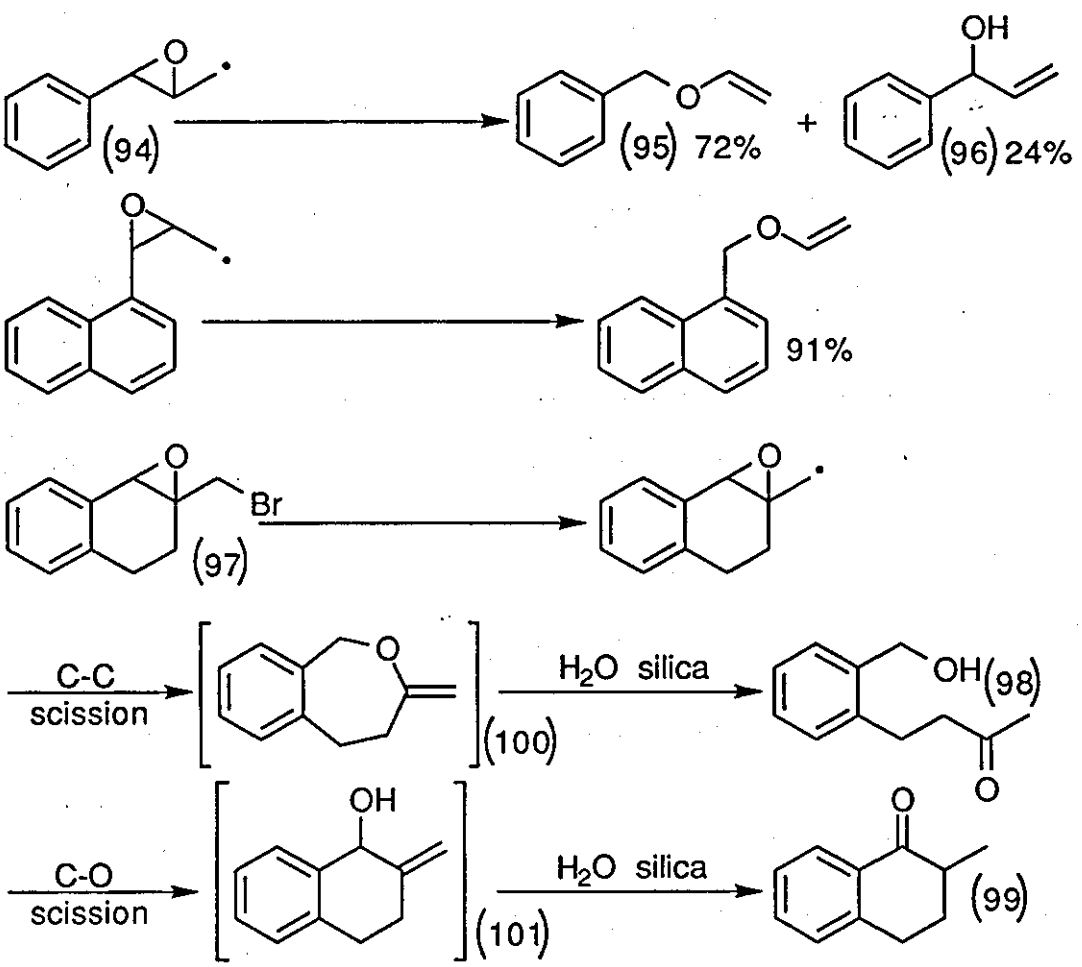
Scheme 26.



Stogryn *et al* observed only the formation of the two enol ether products (92) and (93), with neither of the allylic alcohols, which would have resulted from C-O β-scission, being isolated.

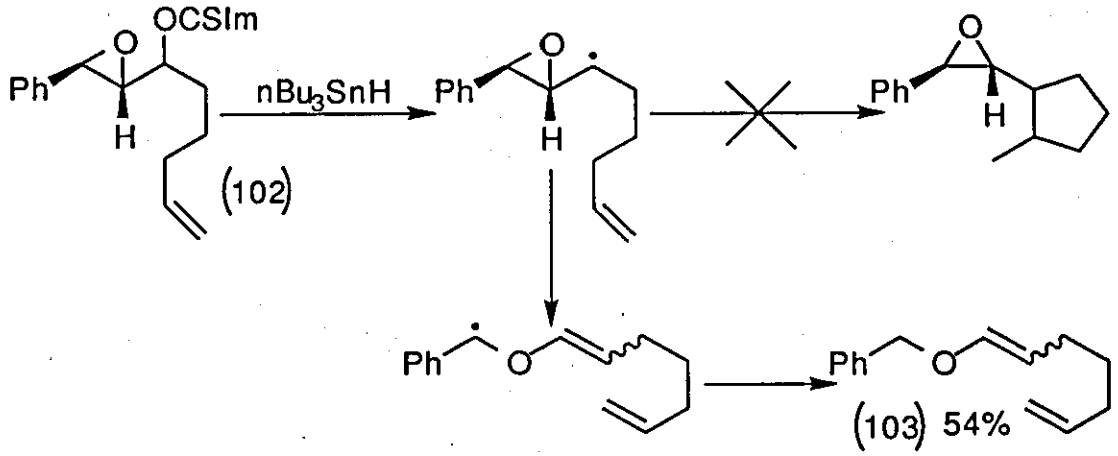
Murphy *et al*[100] demonstrated that cleavage of the oxiranylcarbinyl radical (94) yielded the enol ether (95) as the major product with the allylic alcohol (96), formed from C-O β-scission, being isolated as the minor product (Scheme 27). When the aryl group was naphthalene, the enol ether was formed exclusively in good yield. Treatment of bicycle (97) with tributyltin hydride / A.I.B.N. resulted in isolation of hydroxy ketone (98) in 21% yield and cyclic ketone (99) in 5% yield, following chromatography. Formation of (98) was thought to be formed by silica-catalysed hydrolysis of the oxepane (100). Isomerisation of the allylic alcohol (101) was thought to give (99).

Scheme 27.



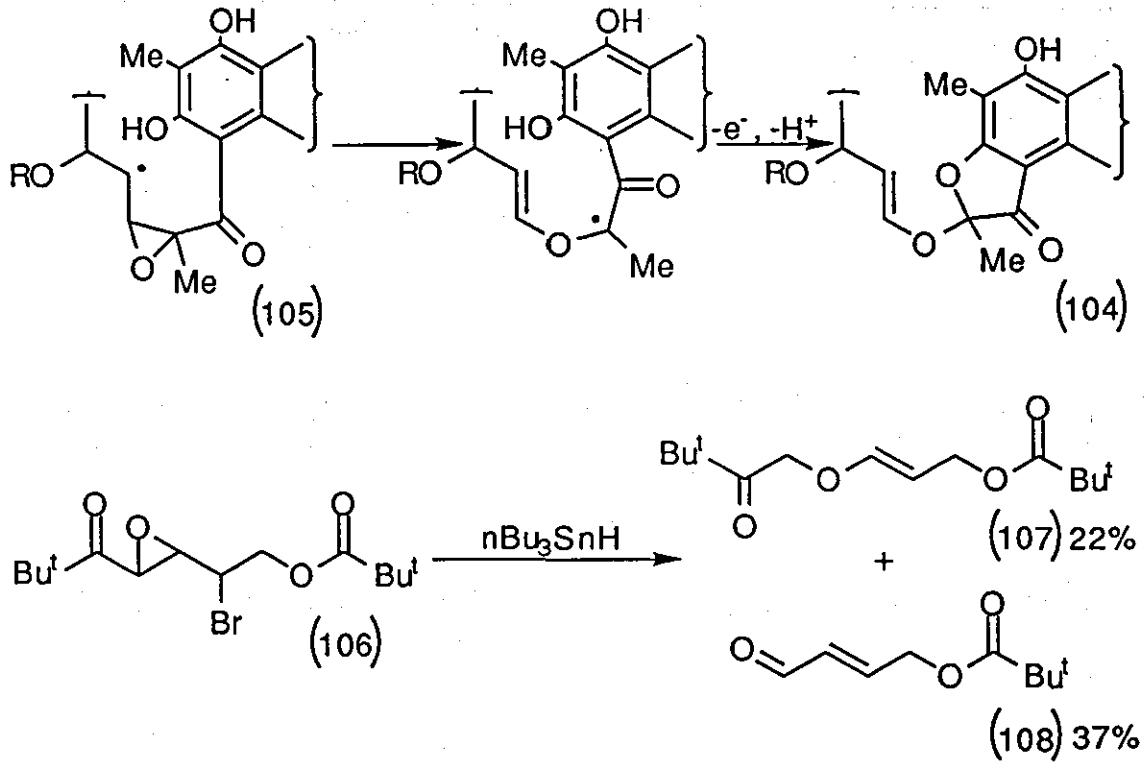
Murphy *et al*[101] demonstrated, through a competition experiment, that epoxide opening occurs faster than ring cyclisation to give cyclopentane formation. Reduction of (102) with tributyltin hydride led to the enol ether (103) being formed as a mixture of *E*- and *Z*-isomers in 54% yield, as shown in Scheme 28.

Scheme 28.



It has been suggested that the C-C bond cleavage of oxiranylcarbinyl radicals may form an important role in the introduction of oxygen atoms in the biosynthesis of various antibiotics.[102] For instance, in the production of rifamycin S, a vinyl ether is required in the side chain of (104), as shown in Scheme 29.

Scheme 29.



It was predicted that this could be formed, as outlined, from the oxiranylcarbinyl radical (105). For this mechanism to be realistic C-C bond cleavage would be required next to a carbonyl group. As has already been seen in Scheme 19, fragmentation of such a compound led to the α,β-unsaturated aldehydes.[92] When the oxiranylcarbinyl radical was prepared from compound (106) a small amount of the enol ether (107) was formed in addition to the α,β-unsaturated aldehydes[102] (108). Although only a low yield was obtained, it was considered that the reaction was occurring in the absence of any enzymatic assistance, which could enhance C-C bond cleavage in *vivo*.

The work described in this thesis intends to extend the applications in synthesis of directed C-O and C-C bond cleavages of oxiranylcarbinyl radicals. Particular targets are medium ring carbocycles and oxygen heterocycles, including spiroketals.

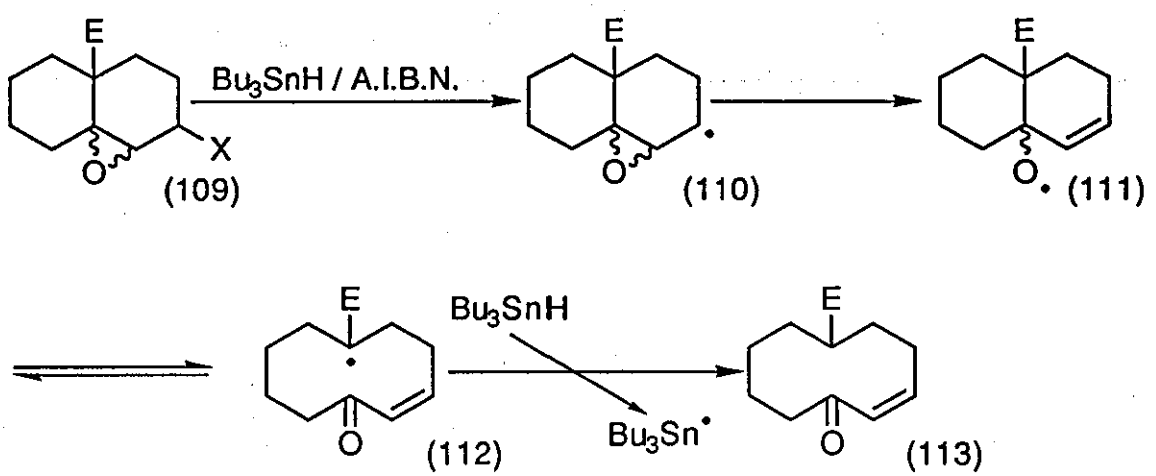
Chapter 5. Radical mediated reactions involving β-scission of the C-O bond of oxiranylcarbinyl radicals.

5.1. Ring expansion reactions of bicyclic systems *via* scission of the bridging C-C bond.

5.1.1. Introduction.

As has already been described in Scheme 18 of **Chapter 4**, Marples *et al* observed that both the α- and β-oxiranylcarbinyl radicals (60) and (61) rearranged to give the single β-alcohol (62).[91] Formation of this single isomer from both compounds, suggested the presence of the discrete radical (63), which cyclised highly selectively to afford the 5β-alkoxy radical (64). We considered that if the half-life of this radical (63) could be extended, it might be possible for it to abstract a hydride radical, resulting in a ring expanded product. Scheme 30 outlines the basic methodology by which it was hope this could be achieved.

Scheme 30.

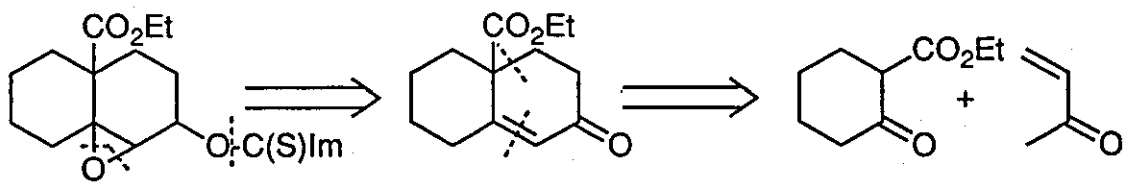


E to be radical stabilising, *e.g.* carboxylate ester, aryl group *etc.*

If compound (109) could be prepared, where E is a radical stabilising group, and X is a halogen or thiocarbonylimidazolide derivative, treatment with tributyltin hydride / A.I.B.N. would afford the oxiranylcarbinyl radical (110). Typical rearrangement of this by C-O bond scission would give the alkoxy radical (111). If this were to undergo the reversible β-scission of the bridging C-C bond, as postulated by Marples *et al*, the now stabilised radical (112) might survive long enough for it to abstract a hydride radical from tributyltin hydride, affording the ring expanded enone (113).

If the radical stabilising group were a carboxylate ester, it is clear from a simple retrosynthetic analysis, that the required bicyclic skeleton could be prepared *via* the Robinson annulation reaction[103] of methylvinylketone and ethyl 2-oxocyclohexanecarboxylate (Scheme 31).

Scheme 31.



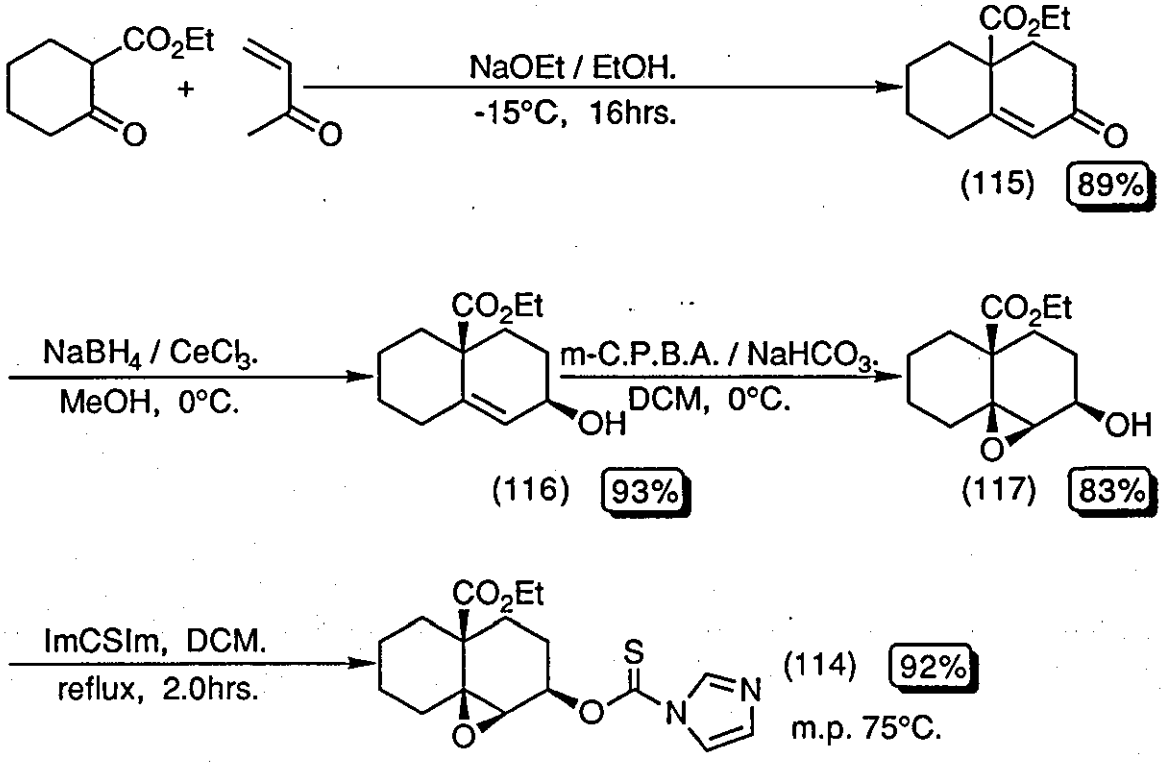
(114)

5.1.2. Preparation of the bicyclic epoxythiocarbonylimidazolide (114).

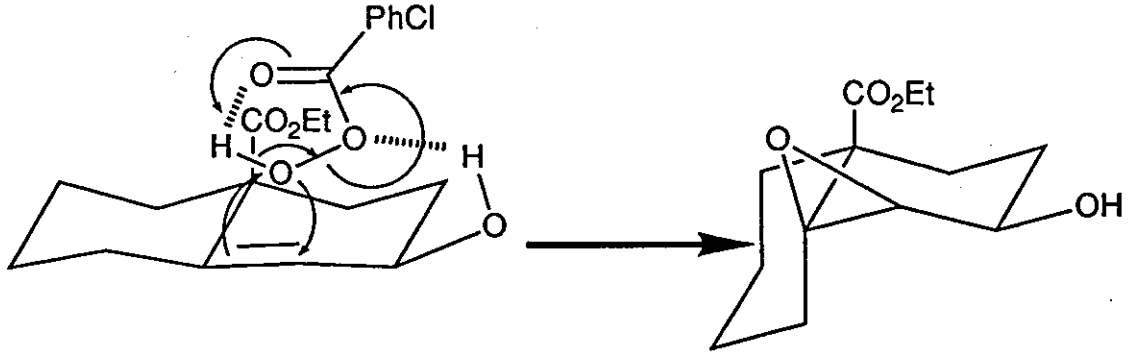
The bicyclic epoxythiocarbonylimidazolide (114) was prepared *via* the route shown in Scheme 32. The bicyclic skeleton was prepared, at -15°C, by the Robinson annulation reaction of ethyl 2-oxocyclohexanecarboxylate and methylvinylketone in anhydrous ethanolic sodium ethoxide solution. The crude bicyclic enone (115) was purified by vacuum distillation, affording the clean product in 89% yield. The allylic alcohol (116) was prepared by the sodium borohydride reduction of ketone (115) in the presence of a one molar equivalent of cerium(III) chloride.[104] The cerium(III) chloride was required as it prevents the reduction of the olefin in enone systems, a process which can occur in the absence of the cerium salt, yielding up to 50% of the fully saturated alcohol.[105] The allylic alcohol (116) was isolated as a clear liquid in 93% yield, after purification by flash chromatography. Only one isomer was evident from the ^{1}H and ^{13}C N.M.R. spectra. This was assigned to be the β-alcohol by comparison of the spectra with the literature compound.[106] m-Chloroperoxybenzoic acid epoxidation of the allylic alcohol proceeded smoothly, with the reaction going to completion in just 30 minutes. After purification by flash chromatography, the epoxy alcohol (117) was isolated as a viscous liquid. It was evident from the ^{1}H and ^{13}C N.M.R. spectra that just one isomer of the epoxide had been formed. In the ^{1}H N.M.R. spectrum the epoxide proton appeared as a well defined doublet at δ 3.11 p.p.m.(J = 4.50 Hz). Although it is difficult to predict what the coupling constant would be for the other geometric isomer of the epoxide, due to the presence of the electronegative groups, it is unlikely that both isomers would have identical shifts and coupling constants, and hence provides good evidence that only one isomer is formed. Henbest *et al*[107] have shown that the peracid epoxidation of allylic alcohols proceeds with high *syn*-stereoselectivity. Which in

the case of the allylic alcohol (116) results in the 8β,8aβ-epoxy-7β-hydroxy product. This *syn*-directing effect is thought to be the result of hydrogen bonds between the hydrogen of the allylic alcohol and one of the oxygens of the peracid in the transition state for the epoxidation, as shown in Scheme 33.

Scheme 32.



Scheme 33.



8β,8aβ-epoxy-7β-hydroxy-(117).

The thiocarbonylimidazolide (114) was simply prepared, following the method of Barton *et al*,[87] by refluxing epoxide (117) with a two molar excess of thiocarbonyldiimidazole in dichloromethane. After recrystallisation the thiocarbonylimidazolide (114) was obtained as colourless crystals; m.p. 75°C.

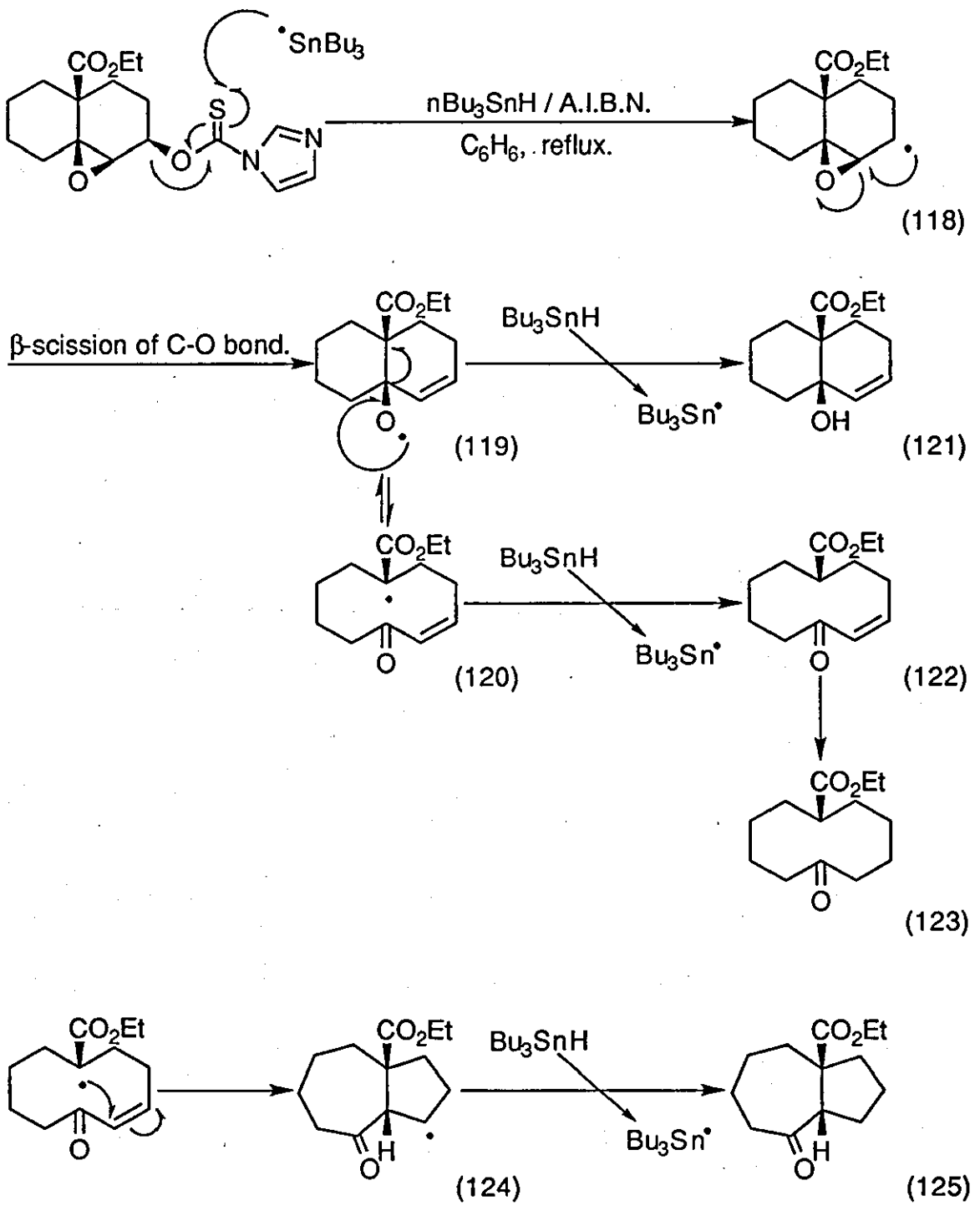
5.1.3. Tributyltin hydride reduction of the bicyclic epoxythiocarbonylimidazolide (114).

The bicyclic epoxythiocarbonylimidazolide (114) was reduced with tributyltin hydride / A.I.B.N. under both normal and inverse modes of addition.

The reduction was initially performed by adding tributyltin hydride / A.I.B.N. to a refluxing benzene solution of the bicyclic epoxythiocarbonyl-imidazolide (114), *via* a syringe pump over a 4 hour period. This normal mode of addition was expected to give the best results as the concentration of tributyltin hydride was kept at a minimum, thus allowing the alkoxy radical (119), formed by β-scission of the oxiranylcarbinyl radical (118), to rearrange to the stabilised tertiary radical (120). Once formed it was expected that the tertiary radical (120) would abstract a hydride radical from tributyltin hydride, resulting in the ring expanded enone (122) (Scheme 34). Table 2, entry 1 gives the results obtained in the tributyltin hydride reduction using the normal mode of addition. A 13% yield of the ring expanded enone (122) was isolated, thus proving that β-scission of the bridging C-C bond was occurring. The presence of the enone was clearly evident from the infrared spectrum (υ_{max} 1686 cm^{-1} C=O, and 1626 cm^{-1} C=C). The two olefinic protons were evident in the ^1H N.M.R. spectrum, and appeared as the expected double-triplet at δ 5.81 p.p.m. (J = 5.26 and 12.00 Hz), and doublet at δ 6.34 p.p.m. (J = 11.96 Hz). The chemical ionisation mass spectrum showed the MH^+ and MNH_4^+ peaks, both with the correct accurate masses.

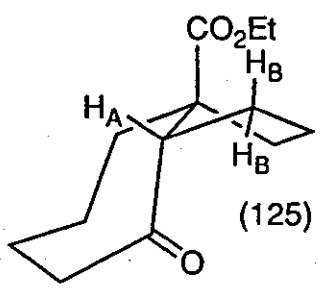
Three other products were isolated from the reaction. The first of these was the tertiary allylic alcohol (121). This resulted from hydride radical abstraction by the alkoxy radical (119). The infrared spectrum showed the presence of the hydroxy group (υ_{max} 3484 cm^{-1}), and the mass spectrum gave the M^+ peak, with the correct accurate mass. The second product was the fully saturated, ring expanded product (123). This was formed by the tributyltin hydride reduction of the alkene of the enone system, a process which has been noted by other workers.[87,90] The fully saturated ring expanded product (123) proved to be the major product, being isolated in 35% yield and was characterised by the carbonyl stretch in the infrared spectrum (υ_{max} 1700 cm^{-1}) and gave the correct accurate mass for the MNH_4^+ ion in the chemical ionisation mass spectrum. The final, unexpected product was the fused *cis*-(5,3,0)-bicyclic compound (125). The mechanism for the formation of (125) is as shown in Scheme 34. The radical (120) adds to the olefinic bond, α to the carbonyl group, affording the secondary radical (124). Once formed this abstracts a hydride radical from tributyltin hydride yielding the bicycle (125). This product was isolated as a single isomer, and was assigned as the *cis*-isomer based on the N.M.R. spectroscopic evidence, which showed the

Scheme 34.


CO2Et
SnBu3
S
O
N
nBu3SnH / A.I.B.N.
C6H6, . reflux.
(118)
β-scission of C-O bond.
Bu3SnH
Bu3Sn•
OH
(119)
(121)
(120)
(122)
(123)
(124)
(125)

bridge head proton (proton H_A in Figure 4) as a well defined triplet, with a chemical shift of δ 3.92 p.p.m. (J = 7.91 Hz). For proton H_A to appear as a triplet, the C-H_A bond must be in a skew conformational relationship with respect to the two C-H_B bonds, as illustrated in Figure 4. If the *trans*- fused bicyclic compound had been formed, the C-H_A bond would not be able to assume this skew conformational relationship with respect to the two C-H_B bonds, and it would probably appear as the double-doublet of an ABX system. As can be seen from Figure 4, in the lowest energy conformation of the *cis*-isomer, the C-H_A and C-H_B bonds are in the required orientation for the signal to appear as a triplet. The low field position of the signal is due to the combined deshielding effects of the carbonyl and ester groups, and also as a result of the ring strain at the fused bridge head position.

Figure 4.



(125)

This simple diagram illustrates the orientation of the bonds of interest in the minimum energy conformation. Of note is the C-H_A bond, which is in a skew relationship with respect to the two C-H_B bonds, and hence the associated signal appears as a triplet in the ^1H N.M.R. spectrum.

It would appear that once formed the tertiary radical (120) has three options:

(I) Direct reduction by tributyltin hydride, affording the ring expanded enone (122). This is the most common process, yielding up to 50% of the enone (122), which may then be further reduced by tributyltin hydride to give (123).

(II) The radical (120) may add to the olefin, affording the *cis*-(5,3,0)-bicycle (125) after reduction of the radical (124). This is the next most common process, yielding 15% of (125).

(III) The radical may add to the carbonyl, affording the alkoxy radical (119). This is the reverse of the β-scission of the bridging C-C bond, and is the least common process as just 8% of the allylic alcohol (121) was isolated. Some, or all of this product may be formed by direct reduction of the alkoxy radical (119), before it undergoes β-scission of the bridging C-C bond.

As the ring expanded compounds (122) and (123) were isolated in reasonable yields, the presence of the radical stabilising carboxylate ester group obviously had the required effect; prolonging the life time of the intermediate radical (120).

Table 2. Results of the tributyltin hydride reduction of the bicyclic epoxythiocarbonylimidazolide (114).

Nº	Mode of addn of tributyltin hydride.	% Yield of product.			
		(121)	(122)	(123)	(125)
1	Normal	8	13	35	15
2	Inverse	15	—	40	—

When performing the reduction of the epoxythiocarbonylimidazolide (114) using the inverse mode of addition of tributyltin hydride / A.I.B.N., only two products were isolated. The tertiary allylic alcohol (121) which was isolated in 15% yield. An increased yield of this product was anticipated as the concentration of reductant was much higher that in the normal mode of addition and as a result it was expected that more of the alkoxy radical (119) would be reduced before β-scission of the bridging C-C bond occurred. Once more, the major product was the ring expanded, fully saturated ketone (123), being isolated in 40% yield. As such a high yield of (123) was obtained under kinetically controlled conditions, where generally the first formed product is obtained, it again demonstrates how effective the carboxylate ester group is at stabilising the radical (120).

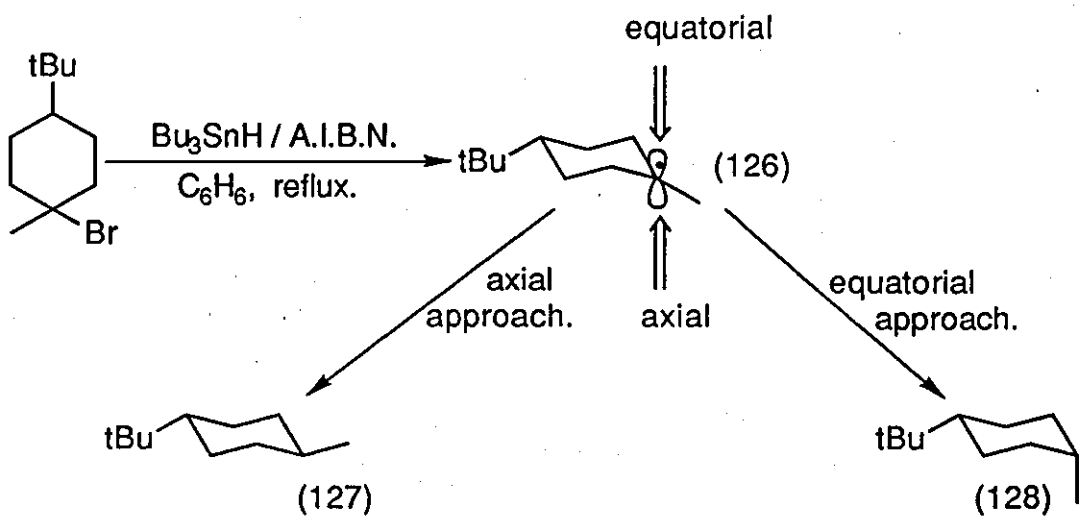
5.2. Ring expansion of a substituted bicyclic epoxythiocarbonylimidazolide, and the diastereofacial selectivity in the reduction of the tertiary cyclodecyl radical.

5.2.1. Introduction.

We considered it interesting to see if the ring expansion observed with the bicyclic epoxythiocarbonylimidazolide (114) would proceed in a similar fashion with an alkyl substituted bicyclic epoxythiocarbonylimidazolide. In particular, we were interested to see whether any diastereofacial selectivity would be seen in the tributyltin hydride reduction of the tertiary cyclodecyl radical. A diastereofacial selectivity has been observed in the reduction of substituted cyclohexyl radicals by Damm *et al.*[108] Scheme 35 shows the results obtained in the tributyltin hydride reduction of the disubstituted cyclohexyl radical (126). Once formed the cyclohexyl radical (126) may be reduced by the tributyltin hydride by either an equatorial attack, resulting in the methyl group assuming the axial position as with cyclohexyl (128), or by the tributyltin hydride *via* an axial approach, affording cyclohexyl (127) which has the methyl in an equatorial position. As can be seen from the results, the tributyltin hydride delivers the hydride radical preferentially *via* the axial

approach. It was hoped that such a selectivity would also be shown in the tributyltin hydride reduction of a disubstituted cyclodecyl radical.

Scheme 35.



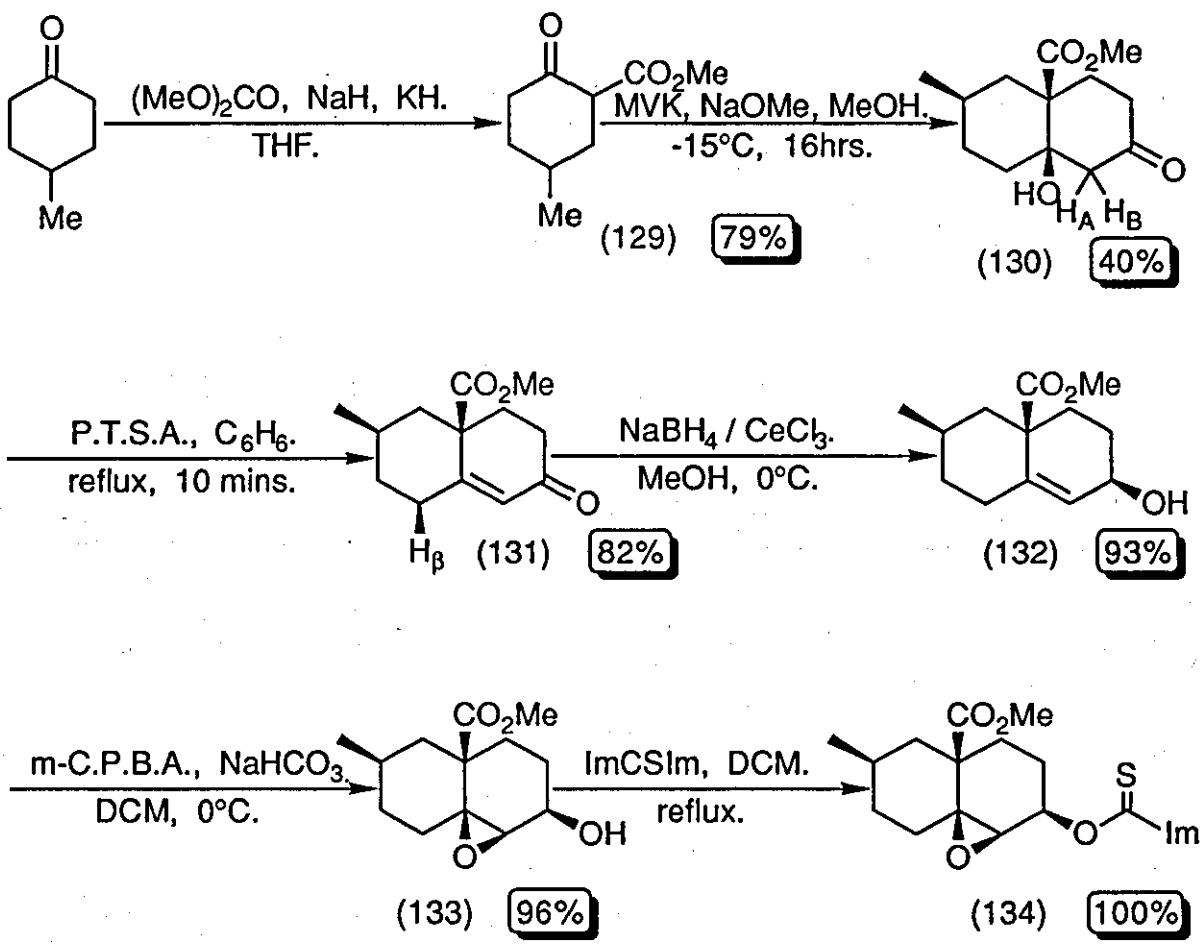
5.2.2. Preparation of the substituted bicyclic epoxythiocarbonylimidazolide (134).

The substituted bicyclic epoxythiocarbonylimidazolide chosen for investigation was the methyl derivative (134). The β-ketoester (129) was prepared employing the method of Ruest *et al.*[109] The Robinson annulation[103] of the β-ketoester (129) was then performed, using methylvinylketone, and sodium methoxide as the base in anhydrous methanol. Rather than obtaining the enone (131) after purification, the bicyclic alcohol (130) was isolated as a crystalline solid, m.p. 60°C. This compound was seen to be a single isomer, and was assigned the stereochemistry shown in Scheme 36, based on the ^1H N.M.R. spectroscopic evidence. The ring junction was assigned as *cis* on the basis of the n.O.e. effects between the hydroxy proton and the protons labelled as H_A and H_B.

The bicyclic alcohol (130) was easily dehydrated to the enone (131) by refluxing it in benzene with a catalytic amount of p-toluenesulfonic acid. The enone (131) was isolated in good yield as a crystalline solid, m.p. 53°C. Again the compound was seen to be a single isomer, with the methyl group assigned as being in the β-position. This assignment was based on n.O.e. effects between the methyl group and the axial proton H_β, and also on the coupling constants of the protons α and β to the methyl group. The enone (131) was reduced with sodium borohydride-cerium(III) chloride, affording the hydroxy compound (132). Epoxidation of (132) with m-chloroperoxybenzoic acid afforded the epoxy alcohol

(133) as a single isomer. The methyl substituted bicyclic epoxythiocarbonylimidazolide (134) was then prepared by refluxing the epoxy alcohol (133) in dichloromethane with a two molar excess of thiocarbonyldiimidazole, affording epoxythiocarbonylimidazolide (134) as a crystalline solid, m.p. 125°C. All of these last four steps went in excellent yields, affording epoxythiocarbonylimidazolide (134) in 73% yield from the alcohol (130).

Scheme 36.



5.2.3. Tributyltin hydride reduction of the methyl substituted bicyclic epoxythiocarbonylimidazolide (134).

The reduction of the methyl substituted bicyclic epoxythiocarbonylimidazolide (134) was performed under both the normal and inverse modes of addition of tributyltin hydride / A.I.B.N. With both modes of addition, just two products were isolated; (I) the ring expanded cyclodecenone (138) and (II) the ring expanded cyclodecanone (139), as shown in Scheme 37 and Table 3. With both modes of addition, the total yield of product was roughly the same, with the cyclodecenone product (138) predominating with the normal mode of addition and

the cyclodecanone product (139) predominating with the inverse mode of addition. These results are as expected, as keeping the concentration of tributyltin hydride low, as is the case with the normal mode of addition, results in less of the olefin being reduced.

Scheme 37.

