*Tetrahedron* Vol 39, No 14, pp 2323 to 2367, 1983
Printed in Great Britain

0040-4020/83 $5.00 + .00
Pergamon Press Ltd.

# TETRAHEDRON REPORT NUMBER 150

# RECENT ADVANCES IN THE PREPARATION AND SYNTHETIC APPLICATIONS OF OXIRANES

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(*Received in the UK 4 November* 1982)

CONTENTS



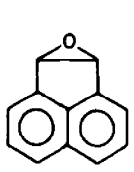
## INTRODUCTION

Biologically important oxiranes include leukotriene A (LTA), the biogenetic precursor of the leukotrienes LTC, LTD and LTE which are important natural mediators of allergic asthma,[2] and arene oxides, postulated as intermediates in the metabolism of aromatic compounds to phenols.[3] The ultimate carcinogenic metabolites of polycyclic aromatic hydrocarbons are the tetrahydrodiol epoxides.[4] The biological activities of aflatoxin $B_1$ and precocenes are due to the oxiranes derived from them.[5,6]

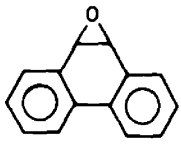
The importance of oxiranes as intermediates in organic synthesis is well-known.[7] Various aspects of reactions of oxiranes have been reviewed by Parker and Isaacs[8] in 1959, Rosovksy[9] in 1964, McDonald[10] in 1971, Buchanan and Sable[11] in 1972, Berti[12] in 1973, Kirk[13] in 1973, Bruice and Bruice[14] in 1976, Dryuk[15] in 1976, Sharpless and Verhoeven[16] in 1979, Adam and Balci[17] in 1980 and Rebek in 1980.[18] The applications of oxiranes for stereoselective synthesis of acyclic systems,[19] reductions of $\alpha$, $\beta$-epoxy ketones and $\delta$, $\epsilon$ epoxyketones,[19] the use of singlet oxygen for the preparation of oxiranes[20] and the deoxygenation[21,22] of oxiranes are discussed in recent reviews. The present review is devoted mainly to the papers on oxiranes published during the period 1976–81. Since a very large number of publications dealing with applications of oxiranes have appeared it has not been possible to present the entire work published during this period. We have tried to include, as far as possible, reactions having wide applicability and furnishing good yields of products which are of current interest. Acid catalyzed rearrangements,[11] hydride reductions[23] and reactions of $\alpha$, $\beta$-epoxysilanes[24] have not been included in this review.

1. *Synthesis of oxiranes from alkenes and arenes*

Oxiranes can be prepared conveniently in the laboratory by reacting olefins with organic peroxyacids, particularly m-chloroperbenzoic acid (MCPBA); several aromatic compounds are also epoxidized by this reagent. Through a proper choice of experimental conditions (particularly control of pH) it has been possible to isolate even sensitive oxiranes, some of which are listed below (**1–3**).[25,26] However, the oxirane **4**, the active metabolite of the carcinogen aflatoxin $B_1$ (**5**), cannot be isolated[27] after MCPBA oxidation of **5**.



**1**



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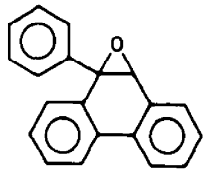
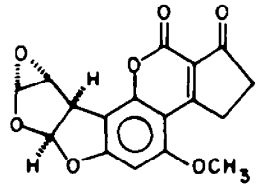


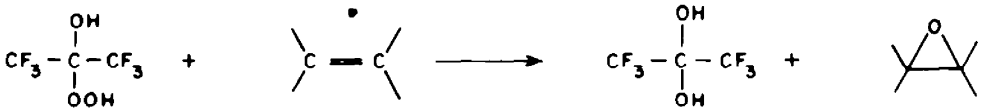
**3**



**4**

**5** = 8,9-deoxy **4**

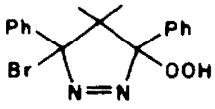
Peroxytrifluoroacetic acid, one of the most electrophilic peroxyacids is used for the epoxidation of electron deficient olefins; a convenient substitute for peroxytrifluoroacetic acid is 3,5-dinitroperbenzoic acid which can be stored for a long time.[28] Olefins are epoxidized with t-butylhydroperoxide (TBHP) in the presence of $Mo(CO)_6$ catalyst;[16] this method is used for the manufacture of propylene oxide. Olefins can be epoxidized with $H_2O_2$ in the presence of one of the following catalysts: o-nitrophenylseleninic acid;[29] 2,4-dinitrophenylseleninic acid;[29] hexafluoroacetone hydrate (**6**);[30] tetrachloroacetone[31] and arsonated polystyrene resins.[32] Hexafluoroacetone hydrate (**6**) reacts with $H_2O_2$ to produce 2-hydro-



**7** **6** (1)

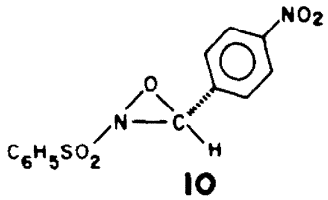
peroxyhexafluoro-2-propanol (**7**) which epoxidizes alkenes (eqn 1).[30] When arsonated polystyrene resin is used as catalyst workup is simple since the catalyst can be separated by filtration and recycled.

Some of the reagents which are suitable for the epoxidation of alkenes are: 3-bromo-4,5-dihydro-5-hydroperoxy-4,4-dimethyl-3,5-diphenyl-3H-pyrazole (**8**)[33] N-benzoyl peroxycarbamic acid (**9**),[34] 2-benzene sulfonyl-3-aryloxaziridine (**10**)[35] and peroxycarboximidic acid (**11**).[36] The reagent **11** epoxidizes arenes also. Alkenes can be epoxidized by treating with potassium caroate and acetone; epoxidation takes place through the intermediate dioxirane (**12**).[37] Polycyclic aromatic hydrocarbons and aza-arenes undergo epoxidation at the K-region when reacted with sodium hypochlorite and a phase transfer catalyst;[38] oxiranes **2**, **13** and **14** have been prepared through this route.




8


9

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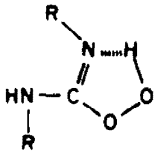
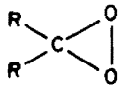



11

R = i-$C_3H_7$

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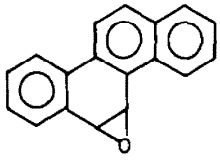


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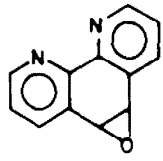
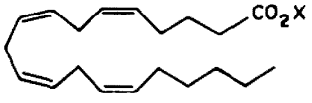



14

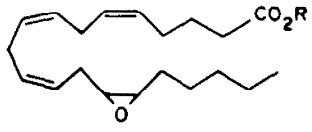
Shimizu and Bartlett[39] have shown that irradiation of an olefin in the presence of molecular oxygen and α-diketone (e.g. benzil) as sensitizer furnishes the corresponding oxirane in high yields. The main advantage of this route is that the reaction proceeds in the complete absence of nucleophiles[40] and thus can avoid formation of byproducts arising from reaction of nucleophiles with sensitive oxiranes. The formation of only the *trans*-epoxide from either *cis* or *trans*-alkene requires a stepwise mechanism by way of a freely rotating intermediate, in contrast to epoxidation with peracids. The photo-epoxidation proceeds via acylperoxy radical as the effective epoxidizing species.[41] Benzil sensitized photo-epoxidation of aflatoxin $B_1$ (**5**) furnishes the epoxide **4** which has been trapped with 3',5'-di-o-butyryl deoxyguanosine and hydrolysed with aqueous acid to give the $N^7$-guanine adduct.[5]

The peroxy acid **16** which can be prepared in a few steps from arachidonic acid (**15**) attacks selectively the 14,15-double bond to furnish the epoxy acid **17** which on esterification with diazomethane gives the ester **18**; in contrast, the intermolecular epoxidation of **15** with peroxy acid reagents is not regioselective.[42]

A recent review[18] by Rebek deals with new epoxidation reagents.



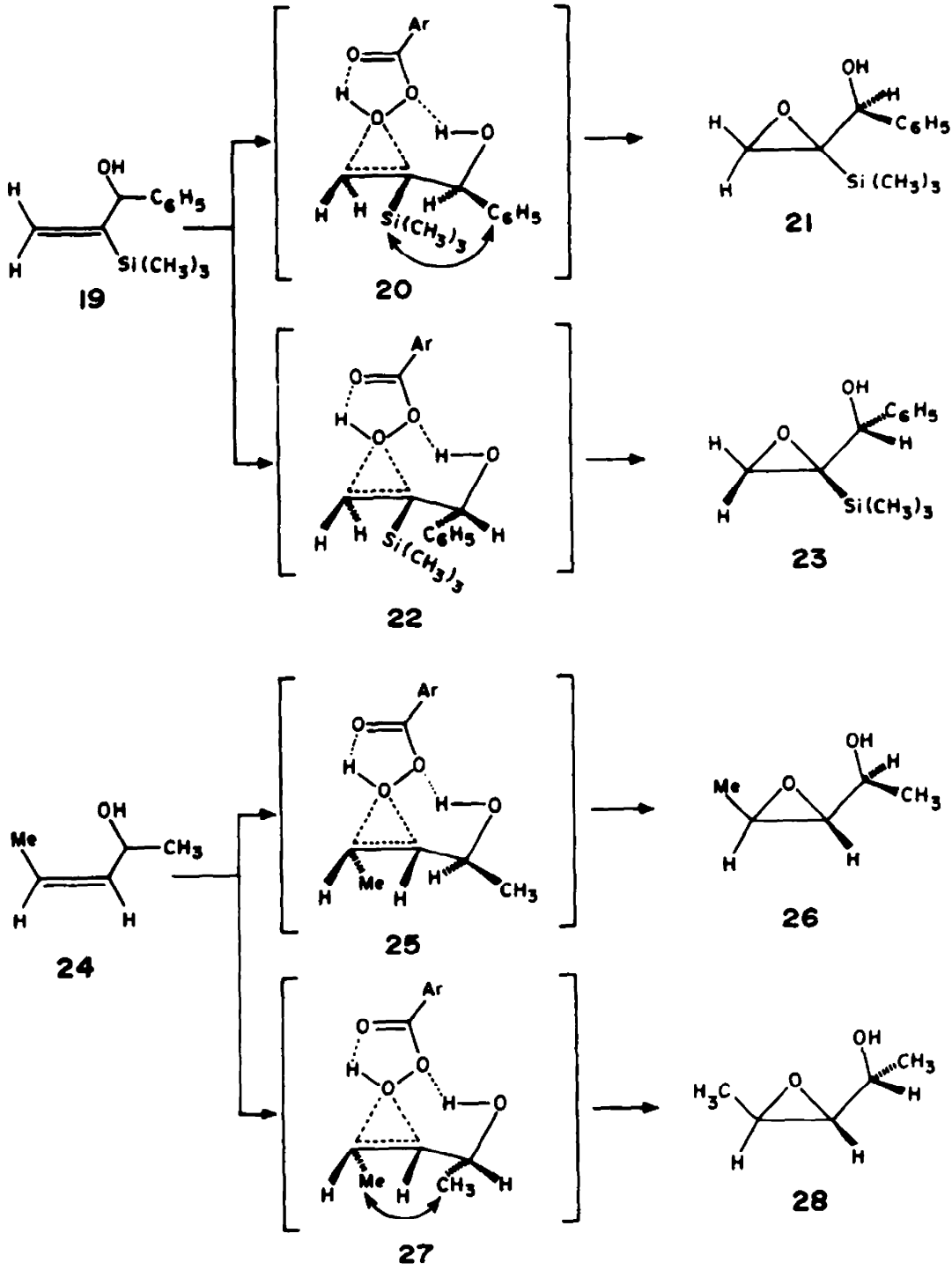

**15** X = H
**16** X = OH




**17** X = H
**18** X = $CH_3$

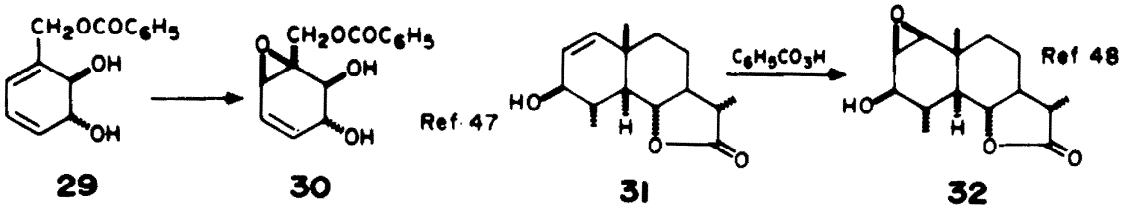
2. *Epoxidations of hydroxy alkenes and alkoxy alkenes.*

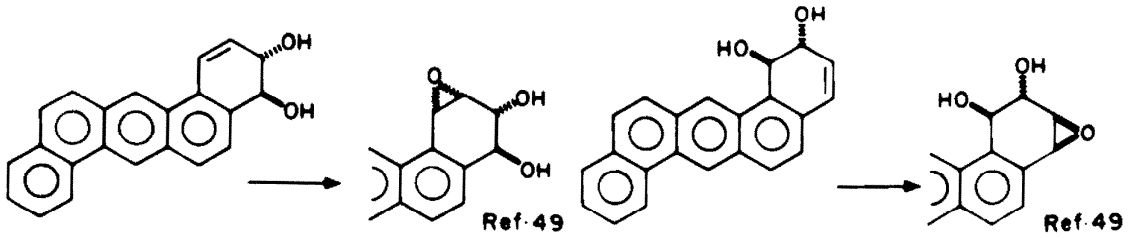
(a) *Epoxidations with organic peracids.* Henbest[43] showed that in the absence of severe steric interference allylic cyclohexenols are epoxidized stereoselectively by organic peracids to furnish *cis*-epoxyalcohols. A homoallylic hydroxyl can direct epoxidation only if it can get sufficiently near the double bond.[12] Epoxidation of medium ring allylic alcohols, e.g. cyclo-oct-2-en-1-ol, furnishes selectively *trans*-epoxy alcohols.[44] Epoxidation of acyclic allylic alcohols has been studied extensively. In many cases it is possible to predict the direction of asymmetric induction by comparing the steric interactions in the transition states leading to erythro and threo epoxy alcohols.[45] For example, epoxidation of **19** will furnish epoxyalcohol **21** through transition state **20** and epoxyalcohol **23** through transition state **22**. Since there is severe steric interference between $SiMe_3$ and $C_6H_5$ in transition state **20** it is to be anticipated that **23** and not **21** will be the major epoxidation product. It has been observed[46] that epoxidation of **19** furnishes exclusively **23**. Similarly in the epoxidation of **24** major diastereomer formed can be predicted to be **26** since the formation of **28** is not favoured due to steric interference between the

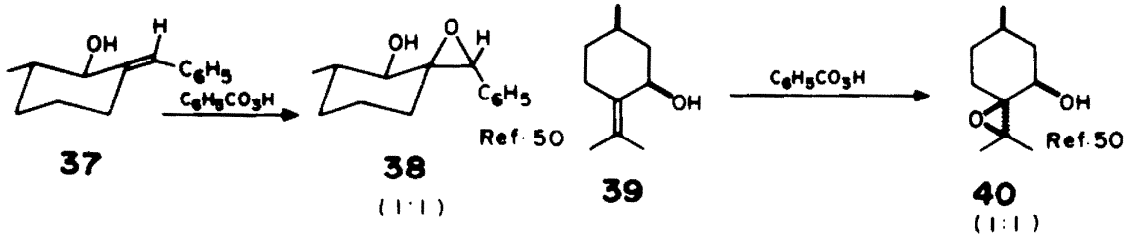


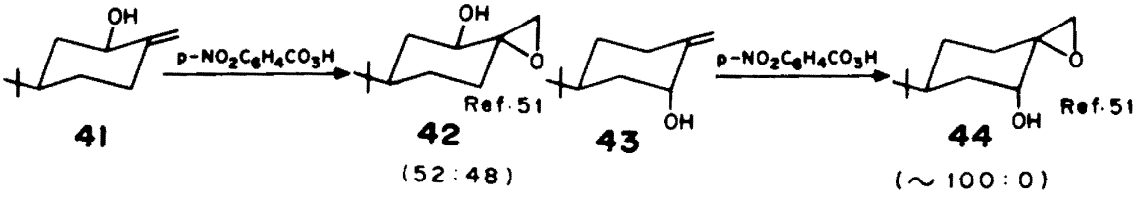

methyl groups in transition state 27. Some of the epoxyalcohols synthesised through peracid epoxidation of hydroxyalkenes are shown in Chart 1.

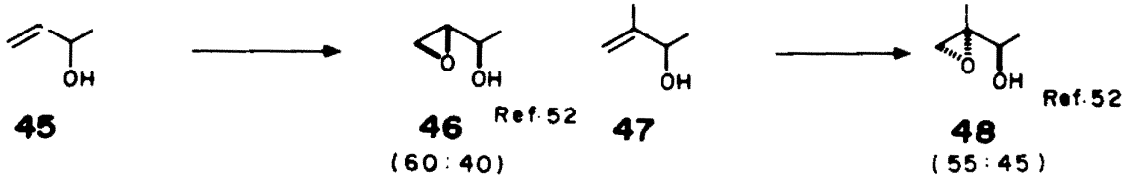
Selective benzoylation of allylic hydroxyl of 30 furnishes pipoxide.[47] The epoxy alcohol 32[48,60] is an intermediate for the synthesis of artecalin and tuberiferine. The stereoselective formation of 34 shows that dihydrodiols of polycyclic aromatic hydrocarbons, e.g. 33 which are sterically free to adopt the pseudoequatorial conformation are epoxidized cis to the allylic hydroxyl.[49] When bay region dihydrodiols, e.g. 35 sterically constrained to exist in the pseudodiaxial conformation are epoxidized, the directing influence of homoallylic hydroxyl which can come close to the double bond is greater than the directing influence of allylic hydroxyl.[49] The epoxidations of 37 and 41 show that allylic alcohols in which the


CH2OCOC6H5
OH
OH
29
CH2OCOC6H5
O
OH
OH
30
Ref. 47
HO
H
O
O
31
C6H5CO3H
Ref. 48
HO
H
O
O
32


OH
OH
33
O
OH
OH
Ref. 49
34
OH
HO
35
OH
HO
O
Ref. 49
36


OH
H
C6H5
C6H5CO3H
37
OH
O
H
C6H5
Ref. 50
38
(1:1)
OH
39
C6H5CO3H
OH
O
Ref. 50
40
(1:1)


OH
p-NO2C6H4CO3H
41
OH
O
Ref. 51
42
(52:48)
OH
43
p-NO2C6H4CO3H
O
OH
Ref. 51
44
(~100:0)


OH
45
O
OH
Ref. 52
46
(60:40)
OH
47
O
OH
Ref. 52
48
(55:45)

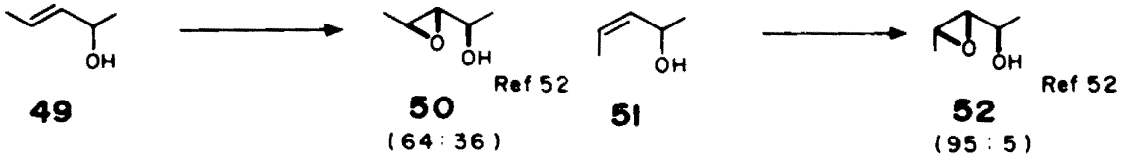
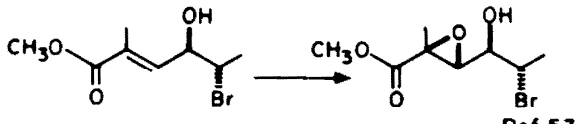
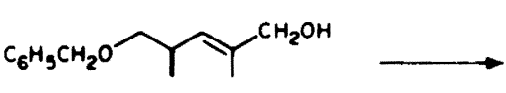

OH
49
O
OH
Ref 52
50
(64:36)
OH
51
O
OH
Ref 52
52
(95:5)

Chart 1.

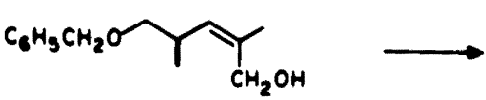
53 → 54 (95:5)



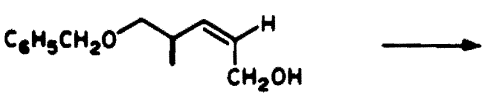
55 → 56 Ref. 53



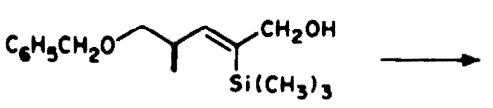
57 → 58 (>25:1) Ref. 54



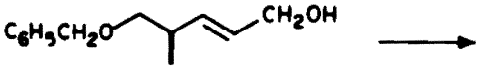
59 → 60 (15:1) Ref. 54



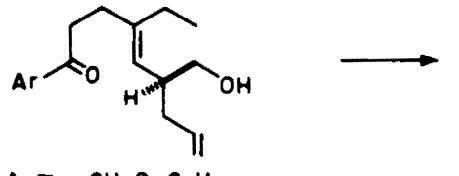
61 → 62 (~100:0) Ref. 55



63 → 64 (~100:0) Ref. 56



65 → 66 (3:2) Ref. 56



67 → 68 (>95:5) Ref. 57

Chart 1 (*Contd.*)

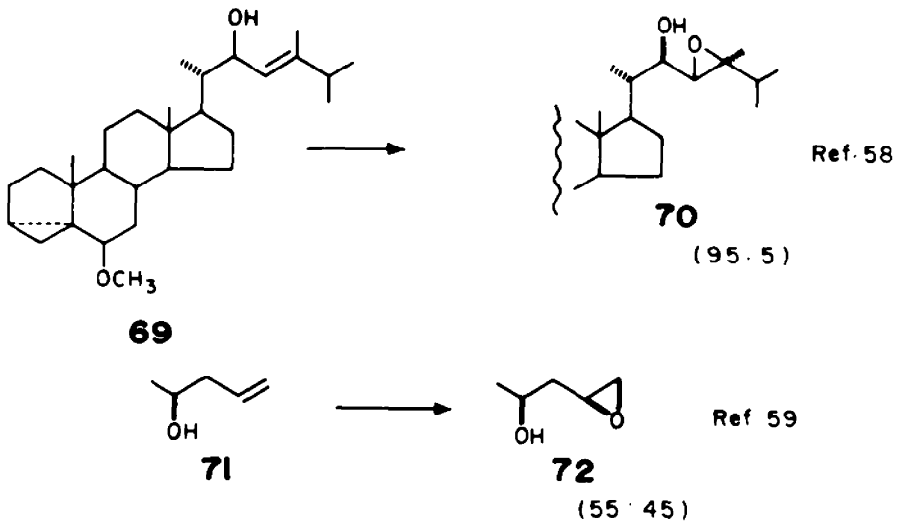
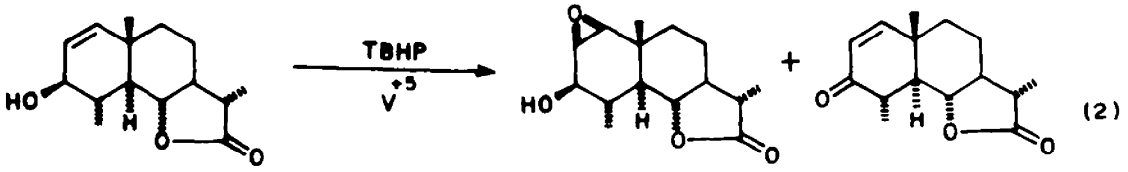


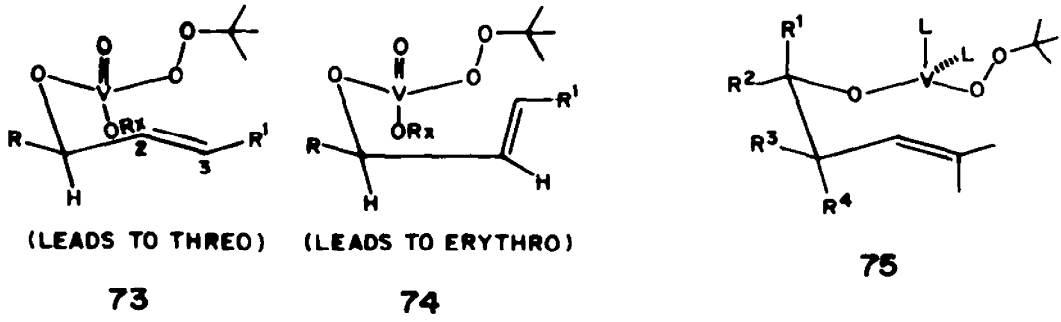

Chart 1. Epoxyalcohols prepared through epoxidation of hydroxyalkenes with peroxyacids; the peroxyacid is MCPBA unless otherwise stated. Diastereomeric ratio is given in brackets; the major diastereomer only is shown.

hydroxyl is almost eclipsed with the double bond do not undergo stereoselective epoxidation. The epoxyalcohol **56** was transformed to a diepoxide which proved useful in assigning the stereochemistry of the side-chain of hedamycin. The epoxy alcohols **64**, **66** and **68** are intermediates for the synthesis of polyether antibiotics. Alcohol (**70**) is an intermediate for the synthesis of brassinolide.

