REVIEW

Saturated oxygen heterocycles

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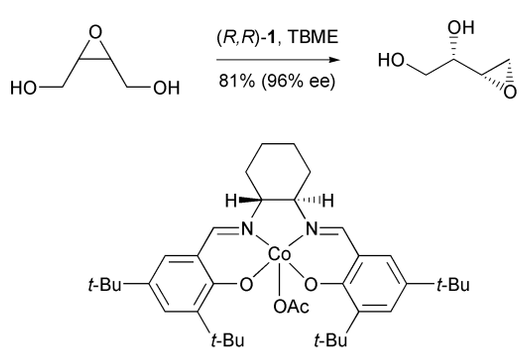
1 Introduction

As with previous reviews in this series, the recent literature on three to nine-membered oxygen heterocycles has been surveyed. Only those systems with a single heteroatom have been covered, with the exclusion of cyclic acetals and ketals. Again, while sugar derivatives have not been generally included, there are inevitably examples of pyran synthesis which owe much to this rich area of chemistry.

Given the large number of publications in this area, no attempt has been made at comprehensive coverage. We have elected to focus on short communications for the most part, with full papers describing work covered in the previous reviews merely being cited and not discussed in detail. Where previous work has been alluded to without citation, these references can be found in the previous reviews.

2 Three-membered rings

The Jacobsen–Katsuki epoxidation has generated interest from a number of groups. Jacobsen's own recent work in this area has concentrated on asymmetric ring-opening of epoxides using cobalt–salen complexes.[2] One particularly useful result from this work is the enantioselective Payne rearrangement shown in Scheme 1.[3] The corresponding chromium complex is more efficient for the kinetic resolution of 2,2-disubstituted epoxides by azide ring-opening.[4] Two groups have reported the asymmetric ring-opening–kinetic resolution of epoxyphosphonates.[5]

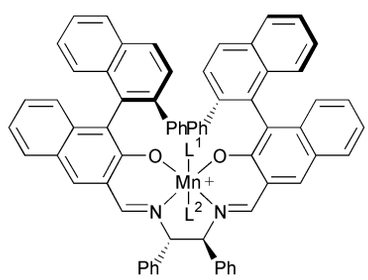


(*R*,*R*)-**1**

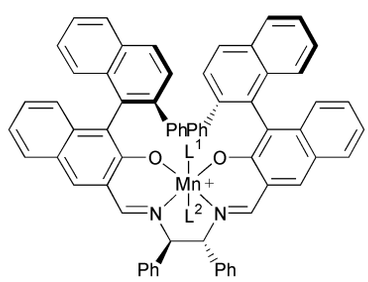
Scheme 1

Dendrimers bearing eight Co–salen complexes show dramatically enhanced catalytic activity in this reaction, which is believed to involve two metal centres, one for activation of the epoxide and one for delivery of the nucleophile (at least in intermolecular epoxide opening).[6] Polymeric manganese–salen complexes have also been used effectively for asymmetric epoxidation.[7]

It is now generally accepted that Mn–salen complexes are not planar, as was initially assumed, but possess stepped conformations. Katsuki and co-workers have extensively investigated complexes such as **2** in which the salen ligand is derived from a binaphthyl aldehyde, and have found that the most effective diastereoisomer of the ligand is dependent on the reaction studied (epoxidation, enol ether oxidation, benzylic oxidation, desymmetrisation of tetrahydrofurans, *etc.*). Complexes **2a**, **2b**, **3a** and **3b** have been studied by single-crystal X-ray diffraction, with **3a** having a more stepped conformation that **2a**, while replacement of an axial water ligand with cyclopentene oxide reverses this trend. Since the salen–Mn(V) oxo complex involved in oxidation is expected to adopt a more distorted conformation than the Mn(III) complex, these effects, not surprisingly, have a profound effect on the level of asymmetric induction observed, and have been rationalised in terms of the direction of substrate approach.[8]



2a, $L^1 = L^2 = H_2O$
2b, $L^1 = H_2O$, L^2 = cyclopentene oxide

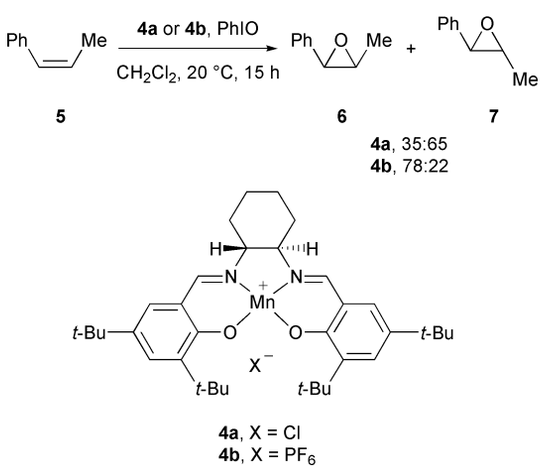


3a, $L^1 = L^2 = H_2O$
3b, $L^1 = H_2O$, L^2 = cyclopentene oxide

In catalytic work, the catalyst possessing *R* stereochemistry at both the binaphthyl and diamine functionalities was more effective for the epoxidation of more nucleophilic alkenes, and indeed, the enantiomer of epoxide formed was determined predominantly by the binaphthyl stereochemistry.[9]

The corresponding ruthenium complexes also catalyse asymmetric epoxidation reactions, but require photoactivation for this to be an efficient process. This reaction was also particularly dependent on the choice of terminal oxidant, with 2,6-dichloropyridine *N*-oxide proving to be the best of those screened.[10] In work with manganese complexes, monopersulfate salts were also shown to be effective terminal oxidants.[11]

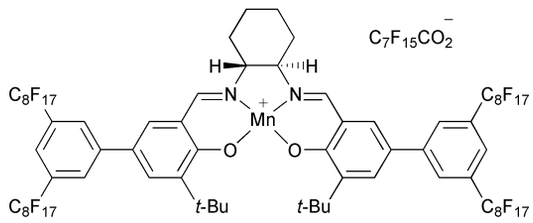
A recent computational study into the mechanism of this reaction using density functional theory points to a mechanism in which direct attack of the olefin at the oxygen of an oxomanganese(V) complex is followed by formation of a free-radical intermediate.[12] Some of the evidence for metallaoxetanes as intermediates in Jacobsen–Katsuki epoxidations could be explained in an alternative manner by the intervention of Mn(IV) species. The presence of manganese(IV) has been established by ESR in the absence of olefin, although the epoxidation of 1,2-dihydronaphthalene by the *in situ* generated Mn(IV) complex gave lower enantioselectivity than in the catalytic process.[13] The observation which gave rise to the initial proposal of a free-radical pathway was the formation of *trans* epoxides from *cis* olefins. A recent study from Adam and co-workers shows that the isomerisation is less pronounced when manganese(III) complexes with non-ligating counter ions are used. Thus, with *Z*-β-methylstyrene **5**, a 65 : 35 mixture favouring the isomerised product **7** was obtained with **4a**, while with **4b** only 22% isomerisation occurred (Scheme 2).[14]



Scheme 2

Methods which allow efficient catalysis followed by easy quantitative recovery of the catalyst in a form which can be readily re-used are particularly attractive. Of these methods, the use of polyfluorinated catalysts in a fluorous phase has received significant attention. Cavazzini *et al.* have shown that **8** is an effective catalyst for epoxidation of alkenes in a two phase (perfluorooctane–acetonitrile) system, allowing the epoxidation of indene with 77% ee.[15] A further method which allows easy recovery of catalyst uses an ionic liquid as co-solvent in conjunction with dichloromethane. After washing the reaction mixture and removal of solvent, the product could be extracted with hexane to leave behind the ionic liquid containing catalyst. This was then reused four times with only a small drop in yield and enantioselectivity. This latter method has the advantage of using the more common commercially available Mn(salen) complex.[16]

Polymer supported catalysts are an obvious development which up until now have met with little success for Jacobsen–Katsuki epoxidation. Reger and Janda have investigated a range of both soluble and insoluble supported catalysts based on general structure **9**. These supported catalysts (R = Merrifield resin, *J*anda*J*el® resin, MeO-PEG$_{5000}$) were competitive in terms of both yield and ee, and despite earlier concerns,



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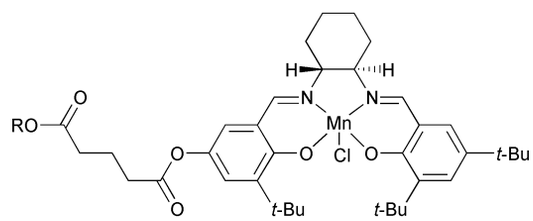
increased catalyst loading did not lead to a reduction in efficiency.[17]



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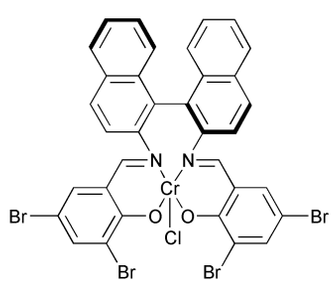
Other Mn-salen complexes have been supported on silica gel[18] and on MCM-41.[19] It is more common for the immobilisation of a homogeneous catalyst onto a solid support to lead to a decrease in enantioselectivity. However, it has been shown that for catalyst **10**, the opposite occurs. In the epoxidation of *Z*-β-methylstyrene, immobilisation of **10** onto a modified MCM-41 leads to an increase in enantioselectivity from 54% to 73% ee.[20] A further related approach is to ion exchange the aluminosilicate Al-MCM-41 with manganese(II) acetate followed by treatment with the salen ligand. Again the results under optimised conditions were comparable with the solution reaction.[21] Manganese complex **11**, with an unusual diaminopyrrolidine backbone, was found to function as an excellent supported epoxidation catalyst when immobilised on NovaSyn® TG amino resin LL.[22]



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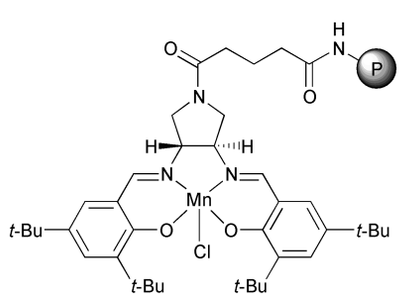

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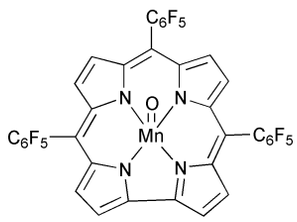
Salen complexes are by no means the only metal complexes which catalyse epoxidation reactions. In other work with manganese, it has long been known that manganese porphyrins are able to catalyse epoxidation reactions. Since corroles are better able to stabilise high oxidation states of transition metals, the epoxidation of styrene by a manganese(III) corrole was investigated. Surprisingly, the catalyst was not particularly

efficient—although an oxomanganese(v) species **12** was characterised spectroscopically, it did not epoxidise styrene, and a higher oxidation state of manganese was proposed to explain the observed slow epoxidation in catalytic experiments.[23]



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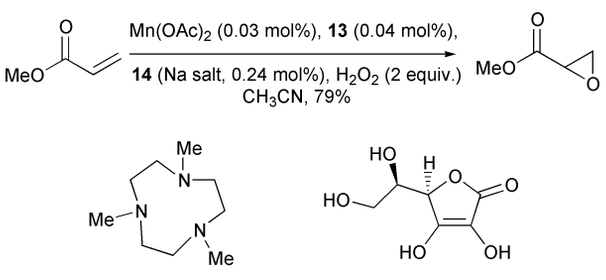
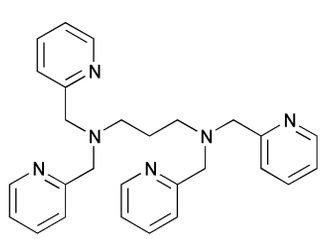
Two other recent methods use hydrogen peroxide as terminal oxidant. Early problems with triazacyclononane **13** complexes catalysing the decomposition of hydrogen peroxide without leading to epoxide formation have been alleviated by the addition of ascorbic acid **14**. Octene and methyl acrylate were epoxidised with equal facility with as little as 0.03 mol% catalyst (Scheme 3).[24] Building on related work, Brinksma *et al.* have designed a dinuclear oxo-bridged complex based on ligand **15** as an effective catalyst for alkene epoxidation. This latter complex, unlike the preceding one, is quite selective for epoxidation over alcohol oxidation.[25]



13 **14**

Scheme 3



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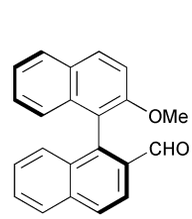
The chiral porphyrin **17** obtained from enantiomerically pure aldehyde **16** can exist in four atropisomeric forms as a result of hindered rotation. These isomers were separated and their metal complexes investigated as catalysts for the epoxidation of styrene. The iron complex of the C2 symmetric atropisomer gave best results (57% ee), with manganese complexes proving less effective.[26] A resin-supported manganese sulfonated tetraphenylporphyrin has also been used for the epoxidation of simple alkenes, giving high yields for styrenes and cycloalkenes, but more modest yields for stilbenes.[27] The same group subsequently reported that this reaction is more efficient when conducted under ultrasonic irradiation.[28]

Methyltrioxorhenium has been used increasingly as an epoxidation catalyst.[29] Sodium percarbonate, an oxidant which is particularly easy to store and handle, can be considered as hydrogen peroxide encapsulated within a sodium carbonate matrix. Treatment of this compound with acid in the presence of an alkene, catalytic pyrazole and catalytic methyltrioxorhenium leads to efficient formation of the corresponding alkene



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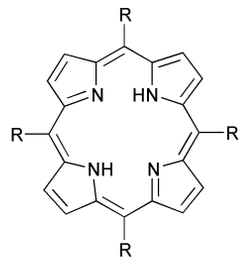

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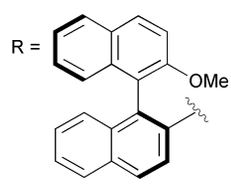
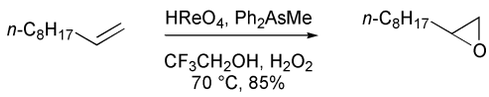


oxide.[30] In fact, sodium bicarbonate itself acts as a catalyst for the epoxidation of alkenes with hydrogen peroxide.[31] Various heterocyclic compounds have been used as additives in methyltrioxorhenium-catalysed reactions, with 3-cyanopyridine proving most effective. A detailed study of these effects led Adolfsson *et al.* to propose that the effect is at least partly due to the heterocycle acting as a phase transfer catalyst in bringing the oxidant into the organic phase.[32] One of the major issues with methyltrioxorhenium-catalysed epoxidation of alkenes by hydrogen peroxide is the subsequent hydrolysis of the epoxide. However, it is possible to carry out the epoxidation in the cage of zeolite NaY, thereby alleviating this problem.[33] (*E*)-Cyclooctene is an interesting mechanistic test bed for epoxidation reactions, due to its strained nature. With methyltrioxorhenium, while epoxidation of the alkene is stereospecific, the oxidised methyltrioxorhenium can deoxygenate the epoxide, and also catalyse double bond isomerisation leading, after re-oxidation, to formation of the *cis* epoxide. In a solution-phase reaction, this problem is partly alleviated by hydrolysis of the catalytically active species, while use of urea–hydrogen peroxide as oxidant, or reaction in the presence of zeolite NaY leads to stabilisation of the oxidant and hence more isomerisation.[34]

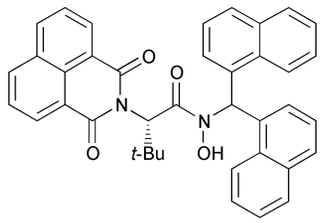
Perrhenic acid offers some potential advantages over methyltrioxorhenium, since it is easier to prepare. Recent work has shown that addition of catalytic amounts of tertiary arsines, particularly methyldiphenylarsine, make this an effective alternative (Scheme 4).[35] Under these conditions the arsine is rapidly oxidised, so that the arsine oxides are just as effective co-catalysts. In fact, tertiary arsines alone also catalyse the epoxidation of alkenes by hydrogen peroxide, but at lower rates, so that the perrhenic acid is clearly active.[36]



Scheme 4

Vanadium hydroxamic acid complexes were some of the earliest reported catalysts for asymmetric epoxidation. Recent studies by Hoshino and Yamamoto have identified a new hydroxamic acid ligand **18** which is particularly effective for the epoxidation of allylic alcohols. The system is most effective for trisubstituted double bonds, with yields and enantiomeric excesses typically over 90%, but with less substituted double bonds extended reaction times (up to 1 week) were needed.[37] The paracyclophane hydroxamic acid **19** shows generally lower selectivity, although with α-methylcinnamyl alcohol, the epoxide was formed in 71% ee and 85% yield.[38] A new achiral vanadium complex **20** has also been reported, and shows excellent catalytic activity over a range of allylic alcohols (reaction times up to 4 hours, yields >90%). Given the widespread use of

oxazolines in asymmetric synthesis, one can only presume that chiral versions of the complex will be forthcoming.[39]



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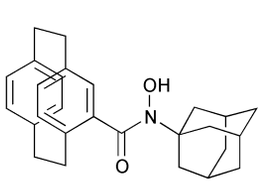

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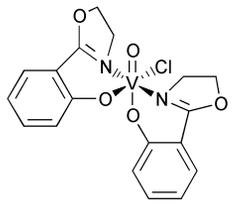

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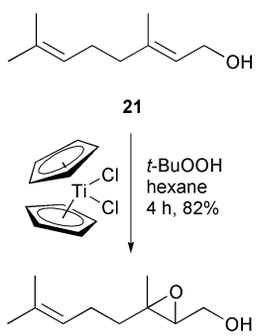
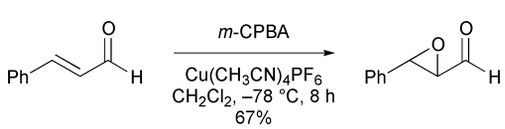
While titanium alkoxides are more commonly associated with epoxidation of allylic alcohols, titanocene dichloride is also suitable if hydrocarbon solvents are used. For instance, the epoxidation of geraniol **21** by *tert*-butyl hydroperoxide proceeds in 82% yield (Scheme 5). Microwave irradiation also had a beneficial effect on the reaction.[40]



Scheme 5

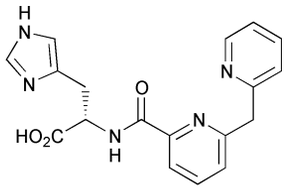
Copper complexes have been seldom used as epoxidation catalysts. Andrus and Poehlein have shown that this reaction is extraordinarily sensitive to the choice of terminal oxidant, so that epoxidation with *m*CPBA proceeded at temperatures as low as −78 °C. Both electron-deficient (Scheme 6) and electron-rich alkenes were epoxidised using this method, although (*Z*)-stilbene gave predominantly *trans*-epoxide.[41] Copper complexes featuring pyrazolylborate counterions show good selectivity for the epoxidation of styrene, with only small amounts of benzaldehyde being produced. These catalysts can also be supported on silica gel, although it is perhaps not surprising in this case that hydrolysis of the epoxide occurred giving rise to 1-phenylethane-1,2-diol as the major product.[42]