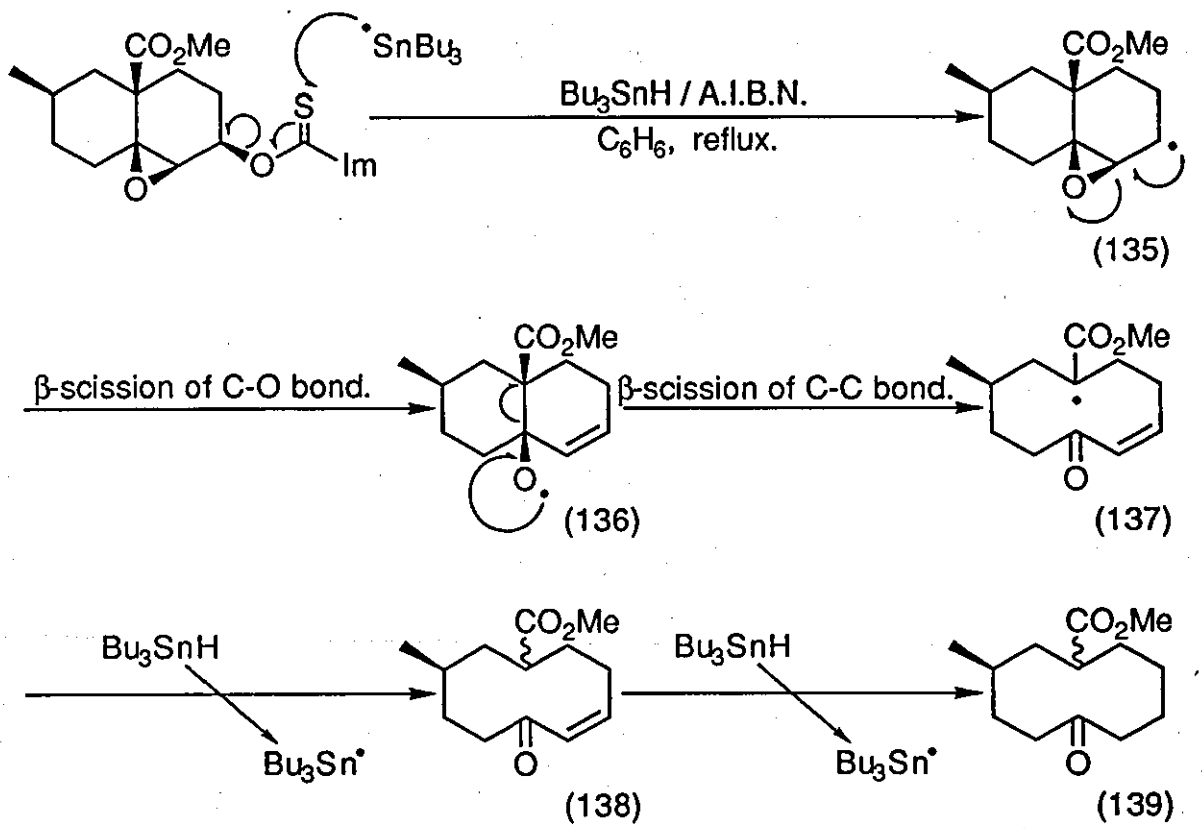


Table 3. Results of the tributyltin hydride reduction of the methyl substituted bicyclic epoxythiocarbonylimidazolide (134).

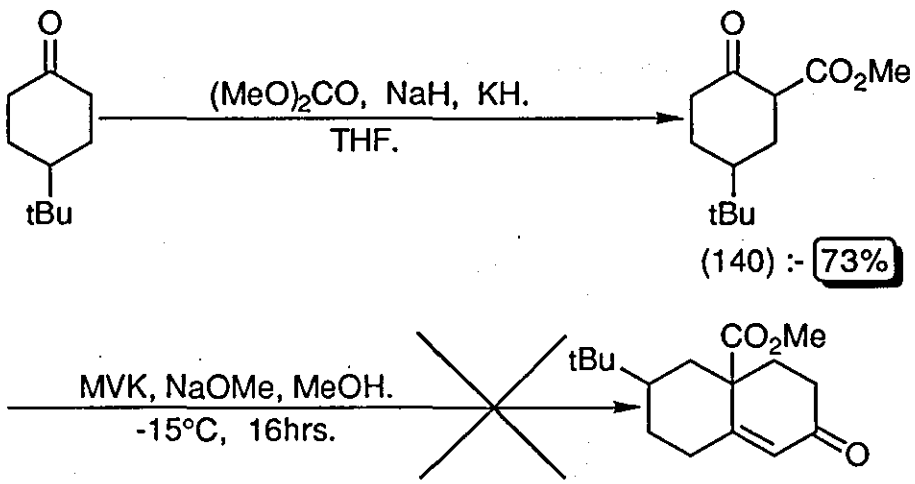
Nº	Mode of addⁿ of. tributyltin hydride.	% Yield of product. (138)	(139)
1	Normal	41	22
2	Inverse	18	41

Interestingly with this reduction, none of the tertiary allylic alcohol, derived from tributyltin hydride reduction of the alkoxy radical (136) was isolated from the reaction mixture. The reason for this is thought to be that in the addition of the tertiary radical (137) to the carbonyl group, affording the *cis*-fused bicycle, the methyl group takes up a pseudo axial position in the transition state. As a result

the energy level of this transition state is raised, due to the increased 1,3-diaxial interactions and hence β-scission of the bridgehead C-C bond is effectively made irreversible. This may also account for the improved yield of the ring expanded products in the tributyltin hydride / A.I.B.N. reduction of epoxythiocarbonyl-imidazolide (134), compared with epoxythiocarbonylimidazolide (114). It is difficult to understand why such an increase in the yield of the enone product was obtained in the reduction of (134), compared with the reduction of (114).

On examining the ^{1}H N.M.R. spectra for both the cyclodecenone (138) and cyclodecanone (139), it is apparent that a 50:50 mixture of diastereoisomers is present, and hence no diastereofacial selectivity was observed in the reduction of the tertiary cyclodecyl radical (137). In the ^{1}H N.M.R. spectrum of cyclodecenone (138), the ring methyl group appeared as two doublets, at δ 0.83 and 0.96 p.p.m., both with a coupling constant of 7.15 Hz. With cyclodecanone (139), the ring methyl group also appeared as two doublets, at δ 0.86 and 0.92 p.p.m., with a coupling constant of 7.21 Hz. The ^{13}C N.M.R. spectrum of both cyclodecenone (138) and cyclodecanone (139) were complex, with all the carbon peaks appearing as doublets due to the mixture of diastereoisomers. Evidently the methyl group was not capable of making the cyclodecyl radical ring adopt a rigid conformational orientation, and thus allow the tributyltin hydride to reduce it selectively. This is perhaps not surprising, as the cyclodecyl radical ring is going to have a large amount of conformational mobility and hence the small methyl group is unlikely to hold it in a rigid orientation. If the methyl group were replaced with a bulkier t-butyl group, a more rigid conformational orientation may be obtained for the cyclodecyl radical ring, hence allowing some diastereofacial selectivity in its reduction with tributyltin hydride. In attempting to prepare such a t-butyl-cyclodecyl radical, the 4-(t-butyl)-cyclohexyl-β-ketoester (140) was first prepared, as shown in Scheme 38. It was considered that the t-butyl-bicyclic epoxythiocarbonylimidazolide could be prepared from the 4-(t-butyl)-cyclohexyl-β-ketoester (140) following a similar reaction path as was set out in Scheme 36. Unfortunately, when the Robinson annulation was attempted with the 4-(t-butyl)-cyclohexyl-β-ketoester (140) and methylvinylketone, no identifiable product was isolated from the reaction mixture. No further attempt was made at forming the t-butyl-bicyclic epoxythiocarbonylimidazolide *via* an alternative route.

Scheme 38.

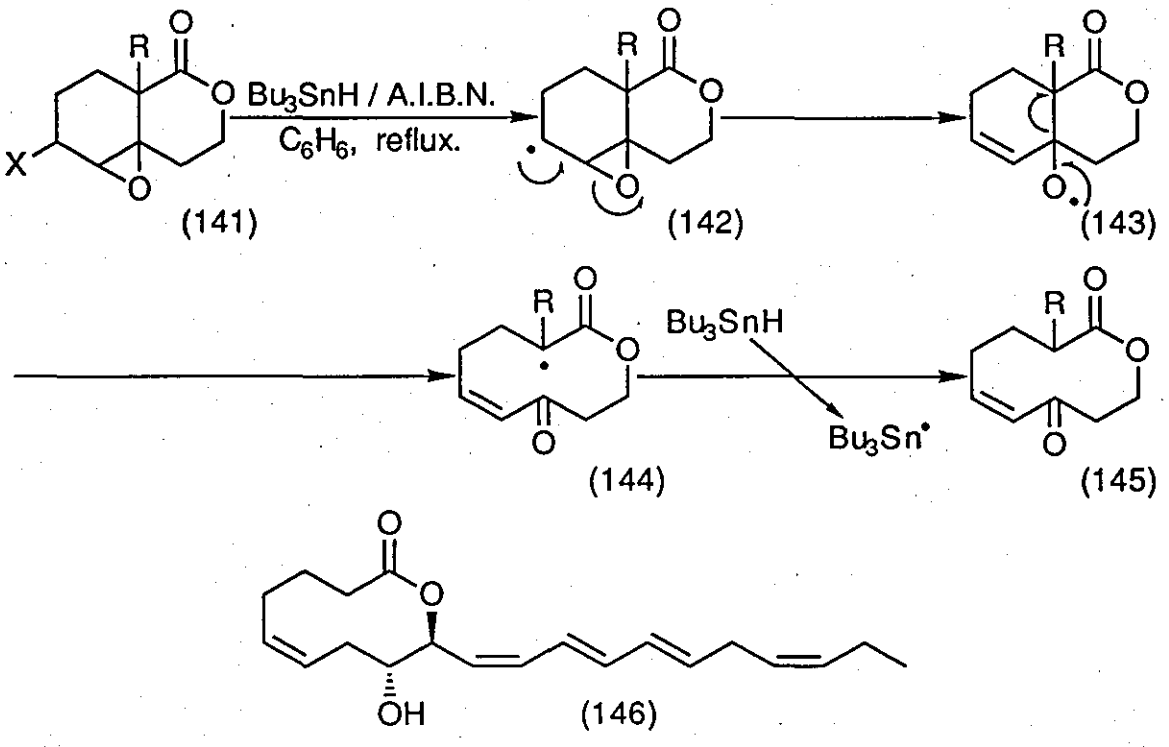


5.3. Attempted preparation of a lactone containing bicyclic epoxythiocarbonyl-imidazolide.

5.3.1. Introduction.

With the ring expansion reactions so far described, the radical stabilising group has been an ester group. We considered it interesting to see whether the ring expansion would still succeed if the stabilising group was part of the ring system, *e.g.* a lactone of the type shown in Scheme 39. It was expected that treatment of (141) with tributyltin hydride / A.I.B.N. would afford the oxiranylcarbinyl radical (142). Rearrangement of (142) to alkoxy radical (143), followed by β-cleavage of the C-C bridging bond of the alkoxy radical would result in the ring expanded lactone (145), after reduction of the stabilised radical (144). The skeleton of the lactone formed is similar to that found in several natural products, *e.g.* the fatty acid metabolite didemnilactone[110] (146), shown in Scheme 39.

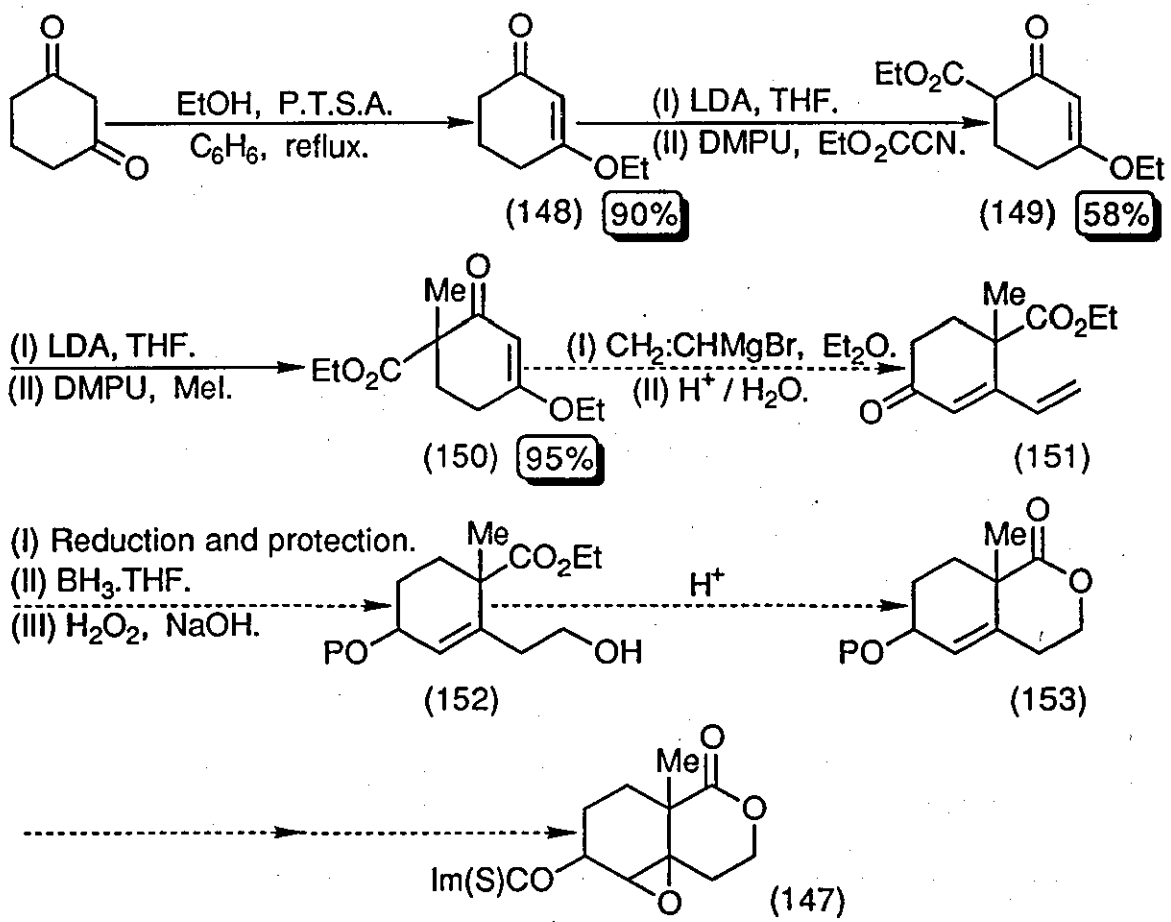
Scheme 39.



5.3.2. Attempted preparation of the lactone epoxythiocarbonylimidazolide (147).

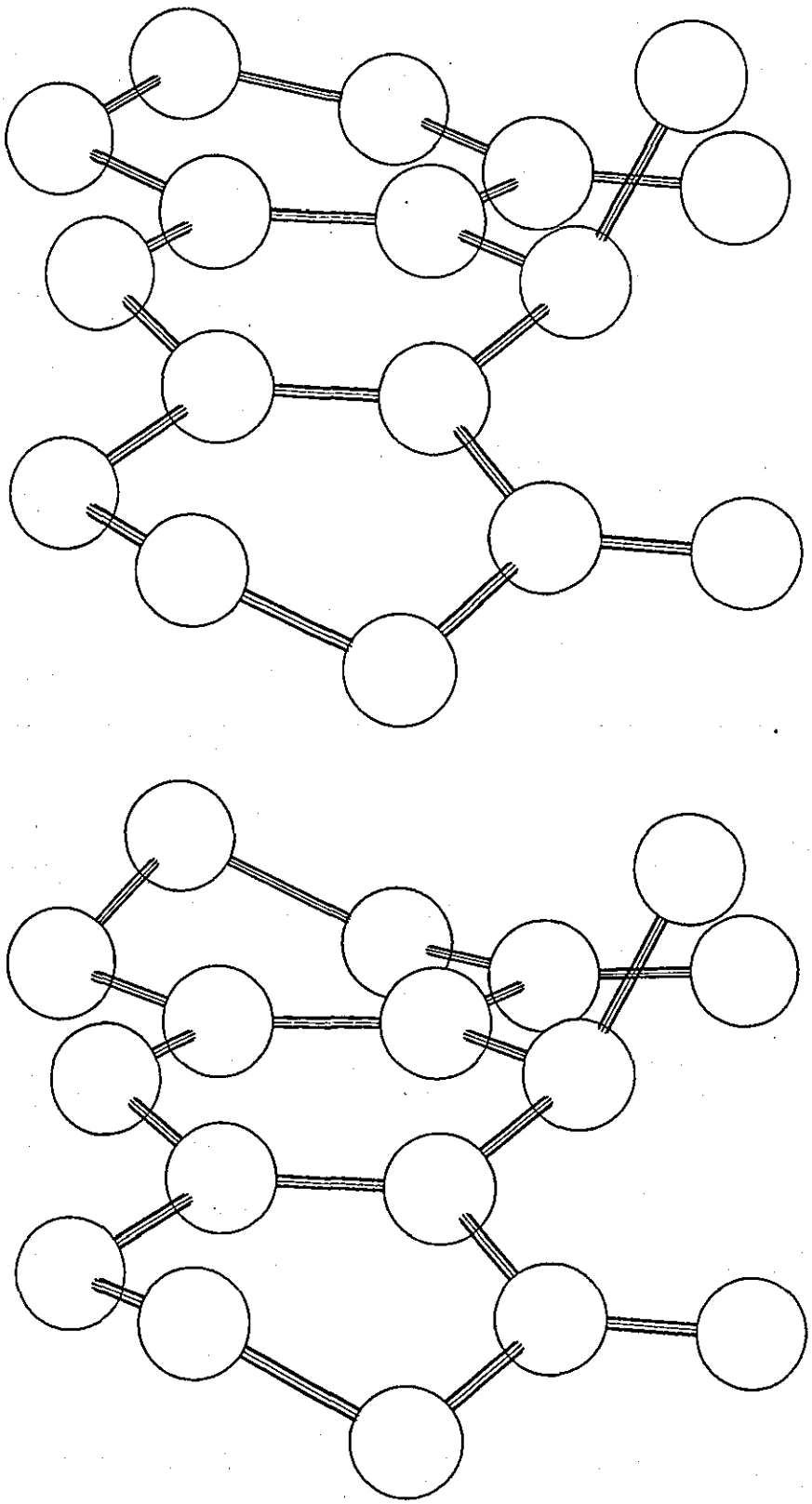
Scheme 40 outlines the proposed route to the preparation of the bicyclic lactone epoxythiocarbonylimidazolide (147). The enol ether (148), of the β-diketone was prepared in good yield following the procedure of Frank and Hall.[111] Initial attempts at preparing the β-ketoester (149) *via* the method of Ruest *et al*[109] proved unsuccessful, so enol ether (148) was treated with methyl cyanoformate with lithium diisopropylamine as the base.[112,113] This afforded the β-ketoester (149) in reasonable yield as a crystalline solid; m.p. 98°C. Alkylation of β-ketoester (149) with methyl iodide gave the methyl derivative (150) in excellent yield. Unfortunately, due to lack of time, the remainder of the proposed reactions were not attempted (Scheme 40). The Grignard reaction, with vinylmagnesium bromide and subsequent reduction of the carbonyl, have been performed successfully on enol ether (148), see section **6.4**, and therefore no problems would be expected for the first steps of proposed reaction path. According to literature precedent, the diene system should undergo hydroboration almost exclusively at the terminal position,[114] affording the alcohol (152) after oxidative work up. Standard transesterification procedures should afford the lactone (153) from which the bicyclic lactone epoxythiocarbonylimidazolide (147) could be prepared following the same reactions that were employed in the preparation of epoxythiocarbonylimidazolide (114) and epoxythiocarbonylimidazolide (134).

Scheme 40.

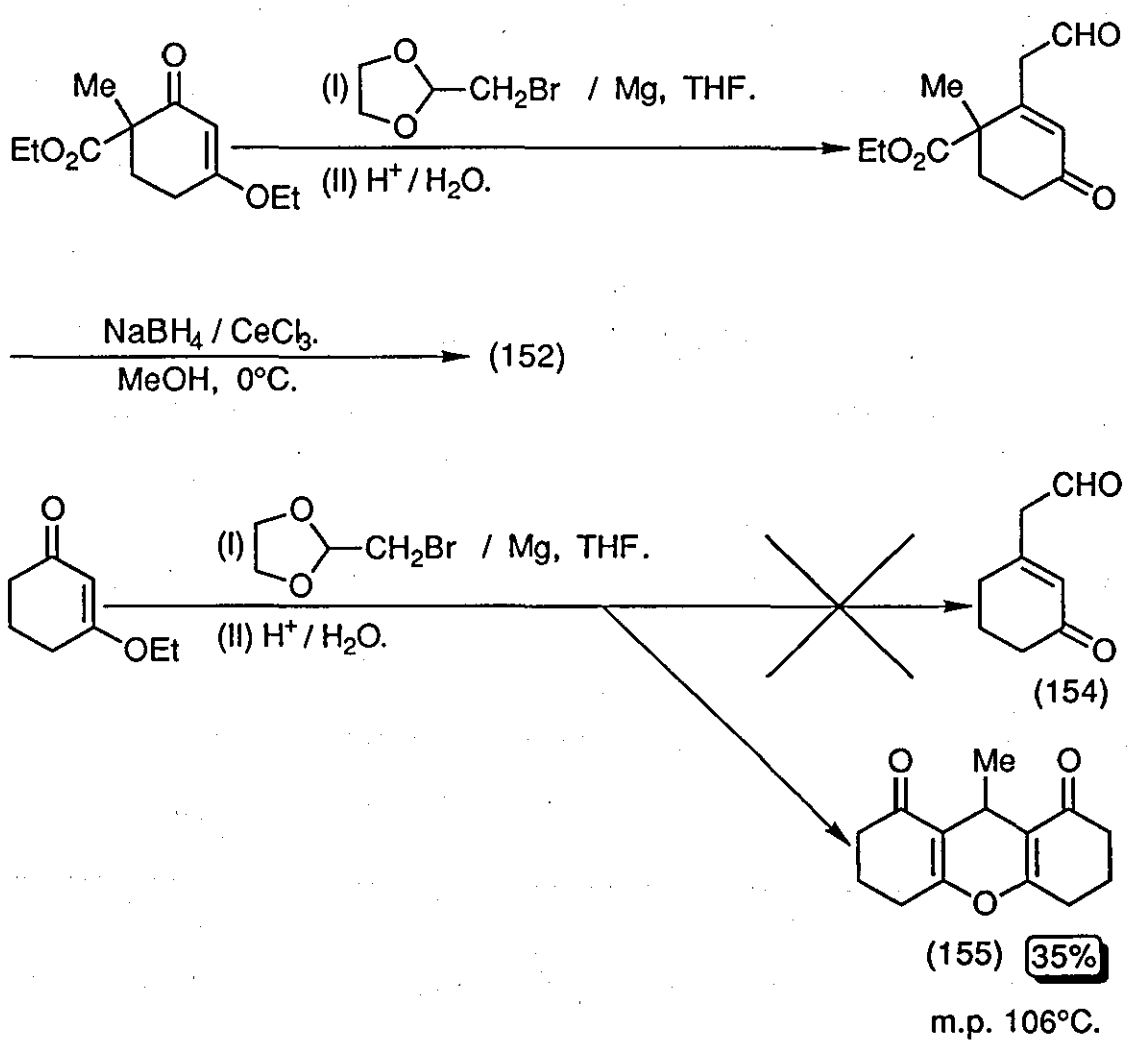


An alternative approach to alcohol (152) was envisaged as indicated in Scheme 41. As a model, the reaction of the Grignard derivative from 2-bromomethyl-1,3-dioxalane with the enol ether (148) was explored. It was evident from the spectra of the crystalline product obtained; m.p. 106°C, that the anticipated aldehyde (154) was not obtained. The product was determined to be the symmetrical tricycle (155)[115] after careful examination of its infrared, N.M.R., mass spectra and elemental analysis. The infrared spectrum showed the presence of the α,β-unsaturated carbonyl groups (υ_{max} 1678 cm^{-1}), and the enol ether groups (υ_{max} 1663 cm^{-1}). The ^{13}C N.M.R. spectrum indicated the presence of two quaternary olefinic carbons, one with a large down field shift of δ 164.49 p.p.m., due to deshielding by the attached oxygen. The ^{1}H N.M.R. spectrum showed the methyl group, appearing as a doublet at δ 1.05 p.p.m. (J = 6.53 Hz) coupled to a single proton, appearing as a quartet at δ 3.62 p.p.m. As this proton had a relatively large down field shift, an X-ray crystal structure was performed which confirmed the structure and showed the proton to be deshielded by the carbonyl groups. Figure 5 shows the X-ray crystal structure of tricycle (155) with two crystallographically non-equivalent molecules being present.

Figure 5. X-ray crystal structure of tricycle (155).



Scheme 41.

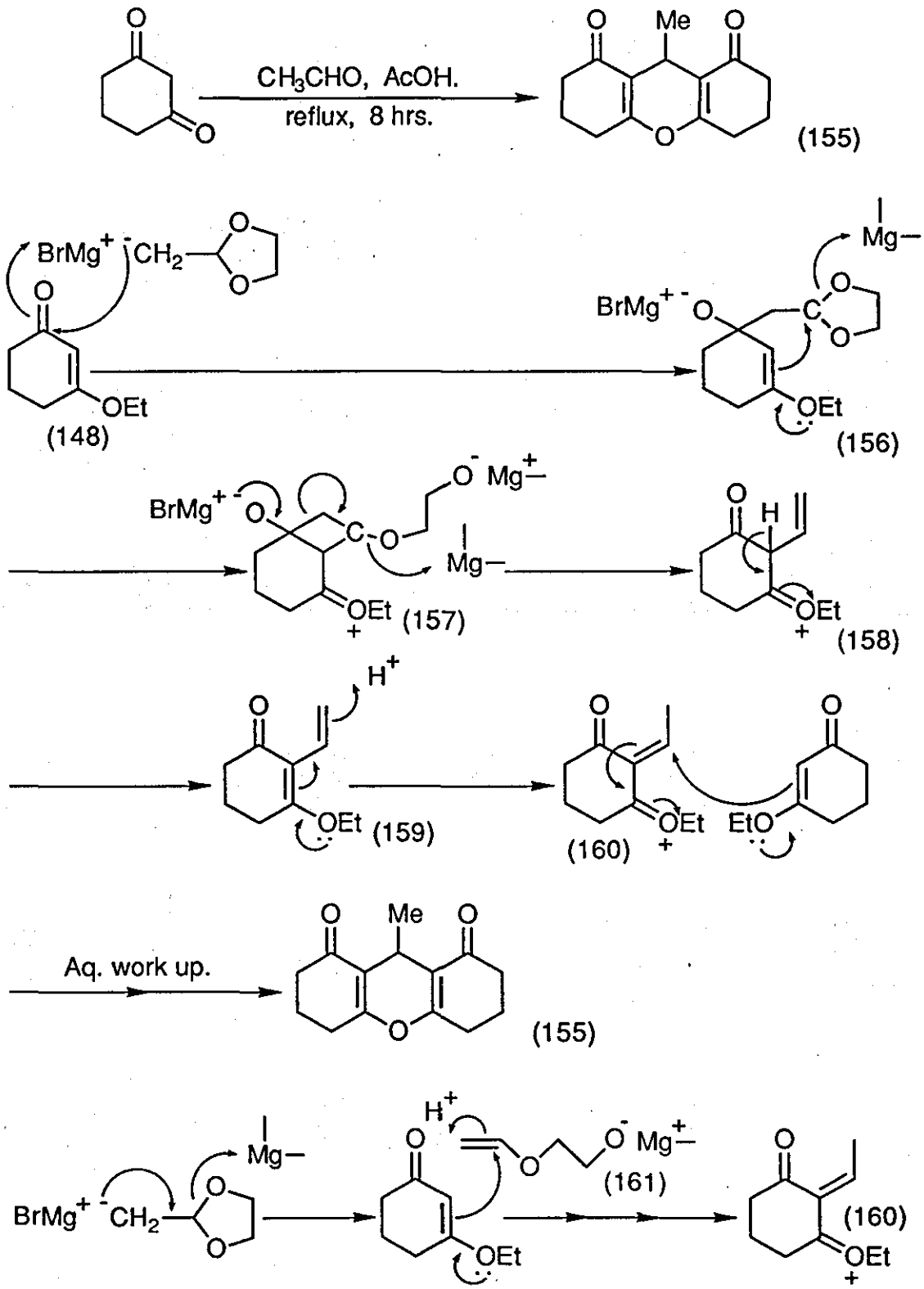


It has been shown[115] that treatment of the β-diketone with acetaldehyde, in acetic acid, affords the tricycle (155) in 41% yield, as shown in Scheme 42.

If the Grignard reagent initially adds as expected to the carbonyl group of the cyclic enol ether (148), it will yield the acetal (156). Intramolecular addition of the olefin to the acetal (156) would afford the bicycle (157), which would be expected to quickly rearrange to give the vinyl derivative (158). Deprotonation of this, followed by reprotonation at the exocyclic position, would yield the electrophile (160). Addition of (160) to the cyclic enol ether (148) would yield the tricycle (155) after aqueous acidic work up. Alternatively the Grignard reagent could rearrange to the vinyl ether (161), a process known to occur on heating.[116] If this were to act as an electrophile for the cyclic enol ether (148), intermediate (160) could again be formed which would yield tricycle (155) after acidic work up. It would be interesting to see whether any of the tricycle (155) would be formed in the reaction between the cyclic enol ether (148) and the vinyl derivative (159),

following an acidic work up. This could at least confirm whether the vinyl derivative (159) is an intermediate in the formation of the tricycle (155).

Scheme 42.

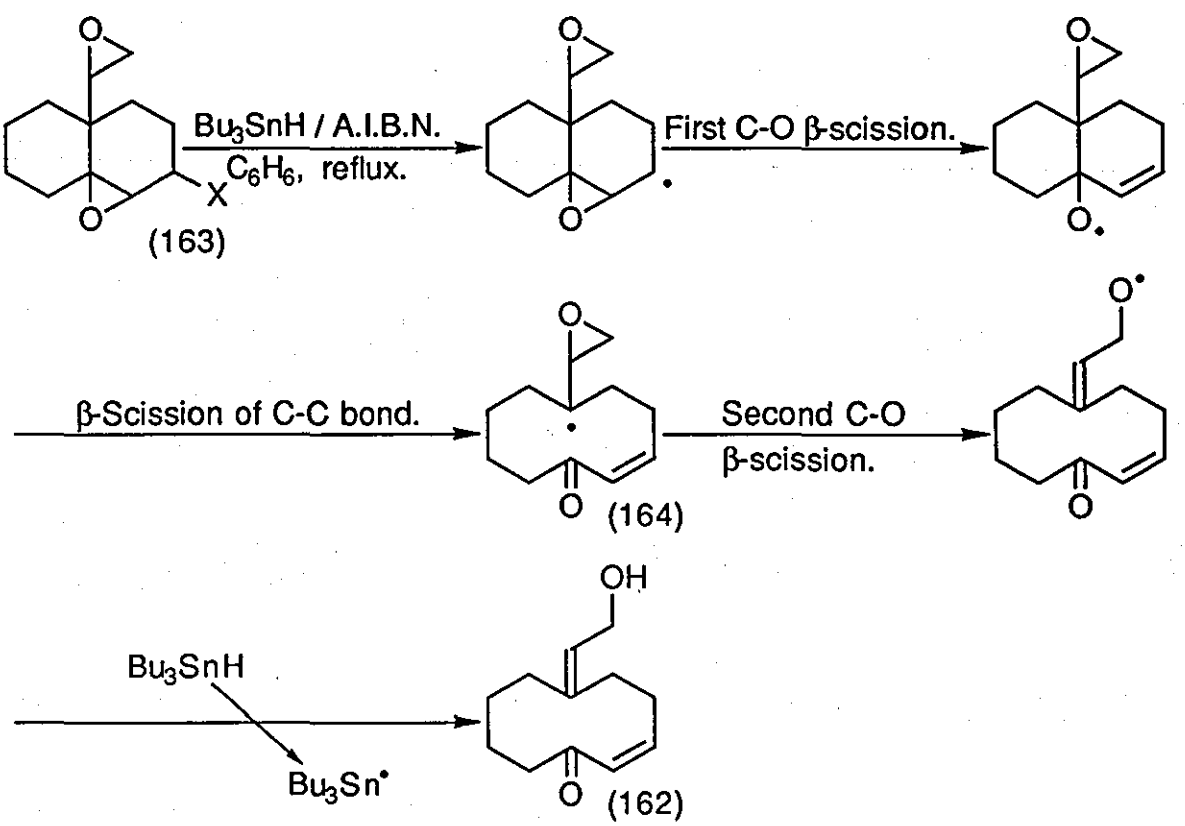


5.4. Preparation and reduction of the bicyclic bis-epoxythiocarbonylimidazolide.

5.4.1. Introduction.

With the ring expansions described so far, an ester moiety has provided the stabilisation required to prolong the life time of the intermediate radical (112), as shown in Scheme 30. If the radical were removed, by a further tandem reaction, it was considered that this would provide another method for obtaining the ring expanded product. As the ring opening of the oxiranylcarbinyl radical is known to be a rapid process, it was considered that if one were formed by β-scission of the bridging C-C bond, β-scission of the C-O bond would occur resulting in the ring expanded product (162) (Scheme 43). The oxiranylcarbinyl radical (164) could be formed by reduction of the bicyclic bis-epoxy-thiocarbonylimidazolide (163).

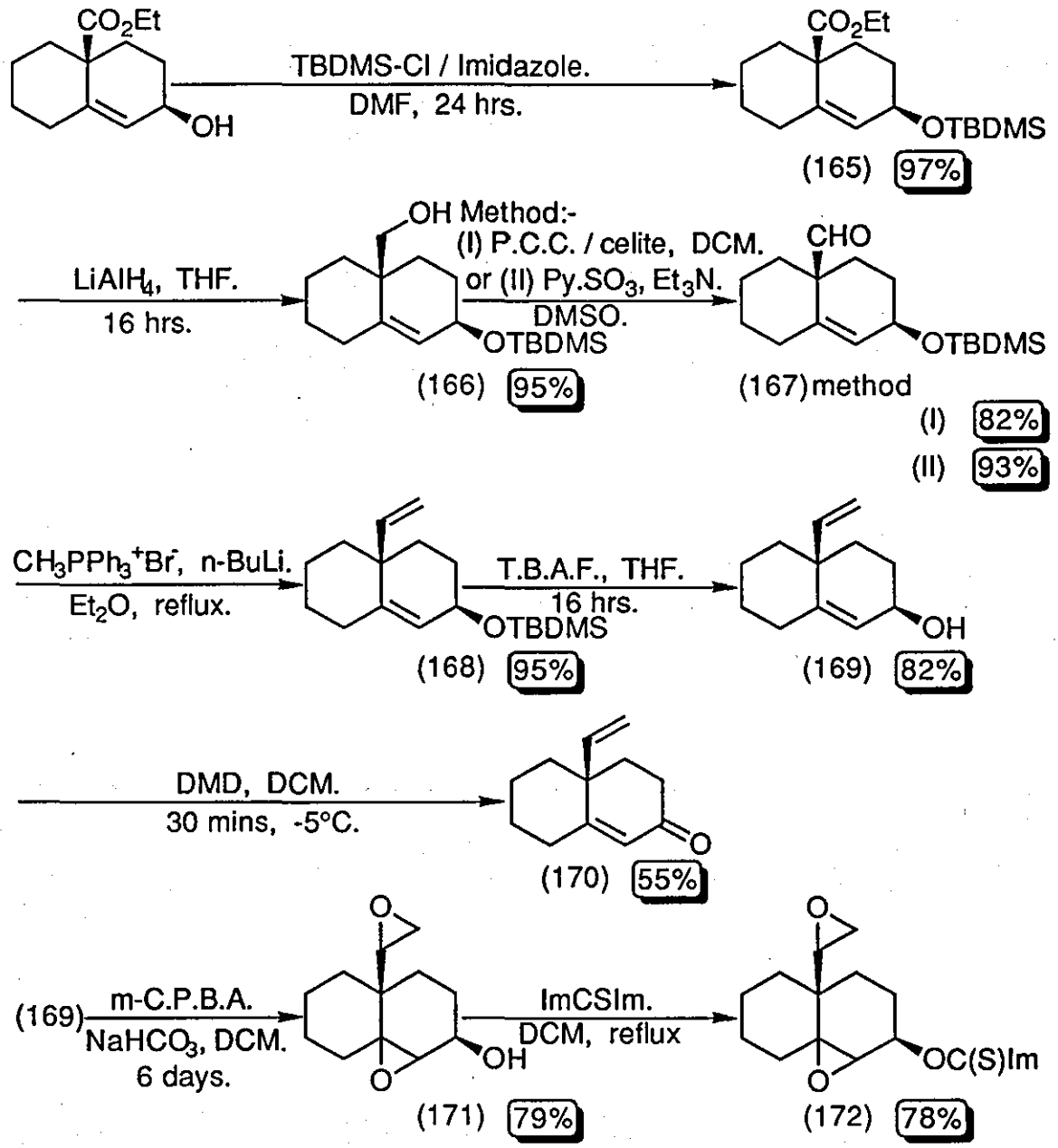
Scheme 43.



5.4.2. Preparation of the bicyclic bis-epoxythiocarbonylimidazolide (172).

The bicyclic bis-epoxythiocarbonylimidazolide (172) was prepared as shown in Scheme 44. The previously prepared allylic alcohol (116) was first protected with a *tert*-butyldimethylsilyl group, affording (165) in excellent yield. Attempts to reduce the ester group of compound (165) to the aldehyde (167) using diisobutylaluminium hydride[117] proved unsuccessful, as only the alcohol (166) was isolated. This alcohol was prepared in better yield by reduction of (165) with lithium aluminium hydride, providing alcohol (166) as a crystalline solid, m.p. 60°C. The alcohol stretch was clearly evident in the infrared spectrum (υ_{max} 3356 cm^{-1}). The protons α to the hydroxy group appeared as a multiplet at δ 3.57 p.p.m. in the ^1H N.M.R. spectrum. The aldehyde (167) was then prepared by pyridinium chlorochromate oxidation[118] or by Swern oxidation,[119] with the sulfur trioxide-pyridinium complex as the activator. Both methods afforded the unstable aldehyde (167) in good yields. The infrared, ^1H and ^{13}C N.M.R. spectra clearly showed the presence of the aldehyde. The Wittig reaction[120] between aldehyde (167) and methyl triphenylphosphonium bromide went in excellent yield, affording olefin (168). In the ^1H N.M.R. spectrum of olefin (168) the ring olefinic proton appeared as a doublet at δ 5.44 p.p.m. (J = 1.40 Hz). The ABX system of the vinyl group protons was clearly visible, with J_{gem} = 1.66 Hz, J_{cis} = 10.53 Hz and J_{trans} = 17.47 Hz. The *tert*-butyldimethylsilyl group was removed with *tetra*-butylammonium fluoride, affording the alcohol (169). As compound (169) contained a terminal alkene, it was expected that this would epoxidise slowly with the normal peroxy acids. Therefore, the epoxidation was initially attempted with an excess of dimethyldioxirane. The dimethyldioxirane solution was prepared following the method of Adam *et al.*[121] When the oxidation was performed at -5°C, only one product was observed by t.l.c. After purification by flash chromatography the product was shown to be the α,β-unsaturated ketone (170). The infrared spectrum showed the typical stretch for an α,β-unsaturated ketone (υ_{max} 1674 cm^{-1}) and olefin (υ_{max} 1618 cm^{-1}). In the ^1H N.M.R. spectrum, the ring olefinic proton appeared as a singlet at δ 5.94 p.p.m. Although this reaction is of little use for the reaction path as set, it demonstrates that dimethyldioxirane is a 'clean reagent', affording just one product in reasonable yield. The bis-epoxidation was achieved in excellent yield by reaction of olefin (169) with m-chloroperoxybenzoic acid, affording (171) as a mixture of isomers. The thiocarbonylimidazolide (172) was then prepared in good yield, following the standard procedure.[87]

Scheme 44.

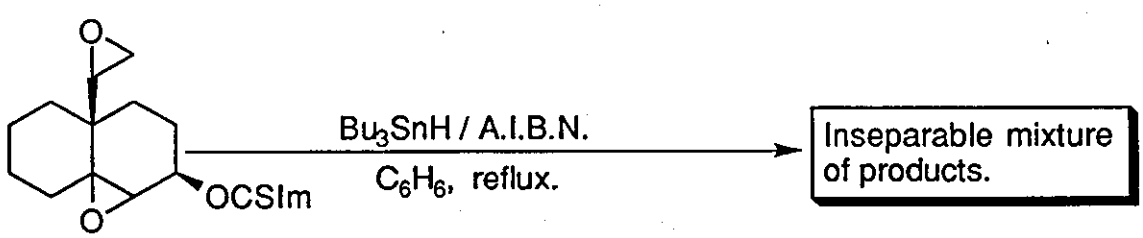


5.4.3. Tributyltin hydride reduction of the bicyclic bis-epoxy-thiocarbonylimidazolide (172).

When the bicyclic bis-epoxythiocarbonylimidazolide (172) was reduced with tributyltin hydride / A.I.B.N., using both modes of addition, a complex mixture of products was observed by t.l.c. analysis. All attempts at isolating a single compound from the reaction mixture, *via* flash chromatography and preparative t.l.c., proved unsuccessful. Examination of the spectra for one band isolated by preparative t.l.c., suggested that the ring expansion might have worked. The infrared spectrum of the band showed a very strong absorption at υ_{max} 3380 cm-1

(hydroxy group). Two absorptions were also visible in the carbonyl region, one at υ_{max} 1693 cm-1 (saturated ketone), the other at υ_{max} 1660 cm-1 (α,β-unsaturated carbonyl). The ^{1}H and ^{13}C N.M.R. spectra showed the presence of several olefinic protons and carbons, but as the spectra were obviously of a mixture of compounds, no structure determination was possible. It could be that this band contained a mixture of the expected α,β-unsaturated cyclodecane (162), along with the saturated cyclodecane product. It seems likely that the ring expansion was occurring, but the reaction was not controlled, resulting in several products being formed and hence the reaction, as it stands, is of little use.

