SOME NOVEL ASPECTS OF CARBOCATION CHEMISTRY
S_N1 RING OPENING OF EPOXIDES

A Thesis Presented by

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ABSTRACT

This thesis concentrates on the study of the S_N1 like ring opening of epoxides, and in particular, it focuses on the formation of allylic alcohols and α,β-unsaturated ketones from epoxides. The work is described in the three main chapters of this thesis.

An introductory chapter reviews the target natural product, *L*-carvone, and its industrial applications. There is a comprehensive review of the existing preparative methods of allylic alcohols from epoxides, with detailed discussion of the types of mechanisms involved. Subsequently, there is a discussion on the transformation of epoxides to α,β-unsaturated ketones.

The chapter covering results and discussion opens with a brief overview of the investigational work previously carried out into the S_N1 like ring opening of a model molecule, 1-methylcyclohexene oxide. This is followed by a description of how a new methodology for the acidic ring opening of epoxides was developed and optimised. This chemistry, leading to the formation of allylic alcohols through an S_N1 like mechanism, involved the use of a urea derivative. The scope and limitations of this novel methodology are then discussed through its application to a wider range of epoxide substrates. The chapter elaborates on the different strategies attempted, based on some adaptation of some of the existing methods of oxidation of alcohols to ketones, to achieve a one-pot synthesis of an α,β-unsaturated ketones from an epoxide. A novel synthesis was subsequently developed using a triflate sulfonium salt. The chapter is rounded off with a summary of the results of this work and of prospective future work.

A concluding chapter provides a formal description of the experimental results and procedures together with appropriate references.

CONTENTS

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ABBREVIATIONS

Ac	Acetyl
AIBN	2,2'-Azobis(2-methylpropionitrile)
Bp	Boiling point
br	Broad
Bu	Butyl
°C	Degrees Celsius
cat	Catalyst
CI	Chemical ionisation
d	Doublet
DCM	Dichloromethane
dd	Double doublet
ddd	Double double doublet
dt	Double triplet
ddt	Double double triplet
DMAP	*N*,*N*-Dimethyl-4-aminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
% ee	% Enantiomeric excess
EI	Electron impact
eq	Equivalent(s)
ESP	Electrospray
Et	Ethyl
EtOAc	Ethyl acetate
FAB	Fast atom bombardment
g	Gram(s)
h	Hours(s)
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
IR	Infrared spectroscopy

IS	Internal standard
J	Coupling constants
L	Liter
LDA	Lithium diisopropylamide
lit	Literature
LRMS	Low resolution mass spectrometry
m	Meta
min	Minute
M	$Mol.l^{-1}$
m	Medium
m	Multiplet
*m*CPBA	*Meta*-chloroperbenzoic acid
Me	Methyl
mg	Milligram(s)
mL	Millilitre(s) l
mmol	Millimole(s)
mol	Mole(s)
Mp	Melting point
NMR	Nuclear magnetic resonance
o	Ortho
p	Para
PE	Petroleum ether
Ph	phenyl
ppm	Part per million
Pr	Propyl
q	Quartet
rac	Racemic
rt	Room temperature
s	Singlet
s	Strong
scss	Strongly coupled spin system
SET	Single electron transfer
t	Tertiary

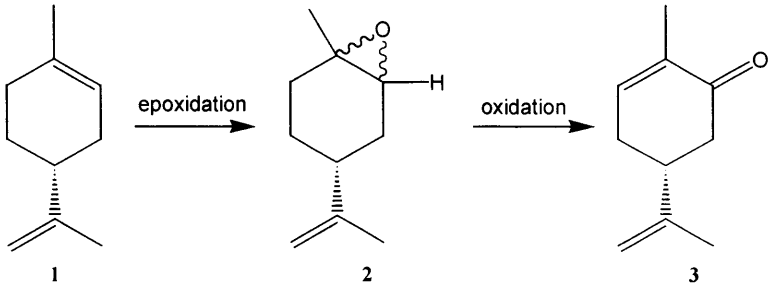
t	Triplet
TBDMS	*Tert* -butyldimethylsilyl
TBDPS	*Tert* -butyldiphenylsilyl
t-Bu	*Tert*-butyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Ts	Tosylate
UV	Ultraviolet spectroscopy
w	Weak

Chapter 1

INTRODUCTION

1. General background

The present thesis focuses on some novel aspects of carbocation chemistry, and in particular on the S_N1 like ring opening of epoxides. Within this framework, a particular problem of industrial relevance was the synthesis of the natural product *L*-carvone **3** from *D*-limonene **1** *via* the diastereoisomeric mixture of epoxides **2** (*Scheme 1*). Hence, in more general terms, this study was directed towards finding a new methodology for the syntheses of α,β-unsaturated ketones and allylic alcohols from epoxides.



Scheme 1

In order to place this area of chemistry in perspective, the following introductory review will highlight previous methods for the synthesis of allylic alcohols from epoxides, and will also present the main synthetic routes to α,β-unsaturated ketones from oxiranes. Within this context, the particular challenge of developing an effective route to *L*-carvone **3** from *D*-limonene **1** will also be emphasised in terms of the limitations of existing processes.

Epoxides, also called oxiranes, are three-membered ring heterocycles bearing an oxygen and two carbon atoms, and are among the most intensively studied functional groups. They are commonly used as synthetic intermediates due to their facile preparation from a variety of starting materials, often with substantial stereochemical control, and because of their high reactivity related to their polarity and strain of the three-membered ring. Indeed, they can undergo a wide range of reactions with electrophiles, nucleophiles, acids,

bases, reducing agents, and some oxidizing agents, and have been the subject of a large number of reviews over the years.[1-9]

The nucleophilic ring opening of epoxides is, of course, a particularly interesting and valuable reaction. The S_N2 opening of epoxides has been widely studied and is well understood, such that product control can be achieved easily.[10-12] By contrast, however, the S_N1 opening of epoxides is still not completely understood by chemists, and therefore remains a fascinating and very challenging area of study. Indeed, in spite of the extensive literature in this area,[13] it is still difficult to make product predictions with confidence. Some processes are clean and occur in high yields,[14] whilst many others give low yields and multicomponent mixture of products.[15] These products range from simple hydride shift to carbonyl isomers, through to structures formed by multistep rearrangements. Epoxides may also be converted, with or without skeletal rearrangement, to unsaturated alcohols, dienes, dimers or oligomers.[1-15] Moreover, a slight change to the reaction conditions can completely alter the product ratios.

Thus, the primary aim of this study was to try to "tame" the carbocations involved in the S_N1 opening of epoxides and thereby predict the outcome of this type of reaction. A few essential guidelines can already be drawn from previous studies on the subject, the main one being that the regioselectivity of epoxide opening in non-symmetrical oxiranes favours the formation of the more stable carbocation (*Figure 1*).

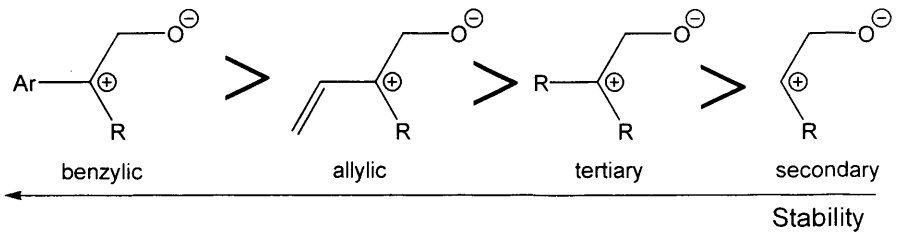


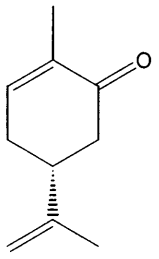
Figure 1

The development of an environmentally friendly and cost effective route for the production of *L*-carvone **3** from *D*-limonene **1** provides a challenge of particular importance to the flavours and fragrances industry. At this stage, it is appropriate to provide a brief overview of the properties and origin of this important monoterpene, and also to focus on the limitations of the existing methodology for its production.

2. *L*-Carvone

2.1. Introduction

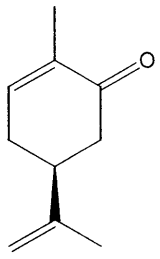
L-Carvone **3** is the major constituent and also the principal odour component of spearmint oil from which it is extracted by steam distillation. Both the oil and synthetic *L*-Carvone **3** are used as perfume and flavour ingredients bearing a refreshingly cool, minty odour and taste. The synthetic material is made industrially from *D*-limonene **1**, which is the major component of orange oil and therefore available as a by-product of orange juice production. *Quest International* is the world's major producer of *L*-carvone **3**. The chirality of the carvone, which is due to the carbon atom from the cyclohexyl ring at which the isopropenyl group is attached, is crucial to the odour, since the enantiomer *D*-carvone **4** has an odour reminiscent of caraway rather than spearmint[16-17] (*Figure 2*). This difference in odour is to be expected, since the odour receptors in the nose are chiral. It is therefore important that any synthesis of carvone leads to an enantiomerically pure product.



3

***L*-Carvone**

Spearmint smell



4

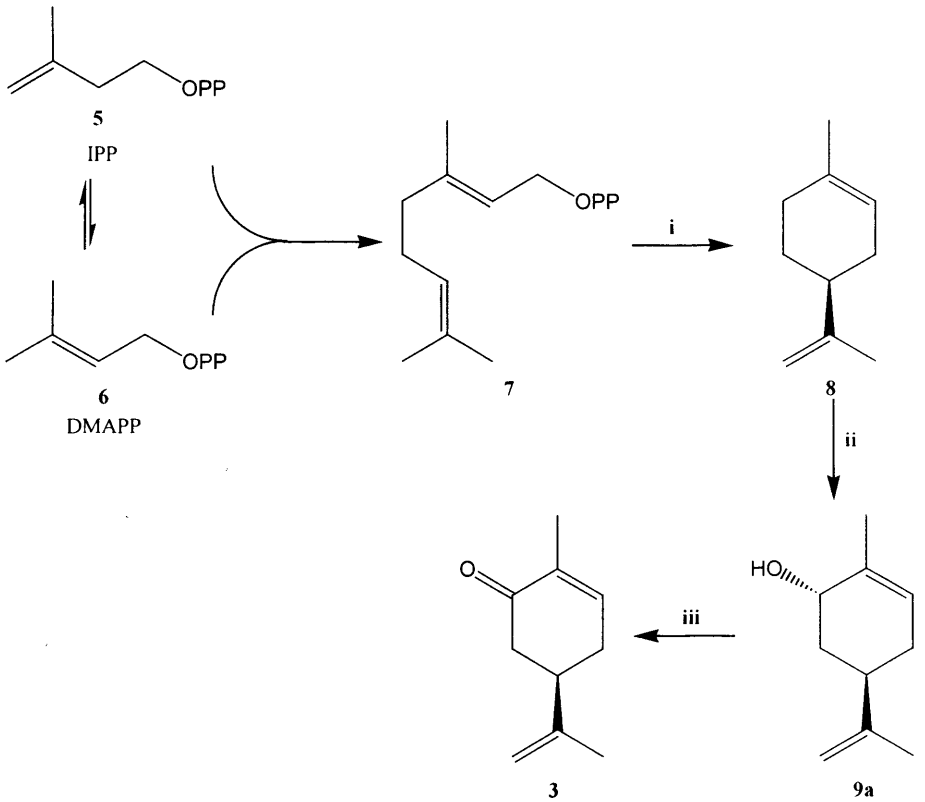
***D*-Carvone**

Caraway smell

Figure 2

2.2. Biosynthesis of *L*-Carvone

Spearmint (*Mentha spicata*) accumulates large quantities of monoterpenes in glandular trichomes, the major constituent of which is *L*-carvone. It is biosynthesised by a four-step sequence, as depicted in Scheme 2. The first step is a coupling reaction between isopentenyl diphosphate (IPP, **5**) and dimethylallyldiphosphate (DMAPP, **6**) to form geranyl diphosphate (7) which is subsequently cyclised to *L*-limonene **8** by a monoterpene synthase. This product is either stored in the leaves or oxidised to *trans*-carveol **9a** by limonene hydroxylase. This hydroxylation step occurs with high regio- and stereospecificity, since *trans*-carveol **9a** makes up to 97% of the total product. Finally, enzymatic oxidation of *trans*-carveol **9a** gives *L*-carvone **3**, which is then stored exclusively in the essential oil ducts of the plant.[18-19]



i)(-)-limonene cyclase, ii)(-)-limonene hydroxylase, iii) (-)-*trans*-carveol dehydrogenase

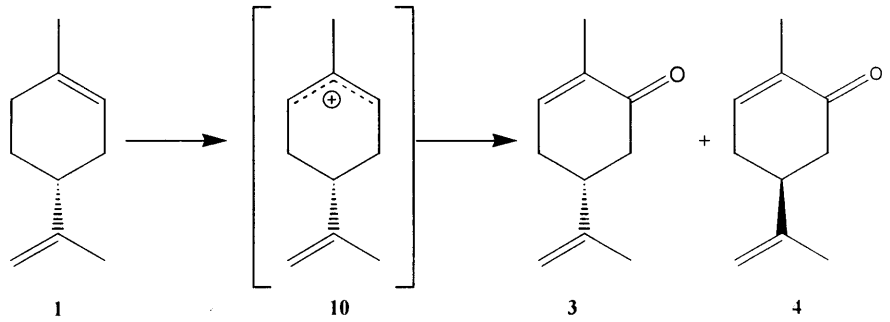
Scheme 2

2.3. Synthetic routes to *L*-Carvone

Due to the high cost of extraction of the naturally occurring carvoniferous oils, a variety of synthetic routes have been developed to provide a "nature identical" product.

D-Limonene **1**, readily available in large quantities as a by-product of the citrus industry, has almost invariably been selected as an excellent starting material for the production of *L*-carvone **3**.

In essence, starting from this abundant raw material **1**, endocyclic allylic oxidation with double bond transposition is required to form the correct enantiomer, *L*-carvone **3**. There is however a critical chirality issue here if this transformation goes *via* the symmetrical allylic cation intermediate **10**. Indeed, such a symmetrical intermediate cannot be considered except in a chiral environment, in order not to end up with a mixture of both enantiomers **3** and **4** (*Scheme 3*).



1 10 3 4

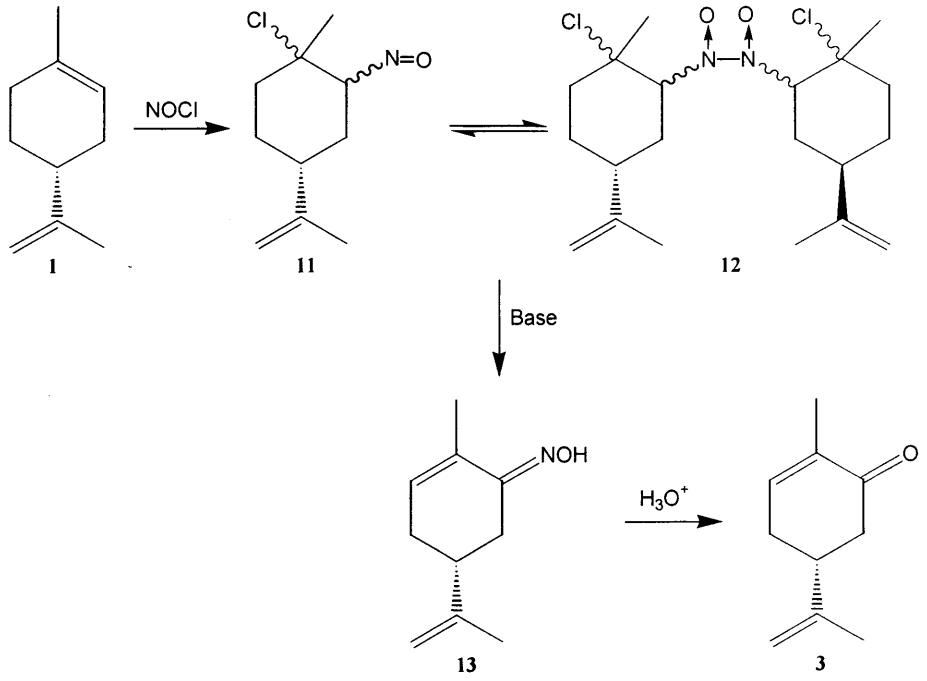
Scheme 3

2.3.1. The nitrosochlorination method

The nitrosochlorination strategy is the most commonly used, and still benefits today from the latest process improvements. The general approach is shown in scheme 4, where *D*-limonene **1** is converted to *D*-limonene nitrosochloride **11**. *D*-limonene nitrosochloride **11** is in equilibrium with its dimeric form **12** which

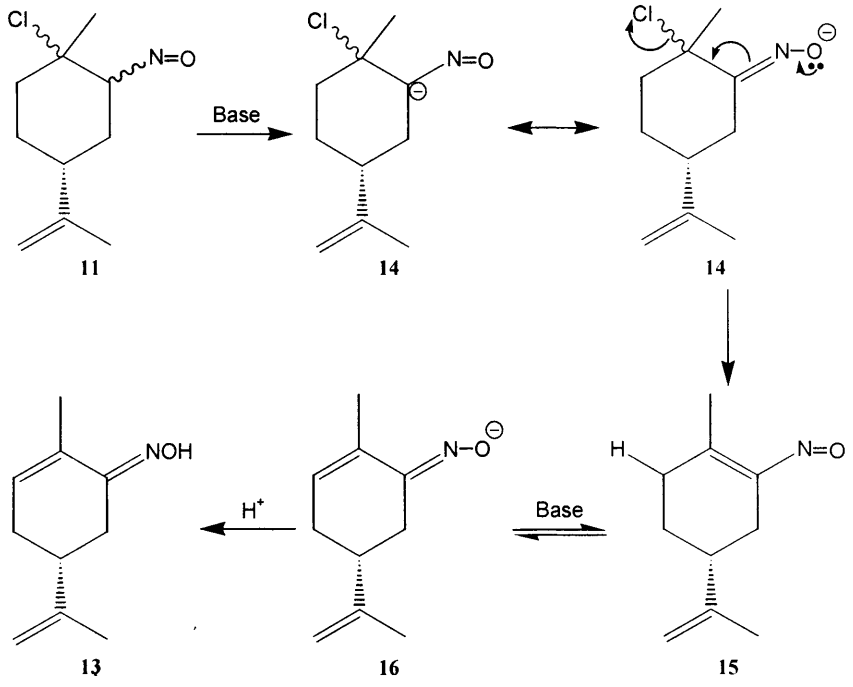
upon basic treatment yields *L*-carvoxime **13**, which is finally converted to *L*-carvone **3**. Different reaction conditions are used for each step of this sequence, as described below.

In the fundamental nitrosochlorination reaction, originally discovered by *Tilden* and *Shenstone*,[20] nitrosyl chloride reacts with the more electron rich endocyclic double bond in an electrophilic addition type reaction. The nitrosyl cation reacts with the less substituted end in a regioselective fashion, thereby generating the more stable carbocation, which is subsequently trapped by the chloride ions. The initial adduct is a blue liquid which is in equilibrium with the dimeric white solid **12** (*Scheme 4*). Various reaction conditions have been developed over the years for this first step, using either gaseous nitrosyl chloride,[21] or generating it *in situ* from methyl nitrite,[22] ethyl nitrite,[22-25] butyl nitrite,[26] amyl nitrite or nitrogen trioxide[27] in the presence of hydrochloric and sulphuric or acetic acids. Common solvents for this step are ethanol,[23] isopropyl alcohol[25] or liquid sulphur dioxide.[21] This first step is problematic as it involves harmful materials. Moreover, nitrosochloride derivatives are unstable, sensitive to heat and acid, and liable to violent decomposition, making them very difficult to handle, especially on a large-scale.



Scheme 4

The dehydrohalogenation step, achieved by the action of a base, requires high dilution in alcoholic solvents such as ethanol[28] or methanol with sodium or potassium hydroxide, pyridine,[23-26,29] urea[21] and dimethylformamide.[25,30] The mechanistic details for the formal elimination of hydrogen chloride from the nitrosochloride are not known in detail. Since the most acidic proton is almost certainly that adjacent to the nitroso group, it could be argued that formation of the oxime, or its derived anion **14** then leads to an assisted elimination of chloride anion to give **15**. Subsequent tautomerisation of the nitrosoalkene intermediate **15** leads exclusively to the endocyclic unsaturated oxime **13** (*Scheme 5*).



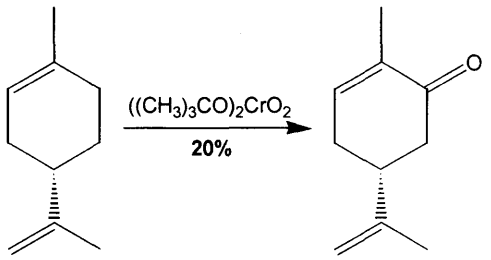
Scheme 5

The final step of the synthesis can be undertaken without purification of the carvoxime **13**, and is generally achieved by hydrolysis[20,22] with hydrochloric, sulphuric, phosphoric or oxalic acid. Under acidic conditions, the isopropylene group can isomerise to an isopropylidene moiety causing isomerisation, and reformation of the isopropylene group is accompanied by racemisation. These transformations can avoided either by maintaining the pH of the medium

between 0.7 and 0.9.[20,23,25] For purification, distillation maybe sufficient if the material is not required to be exceedingly pure.

2.3.2. The allylic oxidation method

Eschinazi has reported a practical laboratory method[22] for the allylic oxidation of *L*-limonene **8** to yield *L*-carvone **3**, through utilising the *tert*-butylchromate reagent of *Oppenauer* and *Oberrauch*[22b] (*Scheme 6*).



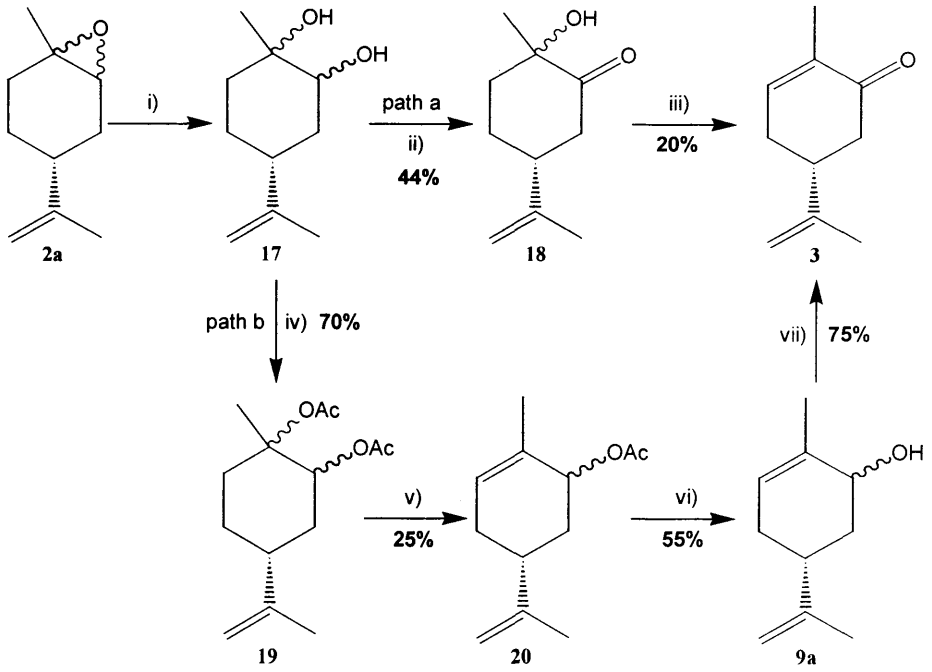
8 3

Scheme 6

The product formed by this allylic oxidation retains optical purity, thus making this method fascinating because of the facile formation of *L*-carvone **3** from inexpensive *L*-limonene **8** without the use of any harmful nitrogenous compounds. Also, the product resulting from this synthesis is claimed to fulfil the high standards of odour purity for perfumery. However, application of this method to flavours remains doubtful, because of the low yields obtained (20%) and the involvement of chromium reagents in the synthetic route.[31]

2.3.3. *Via* epoxidation

Two methods have been reported by *Linder* and *Greenspan*[32,33] for the synthesis of *L*-carvone **3** via epoxidation of *D*-limonene **1**, one by oxidation of limonene glycol **17** (*Scheme 7*, path a), and the other by pyrolysis of limonene glycol acetate **19** (*Scheme 7*, path b).



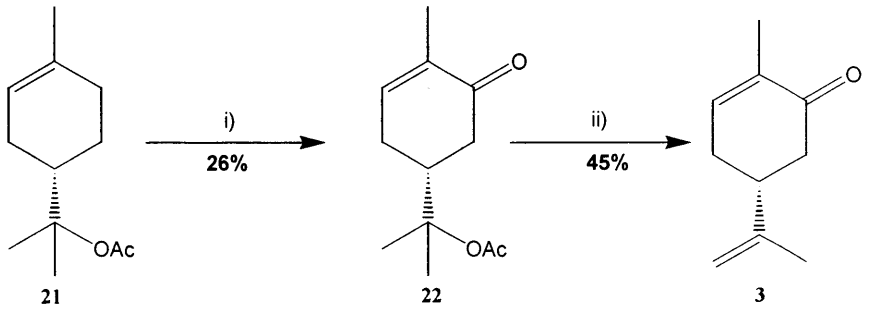
i) 1% H_2SO_4, 0 °C ii) $((CH_3)_3CO)CrO_2$ iii) NH_2OH then 5% oxalic acid iv) AcOH, Ac_2O v) pyrolysis vi) KOH vii) CrO_3

Scheme 7

In the former, epoxide **2a** derived from *D*-limonene **1** was hydrolysed to glycol **17**, by the action of 1% sulphuric acid at 0 °C. Glycol **17** was subsequently oxidised to keto-alcohol **18** using *tert*-butyl chromate, which was the only oxidising agent found by *Linder* and *Greenspan* that did not affect the double bond of the isopropenyl moiety. Since direct dehydration revealed itself to be problematic due to the acid-catalysed interfering reaction leading to carvacrol, preliminary conversion of **18** to the oxime or semicarbazone was necessary. Dehydration of the oxime followed by hydrolysis[32] then afforded *L*-carvone **3**.
In the latter method, glycol **17** was then converted to glycol diacetate **19**, in a 70% overall yield, using acetic acid and acetic anhydride. The diacetate **19** was subsequently pyrolysed to carveol acetate **20**, saponified to carveol **9a**, and finally oxidised with chromium trioxide to *L*-carvone **3**.
Both of these methods suffer once again from the use of chromium reagents and also result in poor overall yields, 9% and 7% respectively.

2.3.4. Synthesis from α-terpinyl acetate

An alternative route for the synthesis of *L*-carvone **3** developed by *Suga*,[34] using α-terpinyl acetate **21** as a starting material once again features the use of *tert*-butyl chromate, to achieve selective formation of enone **22** in low 26% yield after 15 days of reaction time. Further pyrolysis of **22** at 340 °C then affords the desired carvone in 45% yield (*Scheme 8*).



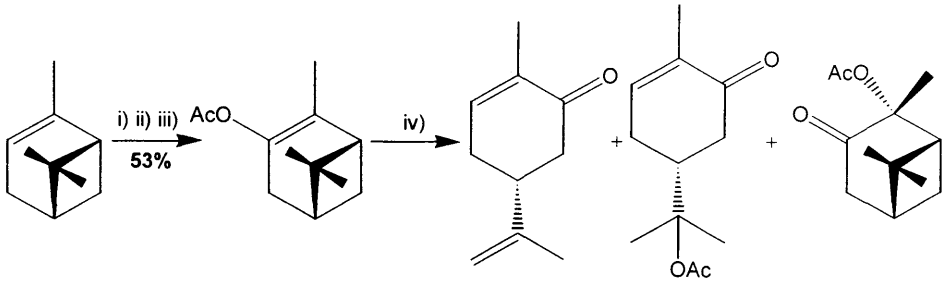
Scheme 8

Thus, the overall yield of this sequence is a poor 12%, and it is reasonable to say that the reaction conditions are not appropriate for large scale production.

2.3.5. Syntheses from α-pinene

2.3.5.1. *Via* electro-oxidation

A more efficient preparation of *L*-carvone **3** can be accomplished in four steps starting from α-pinene **23**. This method consists firstly of the derivatisation of α-pinene **23** to enol acetate **24**, followed by its anodic oxidation using a mixture of dichloromethane and acetic acid as solvent[35] (*Scheme 9*).

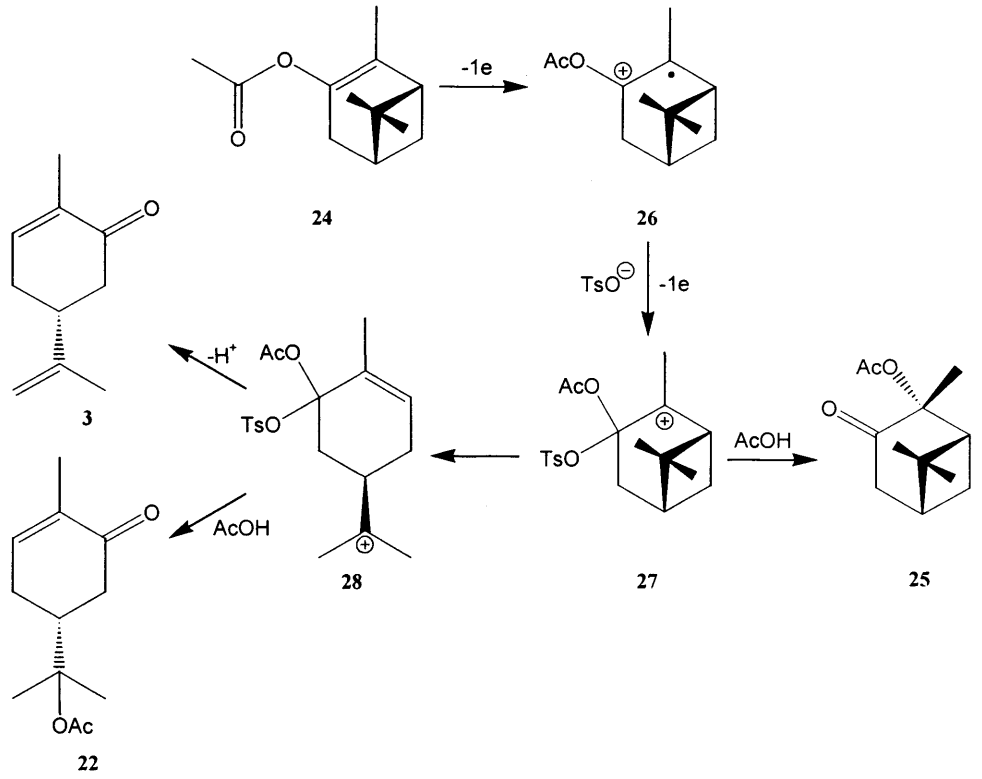


i) BH_3, NaOH-H_2O_2 ii) CrO_3 iii) $AcOC(CH_3)(CH_2)$ iv) anodic oxidation: DCM-AcOH (8:1), Et_4NOTs

Scheme 9

Enol acetate **24** is formed by hydroboration-oxidation[35b] of the double bond followed by further oxidation[35c] with *Jones'* reagent and reaction of the resulting ketone with isopropenyl acetate. Subsequent anodic oxidation of **24** affords the desired α,β-unsaturated ketone **3**. Two by-products are also formed in the anodic oxidation step, 8-acetoxy-*p*-menth-6-en-2-one **22** and the acetoxy ketone **25**. The product ratio is solvent dependent, and an optimal yield of 64% of *L*-carvone **3** is achieved using an 8:1 mixture of dichloromethane and acetic acid.

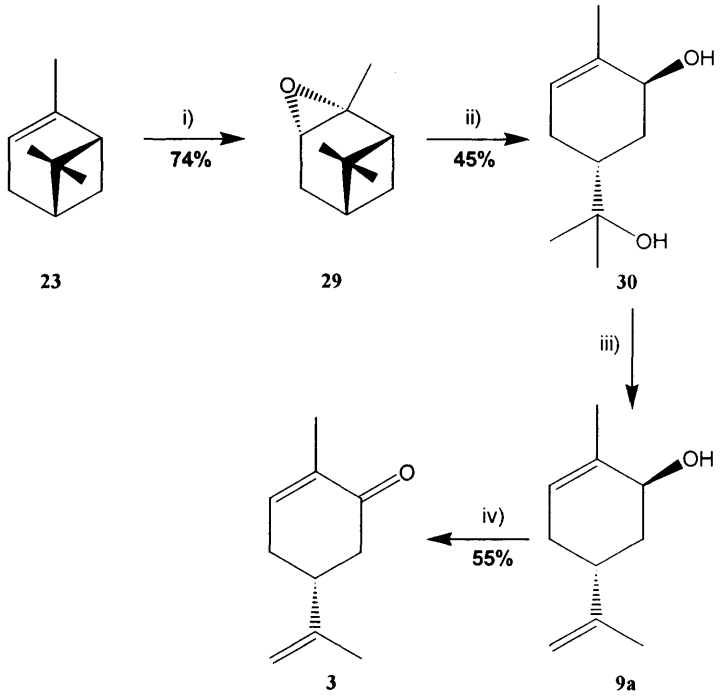
This transformation is of considerable interest, and the formation of the products may be explained by the following proposed mechanism (*Scheme 10*). A first single electron transfer leads to intermediate **26** which carbocation is trapped by *p*-toluenesulfonate anion. A second electron transfer gives carbocation **27** which can either be quenched by acetic acid to give **25**, or rearrange into a less strained carbocation intermediate **28**. This intermediate can subsequently lose a proton to give *L*-carvone **3**, or form an adduct **22** upon addition of acetic acid.



Scheme 10

2.3.5.2. *Via* epoxidation

A second four step transformation from α-pinene **23** involves epoxidation (*Scheme 11*). Subsequent ring opening of α-pinene oxide **29** with aqueous sulphuric acid[36] is followed by rearrangement into a less strained compound bearing a tertiary carbocation which is trapped by water to give sobrerol **30**. Dehydration to **9a** in acidic conditions led preferably to the dehydradation of the tertiary alcohol over the allylic one; oxidation of its allylic alcohol function with chromium trioxide leads to *L*-carvone[37] **3**.



i) *m*-CPBA ii) H_2SO_4 iii) dehydration iv) CrO_3

Scheme 11

2.3.6. Summary

The foregoing overview of the most common synthetic routes to *L*-carvone **3** reveals that the most effective syntheses to date use *D*-limonene **1** as a starting material and follow one of the variations of the nitrosochlorination pathway described in Scheme 4.

The more academic alternatives suffer from different drawbacks. Either the overall yields are low, or they involve toxic and non-environmentally friendly reagents. Therefore, some improvements to the existing routes or a new synthetic pathway are required.

3. Epoxides to allylic alcohols

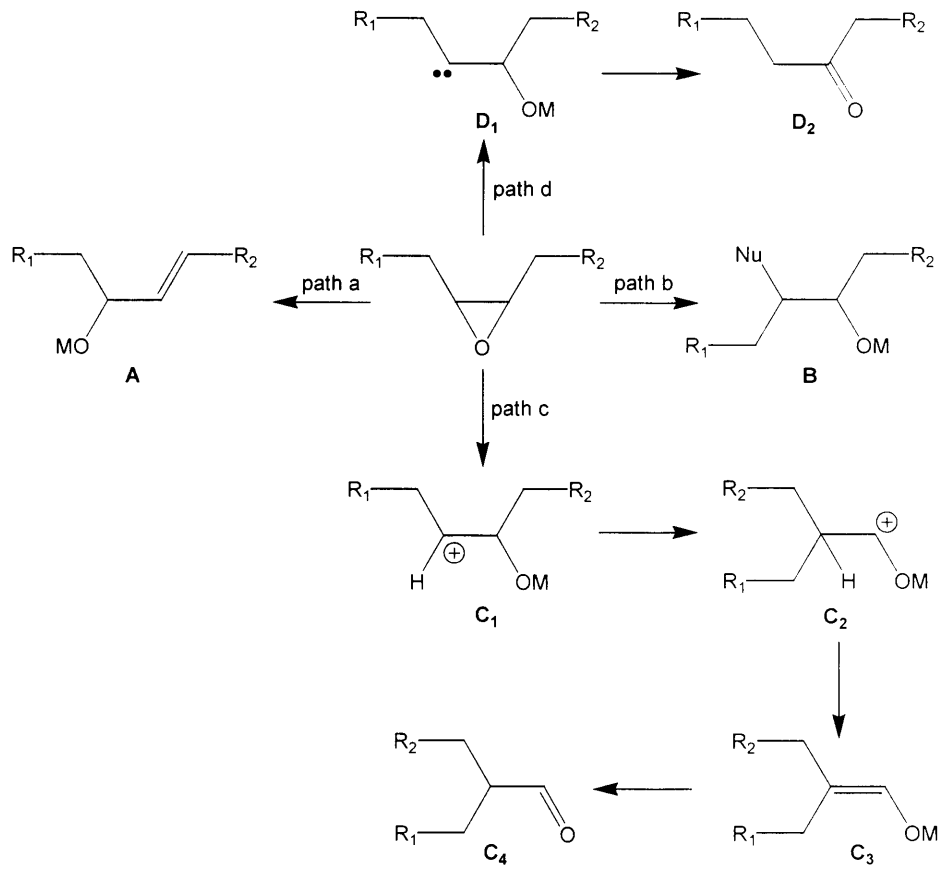
3.1. Introduction

A particularly attractive industrial route to carveol and hence to carvone could well involve controlled isomerisation of limonene oxide to carveol as a first step, and for this reason, it was of interest to examine those reactions already known in the literature which involve selective transformation of epoxides to allylic alcohols.

Over the past five decades, a range of methods have been developed for this transformation,[5,6,13] most of them involving the use of strong non-nucleophilic bases.[38] In most cases, the proton removal in the rearrangement of epoxides to allylic alcohols occurs from the least substituted carbon.[13] A few competing reactions go along with this transformation. A presentation of these competing processes, in the case of both basic and acidic reaction conditions is undertaken below, followed by a review of the major preparative methods which exist for the isomerisation of epoxides to allylic alcohols.

3.2. Mechanistic overview of epoxide ring opening with bases

Base promoted β-elimination leading to an allylic alcohol is a useful and widely used method for the isomerisation of epoxides to allylic alcohols of type **A** (*Scheme 12*, path a). However, there are several other competing mechanistic pathways leading to a range of products. First of all, the base may act as a nucleophile and react with the oxirane either in an S_N2 pathway, or, when a highly electropositive Lewis acidic metal cation is involved, by trapping the incipient carbocation resulting from epoxide opening to give an adduct **B** (path b).



Scheme 12

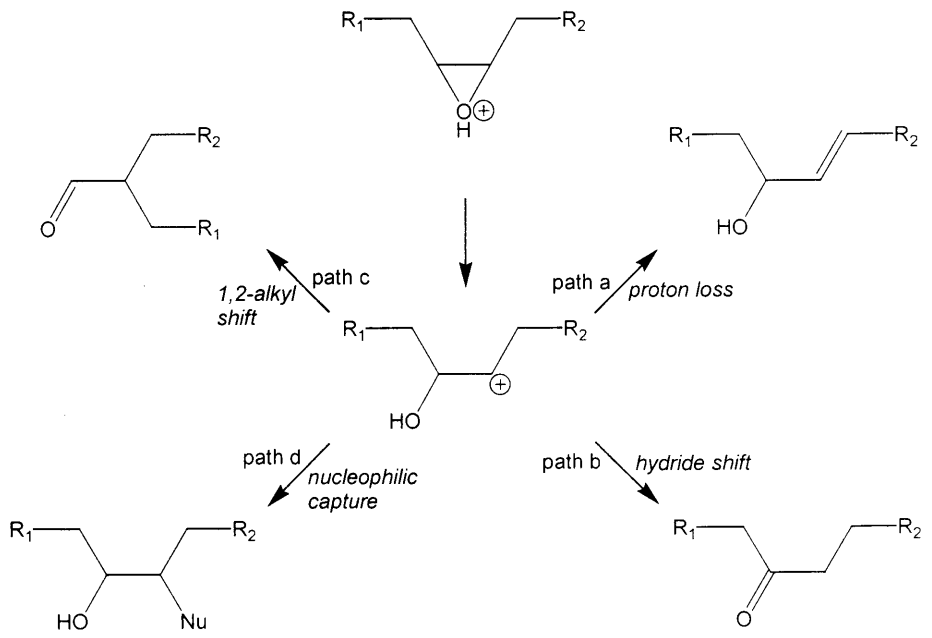
This pathway generally occurs with terminal epoxides, but can also occur with internal ones, as in the case of the reaction of cyclopentene oxide with lithium diethylamide to afford *trans*-2-diethylamino-1-cyclopentanol as the major product.[39] The electrophilic properties of the cation associated with the base can also be deployed in the absence of a strong donor solvent, hence leading to formal formation of a carbocation $\mathbf{C_1}$, which can undergo a 1,2-alkyl migration to form a more stable intermediate $\mathbf{C_2}$. Deprotonation initially leads to the formation of an enolate $\mathbf{C_3}$ and, upon work-up, to the corresponding aldehyde $\mathbf{C_4}$ (path c), as it is observed in the reaction of *trans*-2,3-dipropyloxirane with lithium diethylamide to form 2-propylheptanal in low yield.[40] Finally, a proton adjacent to the oxygen atom may be abstracted by the base, leading to a oxiranyllithium intermediate which generally rearranges to a *β*-

(lithiumoxy)alkylidene $\mathbf{D_1}$ (path d). Such a process is usually followed by a β-hydride shift to produce a ketone $\mathbf{D_2}$ *via* its enolate form.[29,41]

Clearly, in addition to regiochemical issues as a function of substrate structure, the competing sites for deprotonation and the possibilities of reactions evolving with considerable carbocationic character put some limitations on the use of strong "non-nucleophilic" bases for epoxides ring-opening.

3.3. Mechanistic overview of epoxide ring opening with acids or Lewis acids

Although the ring opening of epoxides under acidic or Lewis acidic conditions can actually give similar products as the ones formed under basic conditions, there is a difference between the mechanisms involved. Thus, in general terms, the intermediate carbocation resulting from an S_N1 ring opening of an epoxide, can react *via* four different pathways as described in Scheme 13. However, it is important to note that mixtures of products are often formed under these conditions and it is therefore difficult to compile some simple rules through examination of literature examples.



Scheme 13

The route of greatest interest for our own case, involving "simple" proton elimination leading to an allylic alcohol (path a), seldom happens under acidic conditions, and generally requires the presence of a compatible base to accept the proton which is necessary to form the olefin. This is the case when using aluminium oxide, which contains both acidic and basic sites.[42-47]

The most common, and generally the fastest transformation of the carbocation consists of a hydride shift, when available, leading to a ketone (path b). When working with a non-nucleophilic counteranion, where trapping the carbocation formed is less favoured, this is the preferred route, as exemplified by the reaction of 1-methylcyclohexene oxide with lithium perchlorate to form 2-methylcyclohexanone.[14,48]

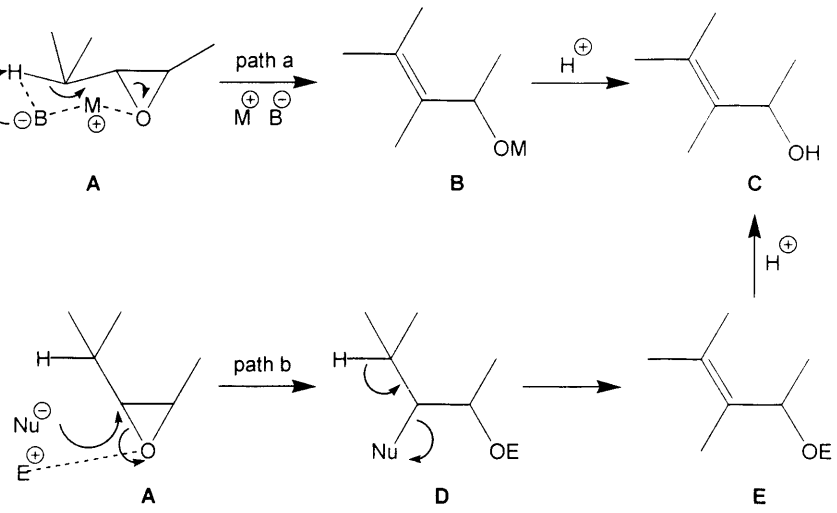
Further rearrangement of the starting carbocation into a more stable carbocation *via* a 1,2-alkyl migration can lead to an aldehyde (path c), and is usually observed when the nucleophilic counteranion can trap the carbocation, and where migration of the alkyl group over hydride is preferable on stereoelectronic grounds to achieve the displacement. This process is seen in the isomerisation of both *cis*- and *trans*-stilbene oxide with boron trifluoride etherate to afford diphenylacetaldehyde as the only product.[49,50] However, if the counter anion is not a good leaving group, an adduct is generally formed (path d). Such a process occurs in the ring opening of 1-methylcyclohexene oxide with trimethylsilyl cyanide in the presence of a catalytic amount of zinc iodide to yield an isonitrile.[51]

The nature of the counter anion is clearly crucial. A non-nucleophilic anion will favour a rearrangement through a hydride shift over alkyl migration,[14,48] whereas a nucleophilic one can give rise to two situations. If it is a good leaving group, its displacement will be performed by migration of the more electron rich substituent, *viz.*, by an alkyl migration over a hydride shift.[49,50] If the counteranion is more nucleophilic, a simple adduct will be the final product.[51]

3.4. Preparatively useful method for the conversion of epoxides to allylic alcohols

3.4.1. General considerations

Two different strategies have evolved for the conversion of epoxides to allylic alcohols, and both are especially applicable to the base-induced mechanism (*Scheme 14*).



Scheme 14

Thus, considering a general epoxide **A** bearing a proton on the carbon adjacent to the ring, treatment with a strong base usually leads, *via* prior coordination of the metal M^+ to the oxygen atom, to β-proton abstraction with concomitant ring opening to form an allylic alkoxide **B** (path a). This then affords an allylic alcohol **C** upon protonation. Alternatively, the epoxide **A** can be attacked by a nucleophile to afford an adduct **D** (path b). The desired double bond can then be generated by elimination of HNu to form **E** which gives the allylic alcohol **C** upon further protonation, if the nucleophile can function as a leaving group. Alternatively, it can simply be transformed into a leaving group in a subsequent chemical reaction.

Many different methods have been developed over the years for the transformation of epoxides to allylic alcohols, and the main procedures will now be presented.

The first two methods, using organolithium and organoaluminium reagents, will receive special attention since they are the most popular ones. Most of the other procedures have the same features, and will therefore have similar mechanisms.

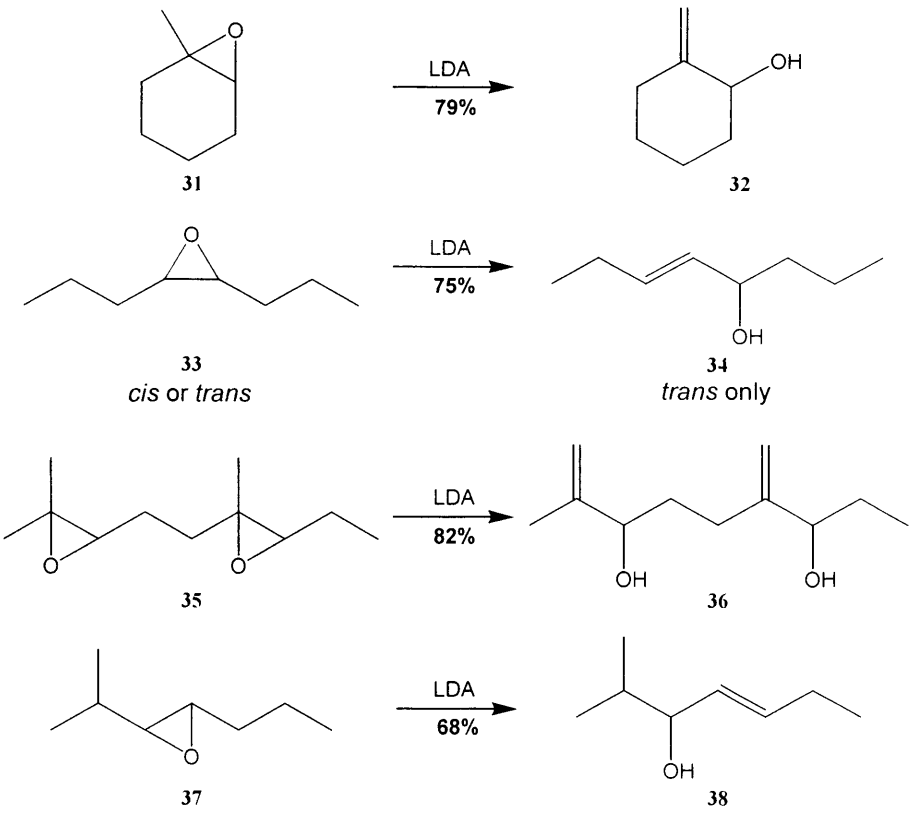
3.4.2. Organolithium reagents

3.4.2.1. Lithium dialkylamide $LiNR_2$

3.4.2.1.1. General features

The most widespread method for the isomerisation of epoxides to allylic alcohols involves the use of a strong non-nucleophilic base $LiNR_2$, at least in equimolar amount, in non-polar solvents. This method has been extensively studied over the last 40 years by *Cope*,[38] *Crandall*[39,53,54] and *Rickborn*,[55-59] and is efficient for both acyclic and cyclic epoxides. In more recent years, some further improvements have been made, especially with the development of chiral lithium dialkylamides for the kinetic resolution of racemic epoxides to allylic alcohols.[60-62] The two lithium bases most commonly used have been lithium diethylamide (LDA) and lithium diisopropylamide (LDIPA).