(b) *Epoxidations with hydroperoxides in the presence of transition metal catalysts.* Sharpless[61] has shown that vanadium catalyzed epoxidation of cyclic allylic alcohols with *tert*-butyl hydroperoxide (TBHP), one of the most stable organic peroxides known, is highly stereoselective, the epoxidation taking place from the side cis to hydroxyl group. Medium ring cyclic allylic alcohols, e.g. cyclo oct-2-en-1-ol, also furnish *cis*-epoxyalcohols.[44] It has been observed that TBHP/V epoxidation of allylic cyclohexenols having quasi-equatorial hydroxyl can in some cases, e.g. eqn (2) furnish the corresponding




α, β-unsaturated ketones besides the expected epoxy alcohols.[44,60] Vanadium catalyzed epoxidation of acyclic allylic alcohols has been studied extensively. The E-allylic alcohol (**49**) furnishes a 60:40 mixture of erythro (**87**) and threo-epoxyalcohols (**50**).[62] Threo-epoxyalcohol is formed in smaller amounts since in the transition state **73** there is steric interaction between $OR_x$ and C-3.[62] The direction of asymmetric



induction during epoxidation of acyclic homoallylic alcohols can be predicted[63] by considering steric interference in the transition state 75; stereoselectivity is high when alkyl groups can be equatorially oriented ($R_2$ and $R_3$) in the transition state. High stereoselectivities have been observed for the epoxidations of some acyclic bishomoallylic alcohols. Some of the epoxy alcohols synthesized through vanadium catalysed TBHP epoxidation of hydroxy alkenes are shown in Chart 2. Oxirane (77) is an

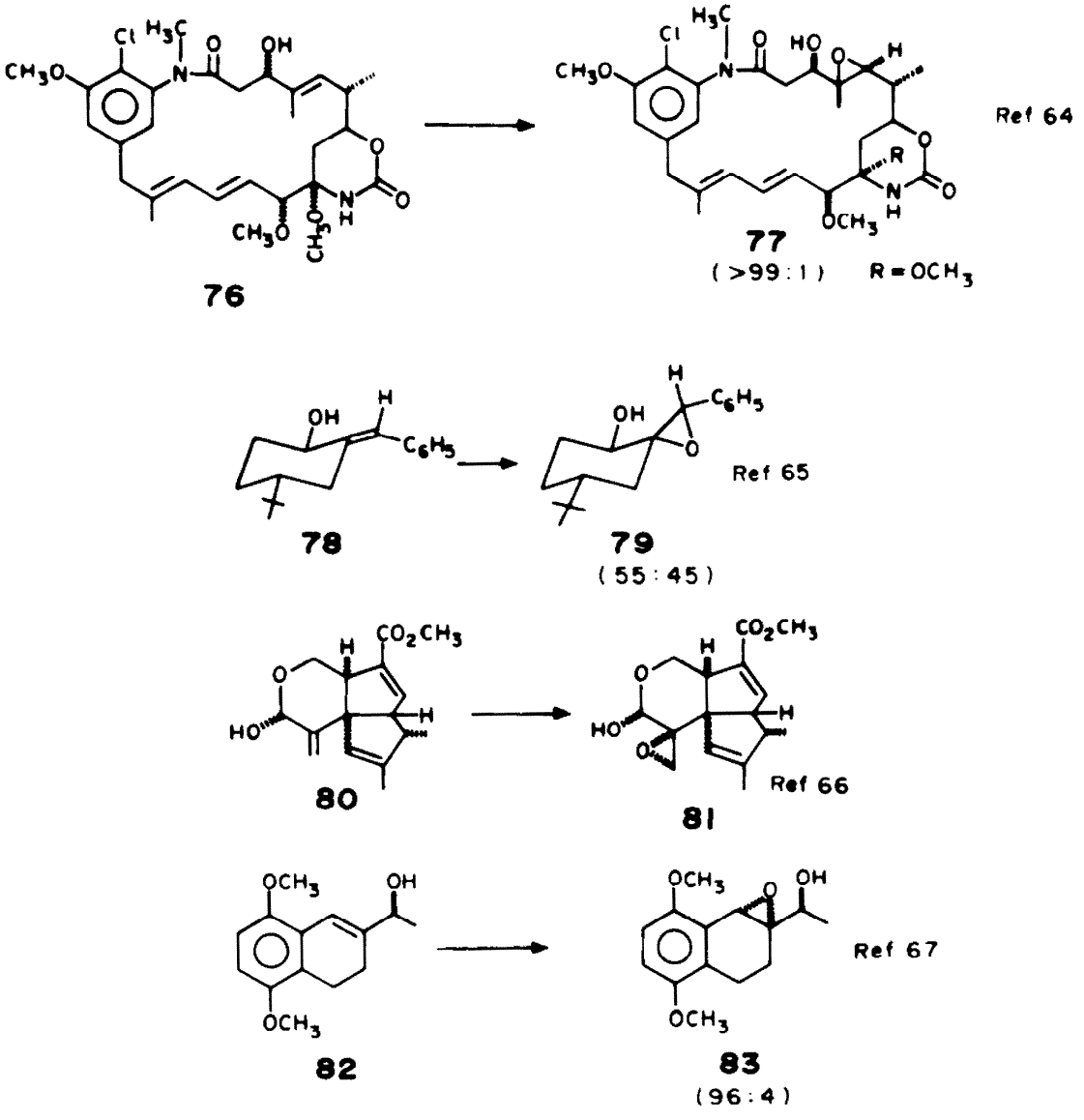



Chart 2.

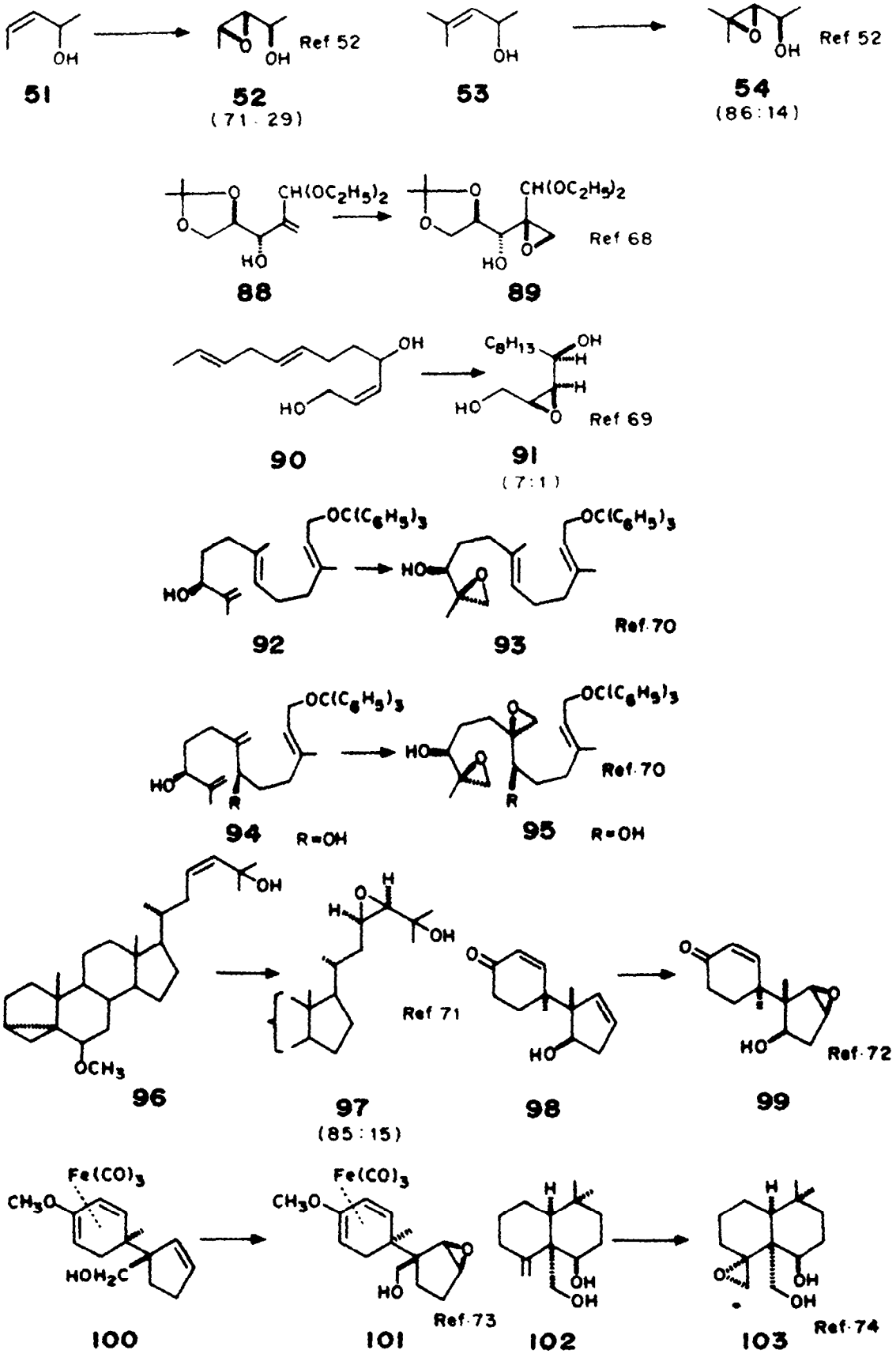



Chart 2 (*Contd.*)

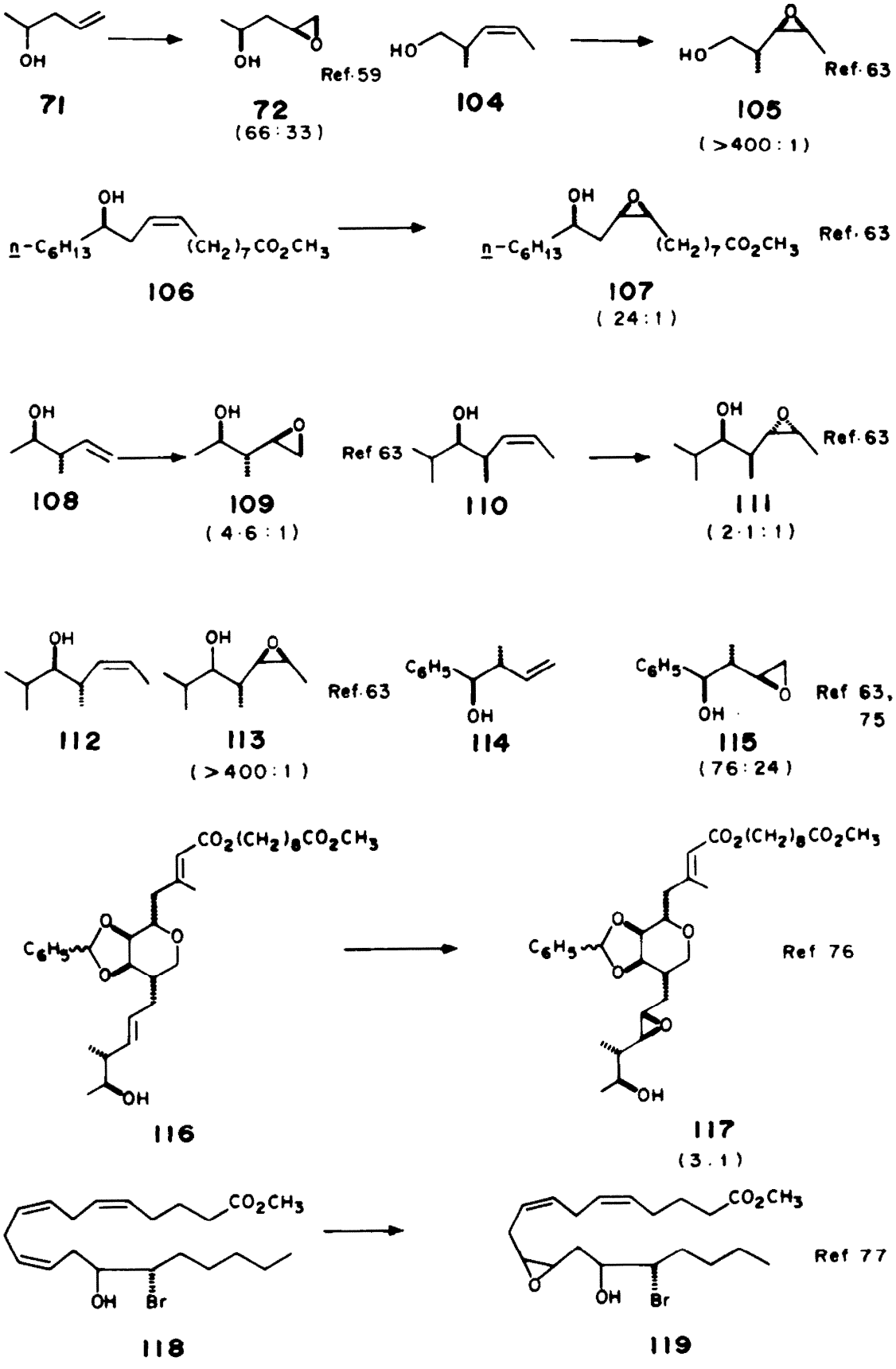



Chart 2 (*Contd.*)

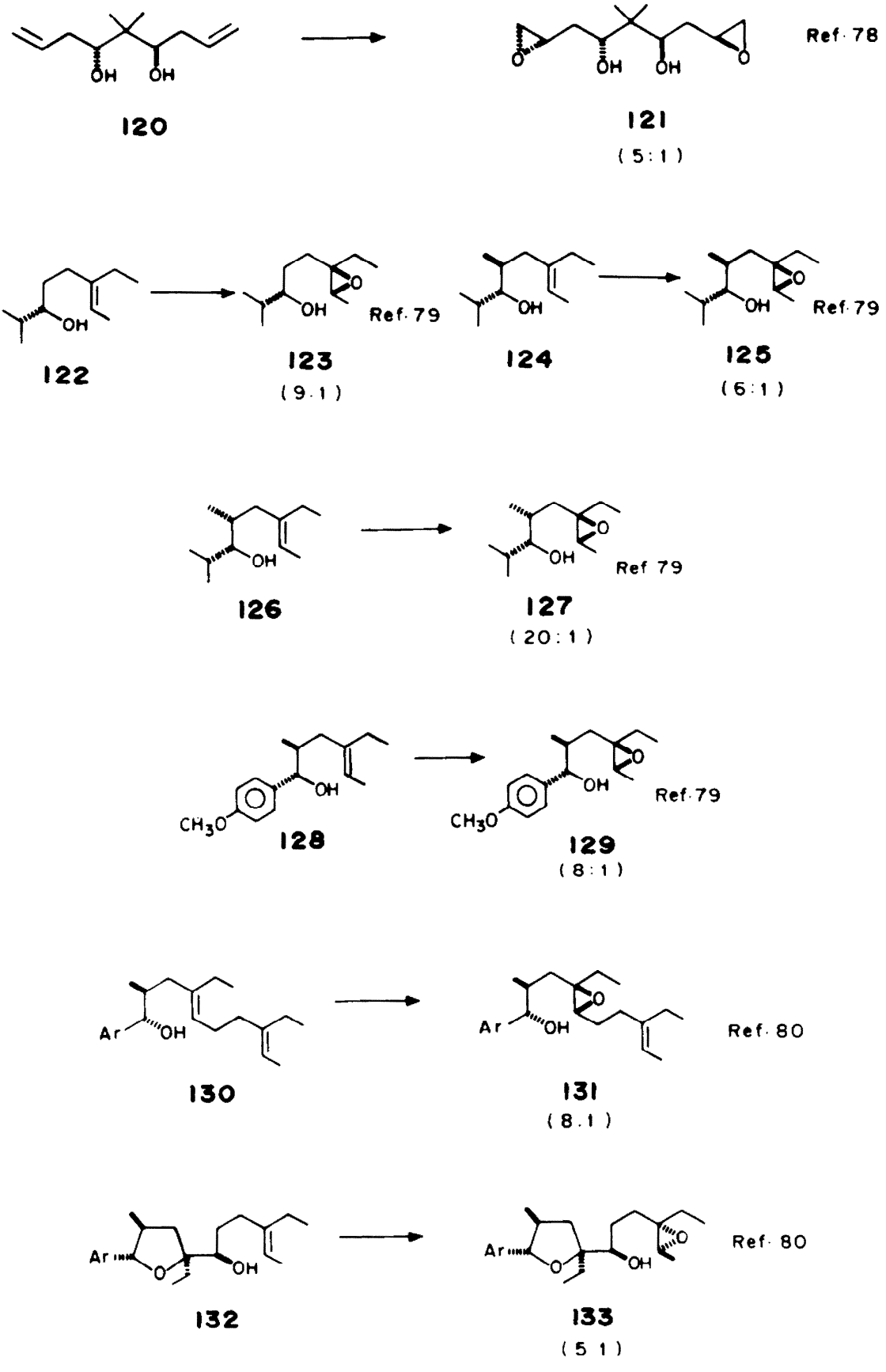


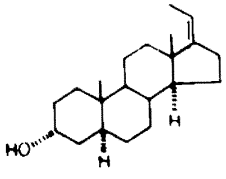

Chart 2. Epoxyalcohols prepared through epoxidation of hydroxyalkenes with TBHP/$V^{+5}$.

intermediate for the synthesis of maytansine.[64] The epoxidation of **78** shows that when hydroxyl group is nearly eclipsed with the ethylenic linkage epoxidation is not stereoselective. The syntheses of dl-pentalenolactone from **81**, optically active anthracyclinones from **83**, 2-epihamamelose from **89**, dl-cerulenin from **91**, juvenile hormone JH-2 from **93**, JH-1 from **95**, 24(R), 25-dihydroxycholesterol from **97**, trichodermol from (**99**), a trichothecin analogue from **101**, pseudomonic acid A from **117**, a mixture of 11-hydroxyeicosatetraenoic acid (11-HETE) and 12-HETE from **119**, pedaldehyde from **121** and lasalocid A from **131** are reported in literature.

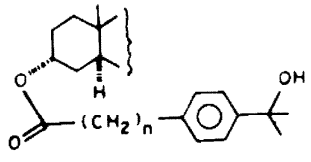
The rate of vanadium catalyzed epoxidation is greatly enhanced by the presence of an allylic hydroxyl group; on the other hand, the introduction of a hydroxyl group into allylic position reduces the rate of peroxy acid epoxidation, compared with the parent olefin.[61] Consequently during epoxidation of polyunsaturated allylic alcohols, e.g. **76** and **90** high regioselectivity is observed with the TBHP/V system but not with MCPBA.

Allylic and homoallylic alcohols are epoxidized with hydroperoxides in the presence of aluminium t-butoxide.[81] In a few cases, the direction of asymmetric induction with Al catalyst has been found to be opposite to the direction of asymmetric induction with vanadium catalyst.

Breslow[82] has shown that a hydroxyl group which is separated from an ethylenic linkage by several C–C bonds can under favourable conditions serve as a convenient handle for directing epoxidation; a suitable template is attached by taking advantage of hydroxyl group as illustrated by the conversion of **134** to **135a**. The alcohol **135a** is epoxidized when heated under reflux with TBHP in toluene in the




**134**

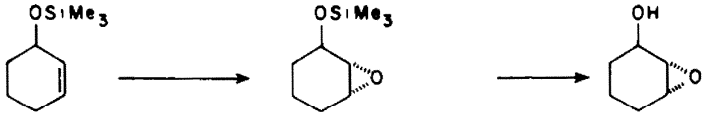



(Ref 82)

**135** a n=1
b n=2

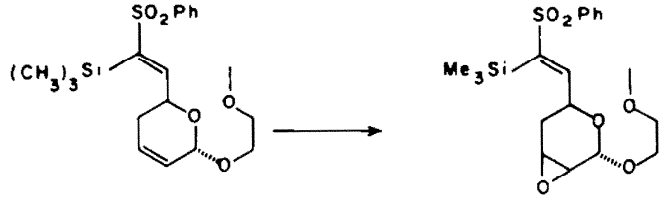
presence of $Mo(CO)_6$; the epoxidation has been shown to be intramolecular. It is obvious that the alcohol **135a** can take up a conformation in which the hydroxyl group is sufficiently close to the ethylenic linkage. The success of this approach depends on the choice of the template. While alcohol **135a** can be epoxidized, the higher homologue **135b** does not undergo epoxidation under similar conditions.

(c) *Epoxidation of alkoxyalkenes.* Ethers of cyclic allylic alcohols undergo stereo-selective epoxidation from the less hindered side, which is trans to alkoxy group. MCPBA epoxidation of **136** furnishes **137** which has been transformed[83] to trans-epoxy alcohol **138**. MCPBA epoxidation of **139** furnishes **140**, an intermediate for the synthesis of maytansine.[84]




Ref 83

**136** **137** **138**

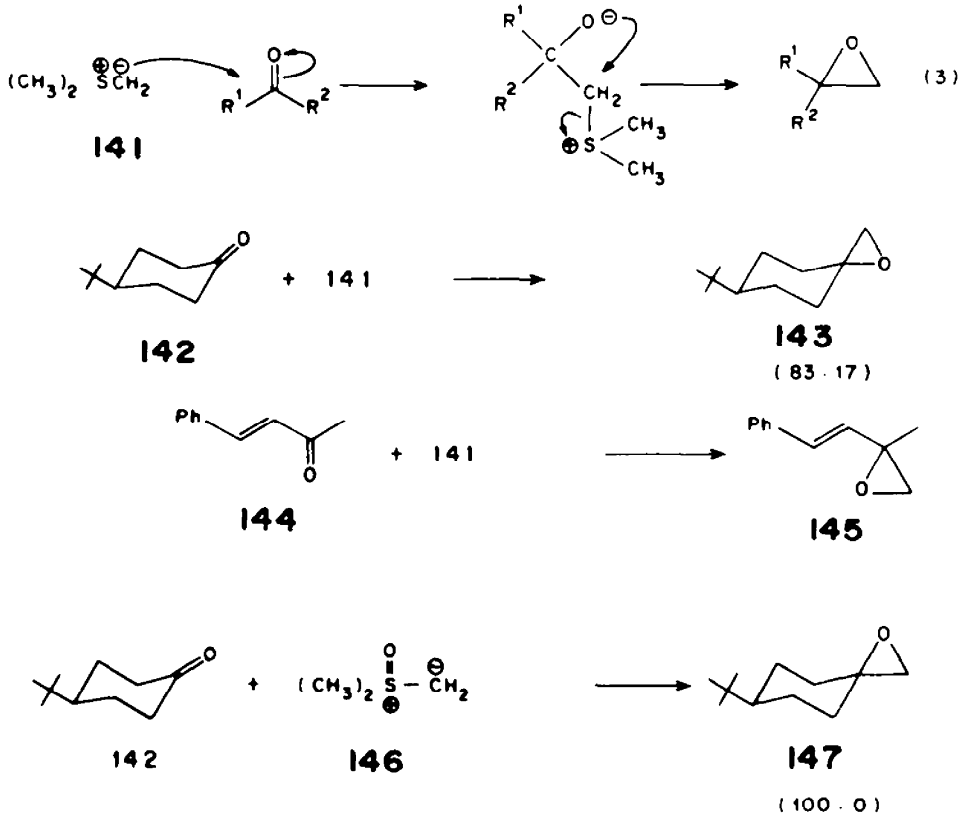



Ref 84

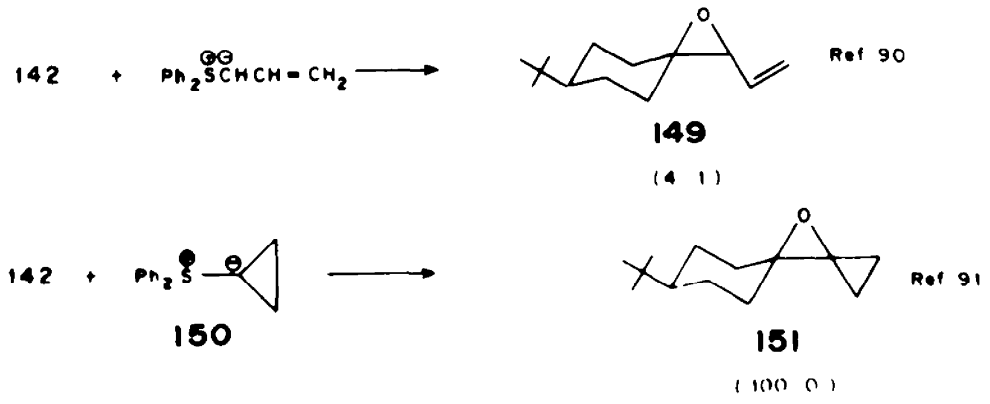
**139** **140**

3. *Synthesis of oxiranes via carbonyl additions*

(a) *Sulphur ylides.* Since carbonyl compounds are readily available they are attractive intermediates for the synthesis of oxiranes. The use of diazomethane[85] and stabilized α-haloanions[86,87] for the synthesis of oxiranes is known for a long time. Synthesis of oxiranes via condensation of aldehydes and ketones with sulphur ylides has become an important synthetic technique.[88] Dimethylsulphonium methylide (**141**) a nucleophilic reagent reacts with ketones to furnish oxiranes through methylene transfer (eqn 3). Saturated ketones as well as α, β-unsaturated ketones are transformed to oxiranes (**143**, **145**). Dimethyloxosulphonium methylide (**146**) is also used for effecting methylene transfer (e.g. **147**). The major product formed by reacting cyclohexanones with **141** involves axial attack by the reagent; in the case of **146** the major product is formed through equatorial attack. α, β-Unsaturated ketones furnish cyclopropane derivatives and not oxiranes when reacted[89] with **146**.