Scheme 45.

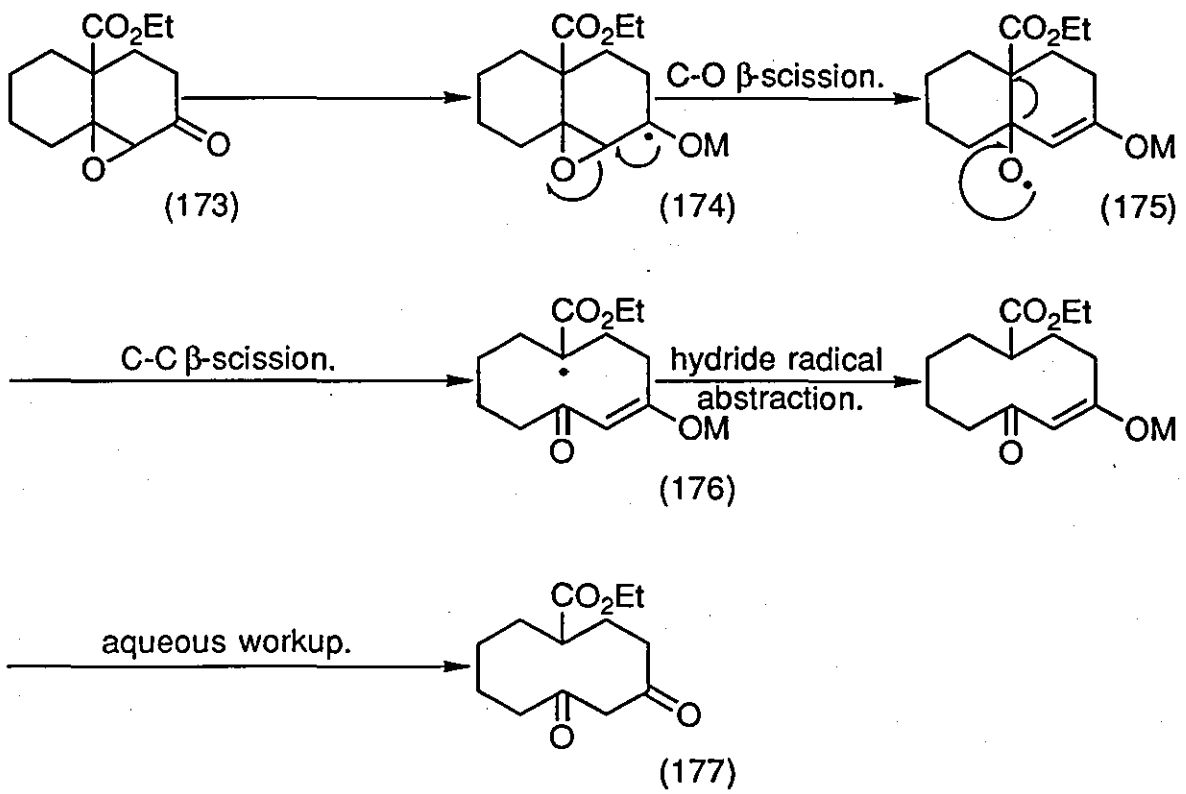


5.5. Preparation and reduction of the bicyclic α,β-epoxyketone (173).

5.5.1. Introduction.

With all the ring expansion examples so far described, the oxiranylcarbinyl radical has been formed by the action of tributyltin hydride / A.I.B.N. on a thiocarbonylimidazolide derivative, resulting in a secondary radical. An alternative, and readily accessible oxiranylcarbinyl radical may be that derived from an α,β-epoxyketone. Rearrangement of such an oxiranylcarbinyl radical (174), formed from the bicyclic α,β-epoxyketone (173) should result in the alkoxy radical (175), as shown in Scheme 46. If alkoxy radical (175) were to undergo β-cleavage of the bridging C-C bond, as was seen with alkoxy radical (119), reduction of the resulting stabilised tertiary radical (176) would afford the ring expanded compound (177), after work up.

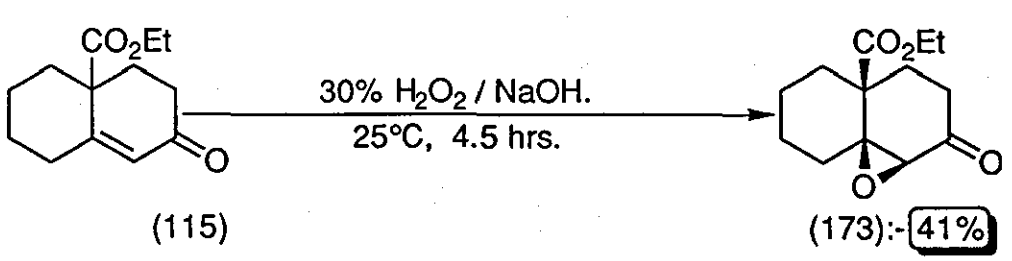
Scheme 46.



5.5.2. Preparation of the bicyclic α,β-epoxyketone (173).

The bicyclic α,β-epoxyketone (173) was simply prepared by the alkaline hydrogen peroxide epoxidation of the enone (115),[122] as shown in Scheme 47. Purification of the crude product afforded the β-epoxide (173) as a single isomer, m.p. 55°C.

Scheme 47.



5.5.3. Tributyltin hydride reduction of the bicyclic α,β-epoxyketone (173).

As previously described in **Chapter 4**, Scheme 23, the tributyltin hydride reduction of α,β-epoxyketones results exclusive in C-O bond cleavage of the formed intermediate oxiranyl(stannyloxy)carbinyl radical. As this is the cleavage required for the ring expansion, the reduction was performed following the conditions of Hasegawa *et al.*[96] The bicyclic α,β-epoxyketone (173) was subjected to the tributyltin hydride / A.I.B.N. reduction, under both normal and inverse modes of addition. The results of the reduction are summarised in Scheme 48 and Table 4.

Scheme 48.

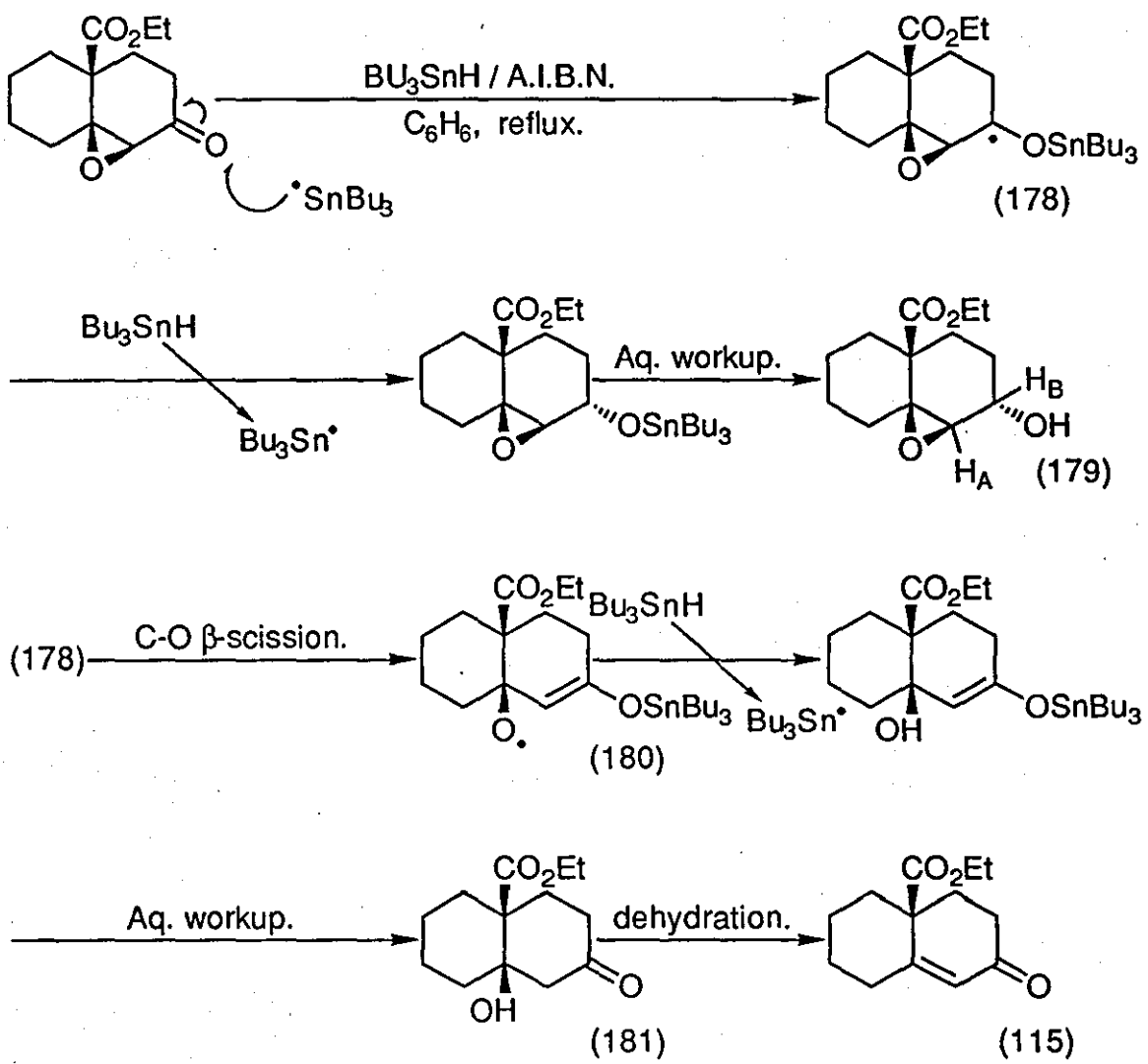
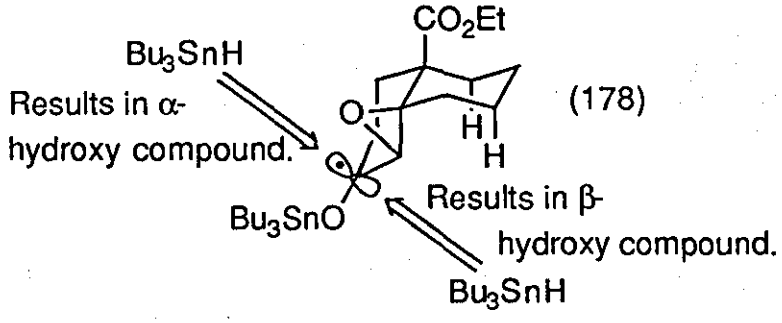


Table 4. Results of the tributyltin hydride reduction of bicyclic α,β-epoxyketone (173).

Nº	Mode of addⁿ of. tributyltin hydride.	% Yield of product. (179)	(181)	(115)
1	Normal	7	23	23
2	Inverse	—	25	36

When epoxide (173) was reduced *via* the normal mode of addition of tributyltin hydride / A.I.B.N., three products were isolated:
(I) The keto alcohol (181), which was shown by n.O.e. experiments to be the β-alcohol.
(II) The enone (115), formed presumably by dehydration of the keto alcohol (181). This product gave identical spectra as for the previously prepared enone.
(III) The epoxy alcohol (179), which was formed by the tributyltin hydride reduction of the oxiranyl(stannyloxy)carbinyl radical (178), before it had time to rearrange. This product was isolated as a single isomer and was assigned to be the α-hydroxy compound, after examination of the ^{1}H and ^{13}C N.M.R. spectra. The ^{1}H N.M.R. spectrum of epoxy alcohol (179) was very similar to that of epoxy alcohol (117). The main difference was that the proton H_A in (179) appeared as a singlet at δ 3.08 p.p.m., where with epoxy alcohol (117) the equivalent proton appeared as a doublet at δ 3.11 p.p.m. (J = 4.50 Hz). This is understandable if the hydroxy group in epoxy alcohol (179) assumes the pseudo equatorial position, the dihedral angle between the C-H_A and C-H_B bond will be roughly 90°, and hence the coupling constant will be zero, according to the Karplus equation. In the ^{13}C N.M.R. spectrum the chemical shifts for hydroxy bearing carbon and adjacent carbons, are all slightly different for epoxy alcohols (117) and (179), as would be expected for the different isomers. Figure 6 shows how the α-epoxy alcohol (179) is formed by reduction of the oxiranyl(stannyloxy)carbinyl radical (178) from the least hindered face.

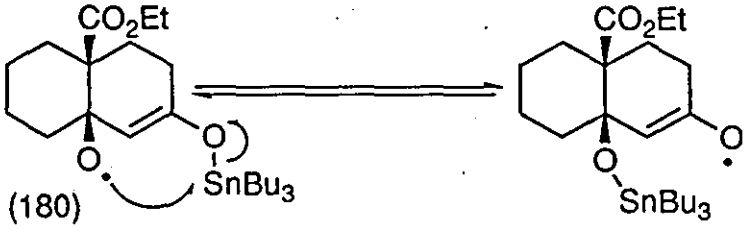
Figure 6.



When the reduction was performed using the inverse mode of addition of tributyltin hydride / A.I.B.N., only the keto alcohol (181) and enone (114) were isolated.

It is apparent that the alkoxy radical (180) is less inclined to undergo β-scission of the C-C bridging bond, leading to the stabilised tertiary radical (176). One process by which the alkoxy radical (180) could be effectively stabilised, would be if there was an intramolecular tributyltin transfer occurring, as shown in Scheme 49. Such a process has been observed by Davies *et al.*[123]

Scheme 49.



If the intramolecular transfer of tributyltin was occurring, as shown, it would effectively stabilise the alkoxy radical (180).

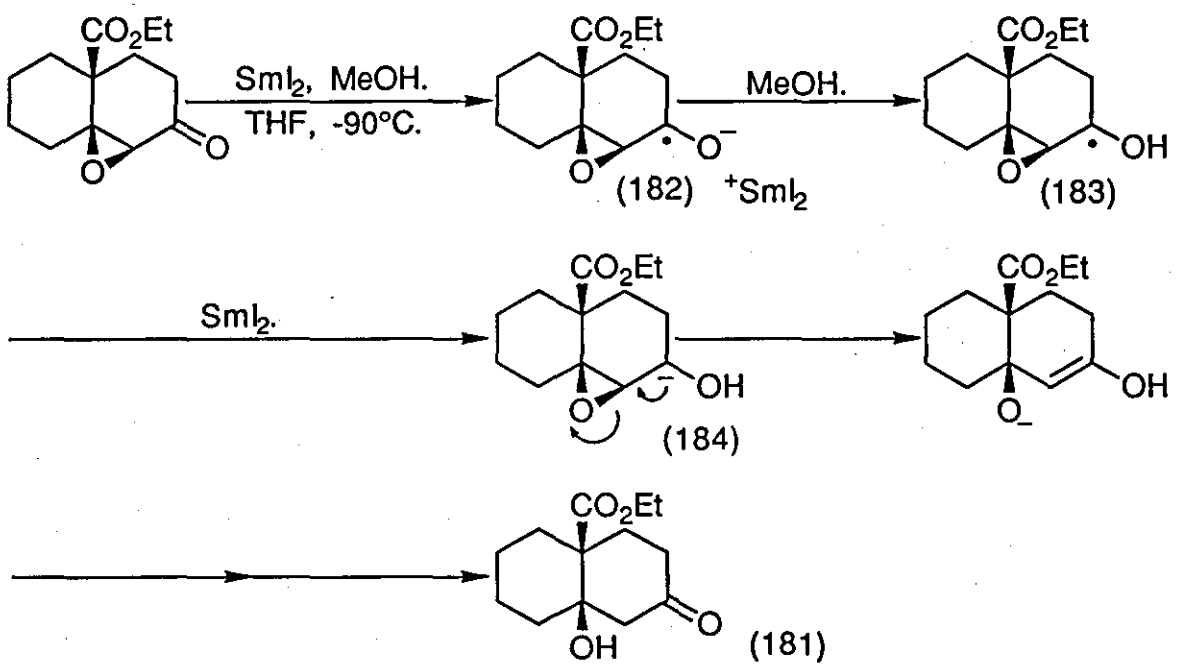
A test experiment which would determine whether the tertiary radical (176) was being formed, would be to carry out the same reduction on the stereoisomeric α-epoxyketone. If none of the tertiary radical, equivalent to (176), was being formed, one would expect to isolate a single isomer of the α-hydroxy ketone. If the tertiary radical, equivalent to (176), were an intermediate, one would expect to isolate atleast some of the β-hydroxy ketone as the product. Unfortunately, lack of time prevented such a reaction being performed.

5.5.4. Samarium(II) iodide reduction of the bicyclic α,β-epoxyketone (173).

The initial samarium(II) iodide reduction of the bicyclic α,β-epoxyketone (173) was performed at -90°C, following the procedure of Molander *et al*,[99] using methanol and a two molar excess of samarium(II) iodide. After 5 minutes at this temperature, an aqueous work up was performed and a single product was separated from unreacted starting material to afford the β-hydroxy ketone (181) in 36% yield. The reaction mechanism, by analogy with that suggested by Molander, is shown in Scheme 50. As can be seen, Molander suggests that the epoxide is cleaved by an anionic rather that *via* a radical mechanism. As no ring expanded product was isolated from the reaction mixture, this tends to support the anion mechanism. However, it is impossible to say whether any of the alkoxy radical, formed by β-scission of either of the oxiranylcarbinyl radicals (182) or (183), was formed as it could have been reduced by more samarium(II) iodide before β-scission of the C-C bridging bond could occur. Reduction of this alkoxy radical

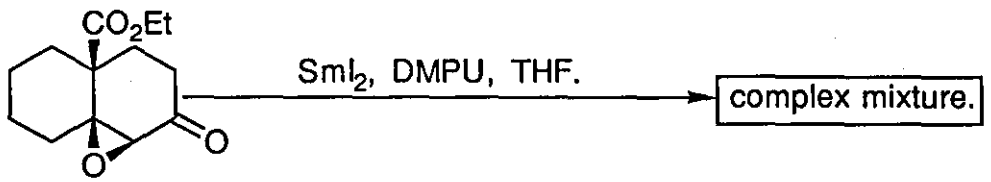
would be favourable, and probably very rapid, as the electrophilic alkoxy radical would be expected to quickly scavenge electrons from samarium(II) iodide.

Scheme 50.



It was considered that removing the proton source from the reaction mixture would prolong the life time of oxiranylcarbinyl radical anion (182), as it was considered unlikely that the samarium(II) iodide would reduce the radical anion to a bis-anion. To test this prediction the reduction was repeated following the conditions of Motherwell *et al*,[77] using a 0.1 M solution of samarium(II) iodide, added over 6 hours to a solution of the bicyclic α,β-epoxyketone (173) and DMPU in anhydrous THF (Scheme 51). By using the above conditions, it was hoped the concentration of reductant would be kept to a minimum, thus allowing the oxiranylcarbinyl radical (182) time to rearrange, and for β-scission of the C-C bridging bond to occur. Examination of the t.l.c. of the crude product showed an extremely complex mixture of products, with no major spot visible. Purification to give any single compound was not feasible, and an infrared spectrum of the crude product showed several absorptions in the carbonyl region, ranging from υ_{max} 1720 to 1790 cm^{-1}. It is possible that the ring expansion, *via* the tertiary radical (176) was occurring, but the reaction was not controlled, leading to a variety of products.

Scheme 51.

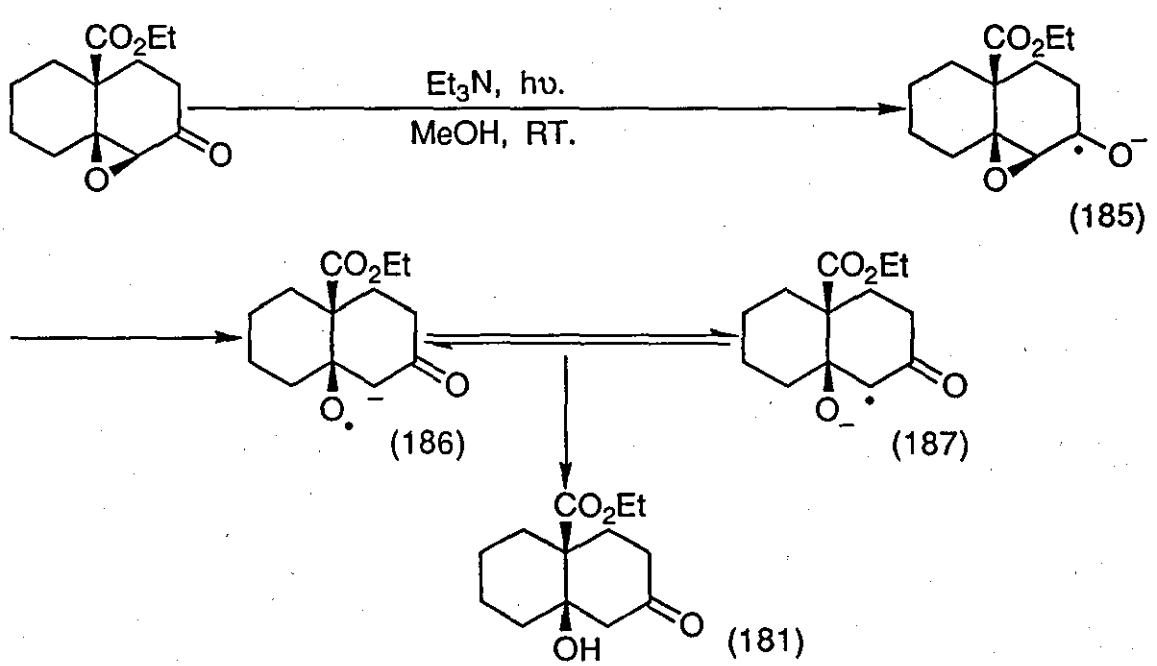


5.5.5. Photoinduced reduction of the bicyclic α,β-epoxyketone (173).

The photoinduced reduction of the bicyclic α,β-epoxyketone (173) was performed following the method of Hasegawa *et al*,[98] using a solution of the bicyclic α,β-epoxyketone (173) and triethylamine in anhydrous methanol, which was irradiated with a 100 W Hanovia ultraviolet lamp. After 3.5 hours all the starting material was seen to have disappeared by t.l.c. analysis, resulting in a single product. This product was again seen to be the β-hydroxy ketone (181) and was isolated in 55% yield.

In Scheme 52 just the key intermediates are shown, namely the oxiranyloxycarbinyl radical anion (185) and the two radical anions (186) and (187). As none of the ring expanded products were isolated, it is difficult to say whether the alkoxy radical anion (186) is in fact being formed, and rearranging to the tertiary radical (176). Again it would have been good to have performed the reduction with the stereoisomeric α-epoxide and to have seen whether it was the α- or β-hydroxy ketone which was isolated after the reduction.

Scheme 52.



To summarise, none of the methods of reduction attempted on the bicyclic α,β-epoxyketone (173) showed any evidence to suggest that the tertiary radical (176) was being formed. Nevertheless, all the methods did provide a route to the β-hydroxy ketone (181). If this product were required, the method of choice would be the photoinduced reduction, as it required relatively simple apparatus and gave a clean reaction, with just one product being formed.

5.6. Preparation and attempted reduction of the bicyclic acetoxyalkenyl epoxide (188).

5.6.1. Introduction.

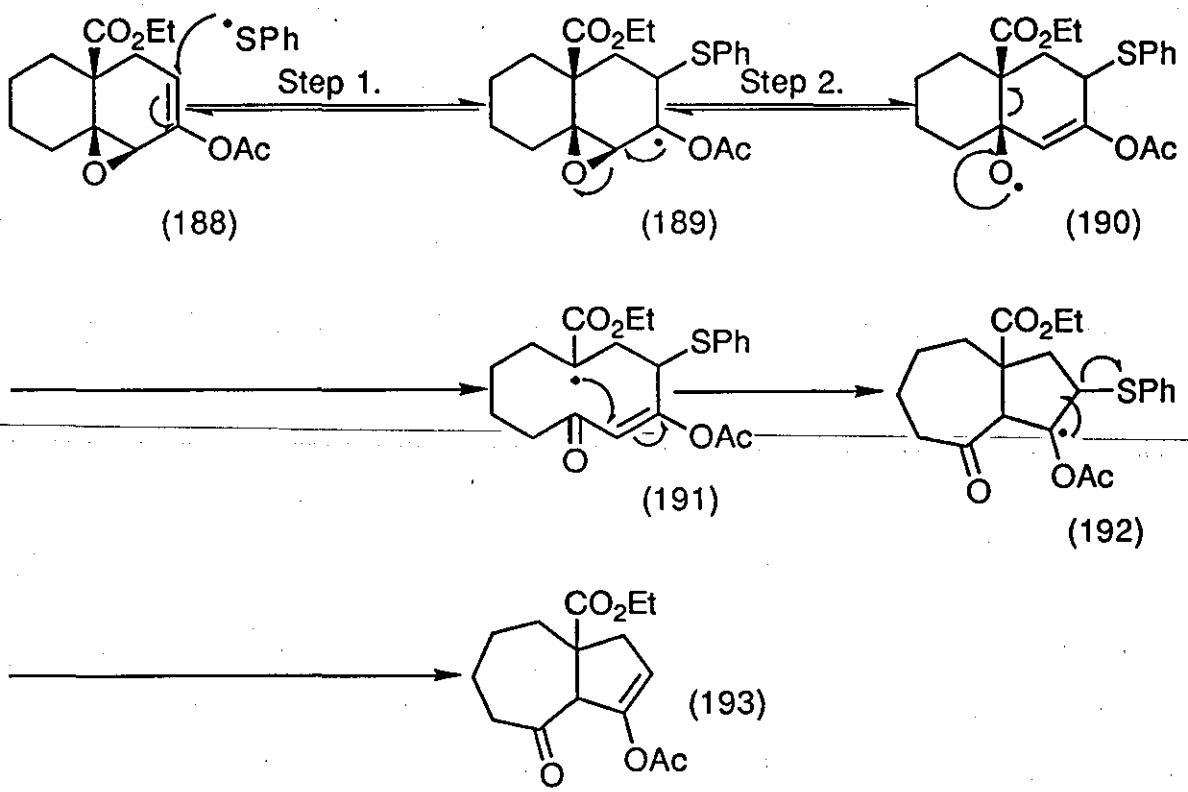
On the basis of the work performed by Rawal *et al*,[124] it was considered that rather than directly reducing the bicyclic α,β-epoxyketone (173) to the oxiranylcarbinyl radical (174), reaction of the bicyclic acetoxyalkenyl epoxide (188) derivative with the phenylthio radical would produce the oxiranyl(acetoxy)carbinyl radical (189), as shown in Scheme 53. Rearrangement of (189) would afford the alkoxy radical (190). As there are no free hydride radicals in the reaction mixture, reduction of (190) to the alcohol would be unlikely. If β-scission of the bridging C-C bond were to occur, hydride radical abstraction by the stabilised tertiary radical (191), yielding the ring expanded product, would also seem unlikely. An alternative process which would seem favourable would be for the electrophilic radical (191) to add to the electron rich olefin. This would yield the (5,3,0)-bicyclic radical (192), which, after loss of the phenylthio radical would afford the acetoxyalkenyl bicyclo-(5,3,0)-decanone (193).

5.6.2. Preparation and attempted reduction of the bicyclic acetoxyalkenyl epoxide (188).

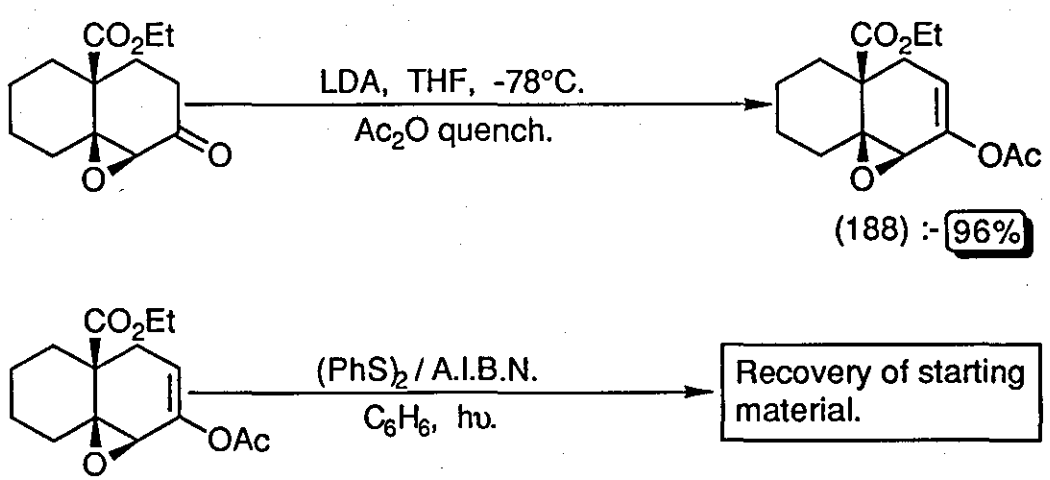
The bicyclic acetoxyalkenyl epoxide (188) was prepared in excellent yield *via* the method of Wender *et al*,[125] as shown in Scheme 54. This compound was rapidly hydrolysed back to the bicyclic α,β-epoxyketone (173) on basic alumina, but could be purified by flash chromatography on silica. The conditions of Rawal *et al*[124] were used, with 0.2 equivalents of diphenyl disulfide being used. After irradiating the reaction mixture with a 450 W medium pressure Hg lamp for 6 hours the starting epoxide (188) was seen to remain unchanged, but the diphenyl disulfide was noted to disappear from the reaction mixture. After an aqueous work up the bicyclic acetoxyalkenyl epoxide (188) was recovered unchanged (Scheme 54). It is difficult to understand the lack of reactivity observed in this reaction, as the diphenyl disulfide was breaking down, presumably to the phenylthio radical.

One possible explanation is that the alkoxy radical (190) is being formed as suggested in Scheme 53. Once formed, β-scission of the bridging C-C bond does not occur. As the olefin is now more electron rich, due to the presence of the acetoxy group, the electrophilic alkoxy radical is more likely to undergo the reverse of Steps 1 and 2, and hence starting material is recovered. The opening and closure of oxiranylcarbinyl radicals has yet to be proved as being reversible,[126] but without such an explanation it is difficult to see why none of the phenylthio radicals add to the olefin.

Scheme 53.



Scheme 54.

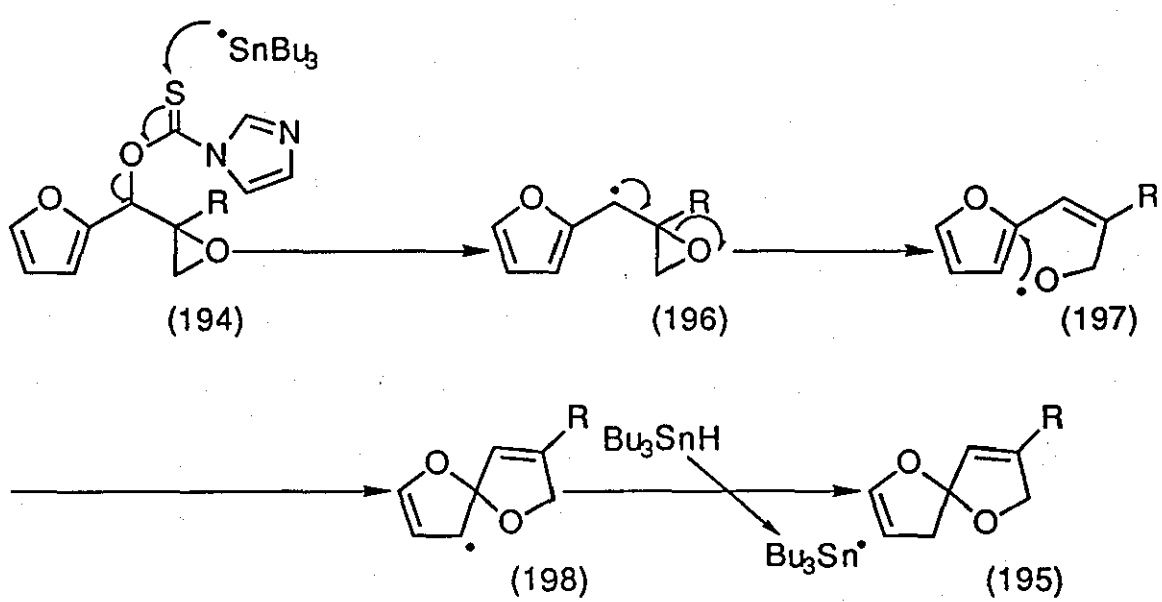


5.7. Attempted preparation of the 2,3-epoxy-1-(2-furyl)-thiocarbonylimidazolide (204).

5.7.1. Introduction.

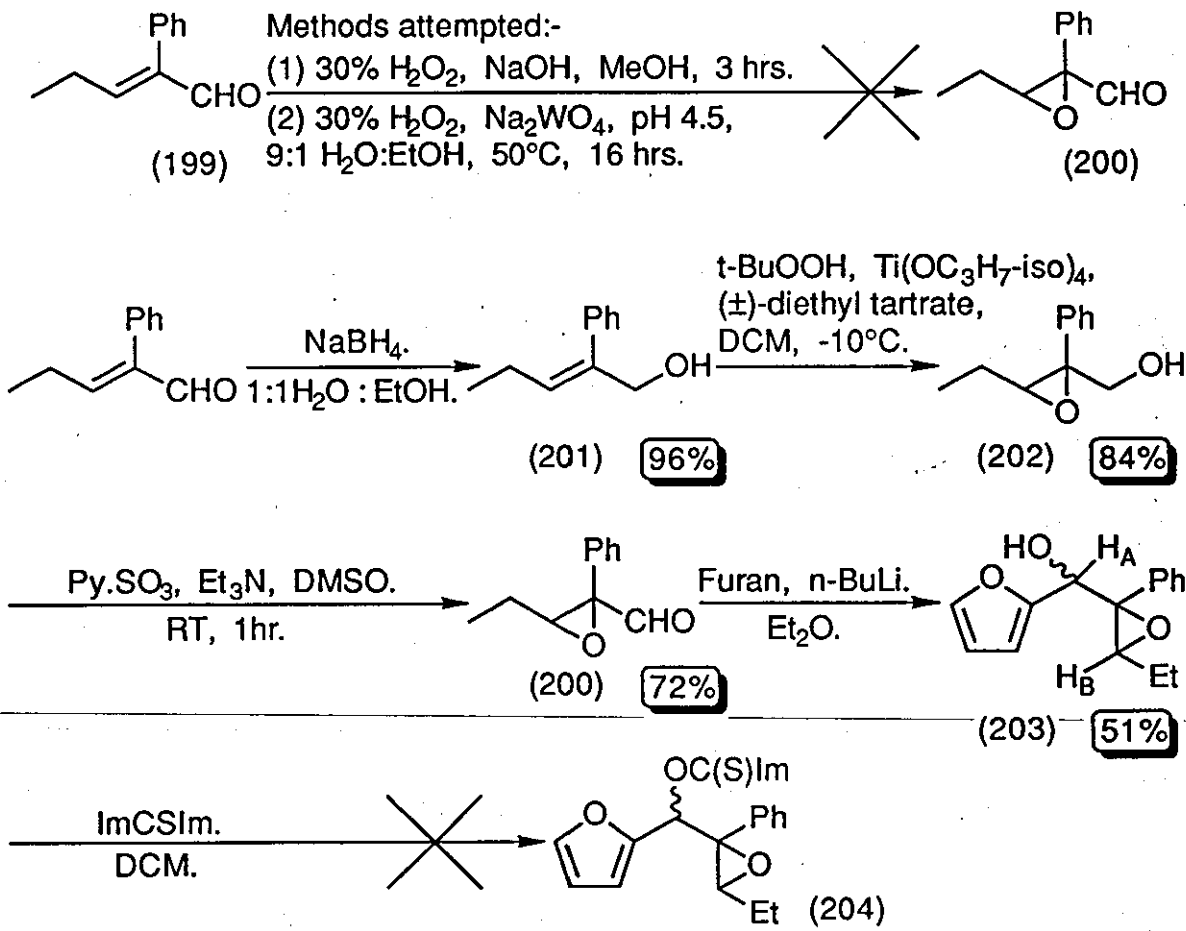
As has been described in **Chapter 4**, the oxiranylcarbinyl radical rearrangement, and subsequent addition of the formed alkoxy radical to an olefin, has proved successful in the preparation of both 5 and 6 membered cyclic ethers.[87,93,94] With an aim to extending the scope of this work, we proposed to prepare a 2,3-epoxy-1-(2-furyl)-thiocarbonylimidazolide derivative, of the type (194), and perform the tributyltin hydride / A.I.B.N. reduction with the aim of forming the spiro-bis-(dihydrofuran) (195) (Scheme 55). Reduction of thiocarbonylimidazolide (194) would afford the oxiranylcarbinyl radical (196). Rearrangement of this in the normal fashion would yield the alkoxy radical (197). As the formation of both the *cis*- and *trans*-isomers of the olefin are possible, of which only the *cis*-isomer (197) would be expected to react in the required manner, inclusion of a bulky R group should promote the formation of the *cis*-isomer (197). The alkoxy radical would then be expected to add to the furan ring, yielding the spiro-bis-(dihydrofuran), vinyl stabilised radical (198). Reduction of this with tributyltin hydride would yield the spiro-bis-(dihydrofuran) (195).

Scheme 55.



5.7.2. Attempted preparation of the 2,3-epoxy-1-(2-furyl)-2-phenylpentane-thiocarbonylimidazolide (204).

Scheme 56.



The simplest method of preparing thiocarbonylimidazolide (204) was considered to be *via* a coupling reaction between an α,β-epoxy aldehyde and 2-furyllithium. The α,β-epoxy aldehyde prepared was 2,3-epoxy-2-phenylpentanal (200). This was chosen as it was considered that the phenyl group would act as the bulky R group, necessary for the reasons given in section **5.7.1.** Also the α,β-unsaturated aldehyde (199) was readily available. Initial attempts at preparing 2,3-epoxy-2-phenylpentanal (200) directly from (199), *via* alkaline hydrogen peroxide epoxidation[122] or sodium tungstate catalysed epoxidation[127] both failed, as shown in Scheme 56. As a result the aldehyde was first reduced to the allylic alcohol (201) in excellent yield. Epoxidation of allylic alcohol (201), using the Sharpless conditions[55] with racemic diethyl tartrate went smoothly, affording the epoxy alcohol (202) in good yield. Epoxy alcohol (201) was oxidised to 2,3-epoxy-2-phenylpentanal (200) under Swern conditions,[119] with pyridinium-sulfur trioxide complex as the activator. 2,3-Epoxy-2-phenylpentanal (200) proved to be

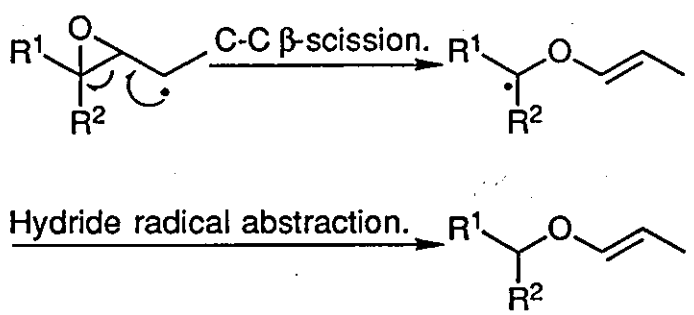
relatively acid labile, and hence was purified by chromatography on basic alumina. Once formed the 2,3-epoxy-2-phenylpentanal (200) was coupled with the 2-furyllithium species following the method of Ramanathan *et al.*[128] The formed 2,3-epoxy-1-(2-furyl)-2-phenylpentanol (203) proved to be extremely acid labile, but could be purified by careful chromatography on basic alumina. Examination of the ^{1}H and ^{13}C N.M.R. spectra of 2,3-epoxy-1-(2-furyl)-2-phenylpentanol (203) clearly showed the compound to be a mixture of isomers. In the ^{1}H N.M.R. spectrum the proton α to the hydroxy group, H_A, was seen as two well separated doublets at δ 4.87 and 5.00 p.p.m. (J = 1.88 and 9.15 Hz respectively), being coupled to the proton on the alcohol. The proton α to the epoxide ring, H_B, also appeared as two triplets, of equal intensity at δ 3.56 p.p.m. (J = 6.22 Hz). All the signals in the ^{13}C N.M.R. appeared as doublets. Unfortunately, attempts at preparing the thiocarbonylimidazolide (204) from this alcohol all failed, resulting in complex mixtures by t.l.c. analysis. Limited time meant that the work was not completed, and no radical cyclisation of the type shown in Scheme 55 were attempted.