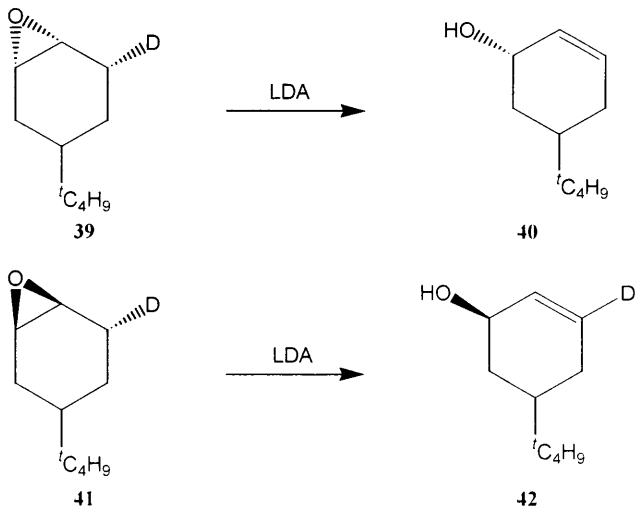
The reaction proceeds predominantly, if not exclusively, by a β-elimination pathway.[38] Formally an elimination, this reaction is actually remarkable for both its high stereoselectivity (exclusive formation of *trans*-olefin in open-chain systems[38,55]) and regioselectivity (quasi-exclusive abstraction of a proton from the least substituted carbon[39,52,55,63-65]), as illustrated in Scheme 15.



Scheme 15

The high degree of regioselectivity is highlighted in the formation of **32**, **36** and **38**, where proton abstraction occurs only from the least substituted carbon. In terms of stereoselectivity, the isomerisation of both *cis*- and *trans*-4,5-epoxyoctane **33** leads only to the *trans*-isomer **34**. In the case of the formation of allylic alcohol **38**, less than 1% of the alternative isomer was formed,[55] and this result, along with observations from further experiments, led to the conclusion that the relative rates of β-proton abstraction were primary:secondary:tertiary, 10^3:10:1. This feature has been attributed to a combination of steric effects and the preferred geometry in the elimination step as outlined below.

Thus, from the results of experiments on selectively deuterated cyclohexene oxides,[56] *Rickborn et al.* demonstrated that isomerisation to allylic alcohols followed a *syn* elimination mechanism, where a *cis* coplanar arrangement of β-hydrogen and epoxide oxygen atom was required (*Scheme 16*).



Scheme 16

In the case of 1-alkylcycloalkene oxides of small and medium sizes, this condition is not easily satisfied within the ring, and *cis* coplanarity is more easily attained with the protons of alkyl substituents, hence leading mainly to the formation of exocyclic allylic alcohols. Therefore, 6, 7 and 8-membered ring epoxides bearing a methyl substituent α to the epoxide oxygen atom gave 2-methylenecycloalkanols as the major products.[52]

The mechanism for this reaction involves the coordination of the oxygen lone pair of the oxirane with the electropositive lithium centre to give complex **43**, as represented in Figure 3. Decomposition of **44** in a cyclic, concerted mechanism gives a reasonable route for the formation of the final allylic alcohol. Removal of a *syn* hydrogen atom in cyclic systems is required in such a process (**44** in *Figure 3*).

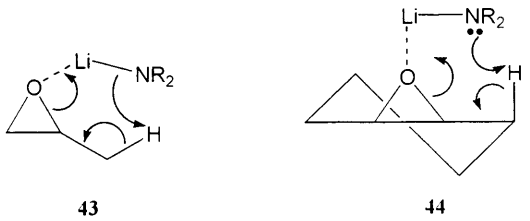
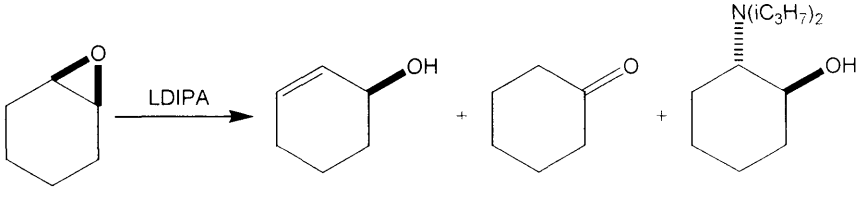


Figure 3

3.4.2.1.2. LDA Derivatives

Due to the low efficiency of LDA and LDIPA with some substrates, some modified methods have been developed. Two main procedures derived from LDA will be presented. The first involves a LDA-HMPA reagent,[41] and the second a mixture of LDIPA and potassium *tert*-butoxide ("LIDAKOR[66] reagent").

A major competitive reaction in the transformation of epoxides to allylic alcohols, which occurs *via* proton elimination, is the α-elimination corresponding to the exchange of a lithium ion and an α-hydrogen atom leading to insertion products. A solution to this issue was to prevent involvement of the cation acting as such by complexing it with the solvent. *Apparu* exploited this concept and discovered that by using HMPA as a solvent which would coordinate the lithium cation, far better results were obtained, the competing α-elimination being suppressed.[41] Accordingly, clean transformation of cyclohexene oxide **45** to cyclohexen-3-ol **46** was accomplished, avoiding the competing formation of the carbonyl compound and the nucleophilic addition of the amide which occurred using LDIPA alone[41] (*Scheme 17*).



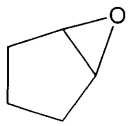
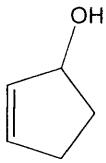
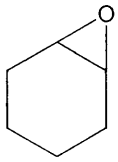
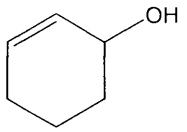
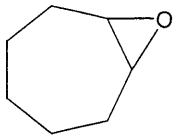
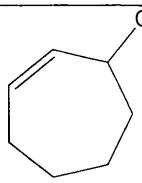
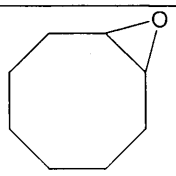
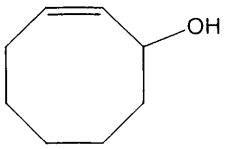
Scheme 17

Schlosser et al. thought that a combination of lithium and potassium bases should be more efficient if mixed together to perform the isomerisation of epoxides to allylic alcohols.[66] Indeed, they considered that due to its

electrophilic properties, the lighter alkali metal could trigger the opening of the oxirane ring whilst the heavier alkali metal would confer maximum basicity to the anionic counterpart and thus permit an easier deprotonation. Furthermore, it was demonstrated that potassium *tert*-butoxide activates organolithium compounds, which led them to mix it with LDIPA to form a new reagent "LIDAKOR".[66]

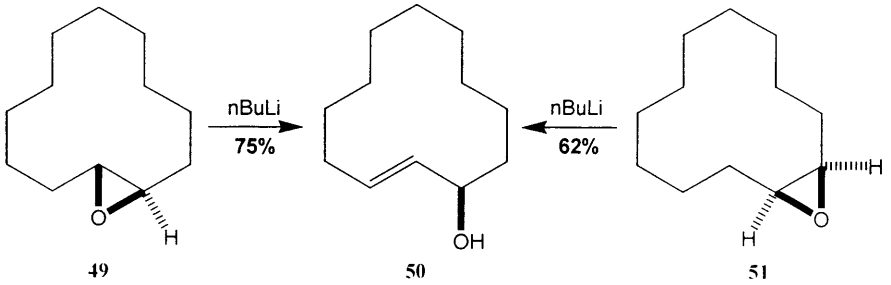
Application of this method gave satisfactory results even at 0 °C (*Table 1*).

Table 1. Preparation of allylic alcohol using the LIDAKOR reagent

Starting material	Product	Yield
		88%
		76%
		40%
		68%

3.4.2.2. n-BuLi

The use of a simple alkyllithium, first reported by *Zakharkin*,[67] has not been extensively investigated and allylic alcohols have been formed in moderate to good yields, but only from a few substrates[68] (*Scheme 18*).



49 50 51

Scheme 18

3.4.3. Aluminium bases

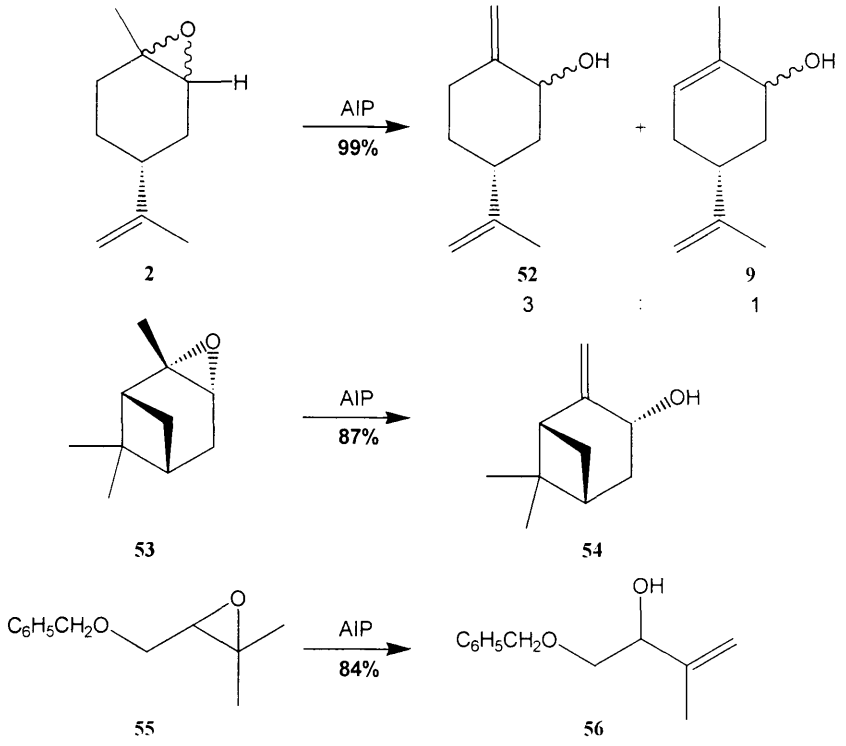
3.4.3.1. Generalities

Aluminium bases have also proven to be particularly useful. The valuable properties of these reagents arise from the high Lewis acidity of the organoaluminium derivatives, and from the tendency of the aluminium atom to form an "ate" complex and hence to complete its electron octet with oxygen atoms. In fact, the aluminium-oxygen bond has a bond strength estimated to be 138 kcal/mol, thus easily forming complexes with oxiranes. This oxophilicity is exploited in the isomerisation of epoxides, especially through the use of three reagents, aluminium isopropoxide, diethylaluminium 2,2,6,6-tertramethylpiperidide and aluminium oxide.

3.4.3.2. Aluminium isopropoxide

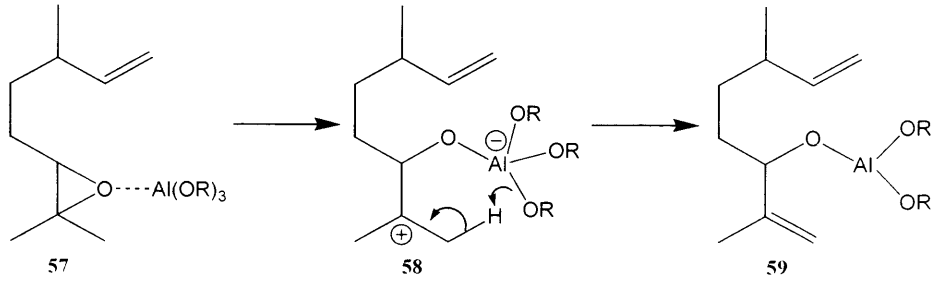
The aluminium isopropoxide (AIP) catalysed rearrangement of epoxides affords a selective way of preparing allylic alcohols in good yields.[69,70] With epoxides derived from trisubstituted alkenes, a facile and specific rearrangement can occur under relatively mild conditions (25 °C to 125 °C) as catalytic amounts of AIP (0.1 mol%) are added to the reaction mixtures. However, more drastic reaction conditions, including equimolar amounts of AIP and higher temperatures, are required when primary or secondary carbons are present at the position α to the oxirane oxygen atom.

In most cases, formation of the least substituted allylic alcohol is observed (*Scheme 19*, formation of **54** and **56**). In the case of the mixture of (+)-(*R*)-limonene oxides **2**, preferential formation of the exocyclic rather than the endocyclic double bond was observed,[70-73] leading to a 3:1 ratio of **52** and **9** (*Scheme 19*).



Scheme 19

The accepted mechanism of the reaction is illustrated with 2,6-dimethyl-2,3-epoxyoct-7-ene **57** (*Scheme 20*). Chelation of the aluminium to the oxygen atom of the epoxide **57** results in a cleavage of the bond at the most substituted α-carbon, hence forming the more stable carbocation **58**. Consequently, a mechanism involving a six membered transition state with a proton transfer from the least substituted carbon β to the oxygen atom was proposed for this reaction, which led therefore to the formation of the least substituted allylic alcohol **59**.

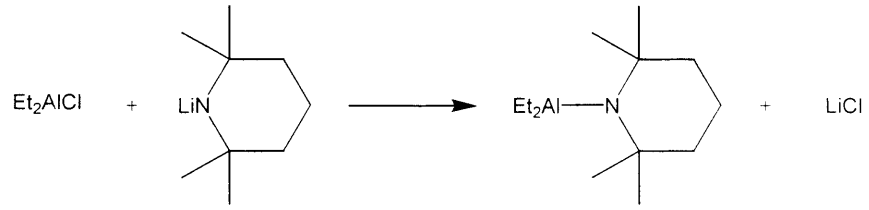


57 58 59

Scheme 20

3.4.3.3. DATMP

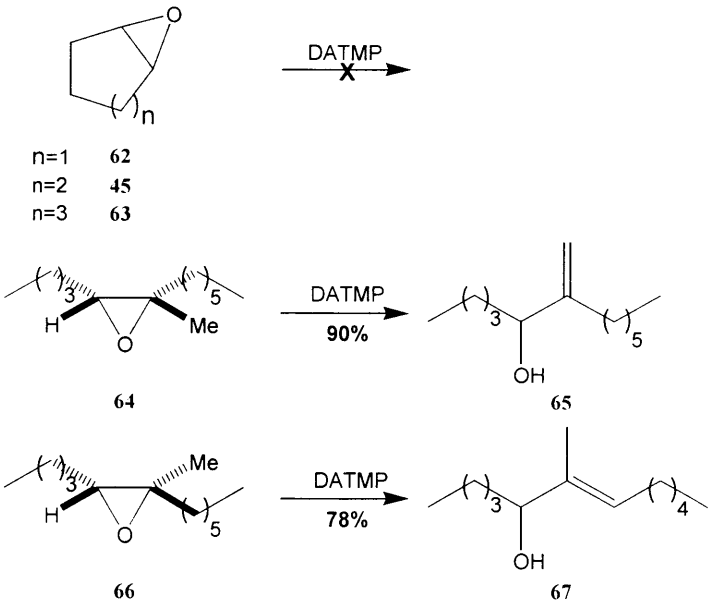
This method is similar to the isomerisation of epoxides with lithium dialkylamides but proceeds under milder conditions. It involves the use of a diethylaluminium dialkylamide, and particularly diethylaluminium 2,2,6,6-tetramethylpiperidide **61** (DATMP), in at least an equimolar amount.[74-76] This reagent is generally prepared *in situ* from diethylaluminium chloride and lithium 2,2,6,6-tetramethylpiperidide **60** in benzene (*Scheme 21*). This method also exploits the affinity of the metal, aluminium, for the oxygen atom.



60 61

Scheme 21

The procedure is very efficient with epoxides derived from trisubstituted alkenes as well as *trans*-2,3-substituted epoxides. However, it is inefficient with *cis*-2,3-disubstituted epoxides, cyclopentene oxide **62**, cyclohexene oxide **45** and cycloheptene oxide **63**, which remain inert upon treatment with DATMP. Moreover, different selectivities were observed with the two diastereoisomers of 6-methyl-5,6-epoxydodecane, **64** and **66** (*Scheme 22*).



Scheme 22

These latter observations were particularly interesting from a mechanistic viewpoint, since aluminium amides preferentially abstract a proton of the alkyl group located on the same side of the hydrogen atom of the oxirane, to give the corresponding allylic alcohol. This is attributed to the attack of the DATMP from the less hindered side of the epoxide, following a "steric approach control".[74] In addition, the double bond formed prefers the *E*-configuration.
Such a high selectivity can be explained by a cyclic *syn* elimination mechanism where the ring opening has substantial stereoelectronic requirements. The favoured direction of elimination can then be explained by preferential proton abstraction providing a greater orbital overlap in the cyclic transition state as shown in Figure 4, with an energetically favourable conformation.

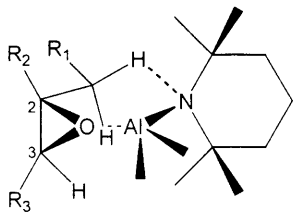
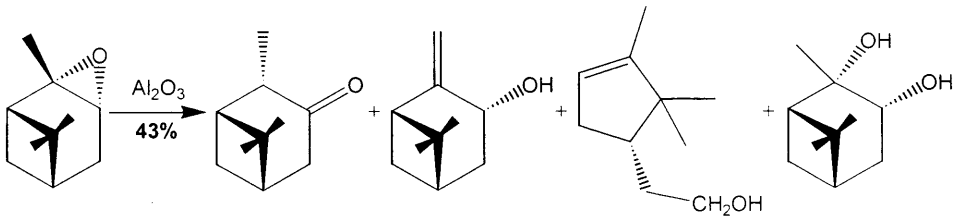


Figure 4

These mechanistic studies by *Yamamoto* and *Nozaki*[75] highlighted three essential rules: (i) the sole product is a secondary allylic alcohol, (ii) the required proton is supplied by the alkyl group on C(2) and located *cis* to the hydrogen of the carbon atom C(3), (iii) the resulting double bond prefers the *E* configuration.

3.4.3.4. Aluminium oxides Al_2O_3

It was discovered in the early sixties that on contact with active alumina, epoxides were isomerised to α,β-unsaturated alcohols.[42-47] Initially, this method was not very efficient and led mainly to mixtures of products containing only small amounts of the desired allylic alcohols, with the major product being the corresponding vicinal diols.[42,43] Nevertheless, as a result of extensive studies, a fairly efficient and selective method was developed.[45] It was actually found that four types of reaction were initiated on the active surface sites of alumina: (i) rearrangement to allylic alcohols, (ii) rearrangement to a ketone, (iii) hydration to form a vicinal diol, and (iv) typical carbonium ion rearrangements.[77,78] This is well illustrated in the reaction of β-pinene oxide with Al_2O_3 doped with KCl[46] (*Scheme 23*).



68 69 36% 70 42% 71 19% 72 1%

Scheme 23

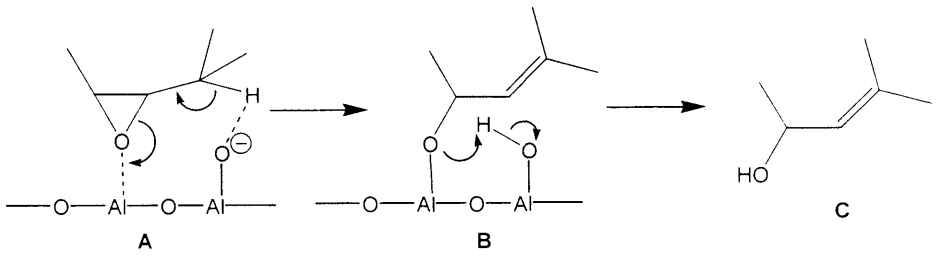
The latter two reactions are relatively insignificant when trisubstituted epoxides are used, and consequently, with such substrates, studies were carried out to favour the formation of allylic alcohols.

Several types of activated alumina with different modified surfaces were studied,[42,44-46] and it was found that doping the surface with a base, and especially sodium hydroxide, increased dramatically the selectivity of the reaction towards formation of the desired allylic alcohol **70** (*Table 2*), in 70% yield with an excellent selectivity over the two other minor products.[46]

Table 2. Opening of pinene oxide with Al_2O_3

Solid matrix	Total recovery (%)	Product composition (%)			
		69	**70**	**71**	**72**
Al_2O_3	52	13	57	27	3
Al_2O_3-LiOH	62	12	75	13	-
Al_2O_3-NaOH	75	4	93	3	-
Al_2O_3-KOH	60	6	90	4	-

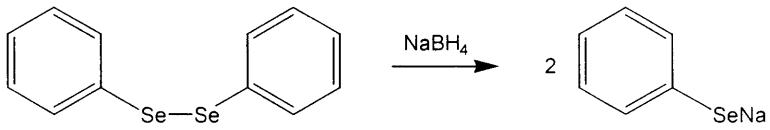
The reactivity of alumina is explained by its dipolar or amphoteric character with the presence of both electron-donor (basic) and electron-acceptor (acidic) sites on its surface. Both these sites are involved in the isomerisation of epoxides to α,β-unsaturated alcohols. Mechanistic studies showed that allylic alcohols were formed by acid-base bifunctional catalysis, whereby the oxygen atom of epoxide **A** is adsorbed onto the Lewis acidic site, and the proton removed by a basic aluminium alkoxide site[44,79] to give **B** (*Scheme 24*). Subsequent hydrolysis finally gives the allylic alcohol **C**.



Scheme 24

3.4.4. Organoselenium reagents

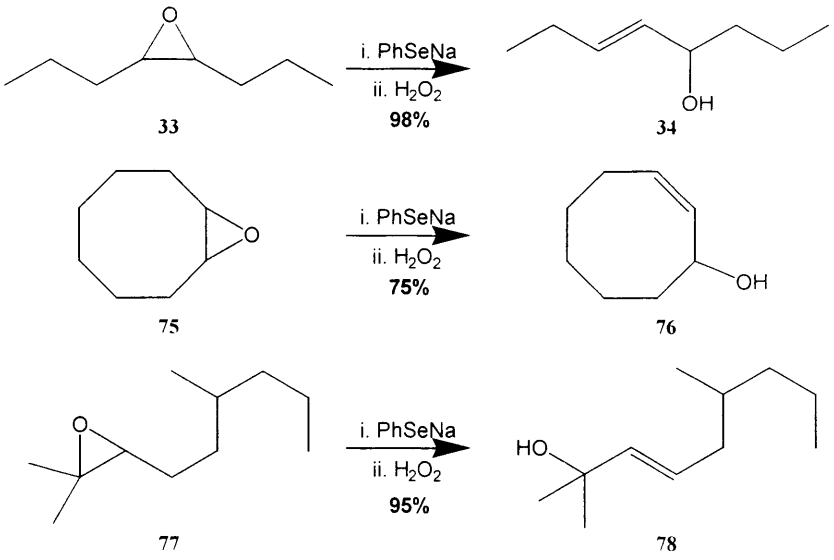
In contrast, to the use of strong non-nucleophilic bases, the essence of this method involves regiospecific epoxide ring opening followed by conversion of the attacking nucleophile into a suitable leaving group for elimination.
Thus, it has been shown that alkyl phenyl selenoxides bearing a β-hydrogen undergo *syn* elimination to form olefins.[80] Based on this facile elimination, a new method for the isomerisation of epoxides to allylic alcohols under relatively mild conditions was developed by *Sharpless*,[81] using an equimolar amount of sodium phenylselenide **74**, prepared from diphenyl diselenide **73** and sodium borohydride in absolute ethanol (*Scheme 25*).



73 **74**

Scheme 25

As a consequence of the fact that selenoxide elimination always occurs away from the alcohol group, this procedure affords good yields of allylic alcohols with di- and tri substituted epoxides with crude mixtures almost free of by-products (*Scheme 26*).

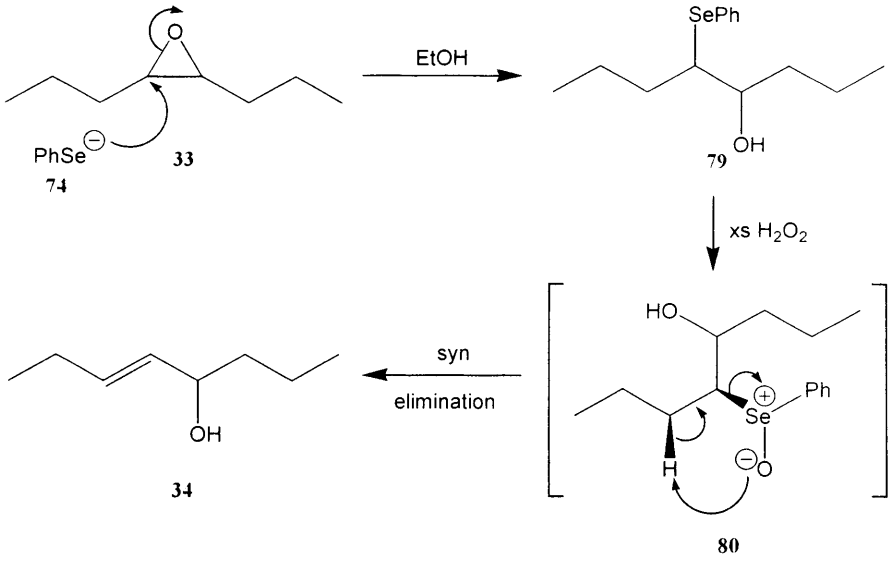


33 34 75 76 77 78

Scheme 26

Moreover, the almost neutral sodium phenylselenide can be used in cases where strong bases like lithium dialkylamide are not tolerated. Nevertheless, two main drawbacks to this method are the expense of the reagent and, more importantly, the toxicity of such compounds.

The mechanism of formation of allylic alcohols is illustrated by the reaction of 4,5-epoxyoctane **33** with phenylselenide anion **74** (*Scheme 27*). The anion **74** is an excellent nucleophile which opens the epoxide **33** easily to form the hydroxy selenide **79**. Direct oxidation of **79** by action of excess hydrogen peroxide affords unstable selenoxide **80**, whose decomposition leads to the *E* allylic alcohol **34**.



Scheme 27

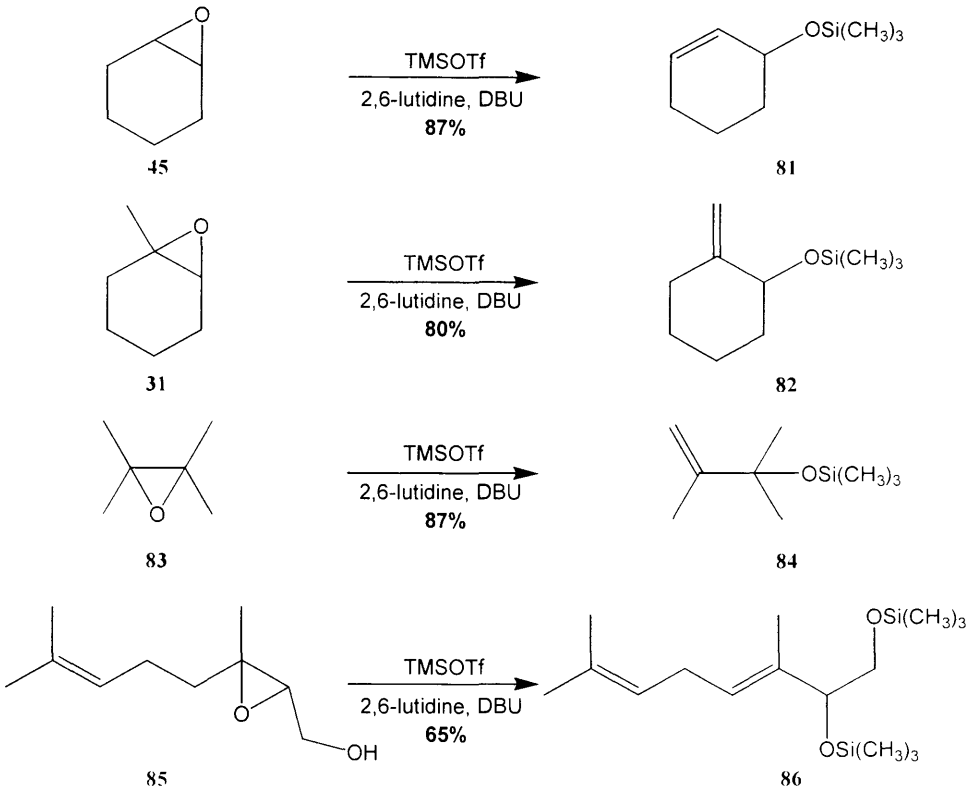
The first step of this mechanism involves an S_N2 type epoxide ring opening on the less hindered carbon atom, hence leading to the opposite regioselectivity which is observed for most of the other methods reported above.

3.4.5. Organosilicon reagents

3.4.5.1. *Noyori*'s method

A very mild method for the conversion of epoxides to allylic alcohols using equimolar amounts of trimethylsilyl trifluoromethanesulfonate in the presence of 2,6-lutidine, followed by treatment with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU), was developed by *Noyori*.[82,83] The reaction affords the allylic alcohol as its protected trimethylsilyl ether, and treatment with either dilute hydrochloric acid or potassium fluoride in methanol then liberates the free hydroxyl group.

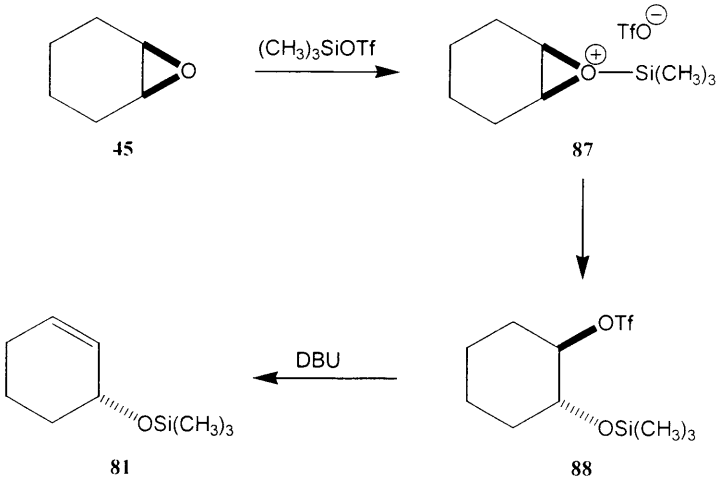
This method works well with cyclic substrates possessing ordinary ring size (5, 6 or 7-membered) as well as with 2,2-di-, tri-, and tetrasubstituted oxiranes. 1-Methylcyclohexene oxide **31** afforded the exocyclic allylic alcohol **82** as the only product (*Scheme 28*).



Scheme 28

However, oxiranes derived from either simple terminal alkenes or from acyclic disubstituted alkenes remained inert under these reaction conditions.

The efficiency of this method is attributed to the affinity of the silicon electrophile for the oxygen atom (*Scheme 29*). When an unsymmetrically trisubstituted oxirane is used, ring opening occurs, as expected, at the more substituted carbon. The elimination step, using DBU as a base, was proposed to follow an E2 mechanism with *anti* stereochemistry rather than intramolecular *syn* elimination.



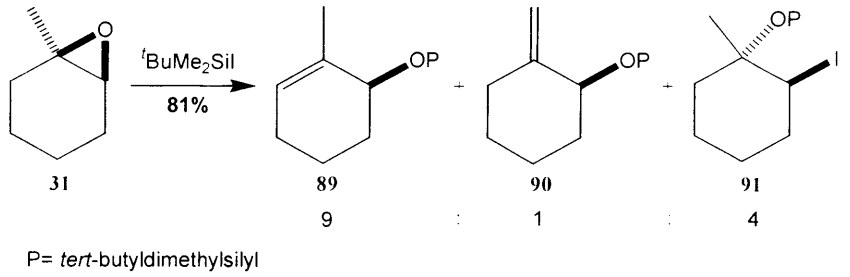
45 87 88 81

Scheme 29.

3.4.5.2. *tert*-Butyldimethylsilyl iodide

A variant of the above sequence involving the reaction of oxiranes with *tert*-butyldimethylsilyl iodide followed by treatment with 1,5-diazabicylo[4.3.0]non-5-ene leading to *tert*-butyldimethylsilyl ether protected allylic alcohols, has been reported by *Detty*.[84]

This method also requires equimolar amounts of reagents, and gives satisfactory results with cyclic di-, tri-, and tertrasubstituted oxiranes. As with most of the methods previously described, when an unsymmetrical trisubstituted oxirane is used, ring opening occurs at the more substituted carbon. However, interestingly and in contrast to other methods, isomerisation of 1-methylcyclohexene oxide **31** gave a mixture of both endo **89** and exocyclic allylic alcohols **90** in a 9:1 ratio in favour of the former, along with an adduct **91** derived by a more S_N2 like ring opening (*Scheme 30*).



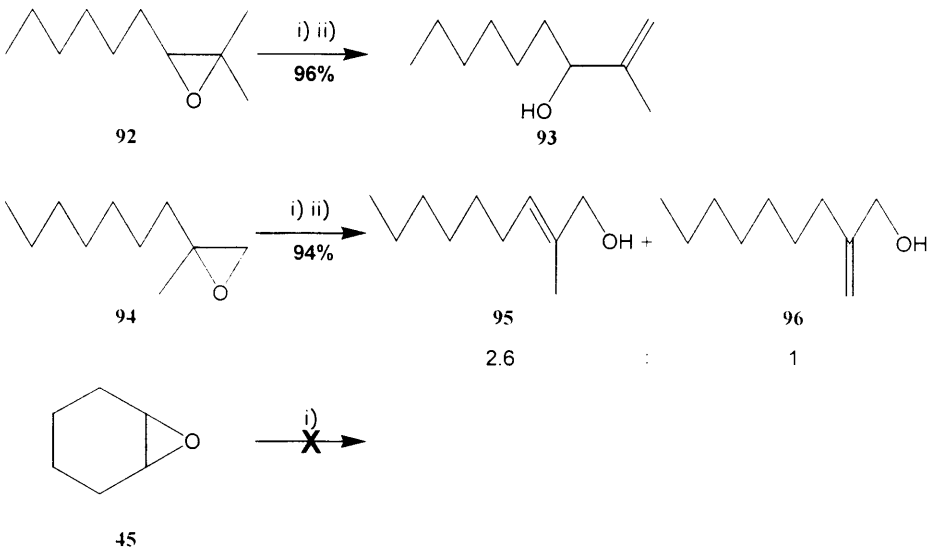
Scheme 30

The mechanism of formation of these protected allylic alcohols is similar to that using trimethylsilyl trifluoromethanesulfonate as described above.

3.4.6. Organoboron reagents

In similar fashion to aluminium and silicon, the oxophilicity of boron for the isomerisation of epoxides to allylic alcohols has also been exploited. The reaction involves treatment with dialkylboryl trifluoromethanesulfonates, especially 9-borabicyclo[3.3.1]non-9-yl trifluoromethanesulfonate, and tertiary amines, as reported by *Inoue et al.*[85] This reaction often proceeds in a regioselective manner and exhibits remarkable reactivity with some types of substrates.

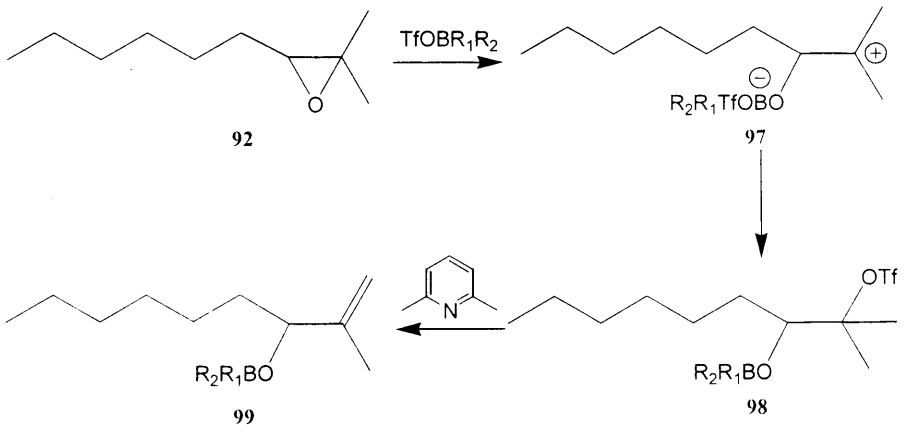
This method works well with 2,2-di-and trisubstituted epoxides, but fails with cyclic substrate (*Scheme 31*). Once again, with unsymmetrical epoxides, opening of the oxirane occurs to give the formation of the more stable carbocation.



i) 9-borabicyclo[3.3.1]non-9-yl trifluoromethanesulfonate ii) hydrolysis

Scheme 31

The mechanism of formation is shown in Scheme 32 for the isomerisation of 2-methyl-2,3-epoxynonane **92**, using 9-borabicyclo[3.3.1]non-9-yl trifluoromethanesulfonate as reagent. Such dialkylboryl triflates possess a strong affinity with oxygen atoms leading to the initial formation of an "ate" complex **97**, which is then converted into the second intermediate **98** following trapping of the carbocation by trifluoromethanesulfonate anion. This intermediate decomposes upon reaction with a tertiary amine to give borate **99**, which can be hydrolysed to produce the final allylic alcohol.

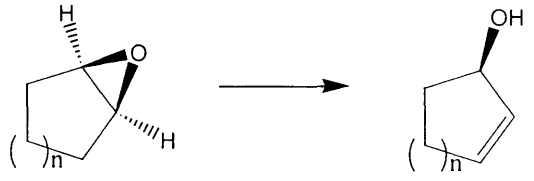


Scheme 32

In contrast to the use of lithium amides, dialkylaluminium amides or sodium phenylselenide, the considerable advantage of this protocol is that the method has also been developed to work catalytically.[85]

3.4.7. Cobalt derivatives

In a more unusual approach, the isomerisation of achiral meso epoxides to optically active allylic alcohols has been achieved through asymmetric catalysis with Vitamin B_{12}.[86-88] The catalytically active species is cob(I)alamin, obtained from vitamin B_{12} by *in situ* two-electron reduction with a reducing agent such as zinc. The disadvantage of this method is the relatively long reaction time which, in most cases, is approximately 40 hours.
This procedure is efficient for the preparation of (*R*)-cycloalk-2-enols, although yields, at present, are moderate for 5- and 6-membered ring substrates (*Scheme 33*). Clearly, further studies on a variety of epoxides would be of considerable interest.

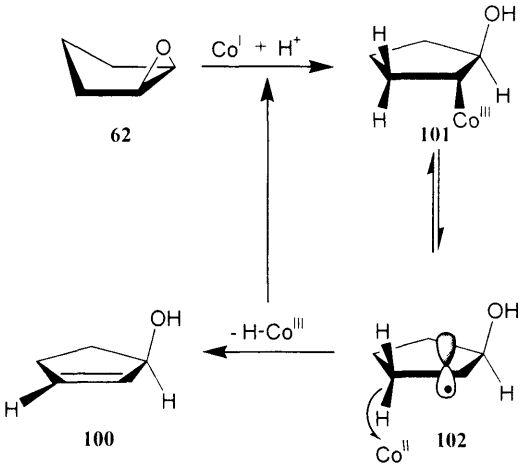


		yield (%)	ee (%)	
n=1	**62**	61	52	**100**
n=2	**45**	52	36	**46**
n=4	**75**	-	-	**76**

Scheme 33

A two-step mechanism was suggested for this transformation, as illustrated in Scheme 34 for the isomerisation of cyclopentene oxide **62** to enantiomerically enriched (*R*)-cyclopent-2-enol **100**. The first step consists of a proton-assisted nucleophilic attack of the chiral Co^{I} catalyst to form (1*R*,2*R*)-(2-hydroxycyclopentyl)cob(III)alamins **101**. This step is responsible for the enantioselectivity of the process, since the absolute configuration of the

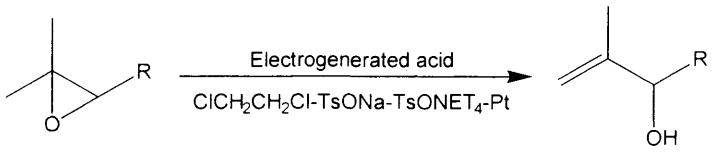
hydroxyl substituted carbon atom is already fixed in this intermediate, whose subsequent decomposition gives the allylic alcohol **100** as well as regenerating the catalyst. This second step, involving formal elimination of the cobalt hydride, is non-selective and is stated to proceed *via* reversible Co-C bond homolysis to form a radical **102**, and subsequent hydrogen-abstraction by the Co^{II} species then affords the desired product **100**.



Scheme 34

3.4.8. Electrogenerated acid catalysis

Most of the methods described in this review use base-catalysed 1,2-elimination, or Lewis acidic types of reagent. In fact, the conventional acid-catalysed reaction of epoxides leads predominantly to the formation of a ketone over an allylic alcohol. In spite of the difficulties encountered when performing this reaction under acidic conditions, *Torii* reported an electrochemical procedure whereby an electrogenerated acid catalysed the formation of α,β-unsaturated alcohols.[89] The method developed involved electrolysis in a $ClCH_2CH_2Cl$-TsONa-$TsONEt_4$-Pt system (*Scheme 35*)



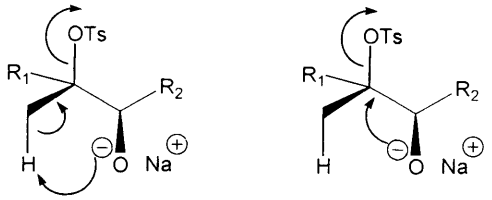
Scheme 35

Table 3. Electrogenerated acid-catalytic ring opening of epoxides

R	Yield of epoxide (%)
$(CH_2)_2CH(Me)CH_2CH_2OCH_2Ph$	74
CH_2OPh	83
$(CH_2)_2C(Me)(OAc)C{\equiv}CH$	70
$(CH_2)_2C(Me){=}CHCH_2OAc$	73
$(CH_2)_2C(Me){=}CHCH_2SO_2Ph$	81

Successful transformations of acyclic epoxides were achieved using this method (*Table 3*). Cyclic substrates however produced poor yields of allylic alcohols because of the unfavourable conformation of the intermediate required for the elimination step.

Opening of the epoxide with the electrogenerated acid generates a carbocation that would be bonded or tightly ion-paired with tosylate anion in non-polar solvent such as 1,2-dichloroethane. Subsequent elimination then requires a specially favoured conformation which is barely accessible from cyclic epoxides on strain grounds[89] (*Figure 5*, **103A**). However, two questions arise from this proposed mechanism. Firstly, no explanation is given on the formation of the alkoxide anion, and secondly, "normal" chemistry suggests the formation of the starting epoxide from intermediate **103** (*Figure 5*, **103B**).



103A 103B

Figure 5

3.4.9. Summary and conclusions

The following table summarises the different features of the foregoing methods leading to allylic alcohols from epoxides and describes the preferred mechanism, when applicable (*Table 4*).

Table 4. Summary of the different methods of formation of allylic alcohols from epoxides

Method (c, s)[a]	Regiochemistry of ring-opening		Regiochemistry of double bond		Preferred stereochemistry	
	Most stable C^+	Less hindered C	Most stabilised	Less stabilised	*E*	*Z*
$LiNR_2$ (s)	✓			✓	✓	
BuLi (s)	✓		-	-	✓	-
AIP (c)	✓			✓	-	-
DATMP (s)	✓		-	-	✓	
$ArSe^-$ (s)		✓	✓	-	✓	-
Al_2O_3 (c)	✓		✓	-	-	-
TMSOTf (s)	✓			✓	✓	
t-$BuSiMe_2I$ (s)	✓		✓		✓	-
$TfOBR_1R_2$ (c)	✓		✓		✓	
Co(I) (c)	✓		✓	-	-	-
Electrogenerated H^+	✓		-	-	-	-

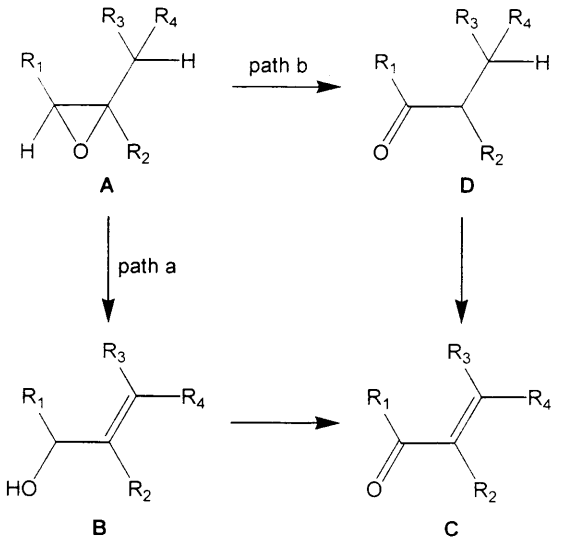
a) c: catalytic, s: stoichiometric

The methods described above include homogeneous catalytic (aluminium isopropoxide), heterogeneous catalytic (alumina), and stoichiometric rearrangements of epoxides to allylic alcohols (lithium dialkyl amides). The common disadvantages of the majority of these procedures are low activities or/and selectivities, harsh reaction conditions (especially high temperatures), the use of strong bases and toxic or expensive materials, and many of these clearly limit their application in terms of industrial use. Improvements in this area of chemistry would therefore be useful.

4. The conversion of epoxides to α,β-unsaturated ketones

4.1. Introduction

In terms of the ideal route for the conversion of the diastereoisomeric mixture of limonene oxides **2** to carvone **3**, an efficient one pot method for the conversion of an epoxide to an α,β-unsaturated ketone is a highly desirable objective. Save for a single exception first reported by *Kolomeyer* and *Oyloe*[90] in 2003 (*vide infra*), this transformation is generally considered to be a multistep operation. In the preceding section, we have reviewed the methods currently available for the transformation of an epoxide **A** to an allylic alcohol **B** which can then, of course, serve as the precursor of an α,β-unsaturated ketone **C** on subsequent oxidation of the hydroxyl group (*Scheme 36*, path a). The alternative approach is to direct the S_N1 like ring opening of an epoxide **A** to a ketone **D** *via* hydride transfer, and then to achieve the introduction of the necessary carbon-carbon double bond in a regiospecific manner (path b).
In the following sections, attention will consequently be focused on the major reactions which are currently used for the transformation of ketones to their α,β-unsaturated congeners.

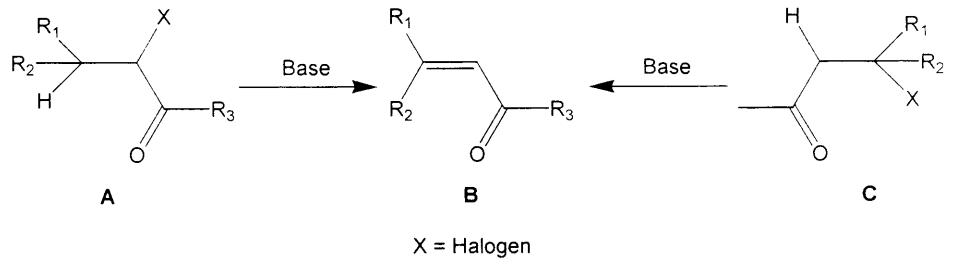


Scheme 36

4.2. *Via* α-bromination-dehydrobromination

This classical method was the most important for the transformation of ketones to α,β-unsaturated carbonyls in spite of early problems related to the control of regioselectivity in the bromination step.[91-98] However, in more recent times, great improvements have been made since, especially with the work of *Stotter* and *Hill* on bromination of various cyclohexanone enolate derivatives[99] (*vide infra*).

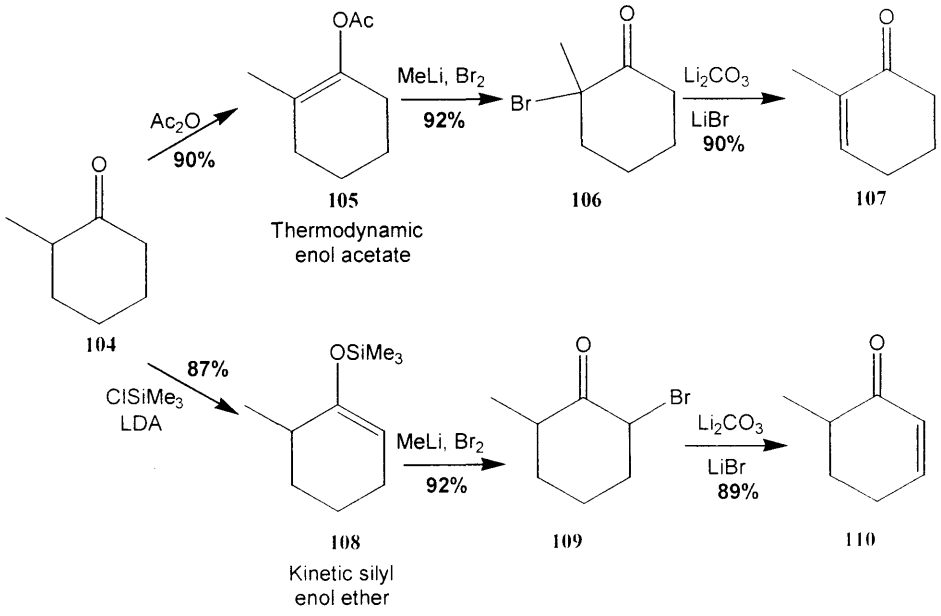
In principle, the halogen leaving group can be either α to the carbonyl moiety (**A**) or β to the carbonyl moiety (**C**) (*Scheme 37*), although base-elimination is easier in the latter instance. However, since β-functionalisation is more difficult, the halogen atom is generally introduced in the α position.



Scheme 37

The control of the regioselectivity in the bromination step may be difficult, and is usually solved by adding a preliminary step from the ketone to form either a thermodynamic or kinetic enol or enolate derivative. The decreased reactivity of the resultant α-bromo derivative compared to the ketone towards further bromination contributes to the ease of selective monobromination. Dehydrobromination is then cleanly achieved in refluxing potassium *t*-butoxide, or other bases depending on the substrate, and leads to either the *E* or the *Z* isomer depending on the substrate.[91-99]

An illustrative example of a selective bromination-dehydrobromination sequence is shown below starting from 2-methylcyclohexanone **104**, (*Scheme 38*), proceeding either through an enol acetate **105** or a silyl enol ether **108** which then react with bromine to give **106** or **109**, respectively. Further dehydrobromination of **106** and **109** leads to 2-methylcyclohex-2-enone **107** and 2-methylcyclohex-5-enone **110**, respectively.[99]

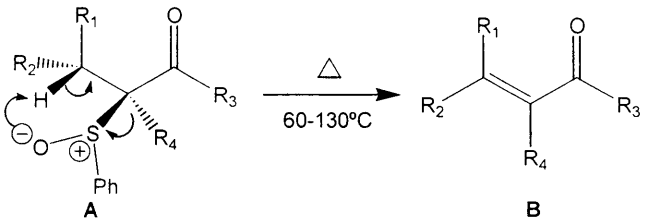


Scheme 38

The main problems in such a method are the use of toxic materials such as bromine, and the formation of mixtures of products in some cases.