Scheme 6

Combinatorial chemistry on a solid support was used to identify potential ligands for ruthenium-catalysed epoxidation. In this way, the ruthenium complex of compound **22** was found to catalyse the epoxidation of (*Z*)-stilbene in 88% yield, although the activity on solid support was much lower.[43]

One of the many problems with a wide range of available epoxidising agents is the use of excess terminal oxidant. For this



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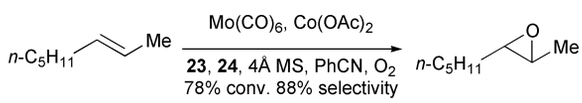
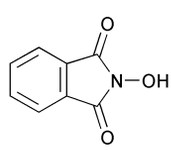
reason, more efficient catalysts are constantly sought. Polybenzimidazole has been used as a support for molybdenum(VI) in the epoxidation of cyclohexene, styrene and 4-vinylcyclohexene with only a single equivalent of *tert*-butyl hydroperoxide.[44] Other studies focus on mechanistic aspects of epoxidation reactions catalysed by oxomolybdenum complexes.[45]

Molecular oxygen is the ideal terminal oxidant, and can be used in a novel tandem process in which autoxidation of an alkane generates a hydroperoxide which can then epoxidise the alkene under the reaction conditions. Thus, reaction of (*E*)-oct-2-ene with molybdenum hexacarbonyl, *N*-hydroxyphthalimide **23** and cobalt(II) acetate in the presence of tetralin® **24** (10 equivalents) under an oxygen atmosphere produced epoxide with high conversion and selectivity (Scheme 7).[46]





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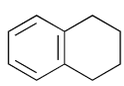

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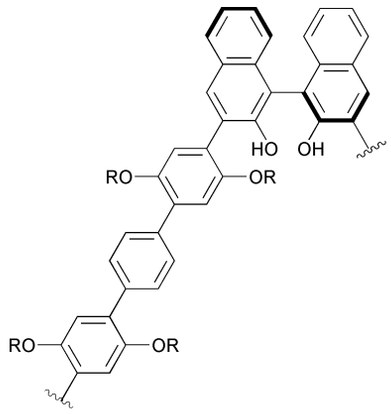
Scheme 7

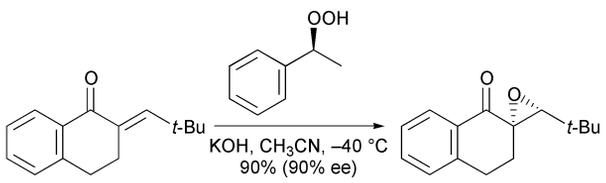
Asymmetric epoxidation of electron-deficient olefins is often more challenging.[47] One recently reported method features the use of diethylzinc in conjunction with a polymeric BINOL **25** in which the selectivity exhibited by polymeric catalyst is higher than that obtained using the monomer. Enantiomeric excesses were typically over 70% for a range of enones.[48]

Poly-L-leucine has been widely used as a catalyst for the epoxidation of electron-deficient alkenes. It is therefore not surprising that a supported version of this polymer (on porous graphitic carbon) is an efficient stationary phase for the separation of these chiral epoxides.[49] An improved protocol for the Juliá–Colonna epoxidation uses sodium percarbonate as terminal oxidant, allowing increased substrate : catalyst ratios without loss of selectivity.[50] In other related work, Carde *et al.* have applied this methodology to the synthesis of arylpropionic acids, making use of polyleucine absorbed onto silica.[51] The importance of an α-helical catalyst structure has been suggested in these reactions, and indeed incorporation of α-aminoisobutyric acid into leucine oligomers does give effective catalysts.[52]

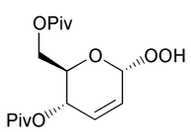
Possibly the simplest protocol for asymmetric epoxidation of an electron-deficient alkene involves base-mediated reaction with a chiral hydroperoxide (Weitz–Scheffer epoxidation). Adam and co-workers have shown that this can indeed be a synthetically useful transformation, with enantiomeric excesses of up to 90% (Scheme 8) being observed.[53] Almost simultaneous with this report, Taylor's group at York showed that sugar hydroperoxides can be used to epoxidise quinones, thus providing a stereocontrolled route to these important biologically active natural products (Scheme 9).[54] A full account of the synthesis of (+)-diepoxin σ, mentioned in the previous review in this series, has also been published.[55]



25, R = *n*-C_6H_{13}



Scheme 8



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Scheme 9

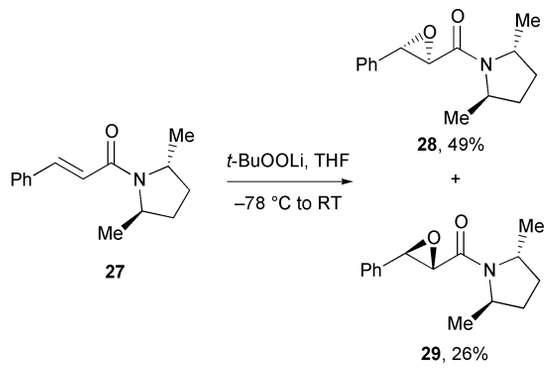
An auxiliary-based approach is shown in Scheme 10, in which chiral unsaturated amide **27** was treated with lithium *tert*-butyl peroxide to give a separable mixture of diastereomeric epoxides **28** and **29**. Treatment with a range of organolithium reagents allowed selective attack at the amide carbonyl, giving rise to enantiomerically pure epoxyketones.[56] Further work centred on the epoxidation of **30**, which produced diastereomerically pure epoxide **31** along with some interesting bicyclic by-products such as **32**.[57] A number of groups have studied the diastereoselectivity of epoxidation of chiral alkenes using a variety of common reagents.[58]

Similar bicyclic compounds have been used to produce epoxides by a combination of cyclisation strategies. Bromocyclisation of **33** gave a single diastereoisomer **34**, treatment of which with benzyl alcohol–sodium hydride permitted formation of epoxide **35** (Scheme 11).[59]

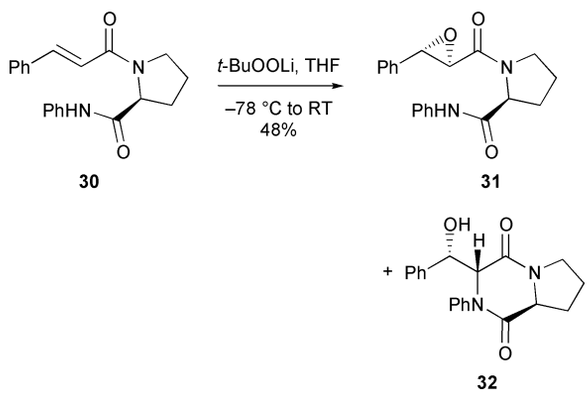
Cinchonidinium salt **36** is an effective phase transfer catalyst for the epoxidation of enones with potassium hypochlorite (Scheme 12), although slightly surprisingly this system shows less selectivity for more rigid enones such as that shown in Scheme 8.[60] An achiral polymer-bound ammonium salt was also used in a triphasic system with comparable efficiency.[61]

Given the range of oxidation reactions of unsaturated carbonyls with iodanes, it is slightly surprising that **37** is able to smoothly epoxidise alkenes such as **38** (Scheme 13). However, the epoxidation of chalcone by this method resulted in much lower conversion.[62]

As an alternative method for the formation of epoxides which would otherwise be derived from electron-deficient alkenes, carbene transfer to carbonyls has been much studied.

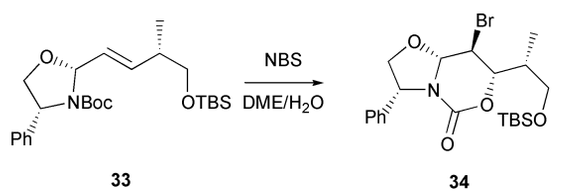


27

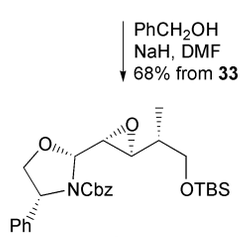


30 **31** **32**

Scheme 10

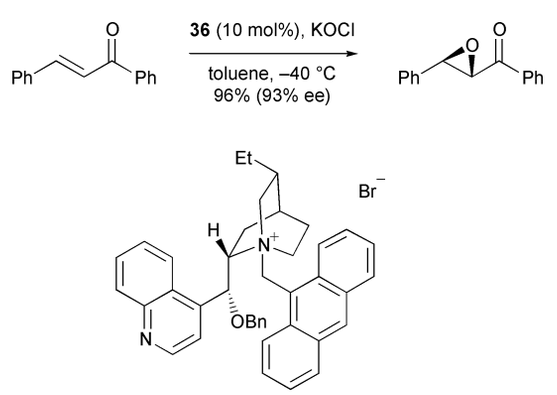


33 **34**



35

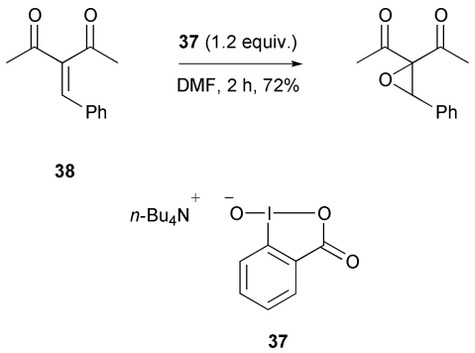
Scheme 11



36

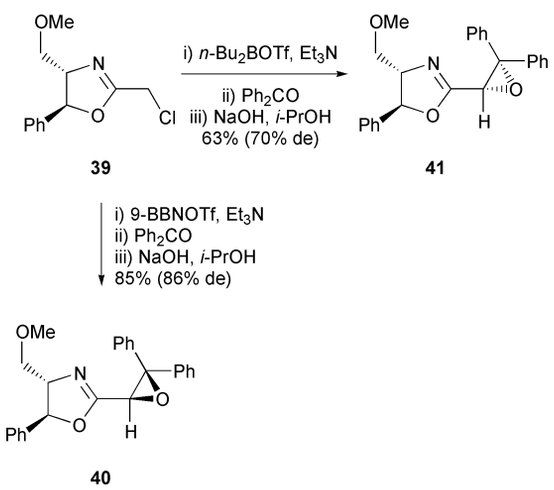
Scheme 12

The classic method in this category, the Darzens reaction, has received attention focusing mainly, not surprisingly, on the production of enantiomerically enriched epoxides. Chloromethyloxazoline **39** serves as substrate in a boron–azaenolate-



Scheme 13

mediated Darzens condensation, with surprising stereochemical differences being observed depending on the choice of borane. Thus, use of 9-BBNOTf gave predominantly (*R*)-epoxide **40**, while Bu_2BOTf gave the opposite diastereoisomer **41** (Scheme 14).[63]

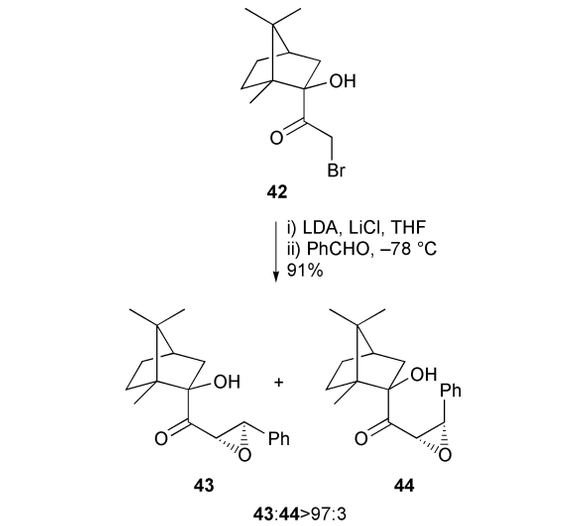


Scheme 14

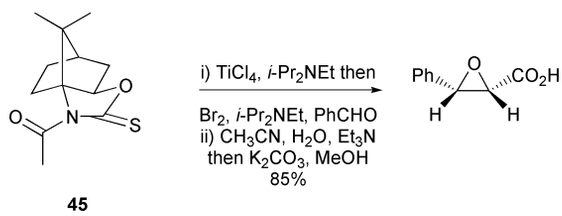
Two independent reports of camphor-based auxiliaries are worthy of note. Reaction of the lithium enolate of **42** with benzaldehyde gave a mixture of diastereoisomers **43** and **44**, corresponding to complete facial stereocontrol in the initial aldol reaction (Scheme 15). Use of acetaldehyde provided excellent selectivity for the *cis* epoxide.[64] As an alternative, Wang *et al.* showed that **45** can be brominated and subjected to aldol reaction in a completely stereoselective one-pot protocol. Treatment as shown in Scheme 16 then allowed epoxide formation and removal of the chiral auxiliary.[65] Diastereoselective Darzens reactions of α-aminoketones have also been reported.[66]

Two enantioselective Darzens reactions were also reported, the first utilising **46** as a phase transfer catalyst.[67] More conventional asymmetric aldol methodology was used as the basis for the epoxide formation reported by Kiyooka and Shahid. Reaction of **47** with benzaldehyde in the presence of **50** gave **48**, as the major component of a 7 : 1 diastereomeric mixture, with 95% ee. Treatment with base then gave **49** (Scheme 17).[68]

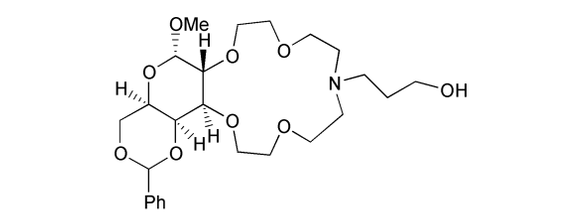
A number of procedures related to the Darzens reaction use ylides, primarily sulfur, but more recently other elements have been demonstrated to be effective. The most prominent reaction in recent years is the rhodium or copper catalysed generation of sulfur ylides reported by Aggarwal and co-workers. A recent variation on this theme, shown in Scheme 18, allows the formation of glycidic amides in moderate yield and enantiomeric excess.[69] A dramatic substituent effect was observed in a related

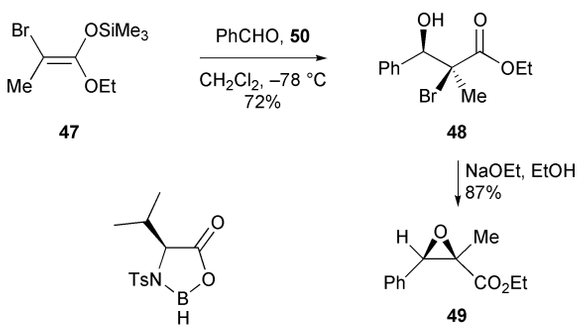


Scheme 15

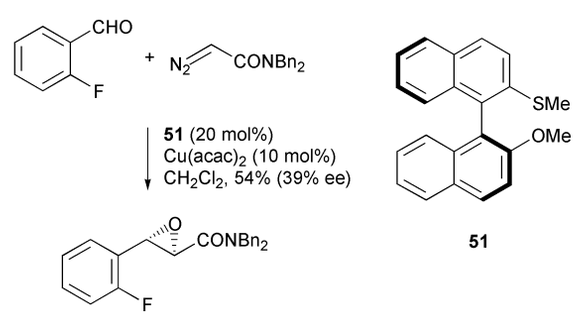


Scheme 16



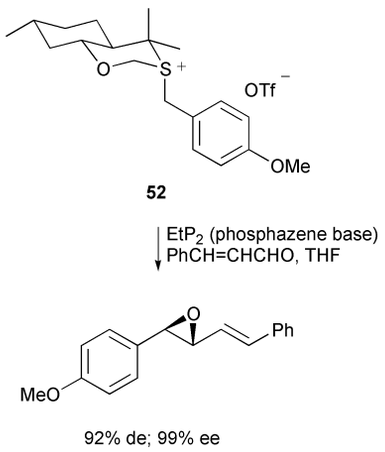


Scheme 17



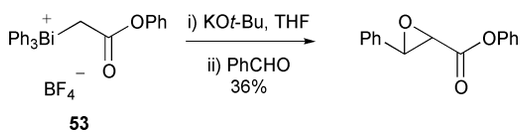
Scheme 18

reaction, in which salt **52** reacted with α,β-unsaturated aldehydes to give only the epoxide (Scheme 19), while without the 4-methoxy group, a cyclopropane derived from conjugate addition and an epoxycyclopropane were isolated in addition to the epoxide.[70] The simplest sulfonium ylide, dimethylsulfonium methanide, can be prepared conveniently from dimethyl sulfide and dimethyl sulfate. Normally this procedure suffers due to the fact that only one of the two methyl groups of dimethyl sulfate is incorporated into the epoxide. A modification from Forrester *et al.*, in which acids are added, allows use of the second methyl group.[71]



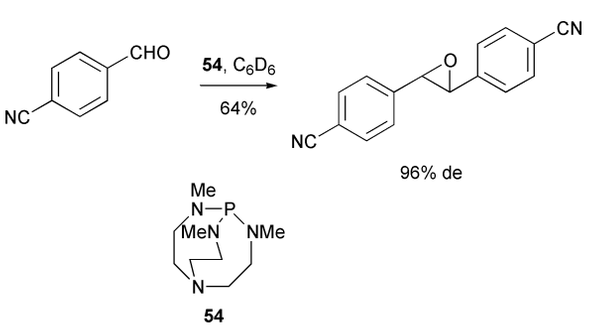
Scheme 19

Bismuth ylides such as **53** undergo similar reactions with aldehydes at low temperature (Scheme 20), although at higher temperatures dimerisation of the ylide predominates. With ketones, an epoxide was formed in one instance, but other reaction pathways were also observed.[72]



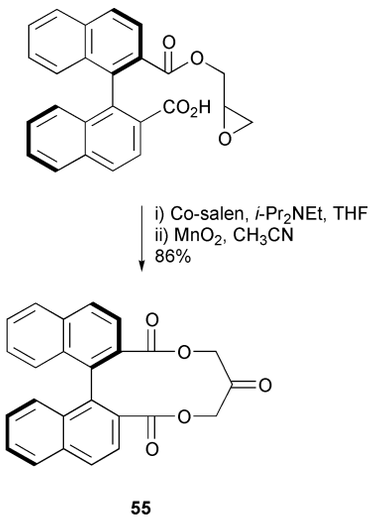
Scheme 20

Finally, for this type of reaction, Liu and Verkade have shown that **54** is superior to $P(NMe_2)_3$ for the dimerisation of aldehydes. For instance, in the reaction shown in Scheme 21 $P(NMe_2)_3$ gave a 1 : 1 mixture of diastereoisomers.[73]



Scheme 21

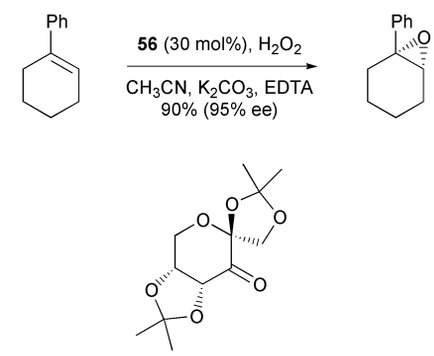
The last five years have seen dioxiranes emerge from being a curiosity to becoming one of the major methods for the epoxidation of alkenes. Naturally, much of this work involved the formation of chiral nonracemic epoxides.[74] Ketone **55** is one of the more prominent dioxirane precursors, with an improved synthesis being reported. The key step, shown in Scheme 22, features the use of the racemic cobalt(II)–salen complex corresponding to **1** as a catalyst for epoxide opening. Simple



Scheme 22

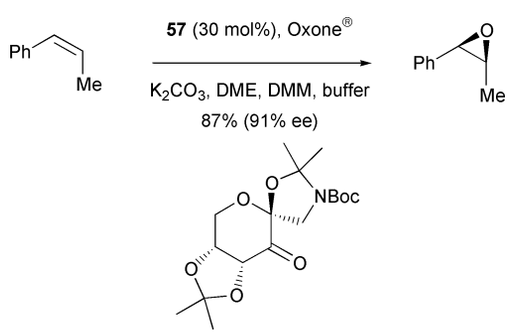
oxidation of the resulting alcohol then provided **55**.[75] Other related synthetic work includes an improved resolution procedure for the dicarboxylic acid precursor.[76] Dioxiranes often offer complementary selectivity to other reagents in epoxidation reactions. For instance, while Δ^5-unsaturated steroids give the α-epoxides using peracids, dioxiranes allow selective access to β-epoxides.[77]

Oxone® is almost universally used as the terminal oxidant in ketone-catalysed epoxidations. However, hydrogen peroxide is more attractive given that the by-product is water. With ketone **56**, hydrogen peroxide can indeed be used as teminal oxidant, but only in acetonitrile as solvent (Scheme 23).[78]



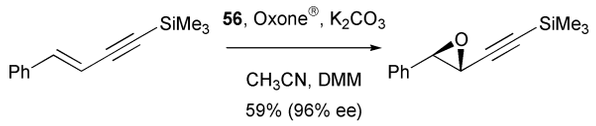
Scheme 23

While **56** gives poor enantioselectivity for the epoxidation of *cis* olefins, the nitrogen analogue **57** performs much better (Scheme 24), although it is less effective for *trans* and trisubstituted olefins. Thus, the two catalysts are complementary.[79]

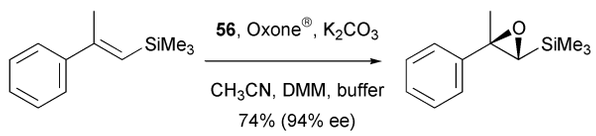


Scheme 24

Shi and co-workers have expanded the scope of epoxidation reactions with **56**. Good asymmetric induction has been obtained with enynes (Scheme 25)[80] and vinylsilanes (Scheme 26).[81] In the latter case, desilylation leads to enantiomerically enriched 1,1-disubstituted epoxides.