Chapter 6. Preparation of cyclic enol ethers *via* β-scission of the C-C bond of oxiranylcarbinyl radicals.

6.1. Introduction.

As described in **Chapter 4**, the oxiranylcarbinyl radical has two distinct ways of rearranging. The most common route is *via* C-O bond cleavage, which results in the allylic alkoxy radical. The other rearrangement is *via* C-C bond cleavage which occurs when there is an aryl or vinyl group α- to the epoxide ring,[84] as shown in Scheme 57.

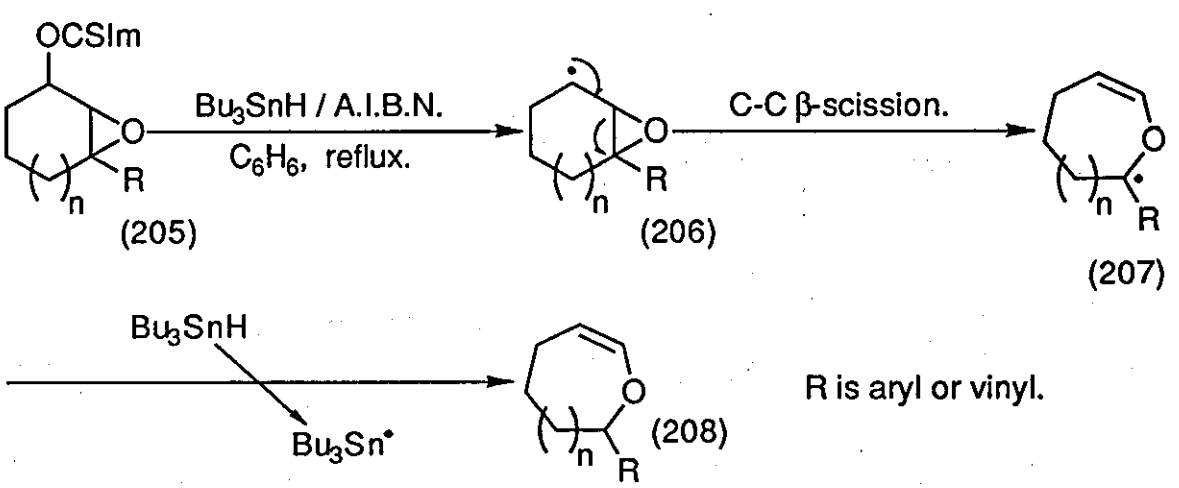
Scheme 57.



β-Scission of the C-C bond tends to predominate when either R^1 or R^2 is aryl or vinyl. Hydride radical abstraction, usually from the reductant, results in the enol ether.

It was considered that if the oxiranylcarbinyl radical were to form part of a ring system, as is the case with oxiranylcarbinyl radical (206) (Scheme 58), β-scission of the C-C bond would lead to the formation of the aryl, or vinyl stabilised enol ether radical (207). Reduction of this with tributyltin hydride would afford the ring expanded enol ether (208). The oxiranylcarbinyl radical (206) could be formed by treatment of the thiocarbonylimidazolide (205) with tributyltin hydride.

Scheme 58.



R is aryl or vinyl.

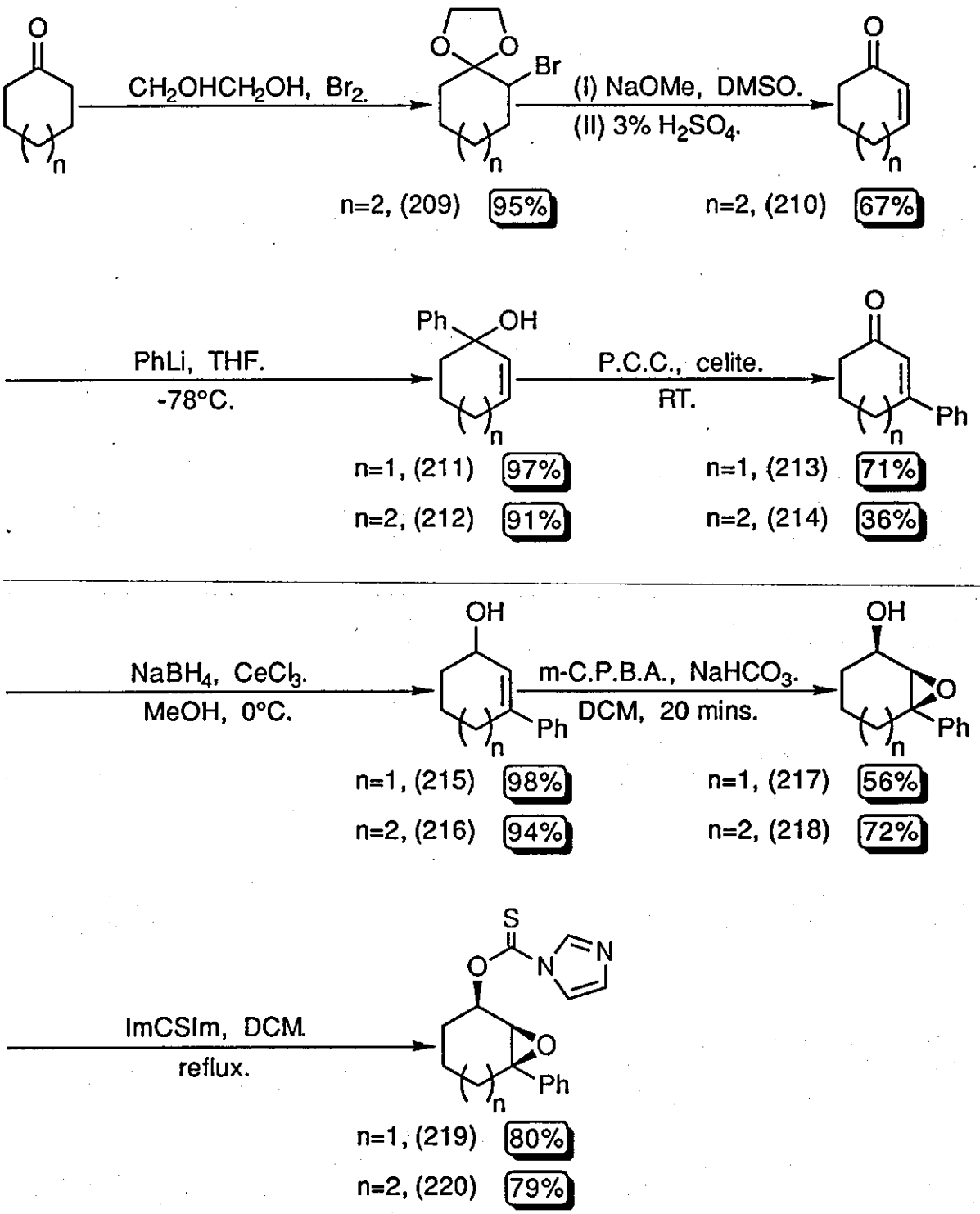
6.2. Preparation and reduction of the thiocarbonylimidazolide derivatives of 2,3-epoxy-3-phenylcyclohexan-1-ol (219) and 2,3-epoxy-3-phenylcycloheptan-1-ol (220).

The thiocarbonylimidazolide derivatives of 2,3-epoxy-3-phenylcyclohexan-1-ol (219) and 2,3-epoxy-3-phenylcycloheptan-1-ol (220) were prepared in a similar fashion, from 2-cyclohexen-1-one and 2-cyclohepten-1-one (210) (Scheme 59). 2-Cyclohepten-1-one (210) was prepared from cycloheptanone following the method of Garbisch[129]. 3-Phenyl-2-cyclohexen-1-one (213) was prepared in good overall yield *via* the 1,3-alkylative carbonyl transposition of Dauben *et al.*[130] The tertiary alcohol (211) was first prepared by the addition of phenyllithium to 2-cyclohexen-1-one. Oxidation of alcohol (211) with pyridinium chlorochromate yielded 3-phenyl-2-cyclohexen-1-one (213) in reasonable yield. Addition of phenyllithium to 2-cyclohepten-1-one (210) afforded the tertiary alcohol (212) in good yield. However, oxidation of this alcohol (212) gave a poor yield of 3-phenyl-2-cyclohepten-1-one (214). The by-product of this reaction was thought to be the unstable α,β-unsaturated aldehyde (221). The ^1H N.M.R. spectrum of this aldehyde (221) showed the aldehyde proton at δ 9.75 p.p.m., the two H_A protons at δ 3.00 p.p.m., and the two H_B protons at δ 2.50 p.p.m. In the ^{13}C N.M.R. spectrum, the two quaternary olefinic carbons were visible at δ 125.50 and 137.00 p.p.m., with the aldehyde carbon appearing at δ 202.50 p.p.m. The Infrared spectrum clearly showed the α,β-unsaturated aldehyde stretch (υ_{max} 1685 cm^{-1}). There was a small quantity of another carbonyl impurity, visible in the infrared spectrum at 1720 cm^{-1}, which could not be removed from this product. The α,β-unsaturated aldehyde (221) could possibly be formed *via* the mechanism shown in Scheme 60. Addition of the chromate ion to the secondary carbonium ion (222) affords the chromate ester (223), which then undergoes oxidative cleavage and rearrangement to the α,β-unsaturated aldehyde (221).

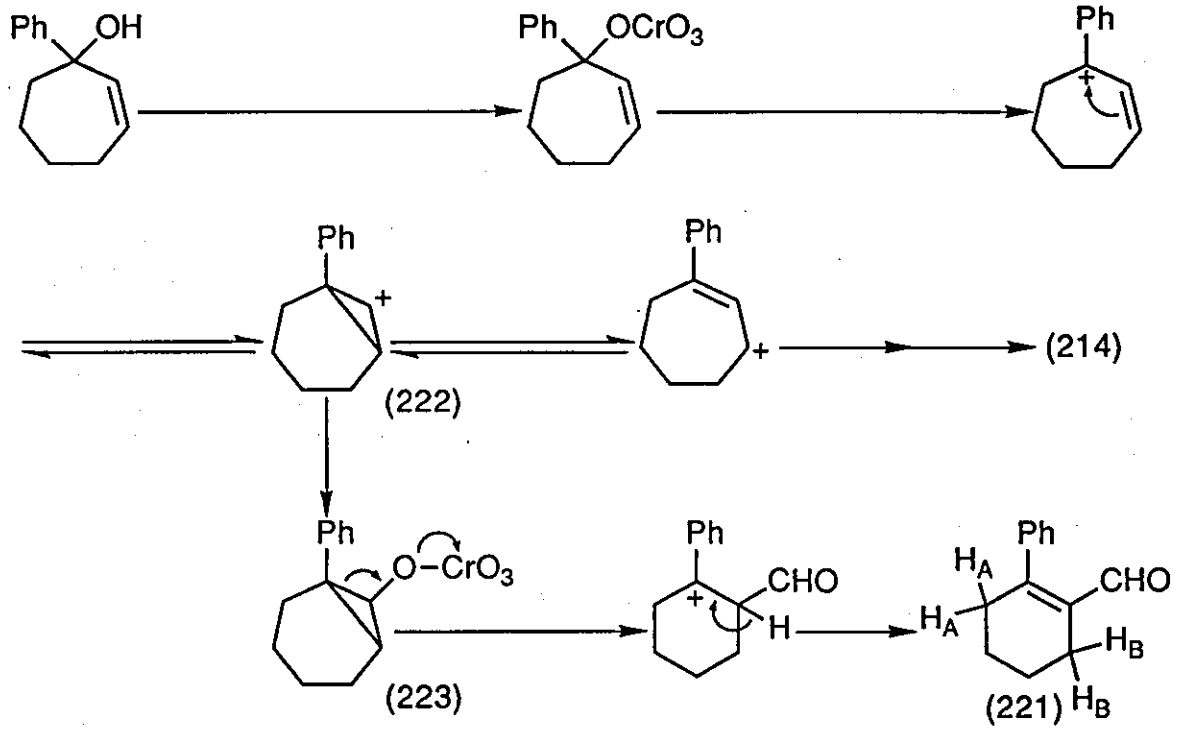
Both 3-phenyl-2-cyclohexen-1-one (213) and 3-phenyl-2-cyclohepten-1-one (214) were reduced with sodium borohydride, in the presence of cerium(III) chloride,[104] to afford the allylic alcohols, (215) and (216), in excellent yields. 3-Phenyl-2-cyclohexen-1-ol (215) was isolated as a viscous liquid, and 3-phenyl-2-cyclohepten-1-ol (216) as a crystalline solid, m.p. 50°C. Both of these allylic alcohols were epoxidised with m-chloroperoxybenzoic acid in the presence of sodium hydrogen carbonate. In the absence of the sodium hydrogen carbonate to buffer the solution, only very poor yields of the epoxides were obtained. Both the epoxides, (217) and (218), were seen by their ^1H and ^{13}C N.M.R. spectra to be single compounds, with the m-chloroperoxybenzoic acid directing the epoxidation onto the same face as the alcohol.[107] Preparation of the epoxythiocarbonylimidazolides, (219) and (220), *via* the normal procedure[87] went

smoothly, affording both products in good yields. All the spectroscopic data agreed with those for the anticipated products.

Scheme 59.



Scheme 60.



The epoxythiocarbonylimidazolides, (219) and (220), were allowed to react with tributyltin hydride / A.I.B.N. using normal and inverse modes of addition. The results obtained are summarised in Scheme 61 and in Table 5.

The reduction of epoxythiocarbonylimidazolides, (219) and (220), proceeded successfully, affording 2-phenyl-2,3,4,5-tetrahydrooxepine (226) and 2-phenyl-3,4,5,6-tetrahydro-2*H*-oxocine (227) respectively, in good yields. In both cases, the tertiary allylic alcohols (225), resulting from C-O β-scission of the oxiranylcarbinyl radical (224) were not isolated. Purification of the enol ethers proved troublesome, as they were extremely acid labile. Purification was achieved by chromatography with basic alumina, but being non-polar compounds they tended to elute quickly with the tributyltin hydride residues. As a result the compounds still contained trace amounts of tributyltin hydride after several columns. The infrared spectra of both compounds exhibited the characteristic enol ether, olefinic stretches at υ_{max} 1644 cm^{-1} for tetrahydrooxepine (226), and υ_{max} 1655 cm^{-1} for tetrahydro-2*H*-oxocine (227). The ^1H N.M.R. spectrum of (226) showed the proton α to the phenyl group, H_A, appearing as a doublet of doublets at δ 4.77 p.p.m. (J_{AX} = 2.69 Hz and J_{BX} = 10.03 Hz). The olefinic proton β to the oxygen, H_B, appeared as a multiplet at δ 4.88 p.p.m., with the olefinic proton α to the oxygen, H_C, appearing as a doublet of doublets at δ 6.40 p.p.m. (J = 1.10 and 6.89 Hz). The ^1H N.M.R. of (227) showed a similar splitting pattern, with the proton α to the phenyl group, H_A, appearing as a doublet of doublets at δ 4.94 p.p.m.

(J_{AX} = 4.06 Hz and J_{BX} = 7.20 Hz). The olefinic proton β to the oxygen, H_B, appeared as a quartet at δ 5.05 p.p.m. (J = 6.32 Hz), with the olefinic proton α to the oxygen, H_C, appearing as a doublet of triplets at δ 6.15 p.p.m. (J = 6.01 and 1.23 Hz). Both compounds gave the correct accurate mass for the MNH_4^+ ion in the chemical ionisation mass spectrum.

Scheme 61.

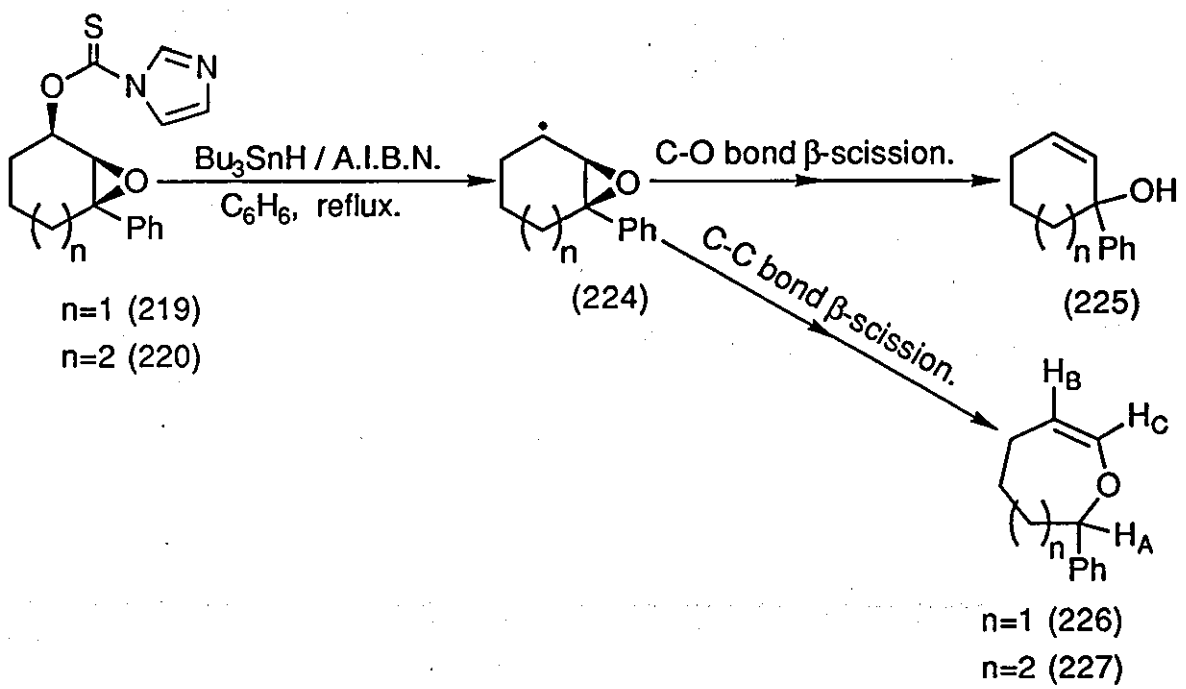


Table 5. Results of the tributyltin hydride reduction of epoxythiocarbonyl-imidazolides (219) and (220).

	Mode of addition of tributyltin hydride.	
	Normal.	Inverse.
% Yield of (226).	62	72
% Yield of (227).	58	66

As both these reactions worked as expected, it shows that the presence of the radical stabilising phenyl group results solely in β-scission of the C-C bond of the oxiranylcarbinyl radicals (224). An increased yield of ~10% was noted when performing the reduction of both epoxythiocarbonylimidazolides, (219) and (220), using the inverse mode of addition of tributyltin hydride / A.I.B.N. In the normal mode of addition, an excess of tributyltin hydride was employed. The extra

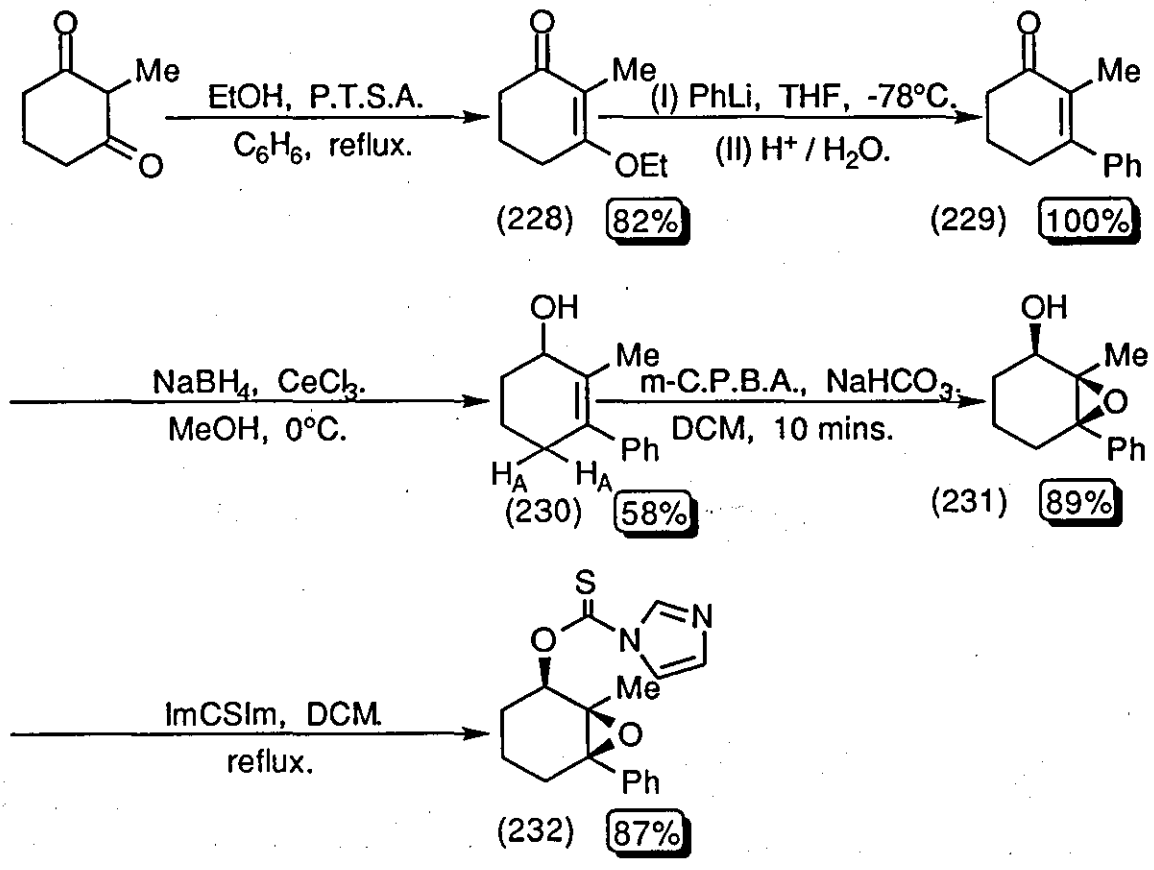
chromatography required to remove this could account for the decrease in yields of tetrahydrooxepine (226) and tetrahydro-2*H*-oxocine (227).

Although the reaction was only attempted on 6 and 7 membered rings, there is no reason why it should be restricted to just these. The only foreseeable problem of performing the reaction on larger rings, is that a mixture of *cis* and *trans* isomers of the enol ether might become evident as the ring constraints, present in the smaller rings, may no longer force the olefin to adopt the *cis* configuration. The generality of this reaction was shown by the reduction of a thiocarbonylimidazolide derivative of a fully substituted epoxide, as described in section **6.3.**

6.3. Preparation and reduction of the thiocarbonylimidazolide derivatives of 2,3-epoxy-2-methyl-3-phenylcyclohexan-1-ol (232).

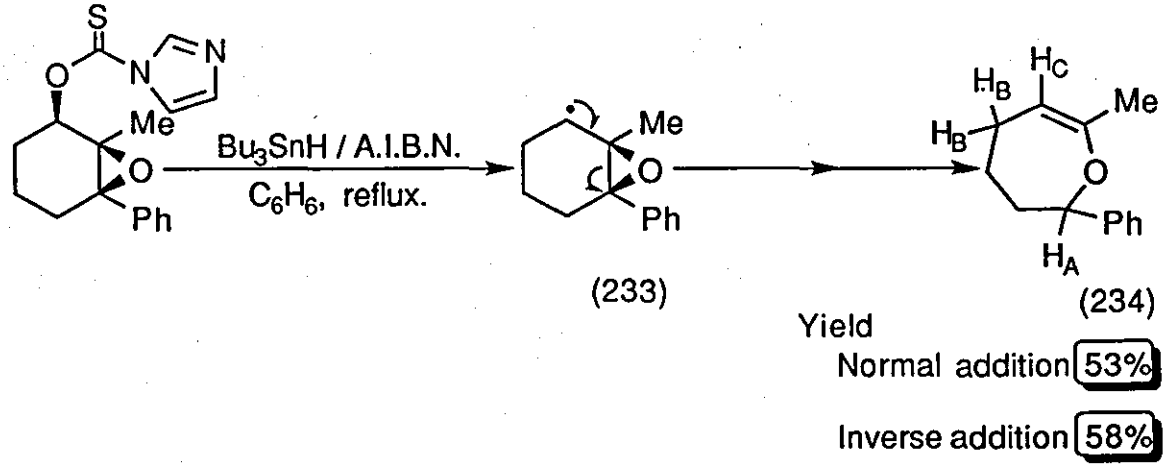
We considered it interesting to investigate how having a fully substituted epoxide would effect the rearrangement of the oxiranylcarbinyl radical formed on the tributyltin hydride reduction of the epoxythiocarbonylimidazolide derivative. The methyl derivative was chosen as a model. The thiocarbonylimidazolide derivative of 2,3-epoxy-2-methyl-3-phenyl-cyclohexan-1-ol (232) was prepared as shown in Scheme 62. The enol ether (228) of the 2-methyl-β-diketone was prepared in good yield following the procedure of Frank and Hall.[111] Enol ether (228) was treated with phenyllithium affording 2-methyl-3-phenyl-2-cyclohexen-1-one (229) in quantitative yield. Reduction of the carbonyl of enone (229) with the sodium borohydride, cerium(III) chloride mixture afforded allylic alcohol (230) as a crystalline solid, m.p. 65°C. In the ^{1}H N.M.R. spectrum of the allylic alcohol (230), the methyl protons appeared as a triplet at δ 1.68 p.p.m. (J = 1.97 Hz), arising from long range coupling to the protons β to the phenyl group H_A. Epoxidation of allylic alcohol (230) with m-chloroperoxybenzoic acid yielded the epoxy alcohol (231) as a crystalline solid, m.p. 73°C. Inspection of the ^{1}H N.M.R. spectrum showed epoxy alcohol (231) to be a single isomer, with the methyl group appearing as a singlet at δ 1.09 p.p.m. The thiocarbonylimidazolide derivative of 2,3-epoxy-2-methyl-3-phenylcyclohexan-1-ol (232) was prepared in good yield following the normal method.[87] Thiocarbonylimidazolide (232) was isolated as a crystalline solid, m.p. 96°C, with all the spectroscopic data in accordance with that anticipated for the product.

Scheme 62.



The thiocarbonylimidazolide ester of 2,3-epoxy-2-methyl-3-phenyl-cyclohexan-1-ol (232) was reduced with tributyltin hydride / A.I.B.N., *via* both modes of addition. The results are summarised in Scheme 63.

Scheme 63.



It is evident from the results that the ring expansion proceeded in the expected manner, with the 7-methyl-2-phenyl-2,3,4,5-tetrahydrooxepine (234) being isolated in reasonable yields. The enol ether proved to be extremely susceptible to hydrolysis, decomposing if left on a basic alumina column for an extended period of time. Again, even after several columns, trace amounts of tributyltin hydride residues remained in the product. The infrared spectrum of tetrahydrooxepine (234) showed the characteristic enol ether olefinic stretch (υ_{max} 1676 cm^{-1}). In the ^1H N.M.R. spectrum, the methyl group appeared as a quartet at δ 1.76 p.p.m. (J = 1.17 Hz), arising from a vicinal and long range coupling to the olefinic proton, H_C, and the protons α to the olefin, H_B. The proton α to the phenyl group, H_A, and the olefinic proton, H_C, appeared as an overlapping multiplet at δ 4.79 p.p.m. Although the yields for this reduction were less than those for epoxythiocarbonylimidazolides, (219) and (220), probably due to loss of tetrahydrooxepine (234) through the hydrolysis of the enol ether, it demonstrates that the ring expansion can be performed on fully substituted epoxides.

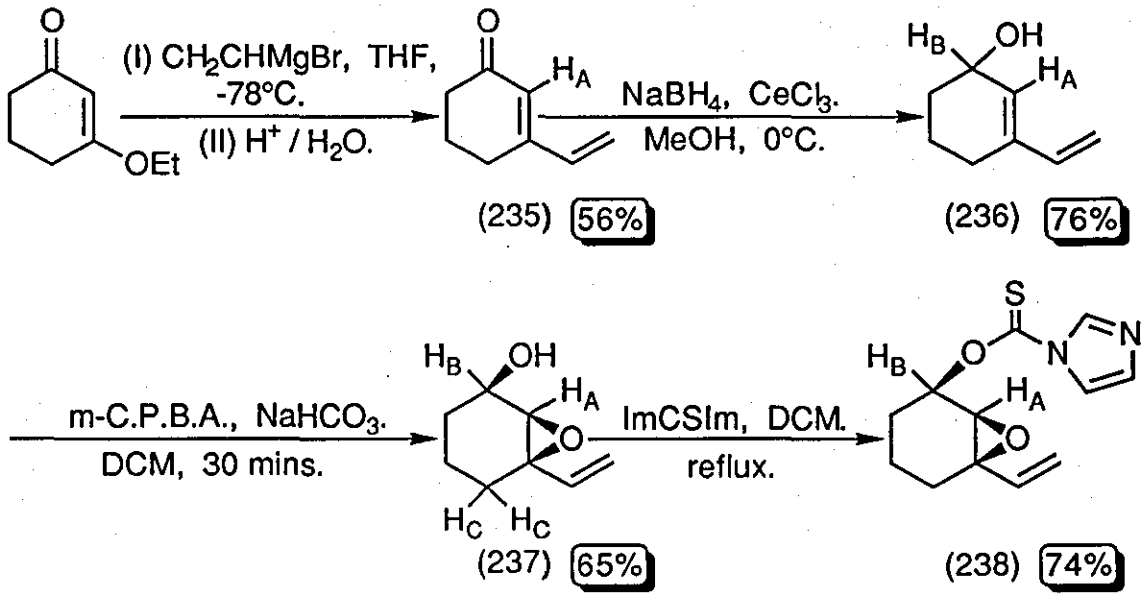
All the examples of the ring expansions, *via* C-C bond β-scission of the oxiranylcarbinyl radical, so far described have had a phenyl moiety as the radical stabilising group. As a vinyl group is also known to promote C-C bond β-scission of the oxiranylcarbinyl radical,[84] it was considered interesting to prepare the thiocarbonylimidazolide derivative of 2,3-epoxy-3-vinylcyclohexan-1-ol and see whether its reduction with tributyltin hydride / A.I.B.N. would result in the ring expanded enol ether.

6.4. Preparation and reduction of the thiocarbonylimidazolide derivative of 2,3-epoxy-3-vinylcyclohexan-1-ol (238).

The thiocarbonylimidazolide derivative of 2,3-epoxy-3-vinylcyclohexan-1-ol (238) was prepared in a similar manner to the thiocarbonylimidazolide ester of 2,3-epoxy-2-methyl-3-phenylcyclohexan-1-ol (232). The first step was the formation of 3-vinyl-2-cyclohexen-1-one (235) *via* the addition of vinylmagnesium bromide to 3-ethoxy-2-cyclohexen-1-one (148), followed by acidic hydrolysis of the resulting tertiary alcohol. This afforded 3-vinyl-2-cyclohexen-1-one (235) in reasonable yield, after purification by flash chromatography. The infrared spectrum of enone (235) showed the α,β-unsaturated carbonyl stretch (υ_{max} 1665 cm^{-1}), with both the olefinic stretches also being visible (υ_{max} 1622 and 1581 cm^{-1}). The ^1H N.M.R. spectrum clearly showed the presence of the vinyl group, with the two methylene protons appearing as doublets at δ 5.47 and 5.69 p.p.m. (J_{cis} = 10.71 Hz and J_{trans} = 17.42 Hz). The methine proton appeared as a doublet of doublets at δ 6.50 p.p.m., with the olefinic proton α to the carbonyl, H_A, as a singlet at 5.96 p.p.m. Reduction of the carbonyl of enone (235) with the sodium

borohydride, cerium(III) chloride mixture[104] afforded the allylic alcohol (236) in good yield. The infrared spectrum showed the hydroxy stretch (υ_{max} 3335 cm^{-1}) and the two olefinic stretches (υ_{max} 1642 and 1606 cm^{-1}). Again the *cis* and *trans* coupling of the vinyl group was clearly visible in the ^1H N.M.R. spectrum, with the olefinic proton β to the alcohol, H_A, showing no signs of any coupling to the proton α to the alcohol, H_B. Selective epoxidation of the ring olefin was achieved in good yield using m-chloroperoxybenzoic acid, with sodium hydrogen carbonate present to buffer the system. The infrared spectrum of the 2,3-epoxy-3-vinylcyclohexan-1-ol (237) showed the hydroxy stretch (υ_{max} 3407 cm^{-1}) and the single olefinic stretch of the vinyl group (υ_{max} 1638 cm^{-1}). The proton α to the epoxide ring, H_A, was seen as a doublet at δ 3.22 p.p.m. (J = 3.29 Hz). In addition to the *cis* and *trans* coupling of the vinyl group, the two methylene protons also exhibited a *geminal* coupling of 1.03 Hz. The epoxythiocarbonylimidazolide (238) was prepared in good yield *via* the normal method.[87] In the ^1H N.M.R. spectrum of epoxythiocarbonylimidazolide (238), the proton α to the epoxide ring, H_A, was seen as a doublet at δ 3.42 p.p.m. (J = 2.54 Hz). With epoxy alcohol (237), the proton α to the hydroxy group, H_B, was seen as a multiplet at δ 4.03 p.p.m., whereas with epoxythiocarbonylimidazolide (238), this proton, H_B, was observed as a doublet of triplets at δ 5.91 p.p.m. (J = 2.64 and 6.10 Hz).

Scheme 64.



On reduction of the epoxythiocarbonylimidazolide (238) using both modes of addition of tributyltin hydride / A.I.B.N., it became apparent that the rearrangement had not proceeded as initially proposed (Scheme 65). It was evident from the ^1H and ^{13}C N.M.R. spectra of the purified product that the vinyl substituted enol ether (240), had not been formed. After careful examination of the

infrared, ^{1}H and ^{13}C N.M.R. spectra of the product, the structure was tentatively assigned as either of the divinyl ethers (245) or (246). The infrared spectrum of the product showed two strong absorptions at υ_{max} 1668 and 1638 cm-1, due to the two enol ether olefinic stretches. As can be seen from Figure 5, the ^{1}H and ^{13}C N.M.R. spectroscopic data for the olefinic protons and carbons are in very close agreement with the structurally similar compound (247),[131] and thus strongly suggests that the divinyl ether structural unit is present in the product.

Such a divinyl ether moiety as (245) or (246) may be formed *via* a radical mechanism as shown in Scheme 65. If the oxiranylcarbinyl radical (239) rearranges *via* C-O β-scission, the resulting alkoxy radical (241) may then add to the *exo*-cyclic vinyl group affording the oxiranylcarbinyl radical (242). As this oxiranylcarbinyl radical (242) has a vinyl group attached to it, C-C β-scission may occur affording the stabilised radical (243). Double bond migration[83] gives the stabilised secondary vinyl radical (244), which abstracts a hydride radical resulting in the divinyl ether (245). Alternatively the stabilised secondary vinyl radical (244) may rearrange to afford the divinyl ether (246), after hydride radical abstraction by the intermediate primary radical. Two possible products are quoted as it is difficult to interpret the up-field region of the ^{1}H and ^{13}C N.M.R. spectra, due to the presence of tributyltin hydride residues. It would appear that the number of methylene and methine carbons in the ^{13}C N.M.R. spectrum fits the divinyl ether (246) structure better. This reaction is very interesting as it strongly suggests that ring opening and closure of the oxiranylcarbinyl radical is reversible, as going from alkoxyl radical (241) to the oxiranylcarbinyl radical (242) is the reverse of C-O β-scission of oxiranylcarbinyl radical (242). A similar process has been observed by Miller *et al.*[126]

The reason why the first oxiranylcarbinyl radical (239) undergoes C-O β-scission, while the second oxiranylcarbinyl radical (242) undergoes C-C β-scission is somewhat perplexing. Assuming the rearrangements are reversible, C-C β-scission of the oxiranylcarbinyl radical (239) could have occurred, but the intermediate radical did not have a long lifetime, and hence no product resulting from its reduction was isolated.

A test to see whether the reaction is going *via* the alkoxy radical (241), would be to form the alkoxy radical (241) by an alternative method and see whether the same product is isolated. The alkoxy radical (241) could be formed by photolysis of the hypoiodite, prepared by treating the tertiary alcohol equivalent of (241) with mercury(II) oxide and iodine.[132]

Scheme 65.

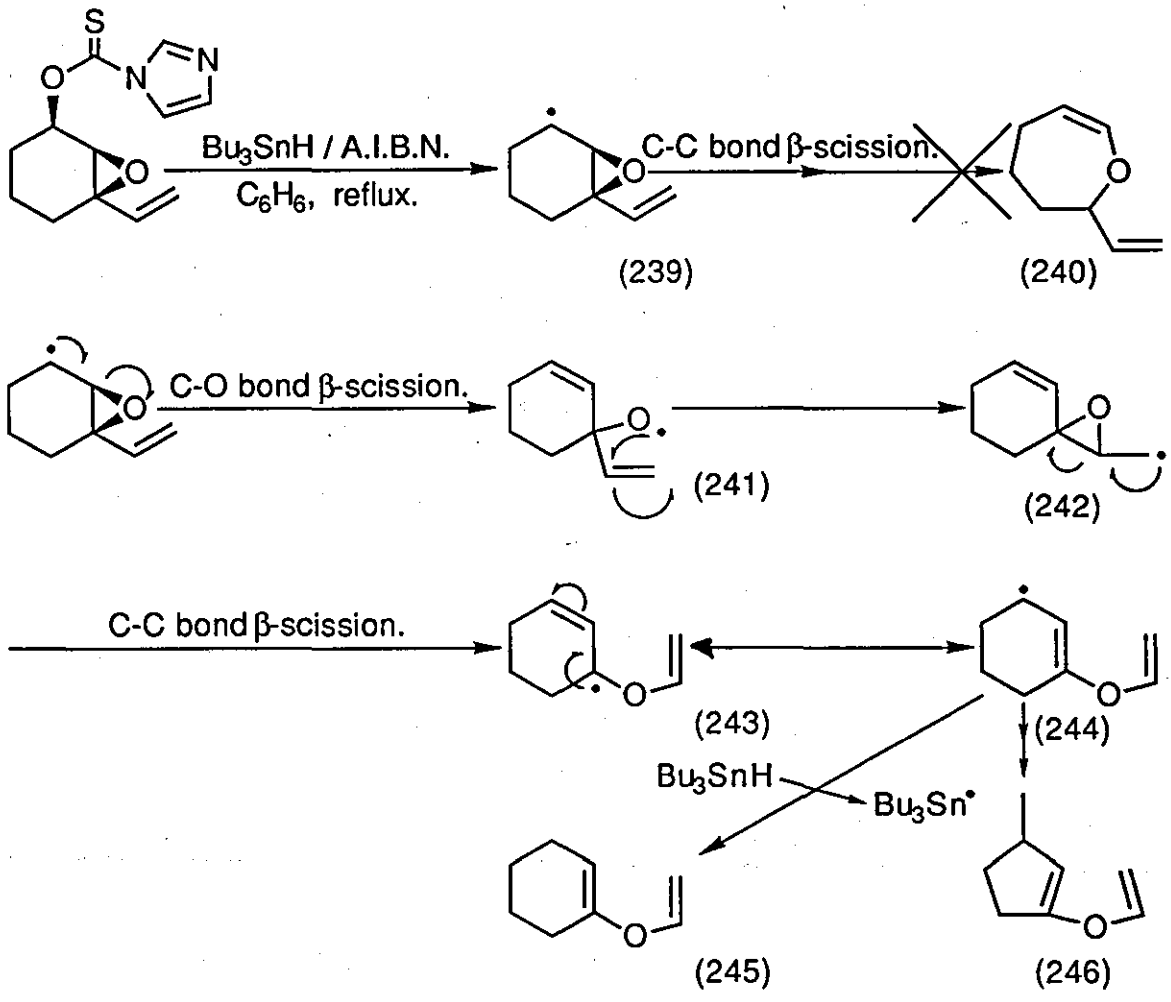
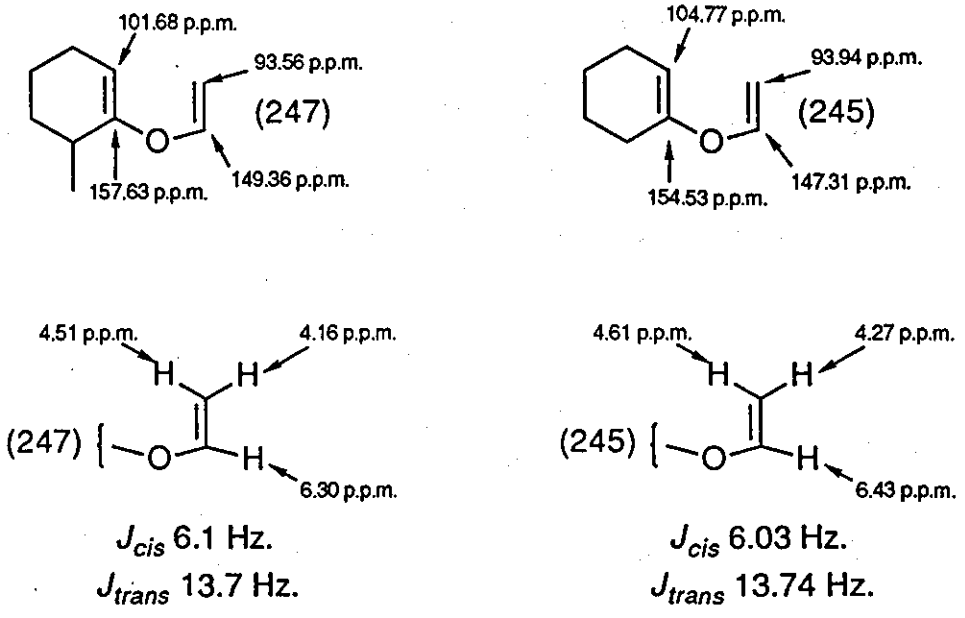


Figure 5. 13C and 1H N.M.R. data for the enol ethers (245) and (247).



