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Oxygen-Directed Carbocyclizations of Epoxides

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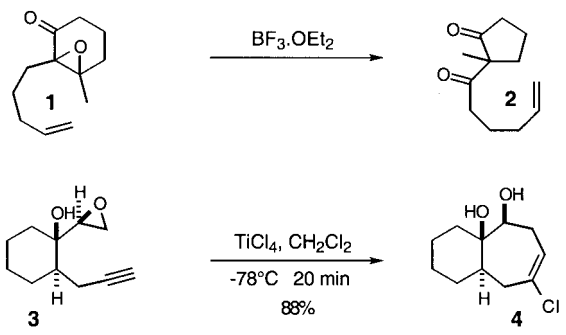
Contents

1. Introduction

Epoxides are among the most important intermediates in organic synthesis[1] chiefly because of their ease of preparation, the ease with which they undergo nucleophilic attack, and the control of relative and absolute configuration of epoxides and products from their reactions. The pronounced electrophilicity of epoxides is attributable to a combination of the polarizing nature of the oxygen atom and the release of strain upon rupture of the three-membered ring. Where a nucleophilic site is present but some atoms away from the epoxide, the possibility exists for stereocontrolled ring formation by internal nucleophilic attack upon the epoxide. Such cyclizations have been extensively studied.[2,3] The cyclization can be initiated by making the epoxide more electrophilic, using either protonic or Lewis acids.[4] Cyclization can be terminated by a variety of nucleophiles, though commonly by a π-system such as an alkene, alkyne or an arene moiety.

The value of hydroxyl-directed processes is amply illustrated by the metal-catalyzed epoxidation of allylic alcohols,[5–8] including its asymmetric version, the Katsuki–Sharpless reaction[8a] that usually provides 2,3-epoxy alcohols of high enantiomeric purity. However, hydroxyl-directed *cyclizations* of 2,3-epoxy alcohols can also display high degrees of regio- and stereocontrol. *The presence of an oxygen atom at the carbon atom adjacent to the epoxide ring can have a marked effect on the constitution and configuration of the products(s), as well as on the yield(s).* This is illustrated in Scheme 1, where treatment of the epoxide **1** with Lewis acids led not to a 6–7 fused system, but instead to **2**, a product of a ring contraction.[9] In contrast, the cyclization of the epoxy alcohol **3** afforded



Scheme 1.

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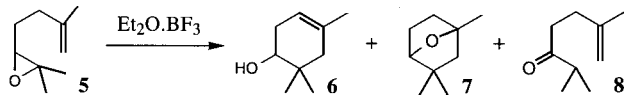
the bicyclic diol **4**, in high yield, and as a single diastereoisomer.[10]

This report concerns the latter types of epoxide cyclizations, in which the possibility exists of directing effects of a neighbouring oxygen atom. It will attempt to provide some understanding of such processes, which in the main have been reported relatively recently. Comparisons will be made with the many classical epoxide cyclizations that do *not* involve an oxygenated function near or adjacent to the epoxide. These latter cyclizations will be considered first, in order to provide the relevant context and background.

2. General Features of Epoxide Cyclizations

2.1. Early biogenetic work

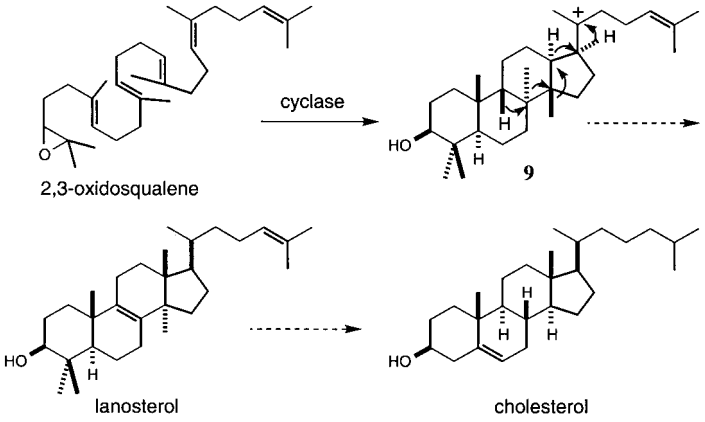
For more than 40 years, mechanistic details of enzymic cyclizations involved in the biosynthesis of steroids and terpenoids have been of continued interest.[2–4,11–14] The idea that cyclizations of epoxide intermediates were implicated in plant and mammalian terpenoid biosynthesis led to in vitro studies of the cyclization of model compounds, pioneering work being reported by Goldsmith and co-workers.[3,15] They used simple epoxy alkene model systems based on the biosynthesis of cholesterol. Geraniolene monoepoxide **5** (Scheme 2) was treated with boron trifluoride etherate to give two cyclized products **6** and **7**, and the ketone **8**. Later, it was shown that the use of tin(IV) chloride as the Lewis acid gave only the cyclized products **6** and **7**.



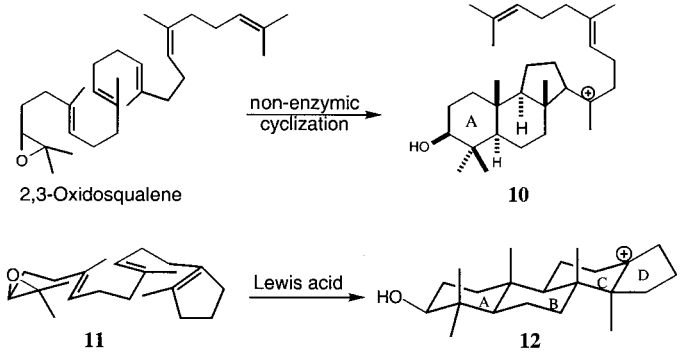
Scheme 2. Cyclization of geraniolene monoepoxide.

Subsequent experiments by the groups of van Tamelen[16] and Corey[17] demonstrated the intermediacy of 2,3-oxidosqualene in the biosynthesis of lanosterol (Scheme 3). 2,3-Oxidosqualene (from in vitro epoxidation of squalene)[18] was cyclized in high yield using pig[16] or rat[17] liver enzymes to give lanosterol. Stork[13b] and Eschenmoser[13c] formulated the hypothesis that polyalkenes could react in a defined conformation which, in combination with antiperiplanar addition to double bonds, allows prediction of the relative stereochemistry of the cyclization products. The chair–boat–chair conformation of 2,3-oxidosqualene secures the stereocontrol during cyclization. The cationic protosterol intermediate **9** undergoes a series of 1,2-shifts to give lanosterol, which affords cholesterol by a biosynthetic pathway established by labelling.

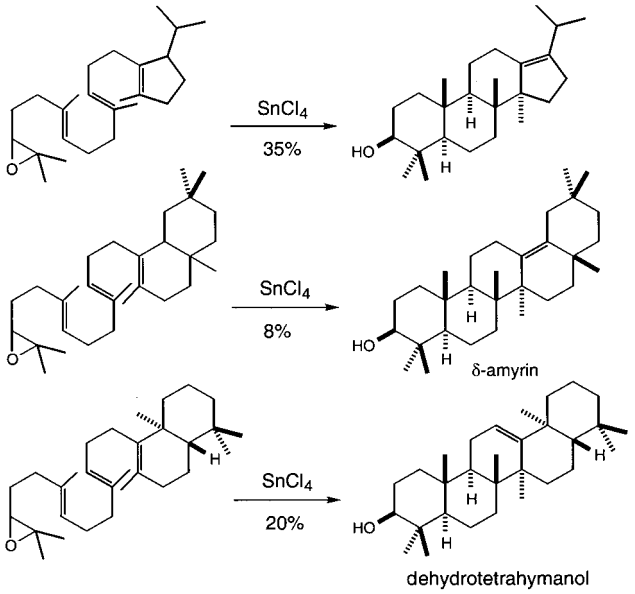
Non-enzymic cyclizations of 2,3-oxidosqualene have been attempted[13a] using conditions normally employed for other cyclizations, but no lanosterol or any other tetracycle was found (Scheme 4). Instead, tricyclic products derived from



Scheme 3. Sterol biosynthesis.



Scheme 4. Tri- and tetra-cyclizations.



Scheme 5. Biomimetic syntheses of naturally occurring polycyclic systems.

the carbocation **10** were isolated, owing to the greater stability of the tertiary carbocation.