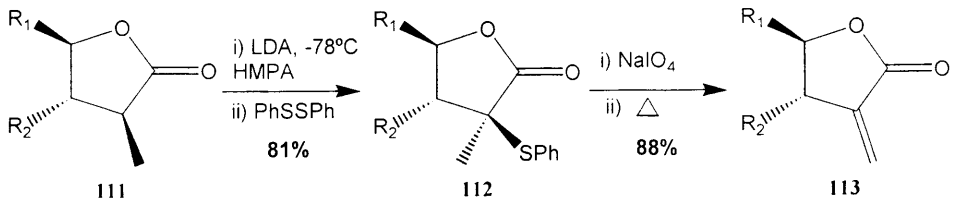
4.3. Sulfur based reagents

Organosulfur reagents have proven to be particularly useful for the introduction of unsaturation,[100] and their efficiency depends on the ease of the *syn* elimination of the sulfoxide moiety from the substrate (*Scheme 39*). Since a particular orientation of the hydrogen atom on the β-carbon to the carbonyl functionality is required (**A**), exclusive formation of the *E* double bond is generally observed in acyclic systems (**B**).



Scheme 39

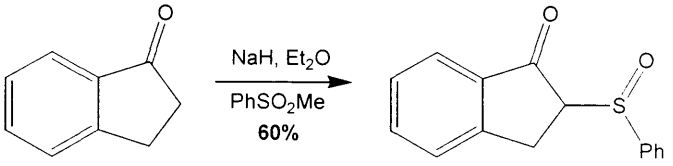
Organosulfur reagents can be selected to introduce the sulphur atom either as sulfur (II) or sulfur (IV), with the former proving more popular, but requiring further oxidation of the sulfide to the sulfoxide to precede the elimination step. Several methods have been reviewed for the introduction of sulfenyl group α to the carbonyl functionality[100] using dialkyl or diaryl sulfides, most of them proceeding *via* a regiospecific enolate form of the ketone and sometimes requiring the presence of HMPA, as shown for the formation of the *exo*-methylene-γ-lactones[101] **113** (*Scheme 40*). Sulfenylation can also be carried out *via* the silyl enol ether form of the ketone.[102]



$R_1 = R_2 = (CH_2)_2$

Scheme 40

Regarding the direct introduction of the sulfinyl moiety, this can be typically achieved by reaction of the enolate form of the ketone **114** with an arylsulfinate ester[103,104] at room temperature to reflux to give **115** (*Scheme 41*).



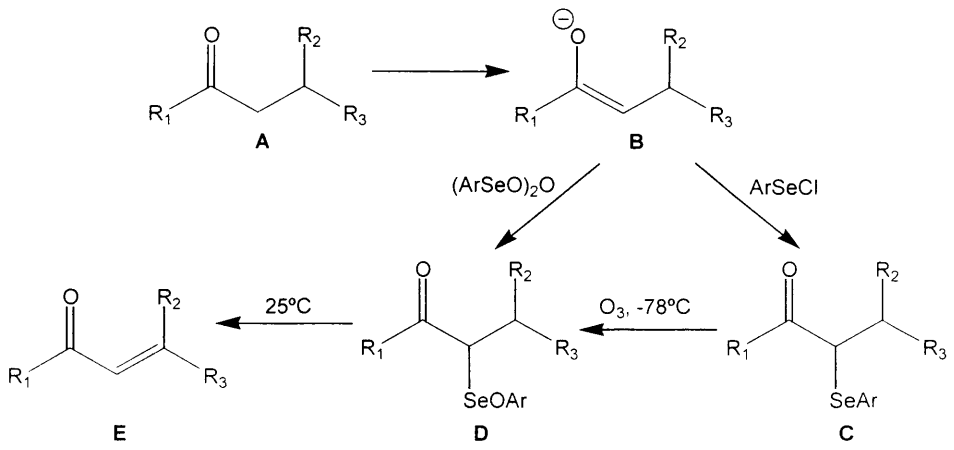
114 115

Scheme 41

4.4. Selenium-based reagents

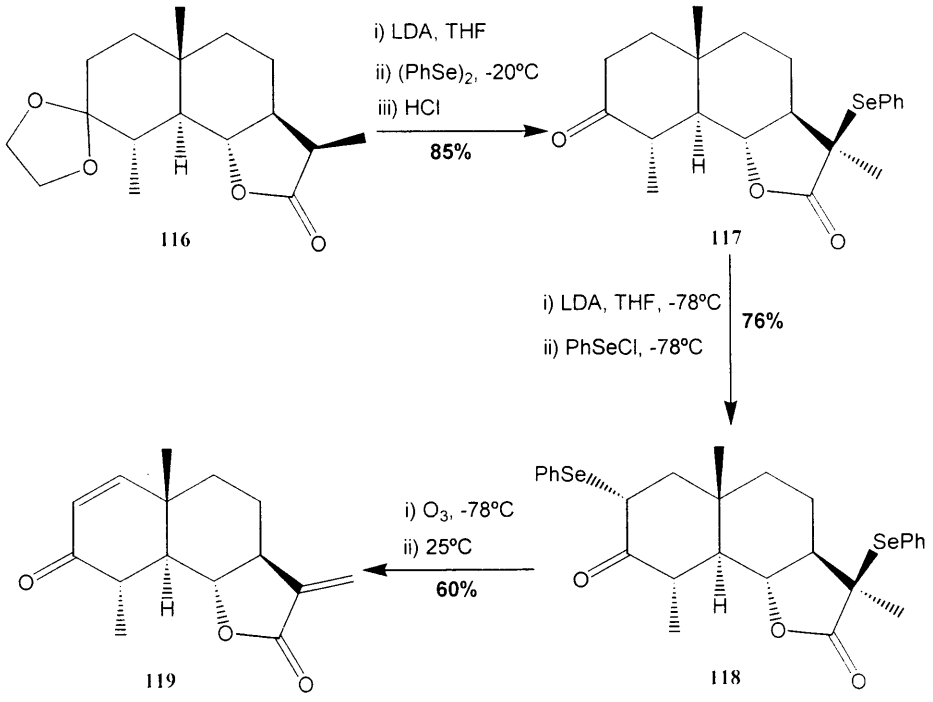
For academic research, the combination of the excellent reactivity of lithium enolates with benzeneselenyl halides to give α-phenylseleno carbonyl compounds and the very mild and rapid *syn* elimination of alkyl phenyl selenoxides bearing a β-hydrogen to form olefins was first discovered by *Sharpless*[81] in the conversion of epoxides to allylic alcohols (*vide supra*). This method was later exploited by *Reich et al*[105-108] to provide a very popular synthesis of α,β-unsaturated carbonyls from ketones.

The most versatile method for introduction of the selenyl moiety is by low temperature reaction of an enolic derivative **B** with a suitable selenium species. As in the case of sulphur reagents, selenium can be introduced either in its selenyl form to give **C** and subsequently oxidised[108] to **D**, or directly as the selenoxide[109] to give **D** (*Scheme 42*). *Syn* elimination at room temperature is then observed to afford α,β-unsaturated ketone **E**.



Scheme 42

This reaction sequence, as illustrated here for the formation of α-methylene-γ-lactones **119**, has seen extensive use in natural product synthesis[110] (*Scheme 43*).

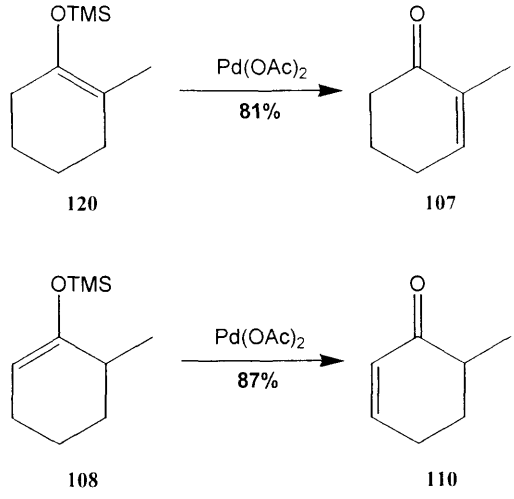


Scheme 43

Obviously, the principal drawback of this methodology resides in the use of toxic selenium reagents.

4.5. Palladium chemistry

Although early studies established that $PdCl_2$ catalyses the dehydrogenation of saturated ketones to give the corresponding α,β-unsaturated derivatives, yields were very low and the reaction was lacking in selectivity for unsymmetrical ketones.[111] *Saegusa et al.*[112] then reported an improved method involving palladium acetate oxidation of the enol ethers derived from carbonyl compounds leading to α,β-unsaturated ketones, and proceeding via an oxo-π-allylpalladium (II) complex. Palladium acetate can be used either alone as a stoichiometric reagent, or as a catalyst with *p*-benzoquinone as a reoxidant. The procedure allows regiospecific introduction of the double bond, according to the geometry of the initial silyl enol ether[112] (*Scheme 44*).

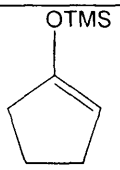
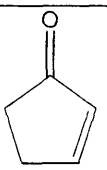
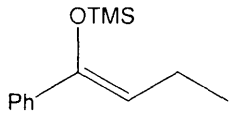
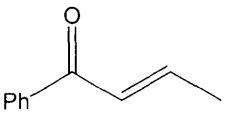
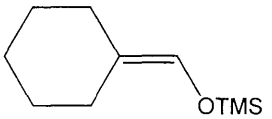
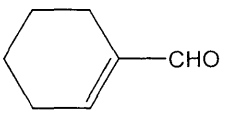
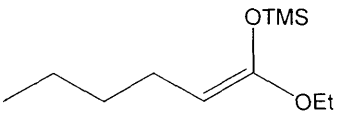
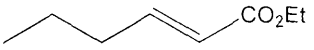


Scheme 44

Another reported regiospecific method for the transformation of silyl enol ethers or enol acetates derived from ketones into α,β-unsaturated carbonyl compounds is by treatment with allyl carbonates using palladium-

bis(diphenylphosphino)ethane (dppe) complex as catalyst.[113,114] This reaction generally proceeds in satisfactory yield, using acetonitrile as solvent (*Table 5*).

Table 5. Palladium catalysed formation of α,β-unsaturated ketones from silyl enol ethers

Starting silyl enol ether	Product	Yield (%)
		69
		66
		74
		79

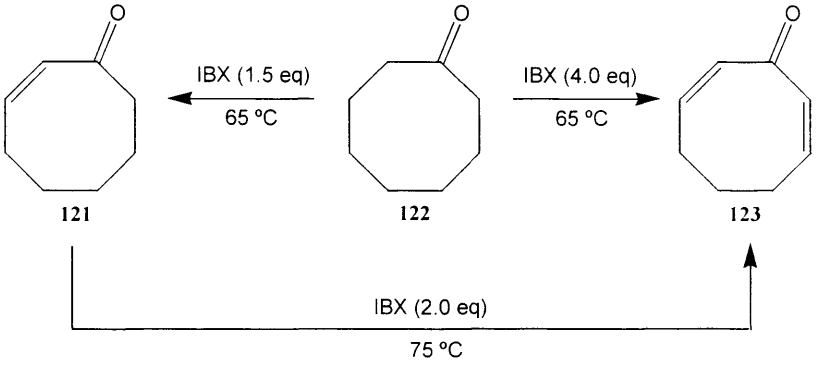
Method: Silyl enolate (1mmol), diallyl carbonate (2 mmol), $Pd(OAc)_2$ (0.05 mmol), and dppe (0.05 mmol) for 1-3 h

The inherent problems of this methodology include variation of the reaction conditions and of the catalyst employed depending on the substrate, the expense of the reagent and the incompatibility with various functional groups. An additional step is also required to form the silyl enol ether or enol acetate derivative.

Finally, for the particular case of dihydrocarvone, it should be noted that further isomerisation reactions involving the isopropenyl group and leading to aromatic systems can occur when transition metals are used.

4.6. *Nicolaou*'s IBX reagent

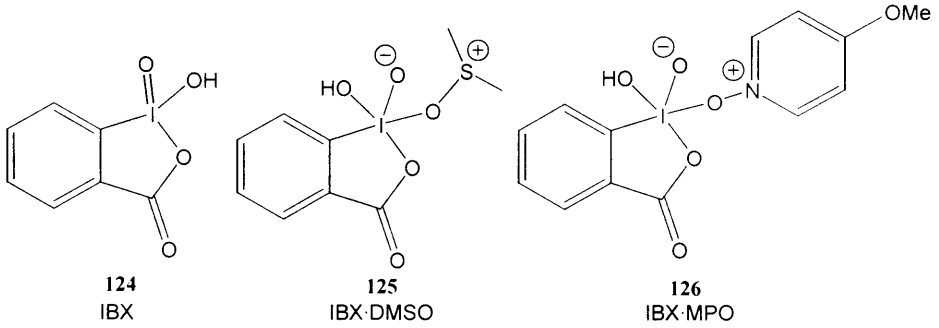
Recently, *Nicolaou* reported a new method for the one-pot synthesis of α,β-unsaturated carbonyl systems from carbonyl compounds using *o*-iodoxybenzoic acid (IBX) and its derivatives.[115-119] The reaction proceeds at high temperature and requires at least stoichiometric amounts of the IBX reagent, which was initially known to perform the oxidation of alcohols to ketones.[120,121] The temperature as well as the quantity of IBX can be controlled to access higher levels of unsaturation as illustrated in scheme 45.



Scheme 45

Different types of ligands were subsequently investigated to complex with IBX **124** and the most reactive proved to be 4-methoxypyridine-*N*-oxide (MPO) over DMSO (*Figure 6*). The complex IBX·MPO **126** is reactive at ambient temperature and is compatible with a wider range of functional groups. Thus, problematic substrates, such as 1-methyl-4-piperidone that contains an alkyl amine which generally decomposes readily when exposed to IBX **124**, perform better under these conditions.[117] However, this method does have some limitations with some substrates, and in such cases a two-step sequence *via* the

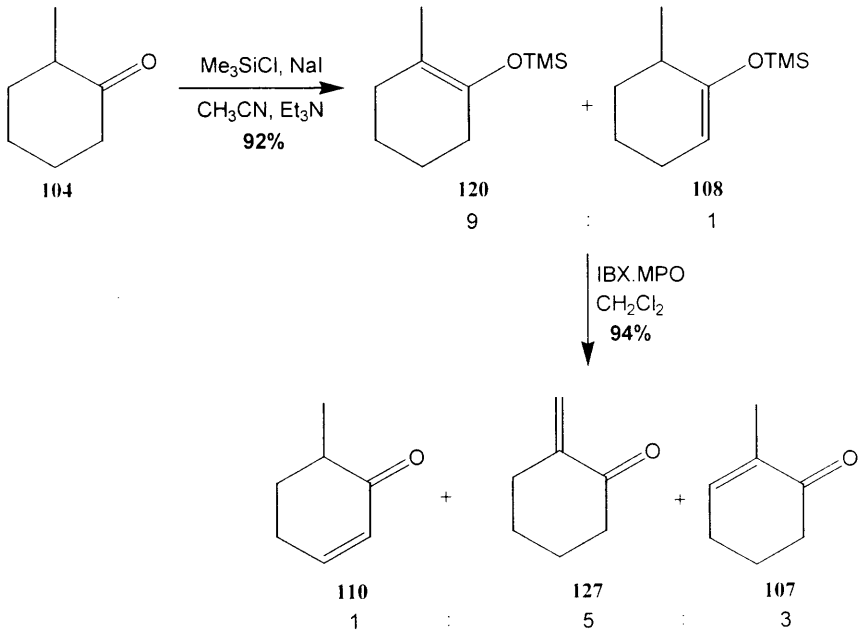
silyl enol ether and using the same reagents, IBX **124** or IBX·MPO **126**, has also been developed.[117]



124 IBX **125** IBX·DMSO **126** IBX·MPO

Figure 6

To some extent, substitutions at the α- and β-sites of the carbonyl do not hinder the reaction nor does it diminish its efficiency. However, the regioselectivity is generally greatly affected, especially in the case of 1-methylcyclohexanone **104**, a crucial example in the scope of our work, where a 1:5:3 mixture of regioisomers **110**, **127** and **107** is formed (*Scheme 46*).



104 → **120** : **108** = 9 : 1

110 : **127** : **107** = 1 : 5 : 3

Scheme 46

In conclusion, this method seems to be mild and efficient, but still suffers from some major disadvantages. Firstly, IBX **124** is reported to be explosive at high temperature. Furthermore, the regioselectivity in the type of substrates of interest to us is poor.

4.7. One-pot synthesis

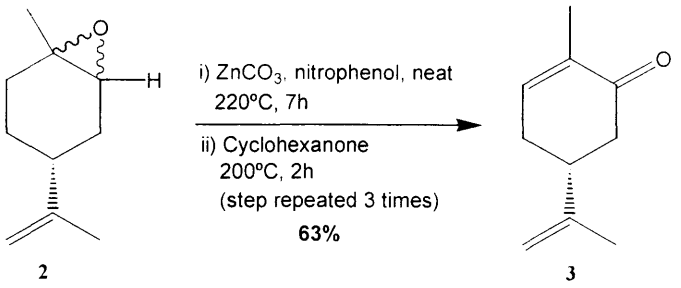
Finally, *Kolomeyer* and *Oyloe*[90] have developed a system based on the combination of an activator/modifier and a catalyst which has the ability to perform both the conversion of an epoxide to an allylic alcohol and its subsequent oxidation to an α,β-unsaturated ketone. This is the only method reported to date for the direct transformation of an epoxide to α,β-unsaturated ketone. The reaction can be stopped at the allylic alcohol step. If not, the presence of an auxiliary carbonyl compound, such as cyclohexanone or dihydrocarvone as a hydrogen acceptor can then induce the *Oppenhauer* oxidation step.

The role of the activator/modifier is to improve the activity and/or selectivity of the catalyst system, particularly in connection with the first step of the sequence. A few examples of heterogeneous inorganic (magnesium oxide, calcium oxide, barium oxide...) and homogeneous organic catalysts (zinc acetate, calcium stearate, and nickel naphthenate) have been studied, combined with phenolic compounds (phenol, monoalkylphenol, hydroxyphenol...) acting as activators or selectivity modifiers for the catalysts.

Depending on the system used, the concentration of catalyst and activator/modifier can vary between 0.05-10 wt% and 0.025-10 wt% based on the epoxide, respectively. The reaction typically occurs without solvent, at reflux, which corresponds to approximately 230 °C in the case of limonene oxide **2**.

A wide range of epoxides has been studied with more or less success, including terminal, cyclic, di- and trisubstituted epoxides. Moreover, the products retain the optical activity of the starting epoxides.

The best catalyst and activator/modifier systems for the preparation of *L*-carvone **3** from limonene oxides **2** are magnesium hydroxide-carvacrol and zinc carbonate-nitrophenol affording 69% and 63% of the desired product respectively (*Scheme 47*).



2 3

Scheme 47

4.8. Conclusions

From the foregoing overview it is clear that the regioselective transformation of an epoxide to an α,β-unsaturated ketone is generally regarded in the research laboratory as a multistep transformation; two distinct approaches are generally adopted involving either isomerisation to an allylic alcohol followed by oxidation or isomerisation to a carbonyl compound followed by dehydrogenation. Furthermore, many of the stoichiometric reagents used would be inappropriate on an industrial scale on grounds of either cost and/or toxicity. The only exception to date appears to be the one pot method developed by *Kolomeyer* and *Oyloe* and, in this instance, a detailed mechanism which explains the clean regioselectivity of the process has not yet been given.

It was with this background in mind that the present project to understand and to control the S_N1 like opening of epoxides was undertaken.

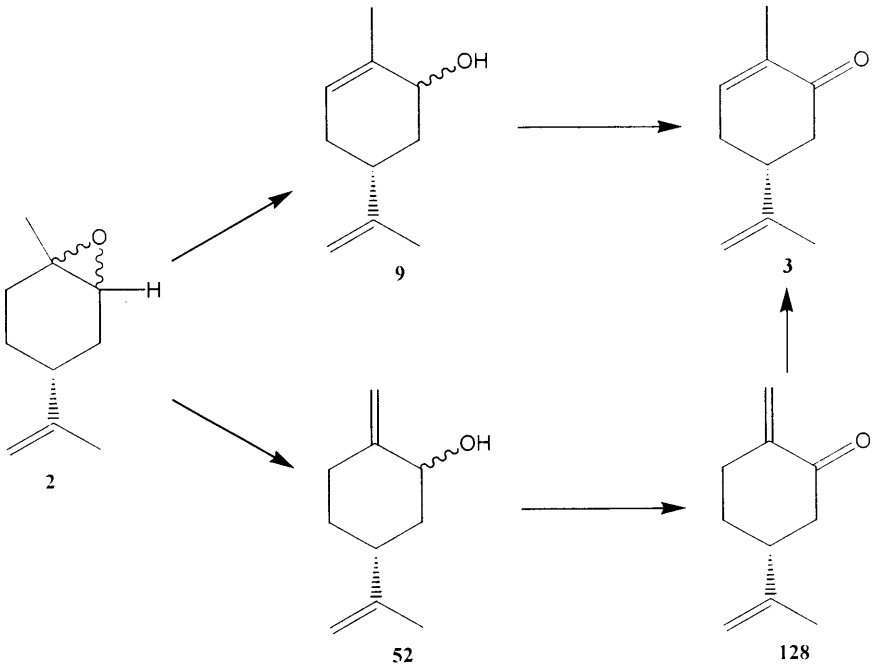
Chapter 2

RESULTS & DISCUSSION

I. The conversion of epoxides to allylic alcohols

1. Introduction

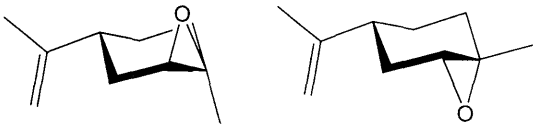
As emphasised in the introductory overviews, a potential commercial solution to the important problem of the stereospecific conversion of (*D*)-limonene **1** to (*L*)-carvone **3** might well be found if a new and effective methodology for the controlled isomerisation of an epoxide to an allylic alcohol could be developed. Thus, as implied in Scheme 48, the synthesis of (*L*)-carvone **3** would ideally involve efficient ring opening of both diastereosisomers of limonene oxide **2** to a mixture of the endocyclic carveols **9** whose subsequent oxidation could be achieved under a wide variety of classical conditions[122] to furnish the desired α,β-unsaturated ketone, (*L*)-carvone **3**. The formation of the exocyclic allylic alcohol **52** would also be of value inasmuch as oxidation to **128** followed by a second isomerisation could be envisaged. In the light of these objectives and in view of our desire to avoid the use of strong non-nucleophilic bases, it was therefore of interest to examine epoxide ring opening under S_N1 like conditions in order to effect the isomerisation to an allylic alcohol.



Scheme 48

1.1. Model studies

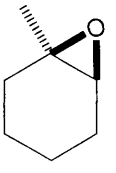
As indicated earlier, the chirality induced by the isopropenyl substituent at the 5-position of limonene oxide **2** has a very significant effect on the chemical and physical properties of this molecule. For our own study of epoxide ring opening under acidic conditions, the selection of (+)-(*R*)-limonene oxides **2** introduced two additional complications. The first of these is that, even although epoxide formation is regiospecific, two diastereoisomers of differing chemical reactivity will be formed (*Figure 7*). In addition, the isopropenyl substituent can also undergo double bond isomerisation particularly in the presence of protons or Lewis acidic metal species. We therefore elected in the first instance to avoid these potential problems linked to the presence of the isopropenyl substituent through selection of a simpler model substrate. Moreover, this should allow us to develop a more general methodology that could subsequently be applied to a wider range of epoxides.



2a **2b**

Figure 7

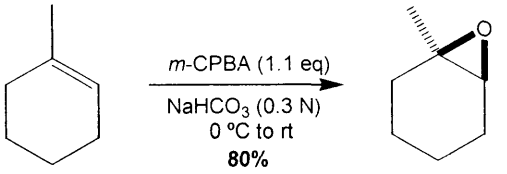
Our work therefore began with an investigation of the acidic ring-opening of 1-methylcyclohexene oxide **31** (*Figure 8*), which allows us to work on a ring-system that also bears a methyl group on the carbon α to the oxygen atom.



31

Figure 8

The preparation of this molecule was most efficiently achieved following *Fringuelli*'s method[123] based on a triphasic system. 1-Methylcyclohexene **129** was stirred in an ice-cold solution of sodium bicarbonate (0.3 N), and 1.1 equivalent of solid *m*-chloroperbenzoic acid was added over a 1 hour period. The triphasic mixture was allowed to stir for a further one hour at room temperature. Organic extraction and washing with ice-cold sodium hydroxide was carried out to eliminate the excess of *m*-chloroperbenzoic acid and of *m*-chlorobenzoic acid formed as a by-product of the reaction. The low temperature of the basic wash is crucial in order to avoid opening of the epoxide and the formation of a vicinal diol. This reaction afforded racemic 1-methylcyclohexene oxide **31** in 80% yield, and required no further purification (*Scheme 49*). Using these conditions gave far better results than the classical use of dichloromethane as a solvent[124,125] where the yield was only 45%.



129 **31**

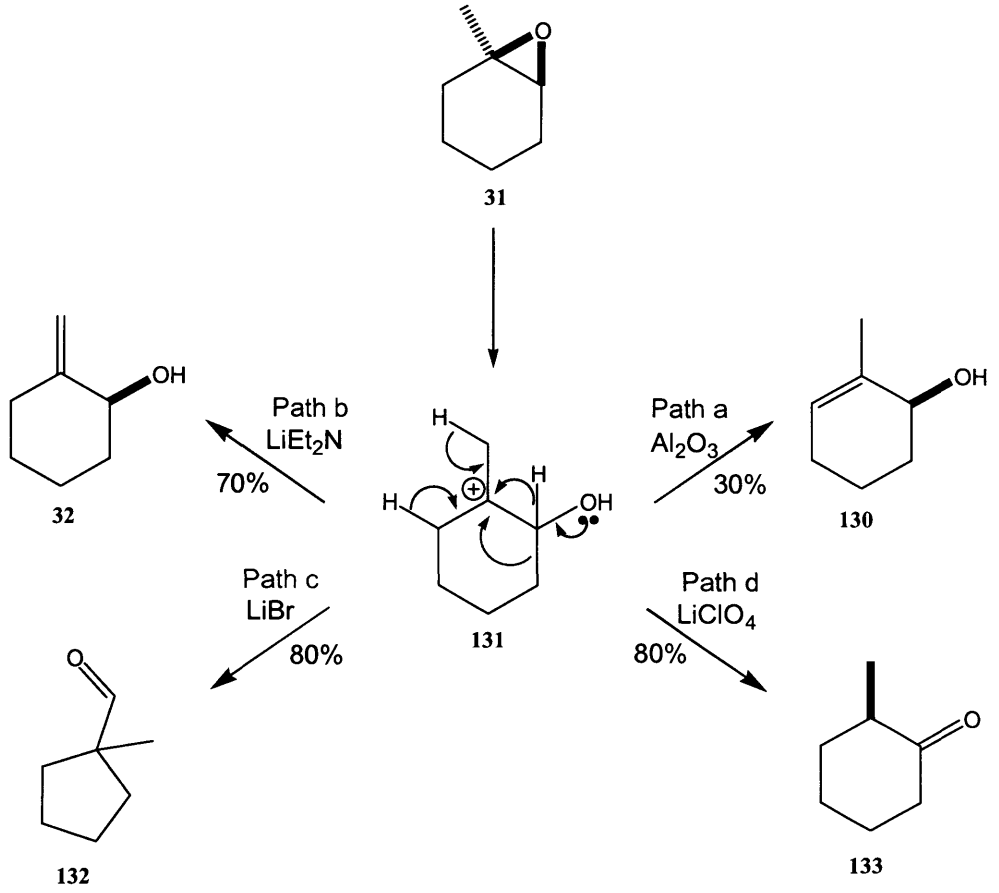
Scheme 49

Moreover, the scaling up of this preparation to 10 grams of starting material was performed accordingly without any problems and afforded similar yields.

1.2. Background studies on the model molecule

The vast majority of the studies carried out on the preparation of allylic alcohols from epoxides have explored cyclohexene derivatives because of the fact that their reactivity is related to conformational constraints and strain problems. Hence, cyclohexene oxide **45** and 1-methylcyclohexene oxide **31** were substrates of choice. *Rickborn* and *Gerkin*[14,48] did some extensive studies on epoxide isomerisations of this type of substrate and especially on the

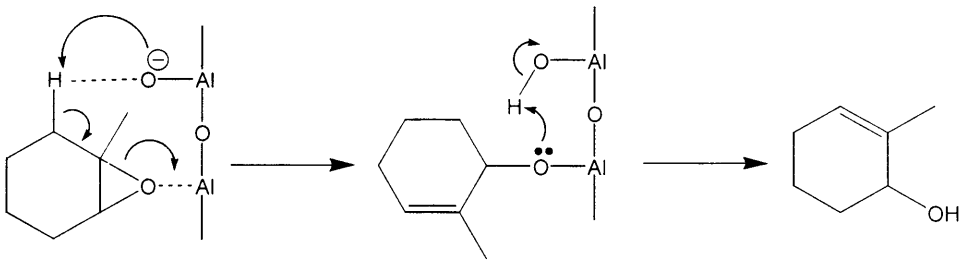
rearrangement of 1-methylcyclohexene oxide **31**.



Scheme 50

The ring opening of 1-methylcyclohexene oxide **31** with a Brønsted acid or a Lewis acid *via* chelation of a metallic cation with the oxygen atom is always considered to involve the formation of a carbocation **131** (*Scheme 50*). Most interestingly however, the evolution of this cation depends critically on the reagent or catalyst used and no less than four different pathways can be followed to varying degrees. Firstly, an E1 type elimination of a *β*-proton within the cyclohexyl ring affords the allylic alcohol 2-methylcyclohex-2-enol **130** (Path a). Thus, treatment of 1-methylcyclohexene oxide **31** with aluminium oxide pretreated with acetic acid and preheated at 450 °C afforded **130** in 30% yield along with 1-methyl-*trans*-cyclohexan-1,2-diol (63%) as the major product.[42,43] This mechanistic pathway is possibly explained by the

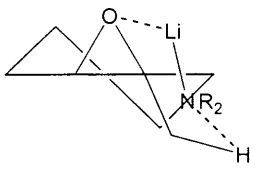
presence of both electron-donor and electron-acceptor sites on the surface of alumina, wherein the epoxide oxygen atom is adsorbed onto an acidic site, leading to ring opening of the oxirane, whereas the β proton is coordinated to a basic site thus allowing its elimination (*Scheme 51*).



31 134 130

Scheme 51

Elimination of a proton can also occur from the methyl substituent, thereby leading to the *exo*-allylic alcohol 2-methylenecyclohexanol **32** (Path b). This is in fact the major product formed in a 70% yield upon treatment of 1-methylcyclohexene oxide **31** with lithium diethylamide in a non-polar solvent.[52-59] Coordination of the oxygen lone pair with the electron deficient lithium centre together with elimination of the proton *via* the nitrogen lone-pair in a concerted cyclic manner leads to **32**. This is not the more stable thermodynamic allylic alcohol but its formation nevertheless occurs due to the free rotation of the hydrogen atoms on the methyl group allowing a favoured conformation to be adopted (*Figure 9*).

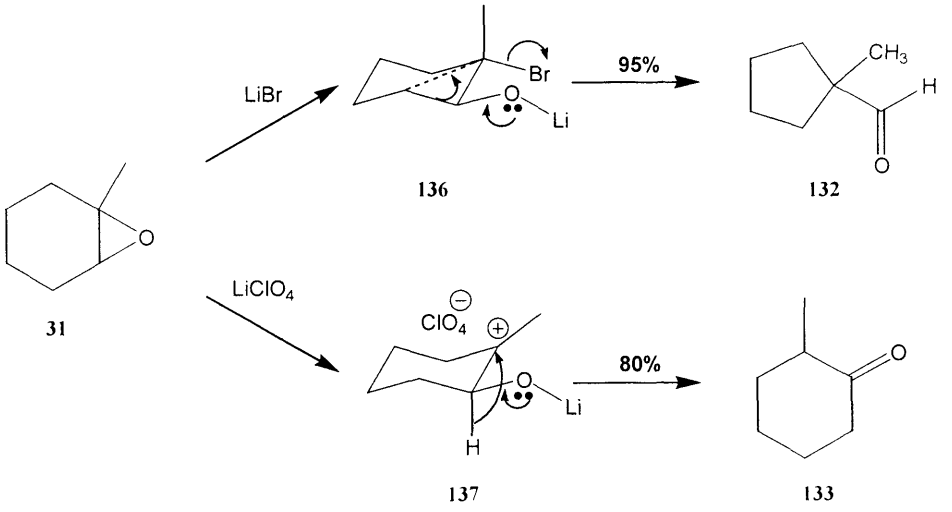


135

Figure 9

As shown on Scheme 50, an apparently slight variation of the reaction

conditions can have a very profound effect on the product distribution. For instance, the variation of the counteranion alone in a reagent can have a huge impact on the product formation. This fact is particularly highlighted by the isomerisation of 1-methylcyclohexene oxide **31** using either lithium bromide or lithium perchlorate,[14] affording respectively 1-methylcyclopentane-carbaldehyde **132** (Path c) and 2-methylcyclohexanone **133** (Path d) as major products. In this instance, whilst the common lithium cation is responsible for the S_N1 like epoxide ring opening, the evolution towards a product is clearly related to the nucleophilicity of the counteranion (*Scheme 52*)



Scheme 52

Thus, for the ring opening reaction involving lithium bromide, capture of the incipient carbocation by the nucleophilic bromide anion can occur in the classical *trans* fashion to give an intermediate **136**, which will preferably exist in the diequatorial conformation shown, thus favouring a stereoelectronically controlled migration of the *trans* coplanar carbon-carbon bond with departure of bromide anion as shown leading to the ring contracted aldehyde **132**. In practice, this reaction was carried out using lithium bromide in the presence of HMPA which solvates the lithium cation and favours participation of naked bromide anion as a nucleophile.[48]

By way of contrast, selection of the non-nucleophilic perchlorate counteranion

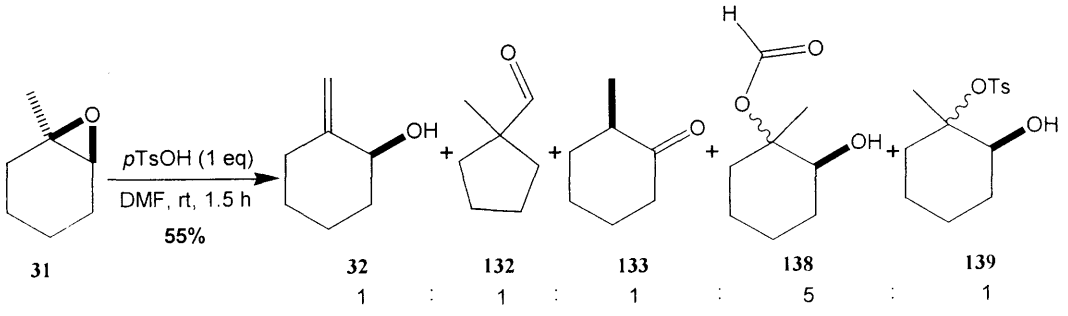
can be considered to involve an essentially classical carbocation **137** whose vacant *p* orbital is perfectly aligned to favour a hydride migration assisted by lithium alkoxide thereby yielding 2-methylcyclohexanone **133** as essentially the sole product.

The four case histories described above indicate that, even for such a simple substrate as 1-methylcyclohexene oxide **31**, controlled ring opening to a single product is not a straightforward process. It is also noteworthy that the *exo* and/or *endo* allylic alcohol products **32** and **130**, which are our desired products, tend to require the presence of a basic site in the reagent and that product evolution *via* a more purely carbocationic pathway favours either ring contraction to **132** or hydride shift to **133**.

With such a background in mind, the simple conversion of an epoxide to an allylic alcohol under acidic or Lewis acidic conditions represents a worthwhile challenge.

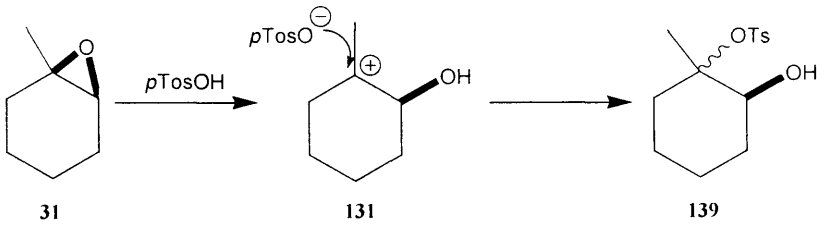
2. Preliminary studies

Our work in this area began with an investigation of the opening of our model epoxide with *p*-toluenesulfonic acid under different reaction conditions, and in particular, trying to establish a pattern between the solvent used and the product distribution. Surprisingly, the opening of 1-methylcyclohexene oxide **31** using a stoichiometric amount of *p*-toluenesulfonic acid in dimethylformamide (20 volumes) at room temperature, gave interesting results. The progress of the reaction was checked by TLC and completion was achieved after 1.5 h.



Scheme 53

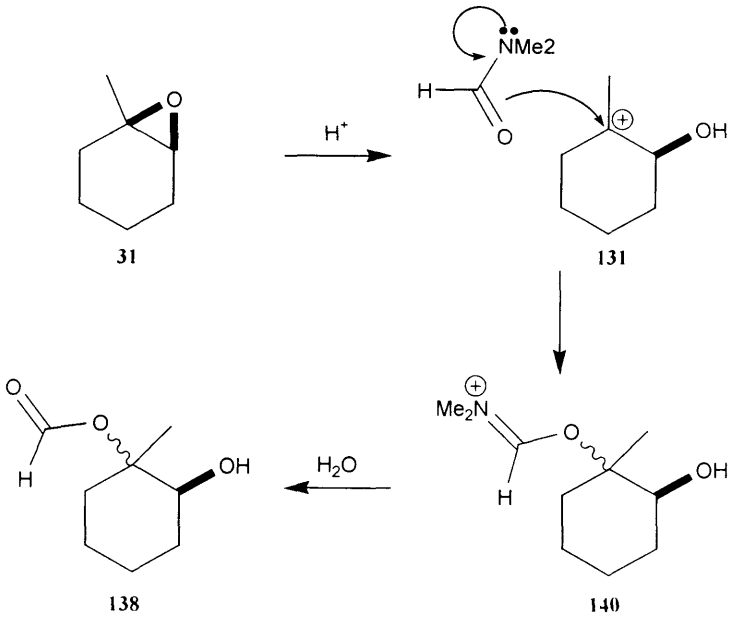
Even although the overall yield is low, probably due to a loss of product during the work-up and problems related to the handling of volatile molecules, five products were isolated from this reaction as illustrated in Scheme 53. The first three were as might be expected from the foregoing examples. Thus, 2-methylenecyclohexanol **32** (7%), 1-methylcyclopentanecarbaldehyde **132** (5%) and 2-methylcyclohexanone **133** (5%) were formed by the mechanisms described previously. Along with these products however, a detectable amount of the tertiary tosylate **139** (5%) was also formed and this may well be an intermediate en route to compounds **32**, **132** and **133** *via* subsequent ionisation. Formation of the tosylate arises from the trapping of carbocation or incipient carbocation **131** most likely by *trans* addition of *p*-toluenesulfonate anion (*Scheme 54*), however, no NMR data confirmed the configuration of the final product. The formation of this product was of limited interest and can possibly be avoided by decreasing the amount of tosic acid used.



31 131 139

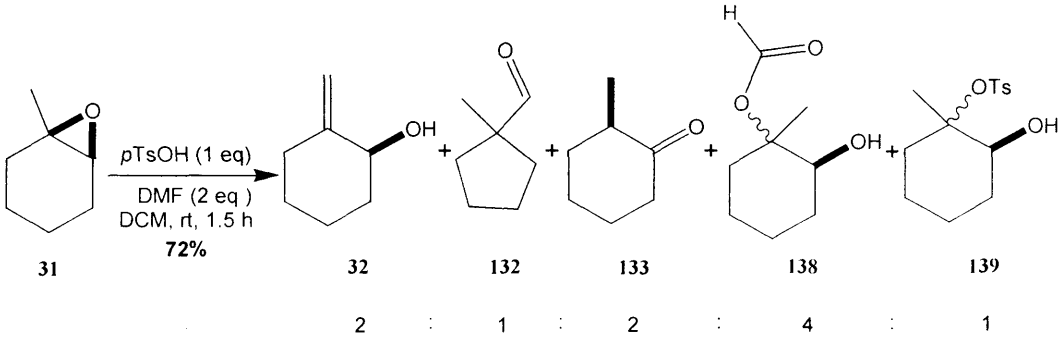
Scheme 54

The major product to be isolated from this reaction, however, was the tertiary formate ester **138** (27%) and its isolation was of significant importance for our project. The mechanism of formation is of great interest and presumably involves trapping of carbocation **131** by *trans* addition of dimethylformamide through its oxygen atom trapping the incipient carbocation to give a formamidinium salt **140**, followed by hydrolysis of this salt on work-up to lead to formate ester **138** (*Scheme 55*). Once again, there are no NMR data confirming the stereoselectivity of this addition.



Scheme 55

The above reaction was then repeated using only two equivalents of dimethylformamide in dichloromethane in order to investigate its impact at a much lower concentration (*Scheme 56*).

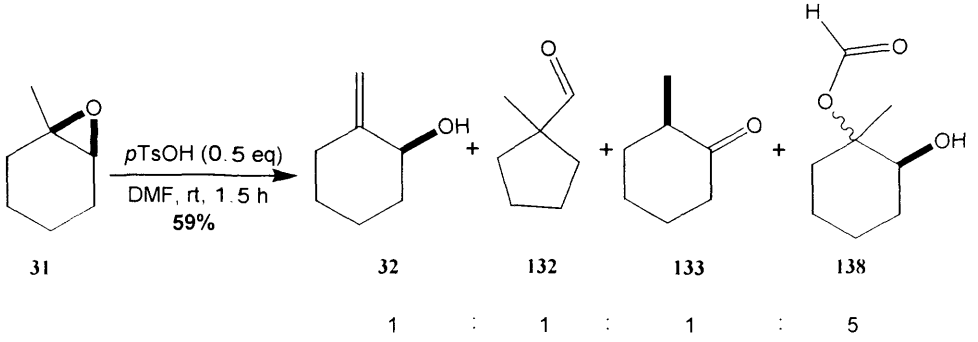


Scheme 56

Although the overall yield was now much better, presumably as a result of the easier work-up, the use of only two molar equivalents of dimethylformamide resulted in a slight decrease in the relative proportion of the formate from 55% of the overall products to 40%.

As further optimisation of the reaction was still required, the reaction conditions were slightly modified aiming to avoid the formation of the tertiary

tosylate **139**. A preliminary screening on the minimum amount of *p*-toluenesulfonic acid necessary to complete the reaction was therefore carried out and, as a result, it was found that the use of 0.5 equivalent of *p*-toluenesulfonic acid was sufficient to bring the reaction to completion. Moreover, it was observed that using this quantity of acid, the formation of tosic acid adduct **139** was successfully eliminated (*Scheme 57*).

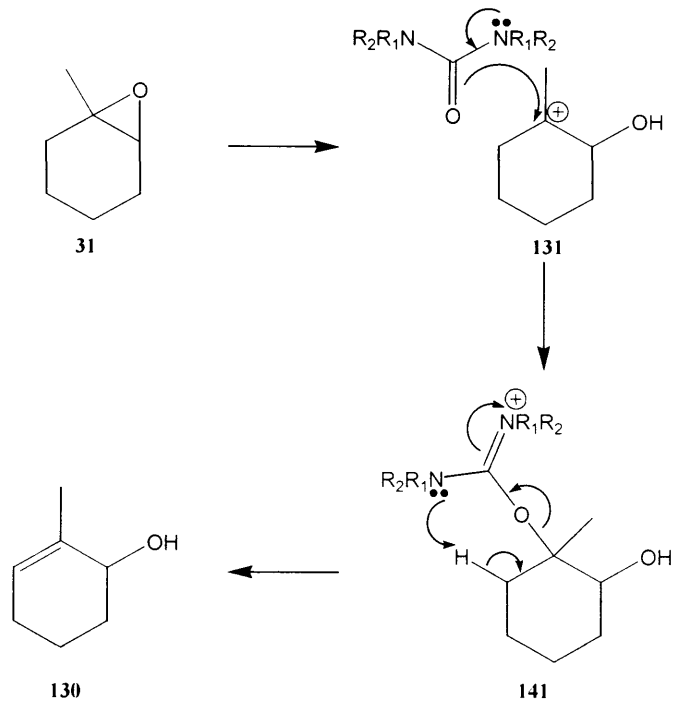


Scheme 57

These preliminary observations proved to be essential in providing insight for a novel strategy.

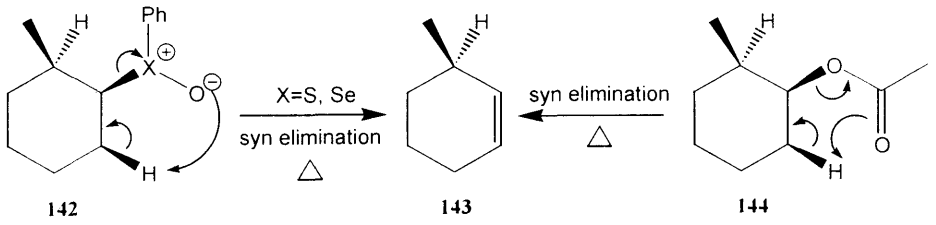
3. Strategy

Based on the outcome of the reactions described above, and especially on consideration of the mechanism of formation of **138** (*Scheme 55*), a conceptually simple strategy was subsequently elaborated. Thus, we reasoned that if the hydrogen atom of the formyl group in **138** is replaced by a functional group capable of triggering the elimination of that moiety, and hence formation of an endocyclic double bond, this would lead to formation of the desired allylic alcohol in a single step (*Scheme 58*). In principle, such a mechanism could be achieved using a urea derivative instead of DMF, but in this instance the urea would function firstly as a nucleophile to quench carbocation **131** to give **141**, and then as a base and a leaving group by triggering its own elimination to provide **130**.



Scheme 58

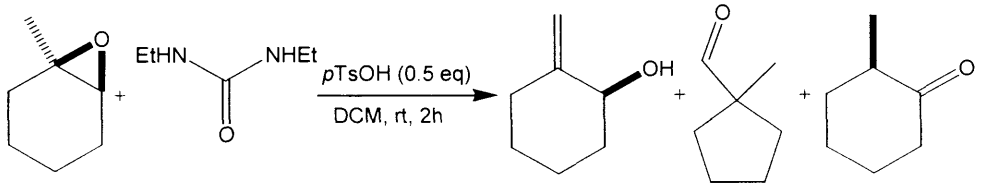
To the best of our knowledge, there are currently no reported uses of urea derivatives that are involved in directing the outcome of ring opening of epoxides in the literature. To some extent however, a parallel can be drawn with reactions such as sulfoxide[126] and selenoxide[127] *syn* eliminations and perhaps even more closely with acetate pyrolysis,[128] even although the exact mechanistic nature remains to be specified (*i.e.* concerted E1 or E2) (*Scheme 59*).



Scheme 59

4. Acid catalysed epoxide ring opening in the presence of a urea derivative

Once again, we elected to study the ring-opening of 1-methylcyclohexene oxide **31** and, of course, to prevent the formation of the formate ester derivative by selecting an alternative solvent to DMF. The use of a relatively polar solvent was considered necessary in order to favour the formation of the carbocation, and it was therefore decided to start the study using dichloromethane. The choice of the urea derivative was then based on solubility considerations. Urea itself was indeed hardly soluble in dichloromethane. However, 1,3-diethylurea **145** proved to be soluble and was consequently the first urea derivative used in the reaction. A two-fold molar excess of this urea derivative **145** was first used in the reaction medium in order to favour trapping of the carbocation. Finally, on the basis of the previous study, 0.5 equivalents of *p*-toluenesulfonic acid were used. A control reaction was also carried out in the absence of any 1,3-diethylurea, and product isolation was as described above. The results of both reactions are summarised in Scheme 60.

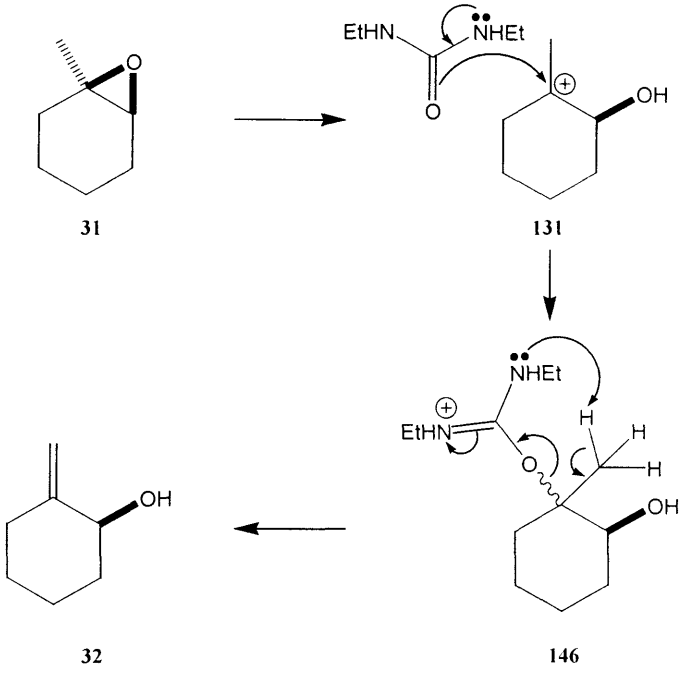


31	145		32		132		133
	0 eq	**59%**	-	:	1	:	4
	2 eq	**54%**	4	:	1	:	4

Scheme 60

A number of interesting conclusions can be drawn from these two reactions. Firstly, for the control reaction, it can be noticed that a 4:1 mixture of 2-methylcyclohexanone **133** and 1-methylcyclopentanecarbaldehyde **132** was formed, and that allylic alcohols were notably absent. To our delight however,

in the presence of 1,3-diethyl-urea **145**, formation of the exocyclic allylic alcohol occurred, finally producing a 4:4:1 mixture of 2-methylene-cyclohexanol **32**, 2-methyl-cyclohexanone **133** and 1-methylcyclopentane-carbaldehyde **132**, respectively. This result confirmed in principle that successful "taming" of the carbocation by 1,3-diethyl-urea was possible as proposed in the mechanism depicted in Scheme 61.