J_{cis} 6.1 Hz.
J_{trans} 13.7 Hz.

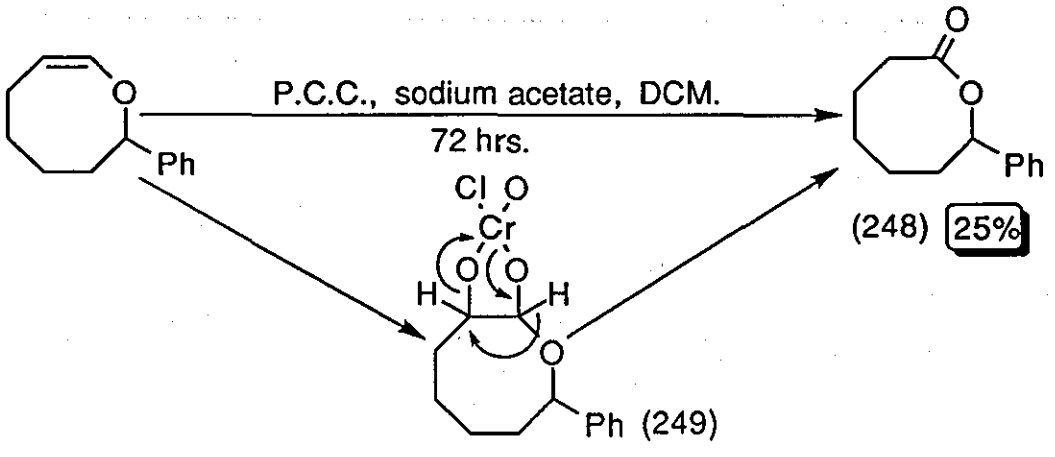
J_{cis} 6.03 Hz.
J_{trans} 13.74 Hz.

6.5. Oxidative manipulations of the enol ether products.

6.5.1. Pyridinium chlorochromate oxidation of 2-phenyl-3,4,5,6-tetrahydro-2*H*-oxocine (227).

It has been shown by Piancatelli *et al*[133] that linear and cyclic enol ethers can be oxidised by pyridinium chlorochromate to afford esters and lactones, respectively. It was considered interesting to perform this oxidation on the ring expanded 2-phenyl-3,4,5,6-tetrahydro-2*H*-oxocine (227). The reaction conditions of Piancatelli *et al* were employed, with 7-phenylheptonic-7-lactone (248) being isolated as a crystalline solid, m.p. 56°C (Scheme 66). The reaction mechanism is shown in Scheme 66, and involves electrophilic attack upon the olefin by pyridinium chlorochromate to afford the unstable intermediate (249). Heterolytic cleavage of the Cr-O bond, accompanied by a 1,2-hydride shift, afforded the carbonyl compound (248). The infrared spectrum of lactone (248) clearly showed the carbonyl stretch of the lactone at υ_{max} 1722 cm^{-1}, with the ^{13}C N.M.R. spectrum showing the carbonyl carbon at δ 176.39 p.p.m.

Scheme 66.



6.5.2. Epoxidation of the enol ethers with dimethyldioxirane and subsequent nucleophilic substitution of the formed epoxides.

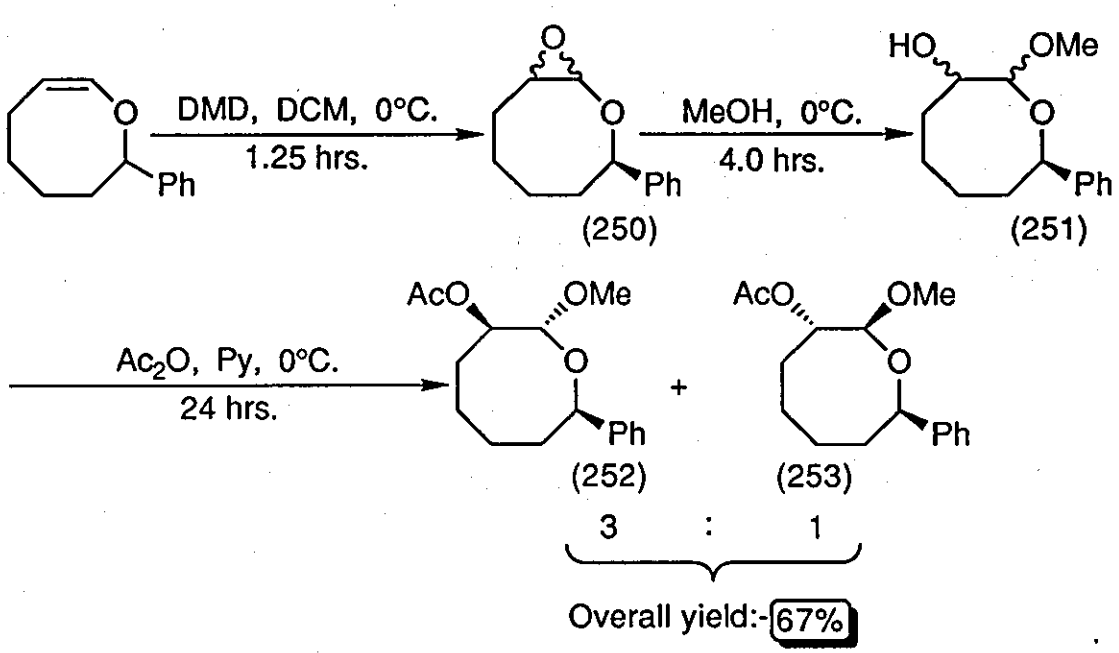
6.5.2-(I). Oxidation and nucleophilic substitution of 2-phenyl-3,4,5,6-tetrahydro-2*H*-oxocine (227).

2-Phenyl-3,4,5,6-tetrahydro-2*H*-oxocine (227) was epoxidised following the procedure of Danishefsky *et al.*[134] The enol ether was first treated with dimethyldioxirane, affording the epoxide (250) after 1 hour. This was not isolated

but rather anhydrous methanol was added to yield the methoxy alcohol (251). The alcohol (251) was immediately esterified with acetic anhydride in pyridine to afford the acetoxy methoxy compounds (252) and (253), in a 3:1 ratio, as shown in Scheme 67. The stereochemistry of the major isomer (252) was assigned on the basis of the coupling constants of the protons α to the phenyl, methoxy and acetoxy groups, and as a result of n.O.e. difference experiments. In these there was no visible n.O.e. effect between the protons α to the phenyl and methoxy groups. As the nucleophile is thought to attack the epoxide ring in a S_N2 fashion, it means that the α and β epoxides (250) are formed in a 1:3 ratio, when the phenyl group is assigned as being in the β-position. No product resulting from the substitution of methanol at the 2-position of the epoxide ring was noted, demonstrating how regioselective the substitution was.

Although this reaction was only attempted with methanol as the nucleophile, there is no reason why it should be restricted to just this nucleophile. If a Grignard reagent, or lithiated species were used, it would provide a good method for the preparation of disubstituted cyclic ethers.

Scheme 67.

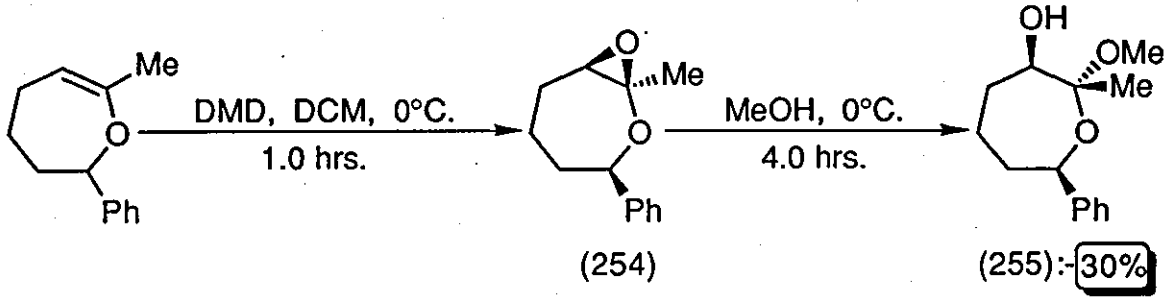


6.5.2-(II). Oxidation and nucleophilic substitution of 7-methyl-2-phenyl-2,3,4,5-tetrahydrooxepine (234).

The 7-methyl-2-phenyl-2,3,4,5-tetrahydrooxepine (234) was epoxidised with the dimethyldioxirane solution to afford the epoxide (254). Addition of methanol to a solution of the epoxide afforded the 3β-hydroxy-2α-methoxy-2β-methyl-7β-phenyloxepane (255) as a single isomer after purification on a basic

alumina column (Scheme 68). The stereochemistry of oxepane (255) was assigned on the basis of the coupling constants around the ring and on n.O.e. difference experiments. There was no observable n.O.e. effect between the methyl group and the proton α to the phenyl group, whereas there was a small n.O.e. effect between the methyl group and the phenyl group.

Scheme 68.



(254) (255):- 30%

This reaction sequence demonstrates the usefulness of the enol ether compounds as precursors for disubstituted and trisubstituted cyclic ethers. Again the methanol in this reaction could be replaced by a different nucleophile, affording trisubstituted cyclic ethers, potentially as single isomers.

The results discussed in **Chapter 5** and **6** have recently been published.[135]

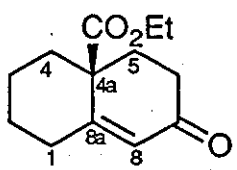
Chapter 7. Experimental.

7.1. General Information.

As for **Chapter 3.1.**

7.2. Experimental for **Chapter 5.**

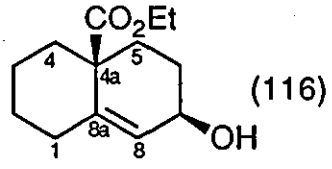
Preparation of *ethyl 1,3,4,5,6,7-hexahydro-7-oxo-4a(2H)-naphthalenecarboxylate* (115).



(115)

To a stirred solution of ethyl 2-oxocyclohexanecarboxylate (15 g, 88 mmol), in ethanolic sodium ethoxide solution (0.1 M, 28 cm^3, 2.8 mmol) at -15°C, methylvinylketone (6.2 g, 88 mmol) in anhydrous ethanol (20 cm^3) was added over 1.5 hours *via* a syringe pump. After the addition was complete, ethanolic sodium ethoxide solution (1 M, 2.8 cm^3, 2.8 mmol) was added and the solution warmed to room temperature. Ethanolic sodium ethoxide solution (1 M, 65 cm^3, 65 mmol) was then added to this and the mixture stirred at room temperature for 16 hours. After this time, hydrochloric acid (2 M) (50 cm^3) was added and the solution extracted with ethyl acetate (3 x 50 cm^3). The extracts were washed with hydrochloric acid (2 M) (x 3), water, a saturated sodium hydrogen carbonate solution, a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving an orange liquid. Kugelruhr distillation yielded (115) as a clear yellow liquid (15.5 g, 89%); b.p. (0.8 mmHg) 130°C;
υ_{max}/cm^{-1} (neat) 1722 (ester C=O), 1676 (α,β-unsaturated C=O) and 1624 (C=C);
δ_H (250 MHz $CDCl_3$) 1.27 (3H, t, J = 6.60 Hz, CH_3), 1.33-1.90 (4H, m, 2 x CH_2), 1.92 (2H, m, CH_2), 2.29-2.46 (6H, m, 3 x CH_2), 4.18 (2H, q, J = 6.40 Hz CO_2CH_2) and 5.92 (1H, s, C=CH);
δ_C (62.9 MHz, $CDCl_3$) 14.26 (CH_3), 23.19 (CH_2), 26.59 (CH_2), 34.23 (CH_2), 34.71 (CH_2), 34.87 (CH_2), 38.45 (CH_2), 48.92 (4a-C), 61.42 (O-CH_2), 126.54 (8-CH), 163.15 (8a-C), 173.37 (CO_2) and 198.85 (C=O).

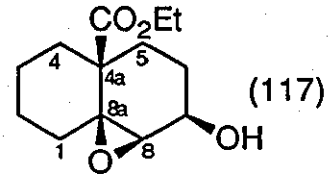
Preparation of *ethyl 1,3,4,5,6,7-hexahydro-7β-hydroxy-4aβ(2H)-naphthalene-carboxylate* (116).



(116)

To a rapidly stirred and cooled (icebath) solution of ethyl 1,3,4,5,6,7-hexahydro-7-oxo-4a(2*H*)-naphthalenecarboxylate (10 g, 45 mmol) and cerium(III) chloride heptahydrate (17.2 g, 45 mmol) in anhydrous methanol (100 cm^3), sodium borohydride (1.7 g, 45 mmol) was added in one portion. After stirring at 0°C for 30 minutes, water was added and the solution extracted with diethyl ether (x 3). The extracts were washed with water, a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness to give a clear yellow liquid. Purification by flash chromatography (3:1 light petroleum (b.p. 40-60°C) : diethyl ether) afforded (116) as a clear liquid (9.0 g, 93%);
υ_{max}/cm^{-1} (neat) 3420 (OH), 1720 (ester C=O) and 1640 (C=C);
δ_H (250 MHz $CDCl_3$) 1.22 (3H, t, J = 7.20 Hz, CH_3), 1.38-2.29 (12H, m, 6 x CH_2), 2.92 (1H, br s, OH), 4.15 (2H, q, J = 7.10 Hz, O-CH_2), 4.15 (1H, m, 7-CH) and 5.55 (1H, d, J = 0.81 Hz, 8-CH);
δ_C (62.9 MHz, $CDCl_3$) 14.20 (CH_3), 23.76 (CH_2), 27.45 (CH_2), 28.97 (CH_2), 33.73 (CH_2), 33.76 (CH_2), 38.30 (CH_2), 48.25 (4a-C), 60.68 ($CO_2\underline{C}H_2$), 66.91 (7-CH), 126.61 (8-CH), 140.12 (8a-C) and 175.73 (CO_2).

Preparation of *ethyl 8β,8aβ-epoxy-7β-hydroxy-octahydro-4aβ(2H)-naphthalene-carboxylate* (117).

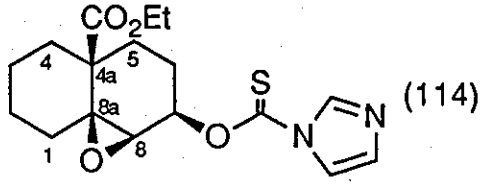


(117)

To a cooled (icebath) and stirred solution of ethyl 1,3,4,5,6,7-hexahydro-7β-hydroxy-4aβ(2*H*)-naphthalenecarboxylate (3.5 g, 15.6 mmol) and sodium hydrogen carbonate (1.7 g, 20 mmol) in anhydrous dichloromethane (100 cm^3), m-chloroperoxybenzoic acid (3.5 g, 20 mmol) was added in one portion. After stirring at room temperature for 1 hour, the solution was washed with a saturated sodium hydrogen carbonate solution (x 4), water, a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a yellow

liquid. Purification by flash chromatography (3:1 light petroleum (b.p. 40-60°C) : ethyl acetate) afforded (117) as a clear viscous liquid (3.0 g, 83%);
υ_{max}/cm^{-1} (neat) 3472 (OH) and 1722 (ester C=O);
δ_H (250 MHz $CDCl_3$) 1.30 (3H, t, J = 7.10 Hz, CH_3), 1.30-2.28 (12H, m, 6 x CH_2), 2.50 (1H, br s, OH), 3.11 (1H, d, J = 4.50 Hz, 8-CH), 4.08 (1H, m, 7-CH) and 4.27 (2H, m, CO_2CH_2);
δ_C (62.9 MHz, $CDCl_3$) 14.22 (CH_3), 22.62 (CH_2), 25.22 (CH_2), 26.22 (CH_2), 26.71 (CH_2), 32.78 (CH_2), 33.39 (CH_2), 47.17 (4a-C), 60.65 ($CO_2\underline{C}H_2$), 60.95 (8-CH), 63.66 (7-CH), 64.72 (8a-C) and 174.68 (CO_2);
m/z (C.I., ammonia) 241.1440 (MH^+, 40%, $C_{13}H_{21}O_4$ requires 241.1440), 258 (20, MNH_4^+) and 223 (100, M^+ minus OH).

Preparation of *ethyl 8β,8aβ-epoxy-7β-(imidazol-1-yl (thiocarbonyl) oxy)-octahydro-4aβ(2H)-naphthalenecarboxylate* (114).



(114)

A stirred solution of ethyl 8β,8aβ-epoxy-7β-hydroxy-octahydro-4aβ(2*H*)-naphthalenecarboxylate (1.5 g, 6.2 mmol) and 1,1-thiocarbonyldiimidazole (2.2 g, 12.4 mmol) in anhydrous dichloromethane (50 cm^3) was heated at gentle reflux for 2.0 hours. After cooling, the solution was washed with a saturated sodium hydrogen carbonate solution (x 3), water, a saturated ammonium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a viscous yellow liquid. All material purified by flash chromatography (3:1 light petroleum (b.p. 40-60°C) : diethyl ether) to afford (114) as a light yellow solid (2.0 g, 92%). Recrystallisation from 2:1 light petroleum (b.p. 40-60°C) : ethyl acetate yielded (118) as colourless crystals m.p. 74-75°C;
found: C, 58.14; H, 6.41; N, 7.98; S, 8.88%. $C_{17}H_{22}N_2O_4S$ requires C, 58.27; H, 6.33; N, 7.98; S, 9.15%;
υ_{max}/cm^{-1} (KBr disc) 1724 (ester C=O);
δ_H (250 MHz $CDCl_3$) 1.82 (3H, t, J = 7.10 Hz, $CO_2CH_2C\underline{H}_3$), 1.28-2.34 (12H, m, 6 x CH_2), 3.32 (1H, d, J = 3.62 Hz, 8-CH), 4.21 (2H, m, $CO_2C\underline{H}_2CH_3$), 5.88 (1H, q, J = 3.73 Hz, 7-CH), 7.01 (1H, br s, Im-CH), 7.64 (1H, br s, Im-CH) and 8.36 (1H, br s, Im-CH);

δ_C (62.9 MHz, $CDCl_3$) 14.23 (CH_3), 22.34 (2-CH_2), 22.60 (3-CH_2), 24.99 (4-CH_2), 28.41 (1-CH_2), 32.47 (5-CH_2), 34.24 (6-CH_2), 46.73 (4a-C), 57.48 (8-CH), 60.67 ($CO_2\underline{C}H_2$), 63.31 (8a-C), 77.49 (7-CH), 117.93 (Im-CH), 130.73 (Im-CH), 136.99 (Im-CH), 174.24 (C=S) and 181.00 (CO_2);
m/z (C.I., ammonia) 351.1379 (MH^+, 30%, $C_{17}H_{23}N_2O_4S$ requires 351.1378), 223 (50, M^+ minus OCSIm) and 69 (100, Im).

Tributyltin hydride reduction of the epoxythiocarbonylimidazolides (general procedure).

(I) Normal addition.

To a stirred and refluxing solution of the epoxythiocarbonylimidazolide in anhydrous benzene, tributyltin hydride (1.2 equivalents) and A.I.B.N. (20 mg) in anhydrous benzene were added over 4 hours *via* a syringe pump. The reaction was followed by t.l.c. until all the starting material disappeared. The crude product was purified as stated in the procedure.

(II) Inverse addition.

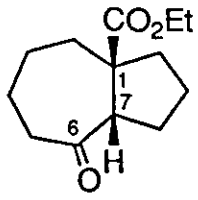
To a stirred and refluxing solution of tributyltin hydride (1.2 equivalents) in anhydrous benzene, the epoxythiocarbonylimidazolide and A.I.B.N. (20 mg) in anhydrous benzene were added over 4 hours *via* a syringe pump. The reaction was followed by t.l.c. until all the starting material disappeared. The crude product was purified as stated in the procedure.

Tributyltin hydride reduction of *ethyl 8β,8aβ-epoxy-7β-(imidazol-1-yl (thiocarbonyl) oxy)-octahydro-4aβ(2H)-naphthalenecarboxylate* (114).

(I) Normal addition.

Method as for general procedure.
All crude purified on flash silica, gradient elution, light petroleum (b.p. 40-60°C) to 1:2 diethyl ether : light petroleum (b.p. 40-60°C). Four products isolated and recolumned on flash silica, listed from least polar to most polar:-

Ethyl 6-oxobicyclo-(5,3,0)-decan-1-carboxylate (125).



(125)

Ethyl 6-oxobicyclo-(5,3,0)-decan-1-carboxylate (125) was isolated as a clear liquid (15%);

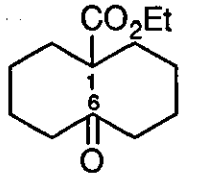
υ_{max}/cm^{-1} (neat) 1720 (ester C=O) and 1700 (C=O);

δ_H (250 MHz $CDCl_3$) 1.30 (3H, t, J = 7.10 Hz, CH_3), 1.30-2.53 (7 x CH_2), 3.92 (1H, t, J = 7.91 Hz, 7-CH) and 4.27 (2H, q, J =7.10 Hz, O-CH_2);

δ_C (62.9 MHz, $CDCl_3$) 14.28 (CH_3), 22.56 (CH_2), 23.43 (CH_2), 24.26 (CH_2), 24.73 (CH_2), 35.53 (CH_2), 41.30 (CH_2), 42.82 (CH_2), 54.95 (7-CH), 55.13 (1-C), 61.14 (O-CH_2), 176.79 (CO_2) and 212.66 (C=O);

m/z (C.I., ammonia) 225.149 (MH^+, 100%, $C_{13}H_{21}O_3$ requires 225.149) and 242 (20, MNH_4^+).

Ethyl 6-oxocyclodecan-1-carboxylate (123).



(123)

Ethyl 6-oxocyclodecan-1-carboxylate (123) was isolated as a clear liquid (35%);

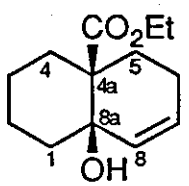
υ_{max}/cm^{-1} (neat)1726 (ester C=O) and 1698 (C=O);

δ_H (250 MHz $CDCl_3$) 1.25 (3H, t, J = 7.16 Hz, CH_3), 1.47-1.84 (12H, m, 6 x CH_2), 2.37 (2H, ddd, J_{AX} = 4.05, $J_{AX'}$ = 8.39 and J_{AB} = 15.66 Hz, 5- and 7-CH_A), 2.50 (1H, t, J = 6.00 Hz, 1-CH), 2.73 (2H, ddd, J_{BX} = 3.73, $J_{BX'}$ = 8.87 and J_{AB} = 15.65 Hz, 5- and 7-CH_B) and 4.16 (2H, q, J = 7.43 Hz, O-CH_2);

δ_C (62.9 MHz, $CDCl_3$) 14.30 (CH_3), 23.12 (2 x CH_2), 23.81 (2 x CH_2), 27.63 (2 x CH_2), 41.67 (1-CH), 41.86 (2 x CH_2), 60.26 (O-CH_2), 176.34 (ester) and 214.31 (C=O);

m/z (C.I., ammonia) 244.191 (MNH_4^+, 100%, $C_{13}H_{26}O_3N$ requires 244.191) and 227 (30, MH^+).

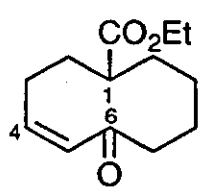
Ethyl 1,3,4,5,6,8a-hexahydro-8aβ-hydroxy-4aβ(2H)-naphthalenecarboxylate (121).



(121)

Ethyl 1,3,4,5,6,8a-hexahydro-8aβ-hydroxy-4aβ(2*H*)-naphthalene-carboxylate (121) was isolated as a clear liquid (8%);
υ_{max}/cm^{-1} (neat) 3484 (OH) and 1700 (ester C=O);
δ_H (250 MHz $CDCl_3$) 1.21 (3H, t, *J* = 7.21 Hz, CH_3), 1.20-2.17 (12H, m, 6 x CH_2), 4.17 (2H, q, *J* = 7.10 Hz, O-CH_2), 4.66 (1H, br s, OH) and 5.58 (2H, br t, *J* = 10.09 Hz, 7- and 8-CH);
δ_C (62.9 MHz, $CDCl_3$) 14.09 (CH_3), 21.76 (2 x CH_2), 24.28 (2 x CH_2), 29.72 (CH_2), 36.91 (CH_2), 49.40 (4a-C), 60.67 (O-CH_2), 70.47 (8a-C), 126.99 (7-CH), 134.90 (8-CH) and 178.51 (CO_2);
m/z (E.I.) 224.141 (M^+, 10%, $C_{13}H_{20}O_3$ requires 224.141) and 207 (100, M^+ minus OH).

Ethyl 6-oxocyclodec-4-en-1-carboxylate (122).



(122)

Ethyl 6-oxocyclodec-4-en-1-carboxylate (122) was isolated as a clear liquid (13%);
υ_{max}/cm^{-1} (neat) 1726 (ester C=O), 1686 (α,β-unsaturated C=O) and 1626 (C=C);
δ_H (250 MHz $CDCl_3$) 1.23 (3H, t, *J* = 7.23 Hz, CH_3), 1.30-2.57 (11H, m, 5 x CH_2 and 1-CH), 2.70 (2H, m, 3-CH_2), 4.15 (2H, q, *J* = 7.25 Hz, O-CH_2), 5.81 (1H, dt, *J* = 12.00 and 5.26 Hz, 4-CH) and 6.34 (1H, d, *J* = 11.96 Hz, 5-CH);
δ_C (62.9 MHz, $CDCl_3$) 14.26 (CH_3), 22.05 (CH_2), 23.54 (CH_2), 23.78 (CH_2), 27.28 (CH_2), 27.89 (CH_2), 39.38 (1-CH), 44.89 (3-CH_2), 60.34 (O-CH_2), 133.09 (4-CH), 137.50 (5-CH), 176.40 (CO_2) and 208.26 (CO);
m/z (C.I., ammonia) 225.149 (MH^+, 70%, $C_{13}H_{21}O_3$ requires 225.149) and 242 (100, MNH_4^+).

(II) Inverse addition.

Method as for general procedure.
All crude purified on flash silica, gradient elution, light petroleum (b.p. 40-60°C) to a 1:2 diethyl ether : light petroleum (b.p. 40-60°C). Two products isolated and recolumned on flash silica, listed from less polar to more polar:-

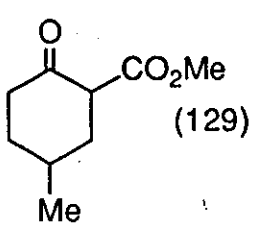
Ethyl 6-oxocyclodecan-1-carboxylate (123).

Ethyl 6-oxocyclodecan-1-carboxylate (123) was isolated as a clear liquid (40%). All spectroscopic data same as for product from normal addition.

Ethyl 1,3,4,5,6,8a-hexahydro-8aβ-hydroxy-4aβ(2H)-naphthalenecarboxylate (121).

Ethyl 1,3,4,5,6,8a-hexahydro-8aβ-hydroxy-4aβ(2*H*)-naphthalene-carboxylate (121) was isolated as a clear liquid (15%). All spectroscopic data same as for product from normal addition.

Preparation of *methyl 2-carboxylate-4-methylcyclohexan-1-one* (129).

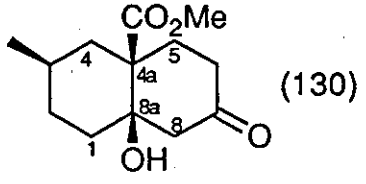


(129)

To a stirred and refluxing solution of methylcarbonate (40 g, 446 mmol) and sodium hydride (60% oil dispersion, 22.5 g, 556 mmol) in anhydrous tetrahydrofuran (200 cm^3), 4-methylcyclohexanone (20 g, 178 mmol) in anhydrous tetrahydrofuran (20 cm^3) was added over 1 hour. After the addition of 3 cm^3 of the solution, potassium hydride (35% oil dispersion, 1.9 g, 17 mmol) was added to initiate the reaction. After refluxing the solution for an hour, acetic acid (200 cm^3) was carefully added, followed by a saturated sodium chloride solution. The solution was then extracted with diethyl ether (3 x 200 cm^3) and the extracts washed with a saturated sodium hydrogen carbonate solution (2 x 50 cm^3), water and a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness. The resulting yellow liquid (25 g) was distilled under vacuum affording (129) as a clear and colourless liquid (23.7 g, 79%); b.p. (0.01 mmHg) 45-48°C;

υ_{max}/cm^{-1} (neat) 1749 (ester C=O), 1719 (C=O), 1660 (C=O, enol tautomer) and 1615 (C=C enol tautomer);
δ_H (250 MHz $CDCl_3$) 0.96 (3H, d, J = 0.55 Hz, ring Me), 1.20 (1H, m, 4-CH), 1.65 (2H, m, 5-CH_2), 2.20-2.60 (5H, m, 2 x CH_2 and 2-CH) and 3.69 (3H, s, -CO_2Me);
δ_C (62.9 MHz, $CDCl_3$) 21.15 (Me), 28.44 (4-CH), 28.80 (5-CH_2), 29.74 (3-CH_2), 30.62 (6-CH_2), 43.52 (2-CH), 51.15 (CO_2Me), 171.80 (CO_2Me) and 214.33 (C=O).

Preparation of *methyl 8aβ-hydroxy-3β-methyl-octahydro-7-oxo-4aβ(2H)-naphthalenecarboxylate* (130).



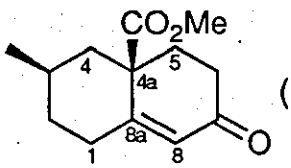
(130)

To a stirred solution of methyl 2-carboxylate-4-methylcyclohexan-1-one (5 g, 31 mmol) in methanolic sodium methoxide solution (0.1 M, 10 cm^3, 1 mmol), at -15°C, methylvinylketone (2.7 g, 32 mmol) in anhydrous methanol (7 cm^3) was added over 1.5 hours *via* a syringe pump. After the addition was complete, methanolic sodium methoxide solution (1 M, 1 cm^3, 1 mmol) was added and the mixture warmed to room temperature. Methanolic sodium methoxide solution (1 M, 65 cm^3, 65 mmol) was then added and the mixture left stirring at room temperature for 16 hours. After this time hydrochloric acid (2 M) (50 cm^3) was added and the solution extracted with ethyl acetate (3 x 50 cm^3). The extracts were washed with hydrochloric acid (2 M) (x 3), water, a saturated sodium hydrogen carbonate solution, a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated affording an orange liquid (4.8 g). Purification by flash chromatography (1:4 ethyl acetate : light petroleum (b.p. 40-60°C)), followed by recrystallisation from 1:1 ethyl acetate : light petroleum (b.p. 40-60°C) gave (130) as colourless needles (2.6 g, 40%); m.p. 60.3-60.6°C;
found: C, 64.81; H, 8.34%. $C_{13}H_{20}O_4$ requires C, 64.98; H, 8.39%;
υ_{max}/cm^{-1} (KBr disc) 3513 (OH), 1716 (ester C=O) and 1713 (C=O);
δ_H (250 MHz $CDCl_3$) 0.92 (3H, d, J = 5.86 Hz, ring-Me), 1.42-1.55 (4H, m, 1-CH_2 and 2-CH_2), 1.60-1.70 (2H, m, 3-CH and 4-CH_A), 1.75 (1H, dd, J_{BX} = 1.50 and J_{AB} =13.40 Hz, 4-CH_B), 2.05-2.35 (4H, m, 5-CH_2 and 6-CH_2), 2.42 (1H, dd, J_{AX} = 2.03 and J_{AB} = 14.11 Hz, 8-CH_A), 2.90 (1H, d, J_{AB} = 14.11 Hz, 8-CH_B), 3.80 (3H, s, OMe) and 4.70 (1H, d, J = 1.70 Hz, OH);

The assigned structure was confirmed by n.O.e. difference spectroscopy.

δ_C (62.9 MHz, $CDCl_3$) 22.04 (CH_3), 26.31 (3-CH), 28.02 (CH_2), 29.06 (CH_2), 33.98 (CH_2), 38.76 (2 x CH_2), 50.99 (4a-C), 52.59 ($CO_2\underline{Me}$), 54.47 (8-CH_2), 73.09 (8a-C), 178.80 ($\underline{C}O_2Me$) and 208.20 (C=O);
m/z (C.I., ammonia) 241 (MH^+, 25%), 223 (100, M^+ minus OH).

Preparation of *methyl 1,3,4,5,6,7-hexahydro-3β-methyl-7-oxo-4aβ(2H)-naphthalenecarboxylate* (131).

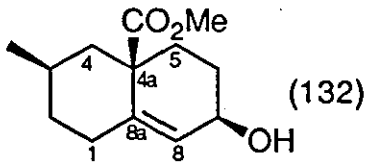


(131)

A solution of methyl 8aβ-hydroxy-3β-methyl-octahydro-7-oxo-4aβ(2*H*)-naphthalenecarboxylate (200 mg, 0.84 mmol) and p-toluenesulfonic acid (50 mg, 0.26 mmol) in benzene (30 cm^3) was heated at reflux for 10 minutes. After cooling, the solution was washed with a saturated sodium hydrogen carbonate solution (2 x 10 cm^3), water, a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness. Purification of the resulting viscous yellow liquid by flash chromatography (1:8 ethyl acetate : light petroleum (b.p. 40-60°C)), followed by recrystallisation from light petroleum (b.p. 40-60°C) gave (131) as colourless needles (162 mg, 82%); m.p. 52.8-53.2°C;
found: C, 69.96; H, 8.11%. $C_{13}H_{18}O_3$ requires C, 70.25; H, 8.16%;
υ_{max}/cm^{-1} (KBr disc) 1723 (ester C=O), 1674 (α,β-unsaturated C=O) and 1623 (C=C);
δ_H (250 MHz $CDCl_3$) 0.98 (3H, d, J = 7.20 Hz, ring-Me), 1.60 (2H, m, 2-CH_β and 5-CH), 1.75 (1H, m, 2-CH_α), 1.96 (2H, m, 3-CH and 6-CH), 2.30 (5H, m, 4-CH_2, 1-CH_α, 5-CH and 6-CH), 2.69 (1H, m, 1-CH_β), 3.74 (3H, s, OMe) and 5.94 (1H, d, J = 1.82 Hz, 8-CH);

The assigned structure was confirmed by n.O.e. difference spectroscopy.
δ_C (62.9 MHz, $CDCl_3$) 18.21 (CH_3), 27.00 (3-CH), 29.33 (1-CH_2), 31.82 (5-CH_2), 34.81 (4-CH_2), 35.97 (6-CH_2), 43.23 (2-CH_2), 46.66 (4a-C), 52.54 ($CO_2\underline{Me}$), 126.80 (8-CH), 163.80 (8a-C), 174.90 ($\underline{C}O_2Me$) and 198.62 (C=O);
m/z (E.I.) 222 (M^+, 45%) and 162 (100, M^+ minus HCO_2Me).

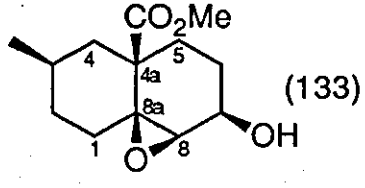
Preparation of *methyl 1,3,4,5,6,7-hexahydro-7β-hydroxy-3β-methyl-4aβ(2H)-naphthalenecarboxylate* (132).



(132)

To a rapidly stirred and cooled (icebath) solution of methyl 1,3,4,5,6,7-hexahydro-3β-methyl-7-oxo-4aβ(2*H*)-naphthalenecarboxylate (7.0 g, 31 mmol) and cerium(III) chloride heptahydrate (11.7 g, 31 mmol) in anhydrous methanol (100 cm^3), sodium borohydride (1.2 g, 31 mmol) was added in one portion. After stirring at 0°C for 30 minutes, water was added and the solution extracted with diethyl ether (x 3). The extracts were washed with water, a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a yellow liquid. Purification by flash chromatography (1:1 light petroleum (b.p. 40-60°C): diethyl ether) afforded (132) as a clear viscous liquid (6.46 g, 93%);
found: C, 68.96; H, 9.04%. $C_{13}H_{20}O_3$ requires C, 69.61; H, 8.99%;
υ_{max}/cm^{-1} (neat) 3410 (OH), 1727 (ester C=O) and 1665 (C=C);
δ_H (250 MHz $CDCl_3$) 0.90 (3H, d, J = 7.37 Hz, ring-Me), 1.31-1.58 (5H, m, CH_2 and 3 x CH), 1.92-2.06 (4H, m, 4 x CH), 2.20 (1H, m, CH), 2.46 (1H, m, 1-CH_β), 2.74 (1H, s, OH), 3.74 (3H, s, OMe), 4.18 (1H, m, 3-CH) and 5.57 (1H, br s, 8-CH);
δ_C (62.9 MHz, $CDCl_3$) 17.86 (CH_3), 27.68 (3-CH), 28.55 (CH_2), 29.24 (CH_2), 32.92 (CH_2), 35.56 (CH_2), 43.55 (CH_2), 45.95 (4a-C), 52.09 ($CO_2\underline{Me}$), 67.40 (7-CH), 127.05 (8-CH), 140.41 (8a-C) and 177.48 ($\underline{C}O_2Me$).

Preparation of *methyl 8β,8aβ-epoxy-7β-hydroxy-3β-methyl-octahydro-4aβ(2H)-naphthalenecarboxylate* (133).



(133)

To a cooled (icebath) and stirred solution of methyl 1,3,4,5,6,7-hexahydro-7β-hydroxy-3β-methyl-4aβ(2*H*)-naphthalenecarboxylate (4.0 g, 17.8 mmol) and sodium hydrogen carbonate (1.9 g, 22.5 mmol) in anhydrous dichloromethane (100 cm^3), m-chloroperoxybenzoic acid (4.1 g, 21.4 mmol) was added in one portion. After stirring at room temperature for 0.5 hour, the solution was washed with a saturated sodium hydrogen carbonate solution (x 4), water, a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to

dryness giving a viscous yellow liquid. Purification by flash chromatography (3:1 light petroleum (b.p. 40-60°C) : ethyl acetate) afforded (133) as a clear viscous liquid (4.1 g, 96%);

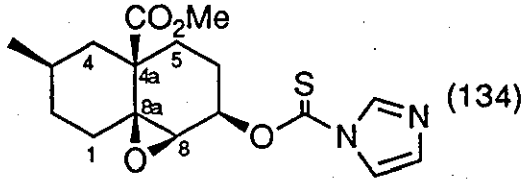
υ_{max}/cm^{-1} (neat) 3443 (OH) and 1731 (ester C=O);

δ_H (250 MHz $CDCl_3$) 0.92 (3H, d, J = 6.15 Hz, ring-Me), 1.00 (1H, m, 2-CH), 1.32 (1H, m, 5-CH), 1.45 (3H, m, 6-CH_β, 2-CH and 4-CH), 1.75 (1H, m, 6-CH_α), 1.90 (4H, m, 5-CH, 1-CH, 3-CH and 4-CH), 2.60 (1H, m, 1-CH), 2.92 (1H, br s, OH), 3.05 (1H, d, J = 2.70 Hz, 8-CH), 3.73 (3H, s, OMe) and 3.98 (1H, m, 7-CH);

δ_C (62.9 MHz, $CDCl_3$) 20.83 (CH_3), 25.12 (3-CH), 25.62 (CH_2), 28.09 (CH_2), 28.35 (CH_2), 29.31 (CH_2), 40.17 (CH_2), 45.15 (4a-C), 51.79 ($CO_2\underline{Me}$), 62.28 (8-CH), 64.90 (8a-C), 66.77 (7-CH) and 175.35 ($\underline{C}O_2Me$);

m/z (C.I., ammonia) 258 (65%, MNH_4^+), 241 (90, MH^+) and 223 (100, M^+ minus OH).