A solution to the above problem of the size of the C-ring formed was found by van Tamelen and co-workers[2] who incorporated a preformed D-ring in the epoxide **11**. This eliminated preferential carbocation stability in the product, by tricyclization, and allowed formation of the normally more stable six-membered C-ring as in **12**. A preformed cycloalkene ring has proved very useful for the synthesis of many polycyclic systems, as exemplified in Scheme 5.[2]

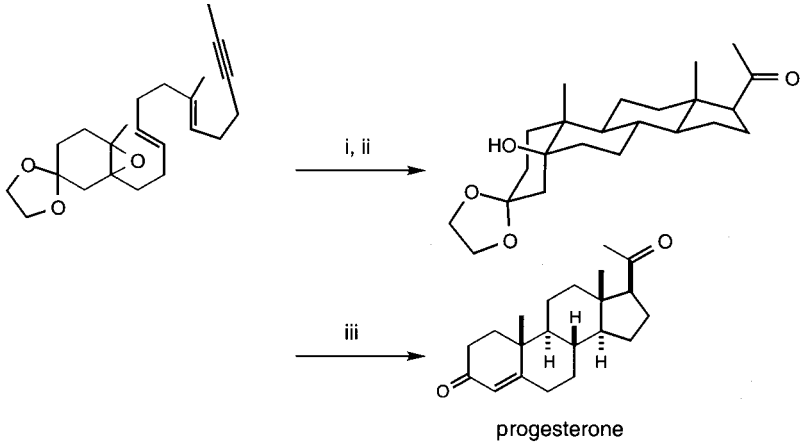
In vitro cyclizations occur through the chair–chair–chair or chair–boat–chair folding of the epoxide chain and always result in *trans*-fused AB rings (Scheme 5). The problem of how to prepare sterol systems with *cis*-fused AB rings was solved by van Tamelen and co-workers[19] by preforming the A-ring. In this way they achieved a succinct route to progesterone (44% from the monocyclic precursor) in which four contiguous stereogenic centres were created in one reaction (Scheme 6).

2.2. Conversion of 2,3-oxidosqualene into lanosterol: a comparison with in vitro cyclizations

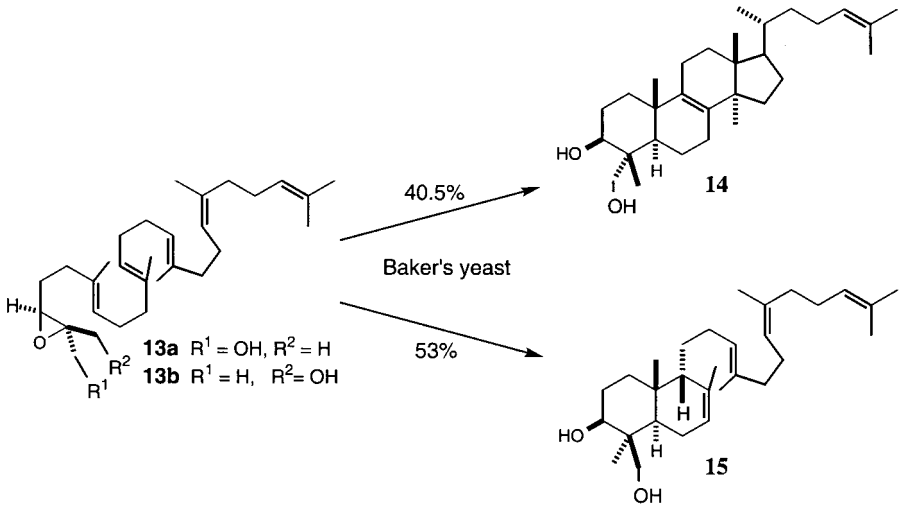
Recently, good evidence has been presented concerning ring closures under *enzymic* conditions that implicate cations and products predicted by Markovnikov's rule. Thus, the non-enzymic formation of ring C of **10** (Scheme 4) is closely analogous to the corresponding step in the biosynthesis of lanosterol. Further steps, including a 1,2-ring expansion of ring C, lead to the protosterol cation, and thence to lanosterol (Scheme 3). Thus, the cyclization of (*S*)-2,3-oxidosqualene to the protosterol cation is probably *not* concerted, but occurs in stages involving discrete carbocationic intermediates, though under tight conformational control.[20]

Comparisons can be made between the above enzymic cyclizations and several of the non-enzymic cyclizations of epoxy alcohols that occupy the following pages. Corey and co-workers have reported[20] the failure of the attempted enzymic cyclization using, inter alia, 20-thia-2,3-oxidosqualene, and propose that the action of lanosterol synthase involves: (i) enzymic binding to induce the correct *folding* of 2,3-oxidosqualene; (ii) a conformational change, dependent upon step (i), that appropriately positions an electrophilic group for *activation* of the epoxide; and (iii) cyclization to give the protosterol cation. In the case of some of the non-enzymic cyclizations of 2,3-epoxy alcohols, the constitution and configuration of the products strongly suggest involvement of the following processes: (i) binding of the Lewis acid to the hydroxylic oxygen atom (by ligand exchange); (ii) coordination of the epoxide oxygen atom to the Lewis acid centre; and (iii) cyclization, presumably as a result of both activation of the epoxide and its alignment with the π-nucleophile in a manner appropriate for the resulting mode of cyclization that is observed.

The outcome of enzymic cyclization of C-1 hydroxylated surrogate squalenoids can depend upon the configuration of the initial epoxy alcohol (Scheme 7).[21] Thus, whereas the complete tetracyclic framework of **14** was enantioselectively formed from the epoxy alcohol **13a**, cyclization of the diastereoisomer **13b** proceeded only as far as the bicyclic system **15**. From these experiments it can be seen that *the effect of a neighbouring hydroxyl group on the*



Scheme 6. A succinct route to progesterone. *Reagents*: (i) $SnCl_4$, $(CH_2O)_2CO$; (ii) aq. K_2CO_3; (iii) *p*-TsOH, aq. acetone.



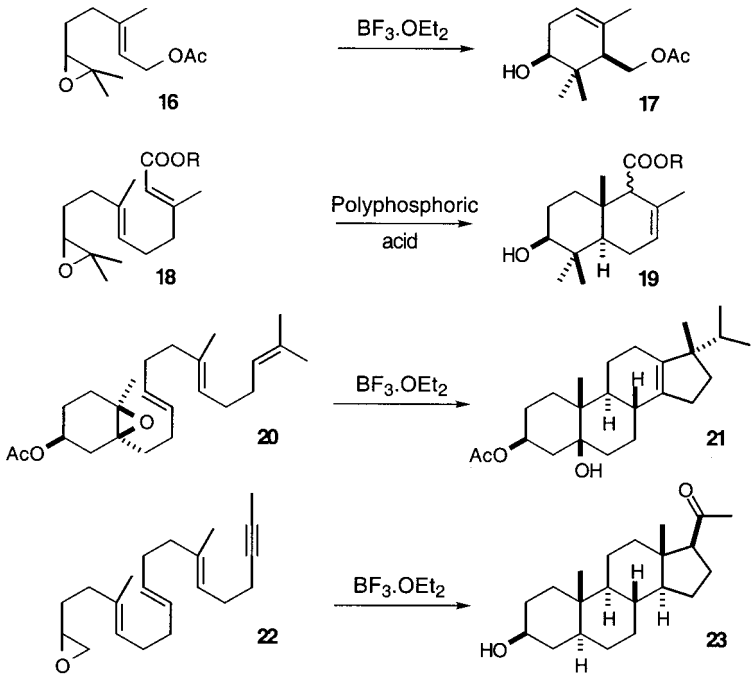
Scheme 7. Enzymic cyclization of surrogate squalenoids.

course of the cyclization of 2,3-oxidosqualene can be considerable. The nature of the products of cyclization presumably depends upon steric and/or electronic effects operating on the β-face of the chair–boat–chair conformer adopted immediately prior to cyclization.