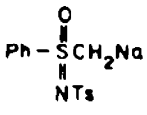

Like methylides, the alkylides react with aldehydes and ketones to give substituted oxiranes (e.g. **149**, **151**).



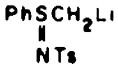
Carbanions derived from *N*-p-toluenesulphonyl sulphoximines (e.g. **152**) and *N*-p-toluenesulphonyl sulphilimines (e.g. **153**) react as methylene transfer agents with aldehydes and ketones.[92]

The preparation of a number of oxiranes using sulphur ylides and utilization of some of the oxiranes as intermediates in organic synthesis has been reviewed.[88]

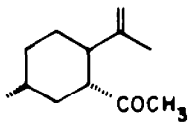
Oxirane formation from **154** proved troublesome with dimethylsulphonium and dimethyloxosulphonium methylides.[93] The less basic anion from dimethylsulphoxide p-toluene sulphoximine afforded **155** in 90% yield as 5:6-mixture of epimers.



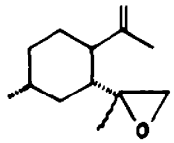
**152**



**153**

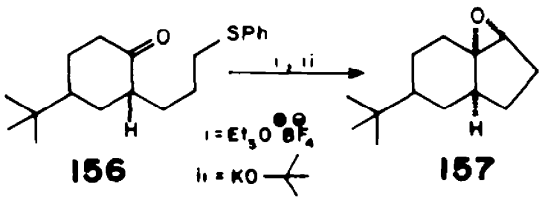


**154**

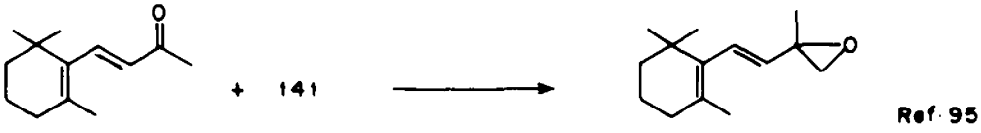


**155**

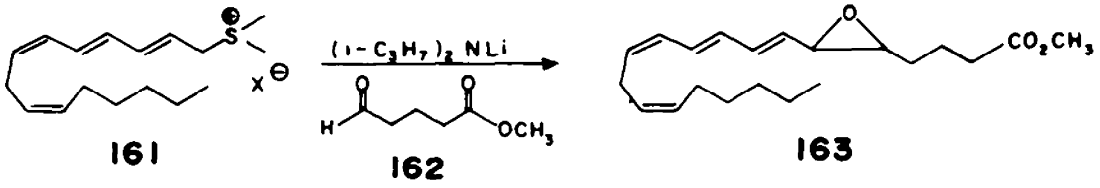
Oxiranes have been prepared through intramolecular sulphur ylide additions to ketones (e.g. eqn 4). Some of the oxiranes synthesised recently using sulphur ylides are given below (**160**, **163**, **166**).



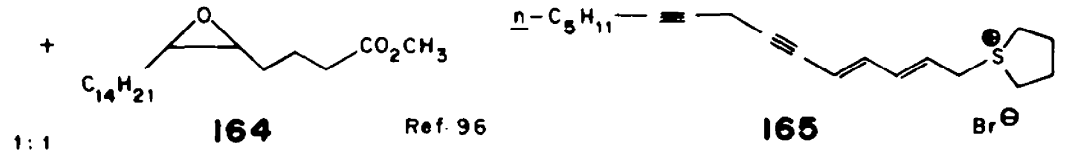
**156** **157** (85:15) **158** (4) Ref 94



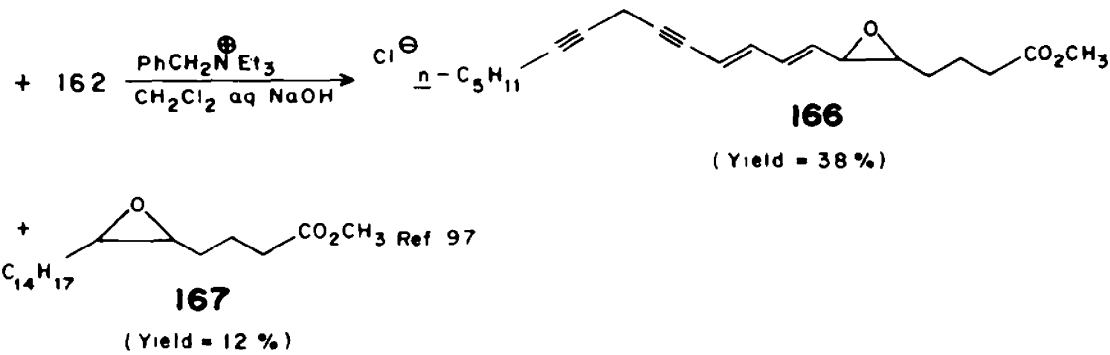
**159** **160** Ref 95



**161** **162** **163**



**164** Ref 96 **165**



**166** (Yield = 38%)

**167** (Yield = 12%)

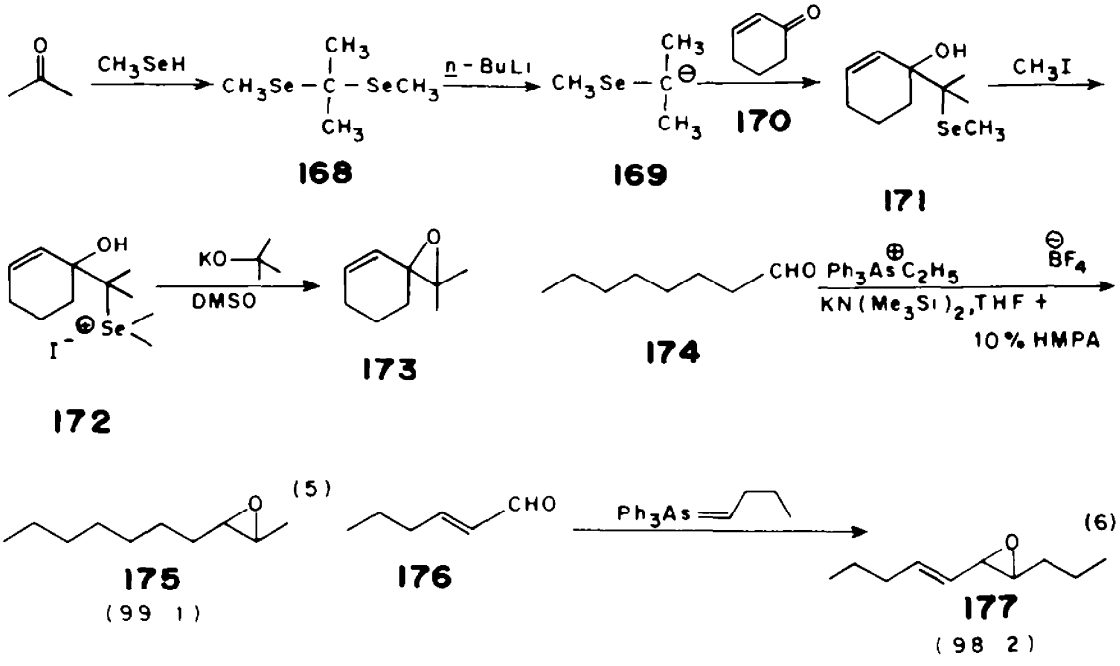
Oxirane **160** is an intermediate for vitamin A synthesis. Since sulphur ylides react with aldehydes and ketones at low temperatures they are well suited for the preparation of sensitive oxiranes. Leukotriene A (LTA) methylester (**163**) an unstable biologically important[98] oxirane has been synthesised[96] from ylide **161**. Hydrogenation[97] of **166** furnishes **163**.

(b) *Selenium ylides.* Selenium ylides have been generated *in situ* and have been found to convert non-enolizable aldehydes and ketones into oxiranes.[99]

(c) *Synthesis of α, β-unsaturated oxiranes via α, β-unsaturated-α'-seleno alcohols.* α, β-Unsaturated oxiranes have been synthesised based on the nucleophilic addition of α-seleno carbanions to α, β-unsaturated ketones and α, β-unsaturated aldehydes.

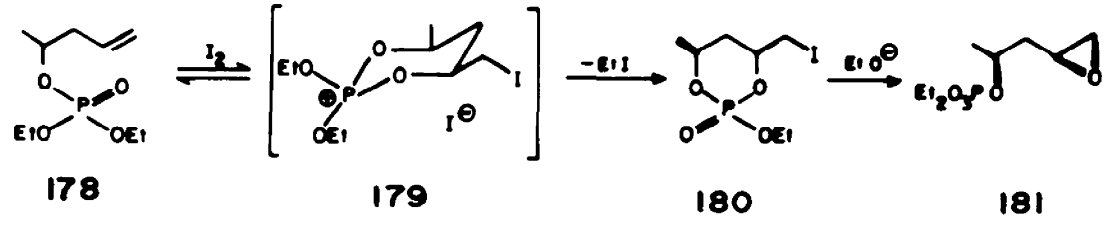
The oxirane (**173**) has been prepared as shown in formulae chart.[100] α-Seleno carbanions are formed readily and normally undergo 1,2-addition when reacted with conjugated ketones and aldehydes.

(d) *Arsonium ylides.* A number of aldehydes react cleanly with arsonium ylides to yield trans oxiranes with stereoselectivity ≥ 50:1 (e.g. eqns 5 and 6). The stereoselectivity depends on the arsonium salt counterion.[101]

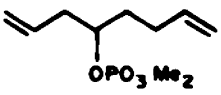



4. *Phosphate extension and halolactonizations*

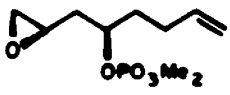
Bartlett has shown that the phosphate **178** which can be prepared from **71** reacts with iodine to furnish the thermodynamically controlled product **180** in which $CH_3$ and $CH_2I$ substituents are cis-related (diequatorial).[59] The electrophilic attack by iodine on the double bond in **178** is very facile due to neighbouring group participation of the nucleophilic phosphate. Treatment of **180** with sodium ethoxide furnishes **181** which contains less than 2% of the diasteromeric oxirane. It may be noted that the stereoselectivity in the synthesis of oxirane **72** via epoxidation of **71** with MCPBA (Chart 1) or TBHP/V (Chart 2) is very poor.




The "phosphate extension" approach has been used to transform the phosphate **182** regio- and stereo-selectively to the oxirane **183**, an intermediate for the synthesis of methyl nonactate.[103]




182

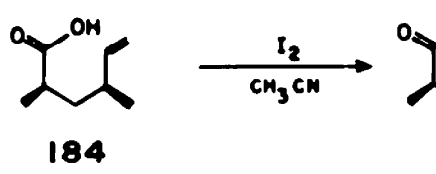



183

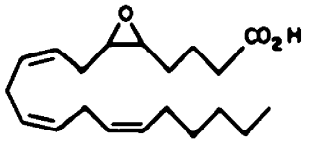
Reaction of γ, δ or δ, ε-unsaturated acyclic carboxylic acids with iodine in acetonitrile in the absence of a base has been shown to furnish stereoselectively the iodolactones with thermodynamic control via cyclic intermediates.[104] This reaction is the basis of an excellent method for the stereoselective epoxidation of acyclic olefinic carboxylic acids.[104] The acid **184** is converted to the iodo lactone **185** contaminated with less than 5% of isomeric material. Alkaline methanolysis of **185** leads to the oxirane **186** an intermediate for the synthesis of α-multistriatin.[105]

Iodolactonization of arachidonic acid (**15**) with $NaHCO_3$–$KI_3$ and treatment of the resulting iodolactone with base furnishes regioselectively *cis*-5,6-epoxy arachidonic acid.[42]

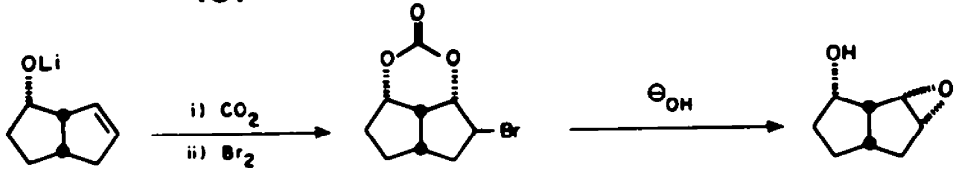
The oxiranes **190** and **193** have been synthesized stereo-selectively employing halolactonization.[107] The oxirane **193** is an intermediate for the synthesis of erythromycin.[108]



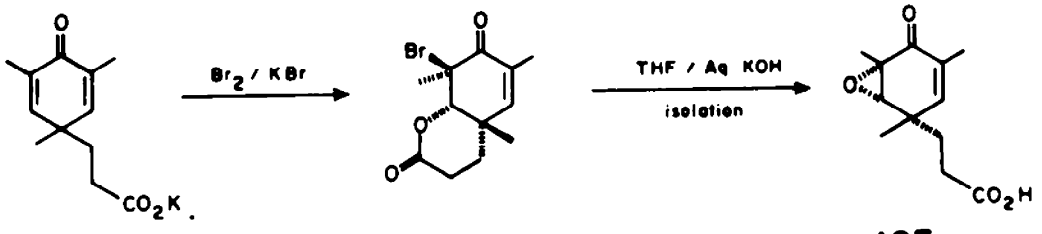

184 185 186




187



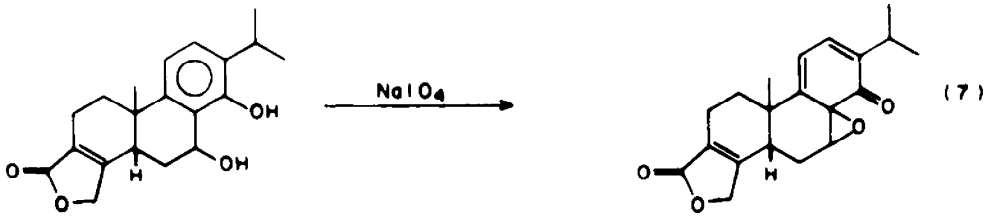

188 189 190




191 192 193

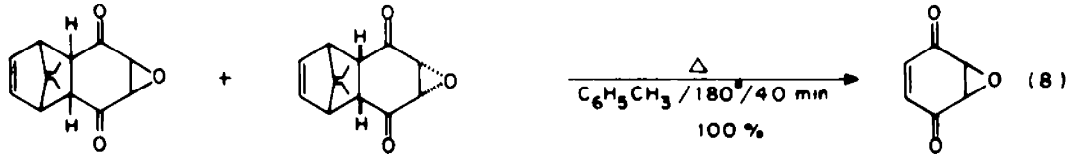
5. *Other methods for preparation of oxiranes*

(a) *o-Hydroxy benzyl alcohols; reaction with sodium periodate.* Oxidation of o-hydroxy benzyl alcohols with sodium periodate furnishes spiro-epoxy-2,4-cyclohexadienones (eqn 7).[109] The parent unsubstituted spiro-epoxy-2,4-cyclohexadienone cannot be prepared by this method as it dimerizes rapidly.[110] Oxirane **195** is an intermediate for the synthesis of triptolide and triptonide.[109]



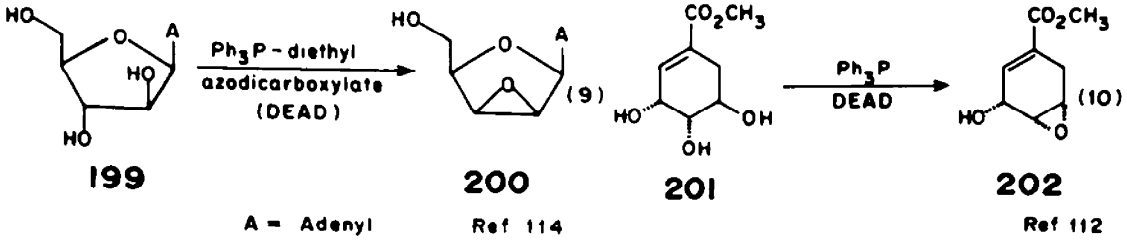

194 195

(b) *Retro-Diels–Alder reaction.* Quinone epoxides have been prepared via the retro-Diels–Alder reaction (eqn 8).[111]




196 197 198

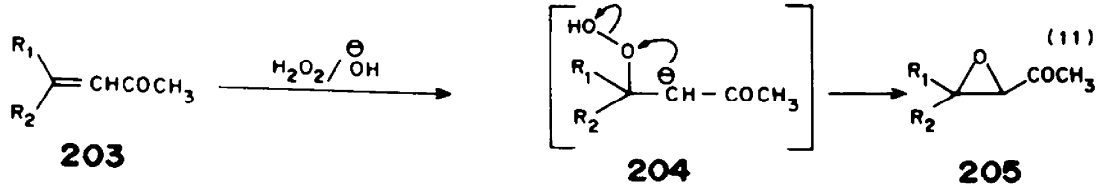
(c) 1,2-*Diols*; *reaction with triphenyl phosphine and diethyl azodicarboxylate.* Oxiranes have been prepared from 1,2-diols through a "one-pot" reaction by employing the reagents triphenylphosphine and diethyl azodicarboxylate.[112] One of the hydroxyl groups is transformed[113] to -$OPPh_3$; the oxirane is then formed according to eqn (16) if the OH and leaving groups are *trans* antiparallel. Some oxiranes prepared by this method are shown below (eqn 9, 10).



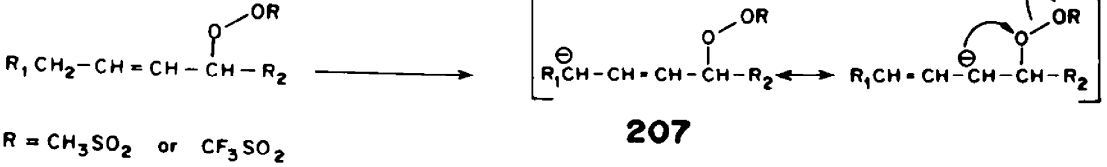

199 200 201 202

A = Adenyl Ref 114 Ref 112

(d) *Oxiranes from unsaturated hydroperoxides.* α, β-Unsaturated ketones react with $H_2O_2$ and alkali to furnish α, β-epoxy ketones. In this reaction the conjugated ketone is initially transformed to the stabilized anion **204** (eqn 11).[115,116] Hence, oxirane formation from an unsaturated activated hydroperoxide can be anticipated if the anion **207** can be generated.

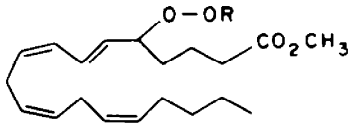



203 204 205

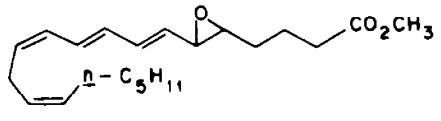



206 207

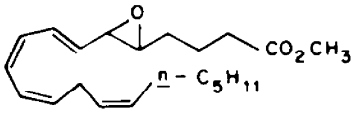
Leukotriene A (LTA) is enzymically derived from arachidonic acid via (*S*)-5 HPETE. Biomimetic conversion of 5-HPETE methyl ester **208** to LTA methyl ester **211** has been carried out.[117,118] This involves transformation of **208** to the mesylate (or triflate) and treatment of the mesylate with a hindered base to furnish a mixture of **211**, **212** and **213**. 15-HPETE methyl ester has also been converted to a mixture of oxiranes.[117]



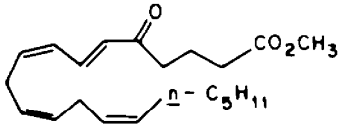
**208** R = H
**209** R = $SO_2CH_3$
**210** R = $SO_2CF_3$



**211**

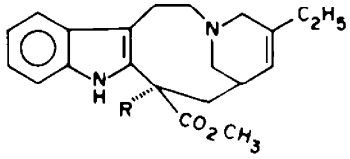


**212**

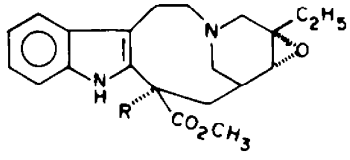


**213**

Anhydrovinblastine is oxidized[119] by air to leurosine (**215**). This transformation can be brought about by agitating a solution of **214** in an organic solvent with air and enzyme systems are not necessary. It has been suggested that a hydroperoxide is an intermediate in this transformation.



R = 10 - Vindolinyl
**214**

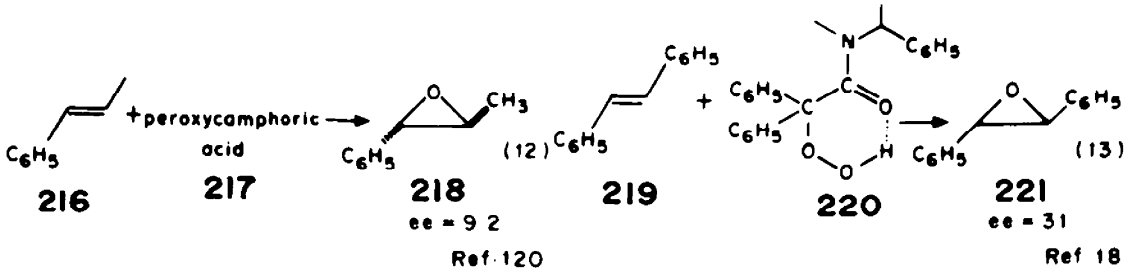


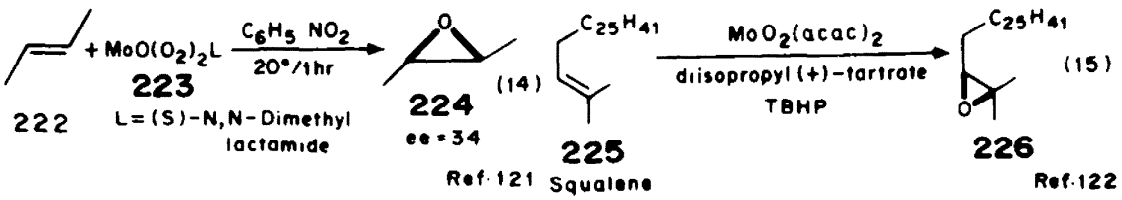
R = 10 - Vindolinyl
**215**

6. *Preparation of optically active oxiranes*

Oxiranes are versatile intermediates in synthetic organic chemistry. Since many of the synthetic targets are biologically active compounds having chiral centers, it is necessary that the compounds synthesised from oxiranes should have high optical purity. This, in turn, requires that the oxiranes used as synthetic intermediates should be optically pure. The methods available for preparing optically pure oxiranes are reviewed.

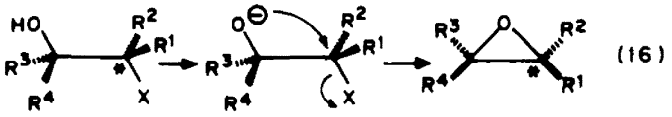
(a) *Enantioselective epoxidation of alkenes.* Optically active oxiranes have been prepared by enantioselective epoxidation of unfunctionalized prochiral alkenes; some of the non-enzymatic routes are given below (eqns 12–15).