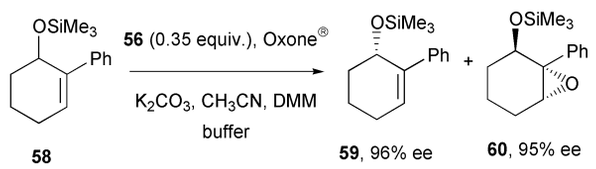


Scheme 25



Scheme 26

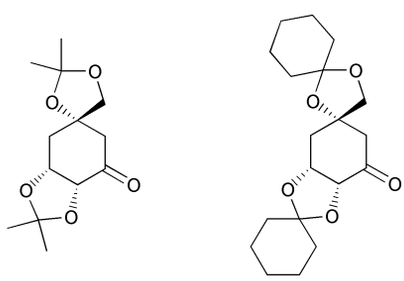
In related work, the same ketone can be used for kinetic resolution of chiral cyclohexenes. For example, carrying out the epoxidation of **58** to 49% conversion allows the formation of **59** and **60**, both with excellent enantiomeric excess (Scheme 27).[82]



Scheme 27

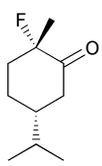
Two new chiral ketones **61** and **62**, derived in only four steps from (D)-(−)-quinic acid, have also been used for asymmetric epoxidation.[83]

Cyclic ketones with α-electron-withdrawing groups are among the most efficient catalysts for dioxirane epoxidation. A direct comparison of ketones **63** and **64** shows that **63**, with an axial fluorine, is far more effective for the epoxidation of cinnamate esters. It seems likely that only the equatorial oxygen is transferred from the dioxirane derived from **63**, and while the authors do not specifically comment, it is possible that the lower selectivity obtained with **64** could be due to axial oxygen transfer as a result of steric hindrance by the axial methyl group.[84] The speculation about equatorial oxygen transfer is supported by a computational study by Armstrong, Washington and Houk.[85]

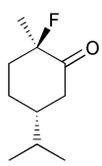


61

62

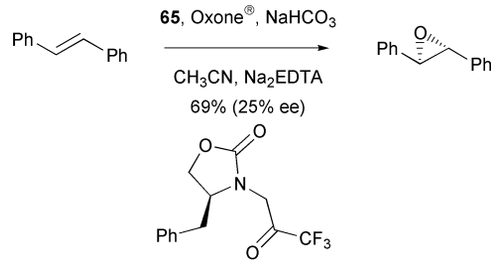


63



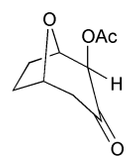
64

Armstrong and Hayter have presented a detailed account of their early studies on the use of functionalised ketones as dioxirane precursors, including the use of **65** as a chiral catalyst (Scheme 28).[86] The same group had previously reported the use of chiral tropinones as catalysts for the same process, and more recently a detailed study has led to the discovery of **66** as a particularly effective catalyst. Using only 20 mol% of **66** (80% ee), stilbene oxide was produced with 74% ee, so that the enantiomerically pure ketone should produce epoxide with an enantiomeric excess of over 90%.[87]



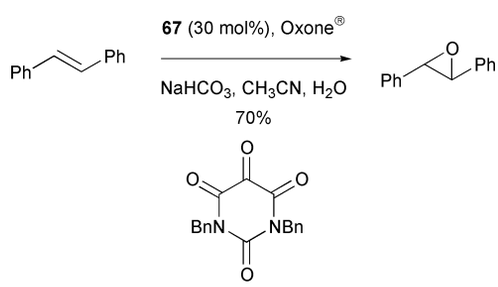
65

Scheme 28



66

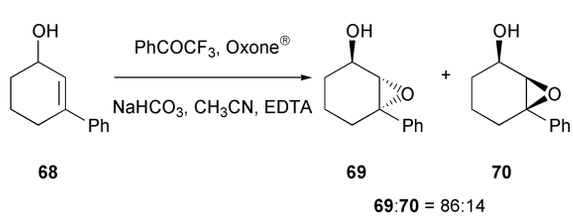
Although the ketones described above can be used in substoichiometric quantities, few of these reactions are truly catalytic, and recovery of the ketone has been seldom demonstrated. In a recent report by Carnell *et al.*, alloxan **67** was introduced as an efficient catalyst, and recovered (70%) after the epoxidation reaction shown in Scheme 29.[88]



67

Scheme 29

Epoxidation of allylic alcohols by *in situ* generated dioxiranes is complicated by direct epoxidation by Oxone®. However, 2,2,2-trifluoroacetophenone is an efficient catalyst, and for the epoxidation of **68** shows good selectivity for the *trans* epoxide **69**, in contrast to Oxone® alone providing predominantly the *cis*-epoxide **70** (Scheme 30).[89] Similar trends are observed for the epoxidation of cyclopent-2-en-1-ol ethers and acetates with dimethyldioxirane and with methyl(trifluoromethyl)dioxirane, although the selectivities are poor and variable with the free alcohols, with significant amounts of cyclopentenone being formed as a by-product.[90]

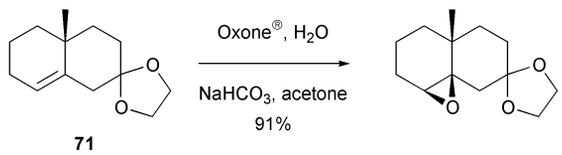


68 **69** **70**

69:**70** = 86:14

Scheme 30

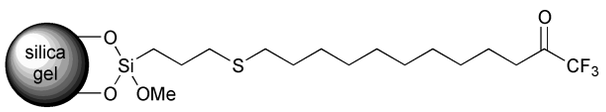
An improved protocol for the *in situ* generation of dimethyldioxirane simply involves dropwise addition of an aqueous Oxone® solution to a mixture of substrate, sodium bicarbonate and acetone at 0 °C. In this way, octalins such as **71** were epoxidised in high yield and with excellent diastereoselectivity (Scheme 31).[91]



71

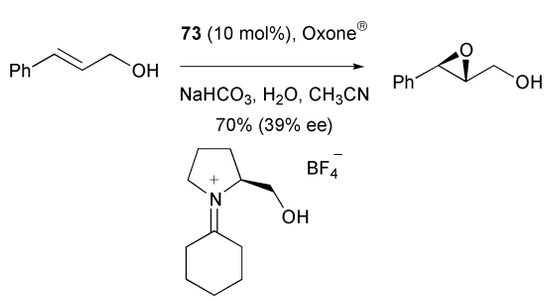
Scheme 31

It has been proposed that Baeyer–Villiger oxidation of ketones may be hindered on a solid support due to a higher activation barrier for migration of the supported chain, and also that formation of tetroxanes in a dimerisation process would be prevented by site isolation of the ketones on the support. These speculations certainly seem to have been borne out by catalyst **72**, which gives spectacular yields compared to the corresponding homogeneous catalyst, and can be easily recovered and re-used without significant loss of activity.[92]



72

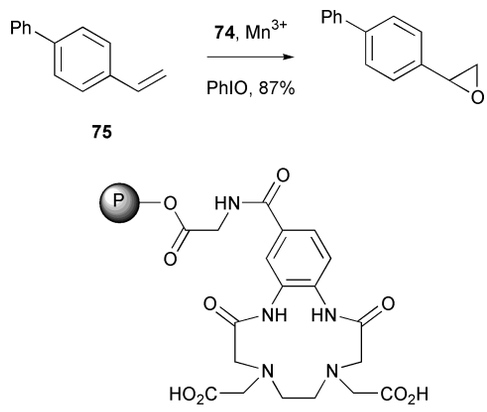
Oxaziridines and oxaziridinium ions are the next logical step from dioxiranes in terms of oxygen transfer from a small-ring heterocycle. The use of dihydroisoquinolinium ions as oxaziridinium ion precursors was described in the previous review in this series. Page *et al.* have now presented a detailed report outlining the effect of various reaction parameters (counter-ion, co-solvent) on the selectivity.[93] Washington and Houk have surveyed the available iminium salts which have been used for asymmetric epoxidation, and calculated transition states for oxygen transfer.[94] A new chiral iminium salt, **73**, has been described (Scheme 32). While the enantioselectivity was modest, the yield in this and related reactions (achiral iminium salts) was good with only 10 mol% of catalyst, boding well for future development.[95] A further new method involves the formation and reaction of *N*-sulfonyloxaziridines from aldehydes and chloramine-M.[96]



73

Scheme 32

Epoxidation reactions using heterogeneous catalysts can be divided broadly into those involving reaction at a solid surface (zeolite, oxide, metal) and those involving immobilisation of catalysts more commonly associated with homogeneous studies. A number of examples of the latter category have been discussed thus far, although one more example should be noted. A parallel screening approach identified **74** as a particularly effective ligand for the epoxidation of **75** catalysed by manganese(III) (Scheme 33). The corresponding homogeneous catalyst was even more effective (96% conversion within 2 minutes!).[97]



75

74

Scheme 33

Various reactions, including epoxidations, involving zeolites have been reviewed.[98] Previously, epoxidations with mesoporous zeolites have been limited by the use of organic peroxides as oxidant. A mesoporous TS-1 was shown to be more effective than conventional TS-1, with hydrogen peroxide being a suitable terminal oxidant.[99] In a further report using the same oxidant, NaY zeolite was first impregnated with titanium(IV) tetraisopropoxide, then with *n*-octadecyltrichlorosilane leading to a particularly effective catalyst.[100]

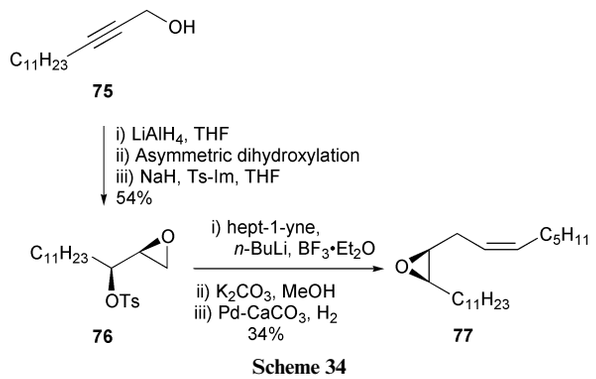
Various silica-supported metal oxides have also been used with good results. These centre mainly on titanium,[101] although photooxidation of propene has used both titanium[102] and zinc[103] oxides. Titanium alkoxides are well-known for homogeneous asymmetric epoxidation of allylic alcohols, while tantalum alkoxides are inefficient. However, when immobilised on silica this situation is reversed as a result of the higher valency of tantalum allowing immobilisation without reducing the number of available coordination sites. In this way, epoxides were prepared in modest to good yields and with up to 94% ee.[104] Tungstate anions have also been used as the basis for heterogeneous catalysts.[105]

Reactions at metal surfaces are also particularly important, including the selective mono-epoxidation of butadiene at Cu{111} surfaces,[106] and the epoxidation of various alkenes by oxygen–isobutyraldehyde in supercritical CO_2 promoted by the stainless steel surface of the reactor.[107]

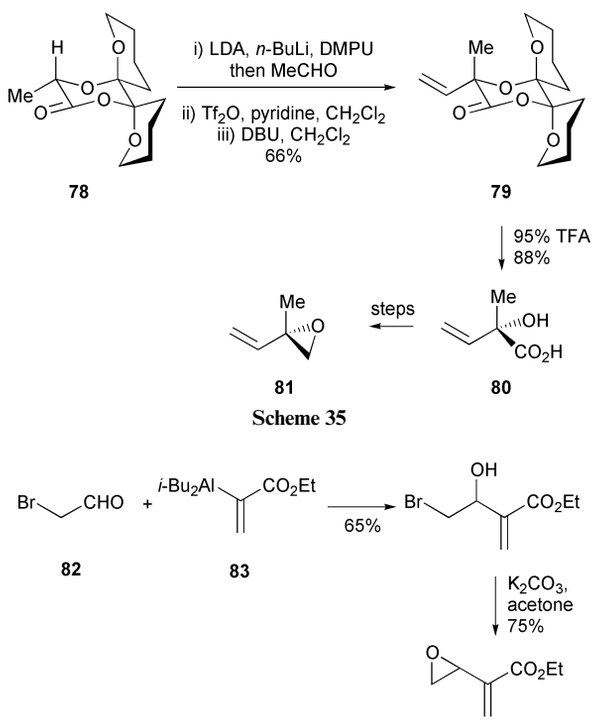
Oxidants such as magnesium monoperoxyphthalate are often used supported on silica or alumina. However, a recent study has shown that in some cases the support is not actually needed.[108]

Hertweck and Boland have expanded on earlier work to provide an asymmetric synthesis of four diastereoisomers of the pheromone lamoxirene using chloroallylboration and ring-closure methodology.[109] In other studies on pheromones, Zhang *et al.* have reported a short synthesis of insect pheromone **77** from **75**. Reduction followed by asymmetric dihydroxylation and subsequent treatment with tosylimidazole gave **76** in 54% yield for the three steps. Nucleophilic attack on the epoxide by an acetylide anion was then followed by ring closure and finally Lindlar reduction to give the pheromone (Scheme 34).[110]

The attraction of epoxides stems from their versatility as synthetic intermediates. Regioselective asymmetric epoxidation of dienes such as isoprene is challenging, and a new method uses chirality transfer from lactic acid to a "dispoke" protecting group to achieve this transformation. Deprotonation of **78** and reaction with acetaldehyde was followed by elimination to provide **79** (Scheme 35). Deprotection to **80** was then followed by standard transformations to give the desired epoxide **81**. A



Scheme 34

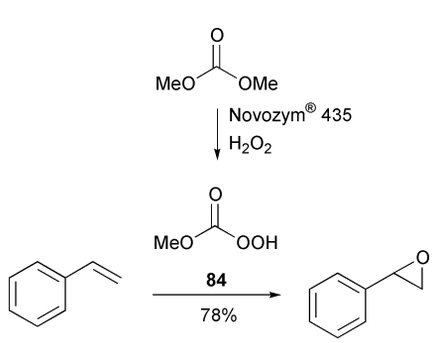


Scheme 35

Scheme 36

similar sequence provided a single enantiomer of the di-epoxide.[111] A further synthesis of vinyloxiranes is provided by reaction of **82** with **83** followed by ring-closure as shown in Scheme 36.[112]

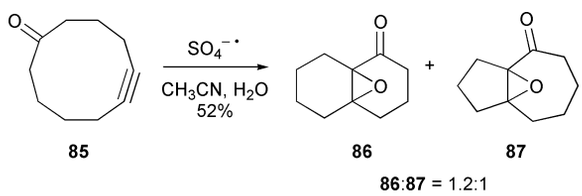
There are a number of biochemical methods which are useful for the resolution of epoxides by selective ring-opening of one enantiomer of a chiral epoxide,[113] or desymmetrisation of a *meso*-epoxide.[114] An immobilised lipase from *Candida antarctica* is able to selectively epoxidise the backbone double bonds of polybutadiene, while leaving the pendant vinyl groups untouched.[115] The same enzyme has also been used in a chemo-enzymic epoxidation in which dimethyl carbonate is perhydrolysed by hydrogen peroxide under influence of the enzyme, to give **84** as the active oxidant (Scheme 37).[116]



Scheme 37

Chloroperoxidase from *Caldariomyces fumago* has been found to catalyse two interesting processes involving epoxides. Although the epoxide was not isolated, epoxidation of cyclohexadiene with *tert*-butyl hydroperoxide occurred to give the ring-opened diols (S_N2 and S_N2') as products.[117] The same enzyme catalyses the kinetic resolution of 2,3-epoxyalcohols by oxidation to the aldehyde.[118]

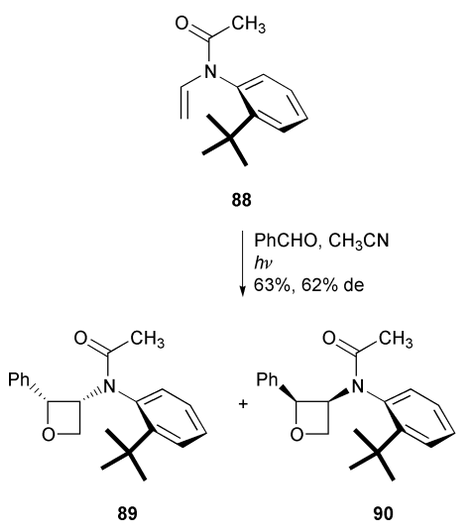
Finally for this section, two epoxides **86** and **87** were obtained from the reaction of **85** with sulfate radical anion (Scheme 38). The proposed mechanism involves attack of the radical anion onto the alkyne followed by cyclisation.[119]