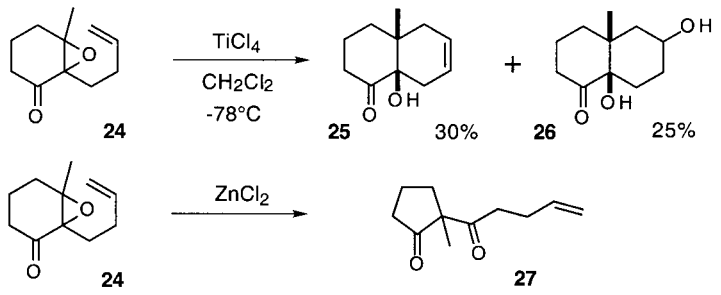
2.3. Further examples of in vitro epoxy alkene cyclizations

Studies have shown that biosyntheses of steroids and polycyclic terpenes proceed through stepwise conversion of acetic acid into polyunsaturated acyclic hydrocarbons. Oxidative cyclization of those intermediates has been shown to proceed via epoxide intermediates, as in the transformation of squalene into lanosterol (Scheme 3). In the context of Goldsmith's pioneering in vitro cyclizations (Scheme 2),[15] and the cyclization to a monocyclic ring A model system **16** with $BF_3{\cdot}OEt_2$ to give **17**, van Tamelen and co-workers showed that polycyclic systems could be assembled (Scheme 8). Cyclization of the dienic epoxide **18** afforded the bicyclic sesquiterpene framework **19** as a mixture of diastereoisomers.[16b] In contrast, the steroids **21** and **23**, prepared from the epoxy alkenes **20** and **22** respectively, were obtained as single diastereoisomers.[16c,16d] In the formation of allopregnanolone **23**, four new carbocyclic rings and seven new chiral centres, all possessing the correct relative configuration of typical non-aromatic steroids, were generated in a single step.

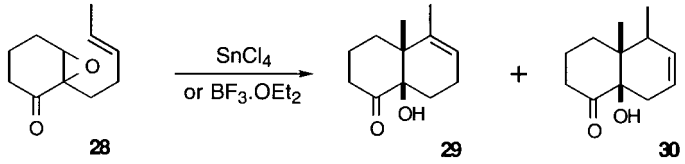
Sutherland and co-workers[9,22–24] have shown that α-keto epoxides are efficient initiators of cyclization, and have used them to investigate various Lewis acid catalysts. Treatment of **24** (Scheme 9) with titanium(IV) chloride gave two cyclization products **25** and **26**.[9] Treatment of



Scheme 8. In vitro epoxy alkene cyclizations.



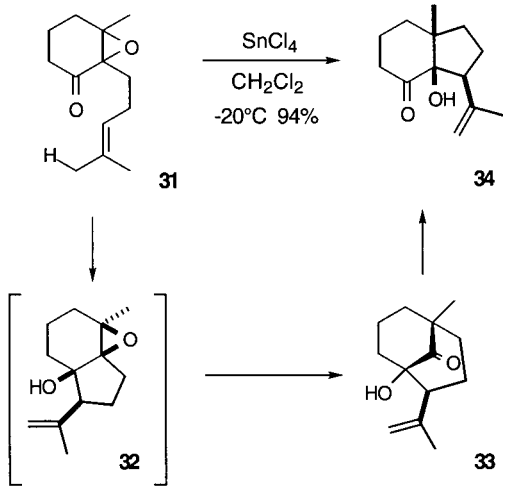
Scheme 9. Cyclization of a terminal alkenic epoxy ketone.



Scheme 10. Cyclization of an internal alkenic epoxy ketone.

24 with weaker Lewis acids produced some ring-contraction product, **27**. The weaker the Lewis acid, the more ring contraction product was formed.

The use of a more electron-rich double bond as in **28** gave only cyclized products **29** and **30** with both weak and strong Lewis acids (Scheme 10).[9] Formation of the five-membered ring on cyclization of **24** was not favoured, because it would lead to a less stabilized carbocation. The additional methyl group in **28** was not sufficient to induce five-membered ring formation. Accordingly, the *gem*-dimethyl analogue **31** was investigated (Scheme 11).[25] This compound underwent cyclization with tin(IV) chloride forming the desired fused five-membered ring, although the propene unit in **34** was found to be located in an unexpected position.[25] This reaction was considered to proceed through an ene reaction of **31** (catalyzed by the Lewis acid)[26] resulting in **32**, which subsequently underwent rearrangement to the ketone **33** which in turn underwent an α-ketol rearrangement to give **34**. Treatment of **33** with tin(IV) chloride gave **34**, confirming that the former was an intermediate to **34**.



Scheme 11. An unexpected cyclization followed by consecutive rearrangements.

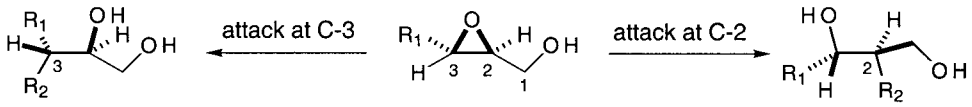
An important conclusion to be drawn from such work is that the outcome of cyclizations involving epoxy ketones *lacking* an adjacent hydroxy group cannot always be predicted. However, the electronic effect of a carbonyl group adjacent to an epoxide can be expected to preclude (direct) cyclization at the α-position, and that is an implicit oxygen-directing influence operating in such carbocyclizations.

The reaction of epoxides with Cp_2TiCl leads to regioselective ring opening and the formation of a β-oxygenated carbon radical that can then cyclize onto an unsaturated terminus.[27] The effect of adjacent oxygen has not been assessed, although the regioselectivity of ring opening is clearly dependent upon the stablility of the radical formed.

2.4. Regioselectivity of epoxide ring opening

Epoxides can be ring opened both intermolecularly and intramolecularly by a wide range of carbon nucleophiles, especially stabilized carbanions and organometallic reagents.[1,28,29] The 'normal' site of attack at a simple epoxide (i.e. one lacking other adjacent functionality) is at the less substituted carbon atom,[28] and this holds for nucleophilic attack under both basic and acidic (including Lewis acidic) conditions. However, in the presence of even weak Lewis acids such as titanium alkoxides, a wide variety of nucleophiles, including cyanide, exhibit a strong preference for attack at C-3 of the epoxy alcohol.[30]

Where the epoxide bears an adjacent electron-withdrawing group, as in an epoxy ketone, that group inhibits attack of the adjacent (C-2) position, attack at the distal position being promoted (e.g. Scheme 15). Conversely, an electron-donating group leads (by cationic stabilization) to attack at the C-2 position. However, the ratio of attack can be fairly evenly balanced, as in the case of 2,3-epoxy

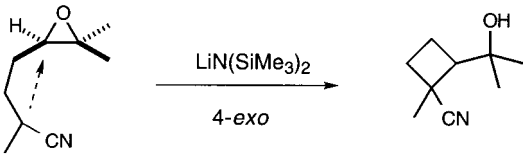


Scheme 12. Modes of ring opening of a 2,3-epoxy alcohol (excluding Payne rearrangement).[33]

ketones. For 2,3-epoxy acids, reactions with *N*- and *S*-nucleophiles favour C-2 in the absence of $Ti(O^iPr)_4$, but attack occurs almost exclusively at C-3 in its presence.[31] Those observations are simply explained in terms of coordination of the epoxy acid to the metal centre in the usual rigid, bidentate manner.[31]

For cyclizations involving epoxide ring opening, several factors influence the site of attack, including: (i) trajectory of approach of the nucleophile; (ii) degree of substitution on the epoxide; (iii) the type of substituents on the epoxide; and (iv) the nature of the reagents, e.g. Lewis acid/protonic acid, or carbanion (either in the absence of a Lewis acid, or in its presence, e.g. $Me_2CuLi–BF_3{\cdot}OEt_2$). For intermolecular processes, nucleophilic attack often occurs at C-3 (Scheme 12). This is also usually the case for intramolecular nucleophilic attack, but there are notable exceptions, such as a few intramolecular Friedel–Crafts alkylations (Scheme 26) and semi-pinacol rearrangements.[32] For 2,3-epoxy alcohols, the consequences for intramolecular nucleophilic attack of co-ordination of the Lewis acid to both oxygen atoms must be carefully considered in each case.

The importance of the trajectory of approach[34] of the (carbon) nucleophile can be seen in the nitrile cyclization of Scheme 13. The epoxide ring opening is facile when the trajectory of the nucleophile can be oriented colinear with the C–O bond being broken.[35] For that reason, 5-*endo* cyclizations of epoxides are not facile, whereas 4-*exo* ones are quite common, and 6-*endo* cyclizations are abundant (Fig. 1).[36]



Scheme 13.