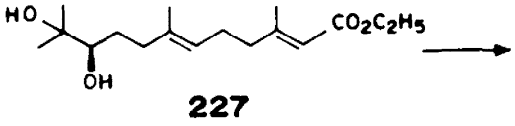


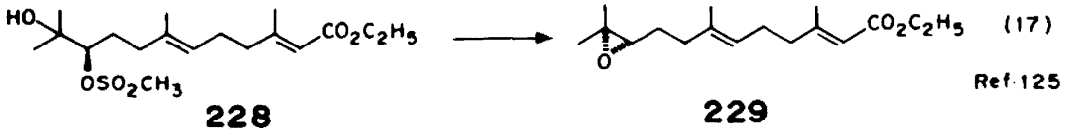

Microbial systems exhibit high enantioselectivity due to enzymes. Epoxidation of 1-octene by *Pseudomonas oleovorans* in a two phase system furnishes 1,2(R)-epoxyoctane of high optical purity (ee = 70).[123] Epoxidation of 1-hexadecene by *corynebacterium equi* IFO 3730 furnishes 100% optically pure 1,2(R)-epoxyhexadecane.[124]

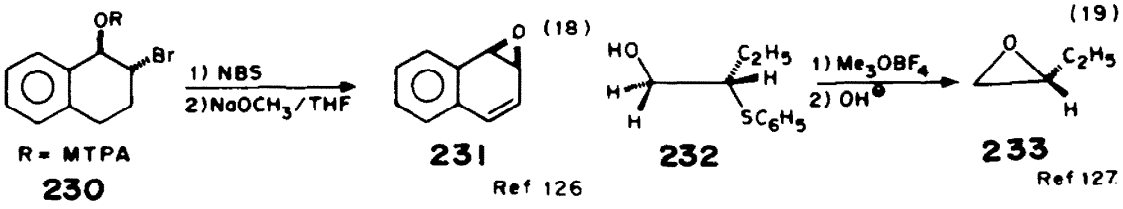
(c) *Optically active oxiranes from racemic precursors.* An alcohol with an appropriate leaving group (X) in the β-position can be transformed to an epoxide by treatment with a suitable base, involving inversion of configuration at the starred carbon atom (eqn 16).

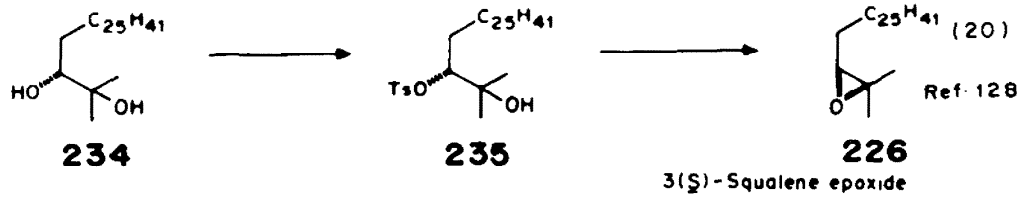


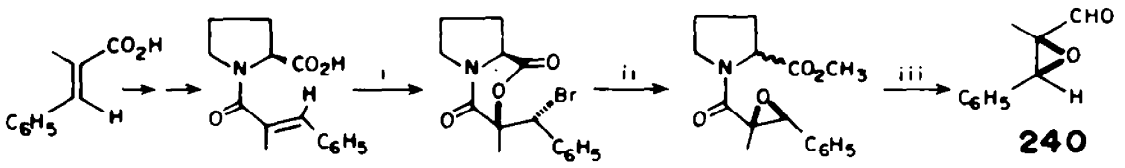

Efficient methods are now available for the resolution of racemic alcohols. The racemic alcohols are converted to: (a) esters of (−)-(S)-α-methoxy-α-trifluoromethyl phenyl acetic acid (MTPA) or (b) esters of 3β-acetoxyetienic acid or (c) reacted with enantiomerically pure 1-(1-napthyl) ethyl isocyanate to furnish carbamate derivatives. The resulting mixture of diastereomeric esters or carbamates are separated employing chromatographic methods and the ester or carbamate thus purified is converted to enantiomerically pure alcohol. Some of the alcohols thus resolved and then transformed to epoxides are shown below (eqns 17–20).



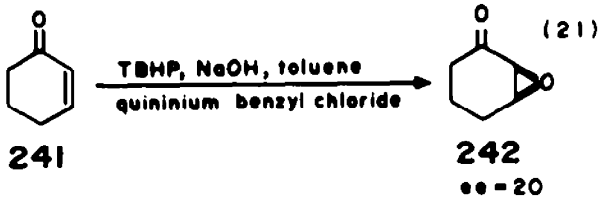





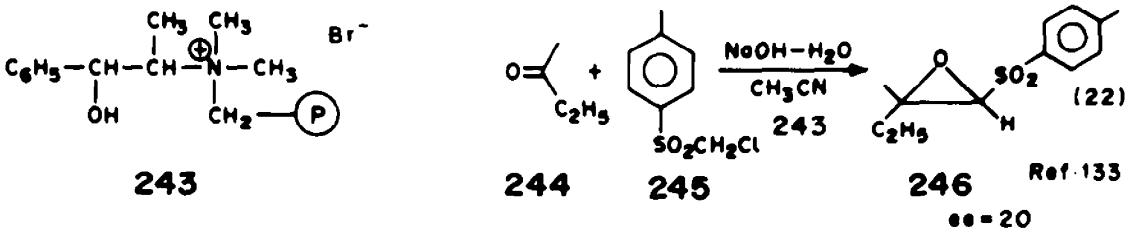

(c) *α, β-Epoxyaldehydes, α, β-epoxyketones and α, β-epoxysulphones.* Efficient asymmetric synthesis of optically active α, β-epoxyaldehydes from α, β-unsaturated acids has been achieved employing a sequence of reactions (e.g. **236**→**240**);[129] the key step in the synthesis is the stereospecific formation of the bromolactone **238**.

2,3-Epoxycyclohexanone has been obtained in optically active form by epoxidation of cyclohexenone (eqn 21).[130] Wynberg has shown that the chiral catalyst, quininium benzylchloride is capable of introducing a considerable degree of asymmetry into products from many different reactions.[131]

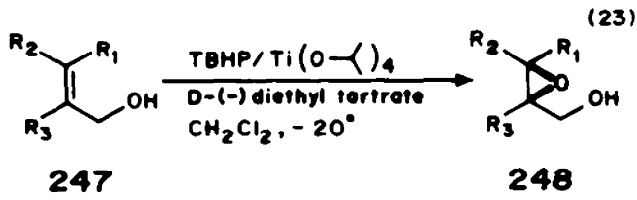



Epoxidation of chalcone with $H_2O_2$–NaOH in a triphase system consisting of toluene, water and the chiral polypeptide poly [(*S*)-alanine] as the phase transfer catalyst furnishes the corresponding α, β-epoxyketone in high (>90%) optical yields.[132]

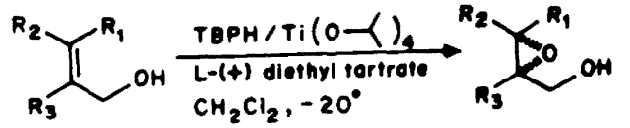
Polystyrene-divinyl benzene-N-methyl-ephedrinium chloride (**243**) prepared from N-methyl-ephedrine has been used as chiral catalyst for the asymmetric synthesis of α, β-epoxysulphones (eqn 22).[133]




(d) *Enantioselective epoxidation of allyl alcohols.* One of the most important developments in enantioselective epoxidations is the recent discovery by Katsuki and Sharpless of a new metal catalyzed asymmetric epoxidation process.[134] A wide variety of prochiral allyl alcohols have been epoxidized with TBHP–Ti $(OPr^i)_4$ and either (+)- or (−)-dialkyl tartrate to furnish enantiomerically pure (ee > 90%) epoxyalcohols (eqns 23, 24). The absolute configuration of the epoxyalcohol can be predicted.

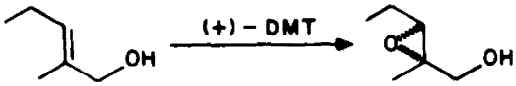


(24)

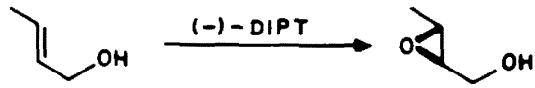



249 250

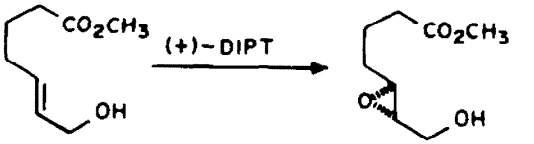
Since both enantiomers of tartaric acid of high optical purity are commercially available, the required enantiomer of the epoxyalcohol can be prepared by choosing the dialkyl tartrate. It is to be noted that the enantiomeric excess of the epoxyalcohol cannot be higher than the enantiomeric excess of the dialkyl tartrate used as chiral director. Some of the epoxyalcohols synthesised according to the method of Katsuki and Sharpless are given in Chart 3.



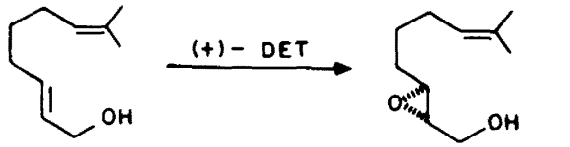

251 252 Ref 135




253 254 Ref 135

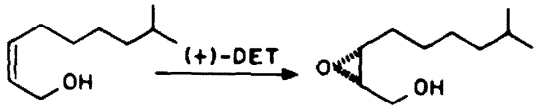



255 256 Ref 135



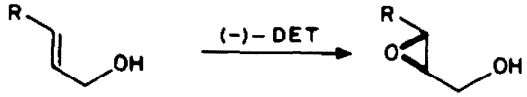

257 258 Ref 136


259 260 Ref 135

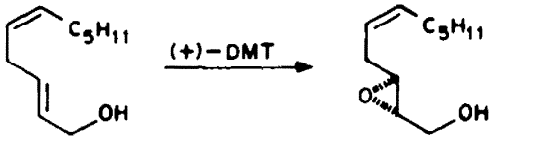



261 262 Ref 137


263 264 Ref 137




265 R = n - C15H31 266 Ref 138




267 268 Ref 139

269 270 Ref 139

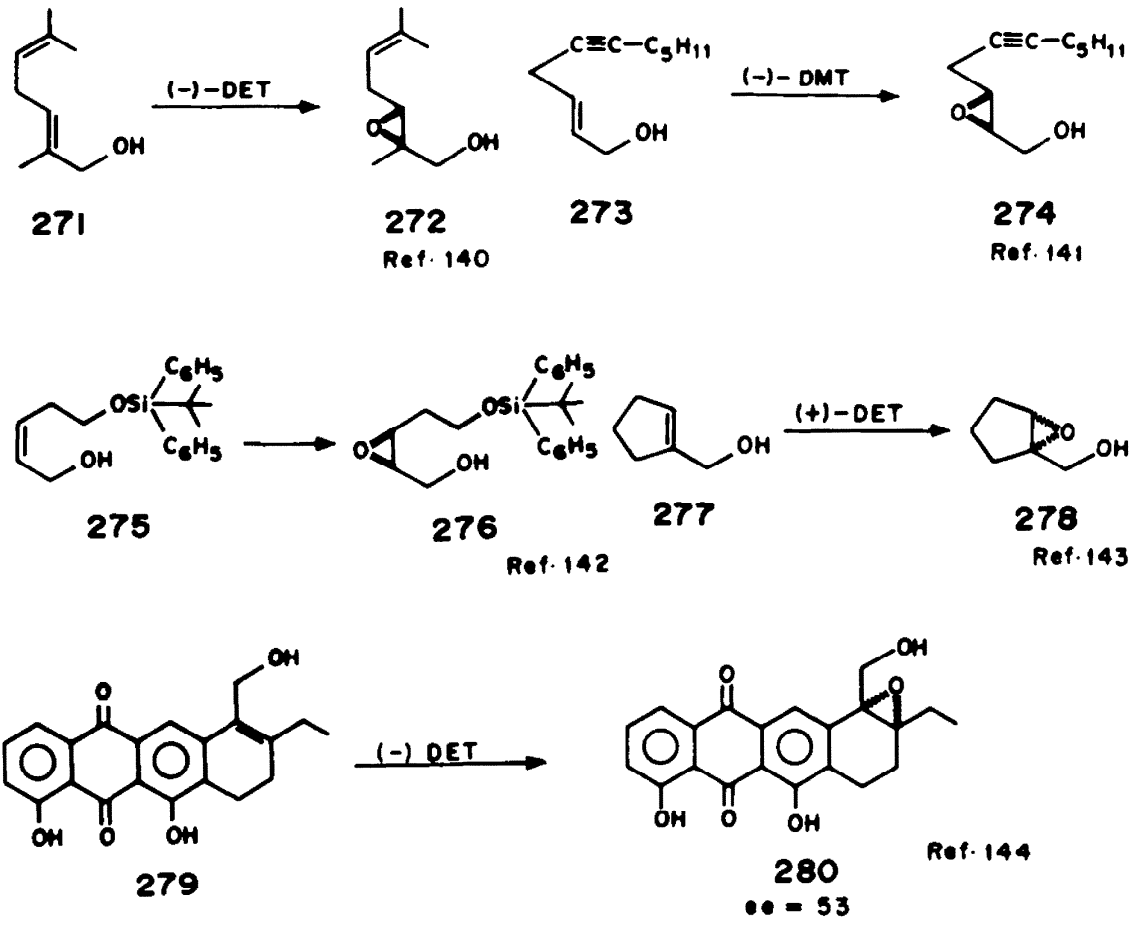



Chart 3. Enantioselective epoxidation of allyl alcohols (see eqns 23, 24). DMT = Dimethyl tartrate; DET = Diethyl tartrate; DIPT = Diisopropyl tartrate.

Epoxyalcohols **252** and **254** are intermediates for the synthesis of methymycin and erythromycin respectively. Epoxides **256** and **258** are intermediates for the synthesis of leukotriene, $LTA_4$. Epoxides **260** and **262** are intermediates for the synthesis of disparlure. Epoxide **268** and its mirror image **270** are intermediates for the synthesis of 5 S, 12 S -di HETE, a human metabolite of arachidonic acid and leukotriene $LTB_4$ respectively. Epoxides **272** and **276** are intermediates for the synthesis of a pheromone of *Pseudococcus comstocki* and verrucarin A respectively.

(e) *Asymmetric epoxidation of optically active allyl alcohols.* Asymmetric epoxidation according to the method of Katsuki-Sharpless (eqns 23, 24) has been carried out using optically active alcohols. In the case of (*S*)-**281** as well as (*R*)-**283** the direction of epoxidation for the major diastereomer is from the side predicted by eqns (23, 24). The stereoselectivity is high for the epoxidation of (S)-**281** on the other hand, the selectivity for epoxidation of (R)-**283** is significantly affected by the chiral centre. The (*S*)-**281** reacts 104 times faster than (*R*)-**283**. The asymmetric epoxidation of chiral allylic alcohols is a convenient method for their kinetic resolution.[145] The chiral centre in the *trans*-allylic alcohol **285** does not significantly affect stereoselectivity for asymmetric epoxidation;[146] on the other hand the stereoselectivity in the asymmetric epoxidation of *cis*-allylic alcohol **288** is reduced due to the presence of the chiral centre.[146] Some of the epoxyalcohols prepared via asymmetric epoxidation of optically active allyl alcohols are shown below (Chart 4). Oxirane 296 is an intermediate for the synthesis of $C_3$–$C_{10}$ fragment of maytansinoids. Oxirane **292** is an intermediate for the synthesis of the aliphatic segment of rifamycin S.

(f) *Oxiranated small chiral fragments.* Optically pure organic compounds which can be isolated readily from natural products, or which are commercially available, can serve as precursors for chiral

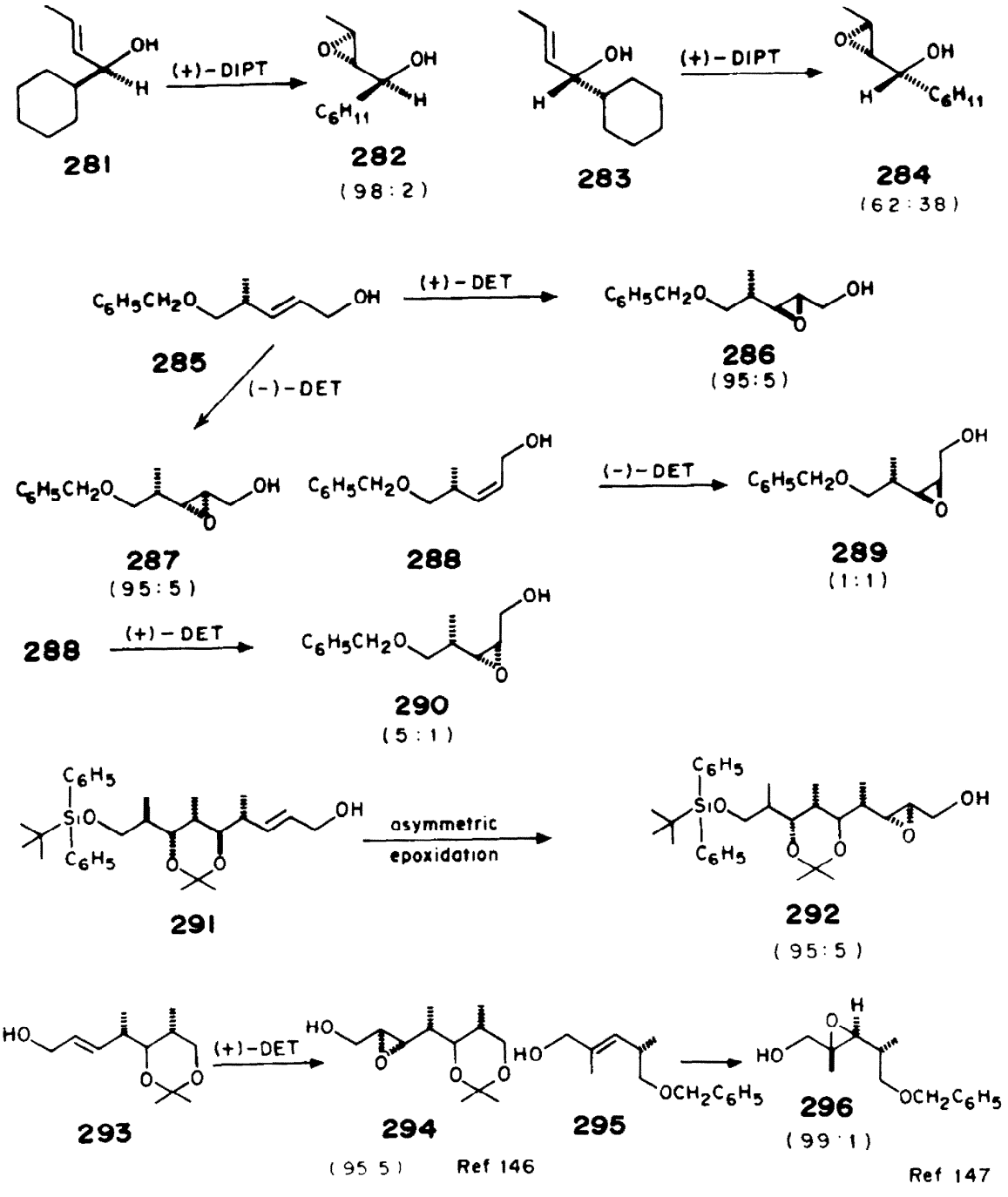
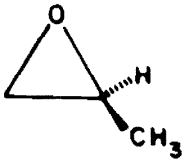


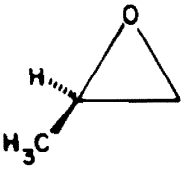

Chart 4. Asymmetric epoxidation (see eqns 23, 24) using optically active allyl alcohols; diastereomeric ratio is given in brackets.

oxiranes if they are 1,2-diols or can be transformed conveniently to 1,2-diols; synthesis of oxiranes would then involve selective conversion of one of the hydroxyl groups to a good leaving group (e.g. OTs) and application of the reaction outlined by eqn (16). A number of small chiral fragments containing the oxirane ring have been made starting from tartaric acid (both enantiomers of tartaric acid are commercially available), lactic acid, D-mannitol, malic acid and other chiral precursors. One of the recent developments in organic chemistry is the application of small chiral fragments for the synthesis of optically pure natural products and pharmaceuticals.[148] Some of the oxiranated small chiral fragments which are either proven or potential intermediates for the synthesis of natural products are depicted in Chart.



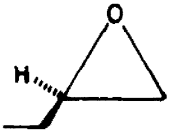
(S)-297

Ref. 150



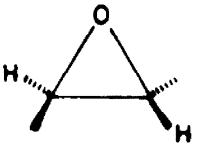
(R)-298

Ref 150

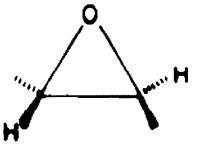


(R)-299

Ref. 152



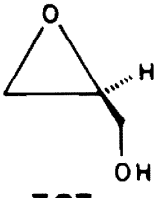
(R,R)-300



(S,S)-301

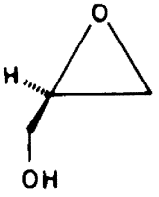
Ref. 113

(S)-302



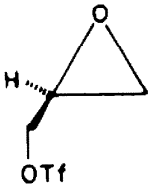
(S)-303

Ref 156



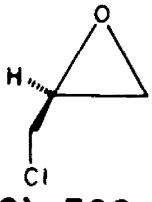
R-(304)

Ref 156



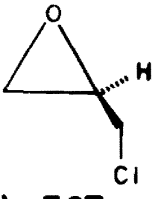
(S)-305

Ref. 157

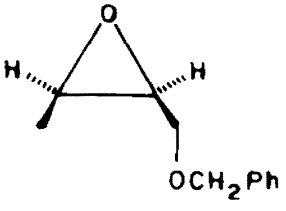


(S)-306

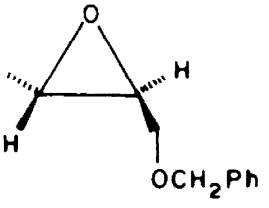
Ref. 158



(R)-307



308



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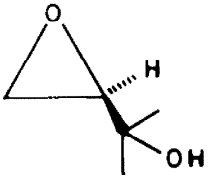

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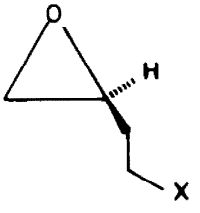
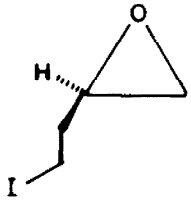


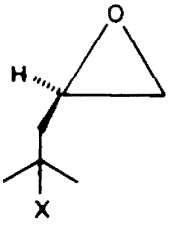
311 a X = I Ref. 162

311 b X = Br



312

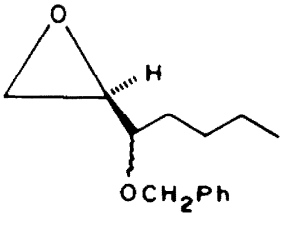
Ref 162



313

a X = H

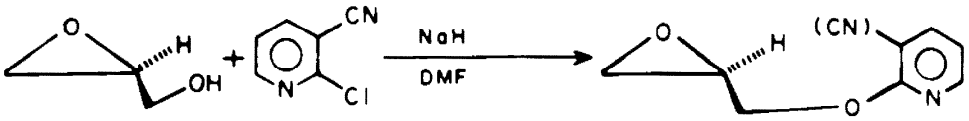
b X = OH



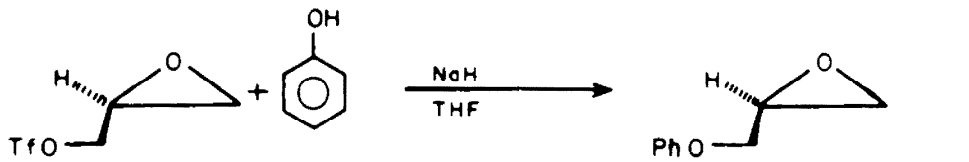
314

The following syntheses have been reported: methyl nonactinates[149] from **297**, (*R*)-recifeiolide from **298**,[151] stereoisomers of sex pheromone of pine sawflies from **300** and **301**, (*S*)-massoilactone[154,155] from **302**, 24(*R*) 24,25-dihydroxy vitamin $D_3$ from **310**,[160] (*R*, *R*)-vermiculin from **311b**, (*S*)-ipsenol from **313a**, (*S*)-ipsdienol from **313b** and (6*R*,-1′*R*)-pestalotin[165] from **314**. An oxirane differing from the antipode of **309** in the blocking group is an intermediate in the erythromycin synthesis.[108,159]

Chiral aryloxymethyloxiranes have been synthesised from chiral oxiranes (eqns 25, 26).