Scheme 38

3 Four-membered rings

As usual, this section is by far the smallest in the review. Bach has described the diastereoselective Paternò–Büchi reaction of an axially chiral enamide. Thus, reaction of **88** with benzaldehyde gave a 4 : 1 mixture of diastereoisomers **89** and **90** (Scheme 39), the major isomer of which (**89**) was characterised crystallographically.[120]



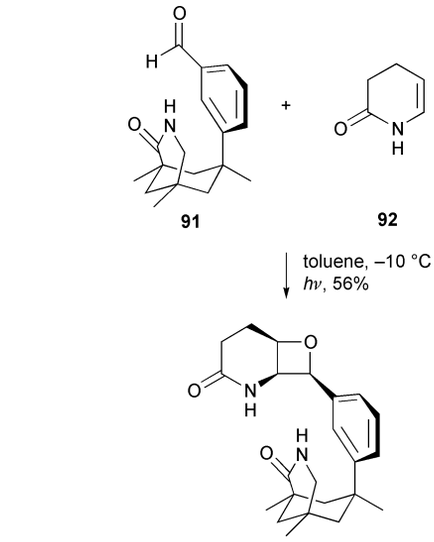
Scheme 39

A template directed approach from the same group is shown in Scheme 40, in which **91** reacts diastereoselectively with dihydropyridone **92** directed by intramolecular hydrogen bonding. The hydrogen bonding could be clearly seen in the crystal structure of **93**, and was also demonstrated by the use of a Job plot for the interaction of **91** with **92**.[121]

A further hydrogen bond-directed Paternò–Büchi reaction involves the carbonyl oxygen directly. Thus, reaction of **94** with benzophenone gave **95** with better than 90% de (Scheme 41).[122]

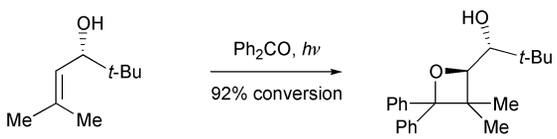
Bach has also presented an overview of his group's work in this area,[123] which includes the synthesis of preussin, now presented in full.[124]

Conceptually the simplest way to prepare an oxetane is cyclisation of a 1,3-diol, but this approach is often hampered by stereoselectivity problems. These problems have been overcome in a novel route from Aftab *et al.*, featuring a double inversion of the diol precursor. Thus, treatment of orthoester **97**, prepared from **96**, with acetyl bromide gave **98** (Scheme 42). At this point the site of bromide attack, although selective, is



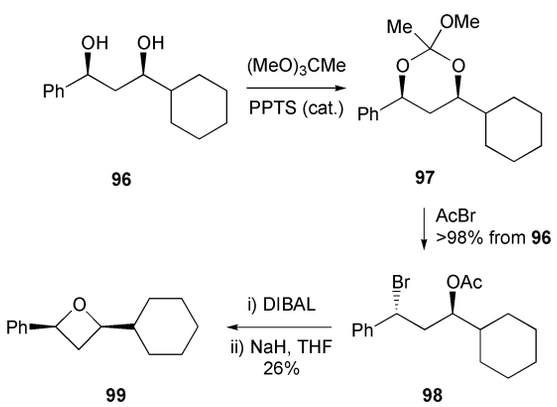
91 **92** **93**, 90% de

Scheme 40



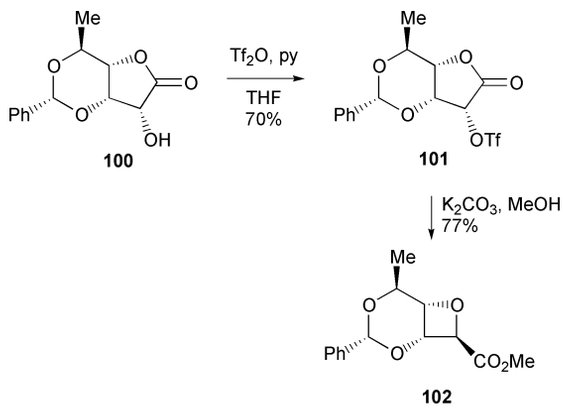
94 **95**, >90% de

Scheme 41



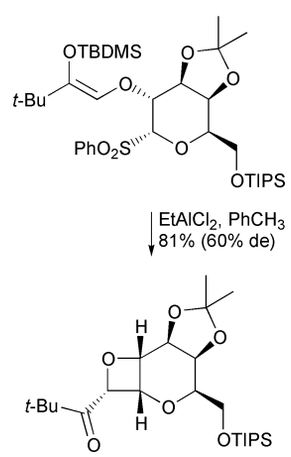
96 **97** **98** **99**

Scheme 42

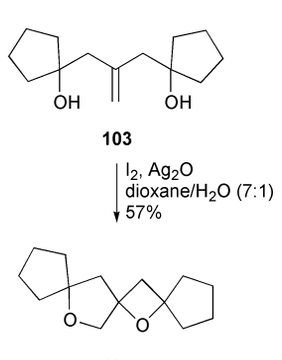


100 **101** **102**

Scheme 43



Scheme 44



103 **104**

Scheme 45

unimportant since this position is inverted by DIBAL reduction of the ester and sodium hydride-mediated cleavage to give the oxetane **99**.[125]

The formation of an oxetane from L-rhamnose is shown in Scheme 43. The key steps, which were amenable to multigram scale, involve formation of the triflate **101** from **100**, followed by treatment with methanolic potassium carbonate giving **102** with complete retention of stereochemistry. Presumably there is clean inversion either of triflate **101** or of the ring opened form after methanolysis but before cyclisation.[126]

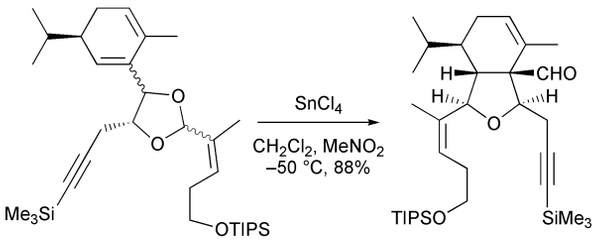
The all-*cis* oxetanes fused onto six-membered rings are clearly accessible, as shown in Scheme 44, although the other substituents on the pyran ring may make a difference in this case.[127]

One further example of oxetane formation involves a novel halocyclisation. Treatment of **103** with iodine and silver oxide in wet dioxane gave **104** directly in a reaction which presumably involves 4-*exo* halocyclisation followed by cyclisation of the resulting 4-iodoalcohol (Scheme 45).[128] Finally, another total synthesis of taxol has been reported, with the oxetane being formed in conventional manner by cyclisation of the appropriate 3-chloroalcohol.[129]

4 Five-membered rings

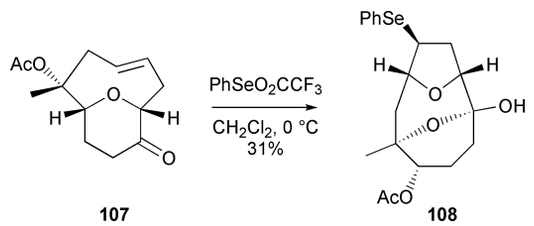
Two total syntheses of the proposed structure of sclerophytin A have been published, leading to a reassignment of the structure of this natural product. Paquette *et al.* began with the tetrahydrofuran ring intact as a lactone,[130] while Overman and Pennington used the Prins–pinacol rearrangement of **105** into **106** (Scheme 46).[131] In studies towards related natural products, Clark and Wong have reported the rearrangement of **107** into **108** (Scheme 47), in which the choice of selenium reagent strongly affects the outcome of the reaction.[132] Other applications of the Prins–pinacol rearrangement during the period of this review include the asymmetric synthesis of citreoviral, of which the key step, generating four contiguous stereogenic centres, is shown in Scheme 48.[133] Further work has shown the use of MOM and MTM ethers allows an effective Prins–pinacol reaction of formaldehyde acetals.[134]

The acetogenins remain popular targets, with a number of new total syntheses and approaches being reported. (+)-Muconin, featuring both tetrahydrofuran and tetrahydropyran



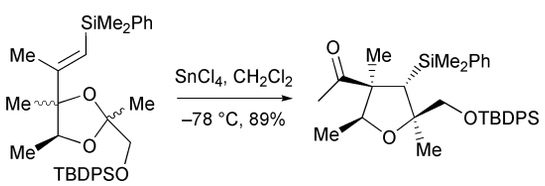
105 106

Scheme 46



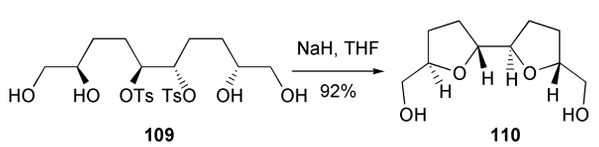
107 108

Scheme 47



Scheme 48

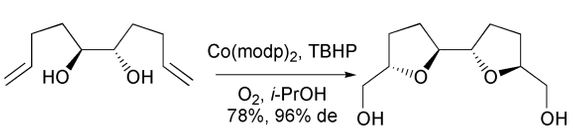
rings, has been prepared by Yang and Kitahara[135] using methodology previously reported by Koert *et al.* Koert's group have themselves prepared the same natural product, also from the same tetrahydrofuran precursor.[136] Emde and Koert have also prepared squamocins A and D starting with acyclic precursor **109**. Treatment with sodium hydride gave the C_2-symmetric bis-THF **110** which was mono-protected prior to further elaboration (Scheme 49).[137] Other work from this group include the synthesis of unnatural acetogenin–quinone hybrids.[138]



109 110

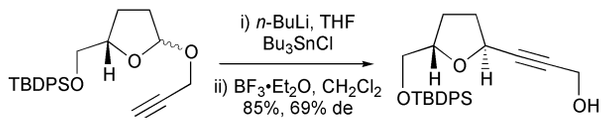
Scheme 49

A similar, although slightly shorter, strategy features a novel oxidative cobalt-mediated cyclisation as shown in Scheme 50. From this compound, the stereochemistry of the bis-THF portion of asimilobin was shown to be enantiomeric with that originally proposed.[139]

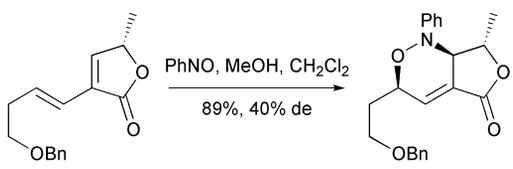


Scheme 50

One common feature of the acetogenins is the presence of a number of stereogenic centres (or groups of stereogenic centres) separated by alkyl chains, so that a modular approach is most effective. Two new syntheses of the muricatetrocins both share similar disconnections,[140] although the approach of Dixon, Ley and Reynolds contains some noteworthy features. Firstly, the tetrahydrofuran was prepared by the anionic rearrangement shown in Scheme 51. Secondly, and although not specifically related to the furan ring, the use of a hetero-Diels–Alder reaction to stereoselectively introduce oxygen functionality into the side chain (**111** to **112**, Scheme 52) is unusual.[141]



Scheme 51

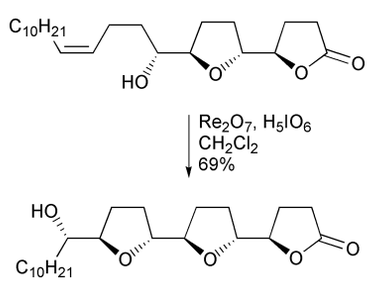


111 112

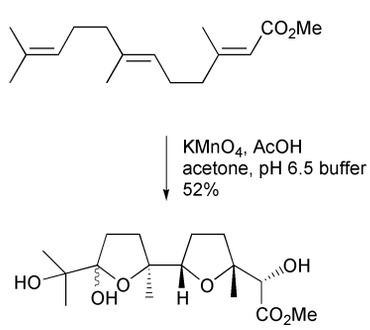
Scheme 52

Squamotacin and bullatacin differ only in the position of the bis-THF on the 34-carbon chain, while asimicin differs at one stereogenic centre. A synthesis of the former makes extensive use of Sharpless oxidation chemistry to provide every stereogenic centre around the bis-THF portion,[142] while syntheses of the latter two compounds also use an oxidative cyclisation, one example of which is shown in Scheme 53.[143] Related chemistry has also been used in the synthesis of (+)-eurylene,[144] while similar permanganate-mediated cyclisations are also known (Scheme 54).[145]

A total synthesis of jimenezin features the use of a cyclic sulfate as an epoxide surrogate. Thus, reaction of diol **113** with thionyl chloride followed by oxidation gave **114** (Scheme 55). Removal of the acetate ester occurred with concomitant cyclisation to give **115**. As a result of this work, the stereochemistry of the natural product was reassigned.[146]

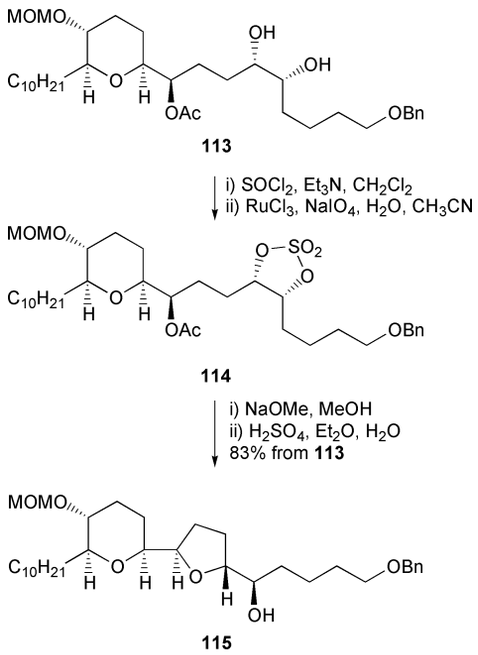


Scheme 53

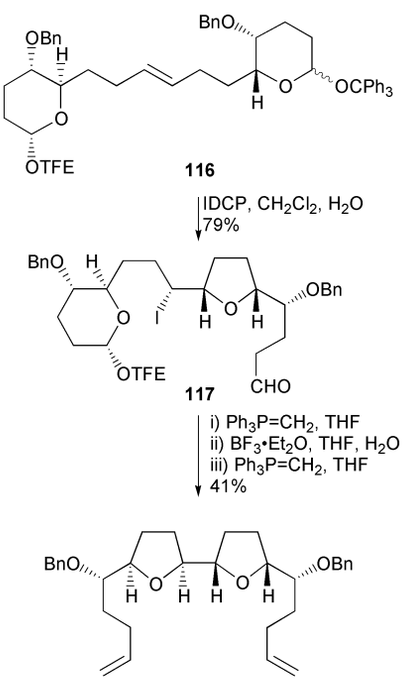


Scheme 54

A synthesis of the core of rolliniastatin makes use of a novel double cyclisation strategy. Iodocyclisation of **116** led to the efficient formation of **117** (Scheme 56). Wittig olefination and hydrolysis was then followed by a second olefination, with the serendipitous cyclisation, to give the near-symmetrical bis-THF **118**.[147]



Scheme 55

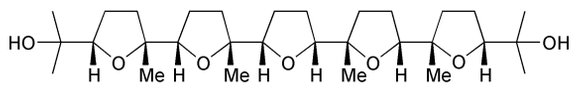


Scheme 56

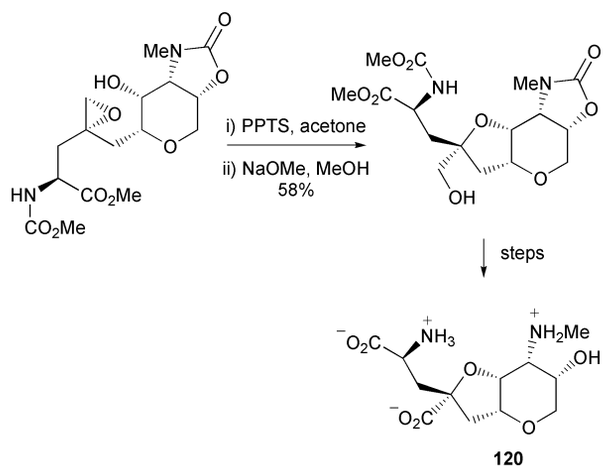
Total syntheses of tonkinecin and annonacin from the group of Wu use THF fragments prepared previously.[148] Finally for these compounds, partially hydroxylated bis-THFs have been prepared using known chemistry of glucose,[149] and a full account of an approach to bis-THFs based on the chemistry of 2-siloxyfurans has also been published.[150]

The triterpene glabrescol was originally assigned structure **119**. However, recent studies from Hioki *et al.* have culminated in the synthesis of this structure using a combination of epoxide opening and S_N2 displacement reactions to ensure stereocontrol. While a diastereoisomer of **119** was also prepared, no alternative structure was proposed for the natural product.[151]

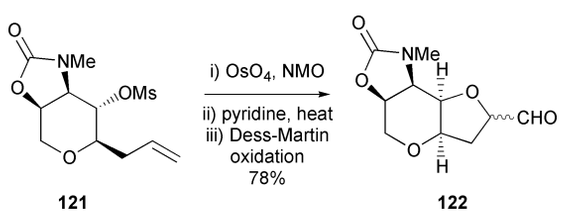
Dysiherbaine **120** is a neuroexcitatory toxin which has now been synthesised three times. The first total synthesis, from Masaki *et al.*, features the epoxide opening shown in Scheme



57 to prepare the tetrahydrofuran ring.[152] The most recent synthesis is similar to this in a number of respects, particularly in the use of an organozinc cross-coupling to introduce the amino-acid side chain, and epoxide opening to prepare the tetrahydrofuran.[153] The final synthesis, from Snider and Hawryluk, uses a simple S_N2 substitution to prepare the same ring (**121** to **122**) followed by enolate allylation to set the stage for completion of the synthesis (Scheme 58).[154]

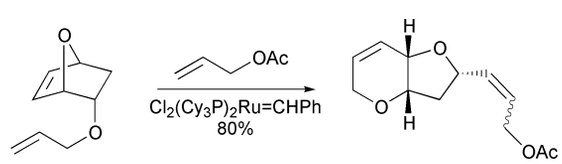


Scheme 57



Scheme 58

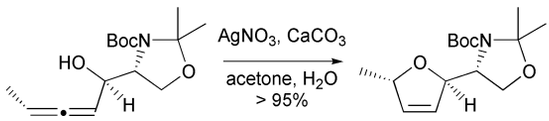
A particularly efficient route to this 6,5-fused ring system is shown in Scheme 59, and features a tandem metathesis reaction using the now-ubiquitous Grubbs' catalyst.[155]