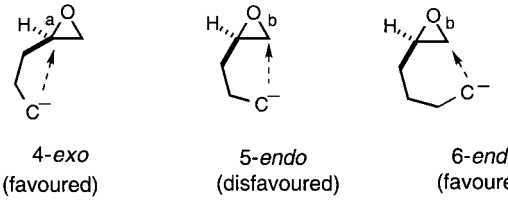


Figure 1.

2.5. The nucleophile

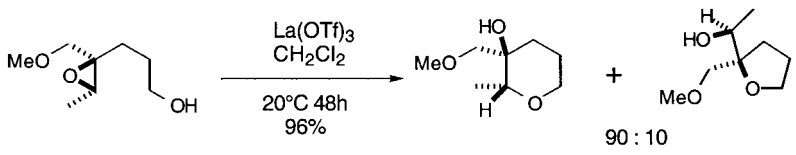
π-Nucleophiles other than simple alkenes have been effectively employed in intramolecular cyclizations involving epoxides. Activated aromatic nucleophiles have been extensively studied. *m*-Substituted methoxybenzene rings are well-known to give a mixture of regioisomers (typically 3:1 *para*:*ortho* coupling to the methoxy group). An unactivated phenyl ring has been found to be sufficiently reactive for the cyclization of keto 2,3-epoxy alcohols (e.g. Scheme 30). Alkynes,[22] furans[37] and activated alkenes[38] have all been shown to participate efficiently in similar cyclizations.

The preparative utility of a cyclization is dependent upon termination to give a single product. One of several efficient processes[23] should occur, common ones being: charge neutralization by deprotonation, either at the *terminus* of an alkene or alkyne, or a site allylic (or propargylic) to the initial alkene or (alkyne); intramolecular nucleophilic attack; or intermolecular nucleophilic attack.

Although this report is primarily concerned with carbocyclizations, it is noteworthy that the same principles of bidentate chelation control have been shown to apply to *O*-nucleophiles (Scheme 14).[39] Selectivity for the 6-*endo* cyclization was carefully optimized; the 6-*endo*: 5-*exo* ratio is strongly influenced by the type of solvent and the amount of water present. 5-*exo*-Cyclization of 2,3-epoxy alcohols has also been achieved with an *N*-nucleophile,[40] although in this example there is no reason to suppose that bidentate chelation control was operating. Indeed, the cyclization was conducted with trifluoroacetic acid, rather than a chelating Lewis acid.

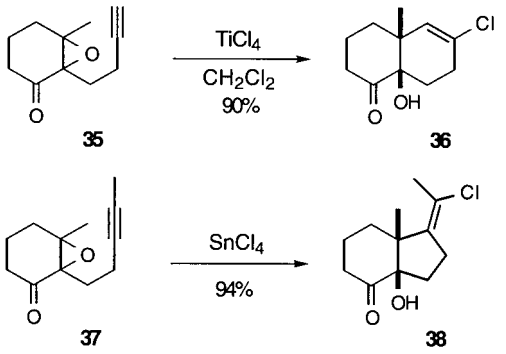
2.6. Epoxy alkyne cyclizations

Although biosynthetic cyclizations involve an alkene unit as the terminating nucleophile, an alkyne also acts as a good terminal π-nucleophile, and has often been used to effect biomimetic polyene cyclizations.[4,12] Sutherland and co-workers carried out epoxy alkyne cyclizations to compare the difference in their behaviour to the alkene counterparts.[22] Treatment of the epoxy alkyne **35** (Scheme 15) with either borontrifluoride etherate or titanium(IV) chloride gave the bicyclodecenone **36** in high yield; in the case of borontrifluoride etherate the chloride must have originated from the solvent, dichloromethane.



Scheme 14. Chelation-controlled intramolecular attack of an *O*-nucleophile upon an epoxide.

Cyclization of the electronically unbiased alkyne **37** gave the bicyclononane **38** with an exocyclic chlorovinyl moiety. This was in accord with Johnson's observation[41] that a five-membered exocyclic halovinyl unit results unless the alkyne is electronically biased in favour of the six-membered ring.



Scheme 15. Epoxy alkyne cyclizations.

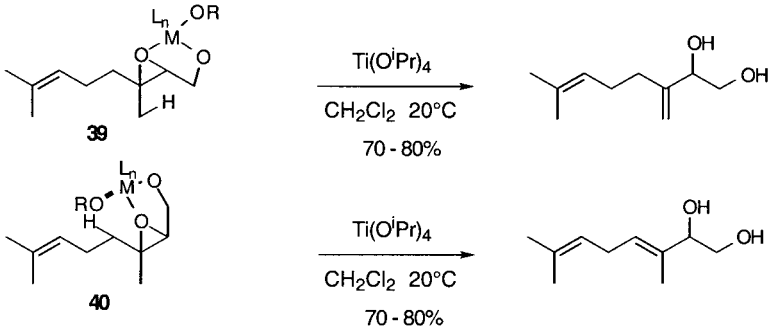
3. 2,3-Epoxy Alcohol Cyclizations

3.1. Early model systems using an alkene terminating group

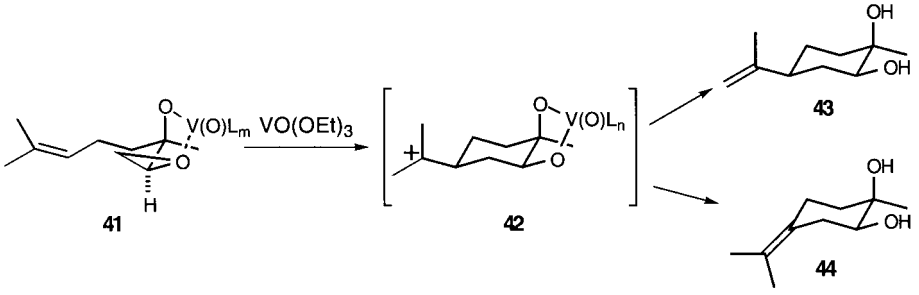
Some of the first clearly recognisable cases of hydroxyl-directed Lewis acid mediated cyclizations of 2,3-epoxy alcohols were reported by Morgans and Sharpless.[42] They used very weak Lewis acids, such as $Ti(O^iPr)_4$ and $VO(OEt)_3$, transition metal alkoxides that display little or no reactivity towards simple epoxides. The earlier work of Sheves and Mazur[43] carries the presumption that binding of Al(III) to both atoms of an allylic alcohol was important in influencing the structure of the resulting spirocyclic diol, but in this work, the precise effect of the hydroxyl group was not established.

The rigidity of the bidentate chelation of a Lewis acid to both atoms of a 2,3-epoxy alcohol can markedly influence the course of a reaction. Thus, the high degree of regio-control during the reaction of 2,3-epoxy geraniol and of its isomer 2,3-epoxy nerol can be accounted for by invoking a rigid arrangement of the respective metal alkoxy complexes **39** and **40**, followed by elimination with proton-transfer to an alkoxy ligand (Scheme 16).[42] Such examples show that an α-hydroxy group in not a sufficient condition for cyclization to occur.

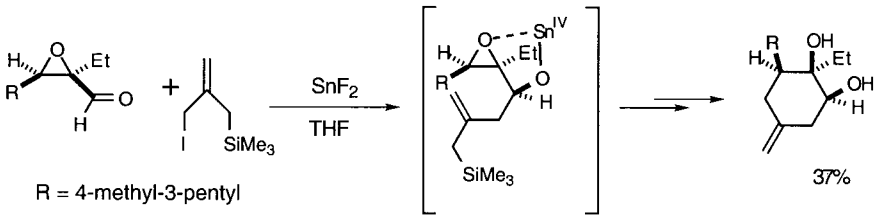
In 1981, a communication by Morgans and Sharpless[42] described how the behaviour of an epoxide participating in an intramolecular cyclization can be substantially altered by the presence of an *internal* α-hydroxyl group. Those investigators treated a mixture of *erythro*- and *threo*-1,2-epoxylinalool (Scheme 17) with $VO(OEt)_3$. The *erythro* isomer gave two cyclized products, each possessing only *cis*-diols (**43** and **44**). Treatment of the *threo/erythro* mixture of 1,2-epoxylinalool with 1.4 equiv. of $Ti(O^iPr)_4$ (CH_2Cl_2, 12 h, 20°C) gave a mixture of **43** and **44** in about 25% yield; the *threo* isomer was recovered unchanged. Those observations can be explained by invoking complexation of the oxygen atoms of the epoxide and hydroxyl group to the metal, thereby restricting the conformation of intermediate **42**. In this arrangement the *erythro* isomer can undergo cyclization owing to proximity of the epoxide and the alkene moieties, and that results in the *cis*-diol products. In the restricted conformation analogous to **42**, the *threo*



Scheme 16. Stereospecific eliminations of 2,3-epoxy geraniol and 2,3-epoxy nerol.