Preparation of *methyl 8β,8aβ-epoxy-7β-(imidazol-1-yl (thiocarbonyl) oxy)-3β-methyl-octahydro-4aβ(2H)-naphthalenecarboxylate* (134).



(134)

A stirred solution of methyl 8β,8aβ-epoxy-7β-hydroxy-3β-methyl-octahydro-4aβ(2*H*)-naphthalenecarboxylate (2.5 g, 10.4 mmol) and 1,1-thiocarbonyldiimidazole (4.1 g, 20.8 mmol) in anhydrous dichloromethane (30 cm^3) was heated at gentle reflux for 3.0 hours. After cooling, the solution was washed with a saturated sodium hydrogen carbonate solution (x 3), water, a saturated ammonium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a viscous orange liquid. Purification by recrystallisation from 2:1 light petroleum (b.p. 40-60°C) : ethyl acetate afforded (134) as colourless crystals (3.6 g, 100%); m.p. 125.4-125.8°C;

found: C, 58.11; H, 6.44; N, 7.85%. $C_{17}H_{22}N_2O_4S$ requires C, 58.27; H, 6.33; N, 7.99%;

υ_{max}/cm^{-1} (KBr disc) 1731 (ester C=O);

δ_H (250 MHz $CDCl_3$) 0.98 (3H, d, J = 6.08 Hz, ring-Me), 1.04 (1H, m, 2-CH), 1.44 (3H, m, 5-CH_β, 2-CH and 4-CH), 1.90 (5H, m, 6-CH_2, 1-CH_α, 3-CH and 4-CH), 2.13 (1H, ddd, J_{AX} = 3.14, $J_{AX'}$ = 5.89 and J_{AB} = 14.00 Hz, 5-CH_α), 2.66 (1H, m, 1-CH_β), 3.27 (1H, d, J = 2.16 Hz, 8-CH), 3.79 (3H, s, OMe), 5.88 (1H, m, 7-CH), 7.02 (1H, q, J = 0.85 Hz, Im-CH), 7.64 (1H, t, J = 2.96 Hz, Im-CH) and 8.35 (1H, t, J = 0.86 Hz, Im-CH);

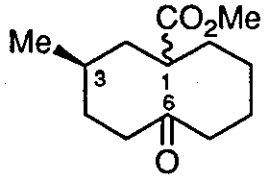
δ_C (62.9 MHz, $CDCl_3$) 21.44 (CH_3), 21.70 (CH_2), 25.13 (3-CH), 28.26 (CH_2), 28.70 (CH_2), 29.16 (CH_2), 40.60 (CH_2), 45.51 (4a-C), 52.25 ($CO_2\underline{Me}$), 58.44 (8-CH), 64.90 (8a-C), 79.92 (7-CH), 117.93 (Im-CH), 130.85 (Im-CH), 137.12 (Im-CH), 174.82 (C=S) and 183.68 ($\underline{C}O_2Me$);
m/z (C.I., ammonia) 351 (90%, MH^+), 223 (95, M^+ minus OCSIm) and 69 (100, Im).

Tributyltin hydride reduction of *methyl 8β,8aβ-epoxy-7β-(imidazol-1-yl (thiocarbonyl) oxy)-3β-methyl-octahydro-4aβ(2H)-naphthalenecarboxylate* (134).

(I) Normal addition.

Method as for general procedure.
All crude purified on flash silica, gradient elution, light petroleum (b.p. 40-60°C) to a 1:1 diethyl ether : light petroleum (b.p. 40-60°C). Two products isolated and recolumned on flash silica, listed from least polar to most polar:-

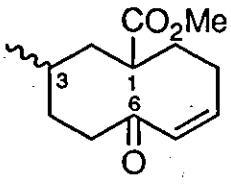
Methyl 3-methyl-6-oxocyclodecan-1-carboxylate (139).



(139)

Methyl 3-methyl-6-oxocyclodecan-1-carboxylate (139) was isolated as a clear and colourless liquid (22%);
υ_{max}/cm^{-1} (neat) 1735 (ester C=O) and 1702 (C=O);
δ_H (250 MHz $CDCl_3$) 0.86 (3H, d, J = 7.21 Hz, ring Me_α), 0.92 (3H, d, J = 7.21 Hz, ring Me_β), 1.05-2.80 (16H, m, 7 x CH_2 and 2 x CH) and 3.66 (3H, s, OMe). Further purification by preparative thin layer chromatography (3:1 light petroleum (b.p. 40-60°C) : ethyl acetate) afforded (139) as a single isomer;
υ_{max}/cm^{-1} (neat) 1735 (ester C=O) and 1702 (C=O);
δ_H (250 MHz $CDCl_3$) 0.92 (3H, d, J = 7.21 Hz, ring Me), 1.10-1.72 (9H, m, 4 x CH_2 and 3-CH), 2.02 (2H, m, CH_2), 2.77 (4H, m, 5- and 7-CH_2), 2.75 (1H, m, 1-CH) and 3.66 (3H, s, OMe);
δ_C (62.9 MHz, $CDCl_3$) 22.16 (CH_3), 22.74 (CH_2), 23.38 (CH_2), 30.35 (CH_2), 30.83 (CH_2), 30.92 (3-CH), 34.20 (CH_2), 40.32 (CH_2), 41.56 (CH_2), 42.09 (1-CH), 51.63 ($CO_2\underline{Me}$), 176.97 ($\underline{C}O_2Me$) and 214.26 (C=O);
m/z (C.I., ammonia) 244 (MNH_4^+, 55%), 227 (45, MH^+) and 149 (100, M^+ minus [CO_2Me and H_2O]).

Methyl 3-methyl-6-oxocyclodec-7-en-1-carboxylate (138).



(138)

Methyl 3-methyl-6-oxocyclodec-7-en-1-carboxylate (138) was isolated as a clear and colourless liquid (41%);
υ_{max}/cm^{-1} (neat) 1733 (ester C=O), 1687 (α,β-unsat C=O) and 1633 (C=C);
δ_H (250 MHz $CDCl_3$) 0.83 (3H, d, J = 7.15 Hz, ring Me_α), 0.96 (3H, d, J = 7.15 Hz, ring Me_β), 1.03-1.97 (7H, m, 3 x CH_2 and 3-CH), 2.08-2.80 (5H, m, 2 x CH_2 and 1-CH), 3.65 and 3.66 (1H, 2 x s, OMe), 5.78 (1H, 2 x t, J = 12.01 Hz, 8-CH) and 6.32 (1H, 2 x d, J = 12.01 Hz, 7-CH);
m/z (C.I., ammonia) 242 (MNH_4^+, 25%), 225 (60, MH^+) and 147 (100, M^+ minus (CO_2Me and H_2O)).

(II) Inverse addition.

Method as for general procedure.
All crude purified on flash silica, gradient elution, light petroleum (b.p. 40-60°C) to a 1:2 diethyl ether : light petroleum (b.p. 40-60°C). Two products isolated and recolumned on flash silica, listed from least polar to most polar:-

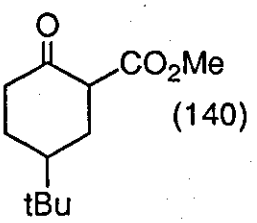
Methyl 3-methyl-6-oxocyclodecan-1-carboxylate (139).

Methyl 3-methyl-6-oxocyclodecan-1-carboxylate (139) was isolated as a clear and colourless liquid (41%). All spectroscopic data as for previously prepared (139).

Methyl 3-methyl-6-oxocyclodec-7-en-1-carboxylate (138).

Methyl 3-methyl-6-oxocyclodec-7-en-1-carboxylate (138) was isolated as a clear and colourless liquid (18%). All spectroscopic data as for previously prepared (138).

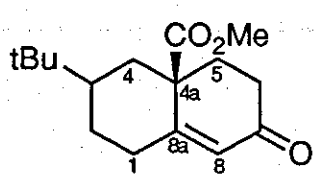
Preparation of *methyl 2-carboxylate-4-(t-butyl)-cyclohexan-1-one* (140).



(140)

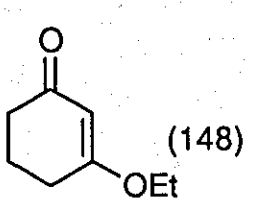
4-(t-Butyl)-cyclohexanone was treated with methylcarbonate as in the preparation of (129). Purification by vacuum distillation afforded (140) as a clear liquid (73%); b.p. (0.05 mmHg) 95°C;
υ_{max}/cm^{-1} (neat) 1745 (ester C=O), 1716 (C=O) and 1658 (C=O, enol tautomer);
δ_H (250 MHz $CDCl_3$) 0.82 (9H, s, t-Bu), 1.13 (1H, m, 4-CH), 1.69 (2H, m, 5-CH_2), 2.12-2.55 (5H, m, 2 x CH_2 and 2-CH) and 3.71 (3H, s, -CO_2Me);
δ_C (62.9 MHz, $CDCl_3$) 26.22 (3 x Me), 28.57 (4-CH), 28.46 (5-CH_2), 29.67 (3-CH_2), 30.68 (6-CH_2), 31.47 (C), 42.68 (2-CH), 51.22 (CO_2Me), 172.23 ($\underline{C}O_2$Me) and 215.12 (C=O).

Attempted preparation of *methyl 1,3,4,5,6,7-hexahydro-3-(t-butyl)-7-oxo-4aβ(2H)-naphthalenecarboxylate.*



Methyl 2-carboxylate-4-(t-butyl)-cyclohexan-1-one (140) was treated with methylvinylketone as in the preparation of (130). Purification of the crude liquid by flash chromatography (1:5 ethyl acetate : light petroleum (b.p. 40-60°C)) did not give any identifiable product.

Preparation of *3-ethoxy-2-cyclohexen-1-one* (148).



(148)

A solution of cyclohexan-1,3-dione (53 g, 470 mmol), p-toluenesulfonic acid (2.5 g) and anhydrous ethanol (300 cm^3) in anhydrous benzene (900 cm^3) was heated at reflux, on a Dean-Stark apparatus for 3 hours. After cooling, the solution was washed with a potassium hydroxide solution (10%) saturated with

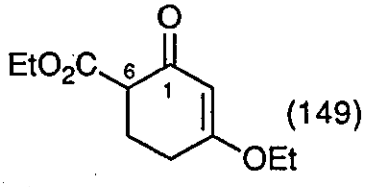
sodium chloride (x 3), water (x 3) and a saturated sodium chloride solution (x 2). After drying (magnesium sulfate), the solvent was evaporated to dryness affording (228) as an orange liquid. Distillation afforded (148) as a clear and colourless liquid (60 g, 90%); b.p. (0.4 mmHg) 60-64°C;

υ_{max}/cm^{-1} (neat) 1651 (α,β-unsaturated C=O) and 1604 (C=C of enol ether);

δ_H (250 MHz $CDCl_3$) 1.37 (3H, t, J = 7.01 Hz, $OCH_2C\underline{H}_3$), 1.98 (2H, quintet, J = 6.51 Hz, 5-CH_2), 2.34 (2H, t, J = 7.00 Hz, 6-CH_2), 2.40 (2H, t, J = 6.30 Hz, 4-CH_2), 3.91 (2H, q, J = 7.05 Hz, $O\underline{C}H_2CH_3$) and 5.35 (1H, s, 2-CH);

δ_C (62.9 MHz, $CDCl_3$) 14.15 ($OCH_2\underline{C}H_3$), 21.30 (5-CH_2), 29.10 (4-CH_2), 36.80 (6-CH_2), 64.17 ($O\underline{C}H_2CH_3$), 102.65 (2-CH), 177.85 (3-C) and 199.52 (C=O).

Preparation of *ethyl 6-carboxylate-3-ethoxy-2-cyclohexen-1-one* (149).



(149)

To a cooled (icebath), and stirred solution of diisopropylamine (8.5 cm^3, 60.6 mmol), in anhydrous THF (100 cm^3), a solution of n-butyllithium (10 M, 6.1 cm^3, 61.0 mmol) was added drop-wise. After 30 minutes, the solution was cooled to -78°C, and 3-ethoxy-2-cyclohexen-1-one (7.1 g, 50.5 mmol) in anhydrous THF (10 cm^3) was added over a 5 minute period. After stirring at 0°C for 45 minutes, D.M.P.U (6.1 cm^3, 50.5 mmol) was added, followed by ethyl cyanoformate (6.0 g, 60.6 mmol) in anhydrous THF (10 cm^3). After stirring at -78°C for 45 minutes, a saturated sodium hydrogen carbonate solution was added, and the solution extracted with diethyl ether (x 2). The extract was washed with a saturated sodium hydrogen carbonate solution (x 2), water, a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness give an orange solid. Recrystallisation from benzene afforded (149) as colourless crystals (6.1 g, 58%); m.p. 98.1-98.3°C;

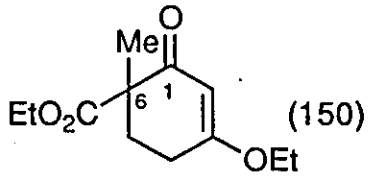
found: C, 62.34; H, 7.78 . $C_{11}H_{16}O_4$ requires C, 62.25; H, 7.60;

υ_{max}/cm^{-1} (KBr disc) 1730 (ester C=O), 1649 (α,β-unsaturated C=O) and 1606 (C=C of enol ether);

δ_H (250 MHz $CDCl_3$) 1.28 (3H, t, J = 7.10 Hz, $OCH_2C\underline{H}_3$), 1.37 (3H, t, J = 7.01 Hz, $CO_2CH_2C\underline{H}_3$), 2.34 (4H, m, 4-CH_2 and 5-CH_2), 3.32 (1H, dd, J_{AX} = 5.30 and J_{BX} = 8.95 Hz, 6-CH), 3.91 (2H, q, J = 7.05 Hz, $OC\underline{H}_2CH_3$), 4.21 (2H, q, J = 7.13 Hz, $CO_2C\underline{H}_2CH_3$) and 5.38 (1H, s, 2-CH);

δ_C (62.9 MHz, $CDCl_3$) 14.10 (CH_3), 14.17 (CH_3), 24.16 (5-CH_2), 27.36 (4-CH_2), 52.31 (6-CH), 61.19 ($O\underline{C}H_2CH_3$), 64.53 ($CO_2\underline{C}H_2CH_3$), 102.08 (2-CH), 170.40 (CO_2), 177.60 (3-C) and 199.50 (C=O);
m/z (C.I., ammonia) 213 (MH^+, 100%).

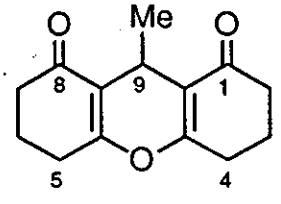
Preparation of *ethyl 6-carboxylate-3-ethoxy-6-methyl-2-cyclohexen-1-one* (150).



(150)

Ethyl 6-carboxylate-3-ethoxy-2-cyclohexen-1-one was treated with methyl iodide, as in the preparation of (149). Ethyl 6-carboxylate-3-ethoxy-6-methyl-2-cyclohexen-1-one (150), was isolated as an orange liquid (95%);
υ_{max}/cm^{-1} (KBr disc) 1731 (ester C=O), 1668 (α,β-unsaturated C=O) and 1607 (C=C of enol ether);
δ_H (250 MHz $CDCl_3$) 1.12 (3H, t, *J* = 7.11 Hz, $OCH_2C\underline{H}_3$), 1.37 (6H, m, ring Me and $CO_2CH_2C\underline{H}_3$), 2.38 (4H, m, 4-CH_2 and 5-CH_2), 3.91 (2H, q, *J* = 7.05 Hz, $OC\underline{H}_2CH_3$), 4.21 (2H, q, *J* = 7.21 Hz, $CO_2C\underline{H}_2CH_3$) and 5.28 (1H, s, 2-CH);
δ_C (62.9 MHz, $CDCl_3$) 13.83 (CH_3), 13.87 (CH_3), 20.27 (ring CH_3), 26.20 (5-CH_2), 31.46 (4-CH_2), 52.00 (6-C), 60.92 ($O\underline{C}H_2CH_3$), 64.16 ($CO_2\underline{C}H_2CH_3$), 101.37 (2-CH), 172.61 (CO_2), 176.31 (3-C) and 196.59 (C=O);

Preparation of *hexahydro-9-methyl-1H-xanthene-1,8(2H)-dione* (155).



(155)

To a stirred solution of magnesium (activated with iodine) (1.45 g, 60.0 mmol) in anhydrous THF (8 cm^3), bromomethyl-1,3-dioxolane (3.1 cm^3, 30 mmol) was added, maintaining the temperature below 30°C. After the addition was completed, the solution was diluted with anhydrous THF (5 cm^3) and cooled to 0°C. 3-Ethoxy-2-cyclohexen-1-one (3.5 g, 25.0 mmol) in anhydrous THF (10 cm^3) was then added drop-wise, with the resulting mixture being stirred at room temperature for 3 hours. Hydrochloric acid (2 M, 60 cm^3) was then added and the solution extracted with diethyl ether (x 2). The extracts were washed with hydrochloric acid (2 M) (x 2), a saturated sodium chloride solution, dried

(magnesium sulfate) and evaporated to dryness giving a viscous yellow liquid. Purification by flash chromatography (1:1 light petroleum (b.p. 40-60°C) : diethyl ether), followed by recrystallisation from 2:1 light petroleum (b.p. 40-60°C) : dichloromethane afforded (155) as colourless crystals (2.0 g, 35%); m.p. 105.8°C [lit.[115] m.p. 104.5°C];

found: C, 72.40; H, 6.91. $C_{14}H_{16}O_3$ requires C, 72.40; H, 6.94;

υ_{max}/cm^{-1} (KBr disc) 1678 (α,β-unsaturated C=O) and 1663 (C=C of enol ether);

δ_H (250 MHz $CDCl_3$) 1.05 (3H, d, J = 6.53 Hz, CH_3), 2.02 (4H, m, 3 and 6-CH_2), 2.26-2.54 (8H, m, 4 x CH_2) and 3.62 (1H, q, J = 6.50 Hz, 9-CH);

δ_C (62.9 MHz, $CDCl_3$) 20.45 (3 and 6-CH_2), 20.88 (9-CH), 22.15 (CH_3), 27.05 (2 and 7-CH_2), 37.53 (4 and 5-CH_2), 117.83 (C), 164.49 (C) and 197.34 (2 x C=O);

m/z (E.I.) 232 (M^+, 10%) and 217 (100, M^+ minus Me).

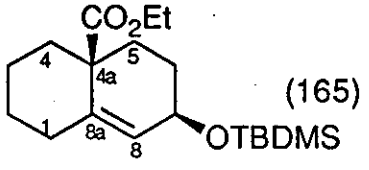
Structure confirmed by X-ray analysis:-

Crystallographic data: Unit cell volume; 2415.32 Å.
Nº of formulaunits per unit cell; 8.
Calculated density; 1.277 ccm^{-1}.

Data collection: Stöe Stadi-2 Weissenberg diffractometer using MoK_α radiation (λ = 0.71069 Å). Temperature 293 K. Range of h, k and l; h 16 to 15, k 0 to 9 and l 0 to 20. 4362 Reflections were measured, of which 4240 were unique and 2915 were classified as 'observed' ($F/\sigma[F]>6$).

Structure solution and refinement: The structure was solved by direct methods (EEES) and all hydrogen atoms except 1 were located by difference maps. The non-hydrogen atoms were resolved anisotropically and one hydrogen atom isotropically. The final conventional R was 0.0788 for the 2915 'observed' reflections.

Preparation of *ethyl 7β-(tert-butyldimethylsilyloxy)-1,3,4,5,6,7-hexahydro-4aβ(2H)-naphthalenecarboxylate* (165).

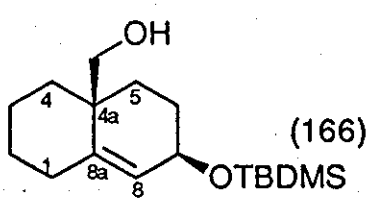


(165)

To a stirred solution of ethyl 1,3,4,5,6,7-hexahydro-7β-hydroxy-4aβ(2*H*)-naphthalenecarboxylate (7.0 g, 31.3 mmol) and imidazole (2.6 g, 38 mmol) in anhydrous *N,N*-dimethylformamide (80 cm^3), *tert*-butlydimethylsilyl chloride (5.7 g, 37.6 mmol) in anhydrous *N,N*-dimethylformamide (20 cm^3) was added in one portion. After stirring at room temperature for 24 hours the solution was diluted with diethyl ether (200 cm^3), washed with water (x 3) and a saturated sodium chloride solution. After drying (magnesium sulfate), the solvent was evaporated

affording a clear liquid. Purification by dry flash chromatography (1:1 toluene : light petroleum (b.p. 40-60°C)) afforded (165) as a clear and colourless liquid (10.5 g, 97%);
found: C, 67.23; H, 10.14 . $C_{19}H_{34}O_3Si$ requires C, 67.41; H, 10.12;
υ_{max}/cm^{-1} (neat) 1724 (ester C=O);
δ_H (250 MHz $CDCl_3$) 0.04 (3H, s, Si-Me), 0.06 (3H, s, Si-Me), 0.89 (9H, s, t-Bu), 1.08-1.77 (8H, m, 4 x CH_2), 1.26 (3H, t, J = 7.09 Hz, $CO_2CH_2C\underline{H}_3$), 2.10-2.30 (4H, m, 2 x CH_2), 4.17 (2H, q, J = 7.09 Hz, $CO_2C\underline{H}_2CH_3$), 4.22 (1H, m, 7-CH) and 5.46 (1H, s, 8-CH);
δ_C (62.9 MHz, $CDCl_3$) -4.41 ($Si\underline{Me}_2$), 14.34 ($CO_2CH_2\underline{C}H_3$), 18.00 (C), 23.86 (CH_2), 26.00 (3 x Me), 27.69 (CH_2), 29.50 (CH_2), 33.93 (CH_2), 34.23 (CH_2), 38.88 (CH_2), 48.15 (4a-C), 60.58 ($CO_2\underline{C}H_2CH_3$), 68.37 (7-CH), 127.72 (8-CH), 139.33 (8a-C) and 175.50 (CO_2).

Preparation of *7β-(tert-butyldimethylsilyloxy)-4aβ-(hydroxymethyl)-1,2,3,4,4a,5,6,7-octahydro-naphthalene* (166).

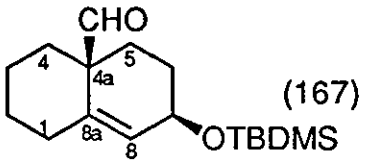


(166)

To a stirred solution of lithium aluminium hydride (790 mg, 20.7 mmol) in anhydrous tetrahydrofuran (100 cm^3), ethyl 7β-(*tert*-butyldimethylsilyloxy)-1,3,4,5,6,7-hexahydro-4aβ(2*H*)-naphthalenecarboxylate (7.0 g, 20.7 mmol) in anhydrous tetrahydrofuran (20 cm^3) was added over a 10 minute period. After stirring at room temperature for 16 hours, the following were carefully added; (I) water (0.8 cm^3), (II) aqueous sodium hydroxide solution (15%, 0.8 cm^3) and (III) water (2.4 cm^3). The resulting mixture was filtered through high-flow, dried (magnesium sulfate) and evaporated to dryness. The resulting clear liquid (5.8 g, 95%) was noted to crystallise on standing in the fridge. Successive recrystallisations from 1:2 ethyl acetate : light petroleum (b.p. 40-60°C) afforded (166) as colourless crystals; m.p. 59.8-60.1°C;
υ_{max}/cm^{-1} (KBr disc) 3356 (OH) and 1652 (C=C);
δ_H (250 MHz $CDCl_3$) 0.05 (3H, s, Si-Me), 0.07 (3H, s, Si-Me), 0.82 (9H, s, t-Bu), 1.06-2.03 (13H, m, OH and 6 x CH_2), 3.57 (2H, m, $C\underline{H}_2OH$), 4.14 (1H, m, 7-CH) and 5.38 (1H, s, 8-CH);
δ_C (62.9 MHz, $CDCl_3$) -4.55 ($Si\underline{Me}_2$), 18.32 (C), 22.13 (CH_2), 26.00 (3 x Me), 28.08 (CH_2), 28.91 (CH_2), 31.21 (CH_2), 32.51 (CH_2), 35.91 (CH_2), 39.96 (4a-C), 63.90 ($\underline{C}H_2OH$), 68.09 (7-CH), 128.05 (8-CH) and 141.87 (8a-C);

m/z (E.I.) 297.225 (MH^+, 1%, $C_{17}H_{33}O_2Si$ requires 297.225).

Preparation of *7β-(tert-butyldimethylsilyloxy)-1,3,4,5,6,7-hexahydro-4aβ(2H)-naphthalenecarbaldehyde* (167).



(167)

(I) Pyridinium chlorochromate oxidation of *7β-(tert-butyldimethylsilyloxy)-4aβ-(hydroxymethyl)-1,2,3,4,4a,5,6,7-octahydro-naphthalene.*

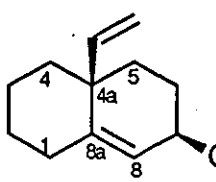
To a stirred solution of 7β-(*tert*-butyldimethylsilyloxy)-4aβ-(hydroxymethyl)-1,2,3,4,4a,5,6,7-octahydro-naphthalene (2.6 g, 8.9 mmol) and celite (~3 g) in anhydrous dichloromethane (70 cm^3), pyridinium chlorochromate (2.9 g, 13 mmol) was added in one portion. After stirring at room temperature for 3 hours, diethyl ether (100 cm^3) was added and the resulting solution filtered through a bed of celite. The resulting solution was washed with hydrochloric acid (2 M) (x 3), a saturated sodium hydrogen carbonate solution (x 4), a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a viscous brown liquid. Purification by chromatography on basic alumina, grade 3, (1:20 diethyl ether : light petroleum (b.p. 40-60°C)) afforded (167) as a colourless liquid (2.1 g, 82%);
υ_{max}/cm^{-1} (neat) 2680 (H-C=O), 1724 (C=O) and 1660 (C=C);
δ_H (250 MHz $CDCl_3$) 0.05 (3H, s, Si-Me), 0.07 (3H, s, Si-Me), 0.90 (9H, s, t-Bu), 1.06-2.03 (12H, m, 6 x CH_2), 4.22 (1H, m, 7-CH), 5.62 (1H, s, 8-CH) and 9.55 (1H, s, CHO);
δ_C (62.9 MHz, $CDCl_3$) -4.50 ($SiMe_2$), 18.32 (C), 23.40 (CH_2), 25.93 (3 x Me), 27.44 (CH_2), 29.08 (CH_2), 30.55 (CH_2), 33.53 (CH_2), 35.64 (CH_2), 51.62 (4a-C), 67.80 (7-CH), 129.55 (8-CH), 137.62 (8a-C) and 204.57 (CHO);
m/z (E.I.) 294.202 (M^+, 1%, $C_{17}H_{30}O_2Si$ requires 294.201).

(II) Swern oxidation of *7β-(tert-butyldimethylsilyloxy)-4aβ-(hydroxymethyl)-1,2,3,4,4a,5,6,7-octahydro-naphthalene.*

To a stirred solution of 7β-(*tert*-butyldimethylsilyloxy)-4aβ-(hydroxymethyl)-1,2,3,4,4a,5,6,7-octahydro-naphthalene (255 mg, 0.82 mmol) and triethylamine (1 cm^3, 7.3 mmol) in anhydrous dimethylsulfoxide (2 cm^3), pyridinium sulfurtrioxide complex (410 mg, 2.46 mmol), in anhydrous dimethylsulfoxide (2 cm^3), was added over 10 minutes. After stirring at room

temperature for 3.5 hours, the solution was diluted with ethyl acetate (50 cm^3), washed with hydrochloric acid (2 M), a saturated sodium hydrogen carbonate solution, a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a colourless liquid. Purification by chromatography on basic alumina, grade 3, (1:20 diethyl ether : light petroleum (b.p. 40-60°C)) afforded (167) as a colourless liquid (225 mg, 93%). All spectroscopic data were the same as for previously prepared (167).

Preparation of *7β-(tert-butyldimethylsilyloxy)-1,2,3,4,4a,5,6,7-octahydro-4aβ-vinyl-naphthalene* (168).



(168)

To a stirred solution of methyl triphenylphosphonium bromide (910 mg, 2.5 mmol) in anhydrous diethyl ether (30 cm^3) at room temperature, a solution of n-butyllithium (2.5 M, 1.0 cm^3, 2.5 mmol) was added drop-wise. After stirring at room temperature for 4 hours, 7β-(*tert*-butyldimethylsilyloxy)-1,3,4,5,6,7-hexahydro-4aβ(2*H*)-naphthalenecarbaldehyde (500 mg, 1.7 mmol), in anhydrous diethyl ether (10 cm^3), was added drop-wise to the bright yellow mixture. The viscous solution was then heated at reflux for 16 hours, cooled, filtered through a bed of celite and the filtrate washed with water (x 4) and a saturated sodium chloride solution. After drying (magnesium sulfate), the solution was evaporated to dryness giving a cloudy yellow liquid. Purification by flash chromatography (20:1 light petroleum (b.p. 40-60°C) : diethyl ether) afforded (168) as a clear and colourless liquid (470 mg, 95%);

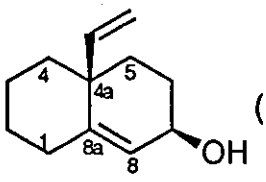
υ_{max}/cm^{-1} (neat) 1663 (cyclic C=C) and 1635 (*exo*-cyclic C=C);

δ_H (250 MHz $CDCl_3$) 0.08 (3H, s, Si-Me), 0.09 (3H, s, Si-Me), 0.90 (9H, s, t-Bu), 1.06-1.75 (10H, m, 5 x CH_2), 2.12 (2H, m, CH_2), 4.24 (1H, m, 7-CH), 4.99 (1H, dd, J_{gem} = 1.66 and J_{trans} = 17.47 Hz, -CH=C$\underline{H}_{trans}$), 5.18 (1H, dd, J_{gem} = 1.66 and J_{cis} = 10.53 Hz, -CH=C$\underline{H}_{cis}$), 5.44 (1H, d, J = 1.40 Hz, 8-CH) and 5.59 (1H, dd, J_{cis} = 10.54 and J_{trans} = 17.43 Hz, -C$\underline{H}$=CH_2);

δ_C (62.9 MHz, $CDCl_3$) -4.41 (Si$\underline{Me}_2$), 18.32 (C), 22.99 (CH_2), 26.05 (3 x Me), 27.88 (CH_2), 28.36 (CH_2), 32.56 (CH_2), 35.73 (CH_2), 41.70 (CH_2), 42.89 (4a-C), 69.00 (7-CH), 116.17 (CH=$\underline{C}H_2$), 127.97 (8-CH), 140.99 (8a-C) and 1.44.42 ($\underline{C}$H=CH_2);

m/z (C.I., ammonia) 292.222 (M^+, 10%, $C_{18}H_{32}OSi$ requires 292.222) and 161 (100, M^+ minus $OSiMe_2Bu^t$).

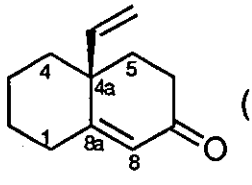
Preparation of *7β-hydroxy-1,2,3,4,4a,5,6,7-octahydro-4aβ-vinyl-naphthalene* (169).



(169)

To a stirred solution of 7β-(*tert*-butyldimethylsilyloxy)-1,2,3,4,4a,5,6,7-octahydro-4aβ-vinyl-naphthalene (1.0 g, 3.42 mmol) in tetrahydrofuran (25 cm^3), a solution of *tetra*-butylammonium fluoride (1.0 M, 10.2 cm^3, 10.2 mmol) was added in one portion. After stirring at room temperature for 16 hours, the solution was diluted with diethyl ether (100 cm^3) and washed with hydrochloric acid (2 M) and a saturated sodium chloride solution. After drying (magnesium sulfate), the solvent was evaporated to give a viscous yellow liquid. Purification by flash chromatography (6:1 light petroleum (b.p. 40-60°C) : ethyl acetate) afforded (169) as a clear viscous liquid (500 mg, 82%);
υ_{max}/cm^{-1} (neat) 3326 (OH), 1662 (cyclic C=C) and 1635 (*exo*-cyclic C=C);
δ_H (250 MHz $CDCl_3$) 1.20-2.22 (13H, m, OH and 6 x CH_2), 4.20 (1H, m, 7-CH), 4.90 (1H, dd, J_{gem} = 1.72 and J_{trans} = 17.40 Hz, -CH=C$\underline{H}_{trans}$), 5.20 (1H, dd, J_{gem} = 1.69 and J_{cis} = 10.50 Hz, -CH=C$\underline{H}_{cis}$), 5.58 (1H, d, J = 1.40 Hz, 8-CH) and 5.59 (1H, dd, J_{cis} = 10.46 and J_{trans} = 17.40 Hz, -C$\underline{H}$=CH_2);
δ_C (62.9 MHz, $CDCl_3$) 22.93 (CH_2), 27.78 (CH_2), 28.22 (CH_2), 32.54 (CH_2), 35.31 (CH_2), 41.57 (CH_2), 43.13 (4a-C), 68.12 (7-CH), 116.26 (CH=$\underline{C}H_2$), 126.80 (8-CH), 142.46 (8a-C) and 144.45 ($\underline{C}$H=CH_2);
m/z (C.I., ammonia) 178.136 (M^+, 10%, $C_{12}H_{18}O$ requires 178.136) and 161 (100, M^+ minus OH).

Preparation of *1,2,3,4,4a,5,6,7-octahydro-7-oxo-4a-vinyl-naphthalene* (170).

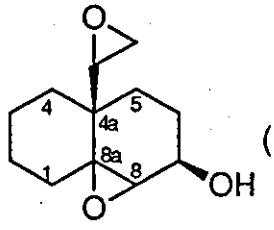


(170)

To a stirred solution of 7β-hydroxy-1,2,3,4,4a,5,6,7-octahydro-4aβ-vinyl-naphthalene (90 mg, 0.5 mmol) in anhydrous dichloromethane (5 cm^3) at -5°C, a solution of dimethyldioxirane (0.073 M, 15.2 cm^3, 1.1 mmol) in acetone was added in one portion. After stirring for 30 minutes the solvent was evaporated to give a light yellow liquid. Purification by flash chromatography (6:1 light petroleum (b.p. 40-60°C) : diethyl ether) afforded (170) as a clear, colourless liquid (56 mg, 55%);

υ_{max}/cm^{-1} (neat) 1674 (α,β-unsat C=O) and 1618 (C=C);
δ_H (250 MHz $CDCl_3$) 1.25-2.48 (12H, m, 6 x CH_2), 4.91 (1H, dd, J_{gem} = 0.93 and J_{trans} = 17.52 Hz, -CH=C<u>H</u>$_{trans}$), 5.28 (1H, dd, J_{gem} = 0.95 and J_{cis} = 10.51 Hz, -CH=C<u>H</u>$_{cis}$), 5.64 (1H, dd, J_{cis} = 10.51 and J_{trans} = 17.47 Hz, -C<u>H</u>=CH_2) and 5.94 (1H, s, 8-CH);
δ_C (62.9 MHz, $CDCl_3$) 22.35 (CH_2), 27.04 (CH_2), 32.98 (CH_2), 33.55 (CH_2), 35.84 (CH_2), 41.15 (CH_2), 44.09 (4a-C), 116.91 (CH=<u>C</u>H_2), 127.08 (8-CH), 141.15 (<u>C</u>H=CH_2), 166.24 (8a-C) and 199.98 (C=O);
m/z (E.I.) 176.120 (M^+, 50%, $C_{12}H_{16}O$ requires 176.120).

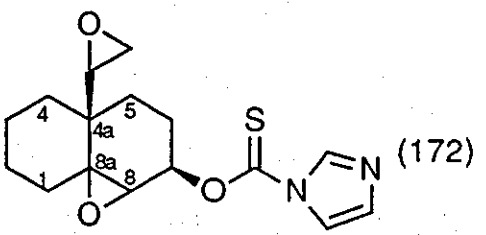
<u>Preparation of *decahydro-8,8a-epoxy-4aβ-(epoxyethane)-7β-hydroxy-naphthalene* (171).</u>



(171)

To a cooled (icebath) and stirred solution of 1,2,3,4,4a,5,6,7-octahydro-7-oxo-4a-vinyl-naphthalene (500 mg, 2.8 mmol) and sodium hydrogen carbonate (710 mg, 8.4 mmol) in anhydrous dichloromethane (60 cm^3), m-chloroperoxybenzoic acid (1.6 g, 8.4 mmol) was added in one portion. After stirring at room temperature for 65 hours, the solution was washed with a saturated sodium hydrogen carbonate solution (x 4), water, a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a colourless solid. Purification by flash chromatography (1:1 light petroleum (b.p. 40-60°C) : diethyl ether) afforded (171) as a clear viscous liquid (460 mg, 79%);
υ_{max}/cm^{-1} (neat) 3428 (OH);
δ_H (250 MHz $CDCl_3$) 0.95-2.20 (12H, m, 6 x CH_2), 2.38 (1H, br s, OH), 2.77 (2H, m, oxirane-CH_2), 3.03 (1H, m, oxirane-CH), 3.20 (1H, m, 8-CH) and 4.08 (1H, m, 7-CH);
δ_C (62.9 MHz, $CDCl_3$) less than 40 ppm very complex due to the existence of isomers; 43.15, 43.76 and 44.61 (oxirane-CH_2), 61.42, 62.83 and 64.00 (oxirane-CH), 64.05, 64.37, 64.86 and 65.19 (7-CH and 8-CH) and 65.23, 65.49 and 67.03 (8a-C);
m/z (C.I., ammonia) 228.160 (MNH_4^+, 75%, $C_{12}H_{22}O_3N$ requires 228.160) and 193 (100, M^+ minus OH).

Preparation of *decahydro-8,8a-epoxy-4aβ-(epoxyethane)-7β-(imidazol-1-yl (thiocarbonyl) oxy)-naphthalene* (172).



(172)

A stirred solution of decahydro-8,8a-epoxy-4aβ-(epoxyethane)-7β-hydroxy-naphthalene (310 mg, 1.47 mmol) and 1,1-thiocarbonyldiimidazole (580 mg, 2.95 mmol) in anhydrous dichloromethane (15 cm^3) was heated at gentle reflux for 2.5 hours. After cooling, the solution was washed with a saturated sodium hydrogen carbonate solution (x 3), water, a saturated ammonium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a viscous oil. Purification by flash chromatography (1:1 light petroleum (b.p. 40-60°C) : ethyl acetate) afforded (172) as a clear viscous liquid (368 mg, 78%);

υ_{max}/cm^{-1} (neat) 1531 (C=C);

δ_H (250 MHz $CDCl_3$) 0.95-2.10 (12H, m, 6 x CH_2), 2.60 (2H, m, oxirane-CH_2), 2.95 (1H, m, oxirane-CH), 3.20 (1H, m, 8-CH), 5.67 (1H, m, 7-CH), 6.90 (1H, s, Im-CH), 7.53 (1H, s, Im-CH) and 8.24 (1H, s, Im-CH);

δ_C (62.9 MHz, $CDCl_3$) less than 40 ppm very complex due to the existence of isomers; 43.40, 43.74 and 44.34 (oxirane-CH_2), 55.03 and 56.08 (8-CH), 57.55, 58.93 and 60.14 (oxirane-CH), 64.00, 64.30 and 65.47 (8a-C), 76.05, 78.00 and 78.23 (7-CH), 117.91 (Im-CH), 130.72 and 130.88 (Im-CH), 136.91 (Im-CH) and 182.55 and 183.03 (C=S);

m/z (C.I., ammonia) 321 (MH^+, 70%) and 69 (100, ImH^+).

Tributyltin hydride reduction of *decahydro-8,8a-epoxy-4aβ-(epoxyethane)-7β-(imidazol-1-yl (thiocarbonyl) oxy)-naphthalene* (172).

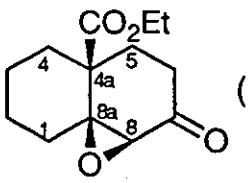
Normal addition.

Method as for general procedure.