Scheme 59

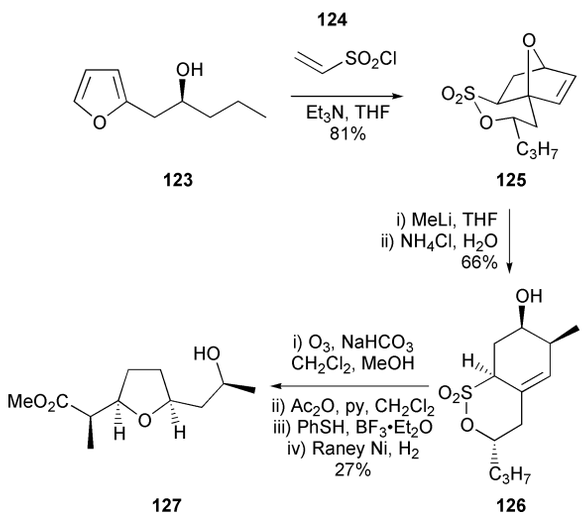
There are a number of relatively simple partially reduced furan derivatives which contain carboxylic acids, amines, or both. For instance, furanomycin is an isoleucine analogue which was been prepared using the allene cyclisation shown in Scheme 60. From this point, completion of the synthesis simply required removal of protecting groups and oxidation of the liberated primary alcohol to the carboxylic acid.[156] Such allenol cyclisations occur with complete transfer of allene chirality to the new stereogenic centre.[157]

The pamamycin group of natural products have been the subject of numerous synthetic studies. Both subunits of pamamycin-607 have been prepared from furan by Metz and co-workers using Diels–Alder chemistry as shown for the



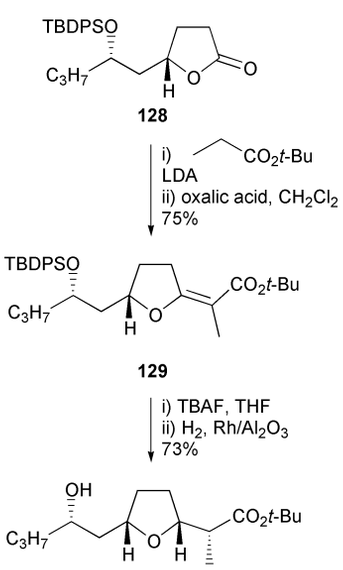
Scheme 60

smaller fragment in Scheme 61. Diels–Alder reaction of **123** with **124** gave **125**, which, upon treatment with methyllithium provided **126** as the major stereoisomer. Ozonolysis of this compound (with concomitant lactol formation) was followed by reaction with thiophenol and reduction over Raney nickel, under which conditions the sultone was also removed, to provide **127**.[158] Mandville and Bloch have also used the 7-oxabicyclo[2.2.1]hept-5-ene ring system in the synthesis of pamamycin fragments, this time as a template for the stereoselective synthesis of the tetrahydrofuran ring.[159]



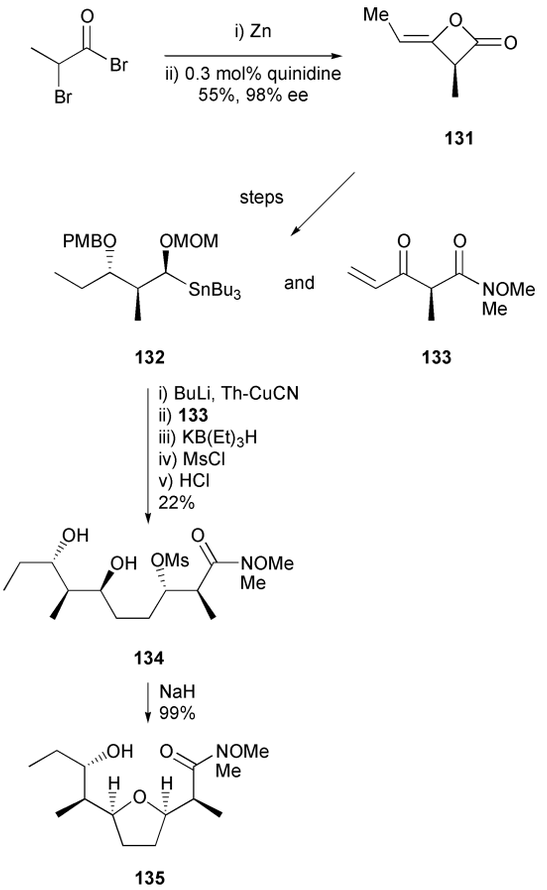
Scheme 61

Another approach to the same compounds uses an interesting modification of a lactone in which **128** provided access to **129** as a single geometrical isomer (Scheme 62). While hydrogenation of **129** gave **130**, it was also shown that compounds such as **129** can be isomerised, so that the alternative stereochemistry at C-2 is also accessible upon hydrogenation.[160]



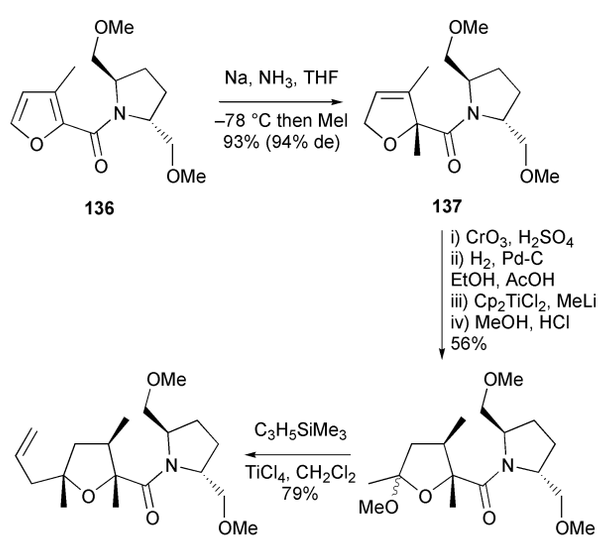
Scheme 62

In studies towards the related pamamycin 621A, Calter and Bi have used the asymmetric dimerisation of methylketene as their source of chirality. Two key fragments, **132** and **133**, were prepared from **131**, and coupled in straightforward manner to provide **134** (after some manipulation of functional groups). From this point, a simple cyclisation gave **135** (Scheme 63).[161] A



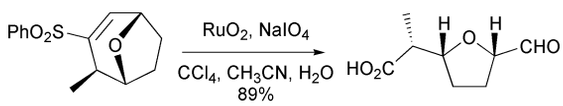
Scheme 63

similar tetrahydrofuran carboxylic acid, nemorensic acid, has been prepared using intramolecular conjugate addition of an alcohol,[162] and also using a diastereoselective Birch reduction of furan **136** to give **137** (Scheme 64). From this point, oxidation to the lactone was followed by double bond hydrogenation and Petasis methylenation. Methanolysis gave a diastereomeric mixture of acetals **138** which were treated with allyltrimethylsilane under Lewis-acidic conditions to give **139**.[163]



Scheme 64

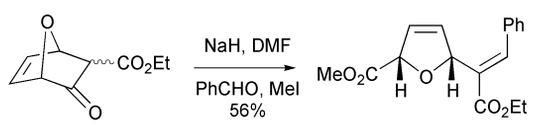
A further approach to related compounds is exemplified by Scheme 65, in which **140**, prepared using asymmetric oxidation of a sulfonylcycloheptadiene and regioselective transannular epoxide opening, is oxidatively cleaved to unveil the tetrahydrofuran **141**.[164]



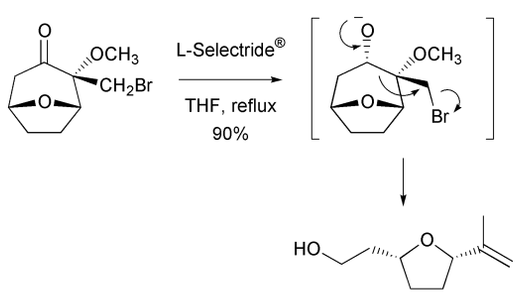
140 **141**

Scheme 65

Fragmentation of bicyclic systems derived from furan Diels–Alder reactions is an attractive method which allows the simultaneous reduction and functionalisation of furans. While oxidative cleavage of alkenes is one obvious method, alternatives have been developed, such as the aldol condensation and fragmentation shown in Scheme 66,[165] and the unusual oxy-anion initiated process shown in Scheme 67.[166]

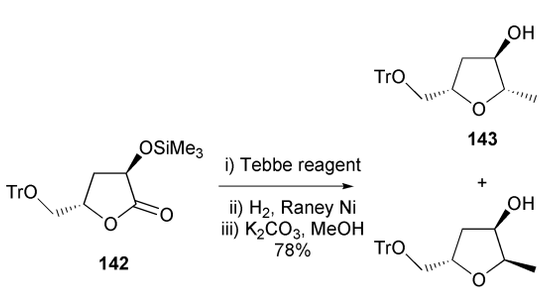


Scheme 66



Scheme 67

Two new total syntheses of muscarine have been disclosed, the former featuring simple cyclisation of a glucose derivative to form the tetrahydrofuran ring.[167] In the latter approach, Tebbe methylenation of **142** was followed by hydrogenation and deprotection to provide a mixture of **143** and **144** (Scheme 68). As is so often the case, if **144** had been required, it could have been prepared with high diastereoselectivity by using palladium on calcium carbonate as the hydrogenation catalyst.[168]

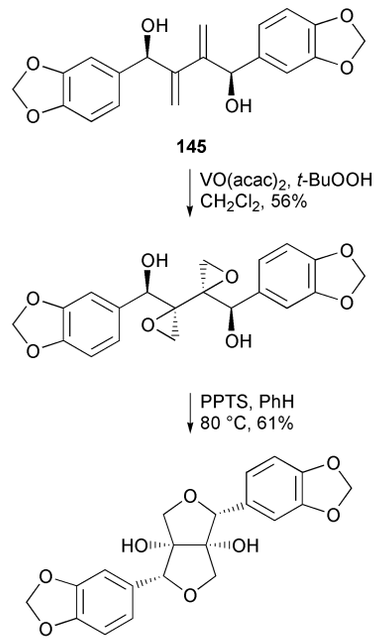


142 **143** **144**

Scheme 68

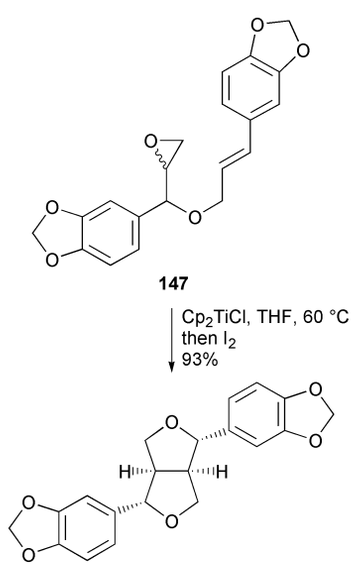
In related work, Koert and co-workers have used epoxide opening and diol cyclisation methodology to prepare tetrahydrofuran carboxylic acids and amino acids[169] which were incorporated into new integrin antagonists.[170] Wang and Metz have resolved methyl nonactate by way of its ester with mandelic acid. This is particularly useful since nonactin is a tetramer of nonactic acid containing both enantiomers.[171]

A concise synthesis of the furofuran lignan wodeshiol has been achieved by Han and Corey as shown in Scheme 69. Diastereoselective epoxidation of **145**, prepared by a symmetrical Pd/Cu catalysed coupling reaction, was followed by a double epoxide opening to give the natural product **146**.[172] A second furofuran lignan synthesis features the stereoconvergent transformation of a 1 : 1 mixture of epoxides **147** into (±)-sesamin **148** (Scheme 70).[173]



145 **146**

Scheme 69

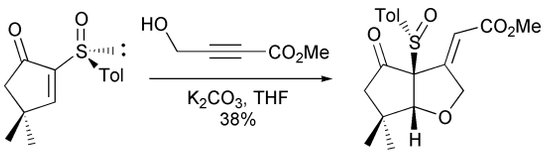


147 **148**

Scheme 70

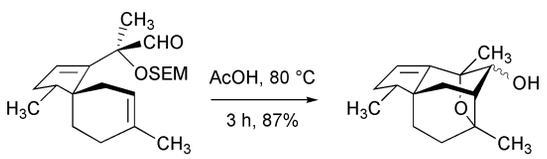
The conversion of lactones into various sized oxygen heterocycles is a relatively common strategy given the ease of preparation of the former. However, in the total synthesis of asteriscanolide, Paquette and co-workers used a reversal of this approach, so that the required lactone was unveiled at the end of the synthesis by oxidation of the corresponding THF, formation of which is shown in Scheme 71.[174]

The final example of total synthesis for this section of the review is the use of a cationic cascade for the preparation of



Scheme 71

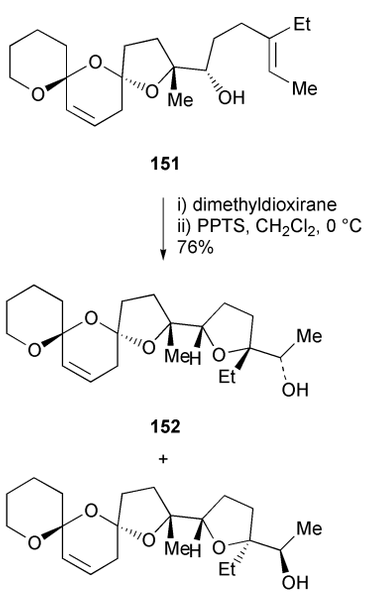
hispidospermidin. Treatment of **149** with acetic acid led to the formation of the cyclohexane and tetrahydrofuran rings of **150** in a manner analogous to the postulated biosynthesis (Scheme 72).[175]



149 **150**

Scheme 72

We have already seen a number of examples of the stereoselective preparation of tetrahydrofuran-2-ylmethanol derivatives by intramolecular ring opening of hydroxyepoxide precursors.[176] This is a common approach due to the ease of preparation of epoxides, and predictable stereochemistry of cyclisation. In studies on polyether antibiotics, Brimble and Prabaharan have used this strategy to prepare **152** and **153** (separable diastereoisomers arising from an inseparable 1 : 1 mixture of epoxides). A number of stereoisomers of the precursor **151** were prepared by attack of a Grignard reagent on a bis-spiroacetal aldehyde under Barbier conditions (Scheme 73).[177]



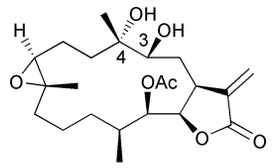
151 **152** **153**

Scheme 73

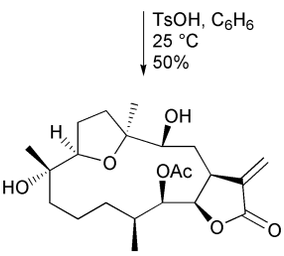
In studies towards the uprolide cembranolides, cyclisation of 14-membered epoxydiol **154** gave a tetrahydropyran (38% yield) as a result of cyclisation of the 3-hydroxy in addition to the tetrahydrofuran **155** shown (Scheme 74). As a result of this work, the structures of uprolides F and G were revised to tetrahydropyrans.[178]

Oxygen transfer from aldehydes to alkenes is important in epoxidation reactions using molecular oxygen as terminal oxidant. In mechanistic studies, Jarboe and Beak observed the following reaction (Scheme 75), which is consistent with the intermediacy of an acylperoxy radical.[179]

One of the more common approaches involving epoxides is the use of a 2,3-epoxyalcohol prepared by Sharpless epoxidation. This has the advantage of introducing further functionality, and has been used a number of times recently,[180] including the formation of diastereoisomers **157** and **158** from **156** (Scheme 76). These compounds were then elaborated to provide naturally occurring tetrahydrofurans isolated from the *Notheia anomala* marine alga.[181]

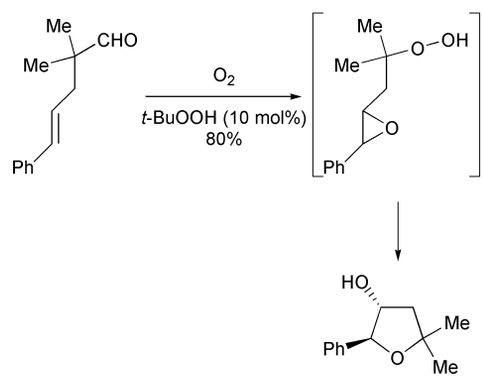


154

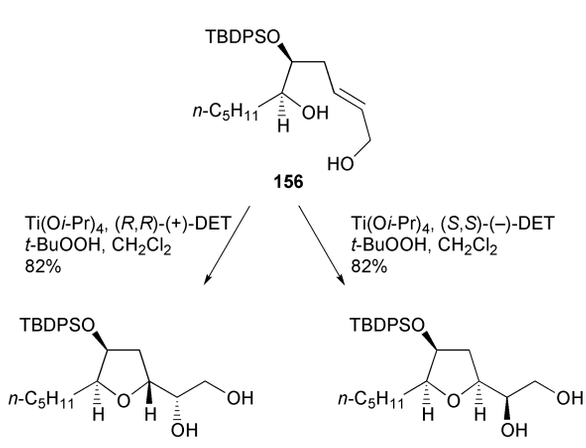


155

Scheme 74



Scheme 75

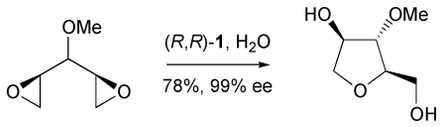


156 **157** **158**

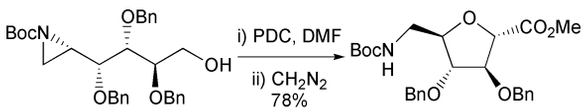
Scheme 76

The use of cobalt complex (*R*,*R*)-**1** in epoxide opening has already been discussed. One further example, in which a tetrahydrofuran is formed, is shown in Scheme 77. This arises from enantioselective hydrolysis of a terminal epoxide followed by cyclisation.[182]

The related ring-opening of aziridines has been used less frequently, but works effectively for the transformation of **159** into **160** (Scheme 78).[183]



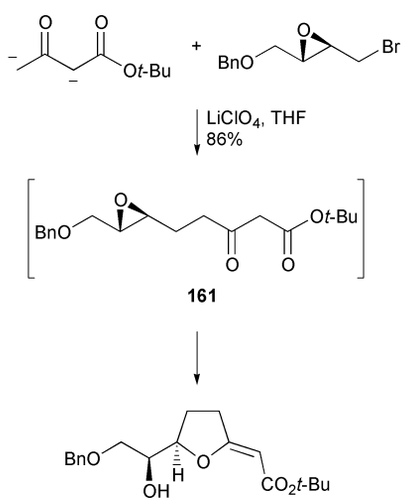
Scheme 77



159 **160**

Scheme 78

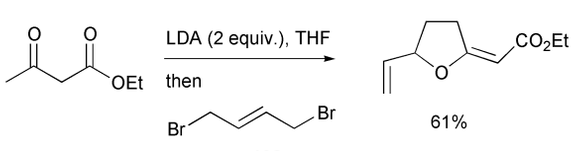
One final example of epoxide opening involves dianion chemistry to generate the requisite epoxide **161**. The addition of lithium perchlorate proved critical, since in the absence of this additive the reaction shown in Scheme 79 gave mainly the tetrahydropyran formed by endocyclic epoxide opening.[184]



161

Scheme 79

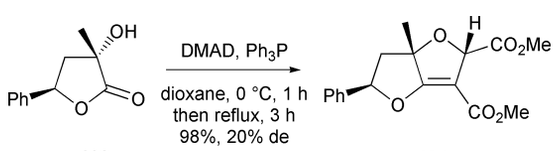
Langer and co-workers have reported an essentially identical reaction,[185] along with the variation shown in Scheme 80 in which **162** was used as a bis-electrophile.[186]