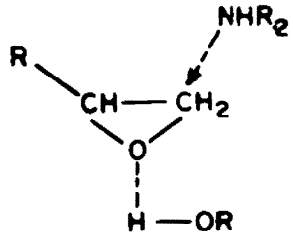

**303** **315** **316** ( Ref 156 ) ( 25 )



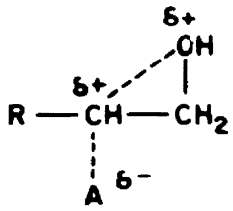

**305** **317** **318** ( Ref 157 ) ( 26 )

7. *Nucleophilic substitution reactions (intermolecular)*

Oxiranes undergo ring-opening when reacted with nucleophilic reagents due to ring strain and the basic nature of oxygen atom in the heterocycle.[167] The nucleophilic opening of the oxiranes has been extensively studied since it provides a convenient route for forming C–C (or C–X where X = N, O, S, Se or Te) $\sigma$-bonds; in most cases it is possible to anticipate the stereochemistry and regiochemistry of ring-opening. The reaction of oxiranes with nucleophiles is facilitated by electrophilic assistance by protic solvents or Lewis acids (**319**, **320**).[11,168]



**319**



**320**

$Fp^- = [(\eta^5-C_5H_5)\,Fe\,(CO)_2]$

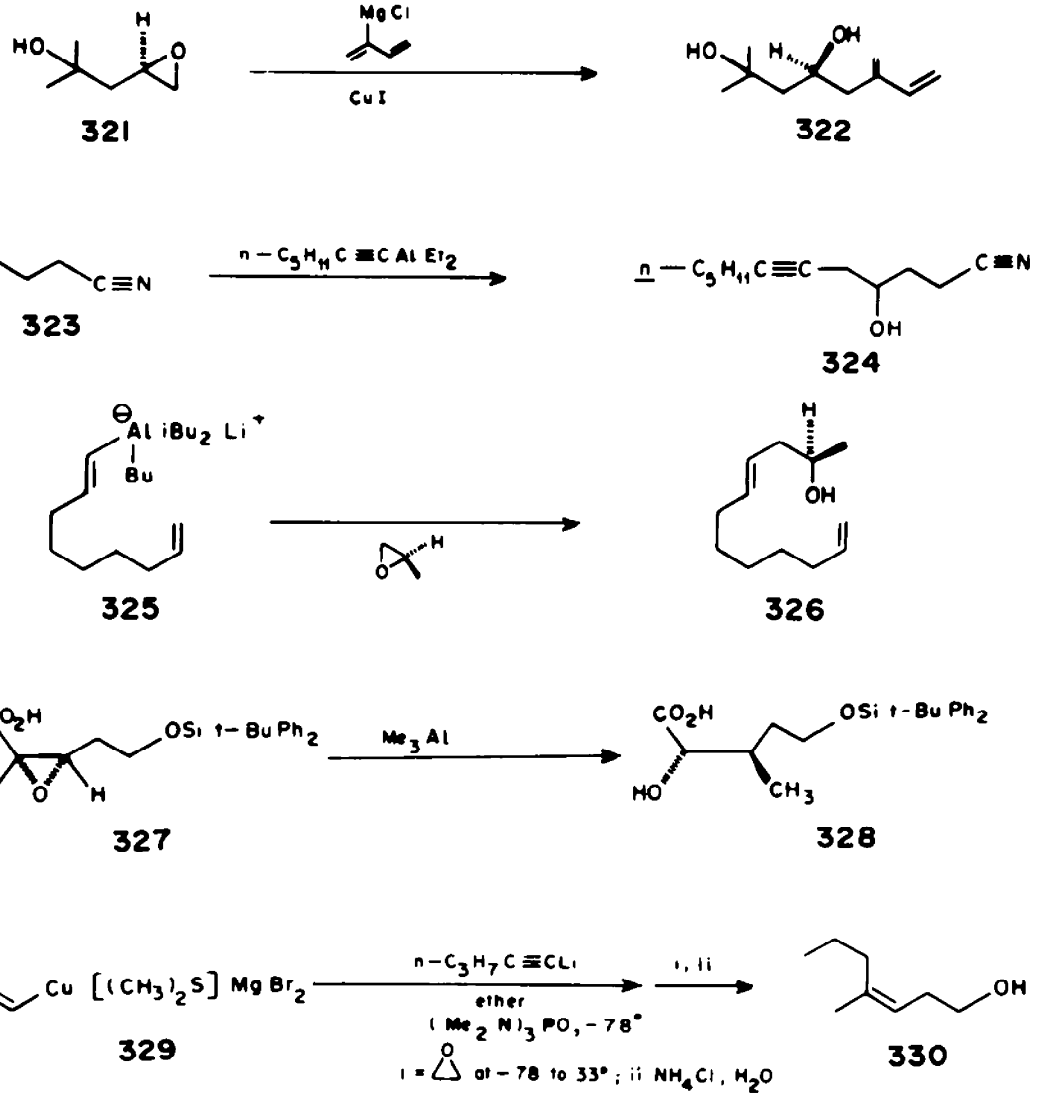
LiFp is more reactive towards oxiranes than the corresponding sodium salt, since $Li^+$ can coordinate more effectively with oxirane oxygen than $Na^+$ ($Li^+$ is known to be a harder acid than $Na^+$). $Fp^-$ is one of the most powerful of organometallic nucleophiles. The greater reactivity of LiFp (as compared with NaFp) clearly demonstrates the importance of Lewis acid promotion in oxirane opening even for anions of high nucleophilicity.[169]

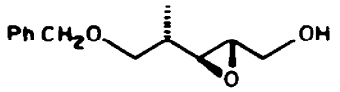
The opening of oxiranes by nucleophiles in basic or neutral media proceeds through the $S_N2$ mechanism and hence the configuration at the carbon atom which is attacked, is inverted. Nucleophilic opening in acidic medium, in most cases, proceeds through transition state (**320**) where both partial bonds are longer than usual (borderline $S_N2$); in these reactions also the configuration at the carbon atom

attacked is inverted.[8] In the extreme, when the substituent is phenyl or vinyl, a stabilized carbonium ion may be formed under acidic conditions resulting in $S_N1$ type ring-opening.[11]

The opening of oxirane involving nucleophilic attack at the less substituted carbon is termed as "normal opening" and opening involving attack at the more substituted carbon is termed as "abnormal opening". Due to steric factors, in basic or neutral medium opening of oxiranes by nucleophiles is normal provided a group having marked polar or conjugative effect is not attached to oxirane. Opening of oxiranes in acid medium proceeds through "borderline $S_N2$" mechanism and hence there is a preference for nucleophiles to attack at a tertiary or benzylic or allylic carbon which is better suited to accommodate $\delta^+$ charge in the transition state. One of the important factors in oxirane opening of cyclohexene oxides is the conformational control; the nucleophile prefers to attack the oxirane carbon along the axial direction.

Nucleophilic opening of oxiranes with Grignard reagents is a well established route; however, it has been limited in scope due to competing reactions arising from Lewis acidity of the Grignard reagents.[8] Recent reports[170] show that the reaction of oxiranes with Grignard reagents proceeds smoothly in the presence of copper catalysts. Lithium dialkylcuprates have been shown to be highly effective reagents for the nucleophilic opening of oxiranes;[171] usually a large excess of the organometallic reagent is required and only one of the alkyl groups is transferred.[172] Lithium organo(cyano)copper(I) reagents, e.g. $CH_3(CN)CuLi$, react with oxiranes to form corresponding alcohols using stoichiometric amounts of cuprate reagents.[172] Organocopper reagents can selectively ring open oxiranes in the presence of unprotected carbonyl functions (ester or ketone).[171] Dimethylethynylaluminium etherate has been used for the ethynylation of base-sensitive oxiranes.[173]



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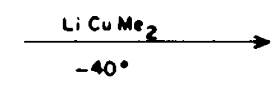


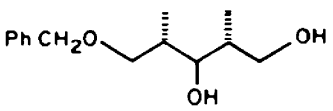


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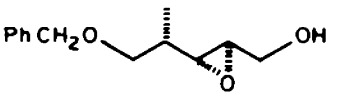


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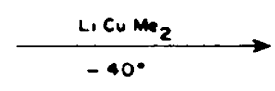


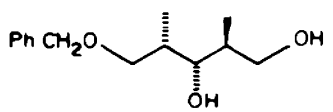


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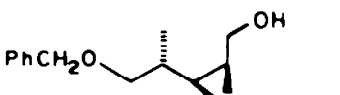


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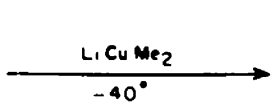


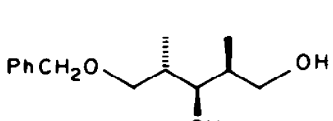


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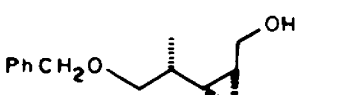


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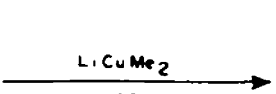


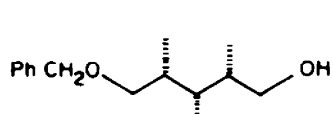


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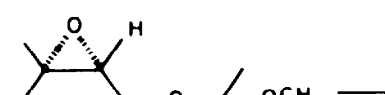


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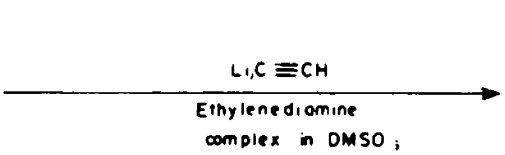



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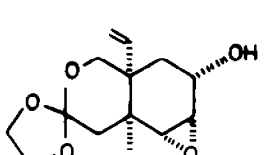


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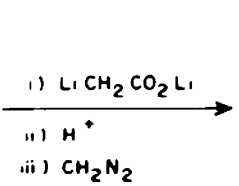


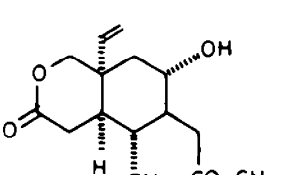


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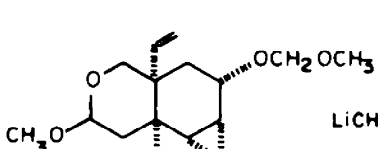


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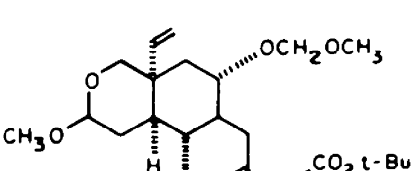


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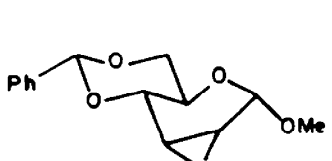


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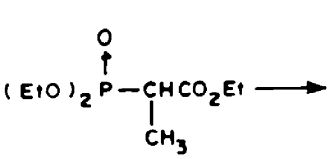


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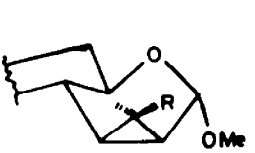


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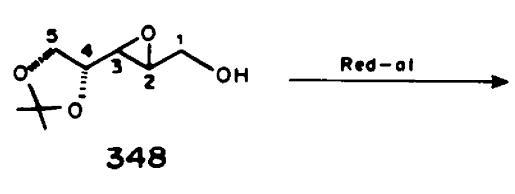
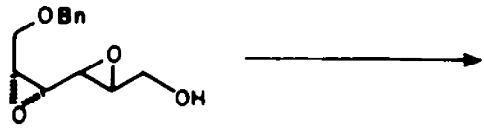
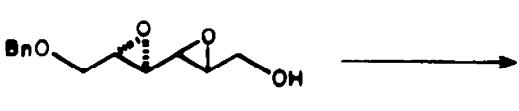
R = $CO_2Et$




348 349 (100:1) (27)




350 351 (>50:1) (28)




352 353 (>100:1) (29)

Some examples of nucleophilic ring-opening of oxiranes, glycidols and glycidic acids are given in chart (**321** to **353**). The synthesis of ipsdienol[164] from **313b**, pheromone of black-tailed deer[174] from **324**, (*R*)-recifeiolide[151] from **326** and verrucarin A[142] from **328** are reported. Homoallylic alcohol **330** has been converted to a constituent of codling moth.[175] The method used for the preparation of **330** has been applied for the stereoselective synthesis of a number of homoallylic alcohols having trisubstituted double bonds. The reaction of the alkynylcopper complex **329** with oxiranes proceeds rather sluggishly; lithium acetylide has been added, to the reaction mixture to generate more reactive mixed cuprates. The diols **332**, **334**, **336** and **338** constitute partial structures of important natural products.[146] The diol **340** is an intermediate in the synthesis of erythromycin.[108] The diol **342** is an intermediate for the synthesis of vernolepin and vernomenin.[176] Dilithioacetate has been widely used for the preparation of γ-lactones from oxiranes.[177] The oxirane ring in **343** cannot be cleaved by dilithioacetate even under forcing conditions; however the ring opening has been brought about by using the more energetic nucleophile, dilithioacetoacetate.[178,179] The keto-ester **344** has been transformed to bisnorvernolepin.[178] Dilithio-2-thiophenyl-propionate,[180] α-anions of N,N-disubstituted carboxamides,[181] aluminium derivatives of t-butyl acetate and ethoxy-acetylene[182] have been employed for the preparation of γ-lactones from oxiranes. Both (+)- as well as (−)-chrysanthemum dicarboxylic acids have been prepared[183] from the ester **347**. Reduction of glycidols carrying an ethereal substituent (or substituents) at C-4 and/or C-5 (see compound **348** for numbering) with sodium bis(methoxyethoxy)aluminium hydride (Red-al) is regioselective (eqns 27–29).[184,185]

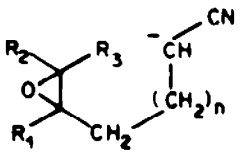
Oxirane ring opening has been utilized in the synthesis of the following compounds: (1) dendrobatid toxin 251D,[186] (2) pederamide,[187] (3) α-tocopherol,[188] (4) a component of california Red Scale Pheremone,[189] (5) ecdysone analogues,[190] (6) prostaglandins,[191] (7) stereoisomers of sawfly pheromone,[153] (8) helenalin,[192] (9) sidechain of α-tocopherol,[193] (10) maytansinoids,[194] (11) lepiochlorin,[180] (12) 24(R)-24,25-dihydroxyvitamin $D_3$,[160] (13) substituted 5,6-dihydro-2H-pyran-2-ones,[195] (14) dihydropalustrin,[196] and (15) an analogue of clerodin.[197] Oxiranes can be opened with oxygen,[84] sulphur,[127] selenium,[22] tellurium[198] and nitrogen nucleophiles.[196,199,200]

Commercially available Woelm 200 neutral chromatographic alumina catalyzes heterogeneous

nucleophilic opening of oxiranes by a few equivalents of alcohols, thiols, amines, acetic acid and benzene selenol under very mild conditions stereo- and regioselectively.[201] Medium ring cycloalkene oxiranes normally furnish cyclized products arising from transannular interactions when reacted with nucleophiles, e.g. acetic acid in the presence of acid catalysts; however, alumina catalyzed ring opening of medium ring cycloalkene oxiranes furnishes in good yields the products arising from 1,2-opening. The alumina catalyzed reactions are facilitated due to electrophilic assistance to ring opening by coordination of oxirane to acid sites on alumina and also due to activation of nucleophiles by the basic sites in alumina.

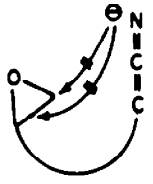
8. *Nucleophilic substitution reactions (intramolecular)*

A systematic study of cyclizations of epoxynitriles (**354**) differing in chain length (n varied from 0 to 3) and degree of substitution of oxirane rings has been carried out by Stork.[202] The nitriles were particularly chosen since nitrile anion is a strong nucleophile which permits ring formation even at a quaternary center. Furthermore, because of the linear allenic structure of nitrile anion the nitrogen end cannot react with oxirane as in **355** since an allene unit cannot be accommodated in normal sized rings



**354**

n = 0, 1, 2, 3



**355**

for geometric reasons. The investigations showed that epoxynitrile cyclization always yields the smaller ring when both ends of oxirane are equally substituted. This is true whether the smaller ring is 3, 4, 5 or 6-membered. Cyclopropane ring is formed in preference to a cyclobutane regardless of relative degree of substitution of oxirane ring.

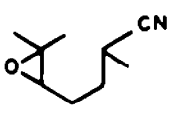
The ring-opening of oxiranes is facile when the nucleophile which is attacking it from the rear side is collinear with the C–O bond which is to be broken. In the case of carbanion **357**, the negatively charged

**356**

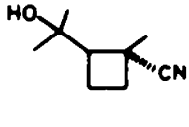
**357**

carbon is not collinear with C–O bond "a" and cyclization to furnish 5-membered ring (*endo* cyclization) is not facile. In carbanion **356**, the negatively charged carbon is collinear with C–O bond "b" and hence can undergo facile exo cyclization to a 4-membered ring. *Endo* cyclization to furnish 6-membered ring and *exo* cyclization to furnish 5-membered ring are facile since the C–O bond to be broken and approaching nucleophile are collinear.

The cyclization of epoxynitrile **358** furnishes stereoselectively the product **359** having CN *trans* to the hydroxyisopropyl substituent. It has been suggested that in the transition state the effective steric hindrance of cyano anion is larger than that of a normal alkyl group as a consequence of the allenic structure of the metal salt. Epoxynitrile **360** has been cyclized to **361** with very high regio- and stereoselectivity. The nitrile **361** is an intermediate for the synthesis of grandisol.



**358**



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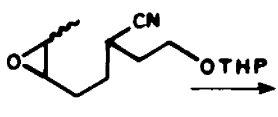
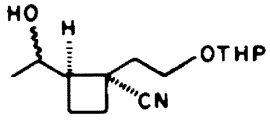


**360**

The transformation of epoxynitrile **362** to the cyclopropane derivative **363** involves nucleophilic attack at a quaternary center.



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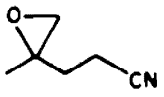

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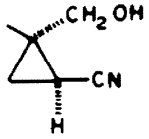
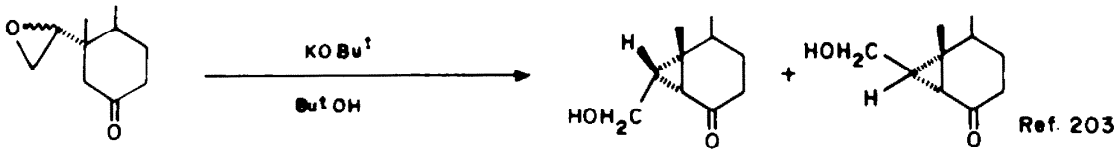
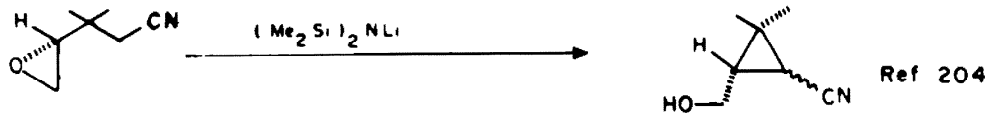


**363**

Some of the compounds synthesised through intramolecular cyclization involving C–C $\sigma$-bond formation and ring-opening of oxiranes are shown as **364** to **384**. In the base catalyzed cyclizations of **364** as well as **367**, cyclopropane ring formation but not cyclobutane ring formation is preferred even though three membered ring formation involves nucleophilic attack at the more substituted end of oxirane; the regioselectivities observed are in agreement with the generalizations of Stork. The ketone **365** and the nitrile **368** are intermediates for the synthesis of eremophilone[203] and *trans* chrysanthemic acid[204]

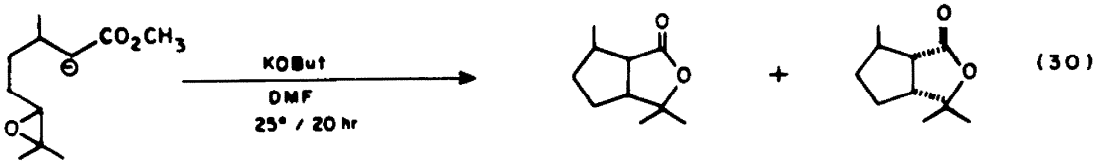



**364** **365** **366**

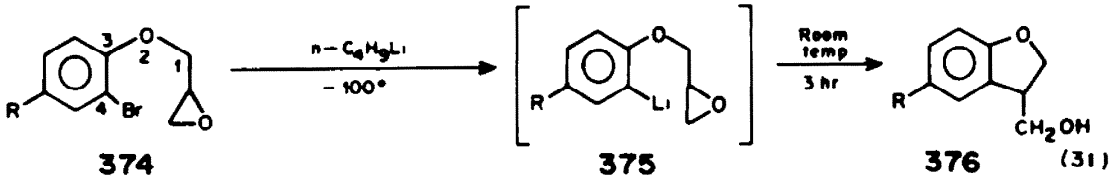



**367** **368**

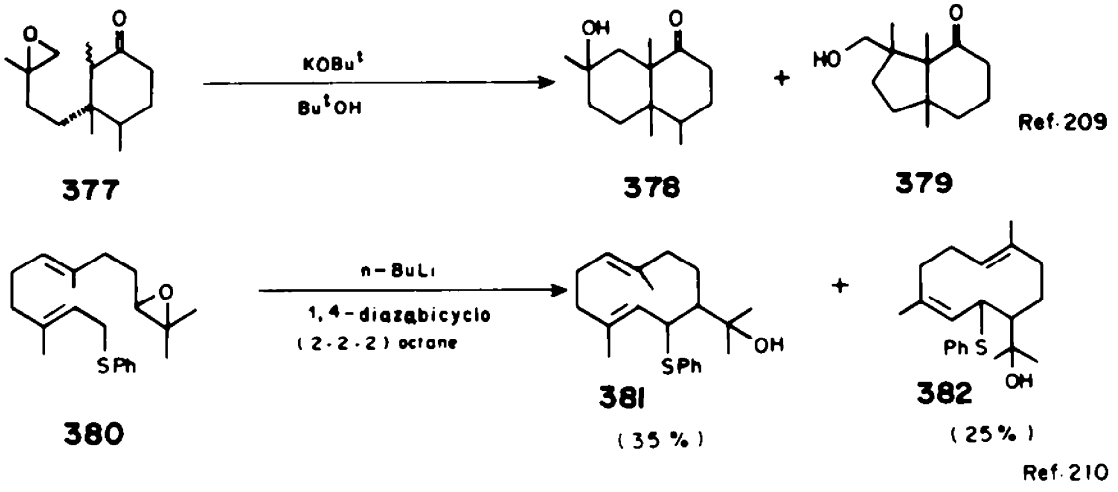

**369** **370**

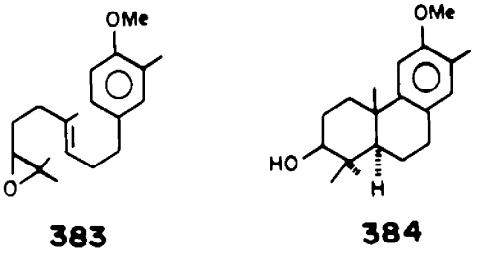



**371** **372** **373**



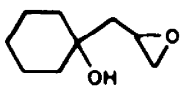

**374** **375** **376**




respectively. A number of cyclopropanes have been synthesised[205] by reacting γ,δ-ethylenic oxiranes with lithium amides in HMPT as solvent. Since α-sulphonyl carbanions are known to be formed by the action of MeMgI on sulphones, cyclopropane ring formation is expected during the reaction of a Grignard reagent with **369**. To explain the observation that a cyclobutane derivative is formed from **369**, it has been suggested[206] that prior to carbanion formation from **369**, the oxirane ring is cleaved to an iodo alkoxide by the Grignard reagent. The reaction shown in eqn (30), provides a convenient method for the synthesis of iridoids.[207] In the cyclization shown in eqn (31), it is of interest to note that endocyclization product is not favoured even though this would have involved attack at the less substituted carbon of the oxirane ring.[208] A comparison of the structure of the 4-membered chain (see numbering in formula **374**) attached to oxirane ring in **374**, with the chains attached to oxiranes investigated by Stork reveals an important difference. Carbon atoms C-3 and C-4 constituting the chain in **374**, form part of a planar ring which decreases the flexibility of the chain and prevents the attainment of collinearity of the anion with that C–O bond of oxirane which must be broken for formation of a 6-membered ring. The keto alcohol **378** is an intermediate in a synthesis of ishwarone.[209] The cyclization reaction shown in eqn (32) provides a convenient route for the synthesis of compounds related to germacrane.[210] A similar approach[211] has been utilized to synthesise cembrenene, a diterpene having a 14-membered ring. When an oxirane group and ethylenic linkage are present in the same molecule, electrophilic activation of the oxirane can lead to cyclization, with the double bond functioning as nucleophile, provided the double bond is suitably located. The oxirane **383** has been cyclized to **384** on treatment with Lewis acid in aprotic solvent.[212]