Scheme 17. Cyclization of *erythro*-1,2-epoxylinalool.



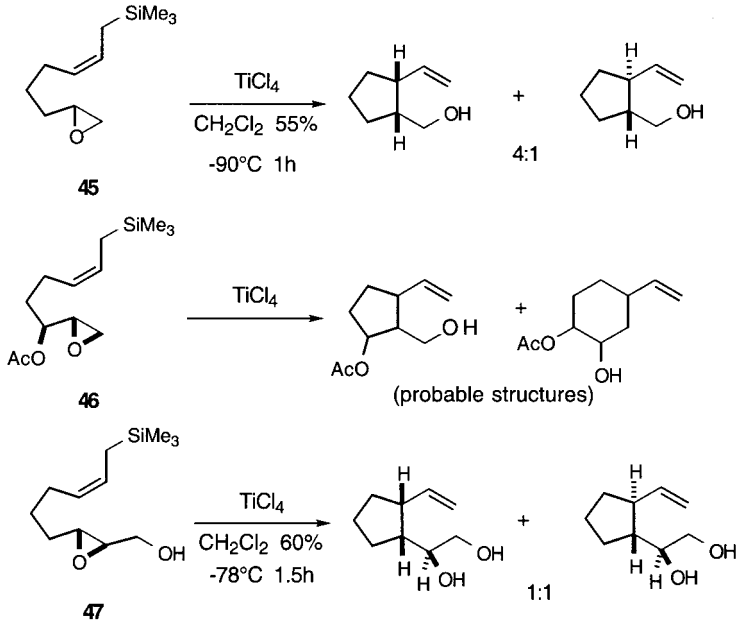
Scheme 18. A tin(IV) promoted [3+3] annulation.

isomer could not cyclize and apparently undergoes decomposition under the reaction conditions.

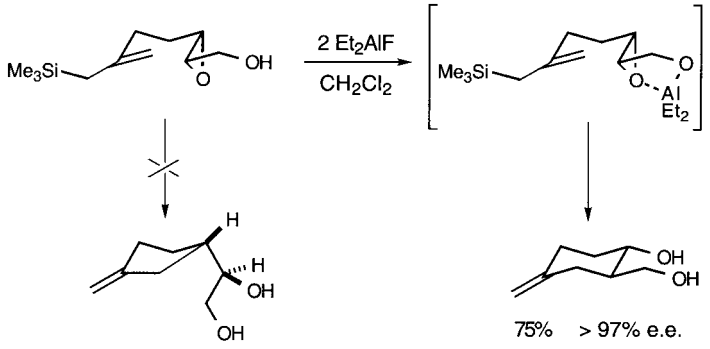
The essential involvement of the hydroxyl group was established by subjecting the methyl ether of *erythro*-1,2-epoxylinalool to the same cyclization conditions. No cyclization was detected, and starting material was recovered. It was also found that related simple epoxides lacking an α-hydroxyl group failed to undergo cyclization.[42]

In a [3+3] annulation,[44] a tin(IV) bound intermediate of an epoxy alcohol is believed to be the key feature that leads to subsequent cyclization (Scheme 18). Chelation control is invoked to account for the 6-*endo* product.

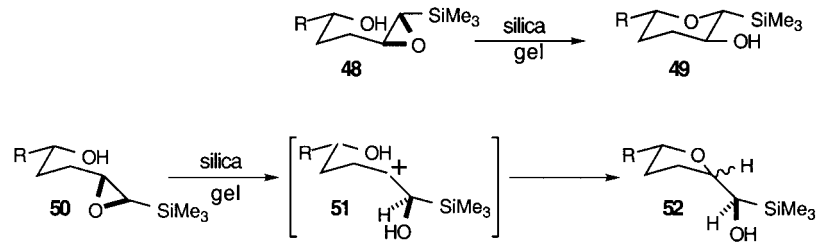
The directing influence of silicon in allylsilanes, through the stablization of a β-carbocations,[45] has been used to prepare cyclic alcohols (Scheme 19). In this study,[46] the use of an epoxy alcohol as the initiating unit was successful, but a terminal hydroxy group provided more definitive results than an internal hydroxy group. Whereas neither the acetate **46** nor the corresponding free epoxy alcohol provided pure products of cyclization, **47** afforded satisfactory yields of cyclopentanoid diols. Notably, the hydroxyl group of **47** did not require protection, and the yield of cyclized products



Scheme 19.



Scheme 20.



Scheme 21.

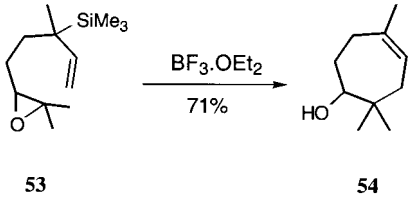
was somewhat greater than that for the non-hydroxylated analogue **45**.

The mode of cyclization of an epoxy alcohol in which the last carbon atom of the chain bears the hydroxy group was shown to lead to the six-membered ring rather than the five-membered ring (Scheme 20).[47] A variety of Lewis acids other than Et_2AlF gave poor results. In terms of orbital overlap during cyclization, the preferred ring closure to the six-membered ring diol (Scheme 20) was likened to a 6-*endo-trig* process (but with the polarity inverted), and the unobserved ring closure to the five-membered ring diol to a disfavoured 5-*endo-trig* process (again with the polarity inverted).

Directive effects of groups other than hydroxy are known; a silyl group attached to the epoxide can lead to ring-closure via stabilization of the β-carbocation by silicon. However, stabilization can be overridden by conformational considerations. Thus, in a cyclization involving a heteroatom acting as a nucleophile, (Scheme 21) proton-induced cyclization of 1,4-*anti*-4,5-epoxy-1-alkanols **48** proceed through a chair-like transition state to give the tetrahydropyran **49**, the silyl and newly formed hydroxy groups residing in equatorial positions.[48] In contrast, the 1,4-*syn*-epoxy alcohol **50** does not give the tetrahydropyran, since the hydroxy group would require attack leading to a (less favoured) boat-like conformation of **50** (Scheme 21). Instead, formation of the epimeric tetrahydrofurans **52** can be explained by proton-induced ring-opening of the epoxide followed by attack of the resulting cation at either side by the hydroxyl group.

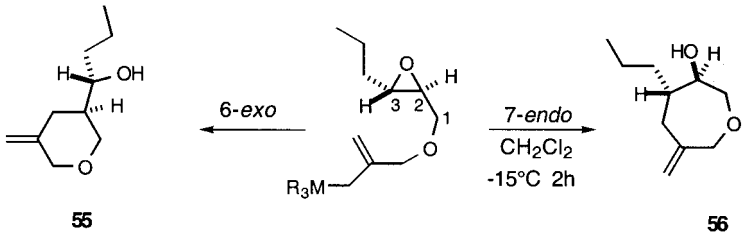
3.2. General aspects of cyclizations to form seven-membered rings

Cyclizations leading to seven-membered rings have often required more forcing conditions than those used for the formation of six-membered rings; the generally lower yields in which cycloheptanoid rings are formed attests to these difficulties. Epoxide cyclizations leading to carbocyclic seven-membered rings are uncommon and usually have particular requirements of design of the terminating group and/or substitution of epoxide ring. For example, the combination of a silyl activated alkene (silicon stabilizing the developing cationic charge) and an epoxide with tetra-substitution (maximizing the stabilization of positive charge) at the site of attack was used by Chan and co-workers (Scheme 22).[49] They treated the epoxide **53** with boron trifluoride etherate to give the seven-membered ring **54** in 71% yield; however, treatment of **53** with titanium (IV) chloride resulted in opening of the epoxide by chloride ion.