Scheme 61

The complete absence of any endocyclic allylic alcohol was also a very significant observation. Since the presence of the urea derivative as a reagent alters the product distribution, it seems reasonable to postulate that the exocyclic allylic alcohol may arise by elimination from intermediate **146** which is formed by trapping of carbocation **131** by 1,3-diethyl-urea **145**. There are however three different types of protons that can be removed, *viz.*, those from the methyl group to give the exocyclic allylic alcohol, those from the adjacent methylene group of the cyclohexyl ring to give the endocyclic allylic alcohol, and finally the methine proton on the carbon atom bearing the hydroxyl group, which would lead, *via* the enol, to 2-methylcyclohexanone **133**. Since the

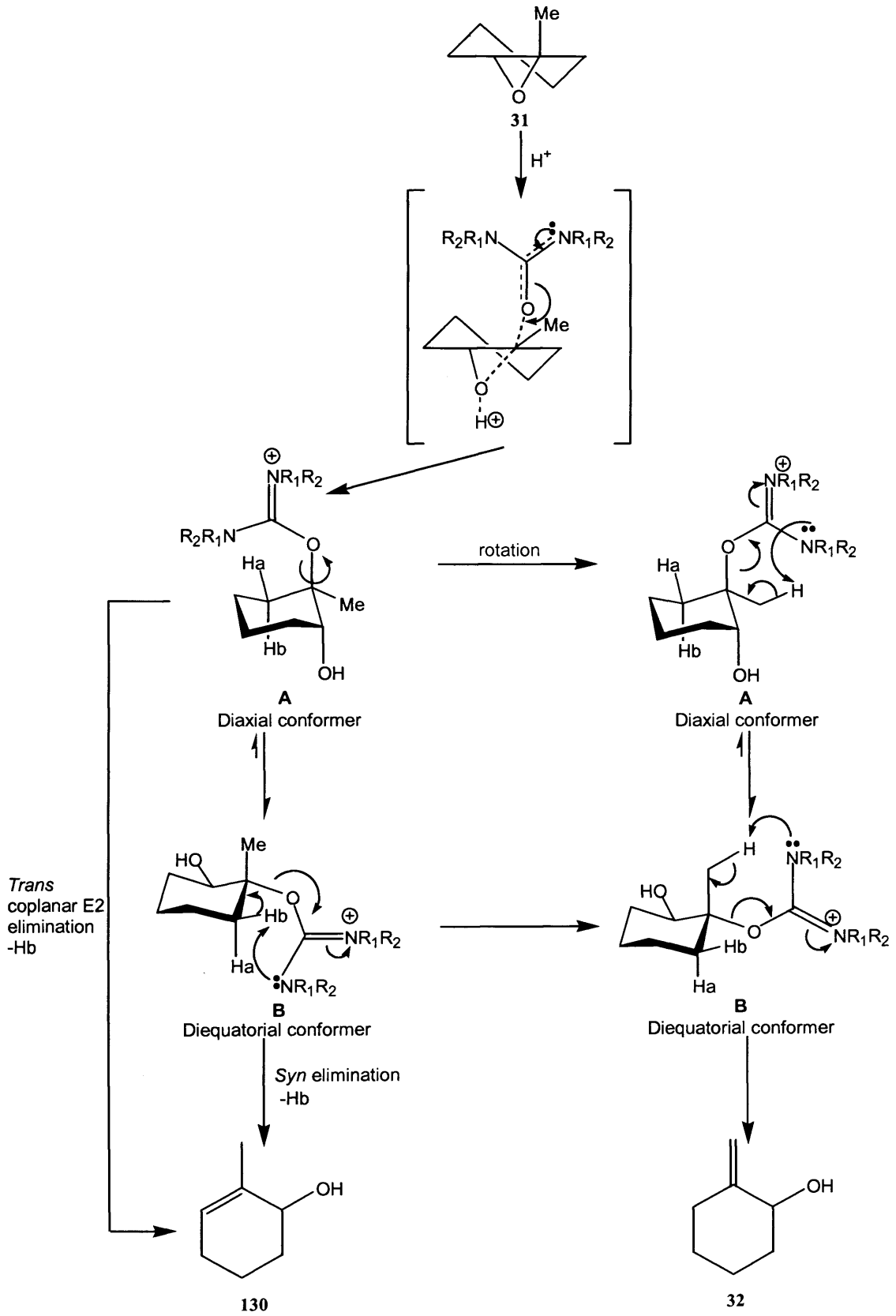
ketone can also be formed in the absence of the urea derivative by the classical hydride shift pathway, it is of course impossible to assess if ketone formation can evolve *via* intermediate **146**.

Prior to discussing the stereochemical implications of this observation, it is however important to note that after completion of the reaction, longer reaction time did not alter the product ratio. In a further control experiment, the products were also left stirring in dichloromethane with 0.5 equivalent of *p*-toluenesulfonic acid for 2 hours, and no reaction was observed, thus definitely proving their stability under the reaction conditions.

5. Stereochemical considerations

Whilst our initial goal was directed towards the formation of the endocyclic allylic alcohol **130**, the isolation of the exocyclic allylic alcohol **32** was nevertheless a very interesting and significant result especially as such products are generally produced from epoxides under strongly basic conditions.

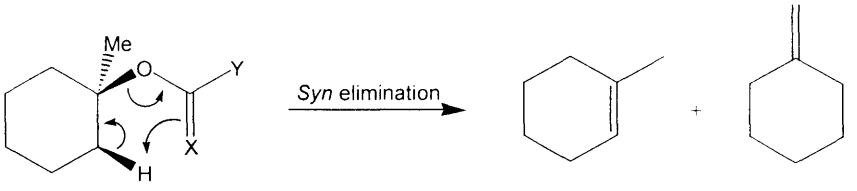
Our attention consequently focused on the mechanism of this reaction in more detail, and in particular it led us to consider the stereochemical aspects. As depicted in Scheme 62, *trans*-diaxial S_N1 like ring opening of 1-methyl-cyclohexene oxide **31** *via* the carbocation or incipient carbocation **131** is most probably followed by *trans* addition of the urea derivative through its oxygen atom to give the diaxial conformer **A** (*Scheme 62*). Although this conformation fulfils the ideal *trans* coplanar *anti* stereoelectronic requirements for an E2 elimination involving loss of the axial proton Hb to give the endocyclic allylic alcohol **130**, this pathway is clearly not followed. Furthermore, the E2 elimination mechanism cannot benefit in an intramolecular way from the presence of the second amino group of the urea derivative acting as a base. Two alternative *syn* elimination pathways, either from the diaxial conformer **A** through removal of the equatorial proton Ha, or from the lower energy diequatorial conformer **B** through removal of the equatorial proton Hb, can also lead to the endocyclic allylic alcohol **130** but are not observed.


Me
O
31
H+
R2R1N
NR1R2
O
Me
O
H⊕
⊕NR1R2
R2R1N
O
Ha
Me
Hb
OH
A
Diaxial conformer
rotation
⊕NR1R2
NR1R2
O
Ha
H
Hb
OH
A
Diaxial conformer
Trans
coplanar E2
elimination
-Hb
Me
HO
O
Hb
⊕NR1R2
Ha
NR1R2
B
Diequatorial conformer
H
NR1R2
HO
O
Hb
⊕NR1R2
Ha
B
Diequatorial conformer
Syn elimination
-Hb
OH
130
OH
32

Scheme 62

Thus, in spite of the fact that such *syn* eliminations potentially benefit from the presence of a positively charged leaving group, an intramolecular base and the thermodynamically favourable creation of two sp^2 centres within the cyclohexyl ring, they are clearly of relatively high energy in the present system.

This result was somewhat surprising inasmuch as the potentially related acetate pyrolysis and *Chugaev* elimination reactions of 1-methylcyclohexanol, both of which are known to proceed *via syn* elimination, both display a 4:1 preference for the formation of the endocyclic alkene[126] **129** (*Scheme 63*).



		129	149
X=O, Y=CH_3	147	80%	20%
X=S, Y=SCH_3	148	79%	21%

Scheme 63

By way of contrast, however, the formation of the *exo* isomer was indeed observed and a mechanism of formation involving simple rotation around the C-O bond on **A** evidently provides a favourable conformation and steric arrangement for proton loss from the methyl group possibly with assistance from the second nitrogen atom acting as a base. Presumably, the concerted mechanism shown in Scheme 62 leads to the formation of 2-methylene-cyclohexanol **32**.

The exclusive formation of the exocyclic isomer of the allylic alcohol remains a very interesting phenomenon.

6. Optimisation of the reaction conditions

With the above results in hand, our aim was then to optimise the reaction conditions towards an increase in the formation of the exocyclic allylic alcohol,

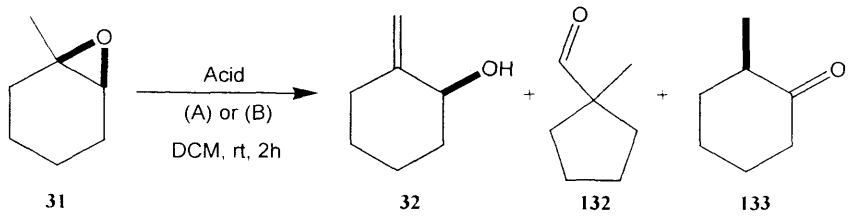
2-methylenecyclohexanol **32**. Different reaction parameters were considered, and a separate screening of each of them was carried out.

The chosen variables are, in order of study, the nature of the "acid", the number of equivalents of the urea derivative, the structure of the urea derivative, the reaction solvent and the temperature. However, it is important to note that each of these parameters were studied independently, meaning that each time one of them was screened, all others remained constant. The best result was then taken and applied in the screening of the next parameter and so on. This will therefore give us a relative optimisation of the reaction conditions since it does not take into account any dependant relationship between two parameters, which is likely to exist. Nowadays, some software, such as *Design of Experiment*, exists and is widely used in industry allowing an efficient reaction condition optimisation, taking into account any dependence between parameters.

At this stage, our progress was supported by GC-analysis, hence decreasing the workload related to the isolation and purification of products. This technique also allowed us to monitor volatile product yields with much higher precision. GC-calibrations of the starting material, 1-methylcyclohexene oxide **31**, and of the three usual products, 2-methylenecyclohexanol **32**, 1-methylcyclopentanecarbaldehyde **132** and 2-methylcyclohexanone **133,** were consequently carried out. Each experiment was ran once.The results of this approach are detailed within the Experimental Section.

6.1. The influence of acids and metal salts on the epoxide ring opening

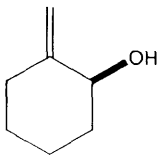
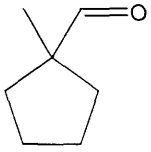
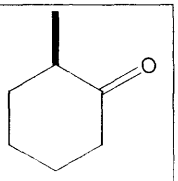
The first parameter to be studied was the influence of the acid both in the presence and in the absence of a urea derivative. Different types of Brønsted acids, spanning a range of structures and acidity strength, and metallic cations of different size, coordination geometry and charge, were therefore studied. The aim was to establish a pattern between the acid strength or the size and charge of the cation used and the formation of allylic alcohol **32**. The reaction conditions used to perform this screening are detailed in Scheme 64.



(A): absence of urea derivative
(B): 2 eq of 1.3-dimethyl-2-imidazolidinone

Scheme 64

Table 6. Influence of the acids and metal salts (pKa are indicated in water)

Acid or metal salt	Conditions	 32 % yield	 132 % yield	 133 % yield
Triflic acid	A	0	0	92
pKa -13.6	B	13	12	68
p-TsOH	A	0	15	52
pKa -6.5	B	46	8	40
F_3C-CO_2H	A	5	11	8
pKa -0.3	B	10	8	14
H_3PO_4	A	4	37	57
pKa 2.12	B	10	29	57
NaOTf	A	15	10	52
	B	17	11	63
$Mg(OTf)_2$	A	6	9	51
	B	15	10	58
$Zn(OTf)_2$	A	16	12	55
	B	16	11	66
$Sc(OTf)_3$	A	0	28	60
	B	16	12	66
$Yb(OTf)_3$	A	9	25	55
	B	13	10	55

A: absence of urea derivative. B: 2 equivalents of 1.3-dimethyl-2-imidazolidinone

Thus, a catalytic or stoichiometric amount of the acid was added to a stirred solution of 1-methylcyclohexene oxide **31** in dichloromethane at room temperature, in the absence (A) or presence (B) of 1,3-dimethyl-2-imidazolidinone **150** as the chosen urea. Some selected results are summarised in Table 6 and a detailed table is available in the Experimental Section.

Throughout this preliminary screening exercise, it was encouraging to note that, with the sole exception of zinc triflate, the use of 1,3-dimethyl-2-imidazolidinone **150** had the expected impact in terms of leading to a slight to significant increase in the formation of 2-methylenecyclohexanol **32**.

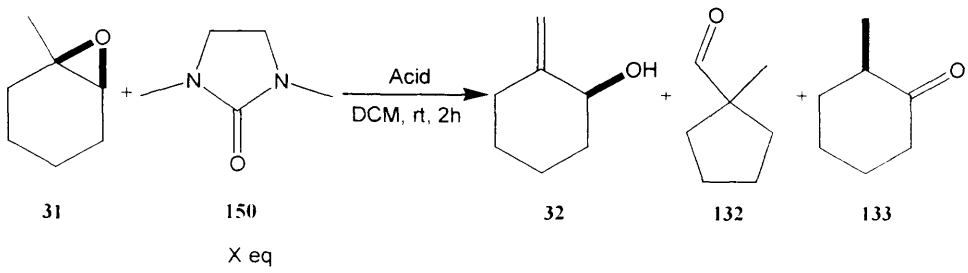
Further scrutinisation of these results clearly demonstrates that the nature of the acid both in terms of its acidity, and also in terms of the structure and nucleophilicity of its conjugated base, has a profound influence on the outcome of the reaction. Thus for example, selection of triflic acid, a powerful proton source with a relatively non-nucleophilic counteranion, apparently guarantees that an extremely rapid hydride shift to give 2-methylcyclohexanone **133** will predominate. By way of contrast, the very low mass balance of rearranged products obtained when trifluoroacetic acid was used may be indicative of carbocation trapping by trifluoroacetate, whilst the implication to be drawn from the use of phosphoric acid is that the phosphate counteranion acts both as a poor nucleophile and a good leaving group inasmuch as both hydride transfer and ring contraction are favoured. Trifluoroacetate counteranion appears to be a better nucleophile than the urea since it seems like the major product of the reaction, which was not isolated, derives from the addition of trifluoroacetate ion to the carbocation. In the event, the selection of *p*-toluenesulfonic acid clearly provides the best balance of acidity, nucleophilicity of counteranion and overall structural features to encourage capture by the urea derivative and formation of the exocyclic allylic alcohol in a particularly dramatic fashion compared to all other Brønsted acids.

In terms of the use of metal triflate salts it would appear that the charge of the cation has little or no impact in formation of the allylic alcohol. It was initially thought, that a highly charged cation would probably have a positive effect since it could coordinate both to the epoxide oxygen atom, consequently

triggering the opening of the oxiran ring, and also to the urea derivative, thus, through a proximity effect, increasing its chance of trapping the carbocation formed. However, the results obtained show that the charge and varying coordination geometry on the Lewis acidic cation is not a critical parameter.
In the final analysis, the use of 1,3-dimethyl-2-imidazolidinone **150** has made an impact on all of the reactions save one, but is most significant with *p*-toluenesulfonic acid, and scandium triflate. These two acids were therefore selected for the following study of the influence of the number of equivalents of the urea derivative.

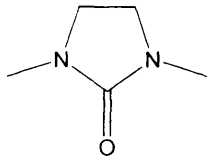
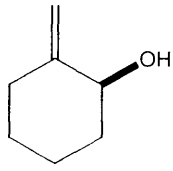
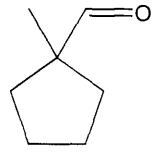
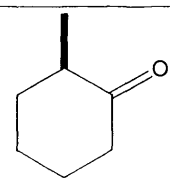
6.2. Influence of the number of molar equivalents of the urea derivative

The urea derivative screened here was 1,3-dimethyl-2-imidazolidinone **150**, which gave the best results in preliminary studies. On the basis of the postulated mechanism leading to the formation of **32**, it would appear logical that the more urea derivative is present in the reaction media, the more chance it has to trap the carbocation formed, hence leading to a better conversion towards the allylic alcohol.
Once again, the positive effect of the urea derivative is obvious, since no 2-methylene-cyclohexanol **32** is formed with either acid catalyst in the absence of 1,3-dimethyl-2-imidazolidinone **150**. However, to our surprise, an increasing concentration of urea did not have the expected effect, since from 2 equivalents onwards the yields of **32** remained stable and even decreased in the case of *p*-toluenesulfonic acid.



Scheme 65

Table 7. Influence of the number of molar equivalents of the urea

	 No equivalents	 32 % yield	 132 % yield	 133 % yield
$Sc(OTf)_3$	0	0	28	60
	1.2	17	16	67
	2.6	16	10	67
	3.8	15	0	73
	8.5	16	0	64
p-TsOH	0	0	17	60
	1	42	8	47
	2	46	7	40
	4	39	8	46
	9	34	8	47

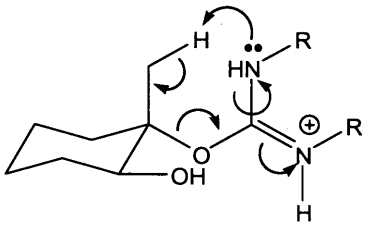
The best two "acids" from the previous section, *viz.*, *p*-toluenesulfonic acid and scandium triflate, were therefore tested at different concentrations of 1,3-dimethyl-2-imidazolidinone **150**, the other reaction parameters remaining unchanged. The above general reaction scheme summarises the reaction conditions (*Scheme 65*), and the results are summarised in Table 7.

This negative effect may be due to some solubility issues of the starting reagents. This is strongly supported by the fact that when the reaction was carried out using 1,3-dimethyl-2-imidazolidinone **150** as a solvent, the reaction did not reach completion. Thus, there are two opposite effects related to an increasing concentration of urea derivative. On the one hand, it gives it more chance to trap the carbocation, and on the other, the solubility of the reagents decreases. A compromise between these two effects seemed to be found when around two equivalents of the urea derivative are used.
Another plausible explanation would be that a first equivalent of urea derivative quenches the carbocation, followed by a second equivalent coming in to trap the proton from the methyl group. This would trigger the elimination of the urea and hence the formation of the double bond. Such a mechanism would then justify the need of two equivalents of urea derivative to perform this transformation.

In the light of these studies, it was decided to use two equivalents of urea derivative from now on, and to select *p*-toluenesulfonic acid since it consistently gave far better results than scandium triflate.

6.3. Influence of the urea derivative

Two types of urea derivatives have already been used in these ring-opening of 1-methylcyclohexene oxide **31**, *viz.*, 1,3-diethylurea **145** and 1,3-dimethyl-2-imidazolidinone **150** and it was significant that these gave different results. Hence, the structure of the urea derivative seemed to have an impact on the outcome of the reaction. In the first instance, we anticipated that the use of an acyclic urea derivative, as opposed to a cyclic one, would allow greater flexibility within the system, thereby facilitating the formation of the *exo*-double bond (*Figure 10*). Thus, since rotation around the C-N bond is indeed permitted in an acyclic system, it should allow an optimum position of the nitrogen lone pair to be adopted for the abstraction of one of the three available protons on the methyl substituent.

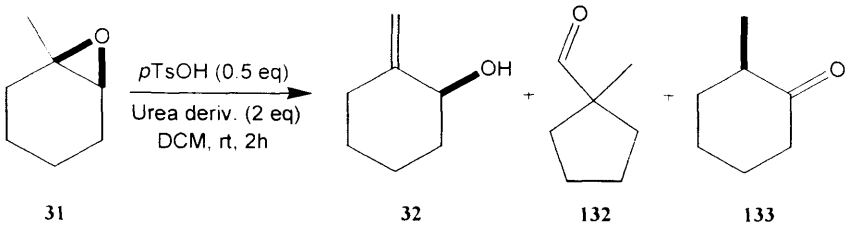


141

Figure 10

Five urea derivatives were accordingly screened, three acyclic and two cyclic, using two equivalents of urea with *p*-toluenesulfonic acid in dichloromethane at room temperature (*Scheme 66*).

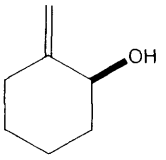
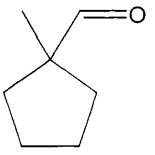
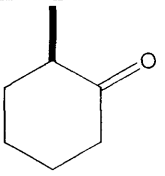
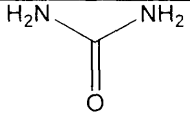
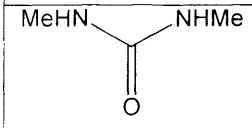
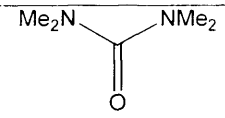
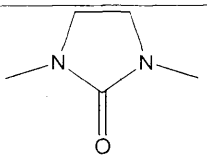
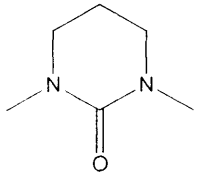
In the event, the results, summarised in Table 8, were not as expected, since the two cyclic urea derivatives 1,3-dimethyl-2-imidazolidinone and DMPU afforded higher yields of 2-methylenecyclohexanol **32**. Since our original assumption that the greater number of degrees of conformational freedom in an acyclic urea would favour the elimination step was obviously not borne out, we therefore turned to possible alternative explanations.



31 32 132 133

Scheme 66

Table 8. Influence of the urea derivative

Urea derivative	 32 % yield	 132 %yield	 133 % yield
	25	13	51
	34	9	43
	35	8	44
	48	5	39
	53	0	47

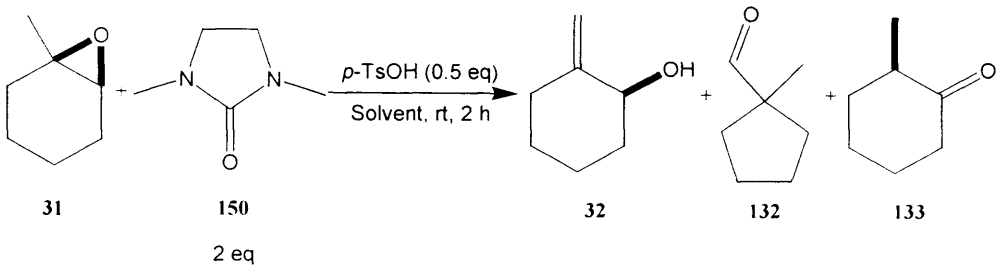
In retrospect, it should be remembered that the urea derivative in this reaction fulfils several successive roles by functioning as a nucleophile, a base, and a

leaving group and that the optimal urea reagent should perform well in each of the categories. When viewed from this perspective, it may well be that the cyclic ureas, by virtue of the fact that they are "tied back" and hence less hindered, act as more effective nucleophiles to trap the carbocation than their acyclic congeners.

Since, the yields of 2-methylenecyclohexanol **32** using either one of the two cyclic ureas were very similar, it was decided to pursue the remaining optimisation investigation using 1,3-dimethyl-2-imidazolidinone **150**.

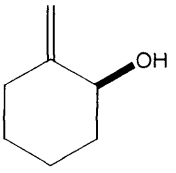
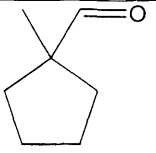
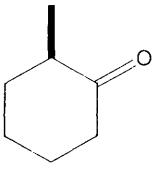
6.4. Influence of solvent

Solvents often have a huge impact in organic synthesis reactions, and their physical properties can often dictate a reaction pathway. It was therefore important to study the influence of the solvent in our reaction, bearing in mind that if it is an S_N1 like mechanism and therefore proceeding *via* a carbocation, such a reaction would probably work better in polar solvents. A wide range of solvents with different polarity were therefore screened. The reaction conditions are detailed in Scheme 67 and the results are summarised in Table 9.



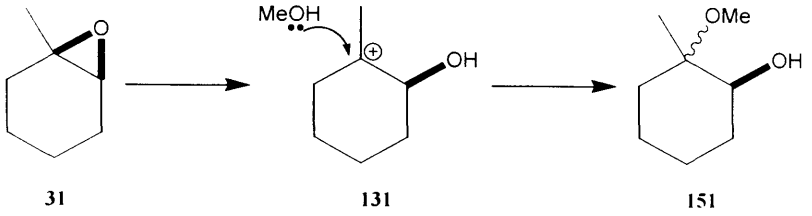
Scheme 67

Table 9. Influence of the solvent

Solvent	 **32** % yield	 **132** % yield	 **133** % yield
Toluene	8	8	55
Et_2O	23	10	47
THF	25	12	48
EtOAc	31	10	50
CH_2Cl_2	48	7	42
$CHCl_3$	33	7	44
MeOH	0	0	6

As might be expected, from toluene to dichloromethane, the yield of 2-methylene-cyclohexanol **32** increased from 8 to 48%. Although surprisingly, it drops back using chloroform.

Also, the presence of a solvent with good nucleophilic properties such as methanol must of course be avoided since the carbocation can be trapped and presumably form an undesired adduct **151** (no product isolation was attempted) (*Scheme 68*). In this instance, the overall yield of our three usual products consequently dropped to 6%.



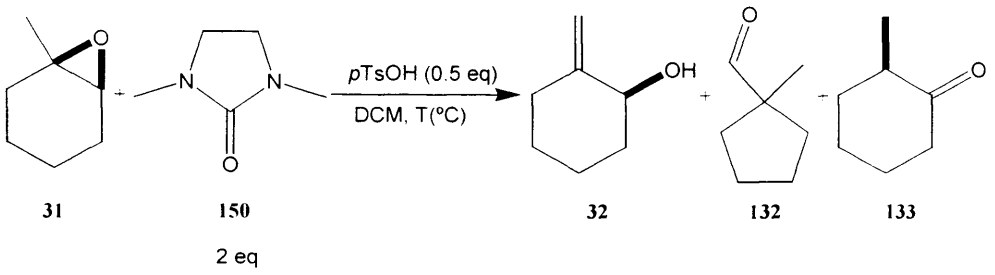
31 131 151

Scheme 68

Following these results, dichloromethane remained the solvent of choice for our reaction.

6.5. Influence of the temperature

The last reaction parameter to be studied for this acidic ring-opening of 1-methylcyclohexene oxide **31** was the temperature. All other parameters were already set, and the reaction was carried out using 0.5 equivalent of *p*-toluenesulfonic acid and 2 equivalents of 1,3-dimethyl-2-imidazolidinone **150** in dichloromethane (*Scheme 69*). The temperature scale which can be investigated in dichloromethane ranges between -78 °C to approximately 40 °C. Five different temperatures were studied within this range, and the results are summarised in Table 10.

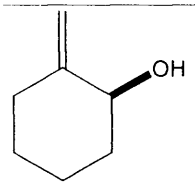
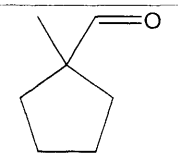
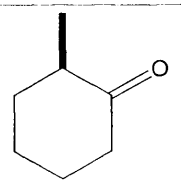


31 150 32 132 133

2 eq

Scheme 69

Table 10. Influence of the temperature

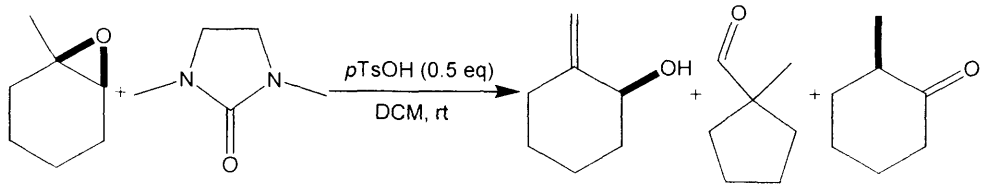
Temperature °C	 32 % yield	 132 % yield	 133 % yield
-78	26	9	42
-30	25	10	47
0	25	10	45
rt	47	8	40
40	49	7	38

The temperature had more of a significant impact on the reaction time than on the product distribution, and completion of the reaction took up to 6 hours at -78 °C. Besides this fact, yields were very comparable in two ranges of temperature, from -78 °C to 0 °C and from room temperature to reflux, the latter affording good yields of 2-methylenecyclohexanol **32**. The slight difference observed between working at room temperature and reflux led us to select the former as the temperature of choice for cost and safety reasons.

6.6. Conclusions

The foregoing reaction parameter screening allowed us to gain some

mechanistic insights and also to set up some optimum reaction conditions. Thus, the acid ring-opening of 1-methylcyclohexene oxide **31** afforded the highest yield of allylic alcohol **32** using half an equivalent of *p*-toluenesulfonic acid and two equivalents of 1,3-dimethyl-2-imidazolidinone **150**, in dichloromethane at room temperature (*Scheme 70*).



31 **150** **32** **132** **133**

2 eq **47%** **8%** **40%**

Scheme 70

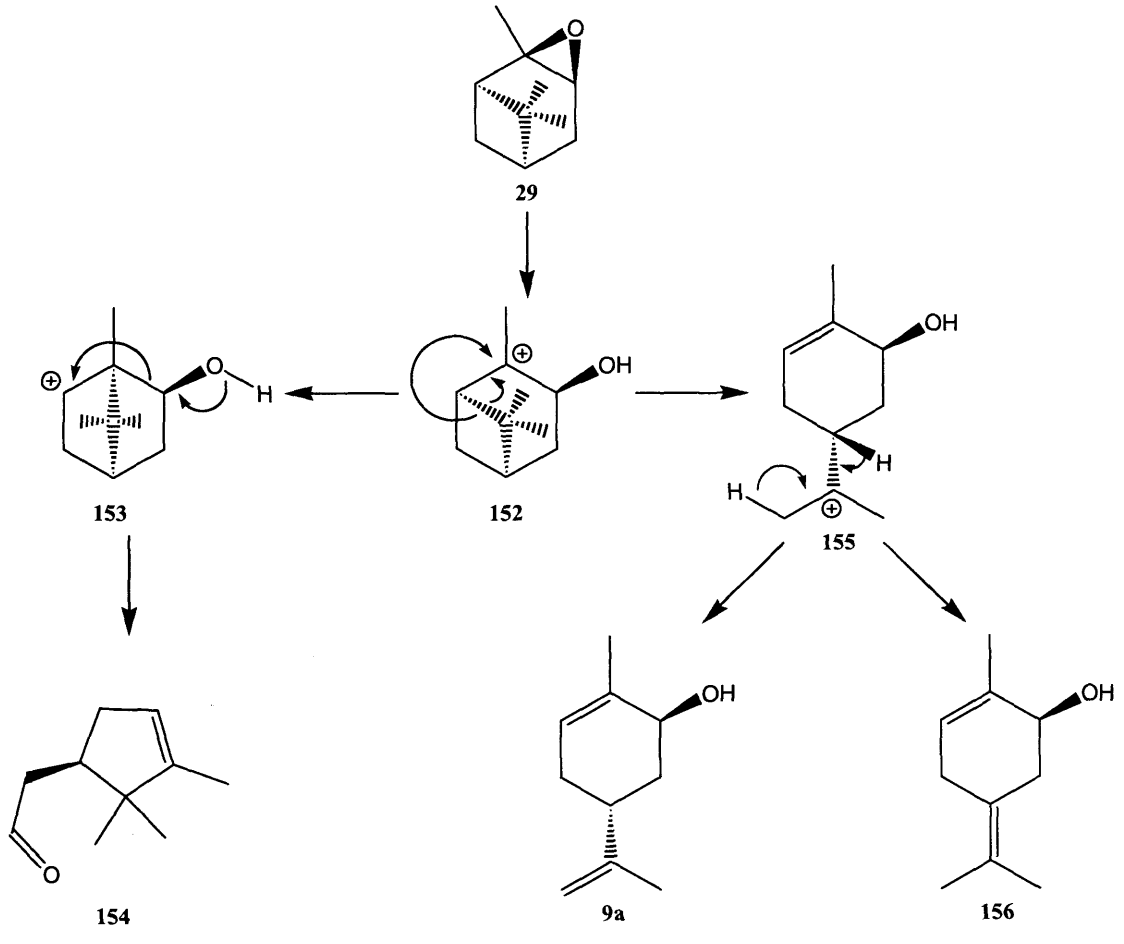
These reaction conditions can now be applied to a variety of epoxides. The syntheses of these substrates are detailed below.

7. An interlude on the ring opening of α-pinene oxide

Throughout our studies, we were always aware that, from an industrial perspective, the epoxide derived from α-pinene **23**, although more expensive, could be used as an alternative to *D*-limonene **1** for the production of carveol **9** by virtue of its ability to participate in more deep seated carbocationic rearrangements. However, since the ring opening of (-)-α-pinene oxide **29** cannot really be considered as similar in nature to the model system studied above, a short optimisation study was also therefore carried out on this particular substrate.

The S_N1 ring opening of (-)-α-pinene oxide **29** is a particularly interesting and unusual one[15,129] and the fate of the carbocation can be difficult to control, as illustrated in Scheme 71, which illustrates that three major products can be formed. Thus, opening of epoxide **29** generates tertiary carbocation **152** which can rearrange by two different pathways both of which involve release of strain

in the four membered ring and both of which remarkably involve movement of the same pair of electrons in the same sigma bond. The first pathway leads to the formation of secondary carbocation **153** *via* a 1,2-alkyl shift, and subsequent ring opening leads to campholenic aldehyde **154**. In the second pathway, a rearrangement leads to tertiary carbocation **155** with the *p*-menthyl skeleton that can be stabilised by forming either an isopropenyl or an isopropylidene moiety depending on the site of proton loss, leading to **9a** or **156**, respectively. It is also noteworthy that the relief of strain dominates over the normally facile hydride transfer pathway.

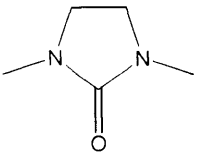
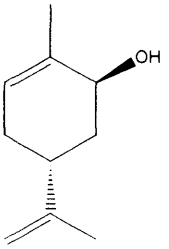
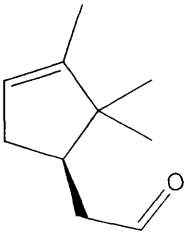
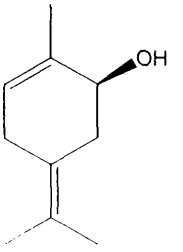


Scheme 71

It was therefore interesting to study the effect of the urea derivative on this substrate and to investigate at which stage it eventually acts. Only two sets of reactions have been carried out with (-)-α-pinene oxide **29**, one of each using a

different class of acid, trifluoromethanesulfonic acid as a Brønsted acid and zinc triflate as a Lewis acid. The choice of the triflate counteranion in both cases was strategic since it is not nucleophilic, and should therefore avoid the formation of adduct products. The use of *p*-toluenesulfonic acid was studied at a later stage. The reaction with the two chosen acids was repeated twice, with and without 1,3-dimethyl-2-imidazolidinone **150**. The results for this set of reactions are detailed in Table 11.

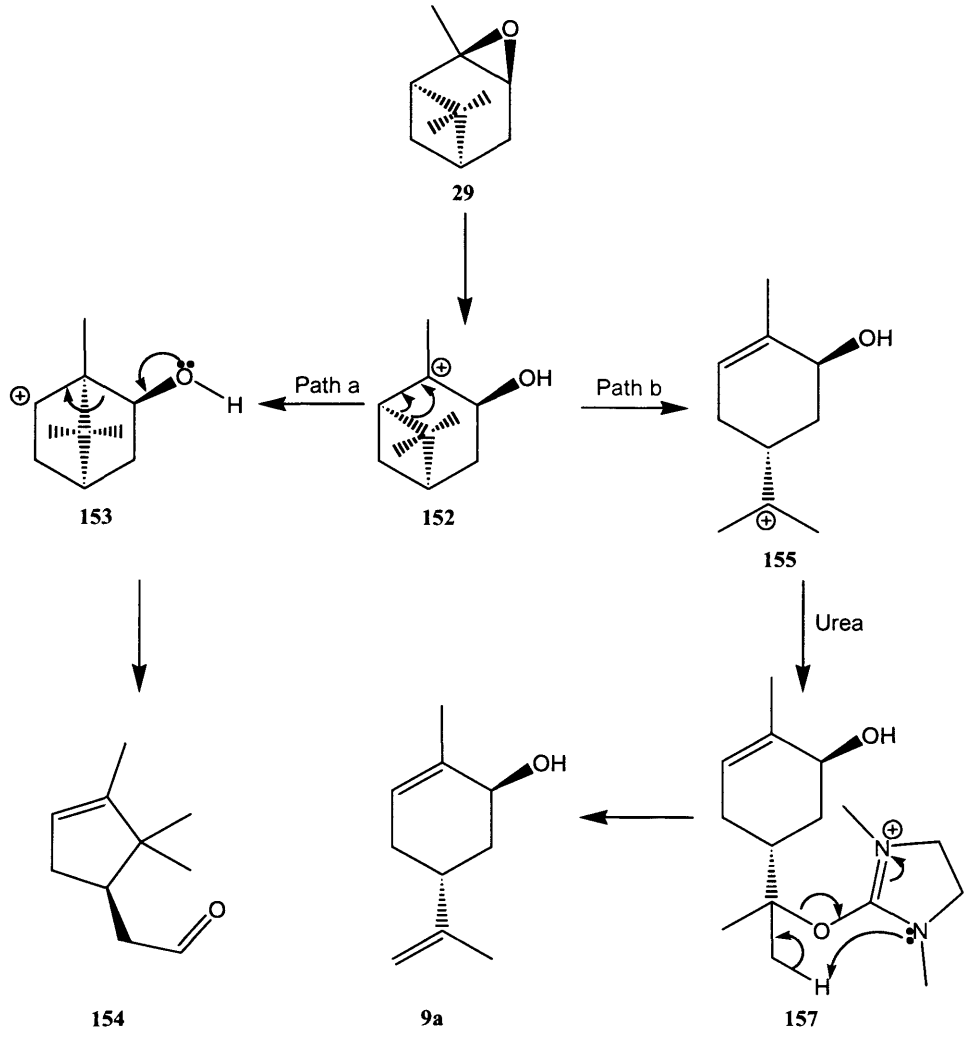
Table 11. Ring opening of *α*-pinene oxide

Acid used	 **150** **No. of eq.**	 **9a** **% yield**	 **154** **% yield**	 **156** **% yield**
Triflic acid	0	27	43	-
	2	29	38	-
Zinc triflate	0	5	54	17
	2	46	39	-

As in the case of 1-methylcyclohexene oxide **31**, the urea did not have a significant effect when triflic acid was used. The use of such a strong acid may be the reason, triggering a fast epoxide opening, which is immediately followed by the rearrangements described above. Pleasingly however, "the urea effect" was successful with zinc triflate, and very considerably altered the selectivity of the reaction towards the desired *L*-carveol **9a**.

Both the formation of the endocyclic double bond and the isopropenyl group are very significant and useful manifestations of the importance of the urea in this reaction. In terms of simple arithmetic for the zinc triflate reactions, the yield of products with the *p*-menthyl skeleton, **9a** and **156**, was effectively doubled in the presence of the urea, at the expense of the alternative path towards campholenic aldehyde **154**. Some mechanistic possibilities are shown

in Scheme 72.



Scheme 72

Thus, as depicted in Scheme 72 above, the urea may influence the rearrangement of the first formed carbocation **152** through formation of a reversible adduct with the urea, which, in turn, appears to favour further rearrangement preferably into carbocation **155** over **153**, and subsequently leads to the endocyclic double bond formation in **9a** (path b), over path a.

8. Applications of the urea methodology

8.1. Synthesis of the substrates

In order to study the efficiency and scope of the developed methodology, it was of interest to examine a wide range of substrates bearing different functionalities and structures. In addition, it would also be of great benefit if these examples could provide further mechanistic detail into the different features of the reaction. The chosen substrates are illustrated in Figure 11 and all of them can potentially proceed through the intermediacy of a tertiary carbocation.

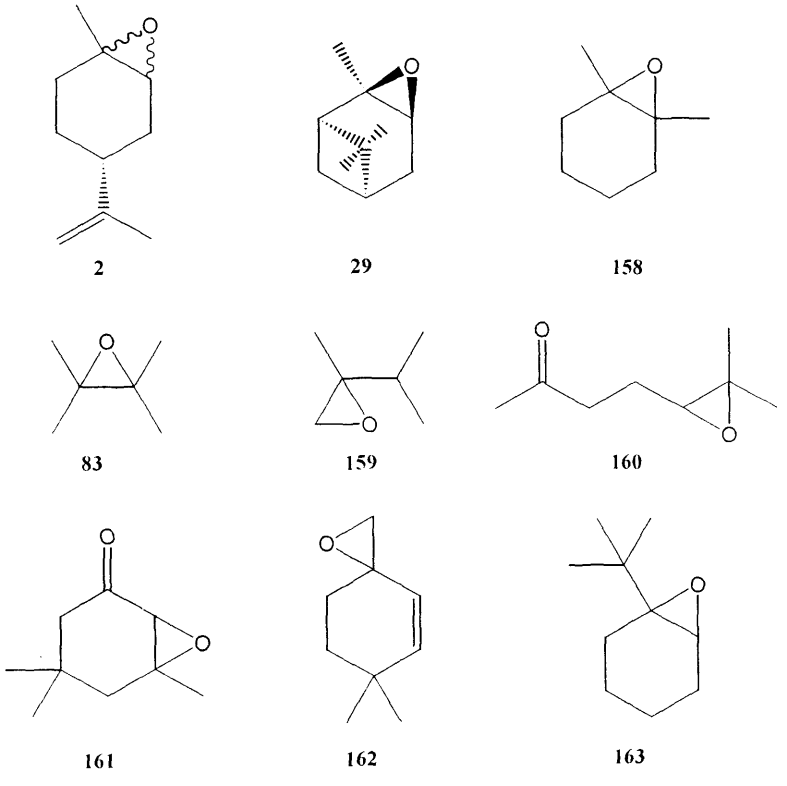


Figure 11

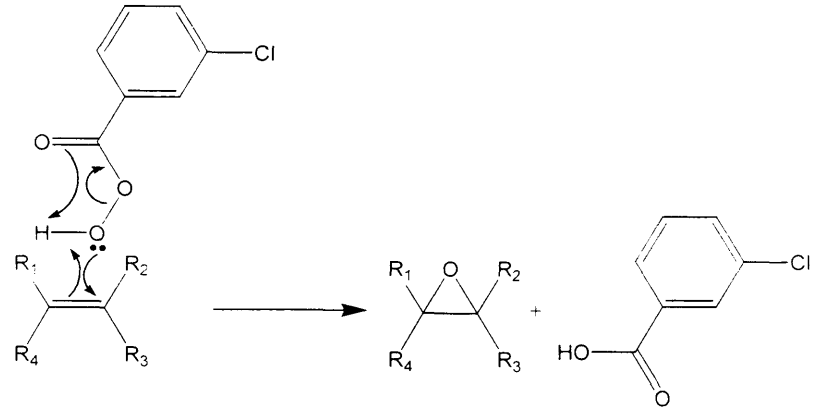
(+)-(*R*)-Limonene oxides **2** and (-)-α-pinene oxide **29** were of course selected as our primary targets because they should in principle lead to the formation of

the desired *endo*, or at least *exo*, carveol, which was one of the original aims of this study. 1,2-Dimethylcyclohexene oxide **158** and tetramethylethylene oxide **83** were chosen to examine the possibly of a 1,2-alkyl shift becoming a competitive process when hydride migration to give a ketone was not possible, in both cyclic and acyclic systems. In contrast to epoxide **83**, oxiran **159** provides further opportunities to examine the regioselectivity of alkene formation in a purely acyclic system. In principle, epoxides **160** and **161** can both probe the influence of the presence of a carbonyl group whilst the spirocyclic system **162** was selected since it should lead to an allylic carbocation on ring opening. The example of *tert*-butylcyclohexene oxide **163** was of interest inasmuch as exocyclic alkene formation is precluded.

The preparation of one of the substrates, 1-methylcyclohexene oxide **31**, has already been described earlier in this thesis,[123] whilst another, (-)-α-pinene oxide **29**, was commercially available. The preparations of the other chosen substrates are summarised in this section. Most of them were prepared by direct epoxidation of the corresponding olefin using different procedures depending on their reactivity and following classical protocols with peracids. Due to the diversity of the procedures employed, each method or multistep synthesis will be described separately.

8.1.1. Epoxidation in dichloromethane

Olefins undergo epoxidations with any of a number of peracids, of which *m*-chloroperbenzoic acid **164** is the most widely used, in a reaction called the *Prilezhaev* reaction.[130,131] This reaction is often carried out in organic solvents and particularly in dichloromethane.[124,125] It follows a one-step mechanism proposed by *Bartlett*[132] and detailed in Scheme 73 below.

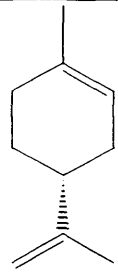
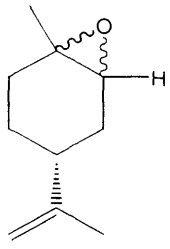
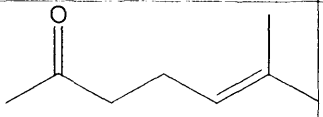
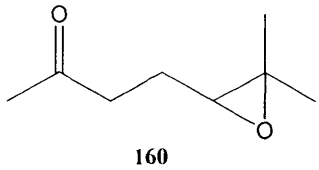
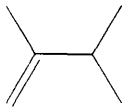
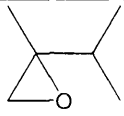


Scheme 73

As mentioned earlier, this reaction is usually carried out in dichloromethane at 0 °C where the olefin is stirred with slow addition of 1.1 equivalent of *m*-chloroperbenzoic acid **164** in solution in dichloromethane. Once the addition is complete, the reaction mixture is allowed to warm up to room temperature and then left stirring until disappearance of the starting material. Generally, no purification is needed as, once the washing is complete, the epoxide remains as the only product of the reaction. Nevertheless, if required, purification by distillation or column chromatography was performed.

This literature reaction was successfully carried out for the epoxidation of three of our substrates, limonene oxides **2**, 4-(3,3-dimethyl-oxiranyl)-butan-2-one **160** and 2-isopropyl-2-methyl-oxirane **159**, starting from the three commercially available olefins, *D*-limonene **1**, 6-methyl-5-hepten-2-one **165** and 2,3-dimethyl-but-1-ene **166**, respectively (*Table 12*). For *D*-limonene **1**, two potential sites can be epoxidised. However, the endocyclic double-bond is more electron-rich making it more reactive, hence leaving the isopropenyl moiety intact,[133,134] and affording two isomers of (+)-(*R*)-limonene oxide **2** (in a 55:45 ratio, according to NMR) in 57% yield. Concerning 2-isopropyl-2-methyl-oxirane **159**, it was easily prepared in an acceptable 56% yield. In the case of 6-methyl-5-hepten-2-one **165**, the ketone moiety remained unreactive, as expected, under the reaction conditions, to finally afford 4-(3,3-dimethyl-oxiranyl)-butan-2-one **160** in 42% yield.

Table 12. Epoxidation in dichloromethane

Starting olefin	Product	Yield (%)	Reaction time (h)
 1	 2	57	2
 165	 160	42	1.5
 166	 159	56	10

8.1.2. Epoxidation in aqueous sodium bicarbonate

Another method was chosen to perform the preparation of three substrates, using a procedure developed by *Fringuelli* and co-workers[123] based on a triphasic system, and achieving the formation of epoxides from olefins by using an aqueous solution of sodium bicarbonate as a solvent. The olefin and solid *m*-chloroperbenzoic acid **164** were simply stirred together in a 3 N aqueous solution of sodium bicarbonate at 0 °C.

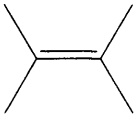
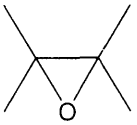
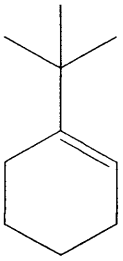
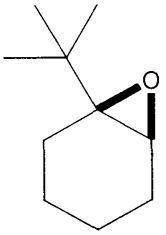
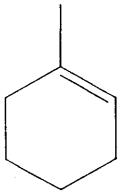
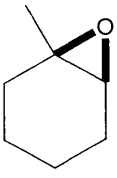
This method proved to be faster with highly reactive substrates. Also, it was observed that the yield of formation of epoxides from alkenes was higher with relatively electron-rich double bonds. For instance, changing the epoxidation conditions of 1-methylcyclohexene **129** in dichloromethane for the latter in aqueous sodium bicarbonate led to a significant improvement in the yield of 1-

methylcyclohexene oxide **31** from 45% to 80% yield.

Three epoxides were formed using this method, 1-methylcyclohexene oxide **31**, 2,3-dimethyl-2,3-epoxy-butane **83** and 1-*tert*-butyl-7-oxa-bicyclo[4.1.0]-heptane **163**.

The synthesis of 2,3-dimethyl-2,3-epoxy-butane **83** following *Fringuelli*'s method was very straightforward, since 2,3-dimethyl-but-2-ene **167** is commercially available. It is however a very volatile starting material and so required careful handling. As a consequence, the yield of the reaction was quite low and indeed, after work-up, only 27% of the desired epoxide was isolated, and required no further purification, (*Table 13*).