162

Scheme 80

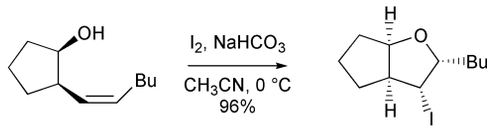
A further approch to 2-alkylidenetetrahydrofurans uses the *in situ* generation of a phosphonium ylide from dimethyl acetylenedicarboxylate and triphenylphosphine. In this way, **164** was produced in excellent yield from hydroxylactone **163** (Scheme 81).[187]



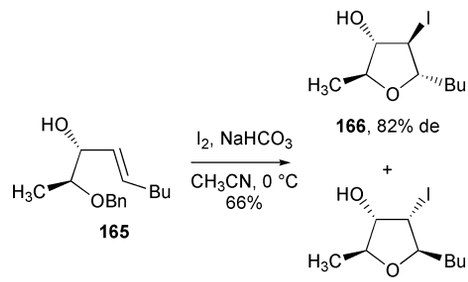
163 **164**

Scheme 81

There are considerable mechanistic parallels between epoxide cyclisations and halo- and selenocyclisations. Knight has developed electrophile-driven 5-*endo-trig* iodocyclisations leading to pyrrolidine and tetrahydrofuran derivatives. A full account has been published detailing the discoveries which led to the initiation of this project and optimisation of the reaction.[188] Further work from the same group demonstrates the formation of fused tetrahydrofurans from cyclohexanol and cyclopentanol derivatives (*e.g.* Scheme 82)[189] and also the incorporation of additional substituents on the tetrahydrofuran ring. For instance, reaction of **165** under standard conditions gave good diastereoselectivity for **166** (Scheme 83).[190] This methodology has been applied to the tetrahydrofuran ring of aplasmomycin.[191]

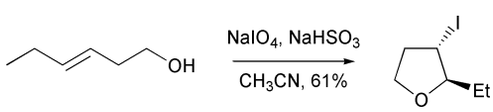


Scheme 82



Scheme 83

A slightly unusual reagent combination for this transformation is shown in Scheme 84, in which $NaIO_4$–$NaHSO_3$ presumably generates IOH *in situ*. However, other cyclisations of homoallylic alcohols resulted in the incorporation of oxygen rather than iodine into the tetrahydrofuran ring. This appears to be a result of intermolecular iodohydroxylation of the double bond followed by cyclisation of the resulting iodo alcohol.[192] While these reactions are only *formally* 5-*endo-trig* cyclisations, Craig *et al.* have previously demonstrated actual 5-*endo-trig* cyclisation reactions of appropriately substituted vinylsulfones.[193]

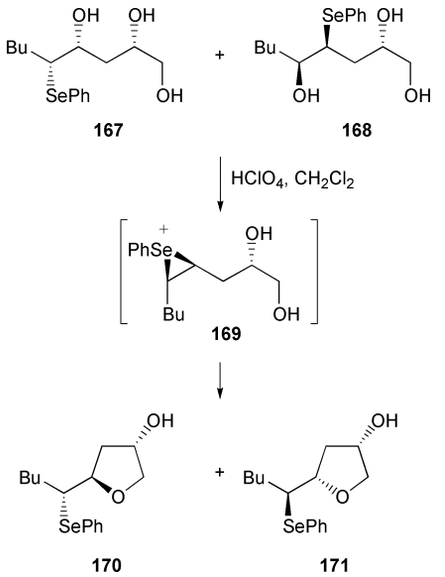


Scheme 84

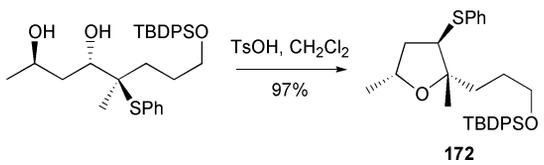
While it is more usual in cyclisations involving selenium that the seleniranium ion is generated intermolecularly,[194] it is also possible to generate this ion intramolecularly as shown in Scheme 85. Treatment of a mixture of **167** and **168** surprisingly gave a 1 : 1 mixture of **170** and **171**. Since both **167** and **168** should give the same stereoisomer of the seleniranium ion **169**, these results have been interpreted as complete removal of the selenium from the double bond and equilibration prior to cyclisation. If the reaction was allowed to proceed for longer, further equilibration took place to give tetrahydropyrans as the sole products.[195]

This last reaction involves a competition between 5-*exo* and 6-*endo* processes. A related reaction from Warren *et al.* sets 4-*exo* against 5-*endo*, so that formation of the tetrahydrofuran **172** is unsurprising (Scheme 86).[196]

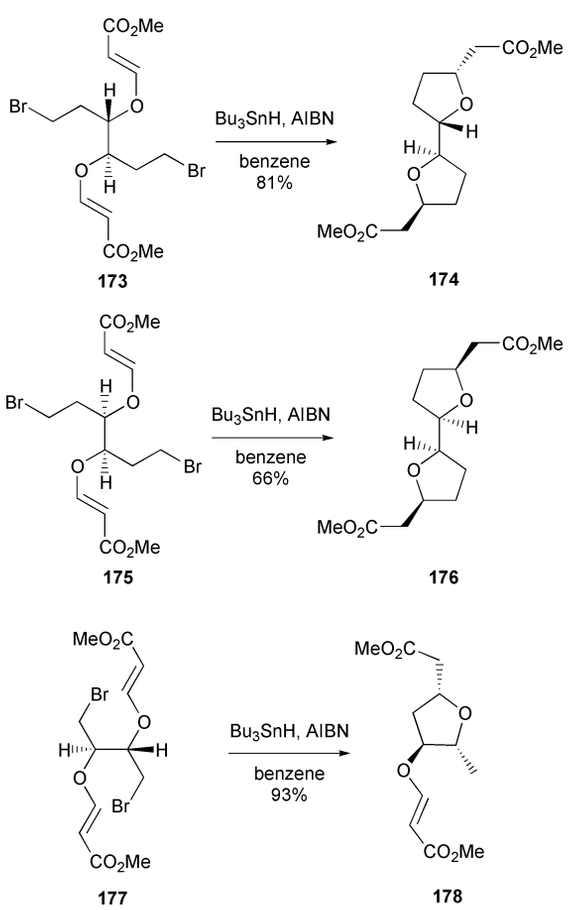
Lee *et al.* have previously reported a formal total synthesis of (−)-kumausallene by double radical cyclisation of an alkoxyacrylate precursor.[197] The same group have now extended the stereochemical scope of this reaction in the reaction of *meso* precursor **173** to give **174**, and of **175** to give **176**. In contrast, **177**, derived from *meso*-erythritol, gave only the product of a single cyclisation **178** (Scheme 87).[198]



Scheme 85



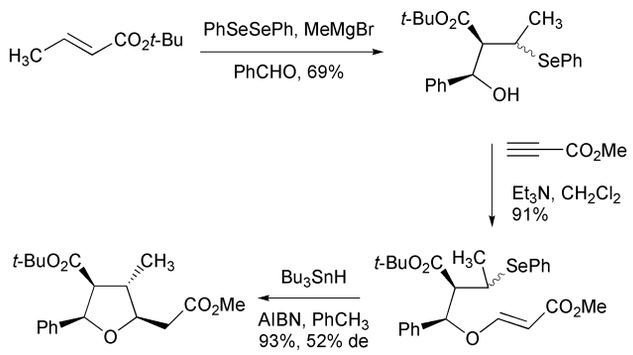
Scheme 86



Scheme 87

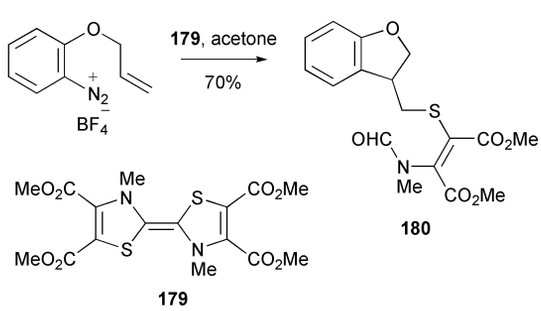
A similar cyclisation to that shown above follows from a tandem Michael addition of magnesium selenolate onto an unsaturated ester and trapping of the resulting enolate with benzaldehyde (Scheme 88).[199]

The generation of radicals by using tin hydrides is routine, but causes problems due to the toxicity of organotin species. In a particularly environmentally benign radical cyclisation, Yorimitsu *et al.* showed that it is possible to use phosphinic acid to generate radicals from aliphatic and aromatic halides, and furthermore that in the presence of sodium carbonate these radicals undergo efficient cyclisation in ethanol solution, thus removing the need for aromatic hydrocarbon solvents.[200] Single electron oxidation adjacent to a nitro group provides another method of carbon-centred radical formation; cyclisation then proceeds in the usual way.[201]



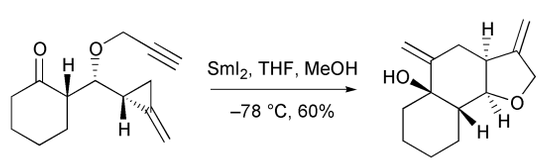
Scheme 88

Recent work on radical-polar crossover reactions has shown that if diazadithiafulvalenes such as **179** are used as initiators, then rather than nucleophilic displacement of the initiator to terminate the reaction, fragmentation may take place leading to products such as **180** (Scheme 89).[202]



Scheme 89

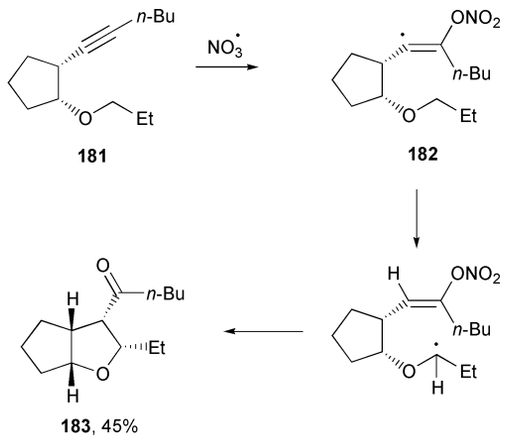
Generation of *O*-stannylketyl radicals from aldehydes using tributyltin hydride has been used to prepare tetrahydrofurans.[203] More commonly, ketyl radicals are prepared using samarium diiodide. One recent use of this approach is the cascade process shown in Scheme 90.[204] In a related example involving final cyclisation onto a double bond, 25% of a dimer was isolated, formed by stereoselective dimerisation of the resulting primary radical.[205]



Scheme 90

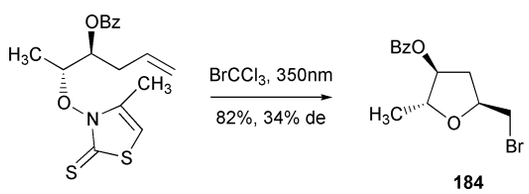
Another interesting, if low yielding, radical cascade begins with addition of the nitro radical (from electrolysis of lithium nitrate) to **181**, giving **182**. Hydrogen radical abstraction is then followed by cyclisation with loss of nitrogen dioxide to give **183** (Scheme 91).[206] A further electrochemical free radical reaction features trapping of the cyclised radical with carbon dioxide.[207]

All of these processes involve cyclisation of carbon-centred radicals. Barton chemistry has been used to provide oxygen-



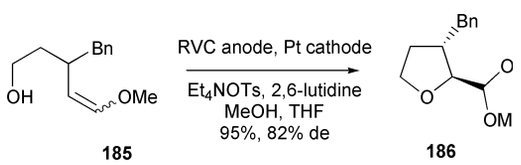
Scheme 91

centred radicals which underwent cyclisation as shown in Scheme 92. From product **184**, (+)-*allo*-muscarine was prepared in two steps.[208]



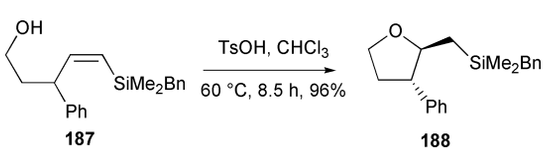
Scheme 92

Anodic oxidation of enol ethers provides a useful method for reversing the polarity of this functional group. Thus, oxidation of **185** provided **186** in excellent yield and good stereocontrol (Scheme 93).[209]



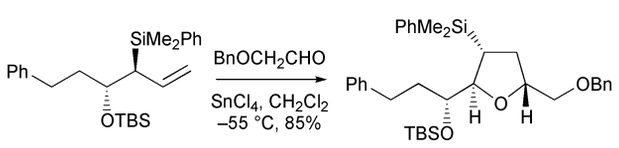
Scheme 93

The electronic effects of silicon are discussed more extensively in the following section. However, there are applications of vinyl and allylsilane chemistry to tetrahydrofuran formation. For instance, treatment of **187** with acid resulted in the formation of a single diastereoisomer **188** in essentially quantitative yield (Scheme 94).[210]



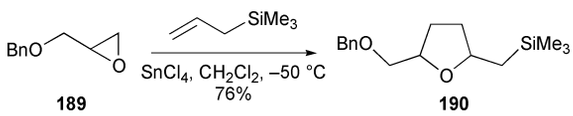
Scheme 94

The tetrahydrofuran formation in Scheme 95 should be contrasted with the reaction in Scheme 145. In this case, addition of the allylsilane to the aldehyde is followed by a 1,2-silyl shift and ring closure.[211]



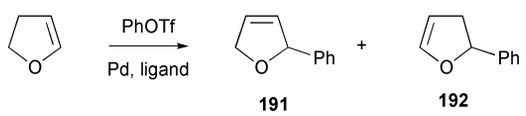
Scheme 95

Every so often a reaction is reported which, given the availability and synthetic utility of starting materials, one would expect to have been discovered before. The reaction of glycidol benzyl ether **189** with allyltrimethylsilane to give **190** is, in the opinion of the reviewers, one such reaction (Scheme 96). Unfortunately, no stereocontrol was observed.[212]

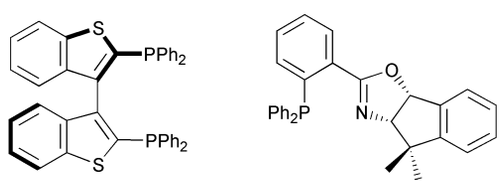


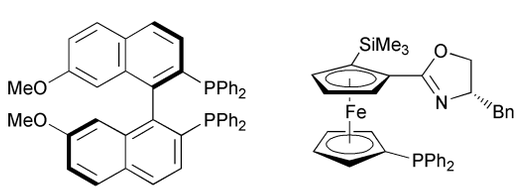
Scheme 96

The asymmetric Heck reaction of dihydrofuran gives rise to products **191** and **192** depending on the extent of double bond migration (Scheme 97). A number of new ligands have been reported for this process, including **193**,[213] **194**,[214] **195**[215] and **196**.[216] 2,2-Dimethyl-2,3-dihydrofuran, in which double bond migration is not possible, has also been used as a test substrate.[217]

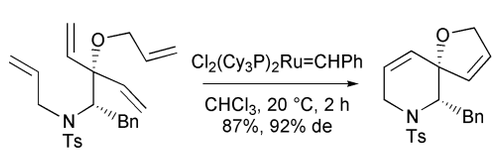


Scheme 97





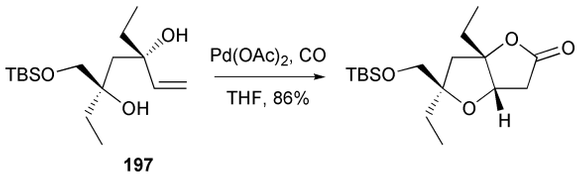
Ring-closing metathesis is discussed more extensively in the context of dihydropyran and medium ring formation.[218] However, there are examples of the use of this reaction in dihydrofuran formation,[219] including the impressive double-metathesis shown in Scheme 98.[220] Single enantiomer substrates for ring closing metathesis can be prepared by zirconium-catalysed ethylmagnesation of allylic ether precursors.[221]



Scheme 98

The palladium-catalysed alkoxycarbonylation of substrates similar to **197** has previously been used to prepare the furanofuranone ring system shown in Scheme 99. Up until this point though, the use of a substrate with two quaternary centres had not been demonstrated.[222]

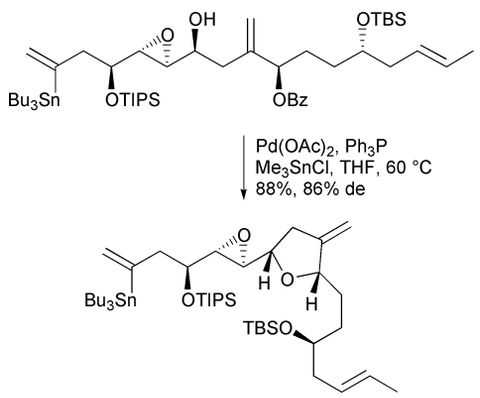
One important facet of organopalladium chemistry is the use of π-allyl complexes. Substantial progress towards the synthesis of amphidinolide K has been made, using the oxygenation of such a complex to prepare the tetrahydrofuran ring, the



197

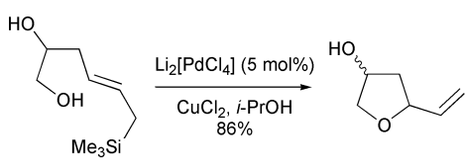
Scheme 99

tolerance of this reaction towards other functional groups within the molecule being particularly impressive (Scheme 100).[223] Similar reactions may also be mediated by iron.[224]



Scheme 100

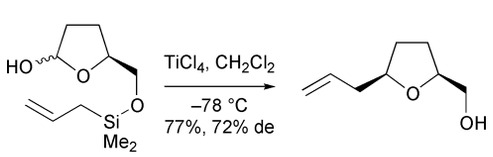
While allyl acetates or allyl benzoates are usually used as substrates in this type of reaction, the use of allylsilanes has recently been reported (Scheme 101). In this case, nucleophilic attack of palladium by the double bond must be followed by re-oxidation to palladium(II).[225]



Scheme 101

Additionally there are a number of transition-metal catalysed intramolecular annulation reactions of alkenes and alkynes in which oxygen heterocycles are formed as a result of the presence of oxygen in a tether.[226]

The generation and allylation of an oxacarbenium ion from a lactol derivative is a fairly general reaction which has been used a number of times over the last 18 months.[227] Intramolecular delivery of the allyl group from **198** is a useful variation which provides predominantly the *cis* isomer (Scheme 102).[228] A further variation provides stereocontrol at two centres by way of Evans aldol chemistry (Scheme 103).[229]