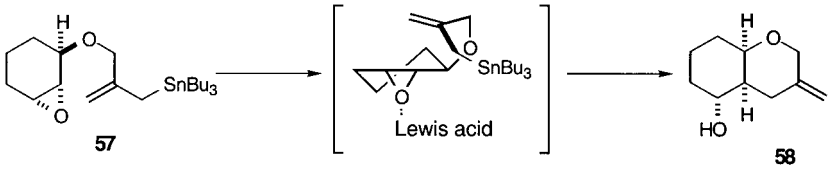
Scheme 22. Cyclization of an acyclic epoxy allylsilane.

An advance in the stereocontrolled synthesis of seven-membered rings (Scheme 23) was made when it was shown that a 7-*endo* cyclization could be efficiently achieved by bidentate chelation to an oxygen atom as part of the ring, in addition to that of the epoxide ring.[50] For cyclization promoted by $BF_3{\cdot}OEt_2$, a strong but non-chelating Lewis acid, substitution at C-1 and lack of substitution at C-3 favours 6-*exo* products, whereas substitution at C-3 (phenyl, alkyl etc.) strongly favours the 7-*endo* product.[50] However, the use of $TiCl_4$ markedly favours the 7-*endo* product, in typical yields of 80–95%; the chelated transition state permits the requisite colinearity between the incoming nucleophilic centre and the polarized epoxide

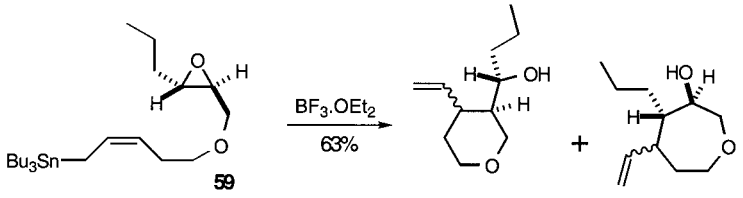


MR_3 = $SnBu_3$, $SiMe_3$ **55:56** 86% overall yield

Scheme 23.



Scheme 24.



Scheme 25.

C–O bond. However, the corresponding chelated transition state that leads to the 6-*exo* product would not allow the required orbital overlap,[34] so the strongly chelating $TiCl_4$ affords an excellent means of regioselection in favour of the 7-*endo* product.

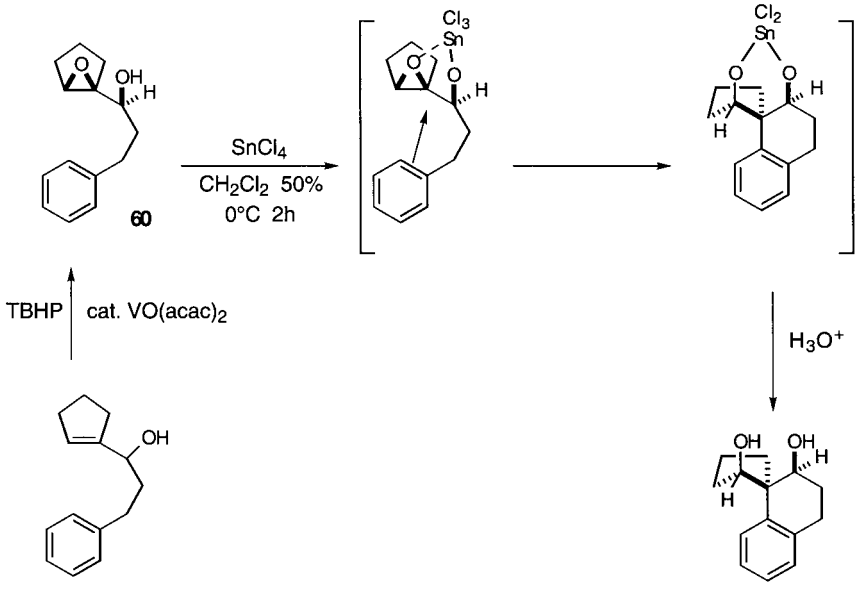
Reaction of **57** either with chelating or non-chelating Lewis acids gave **58** as the only cyclized product,[50] the 7-*endo* process not being observed (Scheme 24).

An attempt to expand the ether-directed methodology showed major limitations; treatment of **59** with $BF_3{\cdot}OEt_2$ gave a 1:1 mixture of regioisomeric products in an overall yield of 63%, each compound being obtained as 1:1 epimers. The use of $TiCl_4$ gave only chlorohydrin products (Scheme 25).[50]

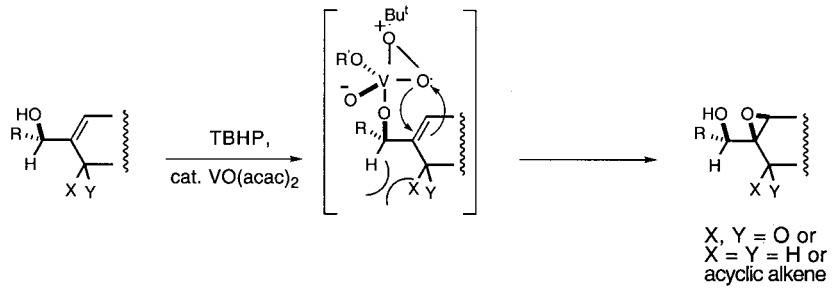
There does not appear to be a report of a direct cyclization of a simple epoxy alcohol to a seven-membered ring. Although interception by an external nucleophile might be expected, at least in the case below (Scheme 26), cyclization of **60** occurred, resulting from attack at the 2-*position*, a rare phenomenon in the cyclization of epoxy alcohols. Cyclization leads to the creation of a spiro ring system flanked by stereogenic centres.[51]

3.3. Synthesis of polycyclic keto diols using Baylis–Hillman-epoxidation–cyclization sequences

2-Cycloalkenones were coupled[52,53] with the requisite aldehydes in a Baylis–Hillman reaction,[54] in which Et_2AlI was used for 2-cyclohexenone, and Me_2AlSPh or its 'ate' complex formed from *n*-BuLi, employed for couplings with 2-cyclopentenone (Scheme 30). Epoxidation of the hydroxy enones with alkaline H_2O_2[55] was appreciably selective, in favour of the *syn*-diastereoisomer (5:2 for m=1; 11:2 for m=2). Epoxidation of the hydroxy enones with other reagents was investigated, notably *tert*-butyl hydroperoxide (TBHP) using $VO(acac)_2$ as the catalyst. Although this reagent was considered to be unreactive towards electrophilic alkenes, it was considered that this might be overridden by ability of the vanadium species to bind to the



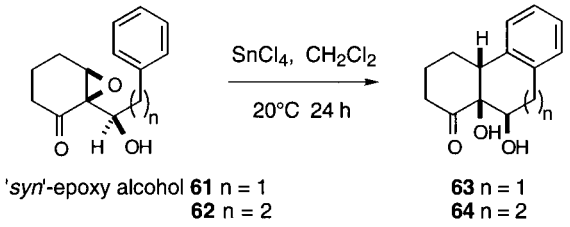
Scheme 26.



Scheme 27. Diastereoselective epoxidation of cyclic allylic alcohols catalyzed by $VO(acac)_2$.

hydroxylic oxygen atom.[56] In fact, this reagent proved to give good yields of the *syn*-diastereoisomers, no *anti*-isomers being detected. (Here, *syn* denotes that the hydroxyl group and the epoxide reside on the same face when R is oriented for cyclization onto the β-epoxide carbon atom, e.g. as in Scheme 27.) At this time, another group reported similar epoxidations that also proceeded with the same exclusive diastereoselection.[57]

A rationale proposed[52,53,58,59] for the diastereoselection using the TBHP-$VO(acac)_2$ system accounts for all the observed results in a wide variety of cyclic epoxy alcohols, particularly X,Y=O and X=Y=H in Scheme 27.[32,53] The principal though not necessarily the exclusive factor is considered to be the minimization of $A^{1,3}$-interactions in the transition state. This can be seen in the vanadium-bound species depicted in Scheme 27; the bulkier (R) substituent lies remote from the CXY flank of the ring, which is nearest to the smaller substituent (here H). The conditions for delivery of the oxygen atom are: (i) covalent binding of the vanadium catalyst to the (former) hydroxy group and (ii) attainment of the appropriate dihedral angle.[58] Unsurprisingly, (and consistent with the above model) two C-1 substituents of similar size lead to low diastereoselection in TBHP-$VO(acac)_2$ epoxidations.[53] The dehydration of such *cis*-diols provides routes to polycyclic hydrocarbons and polycyclic aromatic systems containing a keto group.[51]



Scheme 28. Cyclization to give all *syn*-keto diols.