Table 13. Epoxidation in a sodium bicarbonate solution

Starting olefin	Product	Yield (%)	Reaction time (h)
 **167**	 **83**	27	1
 **168**	 **163**	76	2
 **129**	 **31**	80	1

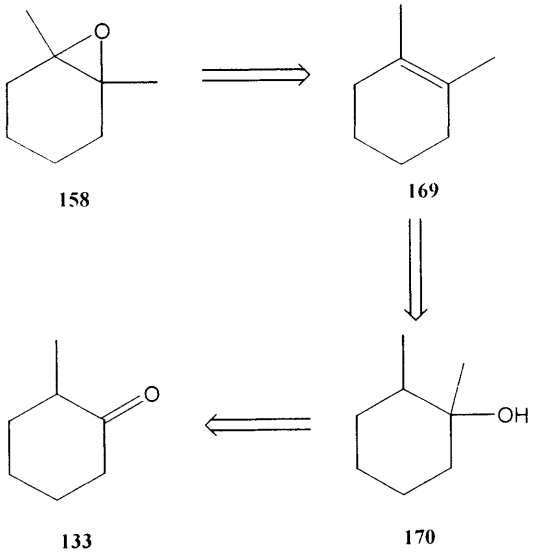
Epoxidation of 1-*tert*-butylcyclohexene **168** was carried out in the same manner but this time in a much better conversion affording **163** in 76% yield. Finally, 1-methylcyclohexene oxide **31** was synthesised in 80% yield following

the same literature procedure. The electron density around the double bond in 1-*tert*-butylcyclohexene **168** is higher than in 1-methylcyclohexene **31**, which should make the former more reactive. However, the observed reaction yield is slightly lower in the former case, and required longer reaction time. This is probably due to the presence of the bulky *tert*-butyl moiety on the former olefin, which causes steric hindrance and hence slows down the reaction.

8.1.3. Preparation of 1,6-dimethyl-7-oxa-bicyclo[4.1.0]heptane

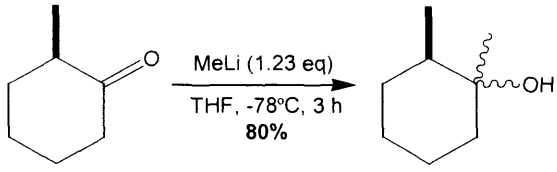
The formation of 2,3-dimethyl-2,3-epoxy-butane **158** required a multistep synthesis because the starting olefin, 1,2-dimethyl-cyclohexene **169**, was not commercially available from our usual suppliers.

The retrosynthetic approach considered to synthesise the desired epoxide is depicted in Scheme 74. 2,3-Dimethyl-2,3-epoxy-butane **158** can be synthesised by direct epoxidation of **169**. This olefin can be formed by dehydration of 1,2-dimethylcyclohexanol **170**, which can be obtained by nucleophilic addition of a methyl group on the carbonyl function of 2-methyl-cyclohexanone **133**.



Scheme 74

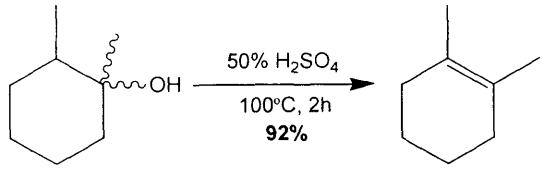
The starting point of this synthesis was consequently 2-methylcyclohexanone **133**. Nucleophilic addition of methyl-lithium at -78 °C in dry tetrahydrofuran afforded the desired alcohol **170** in 80% yield[135] after purification by column chromatography (*Scheme 75*). The stereoselectivity of the addition was determined by comparison with the literature.[135]



133 **170**

Scheme 75

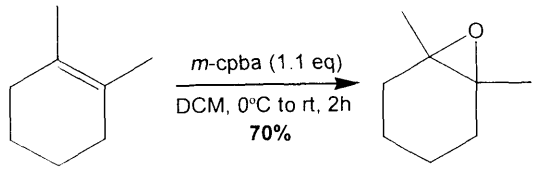
Dehydration of **170** was easily achieved in good yield under strong acidic conditions, in particular, concentrated sulphuric acid[136] at 100 °C for 2 hours to give **169** in 92% yield after purification by column chromatography (*Scheme 76*).



170 **169**

Scheme 76

Finally, facile epoxidation of this electron-rich double-bond using *m*-chloroperbenzoic acid in dichloromethane[124,125] at 0 °C, afforded the desired product **158** in 70% yield (*Scheme 77*).



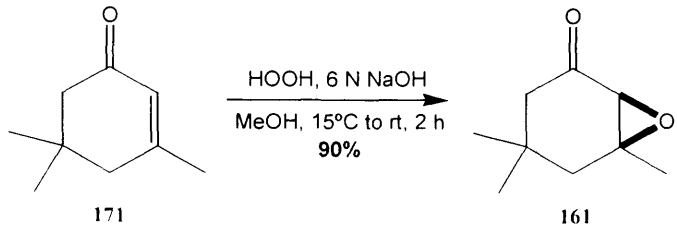
169 **158**

Scheme 77

This non-optimised synthesis finally gave us the desired epoxide **158** in an acceptable 52% overall yield.

8.1.4. Preparation of 4,4,6-trimethyl-7-oxabicyclo[4.1.0]heptan-2-one

The epoxidation of the conjugated enone unit in isophorone **171** was achieved using the classical literature approach[137] involving conjugate addition of hydroperoxide.



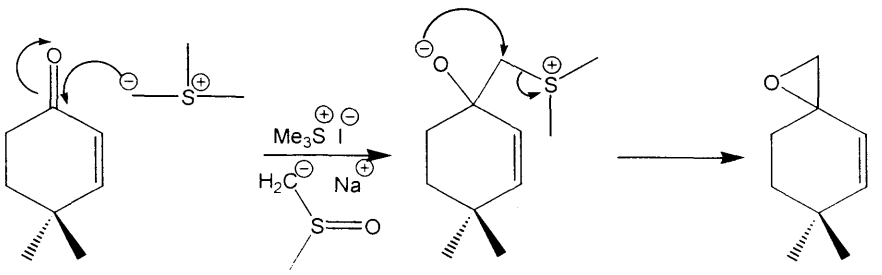
171 161

Scheme 78

The reaction was carried out in methanol for 2 hours affording 4,4,6-trimethyl-7-oxabicyclo[4.1.0]heptan-2-one **161** in an excellent 90% yield (*Scheme 78*). Once again, no purification was required, and the isolated product was ready for use in further reactions.

8.1.5. Preparation of 6,6-dimethyl-1-oxa-spiro[2.5]oct-4-ene

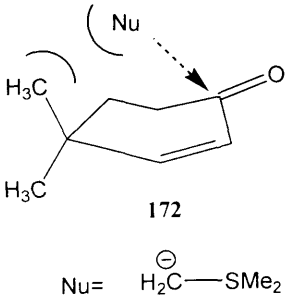
The synthesis of 6,6-dimethyl-1-oxa-spiro[2.5]oct-4-ene **162** was initially considered to be straightforward starting from the relevant α,β-unsaturated ketone **172**. Indeed, epoxides can usually be prepared in one-step following *Corey*'s epoxidation which involves reaction of an unsaturated ketone the sulphur ylide anion generated by deprotonation of a trimethyl sulfonium salt with dimsyl anion.[138] The mechanism is depicted in Scheme 79.



172 173 162

Scheme 79

This reaction was attempted with freshly distilled dimethylsulfoxide, but no reaction occurred and it was first thought that the quality of the sodium hydride used for dimsyl anion generation was doubtful. The reaction was therefore repeated with a new batch of reagent but led to the same result although the reactivity of sodium hydride was successfully tested by a simple control experiment on cyclohex-2-enone, which gave 31% of the expected epoxide. In retrospect, the failure of this reaction can be explained by the operation of two different factors. First of all, α,β-unsaturated ketones are inherently less reactive due to the delocalisation of the electrons over four different centres, thus making the carbonyl moiety less reactive to nucleophilic attack. However, several examples of epoxide formation on this type of substrate have been reported.[138] The second reason is steric. The presence of the gem-dimethyl substituents in the four position relative to the carbonyl group effectively prevent the sulphur ylide reagent from adopting the necessary angle – *Dunitz* angle[139] -of attack for formation of the tetrahedral centre (*Figure 12*).

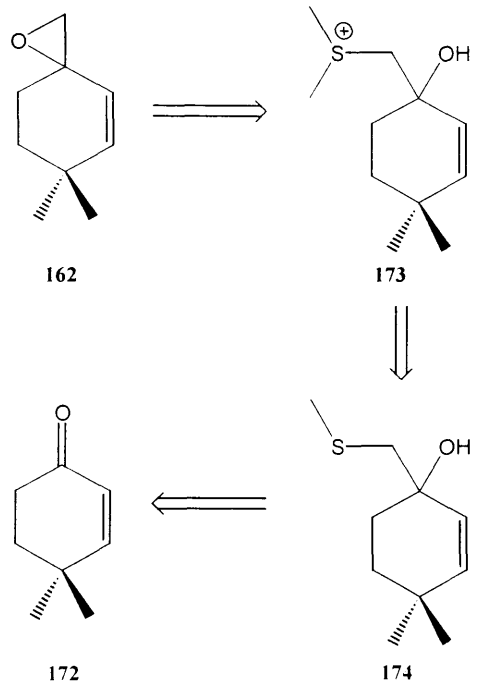


172

Nu= $H_2C^{\ominus}$—SMe_2

Figure 12

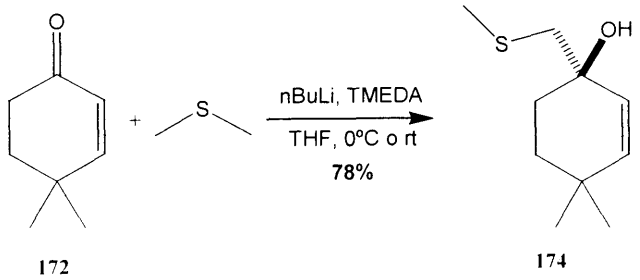
Another route was therefore required to prepare the desired epoxide and a literature search led us to consider the following retrosynthetic approach[140] (*Scheme 80*).



162 **173** **172** **174**

Scheme 80

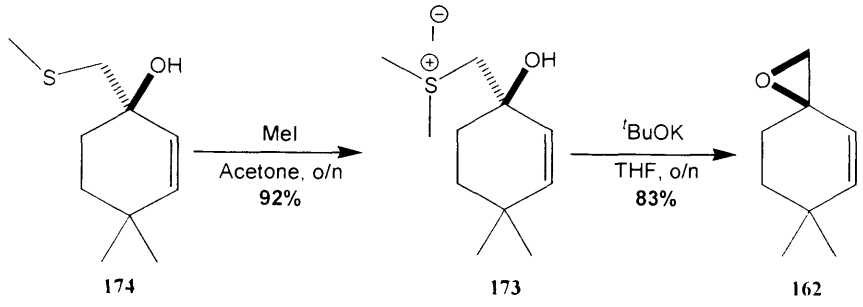
Nucleophilic addition of the anion, generated from dimethylsulfide by deprotonation with n-butyllithium and TMEDA, on 4,4-dimethyl-cyclohex-2-enone **172** gave the desired adduct **174** in 78% yield presumably as a consequence of the smaller size of the nucleophilic sulphur reagent in this case (*Scheme 81*).



172 **174**

Scheme 81

The sulphonium salt **173** was then made by addition of methyl iodide to the sulphide in acetone in 92% yield. No purification was required before the next step. Elimination of dimethylsulfide was then performed by addition of potassium *tert*-butoxide in THF, to afford, after distillation, 83% of the desired 6,6-dimethyl-1-oxa-spiro[2.5]oct-4-ene **162** (*Scheme 82*).



174 173 162

Scheme 82

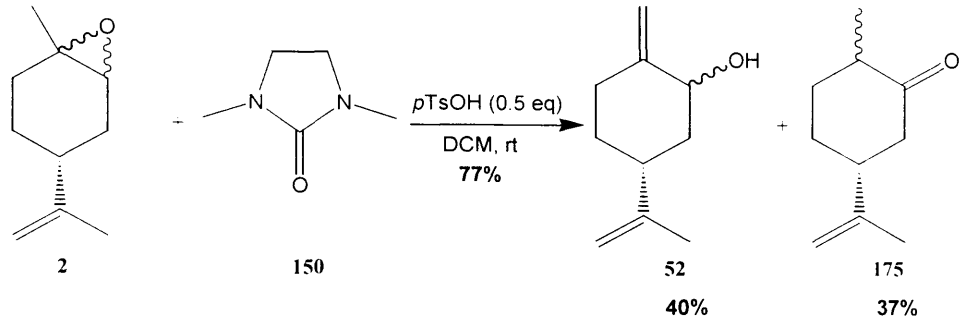
8.2. The scope and limitations of the urea mediated S_N1 epoxide ring opening reaction

With the above substrates in hand, we could start to investigate the scope of our methodology. As indicated earlier, each of these examples was selected to provide insights into the efficiency and robustness of our methodology, and also to highlight possible limitations. In all of the following urea mediated ring opening reactions of epoxides, the experimental conditions used are those which evolved as a consequence of optimisation study, *viz.*, using half an equivalent of *p*-toluenesulfonic acid and two equivalents of 1,3-dimethyl-2-imidazolidinone **150** in dichloromethane at room temperature.

8.2.1. The ring opening of (*R*)-limonene oxide

The first application of this method was targeted towards the formation of carveol **9** from the diastereoisomeric mixture of *cis* and *trans*-limonene oxides **2** (*Scheme 83*). The decision to use the mixture, even although the two epoxides could well evolve to different products at different rates, was of

course taken because separation, especially on an industrial scale is problematic.

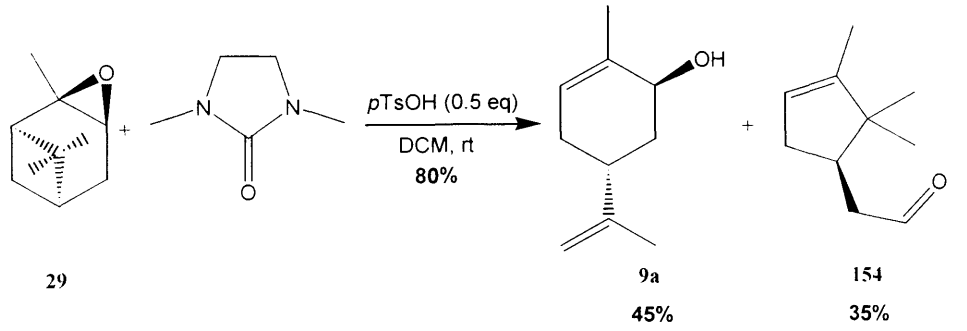


Scheme 83

In the event, the result observed here was in accord with the work carried out on the model system. The isolated yield (77%) was however higher in this case, probably caused by the use of less volatile molecules. A 1:1 mixture of *exo*-carveol **52** and dihydrocarvone **175** was obtained. That was a very encouraging result because we were at this point two steps away from the desired *L*-carvone **3**, and also confirmed the good choice of the model molecule.

8.2.2. The ring opening of α-pinene oxide

Our attention then focused on the second substrate of industrial relevance, *viz.* the ring opening of (-)-α-pinene oxide **29**. It should be noted that this starting material is significantly more expensive than (+)-(*R*)-limonene oxides **2**. The reaction outcome is summarised in Scheme 84.

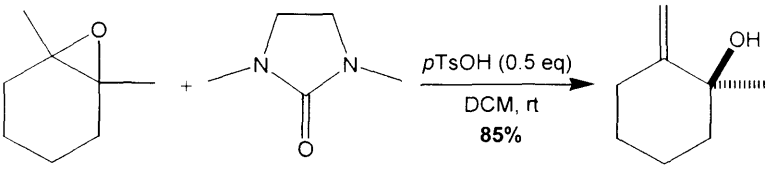


Scheme 84

This was a very successful result since *L*-carveol **9a** was synthesised in a single step in 45% yield, although is still required purification from the other major product campholenic aldehyde **154**. This result essentially parallels our earlier study using zinc triflate in combination with the urea (section 7).

8.2.3. The ring opening of 1,6-dimethyl-7-oxa-bicyclo[4.1.0]heptane

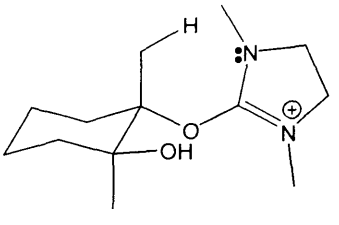
Our methodology was then applied to the ring opening of the symmetrical substrate 1,2-dimethylcyclohexene oxide **158**. This appeared to be an ideal substrate for efficient formation of the *exo*-allylic alcohol, and this was indeed confirmed experimentally (*Scheme 85*).



158 150 176

Scheme 85

From a mechanistic stand point, the major competitive pathway of a hydride shift leading to ketone formation cannot occur, thus permitting the formation of the allylic alcohol as the exclusive product. Moreover, as indicated in Figure 13, the presence of the second methyl group may well produce a buttressing effect which encourages the elimination step in terms of steric acceleration to the departure of the urea.



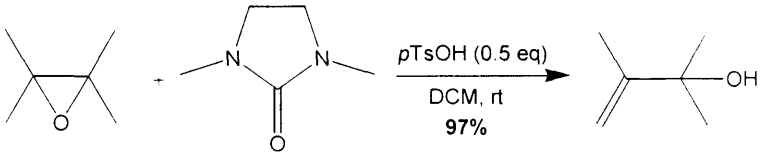
177

Figure 13

Consequently, 1-methyl-2-methylenecyclohexanol **176** was isolated in a promising 85% yield.

8.2.4. The ring opening of 2,3-dimethyl-2,3-epoxy-butane

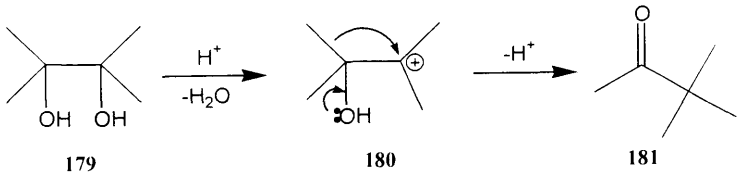
This example is very similar to the previous one, but this time in an acyclic system and, once again, 2,3-dimethyl-2,3-epoxy-butane **83** seemed to be a substrate that would be perfectly suited for our methodology. This was indeed confirmed experimentally by an almost quantitative yield of product **178**, and the fact that the conformationally mobile tertiary allylic alcohol did not dehydrate serves to emphasise the mild reaction conditions of the urea system (*Scheme 86*).



83 **150** **178**

Scheme 86

This example also provides strong presumptive evidence for highly effective trapping of the incipient carbocation by the urea inasmuch as simple proton induced ring opening gives the same classical carbonium ion which is generated in the parent example of the pinacol **179**- pinacolone **181** rearrangement and, undergoes assisted methyl migration in **180** to produce pinacolone[141] (*Scheme 87*).



179 **180** **181**

Scheme 87

8.2.5. The ring opening of 2-isopropyl-2-methyl-oxirane

The ring opening of 2-isopropyl-2-methyl-oxirane **159** was chosen as a strategic example of considerable interest. Indeed, the aim of this reaction was to determine whether the kinetic product **182** or the thermodynamic **183** would be formed (*Figure 14*).

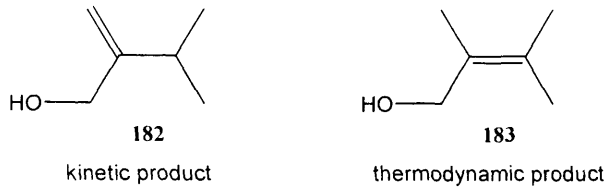
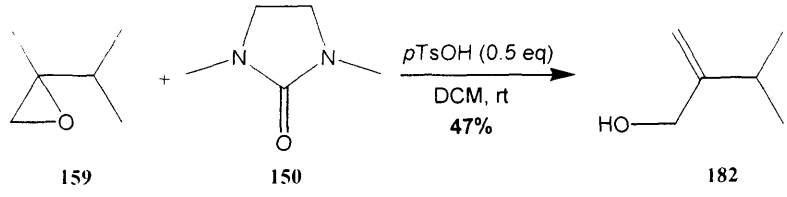


Figure 14

In practise, this reaction afforded a mixture of products, but only one allylic alcohol product, **182**, was cleanly isolable in a relatively modest 47% yield (*Scheme 88*).



Scheme 88

According to the thin layer chromatographic analysis, the remaining mixture of products is much less polar that the isolated 2-isopropyl-prop-2-en-1-ol **182**, suggesting that no thermodynamic allylic alcohol was formed in this reaction. This phenomenon has already been noted in the latter stages of the ring opening of (-)-α-pinene oxide **29**, where formation of 5-isopropenyl-2-methyl-cyclohex-2-enol **9b** over 5-isopropylidene-2-methyl-cyclohex-2-enol **156** was observed. Once again, this example argues for effective carbocation capture by the urea inasmuch as a classical E1 elimination from the carbocation is

expected to evolve *via* a product like transition state and favour the more highly substituted double bond. In the presence of the urea however, examination of the Newman projections **184a** and **184b** (*Figure 15*) which would lead to the tetrasubstituted double bond reveals severe congestion irrespective of whether a *trans* elimination or a *cis* elimination is involved. By way of contrast, formation of the exomethylene group is relatively unhindered.

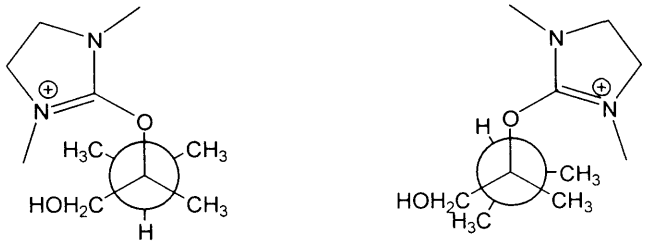
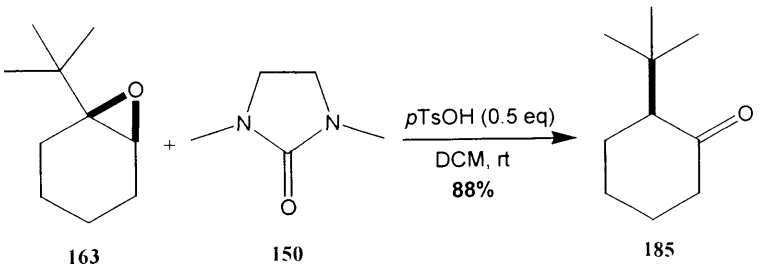


Figure 15

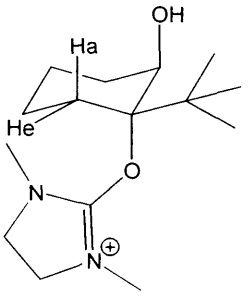
8.2.6. The ring opening of 1-*tert*-7-oxa-bicyclo[4.1.0]heptane

Our attention then turned to the behaviour of 1-*tert*-butylcyclohexene oxide **163** which was selected to examine a situation in which formation of an exocyclic alkene is not possible. In this case, a very clean reaction was observed and 2-*tert*-butylcyclohexanone **185** was the only product to be isolated in 88% yield (*Scheme 89*).



Scheme 89

On the assumption that *trans* diaxial ring opening occurs with interception by the urea of the intermediate which already has the *tert*-butyl group in the favoured equatorial position to give **186** as shown in Figure 16, the E2 elimination reaction involving Ha is clearly not a favourable process and the *syn* elimination which may well require some distortion of the ring is also not observed.



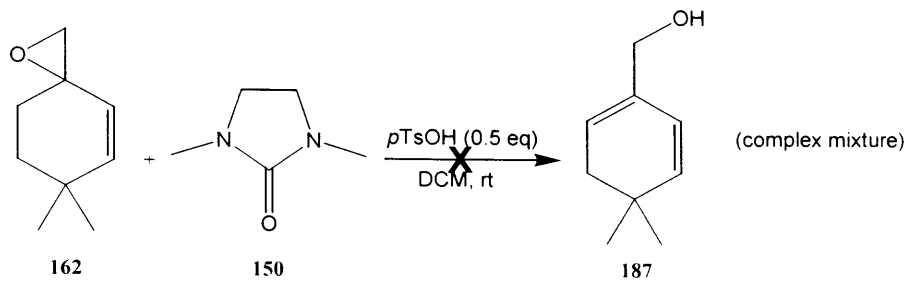
186

Figure 16

The stereoelectronic requirements for hydride migration to give the product 2-*tert*-butylcyclohexanone are also absent however in this intermediate and hence its formation would require departure of the urea to regenerate the carbocation followed by the hydride shift. An alternative explanation may also be that the presence of the *tert*-butyl group effectively prevents carbocation capture on simple steric grounds.

8.2.7. The ring opening of 6,6-dimethyl-1-oxa-spiro[2.5]oct-4-ene

It was also of interest to investigate the fate of the exocyclic epoxide **162** which was expected to evolve through the intermediacy of an allylic cation. In the event however, a highly complex mixture of inseparable products was produced in this reaction and no evidence could be found for the presence of the desired diene alcohol **187** (*Scheme 90*).

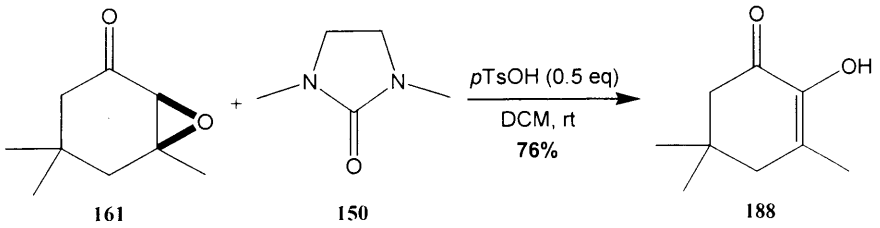


Scheme 90

It is however of interest to note that, as in the case of 2-isopropyl-2-methyl oxirane **159**, where the yield of allylic alcohol was only 47%, the epoxide unit bears a methylene group, *i.e.* it can be considered to derive from a 1,1 disubstituted alkene. Further study of this class is clearly necessary in order to establish if competing process such as rearrangement to an aldehyde are particularly facile.

8.2.8. The ring opening of 4,4,6-trimethyl-7-oxabicyclo[4.1.0]heptan-2-one

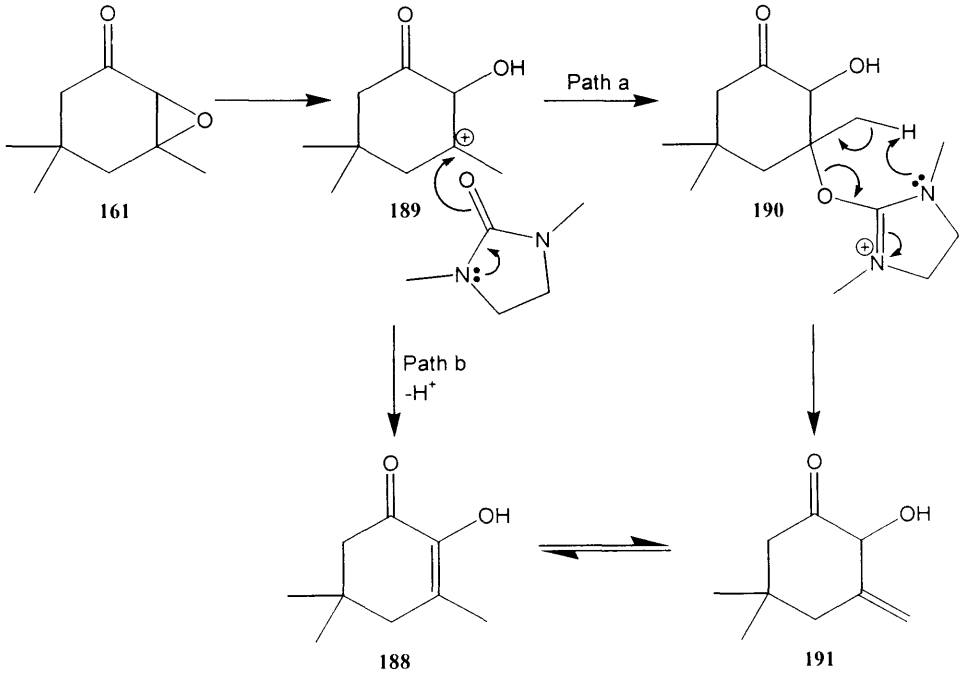
Isophorone epoxide **161** was of interest in terms of probing the influence of the carbonyl group in the urea mediated ring opening reactions. In this instance, the product proved to be 2-hydroxy-3,5,5-trimethylcyclohex-2-enone **188**, which was formed in 76% yield (*Scheme 91*).



Scheme 91

The mechanism of formation of this product **188** may involve the exocyclic allylic alcohol **191**, formed from capture of carbocation **189** by the urea to give **190**. This intermediates would consequently undergo elimination of the urea

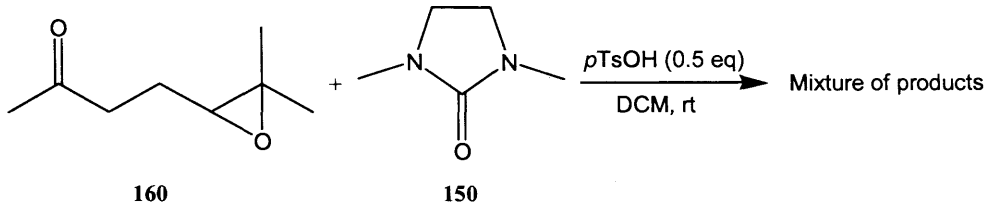
moiety to form **191**. This may be followed by endocyclic isomerisation as shown in Scheme 92 to give **188** (path a). However, it may well be that the urea is not involved in this reaction and that ring opening of the epoxide is followed by direct loss of the acidic proton adjacent to the carbonyl group to give **188** (*Scheme 92*, path b). This two step reaction is nevertheless a simple and useful preparative method of 1,2-diketone **188** in its enolic form from an α,β-unsaturated ketone (*Scheme 92*).



Scheme 92

8.2.9. The ring opening of 4-(3,3-dimethyl-oxiranyl)-butan-2-one

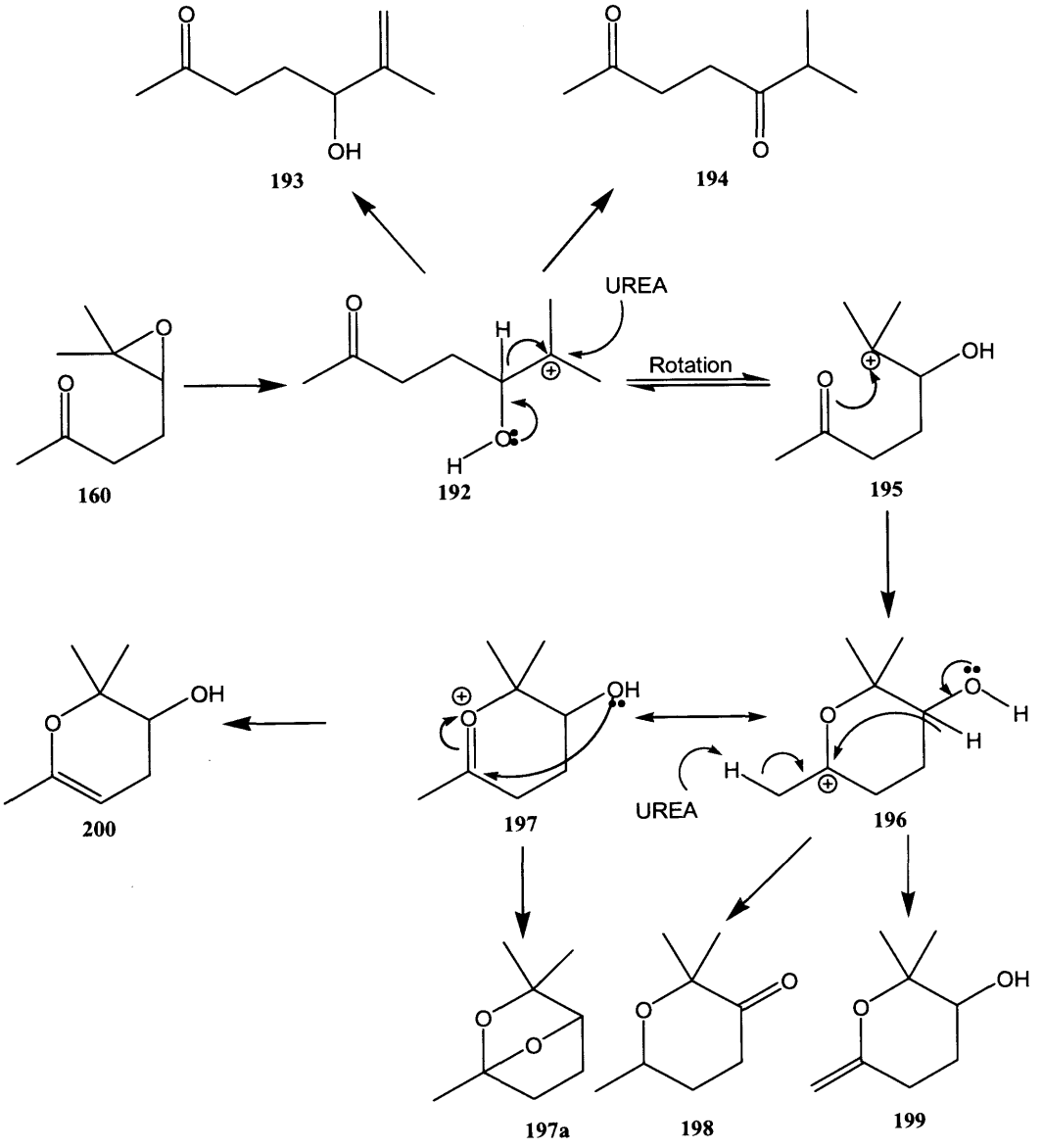
A second substrate to be studied bearing remote ketone functionality was epoxide **160**. Potentially, there is once again the possibility of going through a tertiary carbocation followed by the usual formation of the allylic alcohol. This reaction was attempted but only a very complex mixture of inseparable products was obtained (*Scheme 93*).



160 150

Scheme 93

In retrospect, as shown in Scheme 94 a variety of products could be obtained from this substrate under these reaction conditions.



193 194 160 192 195 200 197 196 197a 198 199

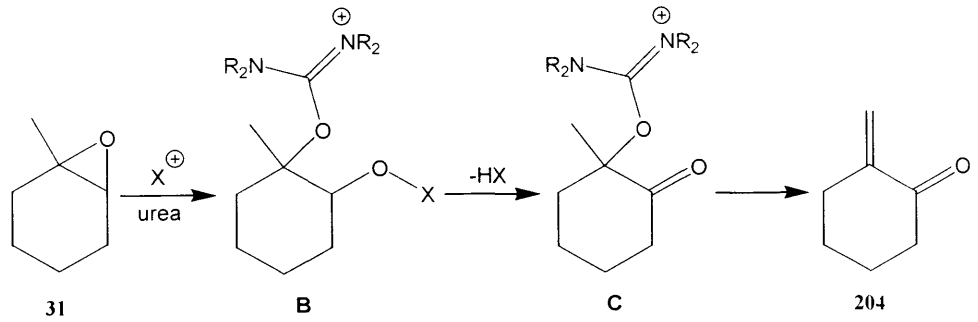
Scheme 94

Thus, as illustrated above, at least five potential products can be formed from this reaction, thereby explaining the results observed. Two of these products arise from mechanisms already discussed previously, the "urea effect" leading to the allylic alcohol **193**, and a hydride shift leading to the diketone **194**. However, the location of the carbonyl group is an issue in this example, since a low energy 6-membered ring oxonium cation can easily be formed, and this intermediate can also evolve in several ways. Three main pathways are described in Scheme **94**, trapping of the carbocation in **197** by the oxygen of the alcohol moiety to afford the cyclic acetal **197a**, hydride shift to give **198**, urea effect to provide **199**, or simple proton loss to give **200**. This may be considered as a limitation in the application of the methodology.

II. Epoxides to α,β-unsaturated ketones

Whilst our studies on the influence of ureas on S_N1 like epoxide ring opening to allylic alcohol were underway, the highly desirable alternative of a one-pot synthesis of an α,β-unsaturated ketone from an epoxide was being investigated. As in the previous section, 1-methylcyclohexene oxide **31** was selected as a suitable model for this study.

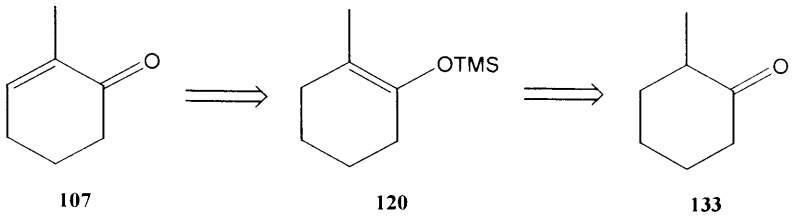
The essential idea in the first instance was to adapt some of the existing methods of oxidation of alcohols to ketones and apply them to the ring opening of epoxides, and to combine this with the methodology developed in the previous section using a urea derivative. These combined methods should, in principle, perform the ring-opening of the epoxide **31** to give **B**, which subsequent oxidation to the carbonyl moiety (**C**) and introduction of a conjugated double bond should provide exocyclic enone **204**, as outlined in Scheme 95.



Scheme 95

1. Preparation of 2-methylcyclohex-2-enone

As discussed in the introductory review, different synthetic pathways were available to synthesise the reference compound, 2-methyl-cyclohex-2-enone **107**. The most typical retrosynthetic approach, depicted in Scheme 96, is to form the enone **107** from silyl enol ether **120**, which can, in turn, be selectively formed from 2-methylcyclohexanone **133**.

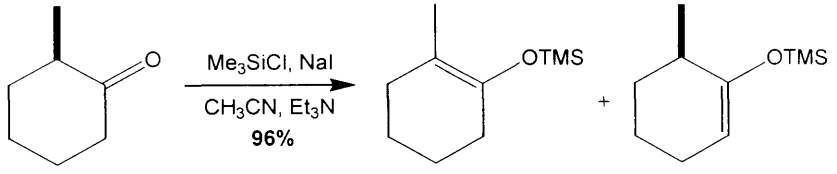


107 **120** **133**

Scheme 96

The transformation of the silyl enol ether **120** to **107** can be achieved by different means. The three most widespread procedures are *Reich*'s method[105-108] using benzeneselenyl halides, *Saegusa*'s palladium chemistry,[112-114] or *Nicolaou*'s IBX.[115-119] The latter was not pursued since it led to a mixture of three regioisomers[116] (*vide supra, Scheme 46*), and it was thus decided to try the former method first.

The starting material for this synthesis was 2-methylcyclohexanone **133**, which had to be regioselectively converted to the desired thermodynamic silyl enol ether **120**. This is typically achieved using a weak and non-hindered base at room temperature by reaction with trimethylchlorosilane. In practical terms, this was carried out using trimethylchlorosilane, triethylamine and sodium iodide in acetonitrile at room temperature[142] (*Scheme 97*).



133 **120** **108**

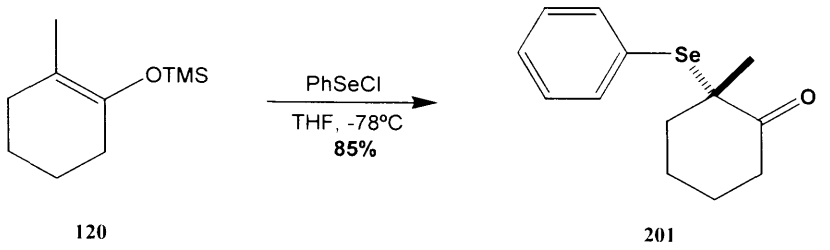
9 : 1

Scheme 97

A 1:9 mixture of regioisomers **108** and **120** was obtained, and purification by distillation afforded the desired silyl enol ether **120** in 91% yield.

The next step required the use of the highly toxic reagent phenylselenyl chloride[143] in THF at -78 °C to form the corresponding selenide derivative **201**

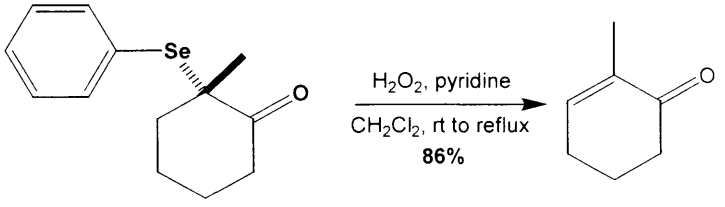
in a very good 85% yield after purification by column chromatography (*Scheme 98*).



120 201

Scheme 98

The final two steps of the synthesis, *viz.*, oxidation to the selenoxide and elimination to form the enone **107**, were achieved in one-pot by addition of hydrogen peroxide to a solution of derivative **201** in dichloromethane, first at room temperature followed by heating to reflux.[143] Purification by distillation afforded the final product 2-methylcyclohex-2-enone **107** in 86% yield (*Scheme 99*).



201 107

Scheme 99

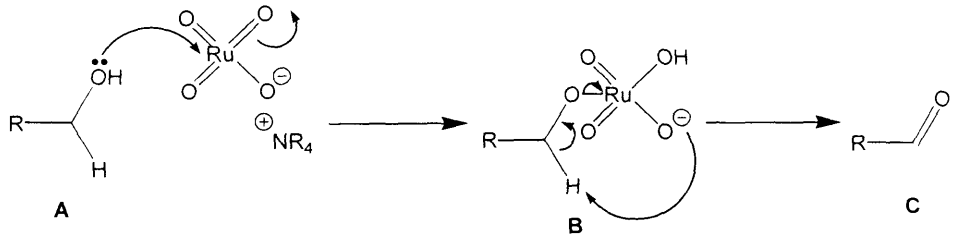
Thus, the synthesis of the reference compound **107** required four steps (two of them in one pot), along with three purifications, two by distillation and one by column chromatography, for an overall 74% yield. This compound was calibrated on a GC (details in the Experimental part), and was used as a GC-reference. Clearly however, such a sequence, whilst acceptable in a research laboratory, is not viable on an industrial scale.

2. Alternative strategies

The direct transformation of an epoxide into an α,β-unsaturated ketones was in consequence a worthwhile challenge, and diverse strategies were attempted throughout our study; the main ones are described hereafter.

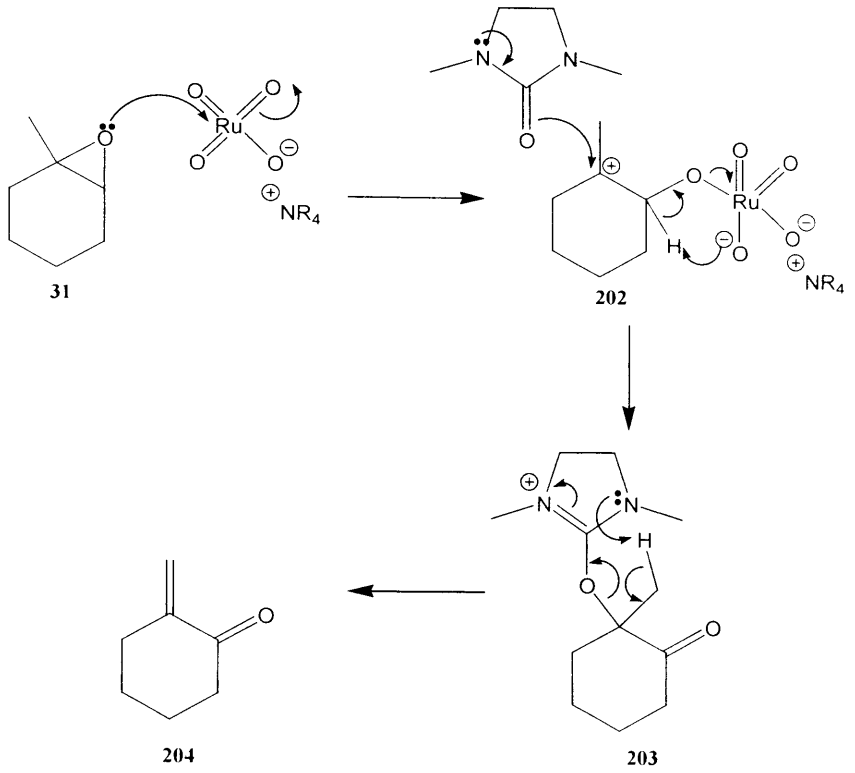
2.1. TPAP

The TPAP reagent introduced by *Ley*[144] is a natural choice for the oxidation of alcohols to aldehydes and ketones. A very wide range of alcohol substrates have indeed been successfully oxidised to the corresponding carbonyl compounds. Moreover, this method is tolerant to a wide range of functional groups, including even epoxides. The mechanism of the reaction in the case of the oxidation of a primary alcohol **A** to an aldehyde **C** and going through a ruthenate ester **B** is depicted in Scheme 100.



Scheme 100

We reasoned however that this reaction could be nicely adapted and applied to the oxidative transformation of epoxides to α,β-unsaturated ketones by working under harsher conditions which could trigger the opening of the epoxide and consequently form both a tertiary carbocation and a ruthenate ester. In the presence of 1,3-dimethyl-2-imidazolidinone **150**, the tertiary carbocation **202** would be trapped, whilst the ruthenate ester moiety would evolve to produce the carbonyl derivative **203**. Subsequent elimination of the urea derivative could then lead to the exocyclic α,β-unsaturated ketone **204** (*Scheme 101*).

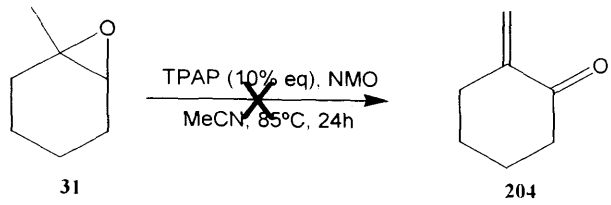


Scheme 101

We also felt that if the final product was the exocyclic α,β-unsaturated ketone **204**, it could subsequently be isomerised to the desired isomer **107**.

In practical terms, this oxidation is generally carried out at room temperature in either dichloromethane or acetonitrile with a co-oxidant to make the reaction catalytic in TPAP, usually, *N*-methylmorpholine *N*-oxide (NMO), and 4 Å molecular sieves to remove the water formed.[144] The aim in our case was to work under more vigorous conditions, such as higher temperatures, which led us to choose acetonitrile as a solvent, thus allowing us to work at 80 °C.

The reaction was first carried out using a catalytic amount of TPAP along with NMO in acetonitrile at reflux, but no reaction was observed after 24 hours of stirring (*Scheme 102*). The reaction was therefore repeated in small scale this time using TPAP stoichiometrically, but once again, no reaction was observed after 1 day of stirring. The reaction was nevertheless carried out in the presence of 1,3-dimethyl-2-imidazolidinone **150** but led to the same unsuccessful result.



31 204

Scheme 102

Unfortunately, these observations merely seemed to confirm the stability of epoxide derivatives towards TPAP. More precisely, it showed that TPAP, as such, was not sufficiently electrophilic to induce the ring opening of epoxides. A possible solution to this problem could therefore be to increase the electrophilic character of TPAP. In principle, this could be achieved by adding a Lewis acid (LA) into the reaction medium which would complex the ruthenium species and pull the electron density away from the central ruthenium atom (*Figure 17*).

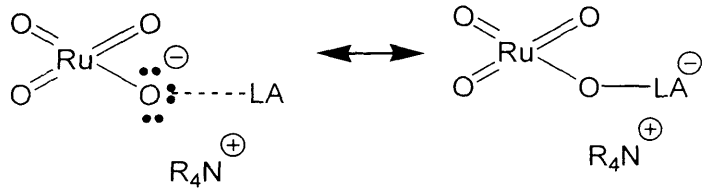


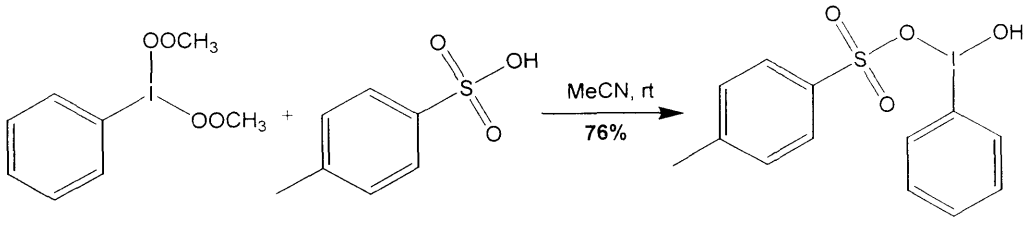
Figure 17

A trial reaction was accordingly carried out on small scale using a stoichiometric amount of a 1:1 mixture of TPAP and boron trifluoride etherate in dichloromethane. A complex seemed to be formed when these two species were stirred together since the colour of the reaction mixture changed from dark blue to dark green. Subsequent addition of 1-methylcyclohexene oxide **31** did not however result in any detectable reaction at all, leaving the starting epoxide untouched after 16 hours of stirring, therefore confirming the existence of a complex between TPAP and boron trifluoride, which also inhibited the Lewis acid character of the latter. Indeed, in the absence of TPAP, boron trifluoride[145] isomerises the starting epoxide to 2-methyl-cyclohexanone **133**.

The reaction was nevertheless repeated in the presence of 1,3-dimethyl-2-imidazolidinone **150**, leading to the same result. No further studies were carried out on this system.

2.2. Hypervalent organoiodine (phenylhydroxytosyloxyiodine)

Hypervalent iodine reagents are nowadays used extensively in organic chemistry as mild and highly selective reagents for the oxidation of alcohols to carbonyl compounds.[146] These type of reagents can be classified in two categories, hypervalent iodine (III), among them phenyliodine diacetate[147-149] or iodosylbenzene,[150-151] and the more successful hypervalent iodine (V), such as 2-iodoxybenzoic acid[120-121] (IBX) or *Dess-Martin* periodinane.[152-153]
Another hypervalent iodine (III) reagent, phenylhydroxytosyloxyiodine **207**, has received little attention[154] in these oxidation reactions, and its structure suggested to us that it could be a potential candidate for the ring opening of epoxides. It was therefore the next system to be studied in our investigation.
Phenylhydroxytosyloxyiodine **207** was synthesised from iodosobenzene diacetate **205** and *p*-toluenesulfonic acid **206** in acetonitrile in 76% yield[154] (*Scheme 103*).