The t.l.c. (1:1 diethyl ether : light petroleum (b.p. 40-60°C)) of the crude product showed it to be a complex mixture, with no major bands evident. Both flash chromatography, and preparative t.l.c., failed to yield any identifiable products.

Performing the reduction under the inverse mode of addition of tributyltin hydride, gave a similar result as the normal mode of addition.

Preparation of *ethyl 8β,8aβ-epoxy-octahydro-7-oxo-4aβ(2H)-naphthalene-carboxylate* (173).



(173)

To a stirred solution of ethyl 1,3,4,5,6,7-hexahydro-7-oxo-4a(2*H*)-naphthalenecarboxylate (2.0 g, 9.0 mmol) and aqueous hydrogen peroxide (30%, 2.7 cm^3, 27 mmol) in methanol (10 cm^3), a sodium hydroxide solution (6 M, 0.8 cm^3, 4.5 mmol) was added drop-wise, maintaining a temperature of 25°C. After stirring for 4.5 hours, water (50 cm^3) was added and the solution extracted with diethyl ether (3 x 50 cm^3). The extracts were washed with hydrochloric acid (2 M) (x 2), a saturated ammonium chloride solution, dried (magnesium sulfate) and evaporated to dryness affording a yellow crystalline solid (1.8 g). Purification by recrystallisation from 1:1 light petroleum (b.p. 40-60°C) : ethyl acetate (x 2) afforded (173) as colourless crystals (41%); m.p. 54.7-55.5°C (lit.[122] m.p. 47-49°C);

found: C, 65.52; H, 7.57%. $C_{13}H_{18}O_4$ requires C, 65.53; H, 7.61%;

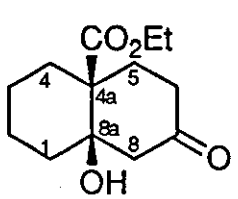
λ_{max} (EtOH)/nm 208.2 and 295.8;

υ_{max}/cm^{-1} (KBr disc) 1720 (ester and ketone C=O);

δ_H (250 MHz $CDCl_3$) 1.25 (3H, t, J = 7.10 Hz, Me), 1.25-1.75 (7H, m, 1-CH_α and 3 x CH_2), 2.04-2.37 (5H, m, 1-CH_β and 3-CH_2 and 2-CH_2), 3.22 (1H, s, 8-CH) and 4.23 (2H, q, J = 7.00 Hz, CO_2CH_2);

δ_C (62.9 MHz, $CDCl_3$) 14.17 (CH_3), 23.16 (CH_2), 23.27 (CH_2), 28.54 (CH_2), 31.36 (CH_2), 33.51 (CH_2), 34.21 (CH_2), 47.72 (4a-C), 61.25 ($CO_2\underline{C}H_2$), 63.16 (8-CH), 65.03 (8a-C), 173.45 (CO_2) and 204.80 (C=O).

Photolysis of *ethyl 8β,8aβ-epoxy-octahydro-7-oxo-4aβ(2H)-naphthalene-carboxylate* (173) in the presence of triethylamine.



(181)

A degased and stirred solution of ethyl 8β,8aβ-epoxy-octahydro-7-oxo-4aβ(2*H*)-naphthalenecarboxylate (150 mg, 0.63 mmol) and triethylamine (2.9 cm^3, 21 mmol) in anhydrous methanol (70 cm^3) was irradiated with a 100 W Hanovia ultraviolet lamp under an argon atmosphere. After 3.5 hours the solvent was

evaporated, and the resulting yellow oil extracted into diethyl ether (50 cm^3). The extract was washed with hydrochloric acid (2 M) (x 5), a saturated ammonium chloride solution, dried (magnesium sulfate) and evaporated to dryness affording a colourless crystalline solid (140 mg). Purification by flash chromatography (4:1 toluene : ethyl acetate), followed by recrystallisation from chloroform, gave (181) as colourless needles (55%); m.p. 142.8-143.1°C;
found: C, 64.83; H, 8.44. $C_{13}H_{20}O_4$ requires C, 64.98; H, 8.39%;
υ_{max}/cm^{-1} (KBr disc) 3513 (OH), 1716 (ester C=O) and 1713 (C=O);
δ_H (250 MHz $CDCl_3$) 1.20 (1H, m, 2-CH_α), 1.29 (3H, t, J = 7.10 Hz, Me), 1.38 (1H, m, 4-CH_β) 1.50-1.68 (3H, m, 3-CH_2 and 2-CH_β), 1.7 (1H, dt, J = 3.00 and 14.00 Hz, 1-CH_α), 1.94 (1H, dt, J = 14.00 and 3.00 Hz, 1-CH_β), 2.05-2.18 (3H, m, 5-CH_2 and 6-CH_β), 2.20 (1H, dd, J = 2.00 and 15.00 Hz, 8-CH_α), 2.33 (2H, m, 4-CH_α and 6-CH_α), 3.10 (1H, br s, OH), 3.42 (1H, d, J = 15.13 Hz, 8-CH_β) and 4.20 (2H, 2 x q, J = 7.10 Hz, CO_2CH_α and H_β);

The assigned structure was confirmed by n.O.e. difference spectroscopy.
δ_C (62.9 MHz, $CDCl_3$) 14.23 (CH_3), 20.32 (CH_2), 22.60 (CH_2), 31.13 (CH_2), 31.56 (CH_2), 35.06 (CH_2), 39.15 (CH_2), 51.04 (4a-C), 52.98 (8-CH_2), 60.68 ($CO_2\underline{C}H_2$), 74.68 (8a-C), 174.72 (CO_2) and 208.20 (C=O);
m/z (C.I., ammonia) 241.144 (MH^+, 95%, $C_{13}H_{21}O_4$ requires 241.144) and 223 (100, M^+ minus OH).

Tributyltin hydride reduction of *ethyl 8β,8aβ-epoxy-octahydro-7-oxo-4aβ(2H)-naphthalenecarboxylate* (173).

(I) Normal addition.

Method as for general procedure.
All crude purified on flash silica, gradient elution, light petroleum (b.p. 40-60°C) to 1:2 diethyl ether : light petroleum (b.p. 40-60°C). Three products were isolated, and recolumned on flash silica. Listed from least polar to most polar:-

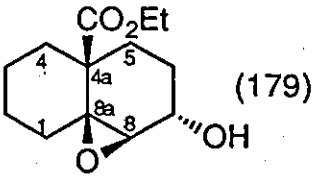
Ethyl 1,3,4,5,6,7-hexahydro-7-oxo-4a(2H)-naphthalenecarboxylate (115).

Ethyl 1,3,4,5,6,7-hexahydro-7-oxo-4a(2*H*)-naphthalenecarboxylate (115) was isolated as a clear liquid (23%). All spectroscopic data were the same as for the previously prepared (115).

Ethyl 8aβ-hydroxy-octahydro-7-oxo-4aβ(2H)-naphthalenecarboxylate (181).

Ethyl 8aβ-hydroxy-octahydro-7-oxo-4aβ(2*H*)-naphthalenecarboxylate (181) was isolated as a colourless crystalline solid (23%), m.p. 142-143°C, after recrystallisation from chloroform. All spectroscopic data were the same as for previously prepared (181).

Ethyl 8β,8aβ-epoxy-7α-hydroxy-octahydro-4aβ(2H)-naphthalenecarboxylate (179).



(179)

Ethyl 8β,8aβ-epoxy-7α-hydroxy-octahydro-4aβ(2*H*)-naphthalene-carboxylate (179) was isolated as a clear liquid (7%);
υ_{max}/cm^{-1} (neat) 3464 (OH) and 1720 (ester C=O);
δ_H (250 MHz $CDCl_3$) 1.30 (3H, t, J = 7.10 Hz, CH_3), 1.30-2.28 (13H, m, OH and 6 x CH_2), 3.08 (1H, s, 8-CH), 4.00 (1H, q, J = 8.10 Hz, 7-CH) and 4.27 (2H, q, J = 7.16 Hz, CO_2-CH_2);
δ_C (62.9 MHz, $CDCl_3$) 14.16 (CH_3), 23.13 (CH_2), 23.38 (CH_2), 27.61 (CH_2), 27.67 (CH_2), 31.49 (CH_2), 33.75 (CH_2), 48.44 (4a-C), 60.71 ($CO_2\underline{C}H_2$), 62.84 (8a-C), 63.84 (7-CH), 65.15 (8-CH) and 175.05 (CO_2);
m/z (C.I., ammonia) 241.144 (MH^+, 40%, $C_{13}H_{21}O_4$ requires 241.144), 258 (20, MNH_4^+) and 223 (100, M^+ minus OH).

(II) Inverse addition.

Method as for general procedure.
All crude purified on flash silica, gradient elution, light petroleum (b.p. 40-60°C) to a 1:2 diethyl ether : light petroleum (b.p. 40-60°C). Two products were isolated and recolumned on flash silica. Listed from least polar to most polar:-

Ethyl 1,3,4,5,6,7-hexahydro-7-oxo-4a(2H)-naphthalenecarboxylate (115).

Ethyl 1,3,4,5,6,7-hexahydro-7-oxo-4a(2*H*)-naphthalenecarboxylate (115) was isolated as a clear liquid (36%). All spectroscopic data were the same as for the previously prepared (115).

Ethyl 8aβ-hydroxy-octahydro-7-oxo-4aβ(2H)-naphthalenecarboxylate (181).

Ethyl 8aβ-hydroxy-octahydro-7-oxo-4aβ(2*H*)-naphthalenecarboxylate (181) was isolated as a colourless crystalline solid (25%), m.p. 142-143°C, after recrystallisation from chloroform. All spectroscopic data were the same as for previously prepared (181).

Samarium(II) iodide reduction of *ethyl 8β,8aβ-epoxy-octahydro-7-oxo-4aβ(2H)-naphthalenecarboxylate.*

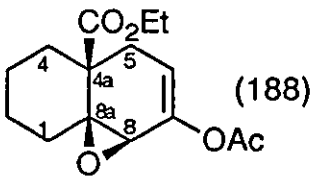
(1) In a protic solvent.

To a stirred solution of samarium(II) iodide (0.88 mmol) in anhydrous tetrahydrofuran (3 cm^3) at -90°C, a solution of ethyl 8β,8aβ-epoxy-octahydro-7-oxo-4aβ(2*H*)-naphthalenecarboxylate (100 mg, 0.42 mmol) and methanol (1 cm^3) in anhydrous tetrahydrofuran (1 cm^3) was added in one portion. After 5 minutes a saturated potassium carbonate solution was added and the solution warmed to room temperature. After extraction with diethyl ether, the extract was dried (magnesium sulfate) and evaporated to dryness affording a colourless solid (100 mg). Purification by flash chromatography (1:2 ethyl acetate : light petroleum (b.p. 40-60°C)), followed by recrystallisation from chloroform, gave (181) as colourless needles (30 mg, 36%); m.p. 142-143°C. All spectroscopic data were the same as for previously prepared (181).

(2) In anhydrous tetrahydrofuran.

To a stirred solution of ethyl 8β,8aβ-epoxy-octahydro-7-oxo-4aβ(2*H*)-naphthalenecarboxylate (120 mg, 0.5 mmol) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (1 cm^3) in anhydrous tetrahydrofuran (9 cm^3), a solution of samarium(II) iodide (0.1 M) was added at a rate of 2.5 cm^3 / hour. After the addition of 17 cm^3 of samarium(II) iodide, the green colouration remained, suggesting complete reduction of starting material. Extraction with diethyl ether, followed by washing with water, a saturated sodium chloride solution, drying (magnesium sulfate) and evaporation to dryness yielded a viscous oil. Analysis by t.l.c. showed this to be a complex, inseparable mixture.

Preparation of *ethyl 7-acetoxy-8β,8aβ-epoxy-1,3,4,5,8,8a-hexahydro-4aβ(2H)-naphthalenecarboxylate* (188).



(188)

To a cooled (icebath), and stirred solution of diisopropylamine (0.18 cm^3, 1.26 mmol) in anhydrous THF (3 cm^3), a solution of n-butyllithium (1.6 M, 0.78 cm^3, 1.26 mmol) was added drop-wise. After 30 minutes, the solution was cooled to -78°C, and ethyl 8β,8aβ-epoxy-octahydro-7-oxo-4aβ(2*H*)-naphthalene-carboxylate (250 mg, 1.05 mmol) in anhydrous THF (3 cm^3), was added over a 5 minute period. After stirring at -78°C for 30 minutes, acetic anhydride (0.2 cm^3) was added and the solution allowed to warm to room temperature. Water was then added and the solution extracted with diethyl ether (x 2). The extracts were washed with hydrochloric acid (0.5 M) (x 2), water, a saturated sodium hydrogen carbonate solution, a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a yellow liquid. Purification by flash chromatography (5:1 light petroleum (b.p. 40-60°C) : diethyl ether) afforded (188) as a clear liquid (370 mg, 96%);
υ_{max}/cm^{-1} (neat) 1761 (acetoxy C=O), 1725 (ester C=O) and 1680 (C=C);
δ_H (250 MHz $CDCl_3$) 1.24 (3H, t, J = 7.10 Hz, Me), 1.25-1.75 (7H, m, 1-CH_α and 3 x CH_2), 2.04-2.37 (5H, m, 1-CH_β and 2 x CH_2), 3.28 (1H, d, J = 2.69 Hz, 8-CH), 4.23 (2H, q, J = 7.00 Hz, CO_2CH_2) and 5.35 (1H, dt, J = 7.04 and 2.88 Hz, 6-CH);
δ_C (62.9 MHz, $CDCl_3$) 14.12 ($CO_2CH_2\underline{C}H_3$), 20.80 (CH_3), 22.93 (CH_2), 23.47 (CH_2), 31.14 (CH_2), 32.24 (CH_2), 34,87 (CH_2), 45.83 (4a-C), 57.74 (8-CH), 60.84 ($CO_2\underline{C}H_2$), 65.00 (8a-C), 111.32 (6-CH), 145.59 (7-CH), 169.02 (CO_2) and 173.97 (CO_2).

Reaction of *ethyl 7-acetoxy-8β,8aβ-epoxy-1,3,4,5,8,8a-hexahydro-4aβ(2H)-naphthalenecarboxylate* (188) with the phenylthio radical.

A stirred solution of ethyl 7-acetoxy-8β,8aβ-epoxy-1,3,4,5,8,8a-hexahydro-4aβ(2*H*)-naphthalenecarboxylate (130 mg, 0.46 mmol), diphenyl-disulfide (30 mg, 0.14 mmol) and A.I.B.N. (15 mg, 0.1 mmol) was irradiated with a 450 W, medium pressure Hg lamp for 6 hours. After this time, the diphenyl-disulfide was noted to disappear by t.l.c. analysis, and the solution was washed with hydrochloric acid (0.5 M) (x 2), water, a saturated sodium hydrogen carbonate solution, a saturated sodium chloride solution, dried (magnesium sulfate) and

evaporated to dryness affording (188) as a colourless liquid (119 mg, 92% recovery). All spectroscopic data were the same as for previously prepared (188).

Attempted epoxidations of *2-phenyl-2-pentenal* (199).

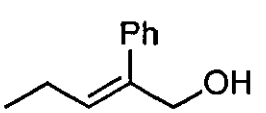
(1) Sodium tungstate catalysed epoxidation.

A vigorously stirred solution of 2-phenyl-2-pentenal (1.5 g, 9.36 mmol) and sodium tungstate (66 mg, 0.2 mmol) in a mixed solvent system of 9:1 water : ethanol (10 cm^3) was warmed to 50°C and had its pH adjusted to 4.5, with aqueous perchloric acid solution (15%) and aqueous triethylamine solution (15%). Aqueous hydrogen peroxide (30%, 1.7 cm^3, 15 mmol) was added in one portion, with the pH being maintained at 4.5 with aqueous triethylamine solution (15%). After stirring for 16 hours, the mixture was extracted with diethyl ether (2 x 40 cm^3), washed with hydrochloric acid (2 M) (x 2), a saturated sodium hydrogen carbonate solution (x 2), a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a yellow liquid (1.4 g). Spectra of this liquid correspond to that of 2-phenyl-2-pentenal.

(2) Alkaline hydrogen peroxide epoxidation.

To a stirred solution of 2-pheny-2-pentenal (1.5 g, 9.36 mmol) and aqueous hydrogen peroxide (30%, 3.2 cm^3, 28 mmol) in methanol (15 cm^3) at 15°C, a sodium hydroxide solution (6 M, 0.8 cm^3, 4.7 mmol) was added drop-wise. After stirring for 3 hours, the mixture was extracted with diethyl ether (60 cm^3), washed with hydrochloric acid (2 M) (x 2), a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a yellow liquid (1.2 g). Spectra of this liquid correspond to that of 2-phenyl-2-pentenal.

Preparation of *2-phenyl-2-pentenol* (201).

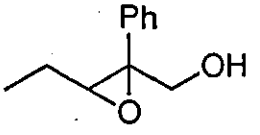


(201)

To a rapidly stirred and cooled (icebath) solution of 2-pheny-2-pentenal (5.0 g, 31 mmol) in 1:1 ethanol : water (20 cm^3), sodium borohydride (600 mg, 15 mmol) was added in one portion. After stirring at 0°C for 4 hours, water was added and the solution extracted with diethyl ether (x 3). The extracts were washed with water, a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness to give a yellow liquid. Purification by Kugelrohr distillation

afforded (201) as a clear and colourless liquid (4.8 g, 96%); b.p. (0.5 mmHg) 140°C;
υ_{max}/cm^{-1} (neat) 3364 (OH);
δ_H (250 MHz $CDCl_3$) 1.41 (3H, t, J = 7.48 Hz, 5-CH_3), 2.17 (1H, br s, OH), 2.47 (2H, quintet, J = 7.46 Hz, 4-CH_2), 4.77 (2H, s, 1-CH_2), 6.17 (1H, t, J = 7.39 Hz, 3-CH) and 7.70 (5H, m, -C_6H_5).

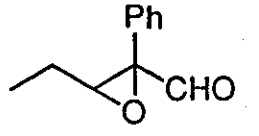
Preparation of *2,3-epoxy-2-phenylpentanol* (202).



(202)

To a stirred solution of racemic diethyl tartrate (950 mg, 4.5 mmol), titanium(IV) isopropoxide (870 mg, 3.0 mmol), powdered 4Å molecular sieves (0.3 g) and anhydrous *tert*-butylhydrogen peroxide (10 cm^3, 45 mmol) in anhydrous dichloromethane (75 cm^3) at -10°C, 2-phenyl-2-pentenol (4.7 g, 30 mmol) in anhydrous dichloromethane (5 cm^3) was added drop-wise. After stirring at 0°C for 4 hours, the solution was washed with hydrochloric acid (2 M) (x 4), a saturated sodium hydrogen carbonate solution (x 2), water, a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a yellow liquid. Purification by flash chromatography (4:1 light petroleum (b.p. 40-60°C) : ethyl acetate) afforded (202) as a clear liquid (4.35 g, 84%);
υ_{max}/cm^{-1} (neat) 3424 (OH) and 1604 (C=C);
δ_H (250 MHz $CDCl_3$) 0.90 (3H, t, J = 7.38 Hz, 5-CH_3), 1.13 (2H, octet, J = 7.32 Hz, 4-CH_2), 2.57 (1H, br s (D_2O exchange), OH), 3.34 (1H, t, J = 6.25 Hz, 3-CH), 3.93 (2H, s, 1-CH_2) and 7.33 (5H, m, -C_6H_5);
δ_C (62.9 MHz, $CDCl_3$) 10.04 (5-CH_3), 21.66 (4-CH_2), 62.39 (3-CH), 64.73 (1-CH_2), 66.34 (2-C), 127.00 (Ar-CH), 127.88 (Ar-CH), 128.34 (Ar-CH) and 136.09 (Ar-C).

Preparation of *2,3-epoxy-2-phenylpentanal* (200).



(200)

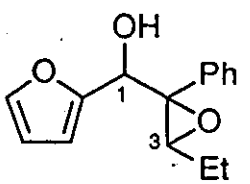
To a stirred solution of 2,3-epoxy-2-phenylpentanol (450 mg, 2.56 mmol) and triethylamine (2.3 g, 24 mmol) in anhydrous dimethylsulfoxide (5 cm^3), pyridinium sulfurtrioxide complex (1.27 g, 7.7 mmol), in anhydrous dimethylsulfoxide (6 cm^3) was added over 10 minutes. After stirring at room temperature for 45 minutes, the solution was diluted with ethyl acetate (50 cm^3)

and washed with hydrochloric acid (2 M), water (x 3), a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness to give a yellow liquid. Purification by chromatography on basic alumina, grade 3, (1:5 diethyl ether : light petroleum (b.p. 40-60°C)) afforded (200) as a colourless liquid (325 mg, 72%);

υ_{max}/cm^{-1} (neat) 1728 (C=O);

δ_H (250 MHz $CDCl_3$) 0.95 (3H, t, J = 7.54 Hz, 5-CH_3), 1.32 (2H, m, 4-CH_2), 3.39 (1H, t, J = 6.12 Hz, 3-CH), 7.40 (5H, m, -C_6H_5) and 9.21 (1H, s, 1-CH).

Preparation of *2,3-epoxy-1-(2-furyl)-2-phenylpentanol* (203).



(203)

To a stirred solution of anhydrous furan (0.74 cm^3, 10 mmol) in anhydrous diethyl ether (4 cm^3) at -78°C, a solution of n-butyllithium (1.6 M, 5.3 cm^3, 8.52 mmol) was added. This solution was heated to gentle reflux and maintained at such for 4 hours. After cooling to -78°C, 2,3-epoxy-2-phenyl-pentanal (1.5 g, 8.52 mmol) in anhydrous diethyl ether (3 cm^3) was added in one portion. The solution was then stirred at room temperature for 14 hours, diluted with diethyl ether (50 cm^3) and washed with a saturated ammonium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a viscous orange liquid (1.84 g). Purification by chromatography on basic alumina, grade 3, (1:10 diethyl ether : light petroleum (b.p. 40-60°C)), afforded (203) as a viscous liquid (980 mg, 51%);

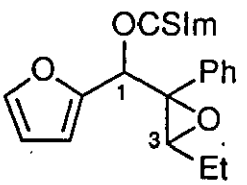
υ_{max}/cm^{-1} (neat) 3448 (OH);

δ_H (250 MHz $CDCl_3$) 0.89 (3H, q, J = 7.25 Hz, 5-CH_3), 1.21 (2H, m, 4-CH_2), 2.48 (0.5H, d (D_2O exchange), J = 9.15 Hz, -OH_α), 2.86 (0.5H, d (D_2O exchange), J = 1.88 Hz, -OH_β), 3.56 (1H, 2 x t, J = 6.22 Hz, 3-CH), 4.87 (0.5H, d (s on D_2O exchange), J = 1.88 Hz, 1-CH_α), 5.00 (0.5H, d (s on D_2O exchange), J = 9.15 Hz, 1-CH_β), 6.10 (0.5H, m, 3-CH_α[furan]), 6.22 (0.5H, m, 4-CH_α[furan]), 6.27 (0.5H, m, 3-CH_β[furan]), 6.36 (0.5H, m, 4-CH_β[furan]), 7.14 (5H, m, -C_6H_5), 7.30 (0.5H, m, 5-CH_α[furan]) and 7.45 (0.5H, m, 5-CH_β[furan]);

δ_C (62.9 MHz, $CDCl_3$) 10.01 (5-CH_3), 21.85 and 22.09 (4-CH_2), 61.92 and 62.28 (3-CH), 66.00 and 66.90 (2-C), 69.03 and 70.14 (1-CH), 107.76 and 110.11 (3-CH[furan]), 110.28 and 110.53 (4-CH[furan]), 127.24 and 127.33 (Ar-CH), 127.68 and 127.70 (Ar-CH), 127.91 and 127.96 (Ar-CH),134.92 and 135.03 (Ar-C),141.92 and 142.65 (3-CH[furan]), 151.80 and 152.32 (2-C[furan]);

m/z (C.I., ammonia) 262.1443 (MNH_4^+, 10%, $C_{15}H_{20}O_3N$ requires 262.1443), 227 (100, M^+ minus OH).

Preparation of *2,3-epoxy-1-(2-furyl)-1-(imidazol-1-yl (thiocarbonyl) oxy)-2-phenyl-pentane* (204).

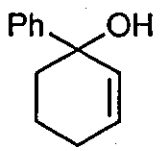


(204)

A stirred solution of 2,3-epoxy-1-(2-furyl)-2-phenylpentanol (950 mg, 3.17 mmol) and 1,1-thiocarbonyldiimidazole (690 mg, 3.5 mmol) in anhydrous dichloromethane (50 cm^3), was heated at gentle reflux for 3.0 hours. After cooling, the solution was washed with a saturated sodium hydrogen carbonate solution (x 3), water, a saturated ammonium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a viscous orange liquid. Attempts at purification by chromatography on basic alumina, and by distillation, failed to produce any identifiable products. Reaction repeated by stirring reactants at room temperature, but again a complex, intractable mixture was formed.

7.3. Experimental for **Chapter 6.**

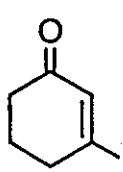
Preparation of *1-phenyl-2-cyclohexen-1-ol* (211).



(211)

To a stirred solution of 2-cyclohexen-1-one (10 g, 104 mmol) in anhydrous tetrahydrofuran (40 cm^3) at -78°C, a solution of phenyllithium (1.8 M, 70 cm^3, 120 mmol) was added over 10 minutes. The resulting clear brown liquid was warmed to room temperature and left at such for 16 hours. After the careful addition of water, followed by extraction with diethyl ether (3 x 40 cm^3), the extracts were washed with a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness affording (211) as a clear orange liquid (17.5 g, 97%);
υ_{max}/cm^{-1} (neat) 3400 (OH), 1600 (C=C) and 1490 (aromatic C=C).

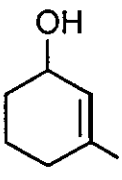
Preparation of *3-phenyl-2-cyclohexen-1-one* (213).



(213)

To a vigorously stirred solution of pyridinium chlorochromate (5.0 g, 23 mmol) in anhydrous dichloromethane (40 cm^3) at room temperature, 1-phenyl-2-cyclohexen-1-ol (2.0 g, 11.5 mmol) was added in one portion. After 4 hours, diethyl ether (40 cm^3) was added and the resulting black mixture filtered through celite. The filtrate was washed with a sodium hydroxide solution (2 M), hydrochloric acid (2 M) , a saturated sodium hydrogen carbonate solution, a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness affording a viscous yellow liquid (1.8 g). Purification by flash chromatography (1:3 diethyl ether : light petroleum (b.p. 40-60°C)) yielded (213) as a clear viscous yellow liquid (1.4 g, 71%);
υ_{max}/cm^{-1} (neat) 1665 (α,β-unsaturated C=O), 1603 (C=C), 1572 and 1493 (aromatic C=C).

Preparation of *3-phenyl-2-cyclohexen-1-ol* (215).



(215)

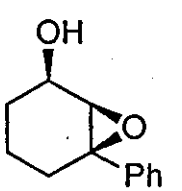
To a rapidly stirred and cooled (ice-bath) solution of 3-phenyl-2-cyclohexen-1-one (2.5 g, 14.5 mmol) and cerium(III) chloride heptahydrate (5.4 g, 14.5 mmol) in anhydrous methanol (30 cm^3), sodium borohydride (550 mg, 14.5 mmol) was added in one portion. After stirring at 0°C for 2 hours, water was added and the solution extracted with diethyl ether (x 3). The extracts were washed with water, a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness affording (215) as a viscous light yellow liquid (2.6 g, 98%);

υ_{max}/cm^{-1} (neat) 3312 (OH), 1596 (C=C), 1492 (aromatic C=C), 908 and 696 (mono-substituted phenyl);

δ_H (250 MHz $CDCl_3$) 1.61 (1H, s, OH), 1.67 (2H, m, 5-CH_2), 1.90 (2H, m, 6-CH_2), 2.42 (2H, m, 4-CH_2), 4.38 (1H, m, 1-CH), 6.11 (1H, m, 2-CH) and 7.35 (5H, m, -C_6H_5);

δ_C (62.9 MHz, $CDCl_3$) 19.47 (5-CH_2), 27.53 (6-CH_2), 31.70 (4-CH_2), 66.34 (1-CH), 125.40 (CH), 126.60 (CH), 127.44 (CH), 128.31 (CH), 140.15 (C) and 141.38 (C).

Preparation of *2,3-epoxy-3-phenylcyclohexan-1-ol* (217).



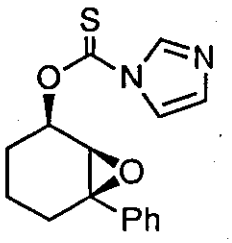
(217)

To a cooled (ice-bath) and stirred solution of 3-phenyl-2-cyclohexen-1-ol (1.0 g, 5.7 mmol) and sodium hydrogen carbonate (720 mg, 8.6 mmol) in anhydrous dichloromethane (40 cm^3), m-chloroperoxybenzoic acid (1.5 g, 8.6 mmol) was added in one portion. After stirring at room temperature for 5 minutes, the solution was washed with a saturated sodium hydrogen carbonate solution (x 4), water, a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a clear yellow liquid. Purification by flash chromatography (1.5:1 light petroleum (b.p. 40-60°C) : diethyl ether) afforded (217) as a clear and colourless liquid (593 mg, 56%);

υ_{max}/cm^{-1} (neat) 3400 (OH), 1492 (aromatic C=C), 906 and 700 (mono-substituted phenyl);

δ_H (250 MHz $CDCl_3$) 1.61 (4H, m, 2 x CH_2), 2.20 (3H, m, CH_2 and OH), 3.28 (1H, d, J = 3.49 Hz, 2-CH), 4.10 (1H, m, 1-CH) and 7.34 (5H, m, -C_6H_5).

Preparation of *2,3-epoxy-1-(imidazol-1-yl (thiocarbonyl) oxy)-3-phenyl-cyclohexane* (219).



(219)

A stirred solution of 2,3-epoxy-3-phenylcyclohexan-1-ol (575 mg, 3.0 mmol) and 1,1-thiocarbonyldiimidazole (1.0 g, 6.0 mmol) in anhydrous dichloromethane (40 cm^3) was heated at gentle reflux for 18 hours. After cooling, the solution was washed with a saturated sodium hydrogen carbonate solution (x 3), water, a saturated ammonium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a viscous orange liquid. Purification by flash chromatography (1:1 light petroleum (b.p. 40-60°C) : diethyl ether) afforded (219) as a colourless solid (720 mg, 80%);

υ_{max}/cm^{-1} (KBr disc) 1530 (aromatic C=C);

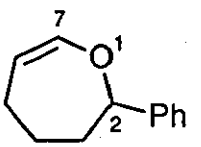
δ_H (250 MHz $CDCl_3$) 1.61 (2H, m, 5-CH_2), 1.94 (2H, m, 6-CH_2), 2.14 (1H, m, 4-CH_α), 2.36 (1H, m, 4-CH_β), 3.47 (1H, d, J = 2.66 Hz, 2-CH), 6.00 (1H, dt, J = 2.72 and 6.60 Hz, 1-CH), 7.06 (1H, s, Im-CH), 7.36 (5H, m, -C_6H_5), 7.70 (1H, s, Im-CH) and 8.40 (1H, s, Im-CH);

δ_C (62.9 MHz, $CDCl_3$) 18.89 (CH_2), 24.81 (CH_2), 27.68 (CH_2), 60.30 (2-CH), 63.25 (3-C), 79.23 (1-CH), 118.18 (Im-CH), 125.35 (Ar-CH), 127.96 (Ar-CH), 128.55 (Ar-CH), 130.85 (Im-CH), 137.12 (Im-CH), 140.37 (Ar-C) and 183.69 (C=S);

m/z (C.I., ammonia) 301.1011 (MH^+, 50%, $C_{16}H_{17}O_2N_2S$ requires 301.1011), 173 (100, M^+ minus OCSIm) and 69 (65, Im).

Tributyltin hydride reduction of *2,3-epoxy-1-(imidazol-1-yl (thiocarbonyl) oxy)-3-phenylcyclohexane.*

(I) Normal addition.



(226)

Method as for general procedure.

All material purified by column chromatography on aluminum oxide, activated, basic, Brockmann grade 3, (light petroleum (b.p. 40-60°C)), yielding the 2-phenyl-2,3,4,5-tetrahydrooxepine (226) as a clear and colourless liquid (62%);

υ_{max}/cm^{-1} (neat) 1644 (C=C enol ether), 916 and 698 (mono-substituted phenyl);

δ_H (250 MHz $CDCl_3$) 1.52 (2H, m, 4-CH_2), 2.04 (3H, m, 3-CH_2 and 5-CH_β), 2.31 (1H, m, 5-CH_α), 4.77 (1H, dd, J_{AX} = 2.69 and J_{BX} = 10.03 Hz, 2-CH), 4.88 (1H, m, 6-CH), 6.40 (1H, dd, J = 1.10 and 6.89 Hz, 7-CH) and 7.32 (5H, m, -C_6H_5);

δ_C (62.9 MHz, $CDCl_3$) 25.86 (4-CH_2), 25.86 (5-CH_2), 38.90 (3-CH_2), 84.47 (2-CH), 110.16 (6-CH), 125.73 (Ar-CH), 127.34 (Ar-CH), 128.34 (Ar-CH), 143.20 (Ar-C) and 147.41 (7-CH);

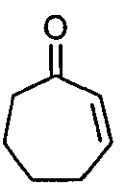
m/z (E.I.) 174.1045 (M^+, 50%, $C_{12}H_{14}O$ requires 174.1044) and 117 (100, M^+ minus C_3H_5O).

(II) Inverse addition.

Method as for general procedure.

All material purified by chromatography on aluminum oxide, activated, basic, Brockmann grade 3, (light petroleum (b.p. 40-60°C)), yielding (226) as a clear and colourless liquid (72%). All spectroscopic data were the same as for the product from normal addition.

Preparation of *2-cyclohepten-1-one* (210).



(210)

To a stirred solution of cycloheptanone (31.6 cm^3, 0.267 mol) in anhydrous ethylene glycol (300 cm^3), bromine (1 cm^3) was added to initiate the

reaction. Once the solution had decolourised (warming required) bromine (13.9 cm^3, 0.288 mmol) was added at such a rate as to maintain the orange colouration. After stirring for 15 minutes, sodium carbonate (80 g) was added and the solution extracted with light petroleum (b.p. 40-60°C) (300 cm^3). The extract was washed with a saturated sodium chloride solution (x 2), dried (magnesium sulfate) and evaporated to dryness giving 2-bromocycloheptanone ethylene ketal (209) (60 g, 95%) as a light yellow liquid.

Sodium methoxide (42 g, 78 mmol) was dissolved in anhydrous dimethylsulfoxide (200 cm^3), at 50°C, and the solution cooled to 40°C. All of the ketal (60 g) in dimethylsulfoxide (20 cm^3) was then added, maintaining a temperature of 45°C. After stirring for an hour at this temperature the solution was cooled, extracted with diethyl ether (3 x 150 cm^3), and the extract washed with a saturated sodium chloride solution (x 2). After drying (magnesium sulfate), the solvent was evaporated to dryness giving 2-cyclohepten-1-one ethylene ketal (209) (26 g, 67%) as a light yellow liquid.

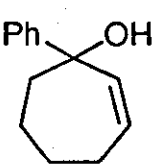
All of this ketal was stirred in aqueous sulphuric acid (3%) for 10 minutes. Extraction with diethyl ether (2 x 100 cm^3) and washing the extracts with a saturated sodium chloride solution, followed by evaporation to dryness, afforded (210) as a clear orange liquid (11.2 g, 100%);

υ_{max}/cm^{-1} (neat) 1663 (α,β-unsaturated C=O);

δ_H (250 MHz $CDCl_3$) 1.84 (4H, m, 2 x CH_2), 2.44 (2H, m, 7-CH_2), 2.60 (2H, dt, J = 0.91 and 7.40 Hz, 4-CH_2), 6.00 (1H, dt, J = 14.5 and 1.02 Hz, 2-CH) and 6.58 (1H, dt, J = 14.4 and 5.46 Hz, 3-CH);

δ_C (62.9 MHz, $CDCl_3$) 21.76 (6-CH_2), 26.16 (5-CH_2), 30.26 (7-CH_2), 43.56 (4-CH_2), 132.56 (2-CH), 146.47 (3-CH) and 204.34 (C=O).

Preparation of *1-phenyl-2-cyclohepten-1-ol* (212).

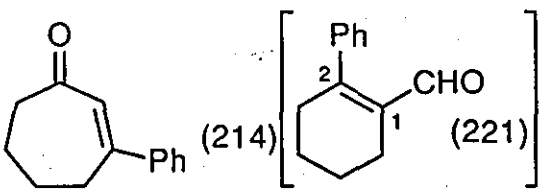


(212)

To a stirred solution of 2-cyclohepten-1-one (3.9 g, 35.4 mmol), in anhydrous tetrahydrofuran (30 cm^3) at -78°C, a solution of phenyllithium (2.0 M, 23 cm^3, 46 mmol) was added over 10 minutes. The resulting clear liquid was warmed to room temperature and left at such for 16 hours. After the careful addition of water, followed by extraction with diethyl ether (3 x 40 cm^3), the extracts were washed with a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness affording (212) as a clear orange liquid (6.1 g, 91%);

υ_{max}/cm^{-1} (neat) 3392 (OH) and 1447 (C=C);
δ_H (250 MHz $CDCl_3$) 1.10-1.82 (4H, m, 2 x CH_2), 2.07 (2H, m, 7-CH_2), 2.22 (2H, t, J = 5.80 Hz, 4-CH_2), 2.48 (1H, br s, OH), 5.77 (1H, d, J = 11.90 Hz, 2-CH), 6.00 (1H, dt, J = 11.78 and 6.69 Hz, 3-CH) and 7.30 (5H, m, -C_6H_5);
δ_C (62.9 MHz, $CDCl_3$) 23.34 (6-CH_2), 26.72 (5-CH_2), 27.52 (7-CH_2), 41.47 (4-CH_2), 78.51 (1-C), 125.70 (Ar-CH), 126.98 (Ar-CH), 128.15 (Ar-CH), 131.76 (2-CH), 137.50 (3-CH) and 146.78 (Ar-C);
m/z (C.I., ammonia) 188.1200 (M^+, 20%, $C_{13}H_{16}O$ requires 188.1201) and 171 (100, M^+ minus OH).

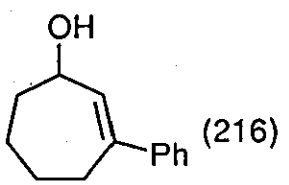
Preparation of *3-phenyl-2-cyclohepten-1-one* (214) and 2-phenyl-1-cyclohexene-carboxaldehyde (221).



To a vigorously stirred solution of pyridinium chlorochromate (11 g, 50 mmol) in anhydrous dichloromethane (120 cm^3) at room temperature, the 1-phenyl-2-cyclohepten-1-ol (4.8 g, 25 mmol) was added in one portion. After 4 hours diethyl ether (120 cm^3) was added, and the resulting black mixture filtered through celite. The filtrate was washed with sodium hydroxide solution (2 M), hydrochloric acid (2 M), a saturated sodium hydrogen carbonate solution, a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness affording a clear green liquid (4.18 g). Purification by flash chromatography (1:6 diethyl ether : light petroleum (b.p. 40-60°C)) yielded two products;
(I) 3-phenyl-2-cyclohepten-1-one (214) was isolated as a clear viscous yellow liquid (1.67 g, 36%);
υ_{max}/cm^{-1} (neat) 1665 (α,β-unsaturated C=O), 1608 (C=C), 1590 and 1445 (aromatic C=C);
δ_H (250 MHz $CDCl_3$) 1.88 (4H, m, 2 x CH_2), 2.67 (2H, t, J = 6.59 Hz, 7-CH_2), 2.88 (2H, t, J = 6.30 Hz, 4-CH_2), 6.30 (1H, s, 2-CH) and 7.40 (5H, m, -C_6H_5);
δ_C (62.9 MHz, $CDCl_3$) 20.99 (6-CH_2), 25.28 (5-CH_2), 31.91 (7-CH_2), 41.96 (4-CH_2), 126.34 (Ar-CH), 128.56 (Ar-CH), 128.91 (Ar-CH), 130.38 (2-CH), 142.46(Ar-C), 157.55 (3-C) and 204.26 (C=O);
m/z (E.I.) 186.1045 (M^+, 30%, $C_{13}H_{14}O$ requires 186.1045).
(II) 2-phenyl-1-cyclohexenecarboxaldehyde (221) was isolated as a colourless solid (1.37 g, 29%);

υ_{max}/cm^{-1} (KBr disc) 1722 (C=O ?), 1685 (α,β-unsaturated C=O) and 1597 (C=C);
δ_H (250 MHz $CDCl_3$) 1.75 (4H, m, 4- and 5-CH_2), 2.50 (2H, m, 3-CH_2), 3.00 (2H, m, 6-CH_2), 7.48 (3H, m, *m* and *p*-C_6H_5),7.93 (2H, m, *o*-C_6H_5) and 9.75 (1H, t, J = 1.02 Hz);
δ_C (62.9 MHz, $CDCl_3$) 21.69 (4-CH_2), 23.55 (5-CH_2), 38.12 (3-CH_2), 43.73 (6-CH_2), 125 50 (2-CH),128.00 (Ar-CH), 128.61 (Ar-CH), 133.02 (Ar-CH), 133.07 (Ar-C), 137.00 (1-C) and 202.38 (C=O).