The fragmentation of the *anti*-isomer, in contrast to the cyclization of the *syn*-isomer (Scheme 28), can only be readily accounted for on the basis of binding of the Lewis acid to *both* the hydroxy and epoxy oxygen atoms (for both isomers). Without the involvement of the hydroxy group, no cyclization to a seven-membered ring is observed. With it, the epoxide of the *syn*-epoxy alcohol **62** is activated, and the termini of **65** (X=O) can evidently adopt the appropriate proximity and alignment for cyclization to occur (Scheme 29). In the case of the *anti*-epoxy alcohol, binding of the Lewis acid to both the hydroxy and epoxy oxygen atoms would prevent the side-chain from being able to achieve proximity with C-3 of the epoxide **62**. Rather than a slow rate of cyclization to the epimeric tricyclic system, it is evident that fragmentation of the bound keto epoxy alcohol **66** (X=O) is a faster process. In other examples, where (i) the hydroxylic carbon atom is tertiary, (ii) X is CH_2 etc. but not carbonyl, and (iii) cyclization is either impossible or unlikely, *C*-migration is observed, a semi-pinacol rearrangement taking place.[32]

The lack of generality in obtaining seven-membered rings by the intramolecular attack of a nucleophilic group upon an epoxide led to an examination of the advantages of using instead an epoxy alcohol electrophilic terminus.[52,53] The first cyclization of an epoxy alcohol to give a cycloheptanoid ring involved an arene π-nucleophile terminating group.[52,53] Treatment of the *syn*-epoxy alcohol **62** (Scheme 28) with tin(IV) chloride gave the tricyclic 6,7,6-fused ring system **64** bearing a *syn*-1,2-diol at the biologically most important position (see Fig. 2). On the other hand, treatment of the *anti*-epoxy alcohol (C-7 epimer of **62**) with tin(IV) chloride caused fragmentation. This observation is most useful, since the absence of similar compounds renders purification of the single diastereoisomer **64** straightforward. Similar fragmentations in many related examples makes the epoxidation–cyclization approach to polycylic systems appealing, when an

Scheme 29. Cyclization and fragmentation of epoxy alcohol epimers.

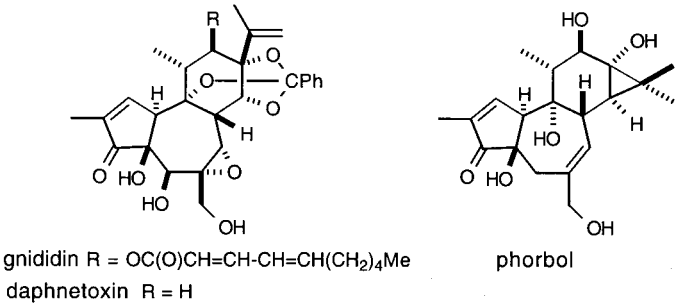
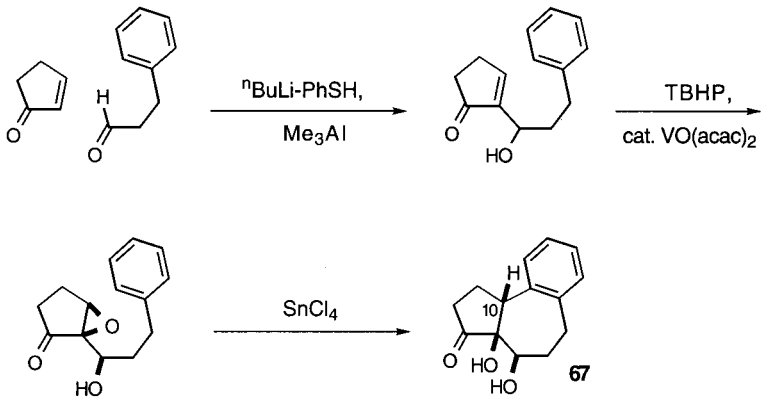


Figure 2.



Scheme 30.

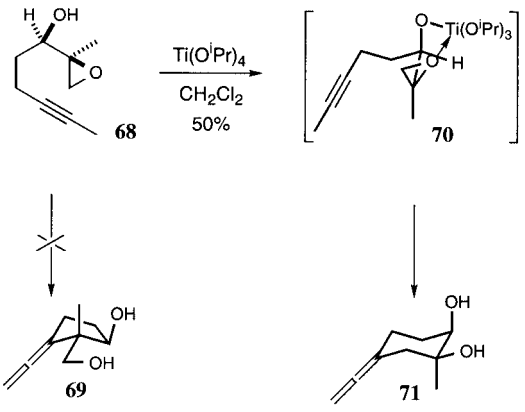
allylic alchol (rather than a simple alkene or enone) is selected as the starting material. *It is often possible to subject the crude mixture of epoxy alcohol diastereoisomers to the chosen Lewis acid, and to obtain a single and diastereoisomerically pure tricyclic product simply by recrystallization*. Additionally, Katsuki–Sharpless epoxidation of the hydroxy enones leads to optically active tricyclic keto diols with good preservation of the enantiomeric excess through the cyclization step.[53]

The stereocontrolled construction of polycarbocyclic rings continues to attract interest[51,60,61] chiefly because of the large number of natural products with different arrangements of the carbon skeleton.[61] Polyhydroxylated natural products which contain a central seven-membered ring present a particular challenge.[62] Compounds with a *cis*-1,2-diol attached to a seven-membered ring with one hydroxy group residing at the 5,7-fused ring junction are of great interest because many exhibit pronounced pharmacological activity.[61,63] They include the antitumourgenic orthoester gnididin (Fig. 2),[62] the irritant esters of ingenol[64] and the cardiotoxic diterpenoid grayanotoxin,[65] and the tumour promoter, phorbol.[66]

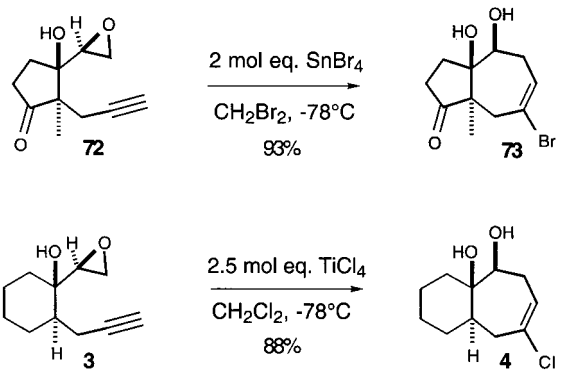
The same strategy as in Scheme 28 led to the analogous 5–7–6 fused system, a single diastereoisomeric keto diol **67** being obtained (Scheme 30).[67] Although most phorbol derivatives possess the 10α-stereochemistry, some have the β-configuration, and subsequent epimerization of a cyclopentenone derivative could be possible. Consequently, this convergent three-step strategy to angularly fused hydroxylated systems offers considerable potential in natural product synthesis.

3.4. Cyclizations of epoxy cycloalkanols with alkene and alkyne terminating groups

Morgans and Sharpless[42] carried out a cyclization of the *acyclic* epoxy alcohol **68** (Scheme 31) using a simple alkyne terminator to give the allene **71**. Complexation between the oxygen atoms and the Lewis acid favours six-membered ring formation rather than the cyclopentanoid product **69**. The third possibility of forming a seven-membered ring (by bonding between the two termini of the alkyne and epoxide



Scheme 31. Allene formation from an alkynic epoxy alcohol.



Scheme 32. Cyclizations of epoxy alcohols to form fused seven-membered rings.

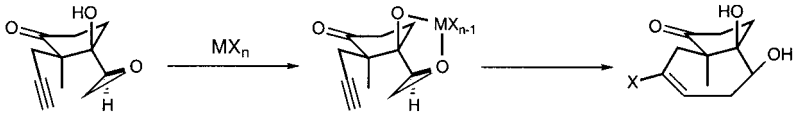
units) is not realized here, presumably because of non-bonding interactions involving the methyl group that arise during alignment prior to cyclization. However, as will be seen below (e.g. Scheme 32), where the alkyne is terminal, its terminus *can* present to the terminus of an epoxy alcohol unit, resulting in the formation of cycloheptanoid rings in very high yields.