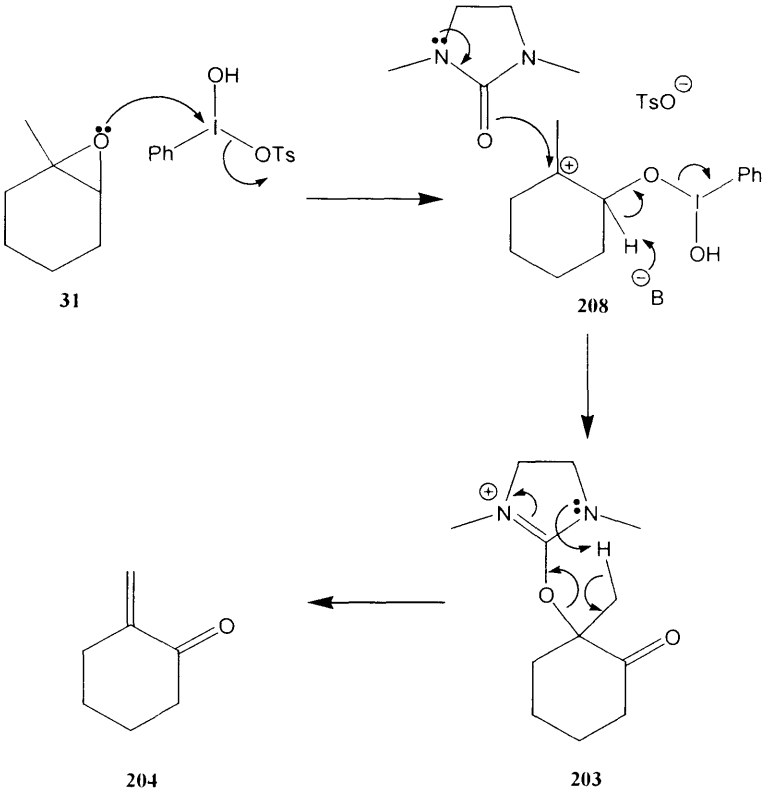


205 **206** **207**

Scheme 103

The reaction between 1-methylcyclohexene oxide **31** and phenylhydroxy-tosyloxyiodine **207** was attempted in the presence of 1,3-dimethyl-2-imidazolidinone **150**. Thus, our model epoxide **31** was expected to displace *p*-toluenesulfonate from phenylhydroxytosyloxyiodine **207**. The intermediate **208**

formed would subsequently lose a proton from the base present in the reaction medium, therefore forming a carbonyl moiety in **203**, while the urea derivative would contribute to form a conjugated double bond, hence affording enone **204** (*Scheme 104*).

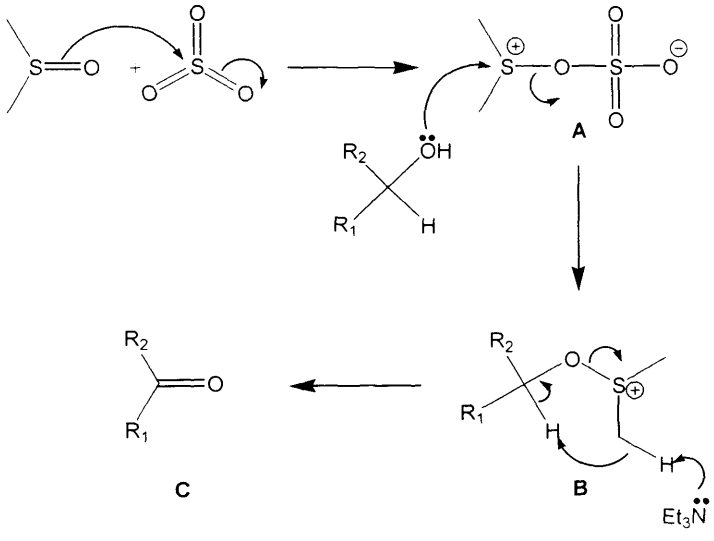


Scheme 104

The ring opening reaction of 1-methylcyclohexene oxide **31** was attempted using one equivalent of phenylhydroxytosyloxyiodine **207** and two equivalents of 1,3-dimethyl-2-imidazolidinone **150**, in dichloromethane at room temperature. A control reaction without any urea derivative was also carried out. The mixture was left stirring for one day but no reaction was observed. The same results were observed when the reaction was carried out without any 1,3-dimethyl-2-imidazolidinone **150**. This system was consequently abandoned.

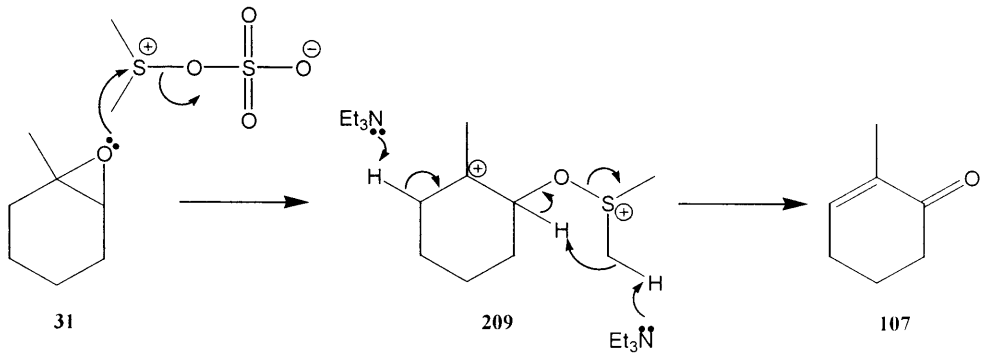
2.3. Sulfur trioxide-pyridine complex

Another method for oxidising alcohols to ketones is to use sulphur trioxide-pyridine complex[155] with triethylamine in dimethylsulfoxide at room temperature. A plausible mechanism[155-156] for this reaction is shown in Scheme 105, in which dimethylsulfoxide and sulphur trioxide first react to give *o*-dimethylsulfoxonium sulphate **A**, followed by attack of the oxygen of the alcohol moiety to produce an *o*-alkyldimethylsulfoxonium intermediate **B**, which suffers base elimination to provide the final carbonyl compound **C**. Epoxides are not known to be ring opened under these reaction conditions.



Scheme 105

Once again, our aim was to work at a higher temperature in order to trigger the ring opening of the epoxide. This time the presence of a urea derivative is not required, since, once the carbocation formed, triethylamine, present in large excess in this reaction, could abstract a proton, consequently forming the endocyclic double bond (*Scheme 106*).

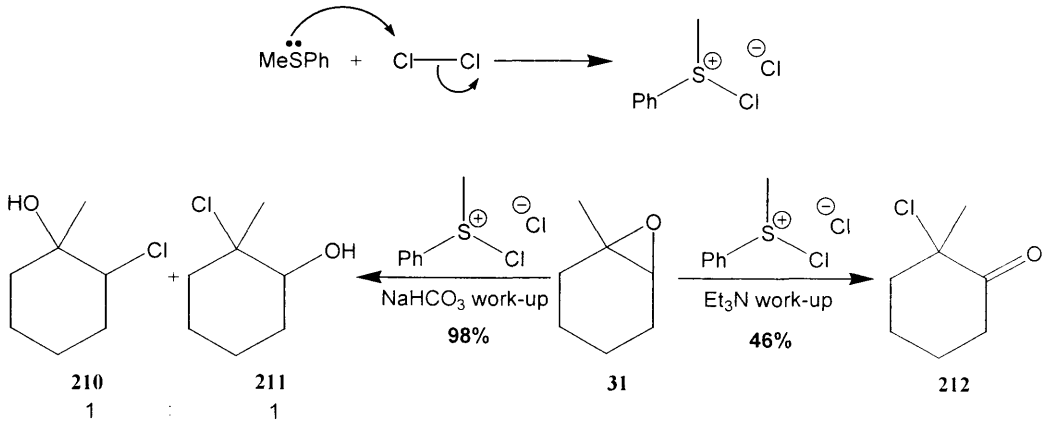


Scheme 106

Reactions were attempted in dimethylsulfoxide with sulphur trioxide-pyridine complex (3 equivalents) and a large excess of triethylamine (8 equivalents), successively at room temperature, 50 °C, 100 °C, 150 °C and 180 °C. At the latter temperature, the opening of epoxide **31** finally occured, only to produce a mixture of a highly complex mixture of products as evidenced by GC analyses. Further investigation on this system was therefore stopped.

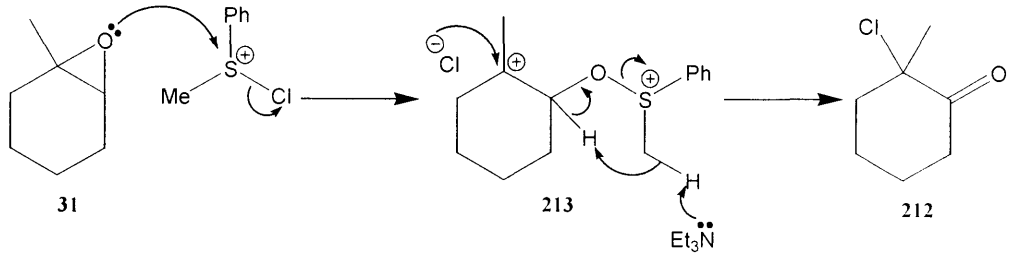
2.4. Extrapolation of *Kurono*'s system: a successful system

At this stage of our investigations, our attention was attracted to a publication by *Kurono et al* which also used an electrophilic sulphur species.[157] In that paper, the ring opening of epoxides was carried out with a chlorosulfonium salt generated *in situ* from methylphenyl sulphide and chlorine, to obtain either a chlorohydrin or an α-chloro-ketone when worked-up with sodium bicarbonate or triethylamine, respectively. Thus, the ring opening of 1-methylcyclohexene oxide **31** gave either a mixture of isomers **210** and **211** in a 1:1 ratio in 98% yield, or 2-chloro-2-methylcyclohexanone **212** in 46% yield (*Scheme 107*).



Scheme 107

The formation of the latter product was of great interest within the scope of our study, given the plausible mechanism of formation shown in Scheme 108.

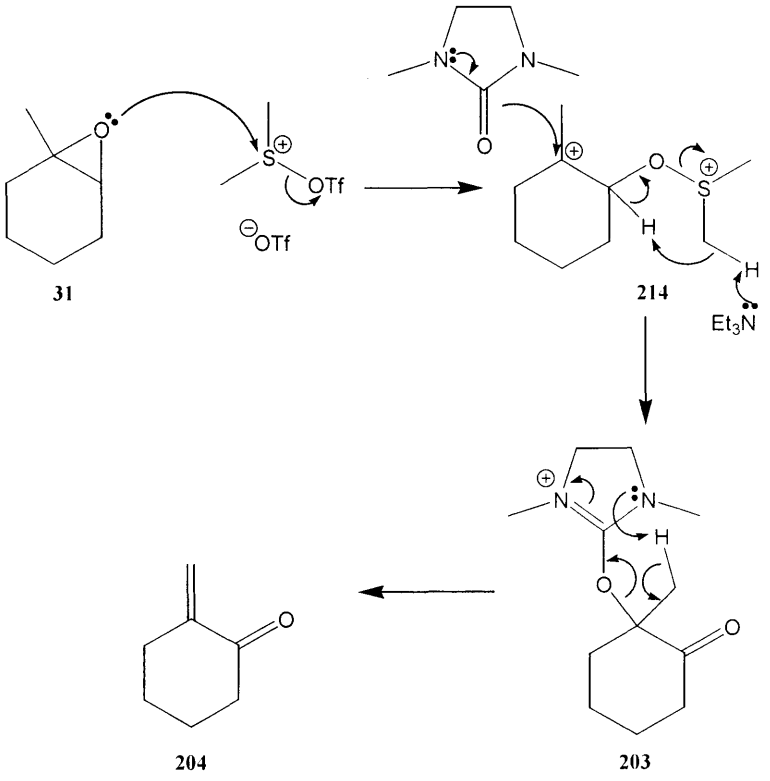


Scheme 108

The *in situ* formation of the chlorosulfonium salt is carried at -20 °C in dichloromethane, and is then followed by addition of 1-methylcyclohexene oxide **31**. The S_N1 like ring opening of epoxide **31** is accompanied by formation of the usual tertiary carbocation **213**, which is then trapped by the chloride counteranion present in the reaction mixture. Since the intermediate at this stage is of exactly the same nature as that generated in *Swern*[156] oxidations, it is not surprising that subsequent work-up with triethylamine as a suitable base to remove a proton consequently leads to the formation of the carbonyl moiety (**212**).

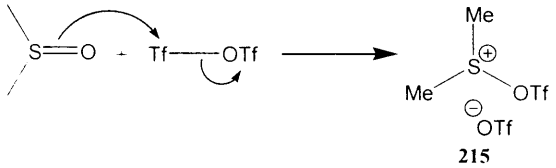
Clearly, these results were very interesting in terms of developing a good

strategy towards the achievement of our goal. In the first instance we decided to replace the chloride ions by a non-nucleophilic anion which could avoid irreversible trapping of the carbocation formed. Thus, we decided to use trifluoromethanesulfonic anhydride to form the reactive sulfonium species instead of using chlorine. Moreover, by working in the presence of 1,3-dimethyl-2-imidazolidinone **150**, we reasoned, as before, that trapping of the carbocation **214** formed followed by its elimination might provide the exocyclic enone **204**. If this strategy works it would therefore provide a good one-pot synthesis of an α,β-unsaturated ketone from an epoxide (*Scheme 109*).



Scheme 109

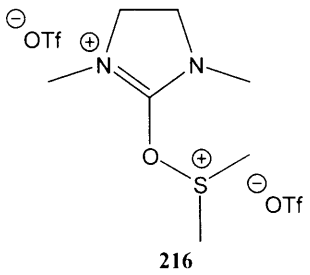
The reactive sulfonium species was accordingly made from dimethylsulfoxide and trifluoromethanesulfonic anhydride in dichloromethane at room temperature to give the sulfonium salt **215** (*Scheme 110*). A white precipitate was immediately formed upon addition of trifluoromethanesulfonic anhydride to dimethylsulfoxide (2 equivalents of each), following an exothermic reaction.



215

Scheme 110

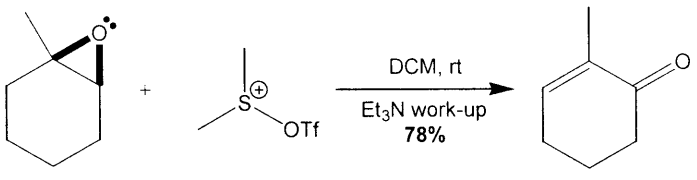
At this stage, two equivalents of 1,3-dimethyl-2-imidazolidinone **150** were added to the reaction mixture, followed by the slow addition of 1-methylcyclohexene oxide **31**. Surprisingly, hardly any starting material was consumed from this reaction after 3 days of stirring. A possible explanation for this result may involve the formation of a less reactive species **216** (*Figure 18*) between the sulfonium salt **215** and 1,3-dimethyl-2-imidazolidinone **150**.



216

Figure 18

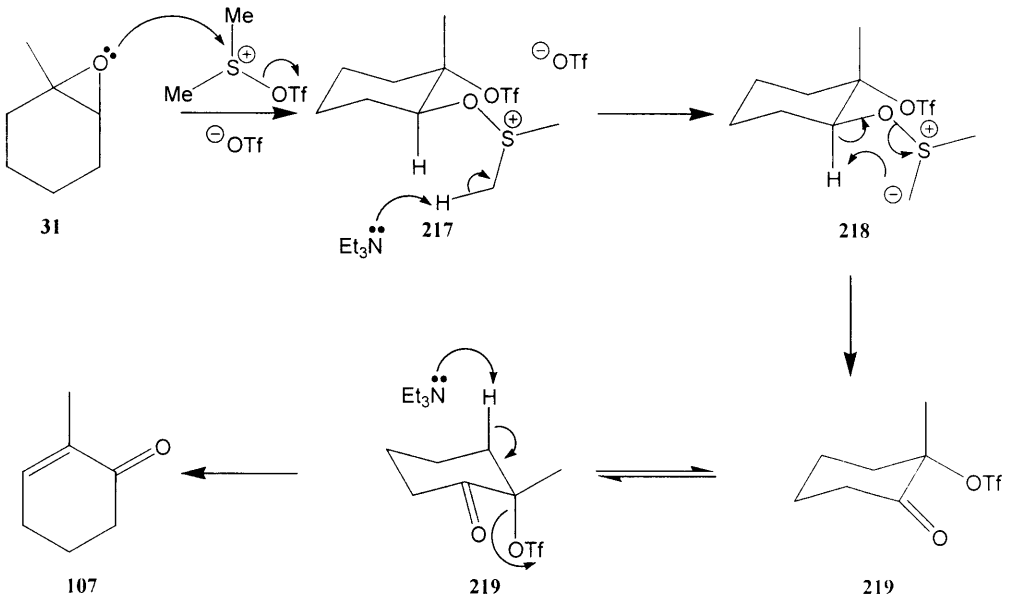
As usual, however, a control reaction in the absence of the urea derivative was also carried out. To our delight, the outcome of this reaction was unexpectedly successful since 2-methylcyclohex-2-enone **107** was formed in 78% yield as estimated by GC analysis of the crude reaction mixture (*Scheme 111*).



31 215 107

Scheme 111

This very successful result may be explained by the mechanism suggested in Scheme 112.



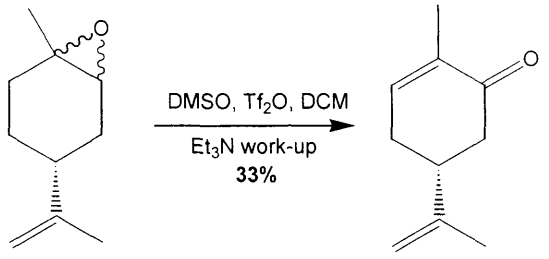
Scheme 112

Thus, S_N1 like ring opening of epoxide **31** in *trans* fashion would lead to intermediate **217** which possesses both a triflate leaving group and an adjacent alkoxysulfonium salt *Swern* intermediate. At this stage, in contrast to the ring contraction observed when lithium triflate or bromide are used, the positively charged sulphur atom effectively prevents participation by the oxygen lone pair of the alkylsulfonium salt. The first equivalent of triethylamine can then removed the most acidic proton adjacent to the positively charged sulphur atom and the resultant sulphur ylide **218** can then evolve in classical fashion to the ketone derivative **219**. The second equivalent of triethylamine can then function as a base in an E2 type elimination, presumably *via* the conformer with an axial triflate group to give 2-methylcyclohex-2-enone **107**. From a practical standpoint, this reaction proved to be frustratingly irreproducible in the first instance and, on several occasions, complex mixtures were produced. Different reaction parameters were then studied including the temperature of formation of the sulfonium triflate salt, the rate of addition of triethylamine

during the work-up, or its presence from the start of the reaction. A reproducible procedure was eventually found, involving dropwise addition of triethylamine which appeared to minimise the formation of alternative degradation products.

2.5 Application to the synthesis of *L*-carvone

Since the primary industrial objective of our work was to find a one-pot synthesis of *L*-carvone **3**, the above optimised conditions were therefore attempted on (+)-*R*-limonene oxides **2**, which consists of a mixture of the two *cis* and *trans* diastereoisomers. To some extent, the reaction was successful since *L*-carvone **3** was indeed formed, but the yield was much lower than expected since only 33% of product was isolated (*Scheme 113*). GC-analyses of the crude reaction mixtures revealed a host of other peaks corresponding to products which could not be separated and characterised by column chromatography.



2 3

Scheme 113

This reaction was repeated several times but again proved to be frustratingly irreproducible. The rate of addition of triethylamine was also varied but had this time no positive impact on the outcome of the reaction, which led to a highly complex mixture of products following GC-analyses of the crude. The reason for such extreme variations are difficult to explain at present but are obviously due to the presence of the isopropenyl moiety in the substrate, and it

will certainly be of interest to examine the behaviour of each of the two epoxides separately.

2.6 Limitations

Unfortunately, time constraints precluded further studies of this reaction. Nevertheless, we can state that a new method for the one-pot formation of α,β-unsaturated ketones has been found. A considerable amount of work is still necessary to understand this reaction and hence to make it efficient and robust. In heterogeneous systems, it is sometimes difficult to reproduce results, and a slight variation of the reaction conditions can have a huge impact on the outcome. At this stage, the methodology is limited to the reproducible application on a single molecule, 1-methylcyclohexene oxide **31**. The presence of other functional groups such as the alkene moiety on (+)-(*R*)-limonene oxide **2** seems to be an issue, although it has been successful on one occasion in low yield, and therefore gives hope that this could be repeated and optimised.

Chapter 3

CONCLUSIONS AND FUTURE WORK

1. Epoxides to allylic alcohols

In summary, a new methodology for the acidic ring opening of epoxides leading to the formation of allylic alcohols, through an S_N1 like mechanism has been developed in this work. This involved the use of a urea derivative, particularly 1,3-dimethyl-2-imidazolidinone, whose role is to control the fate of the carbocation involved in the S_N1 ring opening by "taming" it, and subsequently triggering the formation of a double bond. The main features of interest in this new reaction are the exclusive formation of exocyclic allylic alcohols in ring-systems and the formation of the kinetic double bond over the thermodynamic one. Although, this methodology has been successful for several types of substrate, it does still require improvement to become a more general method of formation of allylic alcohols from epoxides under mild acidic conditions. It would appear that the most dangerous competing pathway is that of hydride shift transfer leading to a carbonyl compound and this may require the design and synthesis of even less sterically demanding and more nucleophilic urea like derivatives. Furthermore, a wide range of epoxide substrates still remains to be investigated and the exact nature of the elimination step still requires clarification.

Some interesting work has to be carried out to optimise this already promising new methodology, and in particular further optimisation of the acid or Lewis acid used. A tuning of the acidity of *p*-toluenesulfonic acid, for example, could be achieved.

2. Epoxides to α,β-unsaturated ketones

A very careful study of the influence of the reaction parameters is clearly required in order to understand the causes of the significant variations from one reaction to another. However, the success of the procedure on the model molecule is very encouraging and should lead to a more general and robust one-pot synthesis of α,β-unsaturated ketones from epoxides. In terms of the

reagents employed, it should certainly be possible to tune the electrophilicity of the sulfonium salt through selection of alternative sulfoxides, for example those derived from alkyl methyl sulfoxides possessing additional electron withdrawing groups. Variation of the nature of the organic base used should also be examined. Comparison of the results obtained with the dimethylsulfoxide-pyridine-SO_3 system which features sulphate anion as the leaving group clearly highlights the importance of the triflate counteranion in this reaction and also implies that other "non-nucleophilic" counteranions of appropriate sulfonium salts, e.g. BF_4^-, could be examined. A very wide range of epoxide substrates also remain to be studied both in cyclic and in acyclic systems. In the first instance, it will be of interest to see if epoxides from mono- and disubstituted alkenes can also be induced to react. Given the remarkable difference in the behaviour of limonene oxides **2** and 1-methylcyclohexene oxide **31**, a study of rigid or conformationally locked epoxides such as **220** and **221** (*Figure 19*) will hopefully shed some light on the stereoelectronic requirements for a successful reaction.

220 **221**

Figure 19

Chapter 4

EXPERIMENTAL

I. General experimental

Proton NMR spectra were recorded on a Bruker Avance 500, Brucker AMX-400 or a Brucker AMX-300 at 500 MHz, 400 MHz or 300 MHz respectively. Carbon NMR spectra were recorded on the same machines at 125.8 MHz or 100.6 MHz or 75.4 MHz. Assignments were supported by DEPT editing, COSY spectra. Proton and carbon NMR chemical shifts are reported as values in ppm from an internal standard (tetramethylsilane) or residual protic solvent. The following abbreviations used to indicate multiplicity are: *s*=singlet, *d*=doublet, *t*=triplet, *m*=multiplet, *dd*=double doublet, *ddd*= double double doublet, *dt*=double triplet, *ddt*=double double triplet, *br*=broad, *scss*=strongly coupled spin system. Residual protic solvent, $CDCl_3$ (δ_H= 7.24 ppm; δ_C= 77.00 ppm) was used as the internal standard. The coupling constants (*J*) are given in Hertz (Hz), and correspond to ^3J couplings unless stated otherwise. Infrared spectra were recorded on a Perkin-Elmer FT-IR 1605 instrument in the medium described in the text. The abbreviations used to denote peak intensity are as follow: *w*=weak, *m*=medium, *s*=strong, b=broad. Mass spectra were recorded either electron impact (EI), or under fast atom bombardment (FAB) at University College London Chemistry Department. Accurate Mass measurements were performed at University College London Chemistry Department. Gas chromatography was performed on a Hewlett-Packard 5890A machine (flame ionisation detector with a 25 m x 0.32 mm BPX5 column using helium or hydrogen as a carrier gas. Boiling points for bulb distillation refer to uncorrected air temperatures. Pressure was recorded on a standard Gallenkamp manometer. Melting points were taken on a Reichert hot stage and are uncorrected.

All reactions using dry solvent were carried out in flame or oven dried glassware under an inert atmosphere of nitrogen. Solvent transfer was performed by canula or syringe. Molecular sieves were activated by microwave irradiation.

Petroleum ethers (b.p.30-40 °C and 40-60 °C) for flash chromatography were distilled prior to use whereas diethyl ether and dichloromethane were used as supplied by the manufacturers. Organic solvents were dried over anhydrous

$MgSO_4$ or Na_2SO_4. Diethyl ether (referred to as ether) and tetrahydrofuran were distilled from sodium with benzophenone ketyl as indicator. Dichloromethane and acetonitrile were pre-dried with 4Å molecular sieves under nitrogen and distilled over calcium hydride. Dimethylformamide was distilled from calcium hydride at reduced pressure and stored over Linde type 4Å molecular sieves under nitrogen. Acetone was pre-dried with $MgSO_4$, distilled and stored under nitrogen. Triethylamine was pre-dried with anhydrous potassium hydroxide and distilled under nitrogen. Chlorotrimethylsilane was distilled from calcium hydride immediately prior to use. For spectroscopic studies, deuterated chloroform was stored over 4Å molecular sieves. All compounds were used as supplied by the manufacturers unless otherwise stated.

Analytical thin layer chromatography (tlc) was performed on pre-coated plastic sheets coated with silica gel $60F_{254}$ (Merck). Visualisation was afforded either using ultraviolet light (254 nm), iodine, basic potassium permanganate [add 6.25 g of Na_2CO_3 in water (1.25 L) to 12.5 g of $KMnO_4$ in water (1.25 L)], acidic ammonium molybdate (IV) [concentrated H_2SO_4 (250 mL), ammonium molybdate.$4H_2O$ in water (2.25 L)] or anisaldehyde [15 mL of anysaldehyde dissolved in EtOH with concentrated H_2SO_4 (25 mL). Flash chromatography was performed at low positive pressure using BDH flash silica gel (40-60 μm), with a silica to crude mass ratio of 30 to 1. Unless otherwise stated, elution was afforded by a graduated solvent system beginning with 40-60 °C or 30-40 °C petroleum and terminating with diethyl ether.

II. GC-Calibration

1. Introduction

The ring opening of 1-methylcyclohexene oxide **31** under acidic conditions was thoroughly studied in this work. It was repeated several times in the optimisation process and led to the same products with different ratios. Therefore, in order to facilitate the quantitative study of the product distributions under several reaction conditions, GC-analyses were carried out. However, it was necessary to perform some preliminary GC-calibrations, of the model molecule - and starting material - 1-methylcyclohexene oxide **31**, and on the reaction products, 2-methylenecyclohexanol **32**, 1-methylcyclopentanecarbaldehyde **132**, and 2-methylcyclohexanone **133**.

Moreover, in the reaction of epoxides to α,β-unsaturated ketones, a GC-calibration of 2-methylcyclohex-2-enone **107** was also required. Both the calibrations and the reactions were carried out in the presence of an internal standard (IS). The choice of this internal standard depends on two main factors. First of all, such a molecule has to be inert towards the starting materials and the products in the reaction conditions; furthermore, it has to have a retention time different to all the species introduced in the reaction and formed in the course of the reaction. In our case, 1,2,4-trichlorobenzene was the internal standard of choice. All these substrates were calibrated in a range of concentration from 0.01 to 0.1 $mol.L^{-1}$, which corresponds to the concentration scale expected in the study for both the starting material and the products.

2. GC- Method

A GC-method was optimised in order to achieve a good separation of the different possible products: the initial temperature was 40 °C and was held for an initial time of 2 min. The temperature was then raised at a constant rate of 10 °C /min until the final temperature of 250 °C was finally reached and held at that temperature for 5 min (*Chart 1*).

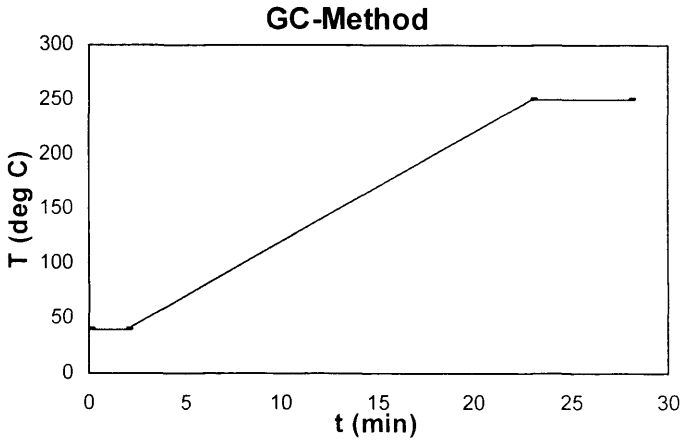


Chart 1

Using this GC-method, the retention time (R_t in min) for the studied substrates are as follow:

- 2-methylenecyclohexanol $R_t = 4.6$
- 1-methylcyclohexene oxide $R_t = 4.8$
- 2-methylcyclohexanone $R_t = 6.4$
- 1-methylcyclopenatnecarbaldehyde $R_t = 6.6$
- 2-methylcyclohex-2-enone $R_t = 7.1$
- 1,3-dimethyl-2-imidazolidinone $R_t = 9.3$
- 1,2,4-trichlorobenzene (IS) $R_t = 10.3$

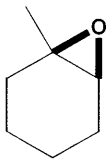
3. Preparation of the solutions

In a 5-mL volumetric flask were mixed an exact known quantity of 1-methylcyclohexene oxide **31** and a constant quantity of internal standard (250 mg exactly). Ethanol was then added to complete to exactly 5 mL.

A constant volume of 0.5 µL of the solution was then injected in the GC-column using the method described above.

4. Results

Calibration of 1-methylcyclohexene oxide



31

The results are summarised in table 14 and illustrated in chart 2.

Table 14. Calibration of 1-methylcyclohexene oxide

m_1 (mg)	C_1 (mol.L^{-1})	m_2 (mg)	C_2 (mol.L^{-1})	C_1/C_2	$Area_1$	$Area_2$	A_1/A_2
7	0.01248	94	0.10361	0.1204	113848	1257778	0.090515
19	0.03387	92	0.101406	0.3340	370934	1317102	0.281628
28	0.04992	91	0.100304	0.4977	502489	1317791	0.38131
38.5	0.06864	91	0.100304	0.6843	841651	1467502	0.573526
45	0.08023	93	0.102508	0.7827	849606	1301552	0.652763

m_1: mass of 1-methylcyclohexene oxide

m_2: mass of internal standard

C_1: concentration of 1-methylcyclohexene oxide

C_2: concentration of internal standard

$Area_1$: area of 1-methylcyclohexene oxide

$Area_2$: area of internal standard

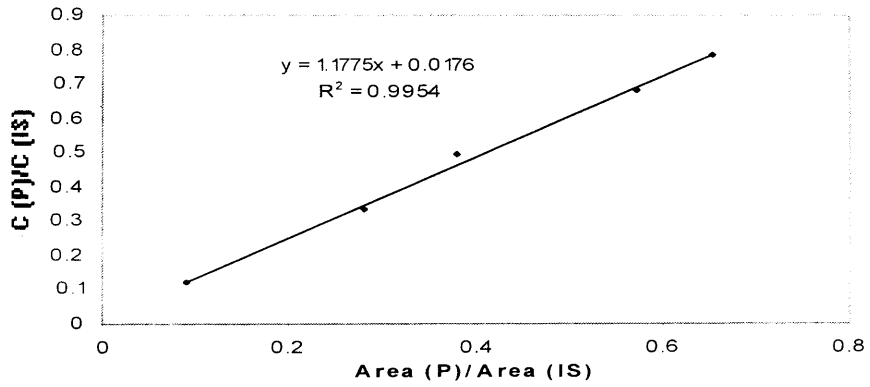
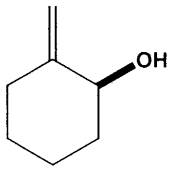


Chart 2. Calibration of 1-methylcyclohexene oxide

Calibration of 2-methylenecyclohexanol



32

The results are summarised in table 15 and illustrated in chart 3.

Table 15. Calibration of 2-methylenecyclohexanol

m_1 (mg)	C_1 (mol.L^{-1})	m_2 (mg)	C_2 (mol.L^{-1})	C_1/C_2	$Area_1$	$Area_2$	A_1/A_2
10.7	0.019078	87	0.095894	0.1989	282378	1794203	0.157384
17	0.030311	96	0.105814	0.2864	388702	1570892	0.24744
32	0.057055	93	0.102508	0.5565	770000	1626338	0.473456
42	0.074885	93	0.102508	0.7305	1137677	1727292	0.658648

m_1: mass of 2-methylenecyclohexanol

m_2: mass of internal standard

C_1: concentration of 2-methylenecyclohexanol

C_2: concentration of internal standard

$Area_1$: area of 2-methylenecyclohexanol

$Area_2$: area of internal standard

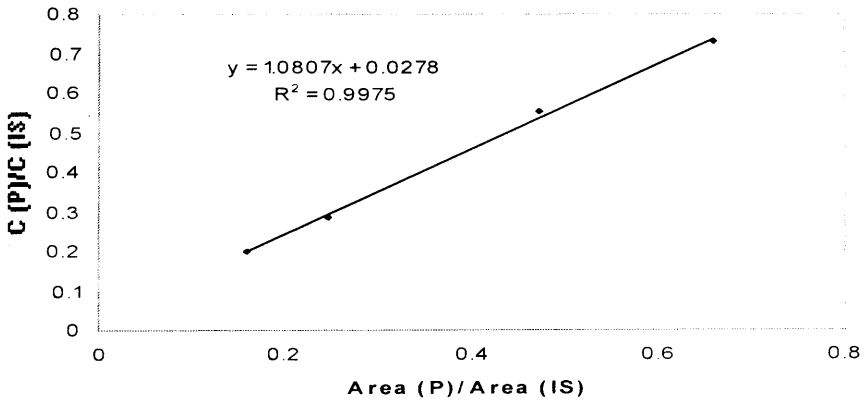
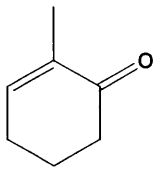


Chart 3. Calibration of 2-methylenecyclohexanol

Calibration of 2-methylcyclohex-2-enone



107

The results are summarised in table 16 and illustrated in chart 4.

Table 16. Calibration of 2-methylcyclohex-2-enone

m_1 (mg)	C_1 (mol.L^{-1})	m_2 (mg)	C_2 (mol.L^{-1})	C_1/C_2	$Area_1$	$Area_2$	A_1/A_2
9	0.01634	89	0.09809	0.166570	91558	1221143	0.07497
11.4	0.02069	90	0.09920	0.208645	143026	1304542	0.109636
21.6	0.03921	92	0.10140	0.38673	250865	1195950	0.209762
28	0.0508	87	0.09589	0.530133	397204	1271808	0.312314
42	0.07625	88	0.09699	0.786163	929346	1793727	0.518108

m_1: mass of 2-methylcyclohex-2-enone

m_2: mass of internal standard

C_1: concentration of 2-methylcyclohex-2-enone

C_2: concentration of internal standard

$Area_1$: area of 2-methylcyclohex-2-enone

$Area_2$: area of internal standard

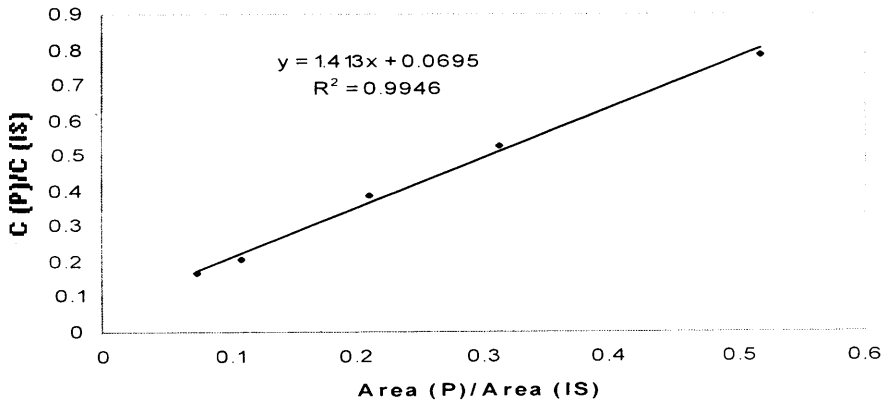
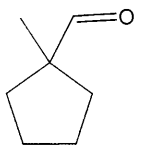


Chart 4. Calibration of 2-methylcyclohex-2-enone

Calibration of 1-methylcyclopentanecarbaldehyde



132

The results are summarised in table 17 and illustrated in chart 5.

Table 17. Calibration of 1-methylcyclopentanecarbaldehyde

m_1 (mg)	C_1 (mol.L^{-1})	m_2 (mg)	C_2 (mol.L^{-1})	C_1/C_2	$Area_1$	$Area_2$	A_1/A_2
12.1	0.021574	90	0.099201	0.2174	405671	1742465	0.232814
21.8	0.038869	92	0.101405	0.3833	632477	1854211	0.341103
33.4	0.059551	90	0.099201	0.6003	941451	1699844	0.553846
45.2	0.080591	93	0.102508	0.7861	1281141	1729541	0.74074

m_1: mass of 1-methylcyclopentanecarbaldehyde

m_2: mass of internal standard

C_1: concentration of 1-methylcyclopentanecarbaldehyde

C_2: concentration of internal standard

$Area_1$: area of 1-methylcyclopentanecarbaldehyde

$Area_2$: area of internal standard

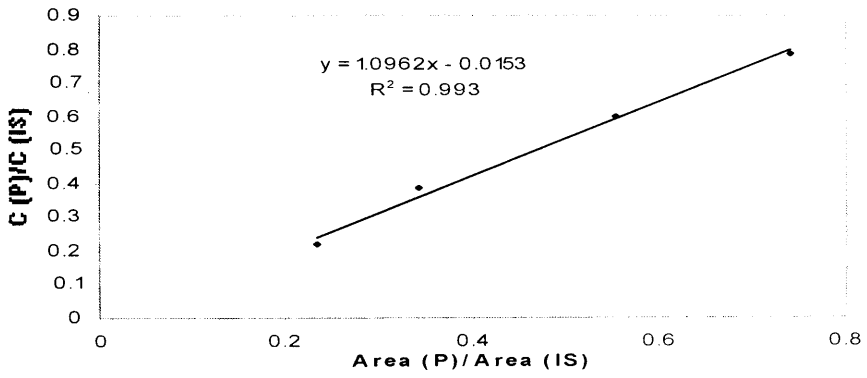
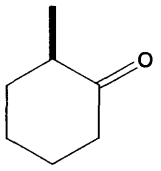


Chart 5. Calibration of 1-methylcyclopentanecarbaldehyde

Calibration of 2-methylcyclohexanone



133

The results are summarised in table 18 and illustrated in chart 6.

Table 18. Calibration of 2-methylcyclohexanone

m_1 (mg)	C_1 (mol.L^{-1})	m_2 (mg)	C_2 (mol.L^{-1})	C_1/C_2	$Area_1$	$Area_2$	A_1/A_2
13.6	0.024248	91	0.100303	0.2417	437976	1930293	0.226896
23.6	0.042078	94	0.10361	0.4061	660800	1784380	0.370325
31.8	0.056699	88	0.096996	0.5845	910462	1665822	0.546554
47.7	0.085048	90	0.099201	0.8573	1328080	1637532	0.811025

m_1: mass of 2-methylcyclohexanone

m_2: mass of internal standard

C_1: concentration of 2-methylcyclohexanone

C_2: concentration of internal standard

$Area_1$: area of 2-methylcyclohexanone

$Area_2$: area of internal standard

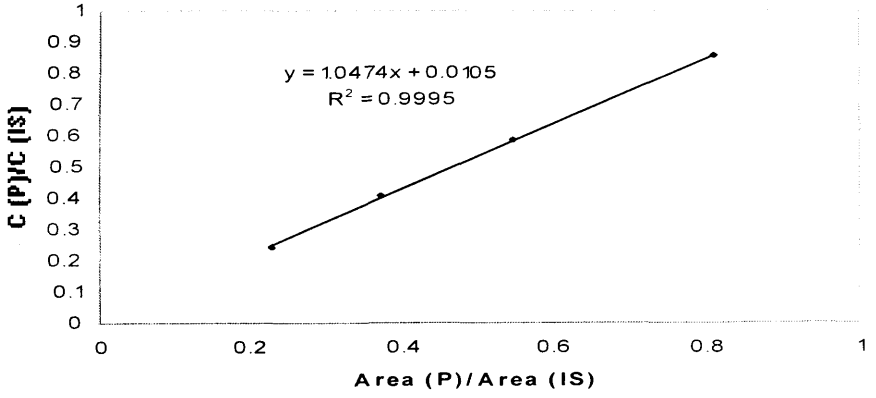


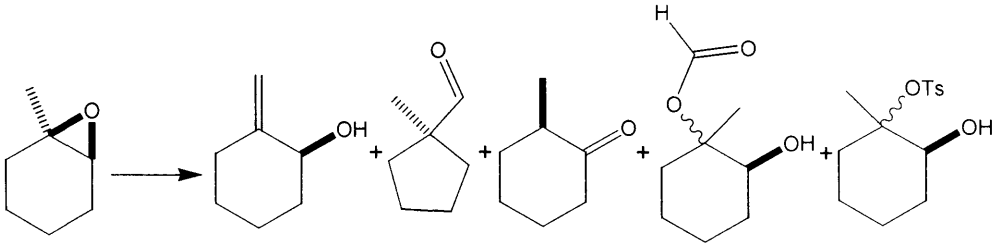
Chart 6. Calibration of 2-methylcyclohexanone

III. Experimental

1. Epoxides to allylic alcohols

1.1. Preliminary work on the acidic ring-opening of 1-methylcyclohexene oxide

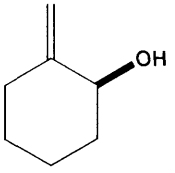
Reaction of 1-methylcyclohexene oxide with *p*-toluenesulfonic acid in dimethyl formamide



31 32 132 133 138 139

A mixture of 1-methylcyclohexene oxide **31** (560 mg, 5.00 mmol, 1eq) and *p*-toluenesulfonic acid monohydrate (0.95 g, 5.00 mmol, 1 eq) was stirred at rt in dimethylformamide (20 mL) for 2 h. The reaction mixture was diluted with dichloromethane (30 mL) and washed with $CuSO_{4(aq)}$ (2 x 40 mL), water (2 x 40 mL), dried (Na_2SO_4) and concentrated. Purification by column chromatography (SiO_2, 20% Ether:petrol 40-60 °C) gave five products, 2-methylene-cyclohexanol **32** (39 mg, 7%), 1-methylcyclopentanecarbaldehyde **132** (27 mg, 5%), 2-methylcyclohexanone **133** (29 mg, 5%), formic acid 2-hydroxy-1-methylcyclohexyl ester **138** (222 mg, 27%) and *p*-toluenesulfonic acid 2-hydroxy-1-methylcyclohexyl ester **139** (42 mg, 3%).

2-Methylenecyclohexanol[158]



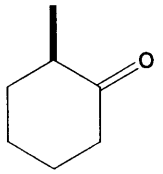
32

$C_7H_{12}O$

MW=112.172 g.mol^{-1}

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 4.89-4.80 (*m*, $=CH_2$, 1 H); 4.72-4.61 (*m*, $=CH_2$, 1 H); 4.10-3.97 (*m*, *CH*OH, 1 H); 2.40-2.26 (*m*, ring *H*, 1 H); 2.01-1.84 (*m*, ring *H*, 2 H); 1.82-1.65 (*s*(br), O*H*, 1 H); 1.65-1.48 (*m*, ring *H*, 2 H); 1.65-1.12 (*m*, ring *H*, 3 H). **^{13}C-NMR** (75.4 MHz, $CDCl_3$) δ_C/ppm: 152.03 (quaternary *C*); 105.42 ($=CH_2$); 73.02 (*C*HOH); 37.04 (CH_2); 33.90 (CH_2); 28.11 (CH_2); 24.17 (CH_2). **IR** (neat): ν_{max}/cm^{-1}: 3336 (*s*, OH), 3084 (*w*), 2962 (*s*), 2912 (*s*), 1639(*m*, C=C), 1431 (*s*), 1375 (*m*), 1264 (*m*), 1166 (*m*), 959 (*s*), 944 (*m*), 882 (*s*). **LRMS** (EIMS): 112 (80%, [M^+]); 97 (100%); 79 (40%).

2-Methylcyclohexanone[159]



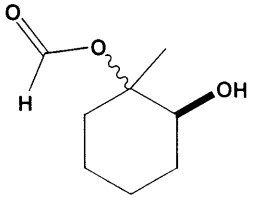
133

$C_7H_{12}O$

MW=112.172 g.mol^{-1}

^{1}H-NMR (500 MHz, $CDCl_3$) δ_H/ppm: 2.39-2.28 (*m*, ring *H*, 2 H); 2.27-2.21 (*m*, ring *H*, 1 H); 2.07-1.95 (*m*, ring *H*, 2 H); 1.83-1.74 (*m*, ring *H*, 1 H); 1.67-1.56 (*m*, ring *H*, 2 H); 1.38-1.25 (*m*, ring *H*, 1 H); 0.97 (*d*, J = 6.54, CH_3, 3 H). **^{13}C-NMR** (125.8 MHz, $CDCl_3$) δ_C/ppm: 213.75 (quaternary *C*); 45.68 (R*C*HCH$_3$); 43.56 (CH_2); 36.51 (CH_2); 28.27 (CH_2); 25.50 (CH_2); 15.05 (CH_3). **IR** (neat): ν_{max}/cm^{-1}: 2964 (*m*), 2933 (*s*), 2862 (*m*), 1713 (*s*), 1450 (*m*), 1429 (*w*), 1377 (*w*), 1313 (*m*), 1215 (*m*), 1145 (*w*), 1124 (*m*). **LRMS** (FABS) m/z: 113 (5%, [M^+]), 111 (20%), 99 (20%), 81 (65%), 55 (20%), 43 (100%).

Formic acid 2-hydroxy-1-methylcyclohexyl ester



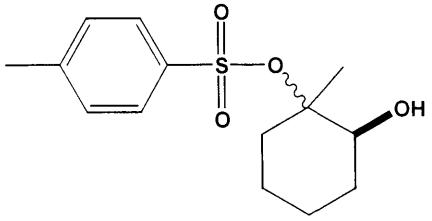
138

$C_8H_{14}O_3$

MW=158.197 g.mol^{-1}

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 8.09 (*s*, C*H*O, 1 H); 4.17-4.09 (*m*, C*H*OH, 1 H); 2.37-2.19 (*m*, ring *H*, 2 H); 1.87-1.71 (*m*, ring *H*, 4 H); 1.63 (*s*, CH_3, 3 H); 1.58-1.35 (*m*, ring *H*, 2 H). **^{13}C-NMR** (75.4 MHz, $CDCl_3$) δ_C/ppm: 160.59 (C=O); 84.17 (quaternary *C*); 71.03 (*C*HOH); 37.31 (*C*H$_2$); 33.98 (*C*H$_2$); 31.11 (*C*H$_2$); 26.20 (*C*H$_2$); 21.48 (*C*H$_3$). **IR** (neat): ν_{max}/cm^{-1}: 3438 (*s*, OH), 3083 (*w*), 2936 (*s*), 2863 (*s*), 1726 (*s*, C=O), 1452 (*m*), 1437 (*m*), 1376 (*m*), 1182 (*s*), 1131 (*m*), 1007 (*m*), 889 (*m*). **HRMS** (EIMS): Theoretical Mass: 158.094294. Measured Mass: 158.094251.

***p*-Toluenesulfonic acid 2-hydroxy-1-methylcyclohexyl ester**



139

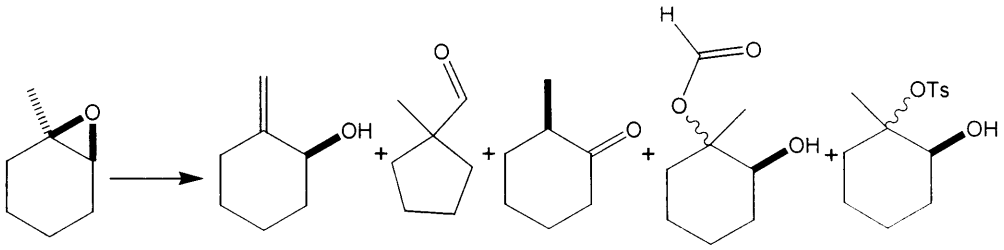
$C_{14}H_{20}O_4S$

MW=284.376 g.mol^{-1}

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.86 (*d*, *J* = 6.65, Ar*H*, 2 H); 7.38 (*d*, *J* = 6.65, Ar*H*, 2 H); 4.42 (*dd*, J_1 = 9.74, J_2 = 4.41, C*H*OH, 1 H); 2.48 (*s*, PhCH_3, 3 H); 1.93-1.23 (*m*, ring *H*, 8 H); 1.21 (*s*, CH_3, 3 H). **^{13}C-NMR** (75.4 MHz, $CDCl_3$) δ_C/ppm: 145.19 (quaternary Ar-*C*); 134.38 (quaternary Ar-*C*); 130.25 (Ar-*C*); 128.19 (Ar-*C*); 87.83 (*C*HOH); 72.16 (quaternary *C*); 37.98 (*C*H$_2$); 29.68 (*C*H$_2$);

23.40 (CH_2): 22.44 (CH_2): 22.40 (CH_3): 22.09 (CH_3). **IR** (neat): ν_{max}/cm^{-1}: 3527 (*m*, OH), 3070 (*w*), 2935 (*s*), 1726 (*s*, C=O), 1452 (*m*), 1363 (*s*), 1176 (*s*), 892 (*s*). **HRMS** (EIMS): Theoretical Mass: 284.108229. Measured Mass: 284.108191.