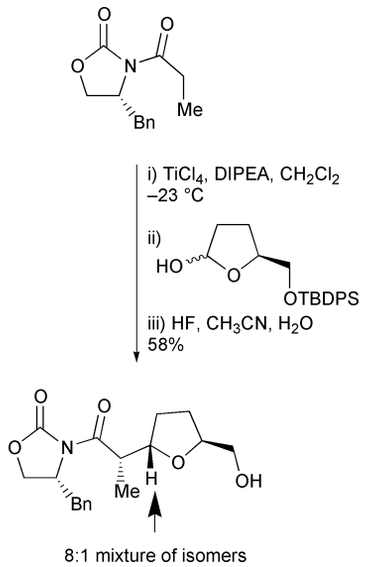


198

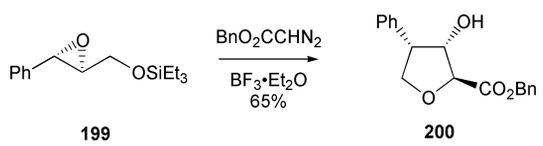
Scheme 102

Intramolecular *C*-glycosidations with enol ethers have been discussed in previous reviews in this series. A full account of this work has been published by Craig *et al.*[230]

In a variation on an earlier reaction,[231] Angle and White have shown that reaction of epoxide **199** with benzyl diazoacetate in the presence of boron trifluoride etherate leads to the stereoselective formation of **200** (Scheme 104). This occurs by initial rearrangement of the epoxide to a 2-siloxyaldehyde.[232]



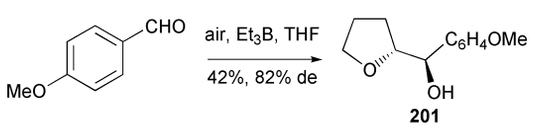
Scheme 103



199 200

Scheme 104

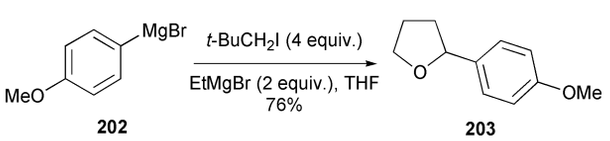
Finally for this section, there are a small number of reactions which involve direct activation of tetrahydrofuran itself. One such method is the addition of the tetrahydrofuranyl radical (generated *in situ* from the reaction of THF with Et_3B in the presence of air) to aldehydes. In this way, 4-methoxybenzaldehyde was converted into a 91 : 9 mixture of **201** and its diastereoisomer (Scheme 105); aliphatic aldehydes gave lower stereoselectivity.[233]



201

Scheme 105

A similar reaction can be accomplished by addition of neopentyl iodide and ethylmagnesium bromide to a solution of **202**. Under optimal conditions this gave **203** in good yield, again presumably *via* the tetrahydrofuranyl radical (Scheme 106).[234]



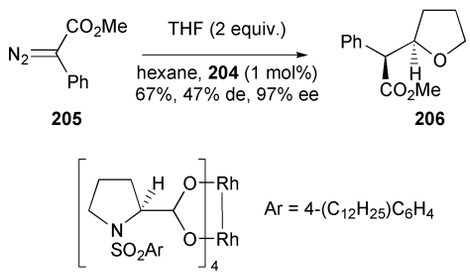
202 203

Scheme 106

It is well known that C–H bonds adjacent to oxygen are activated towards carbene insertion, so that the decomposition of diazo compound **205** by rhodium complex **204** in the presence of THF gave the insertion product as a mixture of diastereoisomers, of which the major isomer, **206** had 97% ee (Scheme 107). The use of THF as solvent proved less selective.[235]

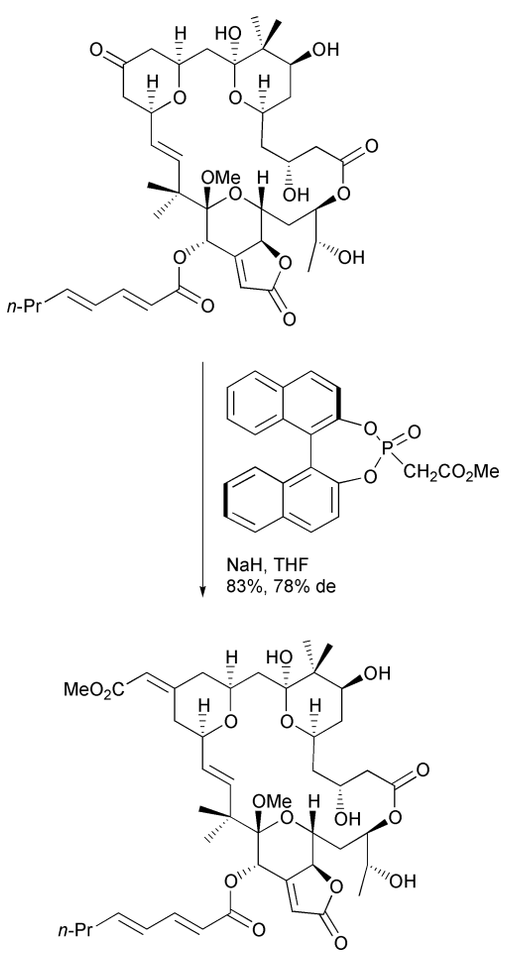
5 Six-membered rings

Forsyth's group have previously reported a total synthesis of okadaic acid. The same methodology has now been applied to 7-deoxyokadaic acid, confirming the structure of this natural product.[236] Overman has completed a total synthesis of racemic



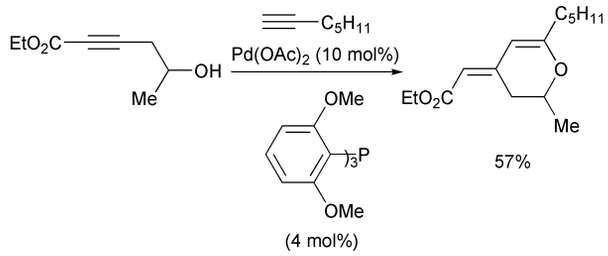
Scheme 107

gelsemine, introducing the tetrahydropyran ring at the end of the synthesis by reduction of the corresponding lactone (DIBAL then Et_3SiH–acid).[237] The first enantioselective synthesis of this natural product uses an intramolecular oxymercuration reaction to form the same ring.[238] The bryostatins contain three tetrahydropyran rings, two of which are present as lactols. The synthesis of bryostatin 3 from Ohmori *et al.* uses an asymmetric Horner–Wadsworth–Emmons reaction to functionalise the tetrahydropyran (Scheme 108),[239] this approach being essentially identical to that used by Evans and co-workers in their total synthesis of bryostatin 2.[240] Trost and Frontier have developed an efficient palladium-catalysed route which addresses the exocyclic double bond geometry found in these natural products (Scheme 109).[241]

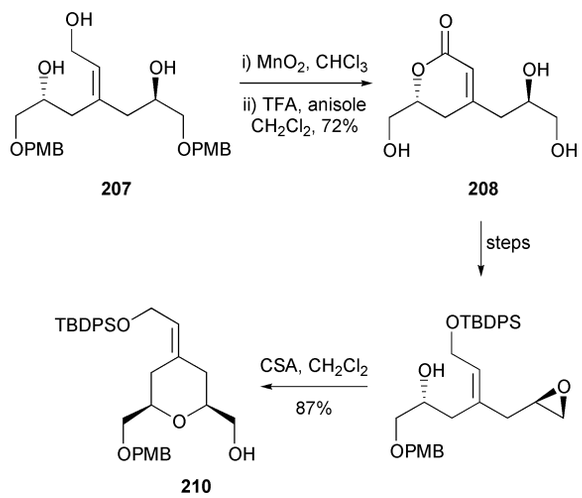


Scheme 108

Hale's approach to the tetrahydropyran ring of the bryostatin natural products uses an efficient symmetry-breaking strategy. Thus, oxidation of **207** provides lactone **208**. Subsequent protecting group manipulations and standard transformations provided epoxide **209** which could be cleanly cyclised to give differentially protected diol **210** (Scheme 110).[242]

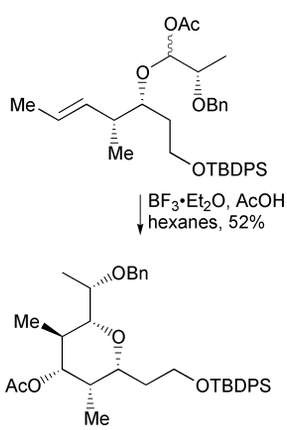


Scheme 109



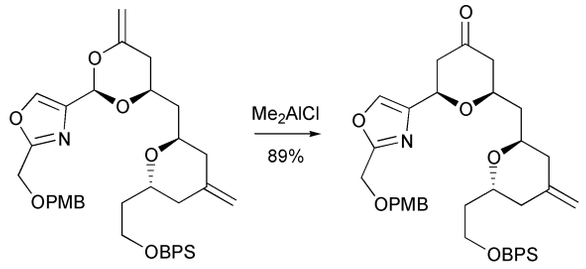
Scheme 110

In another landmark synthesis, Evans *et al.* have completed the first total synthesis of phorboxazole B (Forsyth's synthesis of phorboxazole A was mentioned in previous reviews in this series). In this case, all three tetrahydropyran rings were prepared by functionalisation of lactol precursors.[243] Greer and Donaldson's approach to the bis-oxane ring system is similar in this respect,[244] while Rychnovsky and Thomas have used a stereoselective Prins cyclisation as shown in Scheme 111 to prepare the C22–C26 oxane.[245]



Scheme 111

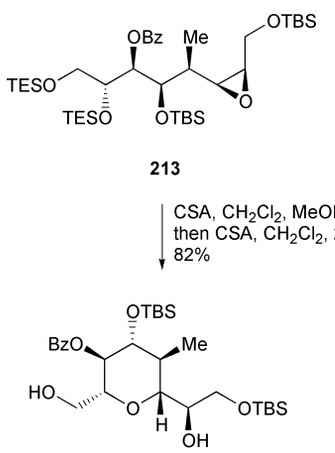
A further approach to the bis-oxane fragment of the phorboxazoles uses a Ferrier rearrangement as shown in Scheme 112. Treatment of **211** with dimethylaluminium chloride provided **212** was a single diastereoisomer in an impressive 89% yield.[246] The C22–C26 oxane was also prepared using the same methodology.[247] Pattenden's approach to a similar fragment uses intramolecular Michael addition to provide the first oxane ring and cyclisation of a hydroxymesylate for the second.[248] Structural analogues of the C15–C26 portion of these natural products have been prepared by Wolbers, Hoffmann and Sasse.[249]



211 **212**

Scheme 112

The altohyrtins are popular synthetic targets. The Evans group have recently published a 56 page epic describing their total synthesis of altohyrtin C,[250] while more recent synthetic studies on the pyran ring of these natural products have been described by a number of groups. Anderson's approach relies on intramolecular attack on epoxide **213**, prepared using Evans' aldol and stereoselective epoxidation (Sharpless and diastereoselective dimethyldioxirane) methodology, to give **214** (Scheme 113).[251] A similar approach provided the tetrahydropyran ring of (+)-ratjadone.[252]



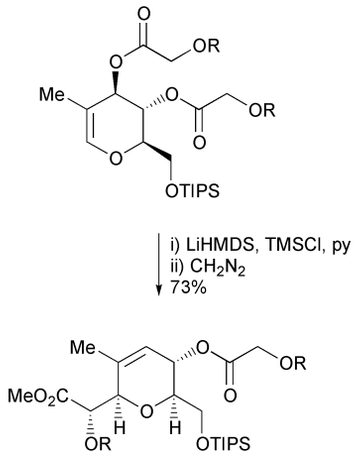
213 **214**

Scheme 113

In an alternative approach, Lemaire-Audoire and Vogel chose to prepare an advanced intermediate containing two of the rings of the natural product in which the pyran ring was present as a lactol. Elaboration then proceeded by way of *C*-glycosidation with an allylsilane.[253] A further approach to this ring uses the Claisen rearrangement shown in Scheme 114. With a 4-methoxybenzyl group as part of the Claisen precursor, stereoselectivity was less than optimal, but use of an (*S*)-methylbenzyl group gave good double-stereodifferentiation to provide a 6 : 1 epimeric mixture favouring **215**.[254] Related Claisen rearrangements have been described by Godage and Fairbanks,[255] while Claisen rearrangements to form the actual pyran ring have been used by Burke and Sametz.[256]

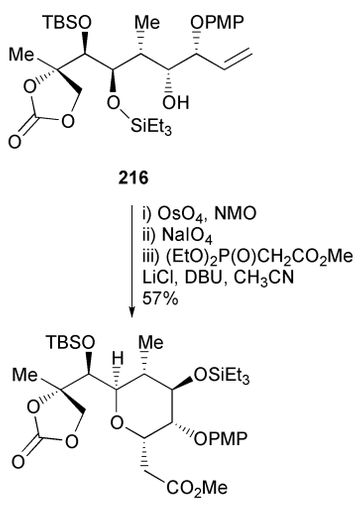
The final approach to this ring system starts with alkene **216**. Oxidative cleavage to the aldehyde was followed immediately by Horner–Wadsworth–Emmons olefination. However, under the reaction conditions (excess LiCl) the triethylsilyl group migrated, allowing spontaneous cyclisation to give **217** (Scheme 115). While this compound contains the incorrect 2,6-stereochemistry at the tetrahydropyran ring, equilibration proved possible after removal of the triethylsilyl group. Based on this observation, an improvement to the sequence was developed in which the olefination was carried out at lower temperature and the silyl group was removed prior to cyclisation.[257]

Further approaches utilising intramolecular Michael addition have also been reported,[258] including the synthesis of



215, R = (*S*)-methylbenzyl

Scheme 114

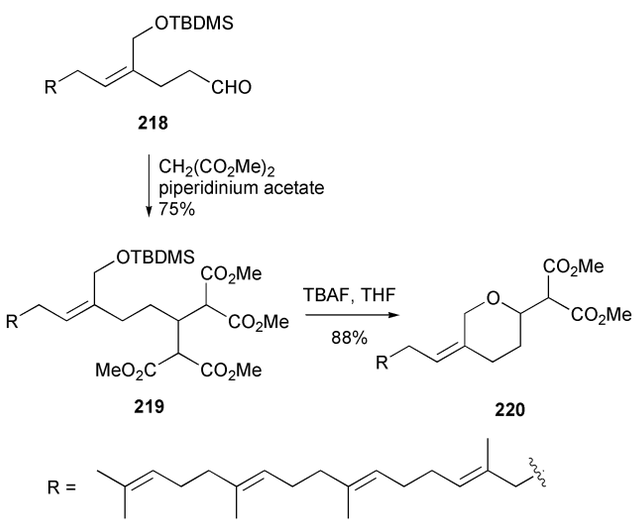


216 **217**

Scheme 115

hippospongic acid A. Treatment of **218** with excess dimethyl malonate gave the double addition product **219** in 75% yield (use of only a slight excess gave this as the major product). Subsequent treatment with TBAF gave **220** by elimination of dimethyl malonate and cyclisation (Scheme 116).[259]

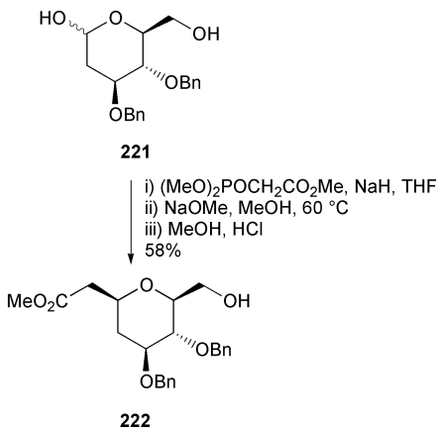
Olefination of the lactol **221** provided a 70 : 30 mixture of stereoisomers of a tetrahydropyran by spontaneous Michael



218 **219** **220**

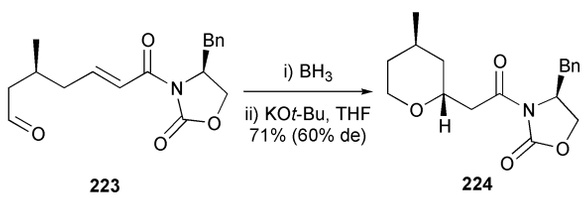
Scheme 116

addition. The reversibility of this reaction allowed thermodynamic equilibration to give a 95 : 5 mixture favouring **222** (Scheme 117), which was then elaborated to provide an analogue of the C1–C12 fragment of (+)-ambrucitin.[260]



Scheme 117

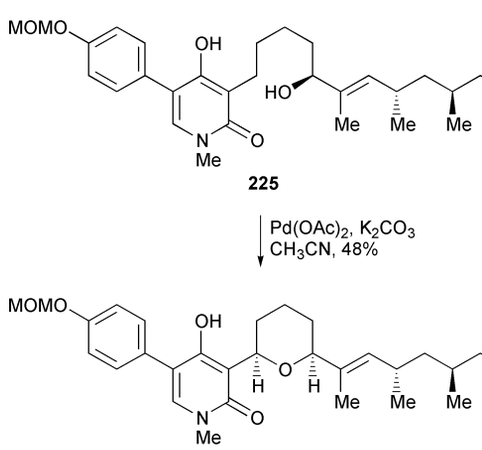
Conjugate addition onto α,β-unsaturated imides such as **223** has also been used to prepare tetrahydropyrans. Compound **223**, prepared by asymmetric aldol reaction followed by Cope rearrangement, was reduced with borane and cyclised as shown to give **224** in good yield (Scheme 118).[261] An essentially identical cyclisation, albeit without the oxazolidinone auxiliary, was used in the total synthesis of (+)-miyakolide in an approach which supports speculation about the biosynthetic origin of this natural product.[262]



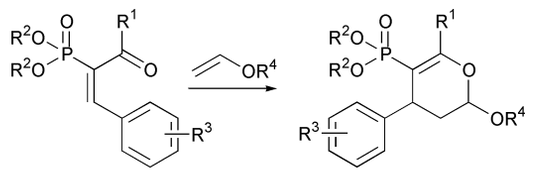
Scheme 118

The final example of conjugate addition is taken from the total synthesis of (+)-sambutoxin, in which **225** is subjected to oxidation by palladium acetate to form the corresponding quinone methide *in situ*. The hydroxy group then cyclises to give the tetrahydropyran **226** (Scheme 119).[263]

Hetero-Diels–Alder reactions have been used on a number of occasions to form dihydropyrans. These reactions can be divided into those using unsaturated ketones as dienes (oxadienes) and carbonyl groups as dienophiles (oxadienophiles). Al-Badri *et al.* have reported the hetero-Diels–Alder reaction of a range of cinnamaldehyde derivatives bearing a phosphonate. Yields were generally over 85% for 41 examples, demonstrating the generality of the method (Scheme 120).[264] Such compounds with an *E*-double bond give the 2,4-*trans* isomer preferentially, although addition of pyridine leads to a reversal of the selectivity.[265]



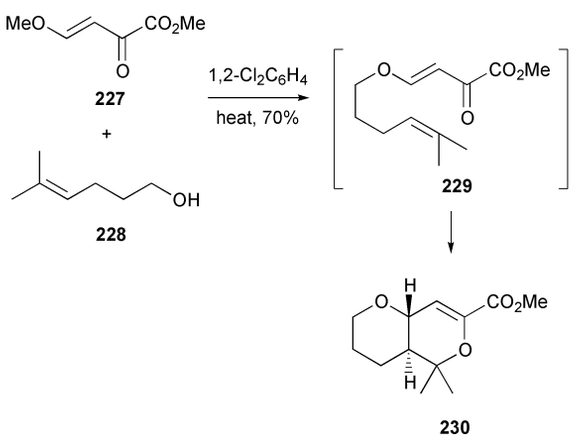
Scheme 119



Scheme 120

As expected, these reactions are inverse electron-demand, and show good correlation in linear free-energy relationships. The reactions of *p*-substituted styrenes with α,β-unsaturated acyl cyanides are particularly sensitive to electronic effects.[266]

Intramolecular reactions are entropically favoured, so that cycloaddition of **229**, generated *in situ* by transetherification of **227** with **228**, gave **230** in 70% yield (Scheme 121).[267]

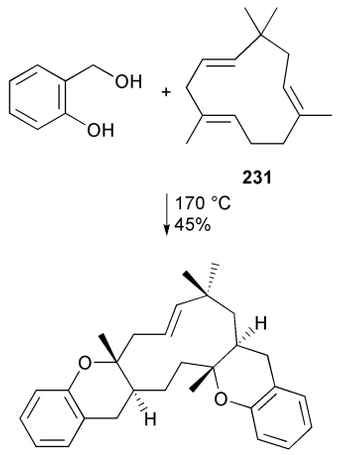


Scheme 121

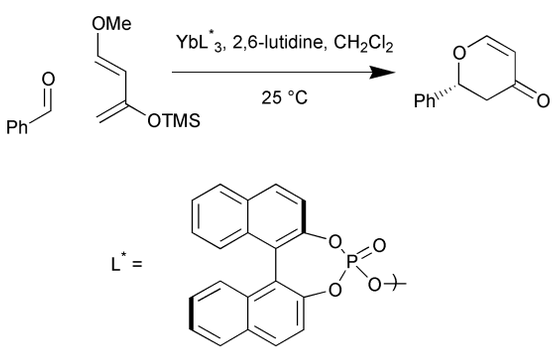
Among the hetero-Diels–Alder reactions of 1-oxadienes, those involving *o*-quinonemethides are particularly prominent. A similar approach to that shown above provided benzo-fused bis-tetrahydropyrans,[268] while studies from the Baldwin group have established a biomimetic route to lucidene[269] and related natural products.[270] Thus, thermolysis of 2-hydroxybenzyl alcohol in the presence of **231** gave a 2 : 1 mixture of the natural product **232** and a stereoisomer in 45% combined yield (Scheme 122).