Treatment of the *trans*,*syn*-epoxide **72** with either tin(IV) bromide or titanium(IV) chloride gave the desired bicyclo [5.4.0] decane system in excellent yields (Scheme 32).[10,67] Cyclization of a cyclohexanoid template also proceeded in excellent yield. The 5,7-fused bromo diol **73** was converted into the sulfite (95%; 1:1 mixture of epimers at sulfur) with thionyl chloride, which enabled confirmation of structure by X-ray crystallography.

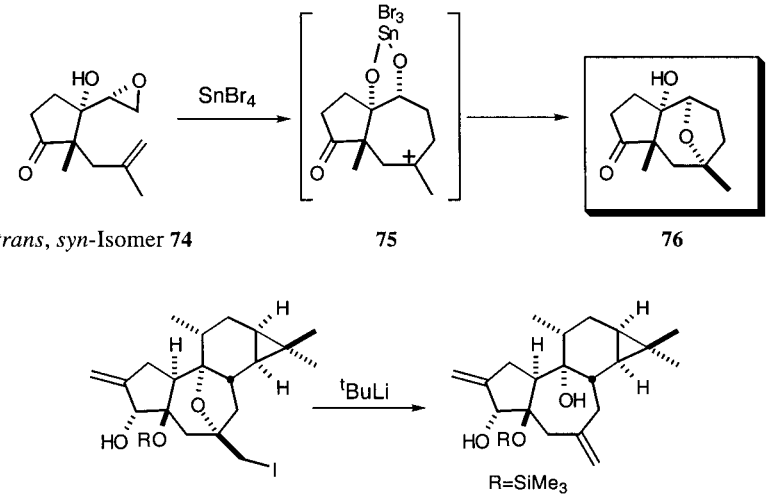
Scheme 33 illustrates the distal attack that leads to the seven-membered ring, rather than a new six-membered ring. The Lewis acid (typically SnX_4) forms a bidentate chelated complex with the hydroxyl and epoxide oxygen atoms, thereby locking the molecule in a conformation in which only the terminal (distal) end of the epoxide can be presented to the (terminal) end of the alkyne. Cyclization then occurs to give the seven-membered ring product. These results show that 7-*endo-tet* cyclizations of certain epoxy alcohols take place in preference to attack at the more substituted carbon atom (6-*exo-tet*, a favoured cyclization process),[33] despite the *exo*-mode of ring opening being generally preferred. This is strong evidence for the involvement of a bidentate chelate. 7-*endo* Selectivity during epoxide ring opening has also been achieved by means of chelation of the Lewis acid usually lanthanum(III) trifluoromethanesulfonate to the methyl ether oxygen atom of 5,6-epoxy-5-methoxymethyl-1-heptanol;[68] although not a carbocyclization, such chelation led to the 3-hydroxylated oxepane, in contrast to many other Lewis acids for which the 6-*exo* product predominated. Previous work achieved activation of 7-*endo* over 6-*exo* epoxide openings by means of substituent control, rather than by chelation control.[69]

It has been shown[10] that an alkene can also participate in these cyclizations but it was found that the intermediate cation **75** (Scheme 34) was trapped intramolecularly by the secondary hydroxyl group to give the cyclic ether **76**.[67] Such cyclizations are of interest in natural product synthesis, since closely related functionalized bridged ethers have been cleaved to liberate key cycloheptanoid intermediates in the total synthesis of phorbol.[62b]

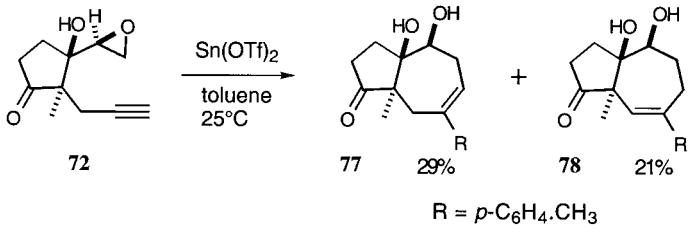
It had been supposed that the formation of vinylic cations (or at least the development of incipient positive charge at the internal site of the alkyne) could be involved, and this is consistent with the trapping by toluene of a cationic species



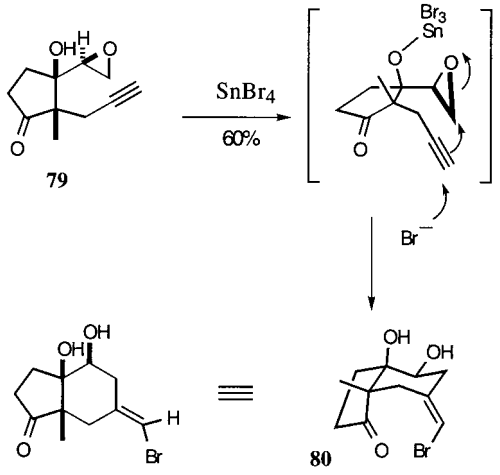
Scheme 33. Bidentate chelation leading to a seven-membered ring.



Scheme 34. Cyclization giving an ether bridge assembly of a precursor of phorbol.



Scheme 35. Solvent participation during seven-membered ring formation.



Scheme 36. Participation of the internal alkyne site in a chelation-controlled cyclization.

to give the arylated cycloheptene rings found in the products **77** and **78** (Scheme 35).[67] The formation of the latter has not been investigated, but might involve direct acid-catalyzed migration of the double bond in **77**. Alternatively, ring opening of a bridged ether might be occurring.

The epimeric epoxide **79** gave a satisfactory yield (60%) of the bicyclo [4.3.0] nonane **80** (Scheme 36).[67] Models show that the internal alkyne site can present in a colinear fashion to the terminus of the epoxide group when that epoxide forms part of a bidentate chelated complex (depicted in Scheme 36 with arbitrary tin ligands). The *cis*-disposition of the epoxide and alkyne substituents does not permit proximity of the termini of the epoxide and alkyne moieties (with or without chelation), and seven-membered ring formation was not detected.

4. Conclusions

Many epoxy alcohol cyclizations provide useful hydroxylated compounds whose configuration can be rationalized. Regiochemical control on the ring opening of epoxides with chelation[70] has been extended to derivatives of 3,4-epoxy alcohols, and it remains to be seen whether oxygen functionality more remote from the cases discussed in this Report can exert useful regio- and stereocontrol in carbocyclizations. Our understanding of epoxide cyclizations continues to grow, as does their utility. The scarcity of (acid) catalyzed epoxide rearrangements[71] is a notable feature in this area. The concept of hydroxy-directed cyclizations of epoxides has become quite well-established, and is a powerful method of obtaining improved cyclization yields, as well as polyoxygenated systems of well-defined stereochemistry. The scope has not been fully determined, and it remains to be seen whether recent developments such as zeolite-promoted biomimetic polyene epoxide cyclizations,[72] or titanium-promoted radical cleavage of epoxides,[27] can broaden the scope of epoxy alcohol cyclizations.

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Biographical Sketch

Charles Marson gained an Open Exhibition to Magdalene College, Cambridge in 1975, and a BA in Natural Sciences in 1978 from the University of Cambridge. His doctoral studies on the synthesis of polycyclic heterocycles under the direction of Professor A. R. Katritzky, FRS, culminated in the synthesis of dodecahydro-18,21-dioxoniakekulene, the first heterocyclic analogue of kekulene, and the award of a PhD from the University of East Anglia. After postdoctoral research on the chemistry of vitamin B_{12}, and on heterocyclic synthesis methodology, Dr Marson was appointed Temporary Lecturer (1986) then Lecturer (1988) at the University of Sheffield. In 1996, he was appointed Senior Lecturer in Chemistry at Queen Mary and Westfield College, University of London and was promoted to Reader in Organic Chemistry in 1998. He was awarded a DSc (University of East Anglia) in 1998. In 1999, he moved to University College London. Dr Marson's research interests concern the invention of new synthetic reactions, particularly with stereocontrol. Major current research themes include: asymmetric synthesis of enantiopure C_2-symmetric compounds; catalytic asymmetric synthesis; the design and synthesis of anticancer compounds; and chiral organofluorine chemistry. Dr Marson is the author of 80 publications and one co-authored research monograph, 'Synthesis using Vilsmeier Reagents'.