Several oxygen containing heterocycles have been synthesised utilizing the attack of oxygen nucleophiles on oxiranes. Some of the cyclizations are shown in chart (**385** to **399**). The cyclization of **385** to furnish the oxetane **386** involves the favoured exo attack by oxygen nucleophile on the oxirane. The five membered heterocycles in **388**, **390**, **392** and **394** are formed with high regio- and stereoselectivities; the exo attack on oxiranes is electrophilically assisted. The polycyclic alcohol **390**, prepared from **389** has been transformed[214] to lasalocid A. The alcohols **392** and **394** are intermediates for the synthesis of isolasalocid ketone[215] and monensin[216] respectively. The synthesis of ionophore antibiotic



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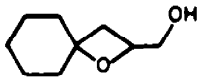

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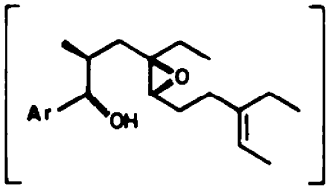

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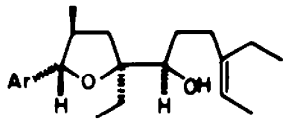
AcOH



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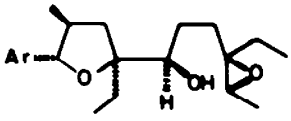

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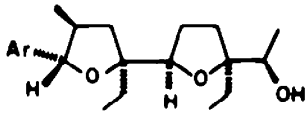
AcOH



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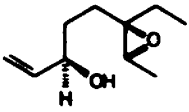

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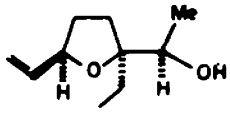
AcOH



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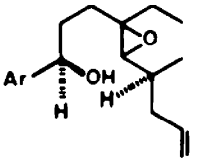
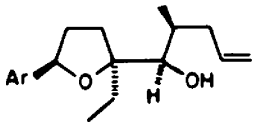


393

$CSA, CH_2Cl_2$



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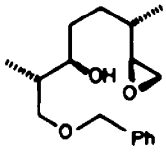
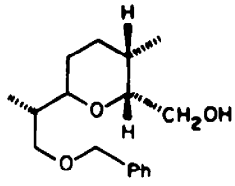


395

CSA Catalyst



396

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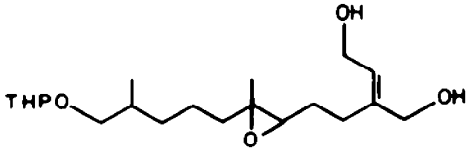


397

(33)

i) $CF_3CO_2H$

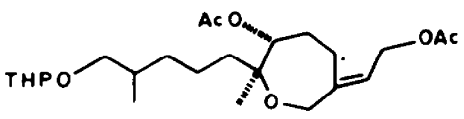
$(CH_2Cl_2, 0°)$

ii) Acetylation

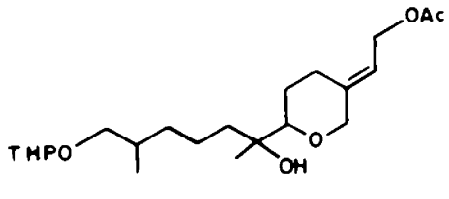
398 + 399

(30%) (17%)

Ref 218



398

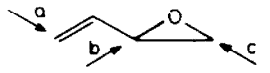


399

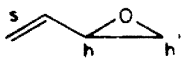
X-14547A[217] and zoapatanol[218] from **396** and **398** respectively are reported. The cyclization shown in eqn (33) provides a convenient route for the synthesis of oxepanes. Nitrogen containing heterocycles, e.g. quinine and dendrobine have been synthesised utilizing the intramolecular attack of nitrogen nucleophiles on oxiranes.[219,220]

9. *Nucleophilic substitution reactions of vinyl oxiranes and benzyl oxiranes*

Nucleophilic ring opening of benzylic oxiranes has been investigated extensively and the results have been rationalized[221] on the basis of hard-soft acid-base (HSAB) theory. In reactions where "hard acid" is not available the softness of an anion and of the two sites on oxirane ring controls regioselectivity of nucleophilic attack. Condensation of substituted styrene oxide with malonate anion represents a soft–soft interaction. In p-methoxy styrene oxide, the benzylic carbon is the "softer" of the two sites and hence is selectively attacked by malonate anion. A hard nucleophile reacts selectively at the sterically less hindered carbon atom.




400

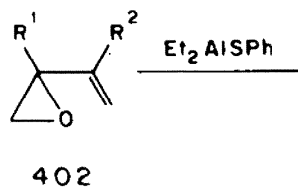



401

s = soft, h = hard, h' = harder

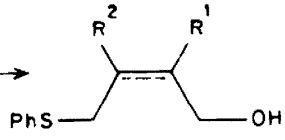
A vinyl oxirane **400** may be attacked by a nucleophile at the region "a" ($S_N2'$ reaction; 1,4-addition) or "b" ($S_N2$ reaction; 1,2-addition) or "c" ($S_N2$ reaction). $S_N2'$ Reaction is favoured when the nucleophile is a soft base and $S_N2$ reaction is favoured with a hard base. Lithium dimethyl cuprate is a softer base than methyl lithium and hence the cuprate reagent reacts in $S_N2'$ fashion while methyl lithium reacts in $S_N2$ fashion with vinyl oxiranes.[171] When an acyclic oxirane, e.g. **402** undergoes an $S_N2'$ reaction, the product has the Z-configuration at the ethylenic linkage if the nucleophile can coordinate with heteroatom and form a cyclic transition state.[222] Similarly, coordination of the attacking nucleophile with the oxygen of a cyclic $\alpha,\beta$-unsaturated oxirane can lead to $S_N2'$ syn attack.[223] When cyclic transition states are not involved, normally $S_N2'$ attack on cyclic $\alpha$, $\beta$-unsaturated oxiranes is anti. The reaction of lithium dimethylcuprate with oxirane **405** is regio- and stereoselective. In contrast, the reaction of lithium dimethylcuprate with the oxirane **406** is not regioselective.[224] The mixed cyano cuprates, e.g. $CH_3Cu(CN)Li$ have been found to react with **406** regio- as well as stereoselectively.[224]

The vinyl oxirane **408** undergoes anti $S_N2'$ attack with lithium isohexylcyanocuprate to furnish **409**; the 15$\beta$-alcohol thus obtained has been shown to contain less than 0.5% of the C-20 epimer.[225] This




402

403

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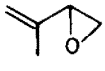


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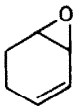


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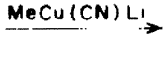


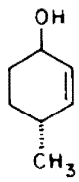


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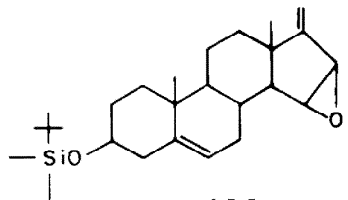


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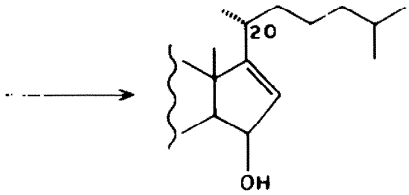


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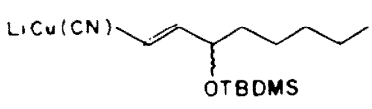


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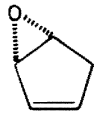



411

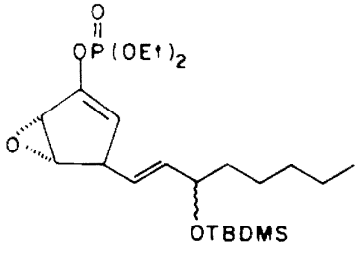
synthesis demonstrates the importance of the cyanocuprate reaction in the stereo-controlled synthesis of acyclic portions of complex molecules. The addition of the cyanocuprate **410** to the oxirane **411** and the cyanocuprate **412** to the oxirane **413** are also regio-(1,4) as well as stereo-($S_N2'$-anti)-selective.[226] The cyclopentane derivative prepared from **413** is an intermediate in the synthesis of prostaglandins.

The reaction of methyl lithium with the enolate **414** involves exclusive 1,2-addition;[227] the methylation product **415** on acidification undergoes $\beta$-elimination to furnish **416**. $S_N2$ attack has been observed in the following reactions: (a) reaction of the oxirane **417** with methylamine,[228] (b) the reaction of the oxirane **418** with anion of methyl malonate[229] and (c) the reaction of 1,3-cycloheptadiene monoepoxide with the cuprate **419**.[230]

Selective $S_N2'$ anti attack has been observed in the following reactions: (a) the reaction of oxirane **420** with methyl cyanocuprate,[231] (b) the reaction of oxirane **421** with methyl cyanocuprate,[232] (c) the reaction of the hetero-cuprate **422** with oxirane **423** (when the product from $S_N2'$ attack was isolated in 43% yield




412

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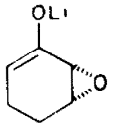


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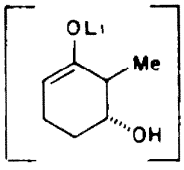


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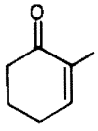

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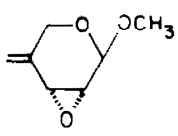


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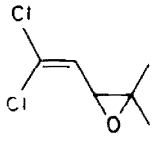


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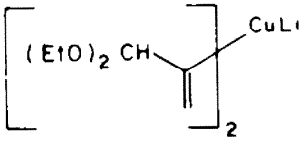


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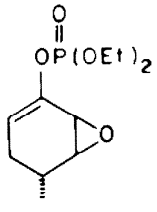


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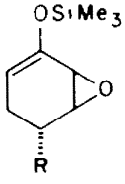


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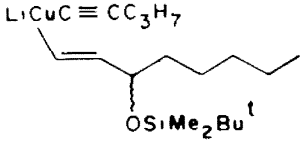


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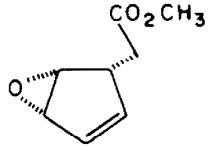


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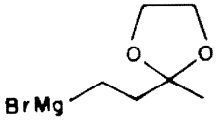


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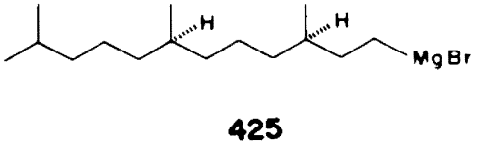



425

and the product from $S_N2$ reaction was isolated in 14% yield),[233] (d) the reaction of the enolate **414** with lithium dimethylcuprate,[227] (e) the copper catalyzed reaction[234] of the Grignard reagent **424** with isoprene oxide (f) the copper catalyzed reaction of Grignard reagents with 5$\alpha$, 10$\alpha$-epoxy-$\Delta^{9(11)}$ steroids.[235] The copper catalyzed reaction of the Grignard reagent **425** with oxirane **405** furnishes phytol;[236] in this reaction the product has the E-geometry (E:Z = 97:3). $S_N2'$ Reaction of alkyl lithium with isoprene oxide furnishes Z-allylic alcohols.[237] Copper enolates derived from tiglic and crotonic acids react

with vinyl oxirane in $S_N2'$ fashion to form 1,5-dienes with entirely E-stereochemistry at 2,3-double bond.[238] Monoepoxides derived from simple cyclic 1,3-dienes possessing ordinary ring size are isomerized to β,γ-unsaturated ketones with Pd(o) catalyst.[239] 1,3-Diene monoepoxides react with nucleophiles (e.g. malonic ester or methyl acetoacetate) in the presence of Pd complex as a catalyst under neutral conditions to give 1,4-adducts selectively.[240]

The oxirane ring of leukotriene A (LTA) methyl ester (**163**) undergoes $S_N2$ attack regioselectively at C-6 with stereoselectivity (inversion of configuration at C-6) when reacted with sulphur nucleophiles. This reaction has been utilized for the synthesis of leukotrienes LTC, LTD and LTE which are important natural mediators of allergic asthma. For the introduction of thio substituents at C-6, a novel, mild and general method for the ring-opening of oxiranes using alkylthiotrimethylsilanes was devised.[241]

10. *Synthesis of allylic alcohols from oxiranes*

One of the important synthetic applications of oxiranes is their rearrangement to allylic alcohols. When oxiranes are treated with a strong base such as lithium diethylamide they can furnish besides allylic alcohols, ketones, substitution products (amino alcohols) and in the case of medium ring compounds transannular cyclization products.[11,242] The rearrangement of cyclohexene oxide to 2-cyclohexenol has been studied employing ether as solvent and changing the base. It has been found that yields are good with lithium diethylamide; lithium di-n-propylamide and lithium di-n-butylamide are excellent reagents.[242] The rearrangement of cyclohexene oxide has been studied with lithium diisopropylamide using either ether or HMPT as solvent.[243] Nearly quantitative yields have been obtained with lithium di-isopropylamide when HMPT is the solvent. The rearrangement with lithium diethylamide can be carried out even when a cyclohexadienone ring system is present.[244]

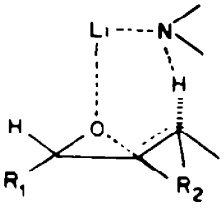
Lithium diethylamide catalyzed rearrangements of deuterated *cis*-4-t-butylcyclohexene oxide as well as the *trans*-isomer have shown that the reaction proceeds through syn elimination process and the β-region quasi axial hydrogen which is *cis* to oxirane is selectively abstracted by the base.[245]

The oxirane to allylic alcohol rearrangement catalyzed by lithium dialkylamide involves a cyclic transition state (**426**). In compound **427**, the axial hydrogen at C-7 is cis to oxirane and the tertiary allylic alcohol **429** is one of the products formed when oxirane **427** is reacted with lithium di-n-propylamide.[246] The β-oxide **428** does not have an axial hydrogen at C-7 cis to oxirane and hence no tertiary allylic alcohol is formed when **428** reacts under similar experimental conditions.

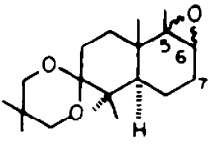
Since the base employed for oxirane rearrangement has substantial steric requirements, the reaction is highly regioselective involving proton abstraction from the least substituted carbon. For example, the oxirane **430** is rearranged to **431** and virtually none of the alcohol **432** is formed.[91]

The regiochemistry of ring opening of tetramethyl-limonene oxide has been controlled by the choice of base.[247] When N-lithio ethylenediamine is the base the product is **434**; however, when lithium di-isopropylamide which has a greater steric requirement is employed the product is **435**.

2,2,3-Trisubstituted oxiranes react readily with diethyl-aluminium 2,2,6,6-tetramethyl-piperidide

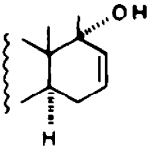



**426**

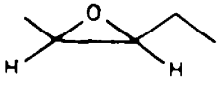



**427** 5,6 α-Oxide

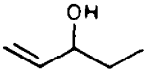
**428** 5,6 β-Oxide




**429**




**430**

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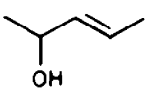
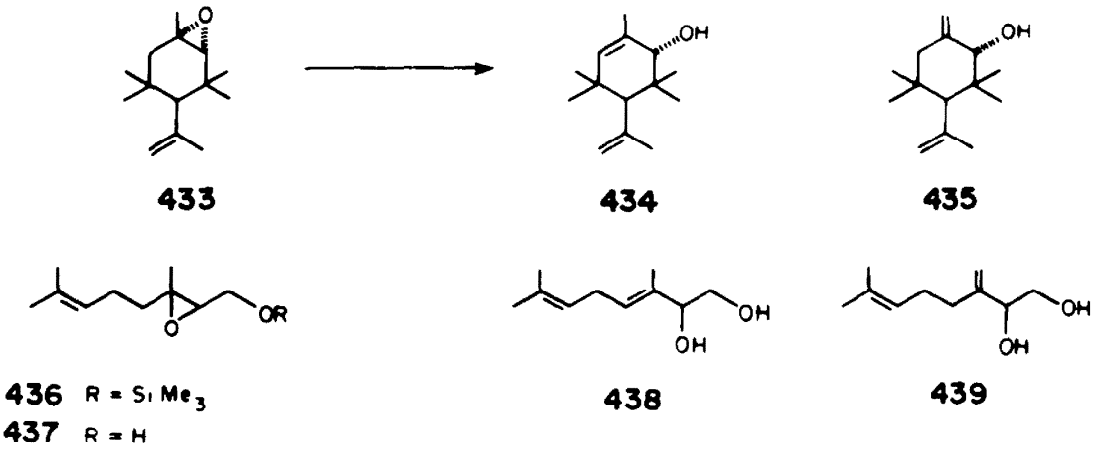


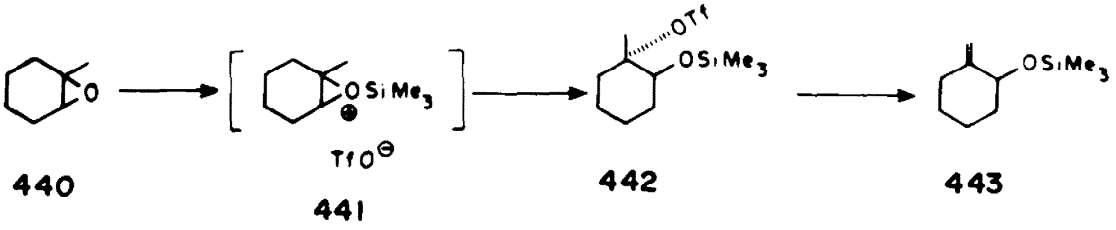

**432**




(DATMP)[248,249,70] to furnish allylic alcohols having E-configuration. The available experimental results support a syn-elimination mechanism. The reaction of the silyl ether **436** with DATMP reagent and subsequent desilylation furnishes the diol **438**; abstraction of hydrogen from methyl group attached to oxirane is not favoured due to steric interference by the trimethylsilyloxy group.

Bromomagnesium derivative of isopropylcyclohexylamine (MICA) prepared by the action of methyl magnesium bromide on isopropylcyclohexylamine is an excellent reagent for the isomerization of oxiranes to allylic alcohols.[77,250] It has been employed for the rearrangement of the oxide **17** to 15-HETE. This rearrangement involves preferential abstraction of allylically activated proton at C-13 leaving the nonallylic protons at C-16 intact.

A number of organosilicon reagents when used in combination with suitable bases transform oxiranes to allyl silyl ethers under mild conditions. When an oxirane, e.g. **440** is treated with trimethyl silyl trifluoromethane sulphonate (TMSOTf) and DBU the allyl silyl ether **443** is obtained.[251] The reaction is



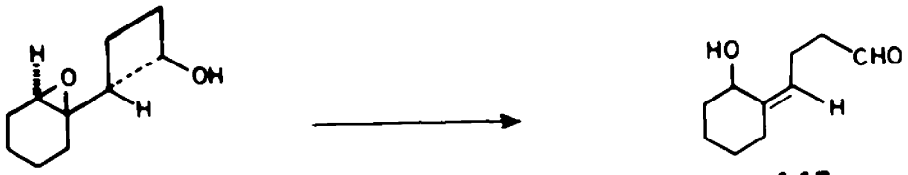

facile due to coordination of trimethylsilyl group to oxirane oxygen. Deblocking of the silyl group furnishes the allylic alcohol. A number of cyclic oxiranes (5, 6 and 7 membered) and trisubstituted oxiranes have been transformed to allylic alcohols using this route. In this case of trisubstituted oxiranes ring opening occurs selectively at the more substituted carbon. This method is not satisfactory for the preparation of allylic alcohols from oxiranes such as cyclooctene oxide, $\alpha$-pinene oxide and humulene oxide which are known to undergo facile acid catalyzed rearrangements.

The reaction of oxiranes with t-butyldimethylsilyl iodide (TBSI) followed by treatment with the base DBN furnishes allyl silyl ethers.[252] Regioselectivity in this reaction is identical with the regioselectivity observed with TMSOTf. In a few cases, e.g. cyclooctene oxide and 2,3-dialkyloxiranes where TMSOTf is not satisfactory, allylic alcohols have been prepared by employing TBDSI reagent. Trimethylsilyl iodide-base (DBU) combination has been used to prepare allyl silyl ethers from oxiranes but in general yields are lower than those reported with TBDSI reagent.[253] Isomerization of oxiranes with dialkyboryl triflates and tertiary amines[254] furnishes borate esters of allylic alcohols which can be hydrolysed to allylic alcohols.

The isomerization of trisubstituted oxiranes to allylic alcohols can be carried out with $Al_2O_3$–NaOH;

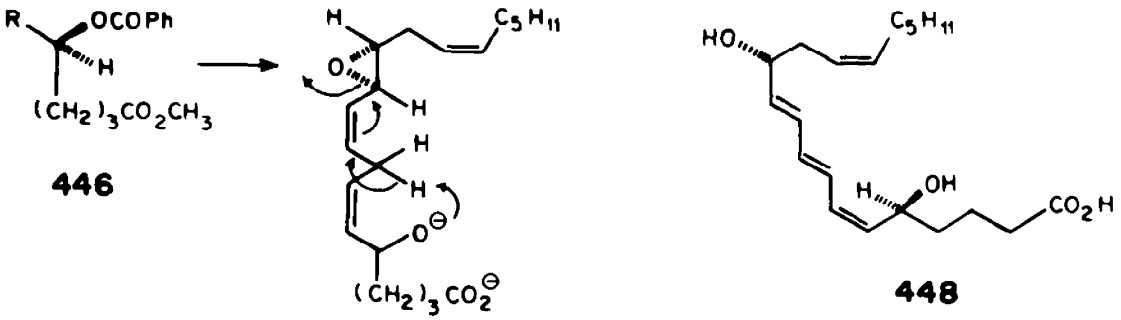
however, this reagent is not satisfactory for the synthesis of allylic alcohols from 2,2-disubstituted oxiranes.[255] Simple oxiranes are not isomerized by titanium isopropoxide in methylene chloride. However, glycidols undergo hydroxyl assisted rearrangement regioselectively. The epoxyalcohol **437** furnishes **439** on treatment with titanium isopropoxide.[256] Organoselenium reagents have been used for transforming oxiranes to allylic alcohols.[22,257]

Epoxycyclobutanols undergo stereospecific anti-fragmentation in the presence of sodium ethoxide to furnish allylic alcohols (e.g. **444**→**445**).[258]




**444** **445**

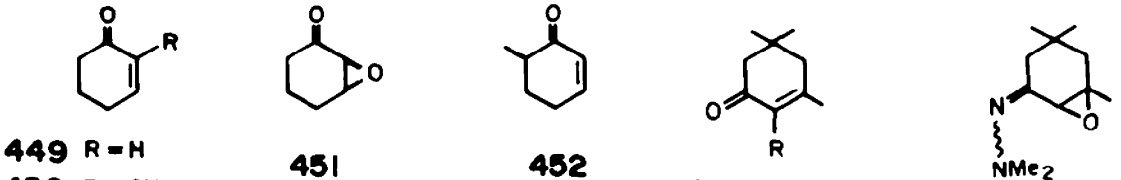
The biologically important leukotriene LTB has been prepared by treating the ester **446** with potassium carbonate in methanol and subsequently acidifying with acetic acid.[259]




**446** **447** **448** (LTB)

11. *Synthetic applications of α, β-epoxy ketones*

α, β-Unsaturated ketones, e.g. cyclohexenone **449** can be regioselectively monoalkylated or arylated at the α-carbon atom through a sequence of reactions. α, β-Epoxycyclohexanone **451**, which can be prepared from cyclohexenone, is transformed to the lithium enolate **414** and then alkylated[227] with methyl lithium; the alkylation product **415** on acid treatment furnishes the α, β-unsaturated ketone **450**. Thus, the sequence of reactions outlined above provides a route for converting cyclohexenone to 2-methylcyclohexenone (**450**). In an alternate approach[260] an α, β-unsaturated ketone, e.g. isophorone (**453**) is transformed to the corresponding α, β-epoxyketone and then the carbonyl group is blocked by reacting with N,N-dimethylhydrazine to give the N,N-dimethylhydrazone **455**. The oxirane ring of hydrazone **455** is cleaved on treatment with phenyl magnesium bromide and the resulting product is deblocked with concomitant dehydration by heating with aqueous ethanol–HCl to furnish the ketone **454** phenylated at the α-position.