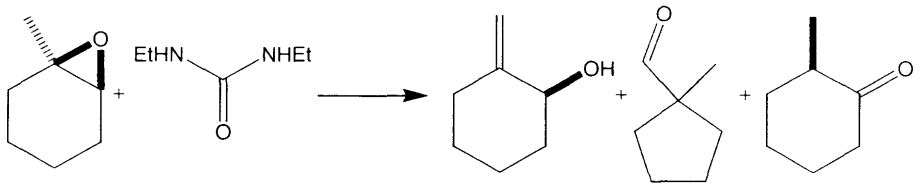
Reaction of 1-methylcyclohexene oxide with *p*-toluenesulfonic acid and dimethylformamide in DCM



31 32 132 133 138 139

A mixture of 1-methylcyclohexene oxide **31** (560 mg, 5.00 mmol, 1 eq), *p*-toluenesulfonic acid monohydrate (0.95 g, 5.00 mmol, 1 eq) and dimethylformide (0.73 g, 10.0 mmol, 2 eq) was stirred at rt in dichloromethane (25 mL) for 2 h. Then the reaction was diluted with dichloromethane (20 mL), and the resulting mixture was extracted with $CuSO_{4(aq)}$ (2 x 40 mL) and water (2 x 40 mL), dried (Na_2SO_4) and concentrated. Purification by column chromatography (SiO_2, 20% Ether:petrol 40-60 °C) afforded five products, 2-methylenecyclohexanol **32** (100 mg, 14%), 1-methylcyclopentanecarbaldehyde **132** (36 mg, 7%), 2-methyl-cyclohexanone **133** (75 mg, 16%), formic acid 2-hydroxy-1-methylcyclohexyl ester **138** (238 mg, 27%) and *p*-toluenesulfonic acid 2-hydroxy-1-methylcyclohexyl ester **139** (98 mg, 8%). **Identical spectroscopic data to that obtained previously.**

Reaction of 1-methylcyclohexene oxide with *p*-toluenesulfonic acid in the presence of 1,3-diethylurea in DCM



31 145 32 132 133

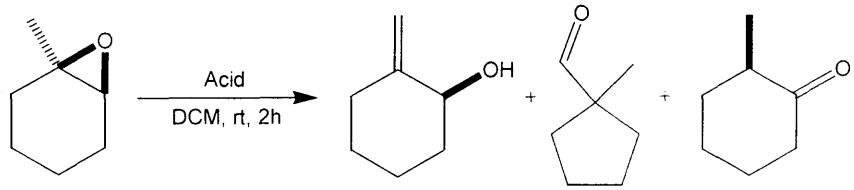
A mixture of 1-methylcyclohexene oxide **31** (1.12 g, 10.0 mmol, 1 eq), *p*-toluenesulfonic acid monohydrate (0.95 g, 5.0 mmol, 0.5 eq) and 1,3-diethylurea **145** (2.32 g, 20.0 mmol, 2 eq) was stirred at rt in dichloromethane (35 mL) for 2 h. The mixture was subsequently washed with brine (2 x 40 mL), dried (Na_2SO_4) and concentrated. Purification by column chromatography (SiO_2, 20% Ether:petrol 40-60 °C) afforded 2-methylenecyclohexanol **32** (235 mg, 25%), 1-methylcyclopentanecarbaldehyde **132** (148 mg, 6%) and 2-methylcyclohexanone **133** (192 mg, 23%). **Identical spectroscopic data to that obtained previously.**

1.2. Optimisation of the reaction conditions

Different reaction parameters of the acidic ring-opening of 1-methylcyclohexene oxide **31** were studied in order to optimise the yield of the desired product, *i.e.* 2-methylene-cyclohexanol **32**. The procedure is described once for each parameter, and is followed by a table summarising the outcome of the reaction sets.

Influence of the acid

Reaction without urea derivative

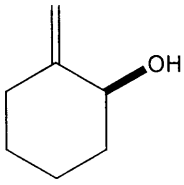
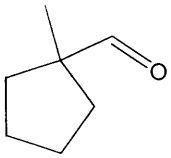
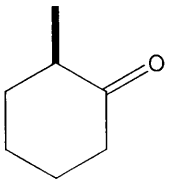


31 32 132 133

A solution of 1-methylcyclohexene oxide **31** (560 mg, 5.00 mmol, 1 eq) in DCM (10 mL) was stirred at room temperature in the presence of a catalytic amount or

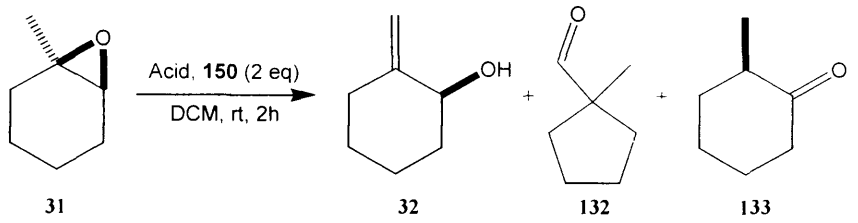
stoichiometric amount (see table 19 below for details) of acid. The resulting mixture was stirred overnight and analysed by GC. The products arising from the reactions are detailed in table 19.

Table 19. Reaction of 1-methylcyclohexene oxide with acids and metal salts

Acid used	 **32** **% yield**	 **132** **% yield**	 **133** **% yield**
Triflic acid (c)	0	0	92
p-TsOH (c)	0	15	52
$F_3C\text{-}CO_2H$ (s)	5	11	8
H_3PO_4 (c)	4	37	57
Na(OTf) (c)	15	10	52
Cu(OTf) (c)	11	14	63
$Mg(OTf)_2$ (c)	6	9	51
$Zn(OTf)_2$ (c)	16	12	55
$La(OTf)_3$ (c)	45	5	50
$Yb(OTf)_3$ (c)	55	9	25
$Sc(OTf)_3$ (c)	60	0	28

(s):stoichiometric: (c): catalytic

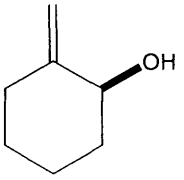
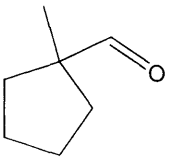
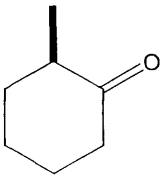
Reaction with urea derivative



31 32 132 133

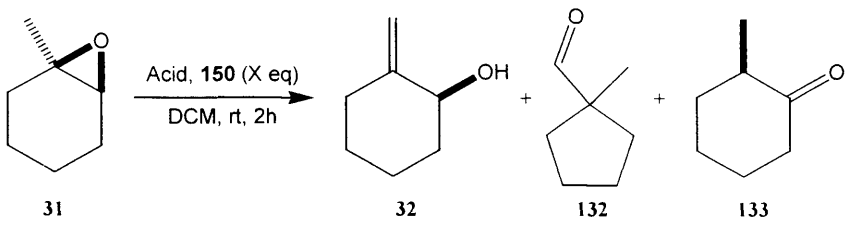
A mixture of 1-methylcyclohexene oxide **31** (560 mg, 5.00 mmol) and 1,3-dimethyl-2-imidazolidinone **150** (2.90 g, 10.0 mmol, 2 eq) in dichloromethane (10 mL) was stirred at rt in the presence of a catalytic or stoichiometric amount (see table 20 below for details) of acid. The resulting mixture was stirred overnight and analysed by GC. The products arising from the reactions are detailed in table 20.

Table 20. Ring opening of 1-methylcyclohexene oxide with different acids and metal salts in the presence of 1,3-dimethyl-2-imidazolidinone

Acid used	 **32** **% yield**	 **132** **% yield**	 **133** **% yield**
Triflic acid (c)	13	12	68
p-TsOH (c)	46	8	40
F_3C-CO_2H (s)	10	8	14
H_3PO_4 (c)	10	29	57
Na(OTf) (c)	17	11	63
Cu(OTf) (c)	14	14	72
$Mg(OTf)_2$ (c)	15	10	58
$Zn(OTf)_2$ (c)	16	11	66
$La(OTf)_3$ (c)	13	17	70
$Yb(OTf)_3$ (c)	13	10	55
$Sc(OTf)_3$ (c)	16	12	66

(s):stoichiometric; (c): catalytic

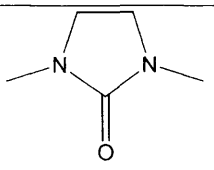
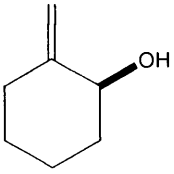
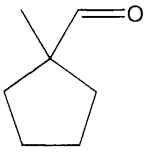
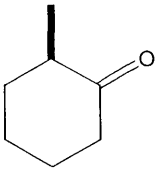
Influence of the number of equivalents of urea derivative



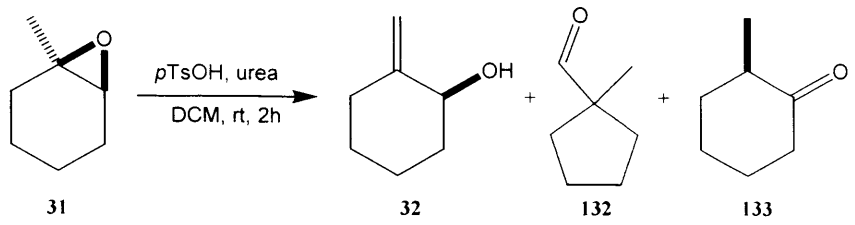
31 32 132 133

A mixture of 1-methylcyclohexene oxide **31** (560 mg, 5.00 mmol, 1 eq) and 1,3-dimethyl-2-imidazolidinone **150** (different amounts, see table 21 for details) in dichloromethane (10 mL) was stirred at rt, as *p*-toluenesulfonic acid monohydrate (465 mg, 2.50 mmol, 0.5 eq) or scandium triflate (245 mg, 0.5 mmol, 0.1 eq) was added. The resulting mixture was stirred for two hours and analysed by GC The products arising from the reactions are detailed in table 21.

Table 21. Influence of the number of molar equivalents of the urea

	 **150** **Nb equivlents**	 **32** **% yield**	 **132** **% yield**	 **133** **% yield**
$Sc(OTf)_3$	0	0	28	60
	1.2	17	16	67
	2.6	16	10	67
	3.8	15	0	73
	8.5	16	0	64
p-TosOH	0	0	17	60
	1	42	8	47
	2	46	7	40
	4	39	8	46
	9	34	8	47

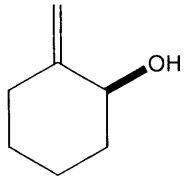
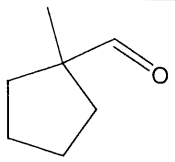
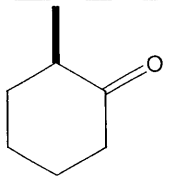
Influence of the urea derivative



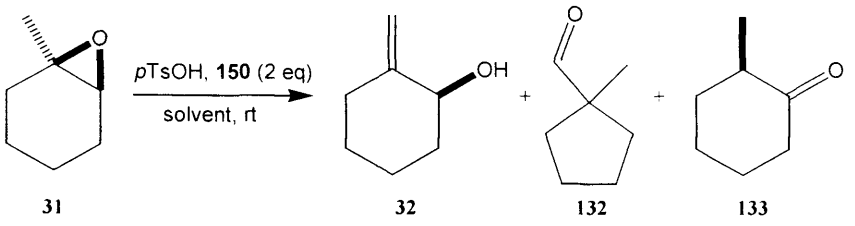
31 32 132 133

A mixture of 1-methylcyclohexene oxide **31** (560 mg, 5.00 mmol, 1 eq) and 2 equivalents of the chosen urea derivative (see table 22 for details) in dichloromethane (10 mL) was stirred at rt, as *p*-toluenesulfonic acid monohydrate (465 mg, 2.50 mmol, 0.5 eq) was added. The resulting mixture was stirred for two hours, and then analysed by GC. The products arising from the reactions are detailed in table 22.

Table 22. Influence of the urea derivative

Urea derivative	 **32** **% yield**	 **132** **% yield**	 **133** **% yield**
Urea	25	13	51
2,3-dimethyl-imidazolidinone	48	5	39
Dimethylurea	34	9	43
DMPU	53	0	47
Tetramethylurea	35	8	44

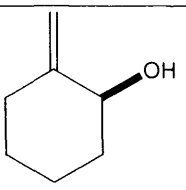
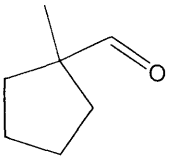
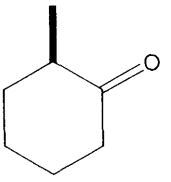
Influence of the solvent



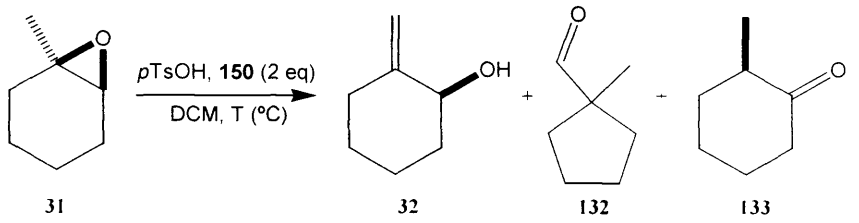
31 32 132 133

A mixture of 1-methylcyclohexene oxide **31** (560 mg, 5.00 mmol, 1 eq) and 1,3-dimethyl-2-imidazolidinone **150** (2.90 g, 10.0 mmol, 2 eq) were stirred in different solvents (10 mL) (see table 23 for details) at room temperature, as *p*-toluenesulfonic acid monohydrate (465 mg, 2.50 mmol, 0.5 eq) was added. The resulting mixture was stirred for 2 h, and then analysed by GC. The products arising from the reactions are detailed in table 23.

Table 23. Influence of the solvent

Sovent used	 **32** **% yield**	 **132** **% yield**	 **133** **% yield**
Dichloromethane	48	7	42
Chloroform	33	7	44
Diethyl ether	23	10	47
Methanol	0	0	6
Ethyl acetate	51	10	50
Tetrahydrofuran	25	12	48
Toluene	31	8	55

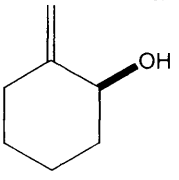
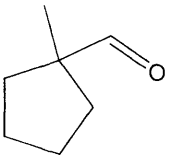
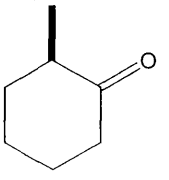
Influence of the temperature



31 32 132 133

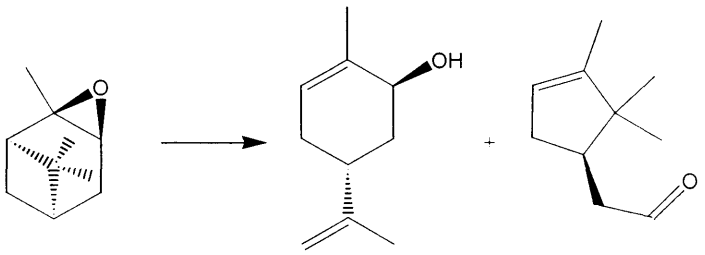
A mixture of 1-methylcyclohexene oxide **31** (560 mg, 5.00 mmol, 1 eq) and 1,3-dimethyl-2-imidazolidinone **150** (2.90 g, 10.0 mmol, 2 eq) in dichloromethane (10 mL) was stirred at different temperatures (see table 24 for details), as *p*-toluenesulfonic acid monohydrate (465 mg, 2.50 mmol, 0.5 eq) was added. The resulting mixture was stirred between 1 and 6 hours (depending on the temperature; the lower the temperature, the longer the reaction time), and then analysed by GC. The products arising from the reactions are detailed in table 24.

Table 24. Influence of the temperature

Temperature (°C)	 **32 % yield**	 **132 % yield**	 **133 % yield**
-78	26	9	42
-30	25	10	47
0	25	10	45
rt	47	8	45
Reflux	48	7	38

1.3. Acidic ring-opening of α-pinene oxide

Reaction of α-pinene oxide with trifluoromethanesulfonic acid

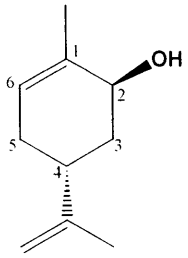


29 9a 154

A mixture of α-pinene oxide **29** (304 mg, 2.00 mmol, 1 eq) and trifluoromethanesulfonic acid (15 mg, 0.1 mmol, 5 mol% eq) in dichloromethane (20 mL) was stirred at rt for 2 h. The resulting mixture was washed with water (2 x 50 mL), dried (Na_2SO_4) and concentrated. Purification by column chromatography (SiO_2, 20% Ether:petrol 40-60 °C) afforded *trans*-carveol **9a** (87 mg, 27%) and campholenic aldehyde **154** (130 mg, 43%).

5-Isopropenyl-2-methyl-cyclohex-2-enol[160]

(*Trans*-carveol)



9a

$C_{10}H_{16}O$

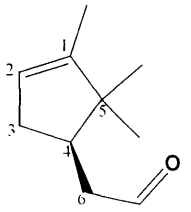
MW=152.237 g.mol^{-1}

Rf 0.3 (SiO_2, 20% EtOAc:petrol 40-60°C). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H/ppm: 5.59 (*dm*, *J*=5.5, =C$_{(6)}$*H*, 1 H); 4.11 (*s*, =C*H*$_2$, 1 H); 4.09 (*s*, =C*H*$_2$, 1 H); 4.02 (*s*(br), C$_{(2)}$*H*, 1 H); 2.32 (*m*, ring *H*, 1 H); 2.14 (*dm*, *J*=13.5, C$_{(4)}$*H*, 1 H); 2.03-1.55 (*m*, ring *H*, O*H*, 4 H); 1.80 (*s*, C*H*$_3$, 3 H); 1.75 (*s*, C*H*$_3$, 3 H). **^{13}C NMR** (100

MHz, $CDCl_3$) δ_C/ppm: 149.2 (*C*=CH_2); 134.3 ($C_{(1)}$); 125.4 ($C_{(6)}$); 109.0 (C=*C*H_2); 68.6 ($C_{(2)}$); 36.7 ($C_{(4)}$); 35.2 (*C*H_2); 31.0 (*C*H_2); 21.2 (*C*H_3); 21.2 (*C*H_3). **IR** (neat): ν_{max}/cm^{-1}: 3333 (*s*, OH), 3082 (*w*), 2966 (*s*), 2916 (*s*), 1645 (*m*, C=C), 1438 (*s*), 1375 (*m*), 1264 (*m*), 1164 (*m*), 1156 (*m*), 1054 (*s*), 1032 (*s*), 962 (*s*), 944 (*m*), 887 (*s*). **LRMS** (EIMS) m/z: 152 (20%, [M^+]), 109 (100%, M-$C_3H_7^+$), 84 (90%), 69 (30%), 54 (50%), 38 (60%).

(2,2,3-Trimethyl-cyclopent-3-enyl)-acetaldehyde[15]

(Campholenic aldehyde)



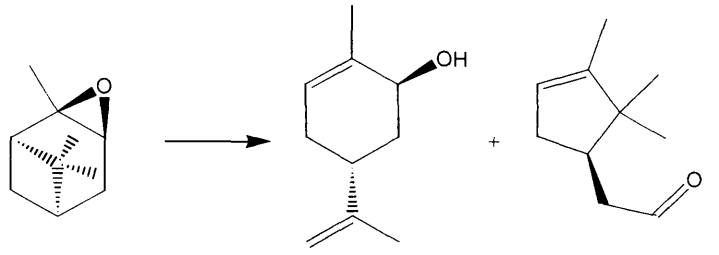
154

$C_{10}H_{16}O$

MW=152.237 g.mol^{-1}

Rf 0.7 (SiO_2, 20% EtOAc:petrol 40-60°C). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H/ppm: 9.80 (*t*, *J*=2.5, C*H*O, 1 H); 5.29 (*m*, C*H*=C, 1 H); 2.55-2.25 (*m*, ring *H*, 4 H); 1.89 (*m*, ring *H*, 1 H); 1.61 (*d*(br), *J*=2.5, =CC*H*$_3$, 3 H); 1.00 (*s*, C*H*$_3$, 3 H); 0.79 (*s*, C*H*$_3$, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C/ppm: 201.8 (*C*HO); 147.8 ($C_{(1)}$); 121.5 ($C_{(2)}$); 46.8 ($C_{(5)}$); 45.0 ($C_{(6)}$); 44.3 ($C_{(4)}$); 35.4 (*C*H_2); 25.5 (*C*H_3); 19.9 (*C*H_3); 12.5 (=C*C*H_3). **IR** (neat): ν_{max}/cm^{-1}: 3038 (*w*), 2957 (*s*), 2716 (*w*, CHO), 1726 (*s*, C=O), 1463 (*m*), 1437 (*w*), 1384 (*w*), 1362 (*m*), 1016 (*w*), 794 (*m*). **LRMS** (EIMS) m/z: 152 (5%, [M^+]), 108 (85%, M-C_2H_4O), 93 (45%), 82 (100%), 67 (30%), 57 (35%).

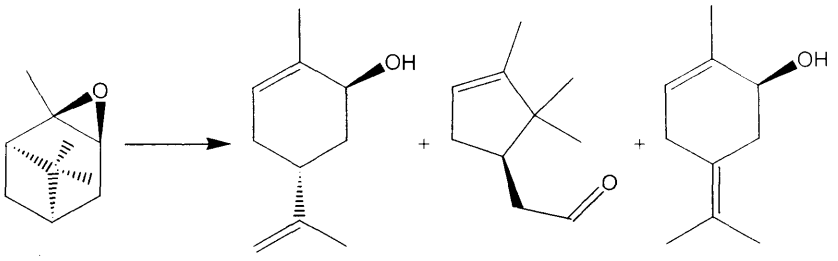
Reaction of α-pinene oxide with trifluoromethanesulfonic acid in the presence of 1,3-dimethyl-2-imidazolidinone



29 9a 154

To a stirred solution of α-pinene oxide **29** (304 mg, 2.00 mmol, 1 eq) and 1,3-dimethyl-2-imidazolidinone **150** (456 mg, 4.00 mmol, 2 eq) in dichloromethane (20 mL) at rt, was added trifluoromethanesulfonic acid (15 mg, 0.1 mmol, 5% mol eq). The resulting mixture was stirred for 2 h, and was washed with water (2 x 50 mL), dried (Na_2SO_4) and concentrated. Purification by column chromatography (SiO_2, 20% Ether:petrol 40-60 °C) afforded *trans*-carveol **9a** (86 mg, 29%) and campholenic aldehyde **154** (117 mg, 38%). **Identical spectroscopic data to that obtained previously.**

Reaction of α-pinene oxide with zinc triflate

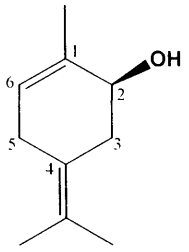


29 9a 154 156

A mixture of α-pinene oxide **29** (549 mg, 3.61 mmol, 1 eq) and zinc trifluoromethanesulfonate (131 mg, 0.36 mmol, 10% mol eq) was stirred overnightin dichloromethane (30 mL), and subsequently washed with water (2 x 20 mL), filtered through celite, dried (Na_2SO_4) and concentrated. Purification by column chromatography (SiO_2, 20% Ether:petrol 40-60 °C) afforded *trans*-carveol **9a** (26 mg, 5%), campholenic aldehyde **154** (296 mg, 54%) and 5-isopropylidene-

2-methyl-cyclohex-2-enol **156** (96 mg, 17%). **Identical spectroscopic data to that obtained previously for the first two compounds.**

5-Isopropylidene-2-methyl-cyclohex-2-enol[15]



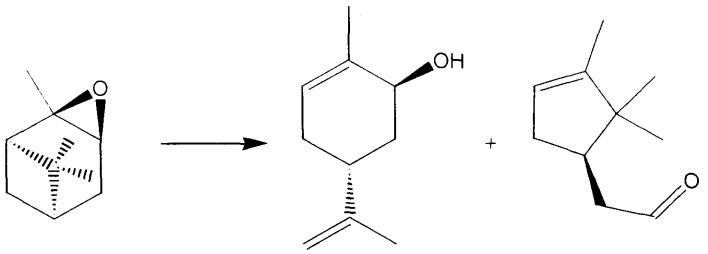
156

$C_{10}H_{16}O$

MW=152.237 g.mol^{-1}

Rf 0.4 (SiO_2, 20% EtOAc:petrol 40-60°C). **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H/ppm: 5.47 (*m*, $C_{(6)}H$, 1 H); 3.97 (*m*, $C_{(2)}H$, 1 H); 2.85 (*d*(br), *J*=20.0, ring *H*, 1 H); 2.65 (*dd*, *J*=13.5, *J*=4.0, ring *H*, 2 H); 2.31 (*dm*, *J*=24, ring *H*, 1 H); 1.77 (*m*, =CCH_3, 3 H); 1.71 (*s*, CH_3, 3 H); 1.66 (*s*, CH_3, 3 H); 1.44 (*s*(br), O*H*, 1 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C/ppm: 135.9 (quaternary *C*); 125.8 (quaternary *C*); 124.3 ($C_{(6)}$); 123.1 (quaternary *C*); 70.4 ($C_{(2)}$); 35.9 (CH_2); 29.8 (CH_2); 20.4 (CH_3); 20.2 (CH_3); 19.9 (CH_3). **IR** (neat): ν_{max}/cm^{-1}: 3257 (*s*, OH), 3160 (*m*), 2966 (*m*), 2935 (*m*), 2884 (*m*), 1607 (*w*), 1436 (*w*), 1366 (*w*), 1320 (*w*), 1058 (*w*), 1014 (*s*), 912 (*w*), 803 (*w*). **LRMS** (FABS) m/z: 152 (45%, [M$^+$]), 149 (100%), 133 (80%), 107 (80%).

Reaction of α-pinene oxide with zinc trifluoromethanesulfonate in the presence of 1,3-dimethyl-2-imidazolidinone



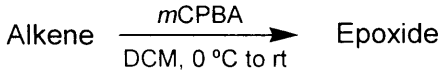
29 **9a** **154**

To a stirred solution of α-pinene oxide **29** (469 mg, 3.10 mmol, 1 eq) and 1,3-dimethyl-2-imidazolidinone **150** (707 g, 6.20 mmol, 2 eq) in dichloromethane (25 mL) at rt, was added zinc trifluoromethanesulfonate (112 mg, 0.31 mmol, 10% mol eq). The resulting mixture was stirred for 2 h, and was subsequently washed with water (2 x 50 mL), filtered through celite, dried (Na_2SO_4) and concentrated. Purification by column chromatography (SiO_2, 30% Ether:petrol 40-60 °C) afforded *trans*-carveol **9a** (216 mg, 46%) and campholenic aldehyde **154** (183 mg, 39%). **Identical spectroscopic data to that obtained previously.**

1.4. Preparation of the epoxides

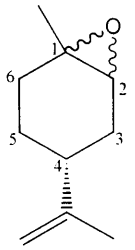
1.4.1. Epoxidation in dichloromethane

The general reaction scheme for this reaction is:



Preparation of 4-isopropenyl-1-methyl-7-oxa-bicyclo[4.1.0]heptane[161]

m-Chloroperbenzoic acid (13.90 g of a 75% dispersion, 0.06 mol, 1.1 eq) was added portionwise over a 45 min period to a stirred solution of *D*-limonene **1** (6.80 g, 0.05 mol, 1 eq) in aqueous $NaHCO_3$ (500 mL of a 0.3 N solution) cooled at 0 °C. Once the addition was complete, the resulting suspension was stirred vigorously at rt for 2 h and extracted with ethyl ether (3 x 70 mL). The combined organic extracts were washed with an ice-cold solution of NaOH (2 x 70 mL of a 10% solution), saturated brine (2 x 70 mL), dried (Na_2SO_4), filtered and concentrated to give a mixture of *cis* and *trans* 4-isopropenyl-1-methyl-7-oxa-bicyclo[4.1.0]heptane **2** (4.56 g, 0.03 mmol, 57%). No further purification was required.



2

$C_{10}H_{16}O$

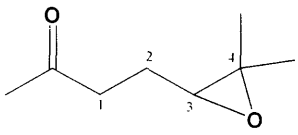
MW=152.237 g.mol^{-1}

Rf 0.3 (SiO_2, 20% EtOAc:petrol 40-60°C). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H/ppm: 4.39-4.31 (*m*, =C*H*$_2$, *cis*+*trans*, 2+2 H); 3.05-2.95 (*m*, C$_{(2)}$*H*, 1 H); 2.86-2.80 (*m*, C$_{(2)}$*H*, 1 H); 2.71-2.63 (*m*, C$_{(4)}$*H*, *cis*+*trans*, 1+1 H); 1.80-1.48 (*m*, ring *H*, *cis*+*trans*, 6+6 H); 1.73 (*s*, C*H*$_3$, 3 H); 1.70 (*s*, C*H*$_3$, 3 H); 1.41 (*s*, C*H*$_3$, 3 H); 1.36 (*s*, C*H*$_3$, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C/ppm: 150.2 (C=CH$_2$); 148.9

(C=CH_2); 109.4 (C=CH_2); 109.0 (C=CH_2); 58.9 ($C_{(1)}$); 59.2 ($C_{(1)}$); 57.7 ($C_{(2)}$); 57.4 ($C_{(2)}$); 38.2 ($C_{(4)}$); 36.1 ($C_{(4)}$); 30.8 ($C_{(3)}$); 30.1 ($C_{(3)}$); 29.9 ($C_{(6)}$); 27.9 ($C_{(6)}$); 24.4 ($C_{(5)}$); 24.1 ($C_{(5)}$); 23.9 (CH_3); 23.2 (CH_3); 21.7 (CH_3); 20.9 (CH_3). **IR** (neat): ν_{max}/cm^{-1}: 2981 (*m*), 2948 (*s*), 1644 (*s*), 1451 (*m*), 1174 (*w*), 1035 (*m*), 888 (*w*). **LRMS** (EIMS) m/z: 152 (8%, $[M^+]$), 109 (100%, M-$C_3H_7^+$), 84 (31%), 69 (70%), 54 (23%), 38 (42%).

Preparation of 4-(3,3-dimethyl-oxiranyl)-butan-2-one[162]

A solution of *m*-chloroperbenzoic acid (3.80 g of a 75% dispersion, 16.5 mmol, 1.1 eq) in dichloromethane (50 mL) was added dropwise over a one hour period to a stirred solution of 6-methyl-5-hepten-2-one **165** (1.89 g, 15.0 mmol, 1 eq) in DCM (50 mL) at 0 °C. The temperature was maintained for 2 h, the ice bath removed and the reaction mixture allowed to stir at room temperature for a further 30 min before extraction with diethyl ether (3 x 50 mL). The combined organic extracts were washed with $NaHCO_3$ (2 x 50 mL of a 10% solution), brine (2 x 50mL), dried ($MgSO_4$) and concentrated to give 2-methyl-2,3-epoxy-heptan-6-one **160** (900 mg, 42%).



160

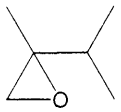
$C_8H_{14}O_2$

MW=142.198 g.mol^{-1}

Rf 0.25 (hexane:ethyl acetate 2:1). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ_H/ppm: 2.71 (*dd*, J = 8.0, J = 4.6, COH, 1 H); 2.60 (*dd*, J = 14.9, J = 8.0, CH_2, 2 H); 2.15 (*s*, CH_3, 3 H); 1.94-1.85 (*m*, CH_2, 1 H); 1.66-1.57 (*m*, CH_2, 1 H); 1.28 (*s*, CH_3, 3 H); 1.25 (*s*, CH_3, 3 H). **^{13}C-NMR** (125.8 MHz, $CDCl_3$) δ_C/ppm: 207.81 (C quarternary, C=O); 63.35 (C_3–O); 58.80 (C_4–O); 40.23 (CH_2); 29.97 (CH_3); 24.77 (CH_3); 22.95 (CH_2); 18.68 (CH_3). **IR** (NaCl, thin film): 2929 (*s*, C–H), 1717 (*s*, C=O), 1363 (*m*), 1166 (*m*), 1124 (*m*), 902 (*w*), 863 (*w*), 678 (*w*). **LRMS** (CI-Methane) m/z: 158 (10%); 157 (100%); 125 (88%); 101 (20%); 83 (25%); 71 (22%); 59 (74%).

Preparation of 2-isopropyl-2-methyl-oxirane[163]

Solid *m*-chloroperbenzoic acid (8.40 g of a 70% dispersion, 33.6 mmol, 1.1 eq) was added portionwise over a one hour period to a stirred solution of 2,3-dimethyl-but-1-ene **166** (1.80 g, 21.4 mmol, 1 eq) and sodium hydrogen carbonate (4.0 g, 48 mmol) in dichloromethane (70 mL) at 0 °C. Once the addition was complete, the ice bath was removed and the resulting suspension allowed to stir at rt for a further 10 h (completion of the reaction was checked by TLC), filtered and the filtrates extracted with diethyl ether (3 x 70 mL). The combined organic extracts were washed with $NaHCO_3$ (2 x 70 mL of a 10% solution), brine (2 x 70 mL), dried ($MgSO_4$) and concentrated to give a yellow oil, which was purified by column chromatography (eluent diethyl ether : PE 30-40, 1:2) to afford 2-isopropyl-2-methyl-oxirane **159** (1.01 g, 56%).



159

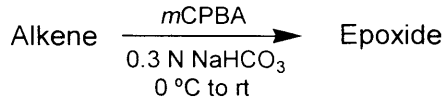
$C_6H_{12}O$

MW=100.161 g.mol^{-1}

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 2.74 (*s*, CH_2, 2 H); 1.27-1.22 (*m*, CH, 1 H); 1.17 (*s*, CH_3, 3 H); 1.04 (*d*, *J*=7.0, CH_3, 3 H); 1.01 (*d*, *J*=7.0, CH_3, 3 H). **^{13}C-NMR** (75.4 MHz, $CDCl_3$) δ_C/ppm: 61.9 (quaternary *C*); 56.5 (CH_2); 37.5 (*C*H); 18.9 (CH_3); 17.3 (CH_3). **IR** (neat): ν_{max}/cm^{-1}: 2929 (*s*), 2860 (*m*), 1718 (*w*), 1441 (*m*), 1377 (*m*), 1125 (*m*), 1051 (*m*), 894 (*m*), 728 (*s*). **LRMS** (EIMS) m/z: 100 (10%, [M$^+$]); 85 (12%); 84 (20%); 69 (100%); 55 (30%).

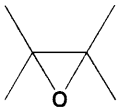
1.4.2. Epoxidation in aqueous sodium bicarbonate

The general reaction scheme for this reaction is:



Preparation of 2,3-dimethyl-2,3-epoxy-butane[164]

m-Chloroperbenzoic acid (8.05 g of a 75% dispersion, 32.7 mmol, 1.1 eq) was added portionwise over a 1 h period to a stirred solution of 2,3-dimethylbut-2-ene **167** (2.50 g, 29.7 mmol, 1 eq) in aqueous $NaHCO_3$ (500 mL of a 0.3 N solution) cooled at 0 °C. Once the addition was complete, the resulting suspension was stirred vigorously at rt for 1 h and extracted with diethyl ether (3 x 100 mL). The combined organic extracts were washed with an ice-cold solution of NaOH (2 x 100 mL of a 10% solution), saturated brine (2 x 70 mL), dried (Na_2SO_4), filtered and concentrated to give 2,3-dimethyl-2,3-epoxy-butane **83** (760 mg, 27%). No further purification was required.



83

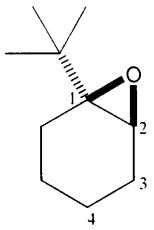
$C_6H_{12}O$

MW=100.161 g.mol^{-1}

^{1}H-NMR (500 MHz, $CDCl_3$) δ_H/ppm: 1.29 (*s*, CH_3). **^{13}C-NMR** (125.8 MHz, $CDCl_3$) δ_C/ppm: 62.03 (CH_3); 21.10 (*C*–O). **IR** (NaCl; thin film) ν_{max}/cm^{-1}: 3008 (*s*), 2959 (*s*), 2930 (*s*), 1787 (*w*), 1377 (*s*), 1203 (*m*), 1169 (*s*), 1136 (*m*), 1018 (*w*), 842 (*s*). **LRMS** (CI-Methane) m/z: 114 (3%); 113 (42%); 93 (13%); 83 (13%); 71 (9%); 69 (10%); 59(12%); 57 (18%).

Preparation of 1-*tert*-7-oxa-bicyclo[4.1.0]heptane[165]

A solution of *m*-chloroperbenzoic acid (1.83 g of a 75% dispersion, 7.97 mmol, 1.1 eq) in dichloromethane (30 mL) was added dropwise over a one hour period to a stirred solution of 1-*tert*-butylcyclohexene **168** (1.00 g, 7.25 mmol, 1 eq) in dichloromethane (25 mL) at 0 °C. Once the addition was complete, the ice bath was removed and the reaction mixture allowed to stir at rt for 2 hours before it was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with $NaHCO_3$ (2 x 50 mL of a 10% solution), brine (2 x 50 mL), dried ($MgSO_4$) and concentrated to give 1-*tert*-7-oxa-bicyclo[4.1.0]heptane **163** (852 mg, 76%).



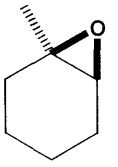
163

$C_{10}H_{18}O$

MW=154.249 g.mol^{-1}

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 3.17-3.09 (*m*, $C_{(2)}H$, 1 H); 2.00-1.81 (*m*, ring *H*, 2 H); 1.77-1.65 (*m*, ring *H*, 2 H); 1.46-1.33 (*m*, ring *H*, 2 H); 1.29-1.13 (*m*, ring *H*, 2 H); 0.97 (*s*, CH_3, 9 H). **^{13}C-NMR** (75.4 MHz, $CDCl_3$) δ_C/ppm: 65.02 (*C*HO); 55.42 (quaternary *C*); 34.19 ($C_{(1)}$); 25.68 ($C(CH_3)_3$); 25.37 ($C_{(6)}$); 24.95 ($C_{(4)}$); 21.20 (CH_3); 19.79 ($C_{(5)}$). **IR** (neat): ν_{max}/cm^{-1}: 2971 (*m*), 2936 (*s*), 2851 (*m*), 1429 (*m*), 1362 (*w*), 917 (*w*), 869 (*w*), 847 (*m*). **LRMS** (EIMS) m/z: 154 (10%, [M$^+$]); 139 (100%); 111 (30%); 98 (45%); 57 (80%); 41 (50%).

Preparation of 1-methyl-7-oxa-bicyclo[4.1.0]heptane[123]



31

$C_7H_{12}O$

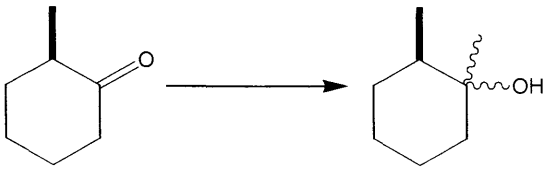
MW=112.172 g.mol^{-1}

m-Chloroperbenzoic acid (25.31 g of a 75% dispersion, 0.11 mmol) was added portionwise over a 50 min period to a stirred solution of 1-methylcyclohexene **129** (9.61 g, 0.10 mol) in aqueous $NaHCO_3$ (500 mL of a 0.3 N solution) cooled to 0 °C. Once the addition was complete, the resulting suspension was stirred vigorously at rt for 40 min and extracted with ethyl ether (3 x 100 mL). The combined organic extracts were washed with an ice-cold solution of NaOH (2 x 100 mL of a 10% solution), saturated brine (2 x 100 mL), dried (Na_2SO_4), filtered and concentrated to give 1-methyl-7-oxa-bicyclo[4.1.0]heptane **31** (8.91 g, 80%). No further purification was required.

^{1}H-NMR (500 MHz, $CDCl_3$) δ_H/ppm: 2.92 (*dm*, *J*=3.52, C*H*OH, 1 H); 1.88-1.77 (*m*, ring *H*, 3 H); 1.66-1.59 (*m*, ring *H*, 1 H); 1.46-1.33 (*m*, ring *H*, 2 H); 1.27 (*s*, C*H*$_3$, 3 H); 1.23-1.10 (*m*, ring *H*, 2 H). **^{13}C-NMR** (125.8 MHz, $CDCl_3$) δ_C/ppm: 59.56 (*C*HO); 57.46 (quaternary *C*); 29.82 ($C_{(3)}$); 24.69 ($C_{(6)}$); 23.93 (*C*H$_3$); 19.98 ($C_{(4)}$); 19.60 ($C_{(5)}$). **IR** (neat): ν_{max}/cm^{-1}: 2974 (*m*), 2937 (*s*), 2860 (*m*), 1718 (*w*), 1448 (*m*), 1435 (*m*), 1379 (*m*), 1213 (*w*), 1182 (*w*), 1118 (*w*), 1032 (*m*), 910 (*w*), 891 (*w*), 760 (*m*). **LRMS** (FABS) m/z: 112 (100%, [M$^+$]), 95 (60%), 73 (70%), 43 (20%), 54 (50%), 38 (60%).

1.4.3. Multistep syntheses

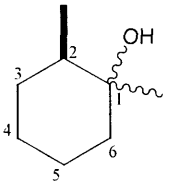
Preparation of 1,2-dimethylcyclohexanol



133 170

A solution of 2-methylcyclohexanone **133** (1.25 g, 11.2 mmol, 1 eq) in tetrahydrofuran (15 mL) was stirred at -78 °C for 30 min. Methyllithium (12 mL of a 1.2 M solution in ether, 13.8 mmol, 1.23 eq) was added dropwise with the temperature maintained at -78 °C. Stirring was maintained at that temperature for a further 3 hours. The reaction mixture was allowed to warm to rt and poured into 1 N HCl (50 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$) and concentrated. Purification by column chromatography (20% diethyl ether : PE 30-40) gave 1,2-dimethyl-cyclohexanol **170** (1.15 g, 80%).

1,2-Dimethylcyclohexanol[135]



170

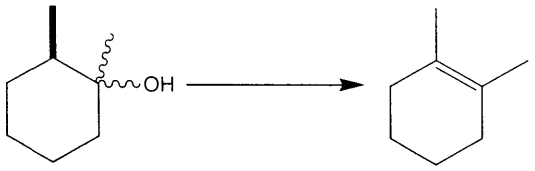
$C_8H_{16}O$

MW=128.215 g.mol^{-1}

^{1}H-NMR (300 MHz, CD_3OD) δ_H/ppm: 1.82-1.66 (*m*, ring CH_2, 3 H); 1.54-1.46 (*m*, CH, 1 H); 1.34-1.12 (*m*, ring CH_2, 7 H); 1.10 (s, CH_3, 1 H); 1.01 (*d*, *J*=7.9, CH_3, 3 H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ_C/ppm: 70.6 ($C_{(1)}$); 42.6 ($C_{(2)}$); 39.8 ($C_{(6)}$)); 30.8 ($C_{(5)}$); 23.5 ($C_{(4)}$); 22.9 (CH_3); 21.4 ($C_{(3)}$); 17.6 (CH_3);. **IR** (NaCl; thin film) ν_{max}/cm^{-1}: 2968 (*s*), 1684 (*w*), 1454 (*w*), 1175 (*w*), 1085 (*m*), 926 (*m*), 811

(*s*). **LRMS** (EIMS) m/z: 128 (10%, $[M^+]$); 113 (10%); 86 (12%); 72 (15%); 71 (100%); 69 (10%); 58 (40%); 41 (25%); 39 (30%).

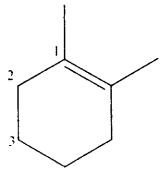
Preparation of 1,2-dimethylcyclohexene



170 **169**

A solution of 1,2-dimethylcyclohexan-1-ol **170** (960 mg, 7.13 mmol) in sulphuric acid (25 mL of 50% solution) was heated at 100 °C for 2 h. The mixture was allowed to cool to room temperature and extracted with diethyl ether (3 x 20 mL). The organic extracts were dried ($MgSO_4$), concentrated and purified by flash chromatography to give 1,2-dimethylcyclohexene **169** (718 mg, 92%).

1,2-Dimethylcyclohexene[136]



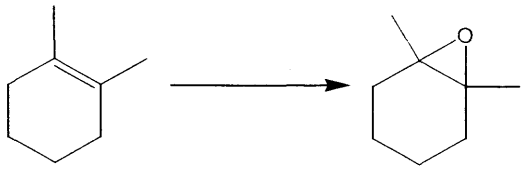
169

C_8H_{14}

MW=110.200 g.mol^{-1}

Rf 0.8 (SiO_2, 80% PE 30-40 : Ether). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ_H/ppm: 1.90-1.86 (*m*, $C_{(2)}H_2$, 4 H); 1.58 (*s*, CH_3, 6 H); 1.57-1.53 (*scss*, $C_{(3)}H_2$, 4 H). **^{13}C-NMR** (125.8 MHz, $CDCl_3$) δ_C/ppm: 125.63 ($C_{(1)}$); 31.70 ($C_{(2)}$); 23.45 ($C_{(3)}$); 19.16 (CH_3). **IR** (NaCl; thin film) ν_{max}/cm^{-1}: 2829 (*s*, C–H)), 1446 (*s*, C=C), 1381 (*m*), 1142 (*m*), 1012 (*w*), 760 (*m*). **LRMS** (CI-Methane) m/z: 123 (31%, $[M^+ + CH_4]$); 109 (16%, M^+); 81 (30%); 69 (54%); 61 (75%); 57 (100%); 45 (50%).

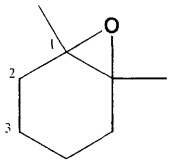
Preparation of 1,6-dimethyl-7-oxa-bicyclo[4.1.0]heptane



169 **158**

Solid *m*-chloroperbenzoic acid (1.50 g of a 70% dispersion, 6.10 mmol, 1.1 eq) was added portionwise over a one hour period to a stirred solution of 1,2-dimethylcyclohexene **169** (700 mg, 5.55 mmol, 1 eq) in dichloromethane (15 mL) cooled at 0-5 °C. The mixture was maintained at 0 °C for 30 min and a solution of sodium bisulfite (1.0 g) in water (10 mL) was added. The resulting mixture was stirred for a further 30 min at rt, diluted with water (10 mL), and the organic phase separated. The aqueous layer was extracted with dichloromethane (15 mL), and the combined organic extracts dried ($MgSO_4$) and concentrated. Distillation of the crude gave 1,6-dimethyl-7-oxa-bicyclo[4.1.0]heptane **158** (505 mg, 70%), **b.p.** 45°C/25 mm Hg. (lit.[167] 152°C/747 mmHg).

1,6-Dimethyl-7-oxa-bicyclo[4.1.0]heptane[166]



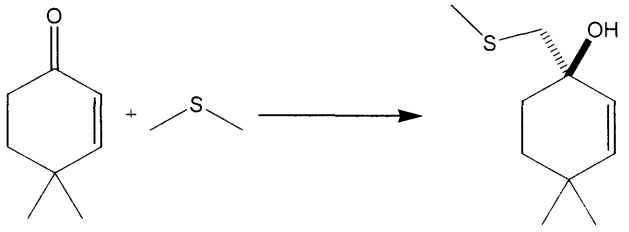
159

$C_8H_{14}O$

MW=126.199 g.mol^{-1}

^{1}H-NMR (500 MHz, $CDCl_3$) δ_H/ppm: 1.85 (*dt*, *J* = 14.9, *J* = 6.5, $C_{(2)}H$, 2 H); 1.64 (*dt*, *J* = 14.9, *J* = 6.5, $C_{(2)}H$, 2 H); 1.46-1.36 (*m*, $C_{(3)}H$, 2 H); 1.26 (*s*, CH_3, 6 H); 1.25-1.18 (*m*, $C_{(3)}H$, 2 H). **^{13}C-NMR** (125.8 MHz, $CDCl_3$) δ_C/ppm: 62.15 (C quaternary); 31.25($C_{(2)}$); 20.76(CH_3); 20.66($C_{(3)}$). **IR** (NaCl, thin film): 2935 (*s*), 2862 (*m*), 1772 (*w*), 1718 (*w*), 1435 (*m*), 1382 (*m*), 1216 (*m*), 1125 (*m*), 1045 (*m*), 908 (*m*), 733 (*s*). **LRMS** (EIMS) m/z: 126 (16%, [M^+]); 110 (60%); 69 (100%).

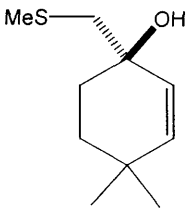
Preparation of 4,4-dimethyl-1-methylsulfanylmethyl-cyclohex-2-enol



172 174

To n-butyllithium (13 mL, 2.13 M solution in hexane, 27.7 mmol, 1 eq) chilled in an ice water bath was added TMEDA (3.22 g, 27.7 mmol, 1 eq). The mixture was allowed to warm up to rt and allowed to stir for 30 min at that temperature. The mixture was cooled to 0 °C over a one-hour period, and dimethylsulfide (1.72 g, 27.7 mmol, 1 eq) was slowly added. The resulting pale yellow solution was stirred for 3.5 h at rt and cooled to -78 °C, and a solution of 4,4-dimethyl-2-cyclohexen-1-one **172** (3.44 g, 27.7 mmol, 1 eq) in THF (15 mL) was added dropwise over a 5 min period. The mixture was allowed to warm up to rt and poured into diethyl ether (70 mL) and saturated aqueous NH_4Cl (70 mL). The organic phase was separated, washed with water (70 mL), dried (Na_2SO_4) and concentrated to provide a viscous yellow liquid. The crude product was purified by fractional distillation affording 4,4-dimethyl-1-methylsulfanylmethyl-cyclohex-2-enol **174** as a colourless oil (4.05 g, 21.7 mmol, 78%), **b.p.** 76°C/0.7 mm Hg.