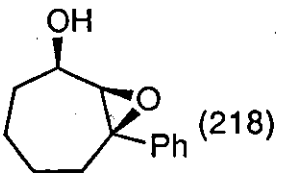
Preparation of *3-phenyl-2-cyclohepten-1-ol* (216).



(216)

To a rapidly stirred, and cooled (ice-bath) solution of 3-phenyl-2-cyclohepten-1-one (1.6 g, 6.8 mmol) and cerium(III) chloride heptahydrate (2.5 g, 6.8 mmol) in anhydrous methanol (40 cm^3), sodium borohydride (260 mg, 6.8 mmol) was added in one portion. After stirring at 0°C for 15 minutes, water was added and the solution extracted with diethyl ether (x 3). The extracts were washed with water, a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a viscous yellow liquid. Purification by flash chromatography (1:3 diethyl ether : light petroleum (b.p. 40-60°C)), followed by recrystallisation from 1:1 diethyl ether : light petroleum (b.p. 40-60°C) afforded (216) as colourless needles (1.21 g, 94%); m.p. 49.7-50.1°C;
found: C, 82.62; H, 8.62. $C_{13}H_{16}O$ requires C, 82.94; H, 8.57%;
υ_{max}/cm^{-1} (KBr disc) 3347 (OH), 1493 and 1446 (aromatic C=C);
δ_H (250 MHz $CDCl_3$) 1.42-2.00 (7H, m, 3 x CH_2 and OH), 2.47 (1H, t, J = 11.00 Hz, 4-CH_α), 2.63 (1H, dd, J_{AX} = 7.20 and J_{AB} = 13.79 Hz, 4-CH_β), 4.58 (1H, m, 1-CH), 5.98 (1H, d, J = 1.94 Hz, 2-CH) and 7.24 (5H, m, -C_6H_5);
δ_C (62.9 MHz, $CDCl_3$) 25.98 (6-CH_2), 27.95 (5-CH_2), 32.53 (7-CH_2), 36.34 (4-CH_2), 72.11 (1-CH), 125.61 (Ar-CH), 126.64 (Ar-CH), 128.11 (Ar-CH), 135.71 (2-CH), 141.70 (Ar-C) and 143.83 (3-C);
m/z (C.I., ammonia) 188.1200 (M^+, 20%, $C_{13}H_{16}O$ requires 188.1201) and 171 (100, M^+ minus OH).

Preparation of *2,3-epoxy-3-phenylcycloheptan-1-ol* (218).



(218)

To a cooled (ice-bath) and stirred solution of 3-phenyl-2-cyclohepten-1-ol (500 mg, 2.65 mmol) and sodium hydrogen carbonate (420 mg, 5.0 mmol) in anhydrous dichloromethane (20 cm^3), m-chloroperoxybenzoic acid (730 mg, 4.3 mmol) was added in one portion. After stirring at room temperature for 20 minutes, the solution was washed with a saturated sodium hydrogen carbonate solution (x 4), water, a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a clear oil. Purification by flash chromatography (1:2 diethyl ether : light petroleum (b.p. 40-60°C)) yielded (218) as viscous liquid (386 mg, 72%);

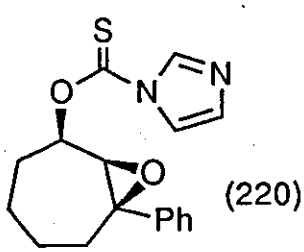
υ_{max}/cm^{-1} (neat) 3401 (OH), 1496 and 1447 (aromatic C=C);

δ_H (250 MHz $CDCl_3$) 1.70 (8H, m, 3 x CH_2, OH and 4-CH_β), 2.58 (1H, dt, J_{AB} = 14.26 and J_{AX} = 8.30 Hz, 4-CH_α), 3.15 (1H, d, J = 5.48 Hz, 2-CH), 3.94 (1H, m, 1-CH) and 7.33 (5H, m, -C_6H_5);

δ_C (62.9 MHz, $CDCl_3$) 24.23 (CH_2), 26.75 (CH_2), 34.36 (CH_2), 34.53 (CH_2), 61.86 (3-C), 69.76 (2-CH), 73.56 (1-CH), 125.73 (Ar-CH), 127.91 (Ar-CH), 128.25 (Ar-CH) and 141.26 (Ar-C);

m/z (C.I., ammonia) 222.1494 ($MNH4^+$, 40%, $C_{13}H_{20}O_2N$ requires 222.1494), 204 (20, M^+) and 187 (100, M^+ minus OH).

Preparation of *2,3-epoxy-1-(imidazol-1-yl (thiocarbonyl) oxy)-3-phenylcycloheptane* (220).



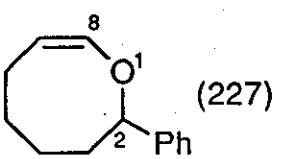
(220)

A stirred solution of 2,3-epoxy-3-phenylcycloheptan-1-ol (350 mg, 1.7 mmol) and 1,1-thiocarbonyldiimidazole (670 mg, 3.4 mmol) in anhydrous dichloromethane (15 cm^3) was heated at gentle reflux for 5 hours. After cooling, the solution was washed with a saturated sodium hydrogen carbonate solution (x 3), water, a saturated ammonium chloride solution, dried (magnesium sulfate) and

evaporated to dryness giving a viscous yellow oil. Purification by flash chromatography (2:1 light petroleum (b.p. 40-60°C) : diethyl ether) afforded (220) as a viscous liquid (420 mg, 79%);
υ_{max}/cm^{-1} (neat) 1530 (aromatic C=C);
δ_H (400 MHz $CDCl_3$) 1.69 (2H, m, 6-CH_2), 1.88 (3H, m, 5-CH_2 and 7-CH_α), 2.10 (2H, m, 7-CH_β and 4-CH_α), 2.67 (1H, dd, J_{AX} = 8.48 and J_{AB} = 15.00 Hz, 4-CH_β), 3.42 (1H, d, J = 5.72 Hz, 2-CH), 5.73 (1H, ddd, J = 2.61, 5.70 and 9.72 Hz, 1-CH), 7.04 (1H, m, Im-CH), 7.36 (5H, m, -C_6H_5), 7.64 (1H, t, J = 1.52 Hz, Im-CH) and 8.36 (1H, br s, Im-CH);
δ_C (62.9 MHz, $CDCl_3$) 24.08 (CH_2), 25.86 (CH_2), 30.74 (CH_2), 34.26 (CH_2), 61.92 (3-C), 65.17 (2-CH), 84.61 (1-CH), 117.86 (Im-CH), 125.47 (Ar-CH), 128.40 (Ar-CH), 128.39 (Ar-CH), 130.70 (Im-CH), 136.63 (Im-CH), 140.65 (Ar-C) and 182.86 (C=S);
m/z (E.I.) 314.1106 (M^+, 1%, $C_{17}H_{18}O_2N_2S$ requires 314.1089), 187 (20, M^+ minus OCSIm) and 69 (100, Im).

Tributyltin hydride reduction of *2,3-epoxy-1-(imidazol-1-yl (thiocarbonyl) oxy)-3-phenylcycloheptane.*

(I) Normal addition.



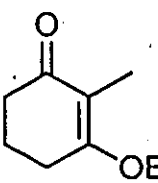
(227)

Method as for general procedure.
All material purified by chromatography on aluminum oxide, activated, basic, Brockmann grade 3, (light petroleum (b.p. 40-60°C)), yielding the 2-phenyl-3,4,5,6-tetrahydro-2*H*-oxocine (227) as a clear and colourless liquid (58%);
υ_{max}/cm^{-1} (neat) 1655 (C=C enol ether) and 698 (mono-substituted phenyl);
δ_H (250 MHz $CDCl_3$) 1.55 (2H, m, 5-CH_2), 1.78 (2H, m, 4-CH_2), 2.04 (3H, m, 3-CH_2 and 6-CH_β), 2.31 (1H, m, 6-CH_α), 4.94 (1H, dd, J_{AX} = 4.06 and J_{BX} = 7.20 Hz, 2-CH), 5.05 (1H, q, J = 6.32 Hz, 7-CH), 6.15 (1H, dt, J = 6.01 and 1.23 Hz, 8-CH) and 7.36 (5H, m, -C_6H_5);
δ_C (62.9 MHz, $CDCl_3$) 24.15 (4-CH_2), 24.79 (5-CH_2), 27.69 (6-CH_2), 33.52 (3-CH_2), 81.53 (2-CH), 117.20 (7-CH), 126.14 (Ar-CH), 127.11 (Ar-CH), 128.16 (Ar-CH), 142.46 (Ar-C) and 143.31 (8-CH);
m/z (C.I., ammonia) 206 (MNH_4^+, 45%), 189 (95, MH^+) and 171 (100, M^+ minus OH).

(II) Inverse addition.

Method as for general procedure.
All material purified by chromatography on aluminum oxide, activated, basic, Brockmann grade 3, (light petroleum (b.p. 40-60°C)), yielding (227) as a clear and colourless liquid (66%). All spectroscopic data were the same as for the product from the normal mode of addition.

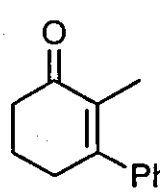
Preparation of *3-ethoxy-2-methyl-2-cyclohexen-1-one* (228).



(228)

A solution of 2-methylcyclohexan-1,3-dione (15 g, 119 mmol), p-toluenesulfonic acid (0.6 g) and anhydrous ethanol (100 cm^3), in anhydrous benzene (300 cm^3), was heated at reflux on a Dean-Stark apparatus for 20 hours. After cooling, the solution was washed with a potassium hydroxide solution (10%) saturated with sodium chloride (x 3), water (x 3) and a saturated sodium chloride (x 2). After drying (magnesium sulfate), the solvent was evaporated to dryness affording (228) as a yellow solid (15 g, 82%). A small sample was recrystallised from benzene giving clear and colourless crystals, m.p. 60.3-60.9°C (Lit.[136] m.p. 60-62°C);
υ_{max}/cm^{-1} (neat) 1639 (α,β-unsaturated C=O) and 1615 (C=C of enol ether);
δ_H (250 MHz $CDCl_3$) 1.36 (3H, t, J = 7.01 Hz, $OCH_2C\underline{H}_3$), 1.70 (3H, s, Me), 1.98 (2H, quintet, J = 6.51 Hz, 5-CH_2), 2.34 (2H, t, J = 6.64 Hz, 6-CH_2), 2.55 (2H, dt, J = 1.20 and J = 6.05 Hz, 4-CH_2) and 4.06 (2H, t, J = 5.84 Hz, $OC\underline{H}_2CH_3$);
δ_C (62.9 MHz, $CDCl_3$) 7.28 (Me), 15.18 ($OCH_2\underline{C}H_3$), 20.88 (5-CH_2), 25.23 (6-CH_2), 36.19 (4-CH_2), 63.34 ($O\underline{C}H_2CH_3$), 114.90 (2-C), 171.30 (3-C) and 198.75 (C=O).

Preparation of *2-methyl-3-phenyl-2-cyclohexen-1-one* (229).

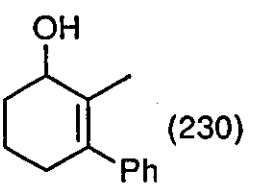


(229)

To a stirred solution of 3-ethoxy-2-methyl-2-cyclohexen-1-one (10 g, 64.9 mmol) in anhydrous tetrahydrofuran (40 cm^3) at -78°C, a solution of

phenyllithium (2.0 M, 36 cm^3, 71 mmol) was added over 10 minutes. The clear brown liquid was warmed to room temperature, and left at such for 16 hours. After the careful addition of hydrochloric acid (2 M) (50 cm^3), followed by extraction with diethyl ether (3 x 40 cm^3), the extracts were washed with a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness affording (229) as a clear red liquid (12.1 g, 100%);
υ_{max}/cm^{-1} (neat) 1665 (α,β-unsaturated C=O), 1619 (C=C of enol ether), 1573 and 1490 (C=C aromatic);
δ_H (250 MHz $CDCl_3$) 1.72 (3H, t, J = 1.82 Hz, Me), 2.06 (2H, quintet, J = 6.18 Hz, 5-CH_2), 2.51 (2H, t, J = 7.25 Hz, 6-CH_2), 2.55 (2H, dt, J = 1.80 and J = 6.10 Hz, 4-CH_2) and 7.32 (5H, m, -C_6H_5);
δ_C (62.9 MHz, $CDCl_3$) 12.77 (Me), 22.67 (5-CH_2), 32.81 (4-CH_2), 37.63 (6-CH_2), 126.97 (Ar-CH), 127.74 (Ar-CH), 128.23 (Ar-CH), 131.00 (2-C), 140.50 (Ar-C), 156.00 (3-C) and 199.92 (C=O);
m/z (E.I.) 186.1039 (M^+, 100%, $C_{13}H_{14}O$ requires 186.1044).

Preparation of *2-methyl-3-phenyl-2-cyclohexen-1-ol* (230).

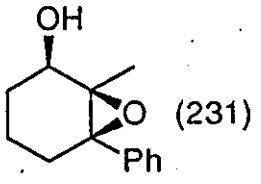


(230)

To a rapidly stirred, and cooled (ice-bath) solution of 2-methyl-3-phenyl-2-cyclohexen-1-one (6.5 g, 35 mmol) and cerium(III) chloride heptahydrate (13 g, 35 mmol) in anhydrous methanol (80 cm^3), sodium borohydride (1.32 g, 35 mmol) was added in one portion. After stirring at 0°C for 45 minutes, water was added and the solution extracted with diethyl ether (x 3). The extracts were washed with water, a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a viscous yellow liquid. Purification by flash chromatography (1:10 ethyl acetate : light petroleum (b.p. 40-60°C)), followed by recrystallisation from 1:1 ethyl acetate : cyclohexane afforded (230) as colourless crystals (3.6 g, 58%); m.p. 65.3-65.4°C;
found: C, 82.74; H, 8.52. $C_{13}H_{16}O$ requires C, 82.94; H, 8.57%;
υ_{max}/cm^{-1} (KBr disc) 3269 (OH) and 1490 (C=C);
δ_H (250 MHz $CDCl_3$) 1.68 (3H, t, J = 1.97 Hz, Me), 1.82 (2H, m, 5-CH_2), 2.11 (2H, m, 6-CH_2), 2.25 (3H, m, OH and 4-CH_2), 4.11 (1H, br s, 1-CH) and 7.24 (5H, m, -C_6H_5);

δ_C (62.9 MHz, $CDCl_3$) 17.67 (Me), 18.69 (5-CH_2), 32.05 (6-CH_2), 32.30 (4-CH_2), 69.36 (1-CH), 126.35 (Ar-CH), 128.07 (2 x Ar-CH), 130.47 (2-C), 136.63 (3-C) and 144.00 (Ar-C);
m/z (E.I.) 188.1199 (M^+, 25%, $C_{13}H_{16}O$ requires 188.1201)) and 173 (100, M^+ minus Me).

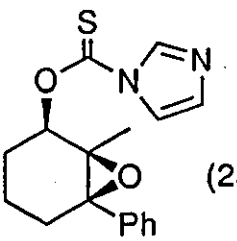
Preparation of *2,3-epoxy-2-methyl-3-phenylcyclohexan-1-ol* (231).



(231)

To a cooled (ice-bath) and stirred solution of 2-methyl-3-phenyl-2-cyclohexen-1-ol (2.6 g, 13.8 mmol) and sodium hydrogen carbonate (1.76 g, 21 mmol) in anhydrous dichloromethane (70 cm^3), m-chloroperoxybenzoic acid (3.6 g, 20.7 mmol) was added in one portion. After stirring at room temperature for 10 minutes, the solution was washed with a saturated sodium hydrogen carbonate solution (x 4), water, a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a viscous yellow liquid. Purification by flash chromatography (20:1 dichloromethane : diethyl ether), followed by recrystallisation from 1:1 ethyl acetate : cyclohexane, afforded (231) as colourless crystals (2.4 g, 89%); m.p. 73.0-73.3°C;
found: C, 76.02; H, 7.84. $C_{13}H_{16}O_2$ requires C, 76.44; H, 7.89%;
υ_{max}/cm^{-1} (neat) 3266 (OH), 1604 and 1496 (C=C);
δ_H (250 MHz $CDCl_3$) 1.09 (3H, s, Me), 1.41 (1H, m, 5-CH_α), 1.60 (3H, m, 5-CH_β and 4-CH_2), 2.07 (2H, t, J = 5.54 Hz, 6-CH_2), 2.18 (1H, br s, OH), 3.89 (1H, br s, 1-CH) and 7.29 (5H, m, -C_6H_5);
δ_C (62.9 MHz, $CDCl_3$) 16.95 (5-CH_2), 18.08 (Me), 30.60 (4-CH_2), 31.63 (6-CH_2), 66.00 (2-C), 69.80 (1-CH), 70.00 (3-C), 126.15 (Ar-CH), 127.23 (Ar-CH), 128.13 (Ar-CH) and 140.50 (Ar-C);
m/z (C.I., ammonia) 204 (M^+, 20%) and 187 (100, M^+ minus OH).

Preparation of *2,3-epoxy-1-(imidazol-1-yl (thiocarbonyl) oxy)-2-methyl-3-phenyl-cyclohexane* (232).



(232)

A stirred solution of 2,3-epoxy-2-methyl-3-phenylcyclohexan-1-ol (2.2 g, 10.7 mmol) and 1,1-thiocarbonyldiimidazole (4.2 g, 21.5 mmol) in anhydrous dichloromethane (20 cm^3) was heated at gentle reflux for 1.5 hours. After cooling, the solution was washed with a saturated sodium hydrogen carbonate solution (x 3), water, a saturated ammonium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a viscous orange liquid. Purification by flash chromatography (1:5 ethyl acetate : light petroleum (b.p. 40-60°C)), followed by recrystallisation from ethyl acetate, afforded (232) as colourless crystals (2.9 g, 87%); m.p. 96.7°C;

found: C, 64.88; H, 5.65; N, 8.87; S, 10.04%. $C_{17}H_{18}O_2N_2S$ requires C, 64.94; H, 5.77; N, 8.91; S, 10.20%;

υ_{max}/cm^{-1} (KBr disc) 1530 (C=C);

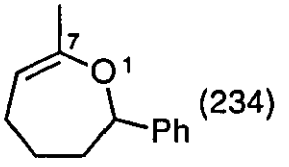
δ_H (250 MHz $CDCl_3$) 1.03 (3H, s, Me), 1.60 (1H, m, 5-CH_α), 1.50-2.16 (3H, m, 5-CH_β and 4-CH_2), 2.20 (2H, m, 6-CH_2), 5.95 (1H, dd, J_{AX} = 5.54 and J_{BX} = 8.25 Hz, 1-CH), 7.06 (1H, t, J = 0.82 Hz, Im-CH), 7.30 (5H, m, -C_6H_5), 7.71 (1H, t, J = 1.45 Hz, Im-CH) and 8.44 (1H, t, J = 0.91 Hz, Im-CH);

δ_C (62.9 MHz, $CDCl_3$) 16.89 (Me), 19.35 (5-CH_2), 25.14 (4-CH_2), 30.77 (6-CH_2), 63.67 (2-C), 69.09 (3-C), 83.92 (1-CH), 117.91 (Im-CH), 126.26 (Ar-CH), 127.61 (Ar-CH), 128.28 (Ar-CH), 130.94 (Im-CH), 137.16 (Im-CH), 139.80 (Ar-C) and 184.50 (C=S);

m/z (C.I., ammonia) 315 (MH^+, 10%), 187 (100, M^+ minus OCSIm) and 69 (80, Im).

Tributyltin hydride reduction of *2,3-epoxy-1-(imidazol-1-yl (thiocarbonyl) oxy)-2-methyl-3-phenylcyclohexane.*

(I) Normal addition.



(234)

Method as for general procedure.

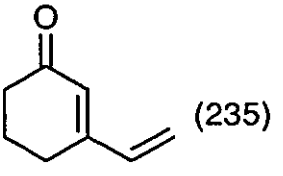
All material purified by chromatography on aluminum oxide, activated, basic, Brockmann grade 3, (light petroleum (b.p. 40-60°C)), yielding 7-methyl-2-phenyl-2,3,4,5-tetrahydrooxepine (234) as a clear and colourless liquid (53%);
υ_{max}/cm^{-1} (neat) 1676 (C=C enol ether) and 698 (mono-substituted phenyl);
δ_H (250 MHz $CDCl_3$) 1.54 (2H, m, 4-CH_2), 1.76 (3H, q, J = 1.17 Hz, Me), 2.20 (4H, m, 3-CH_2 and 5-CH_2), 4.79 (2H, m, 2-CH and 6-CH) and 7.34 (5H, m, -C_6H_5);
δ_C (62.9 MHz, $CDCl_3$) 21.61 (Me), 25 to 30 (impure mix, 4-CH_2 and 3-CH_2), 38.82 (5-CH_2), 82.85 (2-CH), 106.29 (6-CH), 125.68 (Ar-CH), 127.11 (Ar-CH), 128.24 (Ar-CH), 143.68 (Ar-C) and 156.39 (7-C).

(II) Inverse addition.

Method as for general procedure.

All material purified by chromatography on aluminum oxide, activated, basic, Brockmann grade 3, (light petroleum (b.p. 40-60°C)), yielding (234) as a clear and colourless liquid (58%). All spectroscopic data were the same as for the product from the normal mode of addition.

Preparation of *3-vinyl-2-cyclohexenone* (235).

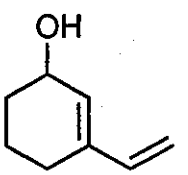


(235)

To a stirred solution of 3-ethoxy-2-cyclohexen-1-one (5 g, 35.7 mmol) in anhydrous tetrahydrofuran (40 cm^3) at -78°C, a solution of vinylmagnesium bromide (1.0 M, 39 cm^3, 39.0 mmol) was added over 10 minutes. The resulting solution was warmed to room temperature, and left at such for 16 hours. After the careful addition of hydrochloric acid (2 M) (50 cm^3), followed by extraction with

diethyl ether (3 x 40 cm^3), the extracts were washed with a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness affording a clear orange liquid. Purification by flash chromatography (1:2 diethyl ether : light petroleum (b.p. 40-60°C)) afforded (235) as a yellow liquid (2.4 g, 56%);
υ_{max}/cm^{-1} (neat) 1665 (α,β-unsaturated C=O), 1622 and 1581 (C=C);
δ_H (250 MHz $CDCl_3$) 2.05 (2H, quintet, J = 6.19 Hz, 5-CH_2), 2.46 (4H, m, 4-CH_2 and 6-CH_2), 5.47 (1H, d, J_{cis} = 10.71 Hz, -CH=C$\underline{H}_{cis}$), 5.69 (1H, d, J_{trans} = 17.42 Hz, -CH=C$\underline{H}_{trans}$), 5.96 (1H, s, 2-CH) and 6.50 (1H, dd, J_{cis} = 10.70 and J_{trans} = 17.50 Hz, -C$\underline{H}$=CH_2);
δ_C (62.9 MHz, $CDCl_3$) 22.22 (5-CH_2), 24.34 (6-CH_2), 37.75 (4-CH_2), 120.70 (-CH=$\underline{C}H_2$), 128.23 (-$\underline{C}$H=CH_2), 137.94 (2-CH), 156.50 (3-C) and 200.50 (C=O);
m/z (E.I.) 122.0721 (M^+, 90%, $C_8H_{10}O$ requires 122.0732) and 94 (100, M^+ minus CH_2CH_2).

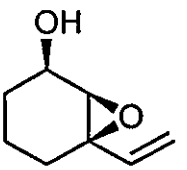
Preparation of *3-vinyl-2-cyclohexen-1-ol* (236).



(236)

To a rapidly stirred, and cooled (ice-bath) solution of 3-vinyl-2-cyclohexen-1-one (2.2 g, 18.0 mmol) and cerium(III) chloride heptahydrate (6.7 g, 35 mmol) in anhydrous methanol (40 cm^3), sodium borohydride (0.68 g, 18.0 mmol) was added in one portion. After stirring at 0°C for 20 minutes, water was added and the solution extracted with diethyl ether (x 3). The extracts were washed with a saturated ammonium chloride solution (x 2), a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness affording (236) as a yellow liquid (1.7 g, 76%);
υ_{max}/cm^{-1} (neat) 3335 (OH), 1642 and 1606 (C=C);
δ_H (250 MHz $CDCl_3$) 1.61 (2H, m, 5-CH_2), 1.82 (2H, m, 6-CH_2), 2.16 (3H, m, OH and 4-CH_2), 4.28 (1H, m, 1-CH), 5.03 (1H, d, J_{cis} = 10.77 Hz, -CH=C$\underline{H}_{cis}$), 5.19 (1H, d, J_{trans} = 17.68 Hz, -CH=C$\underline{H}_{trans}$), 5.74 (1H, s, 2-CH) and 6.35 (1H, dd, J_{cis} = 10.74 and J_{trans} = 17.52 Hz, -C$\underline{H}$=CH_2);
δ_C (62.9 MHz, $CDCl_3$) 18.94 (5-CH_2), 23.79 (6-CH_2), 32.10 (4-CH_2), 66.24 (1-CH), 112.88 (-CH=$\underline{C}H_2$), 130.92 (-$\underline{C}$H=CH_2), 138.61 (3-C) and 139.34 (2-CH);
m/z (E.I.) 124.0876 (M^+, 100%, $C_8H_{10}O$ requires 124.0888).

Preparation of *2,3-epoxy-3-vinylcyclohexan-1-ol* (237).



(237)

To a cooled (ice-bath) and stirred solution of 3-vinyl-2-cyclohexen-1-ol (1.5 g, 12.0 mmol) and sodium hydrogen carbonate (1.68 g, 20.0 mmol) in anhydrous dichloromethane (40 cm^3), m-chloroperoxybenzoic acid (2.7 g, 15.7 mmol) was added in one portion. After stirring at room temperature for 30 minutes, the solution was washed with a saturated sodium hydrogen carbonate solution (x 3), water, a saturated ammonium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a clear liquid. Purification by flash chromatography (6:1 light petroleum (b.p. 40-60°C) : ethyl acetate) afforded (237) as a colourless liquid (1.1 g, 65%);

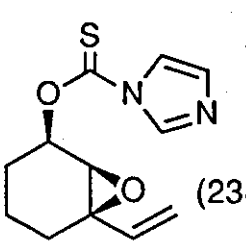
υ_{max}/cm^{-1} (neat) 3407 (OH), 1638 (C=C);

δ_H (250 MHz $CDCl_3$) 1.33 (1H, m, 5-CH_α), 1.55 (3H, m, 5-CH_α and 6-CH_2), 1.90 (2H, m, 4-CH_2), 2.41 (1H, br s, OH), 3.22 (1H, d, J = 3.29 Hz, 2-CH), 4.03 (1H, m, 1-CH), 5.20 (1H, dd, J_{gem} = 1.03 and J_{cis} = 10.70 Hz, -CH=C$\underline{H}_{cis}$), 5.34 (1H, dd, J_{gem} = 1.00 and J_{trans} = 17.36 Hz, -CH=C$\underline{H}_{trans}$) and 5.72 (1H, dd, J_{cis} = 10.70 and J_{trans} = 17.37 Hz, -C$\underline{H}$=CH_2);

δ_C (62.9 MHz, $CDCl_3$) 17.51 (5-CH_2), 25.10 (6-CH_2), 29.22 (4-CH_2), 62.95 (3-C), 63.42 (2-CH), 66.27 (1-CH), 116.42 (-CH=$\underline{C}H_2$), 138.80 (-$\underline{C}$H=CH_2);

m/z (E.I.) 140.0821 (M^+, 1%, $C_8H_{12}O_2$ requires 140.0837).

Preparation of *2,3-epoxy-1-(imidazol-1-yl (thiocarbonyl) oxy)-3-vinylcyclohexane* (238).



(238)

A stirred solution of 2,3-epoxy-3-vinylcyclohexan-1-ol (1.0 g, 10.7 mmol) and 1,1-thiocarbonyldiimidazole (2.7 g, 14.0 mmol) in anhydrous dichloromethane (40 cm^3), was heated at gentle reflux for 2.5 hours. After cooling, the solution was washed with a saturated sodium hydrogen carbonate solution (x 3), water, a saturated ammonium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving an orange liquid. Purification by flash chromatography (1:3

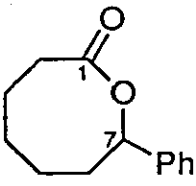
diethyl ether : light petroleum (b.p. 40-60°C)) afforded (238) as viscous orange liquid (1.32 g, 74%);
υ_{max}/cm^{-1} (neat) 1639 (C=C);
δ_H (250 MHz $CDCl_3$) 1.48 (1H, m, 5-CH_α), 1.84 (3H, m, 5-CH_α and 6-CH_2), 1.99 (2H, m, 4-CH_2), 2.41 (1H, br s, OH), 3.42 (1H, d, J = 2.54 Hz, 2-CH), 5.20 (1H, dd, J_{gem} = 0.98 and J_{cis} = 10.68 Hz, -CH=C<u>H</u>$_{cis}$), 5.34 (1H, dd, J_{gem} = 0.97 and J_{trans} = 17.34 Hz, -CH=C<u>H</u>$_{trans}$), 5.72 (1H, dd, J_{cis} = 10.67 and J_{trans} = 17.34 Hz, -C<u>H</u>=CH_2), 5.91 (1H, dt, J = 2.64 and 6.10 Hz, 1-CH), 7.03 (1H, m, Im-CH), 7.67 (1H, t, J = 1.33 Hz, Im-CH) and 8.39 (1H, t, J = 0.99 Hz, Im-CH);
δ_C (62.9 MHz, $CDCl_3$) 18.45 (5-CH_2), 24.56 (2 x CH_2), 59.56 (2-CH), 61.81 (3-C), 79.42 (1-CH), 117.16 (-CH=<u>C</u>H_2), 117.96 (Im-CH), 130.82 (Im-CH), 137.09 (Im-CH), 137.96 (-<u>C</u>H=CH_2) and 183.63 (C=S);
m/z (E.I.) 251.0830 (MH^+, 10%, $C_{12}H_{15}O_2N_2S$ requires 251.0854), 250 (1, M^+) and 123 (100, M^+ minus .OCSIm).

<u>Tributyltin hydride reduction of *2,3-epoxy-1-(imidazol-1-yl (thiocarbonyl) oxy)-3-vinylcyclohexane* (238).</u>

<u>(I) Normal addition.</u>

Method as for general procedure.
All material purified by chromatography on aluminum oxide, activated, basic, Brockmann grade 3, (light petroleum (b.p. 40-60°C)), yielding a colourless liquid (58%);
υ_{max}/cm^{-1} (neat) 1668 and 1638 (C=C of enol ether);
δ_H (250 MHz $CDCl_3$) up-field difficult to interpret due to tributyltin hydride impurities, 4.27 (1H, d, J_{cis} = 6.03 Hz, CH), 4.61 (1H, d, J_{trans} = 13.74 Hz, CH), 4.83 (1H, d, J = 9.67 Hz, CH) and 6.43 (1H, ddd, J = 3.36, J_{cis} = 6.08 and J_{trans} = 13.86 Hz, CH);
δ_C (62.9 MHz, $CDCl_3$) 21.99 (CH_2), 25.82 (CH_2), 39.65 and 39.72 (CH or CH_3), 93.94 (CH_2), 104.77 and 104.99 (CH), 147.24 and 147.31 (CH) and 154.31 and 154.53 (C).
The inverse mode of addition of tributyltin hydride gave a similar result to the normal mode of addition.

Preparation of *7-phenyheptonic-7-lactone* (248).



(248)

To a stirred solution of pyridinium chlorochromate (100 mg, 0.47 mmol) and sodium acetate (20 mg, 0.24 mmol) in anhydrous dichloromethane (2 cm^3) 2-phenyl-3,4,5,6-tetrahydro-2*H*-oxocine (30 mg, 0.16 mmol) in anhydrous dichloromethane (2 cm^3) was added in one portion. After stirring at room temperature for 72 hours, diethyl ether (10 cm^3) was added and the resulting black mixture filtered through celite. The filtrate was washed with hydrochloric acid (2 M) (2 x 10 cm^3), a saturated sodium chloride solution, dried (magnesium sulfate) and evaporated to dryness giving a crude brown solid (80 mg). Purification by flash chromatography (1:10 diethyl ether : light petroleum (b.p. 40-60°C)), followed by recrystallisation from hexane afforded (248) as colourless needles (8 mg, 25%); m.p. 56.6°C;

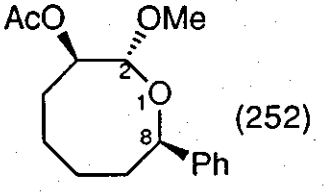
υ_{max}/cm^{-1} (KBr disc) 1722 (ester C=O);

δ_H (250 MHz $CDCl_3$) 1.65 (4H, m, 4-CH_2 and 5-CH_2), 1.92 (4H, m, 3-CH_2 and 6-CH_2), 2.57 (2H, m, 2-CH_2), 5.68 (1H, dd, J_{AX} = 4.82 and J_{BX} = 9.50 Hz, 7-CH) and 7.39 (5H, m, -C_6H_5);

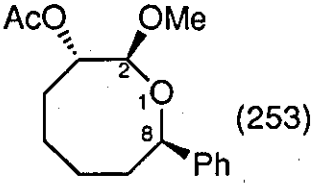
δ_C (62.9 MHz, $CDCl_3$) 24.46 (CH_2), 26.72 (CH_2), 29.46 (CH_2), 33.13 (CH_2), 39.89 (CH_2), 79.79 (7-CH), 125.94 (Ar-CH), 127.91 (Ar-CH), 128.50 (Ar-CH), 140.38 (Ar-C) and 176.39 (CO_2);

m/z (C.I., ammonia) 222 (100%, MNH_4^+), 205 (70, MH^+) and 187 (80, M^+ minus OH).

Preparation of *3β-acetoxy-2α-methoxy-8β-phenyl-oxocane* (252) *and 3α-acetoxy-2β-methoxy-8β-phenyl-oxocane* (253).



(252)



(253)

To a cooled (ice-bath) and stirred solution of 2-phenyl-3,4,5,6-tetrahydro-2*H*-oxocine (60 mg, 0.31 mmol) in anhydrous dichloromethane (1 cm^3) the dimethyldioxirane / acetone solution (0.075 M, 4.8 cm^3, 0.38 mmol) was added drop-wise. The resulting clear solution was stirred at 0°C for 1.25 hours, followed by the addition of anhydrous methanol (4 cm^3). After stirring for 4 hours, the

solvent was evaporated *in vacuo* (4 mmHg) to afford a clear liquid. This was dissolved in pyridine (1.5 cm^3), and acetic anhydride (1.5 cm^3) added. The resulting solution was stirred at 0°C for 24 hours, diluted with ethyl acetate, washed with a saturated sodium hydrogen carbonate solution, a saturated copper sulfate solution (x 5) and a saturated sodium chloride solution. After drying (magnesium sulfate), the solution was evaporated to dryness affording (252) and (253) as a clear oil (80 mg, 67% overall yield). Purification by flash chromatography (1:10 ethyl acetate : light petroleum (b.p. 40-60°C)) afforded (252) as a pure isomer (45 mg, 46%);

υ_{max}/cm^{-1} (neat) 1736 (ester C=O);

δ_H (400 MHz $CDCl_3$) 1.60-1.92 (7H, m, 3 x CH_2 and 7-CH_β), 2.12 (3H, s, $MeCO_2$), 2.12 (1H, quintet, J = 6.25 Hz, 7-CH_α), 3.19 (3H, s, OMe), 4.64 (1H, d, J = 2.88 Hz, 2-CH), 4.73 (1H, m, 8-CH), 4.93 (1H, dt, J = 3.11 and 8.37 Hz, 3-CH) and 7.31 (5H, m, -C_6H_5);

The assigned structure was confirmed by n.O.e difference spectroscopy.

δ_C (62.9 MHz, $CDCl_3$) 21.37 ($\underline{Me}CO_2$), 22.68 (CH_2), 24.59 (CH_2), 27.63, (CH_2), 36.21 (CH_2), 56.41 (OMe), 72.62 (CH), 73.84 (CH), 99.69 (2-CH), 126.14 (Ar-CH), 127.10 (Ar-CH), 128.26 (Ar-CH), 144.70 (Ar-C) and 170.29 (C=O);

m/z (C.I., ammonia) 296 (10%, MNH_4^+) and 279 (45, MH^+).

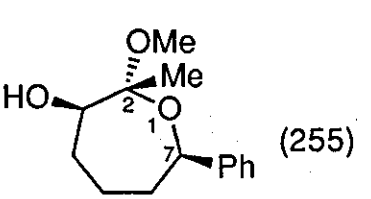
3α-Acetoxy-2β-methoxy-8β-phenyl-oxocane (253) was isolated as a clear liquid (15 mg, 15%), with some (252) impurity still present;

υ_{max}/cm^{-1} (neat) 1738 (ester C=O);

δ_H (250 MHz $CDCl_3$) 1.32-1.94 (7H, m, 3 x CH_2 and 7-CH_β), 2.06 (3H, s, $MeCO_2$), 2.22 (1H, quintet, J = 6.25 Hz, 7-CH_α), 3.00 (3H, s, OMe), 4.69 (1H, d, J = 2.88 Hz, 2-CH), 5.11 (1H, ddd, J = 1.56, 2.85 and 8.40 Hz, 3-CH), 5.20 (1H, dd, J = 3.57 and 11.47 Hz, 8-CH) and 7.31 (5H, m, -C_6H_5);

δ_C (62.9 MHz, $CDCl_3$) 21.29 ($\underline{Me}CO_2$), 22.69 (CH_2), 26.28 (CH_2), 30.18 (CH_2), 36.69 (CH_2), 54.97 (OMe), 75.47 (CH), 85.16 (CH), 106.77 (2-CH), 125.76 (Ar-CH), 126.14 (Ar-CH), 128.28 (Ar-CH), 142.70 (Ar-C) and 170.02 (C=O).

Preparation of *3β-hydroxy-2α-methoxy-2β-methyl-7β-phenyl-oxepane* (255).



(255)

To a cooled (ice-bath) and stirred solution of 7-methyl-2-phenyl-2,3,4,5-tetrahydrooxepine (60 mg, 0.34 mmol) in anhydrous dichloromethane (1 cm^3) the dimethyldioxirane / acetone solution (0.031 M, 16 cm^3, 0.51 mmol) was added

drop-wise. The resulting clear solution was stirred at 0°C for 1.0 hours, followed by the addition of anhydrous methanol (4 cm^3). After stirring for 4 hours, the solvent was evaporated *in vacuo* (4 mmHg) to afford a cloudy liquid. Purification by chromatography on basic alumina, grade 3, (1:3 ethyl acetate : light petroleum (b.p. 40-60°C)), afforded (255) as a single isomer (24 mg, 30%);

υ_{max}/cm^{-1} (neat) 3557 (OH);

δ_H (400 MHz $CDCl_3$) 1.34 (3H, s, ring-Me), 1.55 (1H, m, 5-CH_α), 1.62 (1H, m, 6-CH_α), 1.61 (1H, m, 4-CH_β), 1.63 (1H, m, 6-CH_β), 2.04 (1H, m, 4-CH_α), 2.13 (1H, m, 5-CH_β), 3.11 (3H, s, OMe), 3.20 (1H, br s, OH), 3.92 (1H, d, J = 7.42 Hz, 3-CH), 4.98 (1H, dd, J_{AX} = 1.85 and J_{BX} = 10.36 Hz, 7-CH) and 7.26 (5H, m, -C_6H_5);

The assigned structure was confirmed by n.O.e difference spectroscopy.

δ_C (62.9 MHz, $CDCl_3$) 19.80 (ring-Me), 22.93 (CH_2), 27.89 (CH_2), 38.79 (CH_2), 48.83 (OMe), 73.25 (CH), 75 83 (CH), 100.67 (2-CH), 125.43 (Ar-CH), 126.52 (Ar-CH), 127.93 (Ar-CH) and 144.23 (Ar-C);

m/z (C.I., ammonia) 222 (MNH_4^+ minus (Me and OH), 100%) and 205 (85, MH^+ minus [Me and OH]).

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