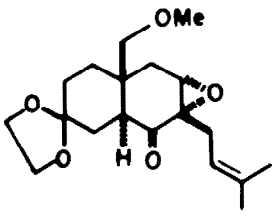



**449** R = H
**450** R = $CH_3$

**451** **452**

**453** R = H
**454** R = Ph

**455**

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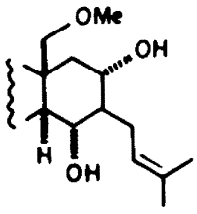



457

Regioselectivemonoalkylation of cyclohexenone at the $\alpha'$-carbon can also be effected via $\alpha$, $\beta$-epoxycyclohexanone.[227] The lithium enolate **414** prepared from **449** is methylated in the $S_N2'$ anti-fashion with lithium dimethylcuprate; the methylation product on acid hydrolysis furnishes the ketone **452**.

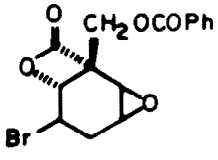
The reduction of acyclic as well as cyclic $\alpha$, $\beta$-epoxyketones to $\alpha$, $\beta$-epoxyalcohols with metal hydrides has been reviewed.[19,261] *Trans* $\alpha$, $\beta$-Epoxycyclohexanols can be prepared stereoselectively by reducing $\alpha$, $\beta$-epoxy cyclohexanones with tri-isobutylaluminium[262] or $NaBH_4$ in the methanol[263] in the presence of $CeCl_3$. The reduction of $\alpha$, $\beta$-epoxyketones with zinc borohydride furnishes[264] stereoselectively *erythro*-$\alpha$, $\beta$-epoxy alcohols; the stereoselectivity in this reaction is not dependent on the substitution pattern of the oxirane. The reduction of $\alpha$, $\beta$-epoxyketones to $\beta$-hydroxyketones employing aluminium amalgam[265] or palladium charcoal–hydrogen[266] has been used to synthesise some biologically important compounds. $\alpha$, $\beta$-Epoxyketone **456** has been reduced[267] to the 1,3-diol **457** with a large excess of lithium–$NH_4Cl$ in liquid ammonia-THF at $-33°$.

The synthesis of acetylenic ketones or aldehydes via fragmentation of tosyl hydrazones or other related derivatives of $\alpha$, $\beta$-epoxyketones is known for a long time and the reaction has been used in several syntheses.[268] The synthesis of allylic alcohols by reacting $\alpha$, $\beta$-epoxyketones with hydrazine has been utilized extensively.[269]

12. *Arene oxides*

There is considerable experimental evidence to support the suggestion that aromatic substrates are enzymatically transformed to arene oxides which rearrange to phenolic metabolites.[3] Some arene oxides are toxic due to their ability to undergo nucleophilic substitution reactions with vital macromolecules.[270] Hence the synthesis of arene oxides and their reactions with nucleophiles has been extensively investigated. The methods employed for the synthesis of arene oxides-oxepins are presented in a review.[271] The synthesis of arene oxides **2**, **3**, **13** and **14** has been discussed in an earlier section of this review. A comparatively stable arene oxide **459** has been synthesised in good yields by refluxing **458** in benzene in the presence of DBU for a short time.[272] The $\beta$-lactone intermediate **458** was prepared in a few steps from 1,4-dihydrobenzoic acid. The arene oxide **459** has been transformed to senepoxide.

Benzene oxide reacts with methyllithium in $S_N2''$ syn fashion as shown[273] by the transformation of the deuterated **460** to the alcohol **461**. The reaction of deuterated benzene oxide **460** with aqueous sodium azide furnishes a 60:40-mixture of **462** and **463**. The alcohol **463** is formed through $S_N2''$ anti-attack. The

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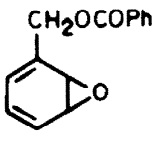


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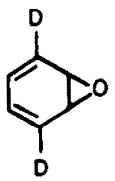


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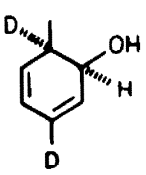


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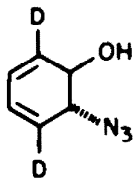


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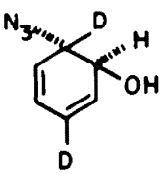
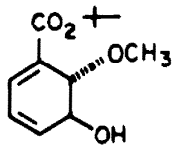



463

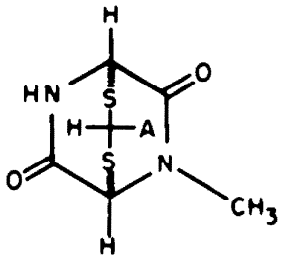
benzene oxide-oxepin **464** reacts[274] with methoxide ion to furnish the methoxy alcohol **465**; the reaction proceeds through the Michael addition of the nucleophile to the α, β-unsaturated ester moiety. The reaction of **464** with the nucleophile **466** in DMSO in the presence of triton B furnishes **467** which has been transformed to gliotoxin.[275]

Arene oxides furnish nucleophilic substitution products by reacting with polarizable nucleophiles such as thiols and azides.[276] On the other hand, arene oxides undergo aromatization faster than substitution reaction with non-polarizable nucleophiles such as amines and oxygen nucleophiles. When naphthalene-1,2-oxide (**468**) is treated with aniline in ether solution at room temperature the only product isolated is 1-naphthol.[277] When the reaction between the oxirane **468** and aniline is carried out in the presence of Woelm-200-basic alumina,[277] the product is a mixture of 1-naphthol (24%) and the substitution products **469** (31%) and **470** (11%). Alumina promoted nucleophilic attack on arene oxides with oxygen and nitrogen nucleophiles is in many cases the only method available for the preparation of substitution products.

**464**



**465**



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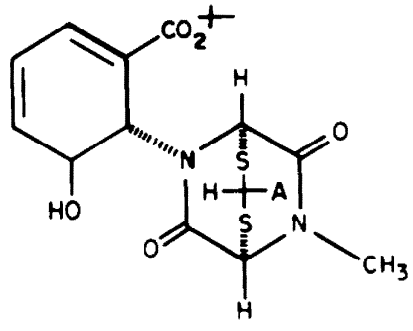

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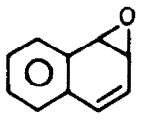
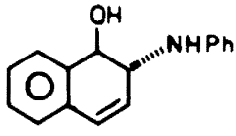
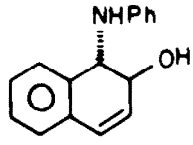


**468**



**469**



**470**

13. *Thermolysis of oxiranes*

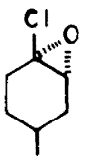
Due to ring strain suitably substituted oxiranes furnish readily, on heating, rearrangement products via cleavage of CC or CO linkages. Since the yields and stereoselectivity are usually good these rearrangement reactions are useful in synthetic studies.

2-Chlorooxiranes rearrange on heating to α-chloro ketones or α-chloroaldehydes.[10] The oxiranes **471** as well as **472** rearrange[278] on heating to the same product **473**. 2-Acetoxyoxiranes (oxiranes of enol acetates) furnish α-acetoxy aldehydes or α-acetoxy ketones on thermal rearrangement.[10] α, β-Unsaturated aldehydes and α, β-unsaturated ketones have been prepared by thermolysis of α, β-epoxysulphoxides; oxiranes **474** and **475** have been transformed to **476** and **477** respectively.[279,280]

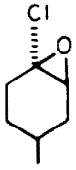
On pyrolysis, oxiranes of δ,ϵ-unsaturated ketones furnish ketals with a high degree of stereoselectivity.[281],[282] The oxirane **478** furnishes, on heating a 9:1 mixture of the exo ketal **479** (brevicomin) and endo ketal **480**.

Thermal rearrangement of styrene oxide furnishes exclusively phenylethanal and none of the isomeric acetophenone.[283] It has been suggested that the reaction probably proceeds through homolytic or heterolytic cleavage of benzylic CO linkage. The oxirane **481** furnishes the enol-acetate **482** on heating.[284]

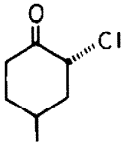
*cis*-2,3-Divinyl oxirane rearranges below 100° to 4,5-dihydrooxipine.[285] Thermal rearrangement[286] of the oxirane **483** furnishes **484**. On heating, suitably substituted oxiranes are transformed to carbonyl ylides through thermally allowed conrotatory electrocyclic opening of the oxirane ring.[287] The carbonyl ylides readily undergo cycloadditions with 1,3-dipolarophiles. The oxirane **485** rearranges to the carbonyl ylide **486** on heating;[288] the oxirane ring opening is facilitated by the phenyl and cyano substituents which stabilize the carbonyl ylide. Trapping of the carbonyl ylide **486** with dimethyl fumarate gives a 58:42 mixture of esters **487** and **488**.



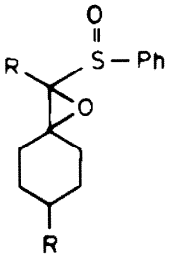

**471**



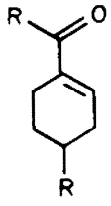

**472**



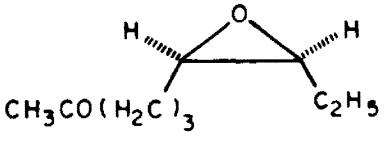

**473**



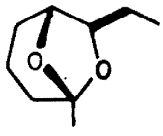

**474** R = H
**475** R = $CH_3$




**476** R = H
**477** R = $CH_3$




**478**

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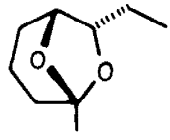
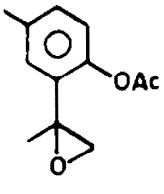
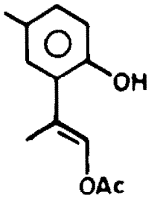


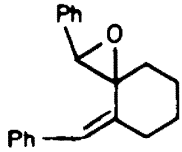

**480**



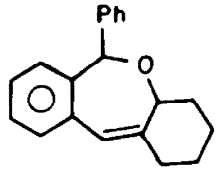

**481**



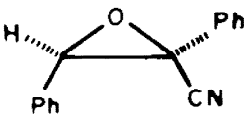

**482**



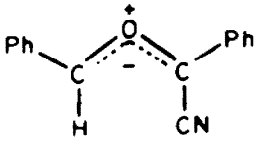

**483**



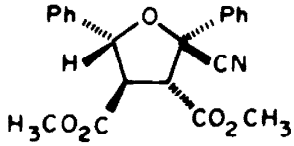

**484**



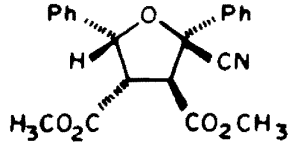

**485**




**486**




**487**




**488**

*Note added in proof.* For a recent review on oxiranes see, M. Bartok and K. L. Lang, *The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and Their Sulphur Analogues* (Edited by S. Patai), Part 2, supplement E, p. 609. Wiley, Chichester (1980).

## REFERENCES


[1]Communication No. 3132 from National Chemical Laboratory, Pune–411008, India.
[2]J. Rokach, R. N. Young, M. Kakushima, C. Lau, R. Seguin, R. Frenette and Y. Guindon, *Tetrahedron Letters* **22**, 979 (1981).
[3]H. S. I. Chao, G. A. Berchtold, D. R. Boyd, J. N. Dynak, J. E. Tomaszewski, H. Yagi and D. M. Jerina, *J. Org. Chem.* **46**, 1948 (1981).
[4]A. R. Becker, J. M. Janusz and T. C. Bruice, *J. Am. Chem. Soc.* **101**, 5679 (1979).
[5]G. Buchi, K. W. Fowler and A. M. Nadzan, *Ibid.* **104**, 544 (1982).
[6]F. Camps, J. Coll, A. Messeguer and M. A. Pericas, *Tetrahedron Letters* **21**, 2361 (1980).
[7]H. O. House, *Modern Synthetic Reactions*, Second Edition, W. A. Benjamin, Menlo Park, California 1972, p. 300.
[8]R. E. Parker and N. S. Isaacs, *Chem. Rev.* **59**, 737 (1959).
[9]A. Rosowsky, *The Chemistry of Heterocyclic Compounds* (Edited by A. Weissberger), Vol. 19, p. 1. Wiley-Interscience, New York (1964).
[10]R. N. McDonald, *Mechanisms of Molecular Migrations* (Edited by B. S. Thyagarajan), Vol. 3, p. 67. Wiley-Interscience, New York (1971).
[11]J. G. Buchenan and H. Z. Sable, *Selective Organic-Transformations* (Edited by B. S. Thyagarajan), Vol. 2, p. 1. Wiley-Interscience, New York (1972).
[12]G. Berti, *Topics in Stereochemistry* **7**, 93 (1973).
[13]D. N. Kirk, *Chemistry and Industry (London)* 109 (1973).
[14]T. C. Bruice and P. Y. Bruice, *Acc. Chem. Res.* **9**, 378 (1976).
[15]V. G. Dryuk, *Tetrahedron* **32**, 2855 (1976).
[16]K. B. Sharpless and T. R. Verhoeven, *Aldrichimica Acta* **12**, 63 (1979).
[17]W. Adam and M. Balci, *Tetrahedron* **36**, 833 (1980).
[18]J. Rebek, *Heterocycles* **15**, 517 (1981).
[19]P. A. Bartlett, *Tetrahedron* **36**, 2 (1980).
[20]H. H. Wasserman and J. L. Ives, *Ibid.* **37**, 1825 (1981).
[21]P. E. Sonnet, *Ibid.* **36**, 557 (1980).
[22]D. L. J. Clive, *Ibid.* **34**, 1049 (1978).
[23]H. C. Brown and S. Krishnamurthy, *Ibid.*, **35**, 567 (1978).
[24]P. F. Hudrlik, A. M. Hudrlik, R. J. Rona, R. N. Misra and G. P. Withers, *J. Am. Chem. Soc.* **99**, 1993 (1977), see also refs 102, 106, 166.
[25]M. Imuta and H. Ziffer, *J. Org. Chem.* **44**, 1351 (1979).
[26]K. Ishikawa, H. C. Charles and C. W. Griffin, *Tetrahedron Letters* 427 (1977).
[27]B. F. Coles, J. R. L. Smith and R. C. Garner, *J. Chem. Soc.* Perkin I, 2664 (1979).
[28]W. H. Rastetter, T. J. Richard and M. D. Lewis, *J. Org. Chem.* **43**, 3163 (1978).
[29]T. Hori and K. B. Sharpless, *Ibid.*, **43**, 1689 (1978).
[30]A. J. Biloski, R. P. Heggs and B. Ganem, *Synthesis* 810 (1980).
[31]C. J. Stark, *Tetrahedron Letters* **22**, 2089 (1981).
[32]S. E. Jacobson, F. Mares and P. M. Zambri, *J. Am. Chem. Soc.* **101**, 6946 (1979).
[33]A. L. Baumstark, D. R. Chrisope and M. E. Landis, *J. Org. Chem.* **46**, 1964 (1981).
[34]J. Rebeck, R. McCready, S. Wolf and A. Mossman, *J. Org. Chem.* **44**, 1485 (1979).
[35]F. A. Davis, N. F. Abdul-Malik, S. B. Awad and M. E. Harakal, *Tetrahedron Letters* **22**, 917 (1981).
[36]S. Krishnan, D. G. Kuhn and G. A. Hamilton, *Ibid.* 1369 (1977).
[37]R. Curci, M. Fiorentino, L. Triosi, J. O. Edwards and R. H. Pater, *J. Org. Chem.* **45**, 4758 (1980).
[38]S. Krishnan, D. G. Kuhn and G. A. Hamilton, *J. Am. Chem. Soc.* **99**, 8121 (1977).
[39]N. Shimizu and P. D. Bartlett, *Ibid.* **98**, 4193 (1976).
[40]M. Malacria and J. Gore, *J. Org. Chem.* **44**, 885 (1979).
[41]Y. Sawaki and Y. Ogata, *J. Am. Chem. Soc.* **103**, 2049 (1981).
[42]E. J. Corey, H. Niwa and J. R. Falck, *Ibid.* **101**, 1586 (1979).
[43]H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.* 1958 (1957).
[44]T. Itoh, K. Jitsukawa, K. Kanada and S. Teranishi, *J. Am. Chem. Soc.* **101**, 159 (1979).
[45]A. S. Narula, *Tetrahedron Letters* **22**, 2017 (1981).
[46]T. H. Chan, P. W. K. Lau and M. P. Li, *Tetrahedron Letters* 2667 (1976).
[47]G. W. Holbert, B. Ganem , D. V. Engen, J. Clardy, L. Borsub, K. Chantrapromma, C. Sadavongvivad and Y. Thebtaranonth, *Ibid.* 715 (1979).
[48]D. N. Bhedi, A. M. Shaligram and A. S. Rao, *Ind. J. Chem.* **14B**, 657 (1976).
[49]H. Lee and R. G. Harvey, *Tetrahedron Letters* **22**, 1657 (1981).
[50]P. P. Sane, V. R. Tadwalkar and A. S. Rao, *Ind. J. Chem.* **12**, 444 (1974).
[51]P. Chautemps and J. L. Pierre, *Tetrahedron* **32**, 549 (1976).
[52]B. R. Rossiter, T. R. Verhoeven and K. B. Sharpless, *Tetrahedron Letters* 4733 (1979).
[53]M. Ceroni and V. Sequin, *Ibid.* 3703 (1979).
[54]M. R. Johnson and Y. Kishi, *Ibid.* 4347 (1979).
[55]M. R. Johnson, T. Nakata and Y. Kishi, *Ibid.*, 4343 (1979).
[56]I. Hasan and Y. Kishi, *Ibid.* **21**, 4229 (1980).
[57]T. Fukuyama, C. L. J. Wang and Y. Kishi, *J. Am. Chem. Soc.* **101**, 260 (1979).
[58]S. Fung and J. B. Siddall, *Ibid.* **102**, 6580 (1980).
[59]P. A. Bartlett and K. K. Jernstedt, *Ibid.* **99**, 4829 (1977).
[60]K. Yamakawa, K. Nishitani and T. Tominaga, *Tetrahedron Letters* 2829 (1975).
[61]K. B. Sharpless and R. C. Michaelson, *J. Am. Chem. Soc.* **95**, 6136 (1973).
[62]E. D. Mihelich, *Tetrahedron Letters* 4729 (1979).
[63]E. D. Mihelich, K. Daniels and D. J. Eickhoff, *J. Am. Chem. Soc.* **103**, 7690 (1981).
[64]E. J. Corey, L. O. Weigel, A. R. Chamberlin, H. Cho and D. H. Hua, *Ibid.* **102**, 6613 (1980).

[65]Y. S. Sanghvi and A. S. Rao, *Ind. J. Chem.* **19B**, 608 (1980).
[66]S. Danishefsky, M. Hirama, K. Gombatz, T. Harayama, E. Berman and P. Schuda, *J. Am. Chem. Soc.* **100**, 6536 (1978).
[67]S. Terashima, N. Tanno and K. Koga, *Tetrahedron Letters* **21**, 2753 (1980).
[68]J. Depezay and A. Dureault, *Ibid.* 2869 (1978).
[69]R. K. Boeckman and E. W. Thomas, *J. Am. Chem. Soc.* 101, 987 (1979).
[70]A. Yasauda, S. Tanaka, H. Yamamoto and H. Nozaki, *Bull. Chem. Soc. Japan* **52**, 1701 (1979).
[71]J. J. Partridge, V. Toome and M. R. Uskokovic, *J. Am. Chem. Soc.* **98**, 3739 (1976).
[72]W. C. Still and M. Y. Tsai, *Ibid.*, **102**, 3654 (1980).
[73]A. J. Pearson and C. W. Ong, *Ibid.*, **103**, 6686 (1981).
[74]W. P. Jackson and S. V. Ley, *J. Chem. Soc.* Perkin Trans. I, 1516 (1981).
[75]T. Hiyama, K. Kimura and H. Nozaki, *Tetrahedron Letters* **22**, 1037 (1981).
[76]A. P. Kozikowski, R. J. Schmiesing and K. L. Sorgi, *Ibid.*, **22**, 2059 (1981).
[77]E. J. Corey, A. Marfat, J. R. Falck and J. O. Albright, *J. Am. Chem. Soc.* **102**, 1433 (1980).
[78]K. Tsuzuki, Y. Nakajima, T. Watanabe, M. Yanagiya and T. Matsumoto, *Tetrahedron Letters* 989 (1978).
[79]T. Fukuyama, B. Vranesic, D. P. Negri and Y. Kishi, *Ibid.* 2741 (1978).
[80]T. Nakata, G. Schmid, B. Vranasic, M. Okigawa, T. Smith-Palmer and Y. Kishi, *J. Am. Chem. Soc.* **98**, 2933 (1978).
[81]K. Takai, K. Oshima and H. Nozaki, *Tetrahedron Letters* **21**, 1657 (1980).
[82]R. Breslow and L. M. Maresca, *Ibid.* 623 (1977).
[83]C. G. Chavdarian and C. H. Heathcock, *Syn. Commun.* **6**, 277 (1976).
[84]M. Isobe, M. Kitamura and T. Goto, *Tetrahedron Letters* **22**, 239 (1981).
[85]C. D. Gutsche, *Org. Reactions* **8** 364 (1954).
[86]M. S. Newman and B. J. Magerlein, *Ibid.* 5, 413 (1949).
[87]W. S. Johnson, J. S. Belew, L. J. Chinn and R. H. Hunt, *J. Am. Chem. Soc.* **75**, 4995 (1953).
[88]B. M. Trost and L. S. Melvin, *Sulfur Ylides.* Academic Press, New York (1975).
[89]E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.* **87**, 1353 (1965).
[90]R. W. La Rochelle, B. M. Trost and L. Krepski, *J. Org. Chem.* **36**, 1126 )1971).
[91]B. M. Trost and M. J. Bogdanowicz, *J. Am. Chem. Soc.* **95**, 5311 (1973).
[92]C. R. Johnson, K. Mosi and A. Nakanishi, *J. Org. Chem.* **44**, 2065 (1979).
[93]N. H. Andersen, D. L. Wadner and A. L. Moore, *Syn. Commun.* **8**, 437 (1978).
[94]J. K. Crandall, H. S. Magaha, R. K. Widener and G. A. Tharp, *Tetrahedron Letters* **21**, 4807 (1980).
[95]M. Rosenberger, W. Jackson and G. Saucy, *Helv. Chim. Acta*, **63**, 1665 (1980).
[96]E. J. Corey, Y. Arai and C. Mioskowski, *J. Am. Chem. Soc.* **101**, 6748 (1979); J. Rokack, Y. Girard, Y. Guindon, J. G. Atkinson, M. Larue, R. N. Young, P. Masson and G. Holme, *Tetrahedron Letters* **21**, 1485 (1980).
[97]M. Rosenberger and C. Neukom, *J. Am. Chem. Soc.* **102**, 5425 (1980).
[98]P. Borgeat and P. Siroris, *J. Med. Chem.* **24**, 121 (1981).
[99]See Ref. 22, p. 1114.
[100]D. V. Ende and A. Krief, *Terahedron Letters* 457 (1976).
[101]W. C. Still and N. J. Novack, *J. Am. Chem. Soc.* **103**, 1283 (1981).
[102]W. E. Fristad, T. R. Bailey and L. A. Paqutte, *J. Org. Chem.* **45**, 3028 (1980).
[103]P. A. Bartlett and J. K. Jernstedt, *Tetrahedron Letters* **21**, 1607 (1980).
[104]P. A. Bartlett and J. Myerson, *J. Am. Chem. Soc.* **100**, 3950 (1978).
[105]*Idem*, *J. Org. Chem.* **44**, 1625 (1979).
[106]W. E. Fristad, T. R. Bailey, L. A. Paquette, G. Gleiter and M. C. Bohm, *J. Am. Chem. Soc.* **101**, 4420 (1979).
[107]M. F. Haslanger and S. Ahmed, *Org. Chem.* **46**, 4808 (1981).
[108]E. J. Corey, E. J. Trybulski, L. S. Melvin, K. C. Nicolaou, J. A. Secrist, R. Cett, P. W. Sheldrake, J. R. Falck, D. J. Brunelle, M. F. Haslanger, S. Kim and S. Yoo, *J. Am. Chem. Soc.* **100**, 4618 (1978).
[109]R. S. Buckanin, S. J. Chen, D. M. Frieze, F. T. Sher and G. A. Berchtold, *Ibid.* **102**, 1200 (1980).
[110]H. D. Becker, T. Bremholt and E. Alder, *Tetrahedron Letters* 4205 (1972).
[111]A. Ichihara, M. Kobayashi, K. Oda, S. Sakamura and R. Sakai, *Tetrahedron* **35**, 2861 (1979).
[112]D. A. McGowan and G. A. Berchtold, *J. Org. Chem.* **46**, 2381 (1981).
[113]V. Schurig, B. Koppenhoefer and W. Buerkle, *Ibid.* **45**, 538 (1980).
[114]R. Mengel and M. Bartke, *Angew. Chem. Int. Ed. Engl.* **17**, 679 (1978).
[115]See Ref. 9, p. 71.
[116]H. O. House and R. S. Ro, *J. Am. Chem. Soc.* **80**, 2428 (1958).
[117]V. Attrache, J. Pai, D. Sok and C. J. Sih, *Tetrahedron Letters* **22**, 3443 (1981).
[118]E. J. Corey, A. E. Barton and D. A. Clark, *J. Am. Chem. Soc.* **102**, 4278 (1980).
[119]N. Langlois and P. Potier, *J. Chem. Soc.* Chem. Commun. 582 (1979).
[120]W. H. Pirkle and P. L. Rinaldi, *J. Org. Chem.* **42**, 2080 (1977).
[121]H. B. Kagan, H. Mimoun, C. Mark and V. Schurig, *Angew. Chem. Int. Ed. Engl.* **18**, 485 (1979).
[122]K. Tani, M. Hanafusa and S. Otsuka, *Tetrahedron Letters* 3017 (1979).
[123]M. de Smet, B. Witholt and H. Wynberg, *J. Org. Chem.* **46**, 3128 (1981).
[124]H. Ohta and H. Tetsukawa, *Agric. Biol. Chem.* **43**, 2099 (1979).
[125]K. Imai, S. Marumo and T. Ohtaki, *Tetrahedron Letters* 1211 (1976).
[126]S. K. Balani, D. R. Boyd, E. S. Cassidy, R. M. E. Greene, K. M. McCombe and N. D. Sharma, *Ibid.* **22**, 3277 (1981).
[127]W. H. Pirkle and P. L. Rinaldi, *J. Org. Chem.* **43**, 3803 (1978).
[128]R. B. Boar and K. Damps, *J. Chem. Soc.* Perkin I, 709 (1977).
[129]S. Terashima, M. Hayashi and K. Koga, *Tetrahedron Letters* **21**, 2733 (1980).
[130]H. Wynberg and B. Marsman, *J. Org. Chem.* **45**, 158 (1980).
[131]J. C. Hummelen and H. Wynberg, *Tetrahedron Letters* 1089 (1978).
[132]S. Julia, J. Masana and J. C. Vega, *Angew Chem. Int. Ed. Engl.* **19**, 929 (1980).
[133]S. Colonna, R. Fornasier and V. Pfeiffer, *J. Chem. Soc.* Perkin I, 8 (1978).
[134]T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.* **102**, 5974 (1980).
[135]B. L. Rossiter, T. Katsuki and K. B. Sharpless, *Ibid.* **103**, 464 (1981).
[136]E. J. Corey, S. Hashimoto and A. E. Barton, *Ibid.* **103**, 721 (1981).