4,4-Dimethyl-1-methylsulfanylmethyl-cyclohex-2-enol



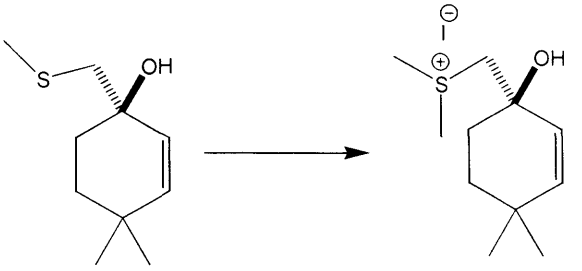
174

$C_{10}H_{18}OS$

MW=186.319 $g.mol^{-1}$

^{1}H-NMR (500 MHz, $CDCl_3$) δ_H/ppm: 5.53 (*d*, *J* = 10.0, $C_{(3)}H$, 1 H); 5.47 (*d*, *J* = 10.0, $C_{(2)}H$, 1 H); 2.71 (*d*, *J* = 13.4, S–C*H*, 1 H); 2.65 (*d*, *J* = 13.4, C*H*–S, 1 H); 2.29 (*s*(br), O*H*, 1 H); 2.17 (*s*, S–CH_3, 3 H); 1.79-1.73 (*m*, ring CH_2, 2 H); 1.65-1.57 (*m*, ring CH_2, 1 H); 1.46-1.39 (*m*, ring CH_2, 1 H); 1.00 (*s*, CH_3, 3 H); 0.94 (*s*, CH_3, 3 H). **^{13}C-NMR** (125.8 MHz, $CDCl_3$) δ_C/ppm: 140.96 (*C*H=); 128.50 (*C*H=); 69.96 (*C* quaternary, *C*–O); 47.27 (*C*H_2–S); 33.61 (*C*H_2); 32.40 (*C*H_2); 32.08 (*C* quaternary); 29.45 (*C*H_3); 28.16 (*C*H_3); 18.12 (*C*H_3–S). **IR** (NaCl; thin film) ν_{max}/cm^{-1}: 3421 (*s*, OH), 2955 (*s*), 2864 (*s*), 2360 (*w*), 1668 (*m*), 1647 (*m*), 1437 (*s*), 1040 (*s*), 773 (*m*). **LRMS** (CI-Methane) m/z: 185 (3%); 153 (5%); 121 (100%). **Anal.** Calcd. for $C_{10}H_{18}OS$: C, 64.47, H, 9.74%. Found: C, 64.67, H, 10.08%.

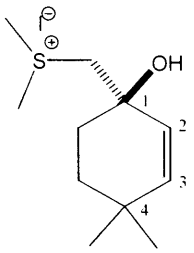
Preparation of (1-hydroxy-4,4-dimethyl-cyclohex-2-enylmethyl)-dimethyl-sulfonium iodide)



174 173

Methyl iodide (5.50 g, 38.6 mmol, 2 eq) was added portionwise to a solution of 4,4-dimethyl-1-methylsulfanylmethyl-cyclohex-2-enol **174** (3.60 g, 19.3 mmol, 1eq) in dry acetone (10 mL). The mixture was allowed to stir at rt overnight and was then concentrated *in vacuo* to provide, without any further purification, the sulfonium salt (1-hydroxy-4,4-dimethyl-cyclohex-2-enylmethyl)-dimethyl-sulfonium iodide) **173** as a white solid (5.82 g, 17.7 mmol, 92%), **m.p.** 154-156°C.

(1-Hydroxy-4,4-dimethyl-cyclohex-2-enylmethyl)-dimethyl-sulfonium iodide)



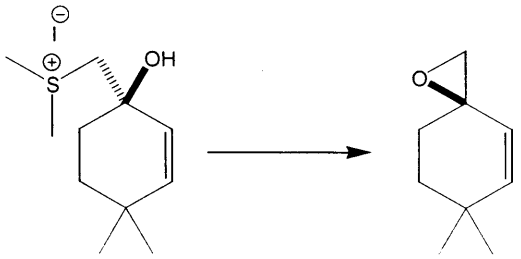
173

$C_{11}H_{21}OSI$

MW=328.254 g.mol^{-1}

^{1}H-NMR (300 MHz, CD_3OD) δ_H/ppm: 5.67 (*d*, *J*=10.0, $C_{(3)}H$, 1 H); 5.54 (*d*, *J*=10.0, $C_{(2)}H$, 1 H); 3.57 (*s*, S–CH_2, 2 H); 3.03 (*s*, CH_3, 3 H); 3.02 (*s*, CH_3, 3 H); 1.96 (*ddd*, ^2J = 13.7, ^3J = 8.5, ^3J=3.9, $C_{(6)}H$, 1 H); 1.88 (*ddd*, ^2J = 13.7, ^3J=8.5, ^3J=3.6, $C_{(6)}H$, 1 H); 1.68 (*ddd*, ^2J=14.0, ^3J=8.5, ^3J=3.6, $C_{(5)}H$, 1 H); 1.54 (*ddd*, ^2J=14.0, ^3J=8.5, ^3J=3.9, $C_{(5)}H$, 1 H); 1.04 (*s*, –CH_3, 3 H); 1.01 (*s*, –CH_3, 3 H). **^{13}C-NMR** (75.4 MHz, CD_3OD) δ_C/ppm: 143.30 ($C_{(3)}$); 128.15 ($C_{(2)}$); 69.77($C_{(1)}$); 56.64 ($C_{(7)}$); 34.37 ($C_{(6)}$); 33.97 ($C_{(5)}$); 33.01 ($C_{(4)}$); 29.16 (CH_3); 28.80 (CH_3); 28.39 (S–CH_3); 27.84 (S–CH_3). **IR** (KBr) ν_{max}/cm^{-1}: 3392 (*m*, OH), 2972 (*s*), 2841 (*s*), 1464 (*s*), 1377 (*m*), 1234 (*w*), 1051 (*m*), 1001 (*w*), 968 (*w*). **LRMS** (FABS) m/z: 201 (M-I, 100%); 154 (15%). **Anal.** Calcd. for $C_{11}H_{21}OSI$: C, 40.25, H, 6.45, S, 9.77, I, 38.66%. Found: C, 40.25, H, 6.51, S, 9.09, I, 38.01%.

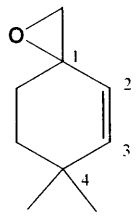
Preparation of 6,6-dimethyl-1-oxa-spiro[2.5]oct-4-ene



173 **162**

KO^{t}Bu (2.44 g, 19.1 mmol, 1.3 eq) was added to a suspension of (1-hydroxy-4,4-dimethyl-cyclohex-2-enylmethyl)-dimethyl-sulfonium iodide **173** (5.50 g, 16.8 mmol, 1 eq) in THF (200 mL). The mixture was allowed to stir overnight, quenched with saturated aqueous $NaHCO_3$ (50 mL) and poured into ether (250 mL). The aqueous phase was separated and extracted with ether (4 x 100 mL), and the combined organic extracts washed with saturated $NaHCO_3$ (500 mL), brine (500 mL), and dried ($MgSO_4$ and K_2CO_3). The solvent was removed by distillation at atmospheric pressure, and the residue was fractionally distilled to afford 6,6-dimethyl-1-oxa-spiro[2.5]oct-4-ene **162** (1.92 g, 13.9 mmol, 83%), as a colourless oil, **b.p.** 26-28°C/0.7 mm Hg.

6,6-Dimethyl-1-oxa-spiro[2.5]oct-4-ene



162

$C_9H_{14}O$

MW=138.210 g.mol^{-1}

^{1}H-NMR (500 MHz, CD_3OD) δ_H/ppm: 5.79 (*d*, ^3J = 9.8, $C_{(3)}H$, 1 H); 5.06 (*d*, ^3J = 9.3, $C_{(2)}H$, 1 H); 2.82 (*d*, ^2J = 4.9, $C_{(7)}H$, 1 H); 2.76 (*d*, ^2J = 4.9, $C_{(7)}H$, 1 H); 2.03-1.88 (*m*, $C_{(5)}H$, 1 H); 1.68-1.58 (*m*, 2 x $C_{(6)}H$ and $C_{(5)}H$, 3 H); 1.05 (*s*, $-CH_3$, 3 H);

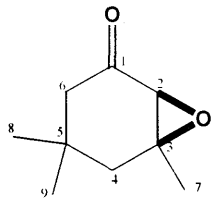
1.01 (*s*, $-CH_3$, 3 H). **^{13}C-NMR** (125.8 MHz, $CDCl_3$) δ_C/ppm: 146.53 ($C_{(3)}$); 126.53 ($C_{(2)}$); 56.77 ($C_{(1)}$)); 55.84 ($C_{(7)}$); 36.36 ($C_{(6)}$); 32.70 ($C_{(4)}$); 29.65 (CH_3); 28.61 (CH_3); 28.46 ($C_{(5)}$). **IR** (NaCl; thin film) ν_{max}/cm^{-1}: 2957 (*s*), 2939 (*m*), 1684 (*w*), 1472 (*w*), 1379 (*w*), 1361 (*m*), 926 (*s*), 806 (*s*). **LRMS** (EIMS) m/z: 138 (10%, [M$^+$]); 123 (10%); 69 (12%). **Anal.** Calcd. for $C_9H_{14}O$: C, 74.21, H, 10.21%. Found: C, 74.24, H, 9.96%.

1.4.4. Epoxidation with hydrogen peroxide

Preparation of 4,4,6-trimethyl-7-oxabicyclo[4.1.0]heptan-2-one

In a 100 mL-three-necked flask, equipped with a dropping funnel, a stirrer, and a thermometer, was placed a solution of isophorone **171** (3.72 g, 26.9 mmol, 1 eq) and 30 wt% aqueous hydrogen peroxide (8 mL, 78.3 mmol, 3 eq) in methanol (25 mL). After the contents of the flask had been cooled to 15 °C by means of an ice-bath, 6M aqueous sodium hydroxide (2.2 mL) was added dropwise with stirring, over 5 min. During the addition, the temperature of the reaction was maintained at 15-20 °C. Once the addition was complete, the resulting mixture was stirred at the same temperature for an additional 30 min, and allowed to warm to rt and stirred for 2 h. The reaction mixture was poured into water (50 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with water (3 x 20 mL), followed by addition of saturated aqueous sodium hydrogen carbonate (10 mL) and 20 wt% aqueous sodium bisulfite (10 mL). The organic layer was then successively washed with water (30 mL) and saturated brine (15 mL), dried (Na_2SO_4), and concentrated to provide 4,4,6-trimethyl-7-oxabicyclo[4.1.0]heptan-2-one **161** (3.72 g, 90%).

4,4,6-trimethyl-7-oxabicyclo[4.1.0]heptan-2-one[168]



161

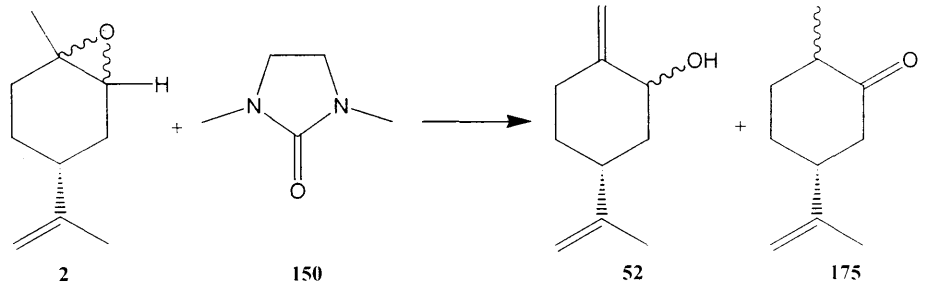
$C_9H_{14}O_2$

MW=154.209 g.mol^{-1}

^{1}H-NMR (500 MHz, $CDCl_3$) δ_H/ppm: 3.01 (*s*, $C_{(2)}H$, 1 H); 2.58 (*d*, ^2J = 13.4, $C_{(6)}H$, 1 H); 2.04 (*d*, ^2J = 14.9, $C_{(4)}H$, 1 H); 1.77 (*d*, ^2J = 13.4, $C_{(6)}H$, 1 H); 1.65 (*d*, ^2J = 14.9, $C_{(4)}H$, 1 H); 1.38 (*s*, $C_{(7)}H_3$, 3 H); 0.98 (*s*, $C_{(8)}H_3$, 3 H); 0.87 (*s*, $C_{(9)}H_3$, 3 H). **^{13}C-NMR** (125.8 MHz, $CDCl_3$) δ_C/ppm: 208.11 ($C_{(1)}$); 64.34 ($C_{(3)}$); 61.44 ($C_{(2)}$); 47.98 ($C_{(6)}$); 42.74 ($C_{(4)}$); 36.18 ($C_{(5)}$); 30.81 ($C_{(8)}$); 27.82 ($C_{(9)}$); 24.03 ($C_{(7)}$). **IR** (NaCl; thin film) ν_{max}/cm^{-1}: 3410 (*w*), 2960 (*s*, C–H), 2872 (*m*, C–H), 1718 (*s*, C=O), 1448 (*m*), 1398 (*s*), 1345 (*m*), 1252 (*m*), 1153 (*w*), 914 (*w*), 809 (*m*), 642 (*w*). **LRMS** (EIMS) m/z: 154 (20%, [M$^+$]); 139 (25%); 111 (10%); 97 (29%); 83 (100%); 69 (54%); 55 (37%); 43 (25%).

1.5. Application of the methodology

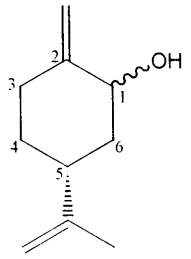
Ring-opening of (*R*)-limonene oxide



2 **150** **52** **175**

A solution of (*R*)-limonene oxide **2** (600 mg, 3.95 mmol, 1 eq) and 1,3-dimethyl-2-imidazolidinone **150** (900 mg, 7.90 mmol, 2 eq) in dichloromethane (20 mL) was stirred at rt as *p*-toluene sulphonic acid monohydrate (375 mg, 1.97 mmol, 0.5 eq) was added in one portion. The mixture was left stirring at rt for 3 hours (completion of the reaction was checked by TLC). It was then washed with brine, dried (Na_2SO_4), and concentrated. Purification by column chromatography (eluent 30% Diethyl ether : PE 30-40) afforded 5-isopropenyl-2-methylene-cyclohexanol **52** (243 mg, 1.60 mmol, 40%) and 5-isopropenyl-2-methyl-cyclohexanone **175** (218 mg, 1.44 mmol, 36%).

5-Isopropenyl-2-methylene-cyclohexanol[169]



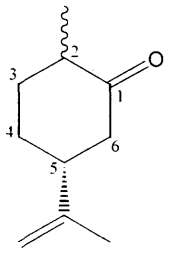
52

$C_{10}H_{16}O$

MW=152.237 g.mol^{-1}

Rf 0.4 (SiO_2, 30% EtOAc:petrol 40-60°C). **^{1}H-NMR** (300MHz, $CDCl_3$) δ_H/ppm: 4.93-4.86 (*m*, =C*H*$_2$, 1 H); 4.78-4.69 (*m*, =C*H*$_2$, 1 H); 4.18 (*s*, =C*H*$_2$, 1 H); 4.13 (*s*, =C*H*$_2$, 1 H); 3.89-3.82 (*m*, C*H*OH, 1 H); 2.40-1.89 (*m*, ring *H*, 2 H); 1.82-1.65 (*s*(br), O*H*, 1 H); 1.79 (*s*, C*H*$_3$, 3 H); 1.65-1.14 (*m*, ring *H*, 5 H). **^{13}C-NMR** (75.4MHz, $CDCl_3$) δ_C/ppm: 152.2 (quaternary *C*); 148.2 (*C*=CH$_2$); 105.9 (=*C*H$_2$); 73.8 (*C*HOH); 37.6 ($C_{(5)}$); 36.6 (*C*H$_2$); 33.8 (*C*H$_2$); 28.1 (*C*H$_2$); 24.5 (*C*H$_2$); 21.4 (*C*H$_3$). **IR** (neat): ν_{max}/cm^{-1}: 3381 (*s*, OH), 3092 (*s*), 1654 (*s*), 1154 (*m*), 906 (*w*), 887 (*w*). **LRMS** (EIMS) m/z: 152 (13%, [M$^+$]), 109 (100%, M-$C_3H_7^+$), 69 (70%), 54 (35%).

5-Isopropenyl-2-methyl-cyclohexanone[170]



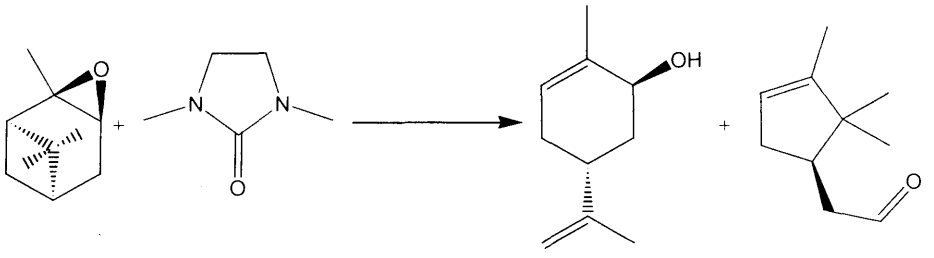
175

$C_{10}H_{16}O$

MW=152.237 g.mol^{-1}

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 4.18-4.13 (*m*, =C*H*$_2$, 2 H); 2.72-2.54 (*m*, ring *H*, 2 H); 2.12-1.86 (*m*, C$_{(5)}$*H*, 1 H); 1.83-1.27 (m, ring *H*, 5 H); 1.69 (*s*, C*H*$_3$, 3 H); 0.97 (*d*, *J*=6.5, C*H*$_3$, 3 H). **^{13}C-NMR** (75.4 MHz, $CDCl_3$) δ_C/ppm: 209.5 (*C*=O); 147.2 (*C*=CH$_2$); 108.9 (=*C*H$_2$); 44.9 (*C*$_{(5)}$); 44.6 (*C*$_{(6)}$); 43.8 (*C*$_{(2)}$); 33.1 (*C*$_{(3)}$); 28.5 (*C*$_{(4)}$); 20.4 (*C*H$_3$); 16.8 (*C*H$_3$). **IR** (neat): ν_{max}/cm^{-1}: 3086 (*s*), 1712 (*s*, C=O), 1641 (*s*, C=C), 1134 (*m*), 906 (*w*), 765 (*w*). **LRMS** (EIMS) m/z: 152 (13%, [M$^+$]), 109 (100%, M-C$_3$H$_7^+$), 69 (70%), 54 (35%).

Ring-opening of *α*-pinene oxide

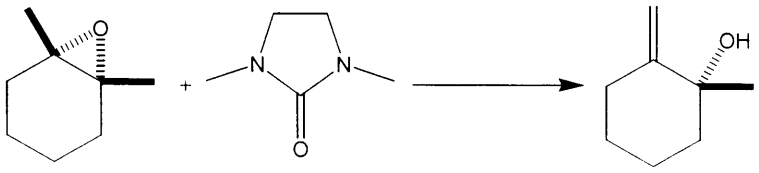


29 **150** **9a** **154**

A solution of *α*-pinene oxide **29** (900 mg, 5.90 mmol, 1 eq) and 1,3-dimethyl-2-imidazolidinone **150** (1.35 g, 11.8 mmol, 2 eq) in dichloromethane (30 mL) was stirred at rt as *p*-toluene sulphonic acid monohydrate (562 mg, 2.96 mmol, 0.5 eq) was added in one portion. The mixture was left stirring at rt for 2 hours (completion of the reaction was checked by TLC). It was then washed with brine,

dried (Na_2SO_4), and concentrated. Purification by column chromatography (eluent 30% Diethyl ether : PE 30-40) afforded *trans*-carveol **9a** (216 mg, 45%) and campholenic aldehyde **154** (183 mg, 35%). **Identical spectroscopic data to that obtained previously.**

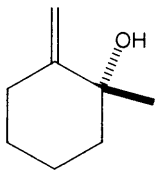
Ring-opening of 1,6-dimethyl-7-oxa-bicyclo[4.1.0]heptane



158 150 176

A solution of 1,6-dimethyl-7-oxa-bicyclo[4.1.0]heptane **158** (410 mg, 3.25 mmol, 1 eq) and 1,3-dimethyl-2-imidazolidinone **150** (740 mg, 6.50 mmol, 2 eq) in dichloromethane (20 mL) was stirred at rt as *p*-toluene sulphonic acid monohydrate (310 mg, 1.63 mmol, 0.5 eq) was added in one portion. The mixture was left stirring at rt for 1 hour (completion of the reaction was checked by TLC, one single product). It was then washed with brine, dried (Na_2SO_4), and concentrated. It was then columned through a short pad of silica using 30% diethyl ether : PE 30-40 as the eluent, to afford 1-methyl-2-methylene-cyclohexanol **176** (348 mg, 2.76 mmol, 85%).

1-Methyl-2-methylene-cyclohexanol[171]



176

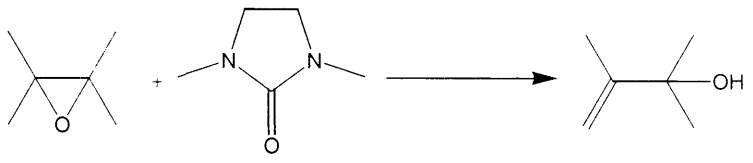
$C_8H_{14}O$

MW=126.199 g.mol^{-1}

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 4.86-4.79 (*m*, =C*H*, 1 H); 4.55-4.49 (*m*, =C*H*, 1 H); 2.36-2.26 (*m*, ring *H*, 1 H); 2.11 (*s*(br), O*H*, 1 H); 2.01-1.84 (*m*, ring

H, 2 H); 1.65-1.12 (*m*, ring *H*, 5 H); 1.26 (*s*, CH_3, 3 H). **^{13}C-NMR** (75.4 MHz, $CDCl_3$) δ_C/ppm: 151.87 (quaternary *C*); 106.52 (=CH_2); 82.58 (*C*OH); 37.21 (CH_2); 34.24 (CH_2); 28.09 (CH_2); 24.09 (CH_3); 23.91 (CH_2). **IR** (neat): ν_{max}/cm^{-1}: 3611 (*s*, OH), 3092 (*s*), 1648 (*s*), 906 (*w*), 887 (*w*). **LRMS** (EIMS) m/z: 126 (6%, [M$^+$]); 111 (42%); 108 (20%); 91 (55%); 69 (100%); 55 (30%).

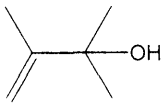
Ring-opening of 2,3-dimethyl-2,3-epoxy-butane



83 **150** **178**

A solution of 2,3-dimethyl-2,3-epoxy-butane **83** (500 mg, 5.00 mmol, 1 eq) and 1,3-dimethyl-2-imidazolidinone **150** (1.14 g, 10.0 mmol, 2 eq) in dichloromethane (20 mL) was stirred at rt as *p*-toluene sulphonic acid monohydrate (380 mg, 2.00 mmol, 0.5 eq) was added in one portion. The mixture was left stirring at rt for 1 hour (completion of the reaction was checked by TLC, one single product). It was then washed with brine, dried (Na_2SO_4), and concentrated. It was finally columned through a short pad of silica using 30% ether : PE 30-40 as the eluent, to afford 2,3-dimethyl-but-3-en-2-ol **178** (487 mg, 4.85 mmol, 97%).

2,3-Dimethyl-but-3-en-2-ol[172]



178

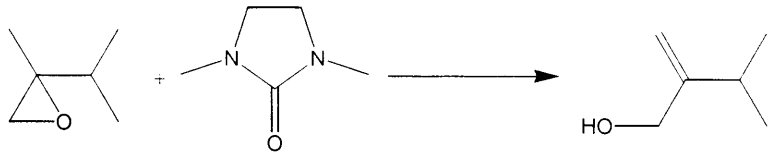
$C_6H_{12}O$

MW=100.161 g.mol^{-1}

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 4.93-4.89 (*m*, =C*H*, 1 H); 4.66-4.59 (*m*, =C*H*, 1 H); 1.81 (*s*(br), O*H*, 1 H); 1.77 (*m*, CH_3, 3 H); 1.31 (*s*, CH_3, 6 H). **^{13}C-NMR** (75.4 MHz, $CDCl_3$) δ_C/ppm: 151.8 (quaternary *C*); 100.5 (=CH_2); 72.6

(*C*OH): 27.21 (*C*H$_3$): 19.91 (*C*H$_3$). **IR** (neat): ν_{max}/cm^{-1}: 3611 (*s*, OH), 3092 (*s*), 1648 (*s*), 906 (*w*), 887 (*w*). **LRMS** (EIMS) m/z: 100 (19%, [M$^+$]); 85 (100%); 59 (55%); 43 (25%).

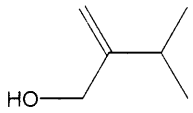
Ring-opening of 2-isopropyl-2-methyl-oxirane



159 **150** **182**

A solution of 2-isopropyl-2-methyloxirane **159** (800 mg, 8.00 mmol, 1 eq) and 1,3-dimethyl-2-imidazolidinone **150** (1.82 g, 16.0 mmol, 2 eq) in dichloromethane (40 mL) was stirred at rt as *p*-toluene sulphonic acid monohydrate (760 mg, 4.00 mmol, 0.5 eq) was added in one portion. The mixture was left stirring at rt for 1 hour (completion of the reaction was checked by TLC). It was then washed with brine, dried (Na_2SO_4), and concentrated. Purification by column chromatography (eluent: 40% diethyl ether : PE 30-40) afforded 2-isopropyl-prop-2-en-1-ol **182** (376 mg, 3.76 mmol, 47%).

2-isopropyl-prop-2-en-1-ol[173]



182

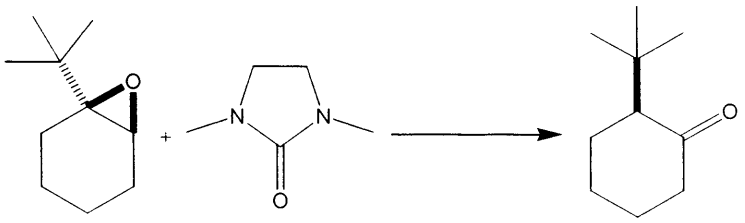
$C_6H_{12}O$

MW=100.161 g.mol^{-1}

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 4.92-4.86 (*m*, =C*H*, 1 H); 4.62-4.56 (*m*, =C*H*, 1 H); 3.98 (*s*, CH_2, 2 H); 2.31-2.19 (*dm*, *J*=7.0, C*H*, 1 H); 1.10 (*d*, *J*=7.0, CH_3, 6 H). **^{13}C-NMR** (75.4 MHz, $CDCl_3$) δ_C/ppm: 150.1 (quaternary *C*); 106.5 (=CH_2); 65.2 (*C*OH); 30.8 (*C*H); 21.0 (*C*H$_3$). **IR** (neat): ν_{max}/cm^{-1}: 3275 (*s*, OH),

1642 (*s*), 1466 (*m*), 1118 (*m*), 916 (*w*). **LRMS** (EIMS) m/z: 100 (15%, [M^+]); 84 (73%); 72 (25%); 39 (100%).

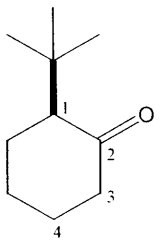
Ring-opening of 1-*tert*-7-Oxa-bicyclo[4.1.0]heptane



163 150 185

A solution of 1-*tert*-7-oxa-bicyclo[4.1.0]heptane **163** (700 mg, 4.54 mmol, 1 eq) and 1,3-dimethyl-2-imidazolidinone **150** (1.04 g, 9.10 mmol, 2 eq) in dichloromethane (40 mL) was stirred at rt as *p*-toluene sulphonic acid monohydrate (430 mg, 2.27 mmol, 0.5 eq) was added in one portion. The mixture was left stirring at rt for 1 hour (completion of the reaction was checked by TLC, one single product). It was then washed with brine, dried (Na_2SO_4), and concentrated. It was finally columned through a short pad of silica using 30% diethyl ether : PE 30-40 as the eluent, to give 2-*tert*-butyl-cyclohexanone **185** (581 mg, 3.77 mmol, 83%).

2-*tert*-Butyl-cyclohexanone[174]



185

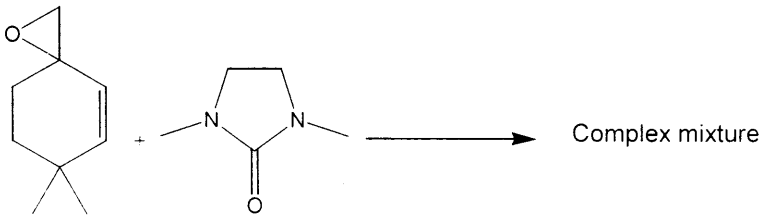
$C_{10}H_{18}O$

MW=154.249 g.mol^{-1}

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 2.41-2.33 (*m*, ring *H*, 2 H); 2.18-2.11 (*m*, ring *H*, 1 H); 2.03-1.89 (*m*, ring *H*, 2 H); 1.80-1.73 (*m*, ring *H*, 1 H); 1.62-1.53 (*m*,

ring *H*, 2 H): 1.39-1.28 (*m*, ring *H*, 1 H): 1.01 (*s*, CH_3, 9 H). **^{13}C-NMR** (75.4 MHz, $CDCl_3$) δ_C/ppm: 213.69 (*C*=O); 46.01 (RCHC$(CH_3)_3$); 43.37 (CH_2); 36.61 (CH_2); 28.78 (CH_2); 26.89 (quaternary *C*); 26.02 (CH_2); 13.99 (CH_3). **IR** (neat): ν_{max}/cm^{-1}: 2971 (*m*), 2931 (*s*), 1712 (*s*), 924 (*w*), 874 (*w*), 845 (*m*). **LRMS** (EIMS) m/z: 154 (4%, [M$^+$]); 98 (100%); 83 (15%); 69 (40%); 39 (15%).

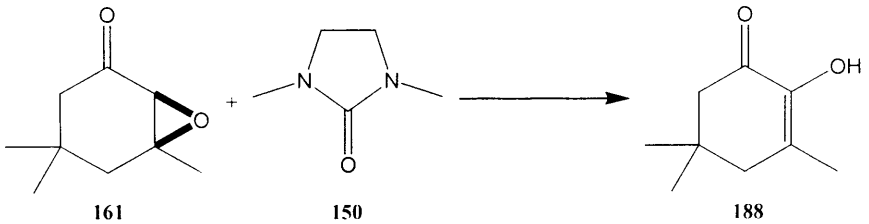
Ring-opening of 6,6-dimethyl-1-oxa-spiro[2.5]oct-4-ene



162 150

A solution of 6,6-dimethyl-1-oxa-spiro[2.5]oct-4-ene **162** (1.50 g, 9.73 mmol, 1 eq) and 1,3-dimethyl-2-imidazolidinone **150** (2.22 g, 19.5 mmol, 2 eq) in dichloromethane (50 mL) was stirred at rt as *p*-toluene sulphonic acid monohydrate (925 mg, 4.86 mmol, 0.5 eq) was added in one portion. The mixture was left stirring at rt for 2 hours (completion of the reaction was checked by TLC, showing a large number of products, at least 5 spots). It was then washed with brine, dried (Na_2SO_4), and concentrated. An attempted purification by column chromatography (15% diethyl ether : PE 30-40 as the eluent) was unsuccessful in isolating any clean product.

Ring-opening of 4,4,6-trimethyl-7-oxabicyclo[4.1.0]heptan-2-one

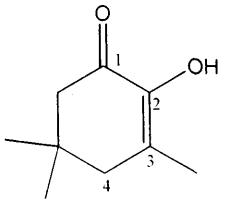


161 150 188

A solution of 4,4,6-trimethyl-7-oxabicyclo[4.1.0]heptan-2-one **161** (1.20 g, 7.78 mmol, 1 eq) and 1,3-dimethyl-2-imidazolidinone **150** (1.78 g, 15.6 mmol, 2 eq) in

dichloromethane (50 mL) was stirred at rt as *p*-toluene sulphonic acid monohydrate (740 mg, 3.89 mmol, 0.5 eq) was added in one portion. The mixture was left stirring at rt for 5 hours (completion of the reaction was checked by TLC, one single product). It was washed with brine, dried (Na_2SO_4), and concentrated. It was then columned through a short pad of silica using 45% diethyl ether : PE 30-40 as the eluent, to afford 2-hydroxy-3,5,5-trimethylcyclohex-2-enone **188** (1.06 g, 6.85 mmol, 88%).

2-Hydroxy-3,5,5-trimethylcyclohex-2-enone[175]



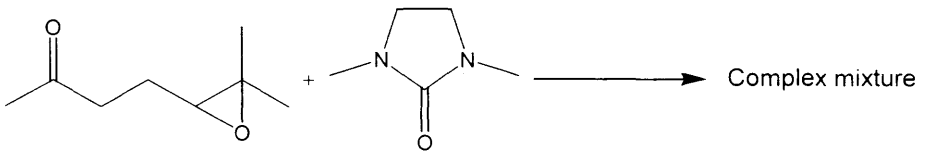
188

$C_9H_{14}O_2$

MW=154.209 g.mol^{-1}

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 2.33 (*s*, $C_{(6)}H$, 2 H); 2.21 (*s*, $C_{(4)}H$, 2 H); 1.86 (*s*, CH_3, 3 H); 1.06 (*s*, CH_3, 6 H). **^{13}C-NMR** (75.4 MHz, $CDCl_3$) δ_C/ppm: 193.92 ($C_{(1)}$); 143.05 ($C_{(2)}$); 127.61 ($C_{(3)}$); 49.32 ($C_{(5)}$); 44.65 ($C_{(6)}$); 33.40 ($C_{(4)}$); 28.31 (CH_3); 17.04 (CH_3). **IR** (neat): ν_{max}/cm^{-1}: 3402 (*s*, OH), 1671 (*s*), 1639 (*s*), 992 (*w*), 817 (*w*). **LRMS** (EIMS) m/z: 154 (91%, [M$^+$]); 139 (52%); 126 (15%); 98 (55%); 83 (35%); 70 (100%); 55 (30%); 43 (35%).

Ring opening of 4-(3,3-dimethyl-oxiranyl)-butan-2-one



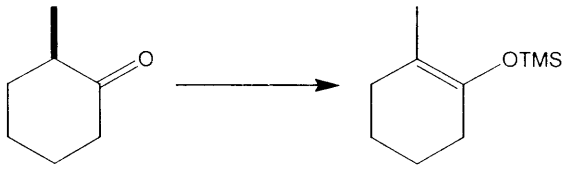
160 **150**

A solution of 4-(3,3-dimethyl-oxiranyl)-butan-2-one **160** (600 mg, 4.22 mmol, 1 eq) and 1,3-dimethyl-2-imidazolidinone **150** (965 mg, 8.45 mmol, 2 eq) in dichloromethane (20 mL) was stirred at rt as *p*-toluene sulphonic acid monohydrate (925 mg, 4.86 mmol, 0.5 eq) was added in one portion. The mixture was left stirring at rt for 2 hours (completion of the reaction was checked by TLC, showing a large number of products). It was then washed with brine, dried (Na_2SO_4), and concentrated. An attempted purification by column chromatography (15% diethyl ether : PE 30-40 as the eluent) was unsuccessful to isolate any clean product.

2. Epoxides to α,β-unsaturated ketones

2.1. Synthesis of the reference

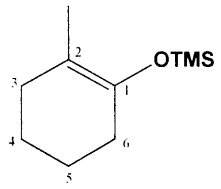
Preparation of trimethyl-(2-methyl-cyclohex-1-enyloxy)-silane



133 120

A solution of sodium iodide (18.60 g, 124 mmol, 1.24 eq) in acetonitrile (100 mL) was added dropwise over a 30 min period at rt to a mixture of 2-methylcyclohexanone **133** (11.21 g, 100 mmol, 1 eq), triethylamine (12.4 g, 124 mmol, 1.24 eq), and trimethylchlorosilane (13.44 g, 124 mmol, 1.24 eq). Stirring was maintained for 2 h. Cold pentane (100 mL) and ice cold water (100 mL) were successively added. After decantating, the aqueous layer was extracted with pentane (2 x 50 mL). The combined organic phases were washed with an aqueous solution of ammonium chloride, dried (sodium sulphate) and concentrated. Distillation under inert atmosphere afforded trimethyl-(2-methyl-cyclohex-1-enyloxy)-silane **120** (16.8 g, 91 mmol, 91%), **b.p** 100-102 °C/70 mmHg (lit.[176] 97-99 °C/65 mmHg) as a clear colourless oil.

Trimethyl-(2-methyl-cyclohex-1-enyloxy)-silane[176]



120

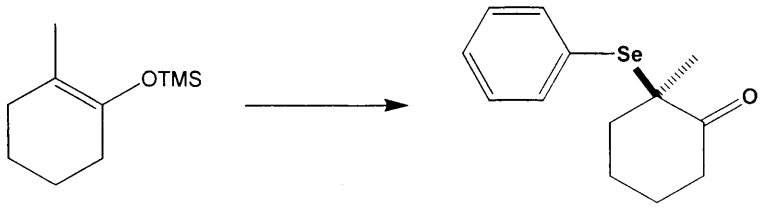
$C_{10}H_{20}OSi$

MW=184.355 g.mol^{-1}

Rf=0.7 (PE 30-40/EtOAc 8:2).^{1}**H-NMR** (300 MHz, $CDCl_3$) δ_H/ppm: 2.03-1.87 (*m*, $C_{(3)}H_2$ and $C_{(4)}H_2$, 4 H); 1.67-1.45 (*m*, $C_{(5)}H_2$ and $C_{(6)}H_2$, 4 H); 1.53 (*s*, CH_3, 3

H): 0.14 (s, Si–CH_3, 9 H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ_C/ppm: 142.78 ($C_{(1)}$); 111.56 ($C_{(2)}$); 30.36 ($C_{(3)}$); 29.96 ($C_{(6)}$); 23.88 ($C_{(5)}$); 22.91 ($C_{(4)}$); 16.32 (CH_3); 0.72 (Si–CH_3). **IR** (NaCl; thin film) ν_{max}/cm^{-1}: 2935 (*s*, C–H), 1716 (*s*, C=C), 1452 (*m*), 1377 (*w*), 1351 (*m*), 1171 (*s*), 844 (*m*). **LRMS** (EIMS): 184 (49%, [M^+]); 169 (M-CH_3, 90); 155 (16); 141 (39); 73 (M-$SiMe_3$, 100)); 45 (25).

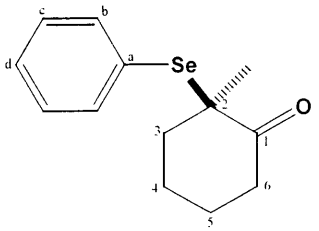
Preparation of 2-methyl-2-phenylselanyl-cyclohexanone



120 201

To a solution of trimethyl-(2-methylcyclohex-1-enyloxy)-silane **120** (3.76 g, 20 mmol, 1 eq) in THF (20 mL) was added dropwise phenylselenylchloride (3.91 g) in THF (40 mL) at -78 °C. After stirring for 10 min, the mixture was quenched with water and extracted with ether (3 x 20 mL). The combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (80% PE 30-40 : Et_2O) to give 2-methyl-2-phenylselanyl-cyclohexanone **201** (4.54 g, 17 mmol, 85%).

2-Methyl-2-phenylselanyl-cyclohexanone[143]



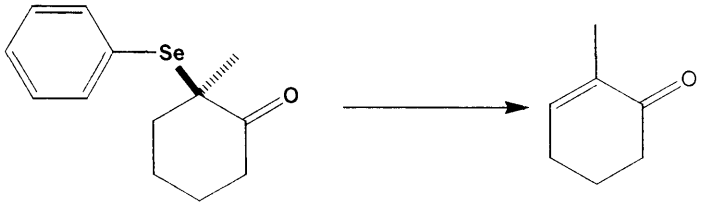
201

$C_{13}H_{16}OSe$

MW=267.230 g.mol^{-1}

Rf (PE 30-40/EtOAc 9:1) = 0.3. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ_H/ppm: 7.44 (*dd*, *J* = 7.4, ^4J = 1.2, Ar-*Hb*, 2 H); 7.35 (*tt*, *J* = 7.4, ^4J = 1.2, Ar-*Hd*, 1 H); 7.26 (*t*, *J* = 7.4, Ar-*Hc*, 2 H); 3.39 (*ddd*, ^2J = 14.8, *J* = 14.0, *J* = 6.3, $C_{(6)}H$, 1 H); 2.38-2.24 (*m*, $C_{(3)}H$, 2 H); 2.21-2.02 (*m*, $C_{(5)}H$, 2 H); 1.98-1.87 (*m*, $C_{(3)}He$, 1 H); 1.79-1.65 (*m*, $C_{(3)}H$, 2 H); 1.37 (*s*, CH_3, 3 H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ_C/ppm: 207.64 ($C_{(1)}$); 137.46 ($C_{(c)}$); 129.23 ($C_{(d)}$); 128.93 ($C_{(b)}$); 126.71 ($C_{(a)}$); 55.28 ($C_{(2)}$); 40.77 ($C_{(6)}$); 37.21 ($C_{(3)}$); 27.05 ($C_{(5)}$); 24.86 (CH_3); 22.43 ($C_{(4)}$). **IR** (NaCl; thin film) ν_{max}/cm^{-1}: 1695 (*s*, C=O), 2931 (*s*, C–H).

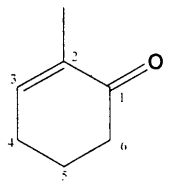
Preparation of 2-methylcyclohex-2-enone



201 107

Hydrogen peroxide (20 mL of a 30%-wt solution in water, 168 mmol, 10 eq) was added dropwise to a solution of 2-methyl-2-phenylselanylcyclohexanone **201** (4.50 g, 16.8 mmol) in pyridine (2.77 g, 35 mmol, 2 eq) and dichloromethane (50 mL) at 0 °C. After 1 h of stirring at rt, the solution was heated at reflux for 5 min, then 2 N HCl was added and the mixture was extracted with diethyl ether (3 x 30 mL). The organic phase was dried (magnesium sulphate) and concentrated. The residue was purified by distillation, to afford 2-methylcyclohex-2-enone **107** (1.6 g, 14.5 mmol, 86%), **b.p.** 74-76 °C/25 mmHg (lit. [£xx] 61 °C/10 mmHg). Rf (PE 30-40/EtOAc 8:2) = 0.35.

2-Methylcyclohex-2-enone[177]



107

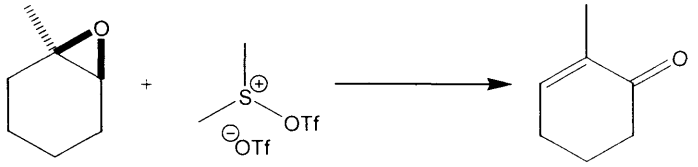
$C_7H_{10}O$

MW=110.156 g.mol^{-1}

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 6.72 (*dt*, J = 4.05, ^4J = 1.25, $C_{(3)}H$, 1 H); 2.40 (*t*, J = 6.7, $C_{(6)}H$, 2 H); 2.34-2.26 (*m*, $C_{(4)}H$, 2 H); 1.96 (*q*, J = 6.7, $C_{(5)}H$, 2 H); 1.75 (*d*, ^4J = 1.25, CH_3, 3 H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ_C/ppm: 199.86 ($C_{(1)}$); 145.85 ($C_{(3)}$); 136.16 ($C_{(2)}$); 38.72 ($C_{(6)}$); 26.43 ($C_{(4)}$); 23.70 ($C_{(5)}$); 16.33 (CH_3). **IR** (NaCl; thin film) ν_{max}/cm^{-1}: 2870 (*s*, C–H), 2833 (*m*), 1674 (*s*, C=O), 1431 (*s*, C=C), 1360 (*s*), 1256 (*m*), 1174 (*s*), 1107 (*m*), 1022 (*m*), 903 (*m*), 881 (*m*). **LRMS** (EIMS): 110 (M+, 30%); 95 (M-CH_3, 3%); 82 (100%); 68 (13%); 54 (20%); 43 (95%); 41 (43%); 39 (54%).

2.2. Application

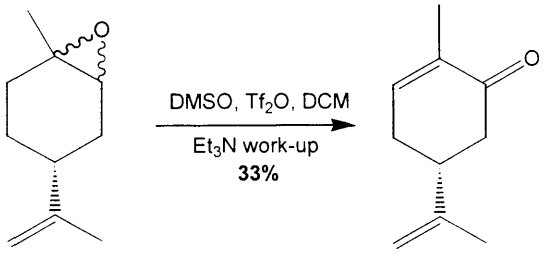
One-pot synthesis of 2-Methylcyclohex-2-enone



31 215 107

A solution of dimethylsulfoxide (633 mg, 85.8 mmol, 2 eq) was stirred at 0 °C in dichloromethane (20 mL). Fresh trifluoromethanesulfonic anhydride (2.40 g, 85.8 mmol, 2 eq) was added dropwise provoking a vigorous reaction and immediate formation of a white precipitate. Upon completion of the addition, the mixture was allowed to warm to room temperature, and 1-methylcyclohexene oxide **31** (470 mg, 42.0 mmol, 1 eq) was added dropwise forming a red solution. The mixture was stirred for one day. Dropwise addition of triethylamine (1 g, 99 mmol, 2.4 eq), followed by washing with water (2 x 30 mL), sat. $NaHCO_3$ (3 x 30 mL), brine (3 x 30 mL), and drying (Na_2SO_4), afforded a crude product that was purified by column chromatography to afford 2-methylcyclohex-2-enone **107** (360 mg, 32.8 mmol, 78%). **Identical spectroscopic data to that obtained previously.**

One-pot synthesis of 5-isopropenyl-2-methyl-cyclohex-2-enone

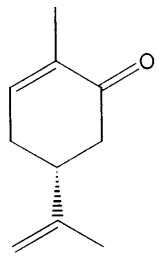


2 3

A solution of dimethylsulfoxide (487 mg, 66.0 mmol, 2 eq) was stirred at 0 °C in dichloromethane (15 mL). Fresh trifluoromethanesulfonic anhydride (1.85 g, 66.0

mmol, 2 eq) was added dropwise provoking a vigorous reaction and immediate formation of a white precipitate. Upon completion of the addition, the mixture was allowed to warm up to room temperature, and (*R*)-limonene oxide **2** (500 mg, 32.9 mmol, 1 eq) was added dropwise forming a red solution. The mixture was stirred for one day. Dropwise addition of triethylamine (1 g, 99 mmol, 3 eq), followed by washing with water (2 x 30 mL), sat. sodium bicarbonate (3 x 30 mL) and brine (3 x 30 mL), and drying (Na_2SO_4), afforded a crude product that was purified by column chromatography to give 5-isopropenyl-2-methylcyclohex-2-enone **3** (162 mg, 33%).

5-Isopropenyl-2-methyl-cyclohex-2-enone



3

$C_{10}H_{14}O$

MW=150.221 g.mol^{-1}

^{1}H-NMR (300 MHz, $CDCl_3$) δ_H/ppm: 6.76-6.70 (*m*, $C_{(3)}H$, 1 H); 4.06 (*s*, $=CH_2$, 1 H); 4.02 (*s*, $=CH_2$, 1 H); 2.46-2.41 (*m*, $C_{(6)}H$, 2 H); 2.37-2.28 (*m*, $C_{(4)}H$, 2 H); 1.96 (*m*, $C_{(5)}H$, 1 H); 1.80 (s, CH_3, 3 H); 1.72 (*d*, ^4J = 1.25, CH_3, 3 H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ_C/ppm: 199.9 ($C_{(1)}$); 149.1 (C=CH_2); 145.8 ($C_{(3)}$); 136.2 ($C_{(2)}$); 109.6 (C=CH_2); 38.7 ($C_{(6)}$); 26.4 ($C_{(4)}$); 23.7 ($C_{(5)}$); 21.2 (CH_3); 16.3 (CH_3). **IR** (NaCl; thin film) ν_{max}/cm^{-1}: 2876 (*s*, C–H), 2841 (*m*), 1674 (*s*, C=O), 1431 (*s*, C=C), 1360 (*s*), 1174 (*s*), 1101 (*m*), 917 (*m*), 875 (*m*). **LRMS** (EIMS) m/z: 150 (6%, [M$^+$]), 107 (100%, M-$C_3H_7^+$), 84 (60%), 69 (38%), 54 (72%).

2.3. Attempted reactions

Reaction of 1-methylcyclohexene oxide with TPAP and boron trifluoride

A mixture of TPAP (10 mol%), and boron trifluoride etherate (10 mmol%) was stirred at rt in dry ether (5 mL) under nitrogen. The mixture rapidly changed colour from dark blue to dark green. Then, 1-methylcyclohexene oxide **31** (100 mg, 8.93 mmol, 1 eq) was added dropwise , and the resulting mixture was stirred at rt for 1 day. GC analyses were regularly performed to notice any consumption of the starting material. However, after 1 day, the starting epoxide remained unreacted.

Reaction of 1-methylcyclohexene oxide with sufur trioxide-pyridine complex

A mixture of 1-methylcyclohexene oxide **31** (450 mg, 4.02 mmol, 1 eq) and triethylamine (3.03 g, 30.0 mmol) in dimethylsulfoxide (10 mL) was stirred at room temperature as sulphur trioxide-pyridine complex (1.90 g, 12.0 mmol, 3 eq) was added. The mixture was left stirring at rt for 3 h. Advancement of the reaction was followed by GC-analyses, looking for the disappearance of the starting material and formation of the desired enone. No reaction was taking place, so the mixture was successively heated to 50 °C for 30 min(no reaction observed), 100 °C for 30 min (no reaction observed), 150 °C for 30 min (no reaction observed) and finally to reflux (180 °C) for 2 hours. Opening of the epoxide was finally achieved but led to the formation of a mixture of several products (from GC-analyses and TLC) that could not be isolated by column chromatography.

Chapter 5

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