[137]K. Mori and T. Ebata, *Tetrahedron Letters* **22**, 4281 (1981).
[138]K. Mori and T. Umemura, *Ibid.* **22**, 4433 (1981).
[139]E. J. Corey, A. Marfat and B. C. Laguzza, *Ibid.* **22**, 3339 (1981).
[140]K. Mori and H. Ueda, *Tetrahedron* **37**, 2581 (1981).
[141]E. J. Corey, P. B. Hopkins, J. E. Munroe, A. Marfat and S. Hashimoto, *J. Am. Chem. Soc.* **102**, 7986 (1980).
[142]W. C. Still and H. Ohmizu, *J. Org. Chem.* **46**, 5242 (1981).
[143]P. Sundararaman, G. Barth and C. Djerassi, *J. Am. Chem. Soc.* **103**, 5004 (1981).
[144]A. S. Kende and J. P. Rizzi, *Ibid.* **103**, 4247 (1981).
[145]V. S. Martin, S. C. Woodard, T. Katsuki, Y. Yamada, M. Ikeda and K. B. Sharpless, *Ibid.* **103**, 6237 (1981).
[146]H. Nagaoka and Y. Kishi, *Tetrahedron* **37**, 3873 (1981).
[147]A. I. Meyers and J. P. Hudspeth, *Tetrahedron Letters* **22**, 3925 (1981).
[148]D. Seebach and H. O. Kalinowski, *Nachr. Chem. Tech.* **24**, 415 (1976).
[149]U. Schmidt, J. Gombos, E. Haslinger and H. Zak, *Chem. Ber.* **109**, 2628 (1976).
[150]L. R. Hillis and R. C. Ronald *J. Org. Chem.* **46**, 3348 (1981).
[151]K. Utimoto, K. Uchida, M. Yamaya and H. Nozaki, *Tetrahedron Letters* **3641** (1977).
[152]K. Mori, M. Sasaki, S. Yamada, T. Suguro and S. Masuda, *Tetrahedron* **35**, 1601 (1979).
[153]K. Mori and S. Yamada, *Ibid.* **35**, 1279 (1979).
[154]K. Mori, *Agric. Biol. Chem.* **40**, 1617 (1976).
[155]U. Schmidt, J. Talbiersky, F. Bartkowirk and J. Wid, *Angew. Chem. Int. Ed. Engl.* **19**, 198 (1980).
[156]D. E. McClure, E. L. Engelhardt, K. Mensler, S. King, W. J. Saari, J. R. Huff and J. J. Baldwin, *J. Org. Chem.* **44**, 1826 (1979).
[157]D. E. McClure, B. H. Arison and J. J. Baldwin, *J. Am. Chem. Soc.* **101**, 3666 (1979).
[158]J. J. Baldwin, A. W. Raab, K. Mensler, B. H. Arison and D. E. McClure, *J. Org. Chem.* **43**, 4876 (1978).
[159]E. Hungerbuhler, D. Seebach and D. Wasmuth, *Angew. Chem. Int. Ed. Engl.* **18**, 958 (1979).
[160]H. Takayama, M. Ohmori and S. Yamada, *Tetrahedron Letters* **21**, 5027 (1980).
[161]D. Seebach, B. Seuring, H. O. Kalinowski, W. Lubosh and B. Renger, *Angew. Chem. Int. Ed. Engl.* **16**, 264 (1977).
[162]D. L. Boger and J. S. Panek, *J. Org. Chem.* **46**, 1208 (1981).
[163]K. Mori, *Tetrahedron* **32**, 1101 (1976).
[164]K. Mori, T. Takigawa and T. Matsuo, *Ibid.* **35**, 933 (1979).
[165]K. Mori, M. Oda and M. Matsui, *Tetrahedron Letters* 3173 (1976).
[166]C. Burford, F. Cooke, E. Ehlinger and P. Magnus, *J. Am. Chem. Soc.* **99**, 4536 (1977).
[167]H. Kakiuchi and T. Ijima, *Tetrahedron* **36**, 1011 (1980).
[168]H. Kakiuchi, T. Ijina and H. Horie, *Ibid.* **35**, 303 (1979).
[169]M. Nitaya nd M. Rosenblum, *J. Organometal. Chem.* **136**, C23–C26 (1977).
[170]C. Huynh, F. Derguini-Boumechal and G. Linstrumelle, *Tetrahedron Letters* 1503 (1979).
[171]C. R. Johnson, R. W. Herrand D. M. Wieland, *J. Org. Chem.* **38**, 4263 (1973).
[172]R. Acker, *Tetrahedron Letters* 3407 (1977).
[173]T. E. Murray, E. G. Samsel, V. Varma and J. R. Norton, *J. Am. Chem. Soc.* **103**, 7520 (1981).
[174]W. H. Pirkle and P. E. Adams, *J. Org. Chem.* **44**, 2169 (1979).
[175]A. Marfat, P. R. McGuirk and P. Helquist, *Ibid.* **44**, 3888 (1979).
[176]S. Danishefsky, P. F. Schuda, T. Kitahara and S. J. E. Etheradge, *J. Am. Chem. Soc.* **99**, 6066 (1977); F. Zutterman, H. D. Wilde, R. Mijngheer, D. DeClercq and M. Vandewalle, *Tetrahedron* **35**, 2389 (1979).
[177]S. Danishefsky, M. Tsai and T. Kitahara, *J. Org. Chem.* **42**, 394 (1977); M. R. Roberts and R. H. Schlessinger, *J. Am. Chem. Soc.* **103**, 724 (1981).
[178]G. R. Kieczykowski, M. L. Quesada and R. H. Schlessinger, *Ibid.* **102**, 782 (1980).
[179]G. R. Kieczykowski, M. R. Roberts and R. H. Schlessinger, *J. Org. Chem.* **43**, 788 (1978).
[180]J. R. Donaubauer and T. C. McMorris, *Tetrahedron Letters* **21**, 2771 (1980).
[181]P. Hullot, T. Cuvigny, M. Larcheveque and H. Normant, *Can. J. Chem.* **55**, 266 (1977).
[182]S. Danishefsky, T. Kitahara, M. Tsai and J. Dynak, *J. Org. Chem.* **41**, 1669 (1976).
[183]B. J. Fritzsimmons and B. Fraser-Reid, *J. Am. Chem. Soc.* **101**, 6123 (1979).
[184]P. Ma, V. S. Martin, S. Masamune, K. B. Sharpless and S. M. Viti, *J. Org. Chem.* **47**, 1378 (1982).
[185]N. Minami, S. S. Ko and Y. Kishi, *J. Am. Chem. Soc.* **104**, 1109 (1982).
[186]L. E. Overman and K. L. Bell, *Ibid.* **103**, 1851 (1981).
[187]M. A. Adams, A. J. Duggam, J. S. Molanoff and J. Meinwald, *Ibid.* **101**, 5364 (1979).
[188]G. L. Olson, H. Cheung, K. Morgan and G. Saucy, *J. Org. Chem.* **45**, 803 (1980).
[189]R. J. Anderson, K. G. Adams, H. R. Chinn and C. A. Henrick, *Ibid.* **45**, 2229 (1980).
[190]B. M. Trost and Y. Matsumura, *Ibid.* **42**, 2036 (1977).
[191]D. R. Kelly and S. M. Roberts, *J. Chem. Soc.* Perkin I, 852 (1980).
[192]Y. Ohfune, P. A. Grieco, C. L. J. Wang and G. Majetich, *J. Am. Chem. Soc.* **100**, 5946 (1978).
[193]B. M. Trost and T. P. Klun, *Ibid.* **103**, 1864 (1980).
[194]E. J. Corey and M. G. Bock, *Tetrahedron Letters* 2643 (1975); W. J. Elliott and J. Fried, *J. Org. Chem.* **41**, 2469 (1976).
[195]R. M. Carlson, A. R. Oyler and J. R. Peterson, *Ibid.* **40**, 1610 (1975).
[196]E. Walchli-Schaer and C. H. Eugster, *Helv. Chim. Acta*, **61**, 928 (1978).
[197]Y. Kojima and N. Kato, *Tetrahedron Letters* **21**, 5033 (1980).
[198]D. L. J. Clive, G. J. Chittattu, V. Farina, W. A. Kiel, S. M. Menchen, C. G. Russell, A. Singh, C. K. Wong and N. J. Curtis, *J. Am. Chem. Soc.* **102**, 4438 (1980).
[199]D. R. Burfield, S. Gan and R. H. Smithers, *J. Chem. Soc.* Perkin I, 666 (1977).
[200]W. L. Nelson and T. R. Burke, *J. Org. Chem.* **43**, 3641 (1978).
[201]G. H. Posner and D. Z. Rogers, *J. Am. Chem. Soc.* **99**, 8208 (1977).
[202]G. Stork, L. D. Cama and D. R. Coulson, *Ibid.* **96**, 5268 (1974); G. Stork and J. F. Cohen, *Ibid.* **96**, 5270 (1974).
[203]F. E. Ziegler, G. R. Reid, W. I. Studt and P. A. Wender, *J. Org. Chem.* **42**, 1991 (1977).
[204]T. Matsuo, K. Mori and M. Matsui, *Tetrahedron Letters*, 1979 (1976); J. H. Babler and A. J. Torterello, *J. Org. Chem.* **41**, 885 (1976).
[205]M. Apparu and M. Barrelle, *Tetrahedron* **34**, 1691 (1978).
[206]B. Corbel and T. Durst, *J. Org. Chem.* **41**, 3648 (1976).
[207]J. Wolinsky, P. Hull and E. M. White, *Tetrahedron* **32**, 1335 (1976).

[208]C. K. Bradsher and D. C. Reames, *J. Org. Chem.* **43**, 3800 (1978).
[209]R. M. Cory, D. M. T. Chan, F. R. McLaren, M. H. Rasmussen and R. M. Renneborg, *Tetrahedron Letters* 4133 (1979).
[210]M. Kodama, Y. Matsuki and S. Ito, *Ibid.* 1121 (1976).
[211]K. Shimada, M. Kodama and S. Ito, *Ibid.* **22**, 4275 (1981).
[212]E. E. Vantamelen, J. G. Carlson, R. K. Russell and S. R. Zawacky, *J. Am. Chem. Soc.* **103**, 4615 (1981); see also D. Nasipuri and G. Das, *J. Chem. Soc.* Perkin I, 2776 (1979).
[213]T. Masamune, M. Ono, S. Sato and A. Murai, *Tetrahedron Letters* 371 (1978).
[214]T. Nakata, G. Schmid, B. Vranesic, M. Okigawa, T. Smith-Palmer and Y. Kishi, *J. Am. Chem. Soc.* **100**, 2933 (1978).
[215]T. Nakata and Y. Kishi, *Tetrahedron Letters* 2745 (1978).
[216]T. Fukuyama, C. L. J. Wang and Y. Kishi, *J. Am. Chem. Soc.* **101**, 260 (1979).
[217]K. C. Nicolaou, D. P. Papahatjis, D. A. Claremon and R. E. Dolle, *Ibid.* **103**, 6967 (1981).
[218]R. Chen and D. A. Rowand, *Ibid.* **102**, 6609 (1980).
[219]J. Gutzwiller and M. R. Uskokovic, *Ibid.* **100**, 576 (1978).
[220]W. R. Roush, *Ibid.* **100**, 3599 (1978).
[221]M. M. Kayser and P. Morand *Can. J. Chem.* **58**, 302 (1980).
[222]A. Yasuda, M. Takahashi and H. Takaya, *Tetrahedron Letters* **22**, 2413 (1981).
[223]J. C. Saddler and P. L. Fuchs, *J. Am. Chem. Soc.* **103**, 2112 (1981).
[224]J. P. Marino and D. M. Floyd, *Tetrahedron Letters* 675 (1979).
[225]J. P. Marino and H. Abe, *J. Am. Chem. Soc.* **103**, 2907 (1981).
[226]J. P. Marino and M. G. Kelly, *J. Org. Chem.* **46**, 4389 (1981).
[227]P. A. Wender, J. M. Erhardt and L. J. Letendre, *J. A. Chem. Soc.* 103, 2114 (1981).
[228]*H. W. Pauls and B. Fraser-Reid, Ibid.* **102**, 3956 (1980).
[229]P. D. Klemmensen, H. Kolind-Andersen, H. B. Madsen nnd A. Svendsen, *J. Org. Chem.* **44**, 416 (1979).
[230]J. P. Marino and J. S. Farina, *Ibid.* **41**, 3213 (1976).
[231]J. P. Marino and H. Abe, *Ibid.* **46**, 5379 (1981).
[232]J. P. Marino and N. Hatanaka, *Ibid.* **44**, 4467 (1979).
[233]R. F. Newton and S. M. Roberts, *Tetrahedron*, **36**, 2163 (1980).
[234]J. Gras, *J. Org. Chem.* **46**, 3738 (1981).
[235]G. Teutsch and .A. Belanger, *Tetrahedron Letters* 2051 (1979).
[236]T. Fujisawa, T. Sato, T. Kawara and K. Ohashi, *Ibid.* **22**, 4823 (1981).
[237]M. Tamura and G. Sazukamo, *Ibid.* **22**, 577 (1981).
[238]P. M. Savu and J. A. Katzenellenbogen, *J. Org. Chem.* **46**, 239 (1981).
[239]M. Suzuki, Y. Oda and R. Noyori, *J. Am. Chem. Soc.* **101**, 1623 (1979).
[240]J. Tsuji, H. Kataoka and Y. Kobayashi, *Tetrahedron Letters* **22**, 2575 (1981).
[241]Y. Guindon, R. N. Young and R. Frenette, *Synth. Commun.* **11**, 391 (1981).
[242]C. L. Kissel and B. Rickborn, *J. Org. Chem.* **37**, 2060 (1972).
[243]M. Apparu and M. Barrele, *Tetrahedron* **34**, 1541 (1978).
[244]K. Yamakawa, M. Kobayashi, S. Hinata and T. Satoh, *Tetrahedron Letters* 3871 (1979).
[245]R. P. Thummel and B. Rickborn, *J. Am. Chem. Soc.* **92**, 2064 (1970).
[246]J. S. Dutcher, J. G. Macmillan and C. H. Heathcock, *J. Org. Chem.* **41**, 2663 (1976).
[247]R. J. Giguere and H. M. R. Hoffman, *Tetrahedron Letters* **22**, 5039 (1981).
[248]S. Tanaka, A. Yasuda, H. Yamamoto and H. Nozaki, *J. Am. Chem. Soc.* **97** 3252 (1975).
[249]H. Yamamoto and H. Nozaki, *Angew. Chem. Int. Ed. Engl.* **17**, 169 (1978).
[250]E. J. Corey, P. B. Hopkins, J. E. Munroe, A. Marfat and S. Hashimoto, *J. Am. Chem. Soc.* **102**, 7986 (1980).
[251]S. Murata, M. Suzuki and R. Noyori, *Ibid.* **101**, 2738 (1979); R. Noyori, S. Murata and M. Suzuki, *Tetrahedron*, **37**, 3899 (1981).
[252]M. R. Detty, *J. Org. Chem.* **45**, 924 (1980); M. R. Detty and M. D. Seidler, *Ibid.* **46**, 1283 (1981).
[253]G. A. Kraus and K. Frazier, *Ibid.* **45**, 2579 (1980); H. Sakurai, K. Sasaki and A. Hosomi, *Tetrahedron Letters* **21**, 2329 (1980).
[254]T. Inoue, T. Uchimaru and T. Mukaiyama, *Chemistry Letters* 1215 (1977).
[255]V. S. Joshi and Sukh Dev, *Tetrahedron* **33**, 2955 (1977).
[256]D. J. Morgans, K. B. Sharpless and S. G. Traynor, *J. Am. Chem. Soc.* **103**, 462 (1981).
[257]K. B. Sharpless and R. F. Lauer, *Ibid.* **95**, 2697 (1973).
[258]B. M. Trost and L. N. Jungheim, *Ibid.* **102**, 7910 (1980).
[259]E. J. Corey, A. Marfat, J. Munroe, K. S. Kim, P. B. Hopkins and F. Brien, *Tetrahedron Letters* **22**, 1077 (1981).
[260]G. Stork and A. A. Ponaras, *J. Org. Chem.* **41**, 2937 (1976).
[261]E. Toromanoff, *Tetrahedron* **36**, 2809 (1980).
[262]M. R. Roberts, W. H. Parsons and R. H. Schessinger, *J. Org. Chem.* **43**, 3970 (1978).
[263]G. Rucker, H. Horster and W. Gajewski, *Synth. Commun.* **10**, 623 (1980).
[264]T. Nakata, T. Tanaka and T. Oishi, *Tetrahedron Letters* **22**, 4723 (1981).
[265]G. R. Weihe and T. C. McMorris, *J. Org. Chem.* **43**, 3942 (1978); E. J. Corey and H. E. Ensley, *Ibid.* **38**, 3187 (1973); see also ref. 108.
[266]E. J. Corey, S. Kim, S. Yoo, K. C. Nicolaou, L. S. Melvin, D. J. Bundle, J. F. Falck, E. J. Trybulski, R. Lett and P. W. Sheldrake, *J. Am. Chem. Soc.* **100**, 4620 (1978).
[267]P. A. Grieco, M. Nishizawa, T. Oguri, S. D. Burke and N. Marinovic, *Ibid.* **99**, 5773 (1977).
[268]D. Felix, R. K. Muller, U. Horn, R. Joos, J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta*, **55**, 1276 (1972); M. Tanabe, D. F. Crowe and R. L. Dehm, *Tetrahedron Letters* 3943 (1967); T. Kametani, M. Tsubuki and H. Nemoto, *Ibid.* **21**, 4855 (1980); T. Kametani, K. Suzuki and H. Nemoto, *Ibid.* **21**, 1469 (1980); R. V. Stevens, J. M. Fitzpatrick, P. B. Germaraad, B. L. Harrison and R. Lapalme, *J. Am. Chem. Soc.* **98**, 6313 (1976); R. Stevens, R. E. Cherpeck, B. L. Harrison, J. Lai and R. Lapalme, *Ibid.* **98**, 6317 (1976); F. H. Batzold and C. H. Robinsonl, *J. Org. Chem.* **41**, 313 (1976); P. J. Kocienski and G. J. Cernigliaro, *Ibid.* **41**, 2927 (1976).
[269]P. Wharton and D. Bohlen, *J. Org. Chem.* **26**, 3615 (1961); also see Ref. 203.
[270]A. R. Becker, J. M. Janusz and T. C. Bruice, *J. Am. Chem. Soc.* **101**, 5679 (1979).
[271]E. Vogel and H. Gunther, *Angew. Chem. Int. Ed. Engl.* **6**, 385 (1967).
[272]B. Ganem, G. W. Holbert, L. B. Weiss and K. Ishizumi, *J. Am. Chem. Soc.* **100**, 6483 (1978).
[273]A. M. Jeffrey, H. J. C. Yeh, D. M. Jerina, R. M. Demarinis, C. H. Foster, D. E. Piccolo and G. A. Berchtold, *Ibid.* **96**, 6929 (1974).
[274]R. M. Demarinis, C. N. Filer, S. M. Waraszkiewicz and G. A. Berchtold, *Ibid.* **96**, 1193 (1974).
[275]T. Fukuyama, S. Nakatsuka and Y. Kishi, *Tetrahedron*, **37**, 2045 (1981).
[276]P. Y. Bruice, T. C. Bruice, H. Yagi and D. M. Jerina, *J. Am. Chem. Soc.* **98**, 2973 (1976).

[277]G. H. Posner and D. Z. Rogers, *Ibid.* **99**, 8214 (1977).
[278]R. N. McDonald and T. E. Tabor, *Ibid.* **89**, 6573 (1967).
[279]V. Reutrakul and W. Kanghae, *Tetrahedron Letters* 1377 (1977).
[280]D. F. Taber and P. P. Gunn, *J. Org. Chem.* **44**, 450 (1979).
[281]H. H. Wasserman and E. H. Barber, *J. Am. Chem. Soc.* **91**, 3674 (1969).
[282]J. L. Coke, H. J. Williams and S. Natarajan, *J. Org.Chem.* **42**, 2380 (1977).
[283]J. M. Watson and B. L. Young, *Ibid.* **39**, 116 (1974).
[284]V. V. Dhekne and A. S. Rao, *Ind. J. Chem.* **19B**, 852 (1980).
[285]E. L. Stogryn, M. H. Gianni and A. J. Passannante, *J. Org. Chem.* **29**, 1275 (1964).
[286] W. Elerbach, B. Burchardt and V. Trostmann, *Tetrahedron Letters* 4049 (1979).
[287]K. N. Houk, N. G. Rondan, C. Santiago, C. J. Gallo, R. W. Gandour and G. W. Griffin, *J. Am. Chem. Soc.* **102**, 1504 (1980).
[288]V. Markowski and R. Huisgen, *Tetrahedron Letters* 4643 (1976).