The test bed for aldehyde oxa-Diels–Alder chemistry is the reaction of benzaldehyde with the Danishefsky–Kitahara diene.[271] A dramatic asymmetric amplification effect was observed in this reaction, in that a catalyst produced from ligand of only 20% ee gave product of 90% ee. This effect has been attributed to the greater solubility of the catalyst derived from only a single enantiomer of ligand (Scheme 123).[272]

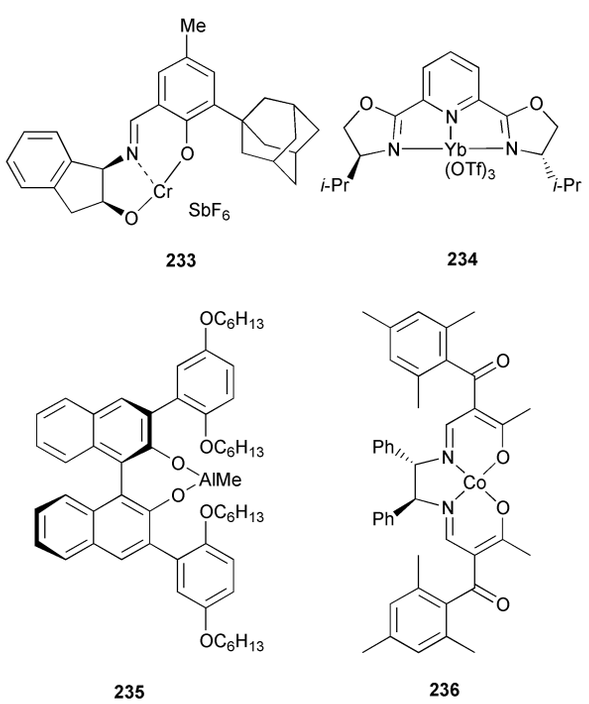
A range of new catalysts have been reported for this and related reactions, including **233**,[273] **235**[274] and **236**.[275] In the case of $[Cp^*_2Ce][BPh_4]$ a Mukaiyama aldol pathway was excluded,[276] while with **234** a competing aldol reaction was demonstrated.[277] Reactions using ruthenium–salen complexes have been shown to be promoted by sunlight.[278] Catalyst **233** has been used in synthetic studies towards apicularen A,[279] while more conventional Co–salen complexes have been used to catalyse the reaction of ethyl glyoxylate with an electron-rich diene in the synthesis of an unusual nine-carbon sugar derivative.[280]



Scheme 122

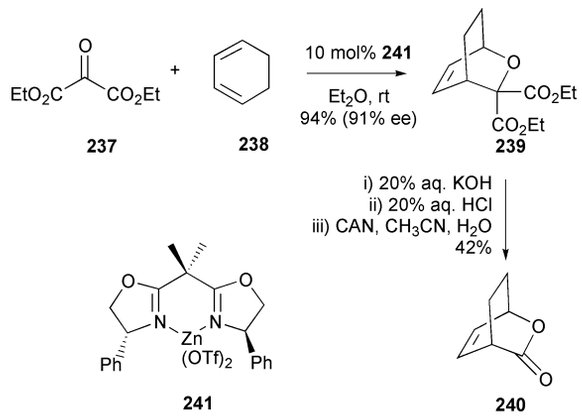


Scheme 123



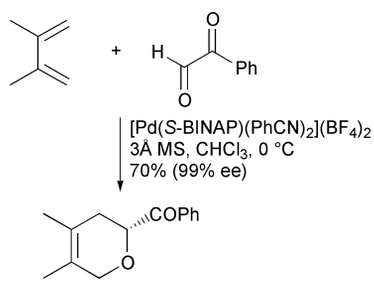
The synthetic utility of these reactions, albeit in lactone formation, is shown in the reaction of **237** with cyclohexa-1,3-diene **238** to give **239** enantioselectively and in good yield (Scheme 124). Hydrolysis and oxidative decarboxylation then provided **240**, so that **237** can be considered a CO_2 synthon.[281]

With 1-amino-3-siloxybutadienes, reaction takes place under particularly mild conditions (room temperature in $CHCl_3$) in a strictly thermal reaction. Even aliphatic aldehydes react efficiently within 8 hours.[282]



Scheme 124

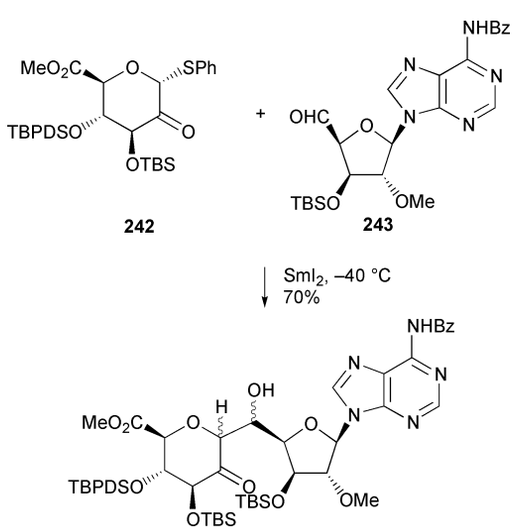
There are considerably fewer reports of asymmetric hetero-Diels–Alder reactions of aldehydes with other dienes. However, the reaction shown in Scheme 125, catalysed by a palladium BINAP complex, is particularly efficient, and applicable to a range of dienes, although only glyoxal and glyoxylate derivatives were used as dienophiles.[283]



Scheme 125

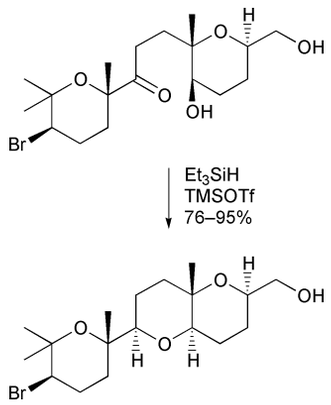
Vinylallenes are more reactive than normal dienes, and also react well with aliphatic aldehydes, although in this case a Lewis acid catalyst is needed.[284]

The first total synthesis of one of the herbicidin group of nucleoside antibiotics has been achieved by Ichikawa, Shuto and Matsuda. A number of stereochemical issues arose as a result of the conformation of various intermediates. However, for the purpose of this review, only the actual tetrahydropyran formation will be presented, this being achieved by way of *C*-glycosidation of **242** with aldehyde **243** in the presence of samarium(II) iodide (Scheme 126). Elimination of the alcohol, hydrogenation and global deprotection then provided the natural product.[285]



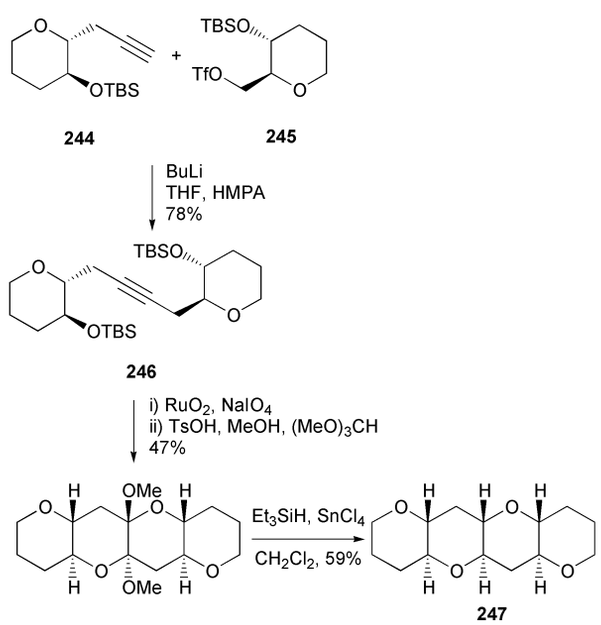
Scheme 126

Thyrsiferyl 23-acetate is a marine natural product containing an isolated tetrahydropyran ring, two fused tetrahydropyrans and an isolated tetrahydrofuran. González and Forsyth have prepared this compound using a combination of methods, including halocyclisation, epoxide opening and the reductive cyclisation shown in Scheme 127, to eventually prepare the bis-oxane fragment.[286]



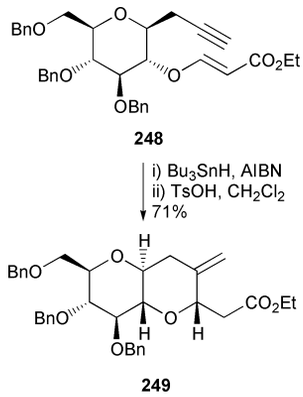
Scheme 127

The most prominent group of natural products containing fused oxygen heterocycles are the brevetoxins. Much of the synthetic work on these compounds is discussed in the following section as a result of the presence of medium-sized rings, but some approaches have focused on the fused tetrahydropyrans, and so will be described here. Mori and co-workers have previously described the use of optically pure oxiranylsulfones in an iterative approach to these ring systems. More recently the same group have shown that a racemic epoxide will serve the same purpose admirably, with stereochemical convergence during the cyclisation step.[287] Extensions to this methodology permit the introduction of angular methyl groups which are often found in the natural product targets.[288] Recently three groups have independently reported an essentially identical approach to a tetra-THP subunit. The example shown in Scheme 128 is taken from the work of Fujiwara *et al.*, in which the acetylide derived from **244** is allowed to react with **245** to give **246**. Alkyne oxidation and acetal formation was then followed by reduction to give **247**.[289]



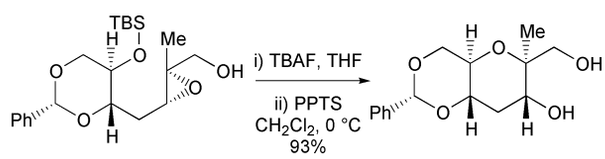
Scheme 128

A free-radical cyclisation also provides access to similar fused tetrahydropyrans (and oxepanes) as shown in Scheme 129. Treatment of **248** with tributyltin hydride followed by acidic destannylation gave **249** in good overall yield.[290] Related free-radical cyclisation reactions allow access to exocyclic dienes,[291] while contributions from the Evans' group have been described in previous reviews in this series.[292]



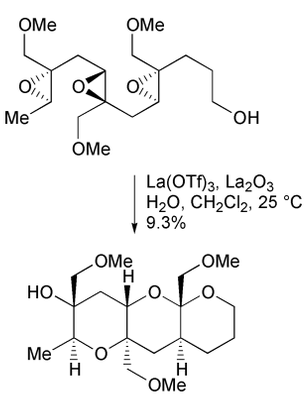
Scheme 129

In new studies towards brevetoxin B, a fragment corresponding to the ABC rings was prepared by intramolecular epoxide opening as shown in Scheme 130 to form the B ring, followed by ring-closing metathesis to form the A ring, and finally samarium-mediated cyclisation of an aldehyde with an unsaturated ester (as described in more detail in the following section) to append the C ring.[293] Similar epoxide opening was used to prepare an IJK ring fragment of the same natural product,[294] while the approach to the EFG rings is discussed in the following section.



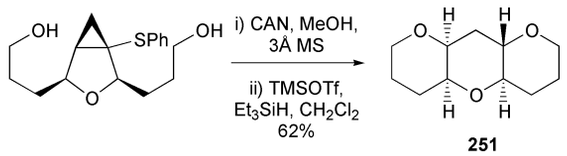
Scheme 130

An impressive, although low yielding, triple cyclisation was also used to prepare three tetrahydropyran rings in a single step, although initial 5-*exo* cyclisation predominated to give a tetrahydrofuran (15%) in addition to the product **250** shown in Scheme 131.[295] Successful attempts to favour the 6-*endo* pathway at the expense of the normally favoured 5-*exo* mode of cyclisation have used catalytic antibodies. More recently it has been shown that tripeptides identified combinatorially can also accelerate this pathway.[296] Intramolecular opening of an epoxide has also been used in synthetic studies towards methyl sartortuoate.[297]



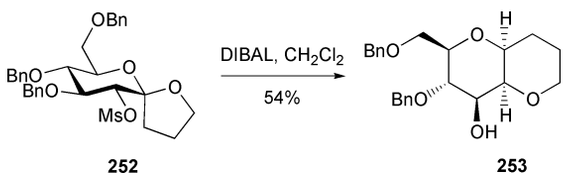
Scheme 131

Tandem oxidative cyclisation of cyclopropyl sulfides has been used to prepare polycyclic oxygen heterocycles, including the tris-tetrahydropyran **251** shown in Scheme 132.[298] Oxidative cyclisation of dienes has also been used, although in variable yield.[299]



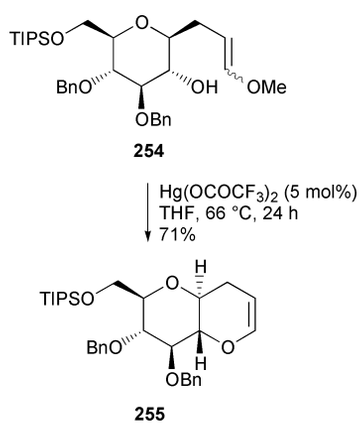
Scheme 132

A slightly unusual reductive rearrangement allows access to bis-tetrahydropyran **253** from **252** (Scheme 133). A reasonable mechanism is proposed to account for the unprecedented reductive debenzylation.[300]



Scheme 133

Finally for the brevetoxins, mercury-catalysed transetherification provides an efficient way to cyclise hydroxy-enolethers such as **254** to the corresponding dihydropyran **255** (Scheme 134).[301]

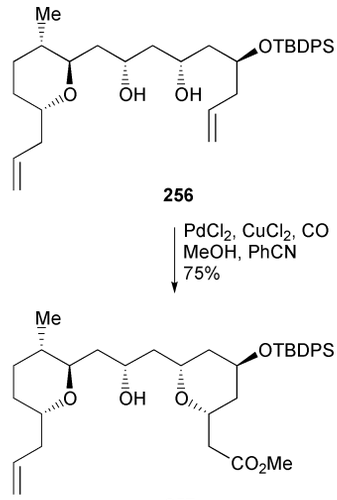


Scheme 134

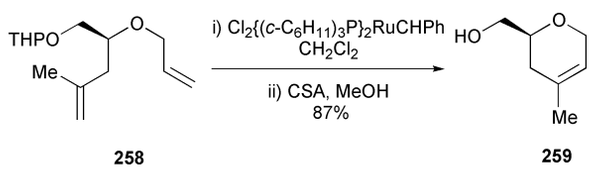
The total synthesis of leucascandrolide A features allylation of a lactol to introduce the first THP ring, although the lactol in this case is formed unusually by carbonylation of an alkene. Intramolecular alkoxycarbonylation of **256** formed the second THP ring to give **257** as shown in Scheme 135.[302] Another approach to the same target features a chelation controlled selective cleavage of a spiroketal followed by silane reduction to give the right hand tetrahydropyran.[303]

Laulimalide, an antitumour macrolide isolated from an Indonesian sponge, has recently attracted synthetic attention leading to a total synthesis from Ghosh and Wang. One of the dihydropyran rings was prepared by reduction and subsequent elaboration of a lactone, while the other originates in a ring-closing metathesis of **258** to give **259** as shown in Scheme 136.[304] An essentially identical route to the former ring was reported by Mulzer and Hanbauer, albeit at a lower oxidation level so that reduction to the lactol was not needed.[305]

Hoveyda, Schrock and co-workers have described new catalysts such as **260** which promote the efficient asymmetric ring-closing metathesis of *meso* precursors. For instance, **261** underwent ring closure to provide a single enantiomer

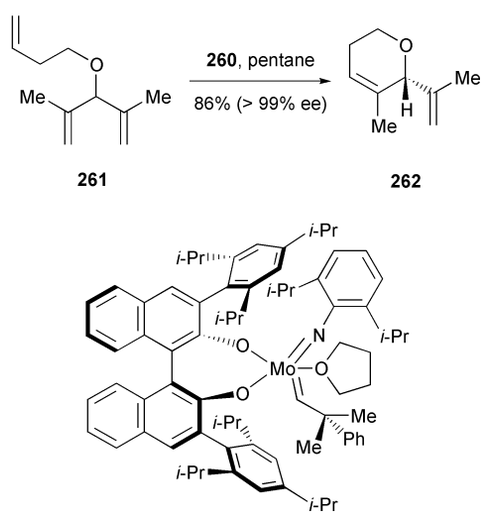


Scheme 135



Scheme 136

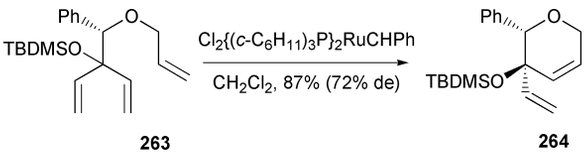
262 (Scheme 137). Kinetic resolution was also described, although not for simple oxygen heterocycles.[306] A related procedure involving tandem ring-opening metathesis/ring-closing metathesis also utilised similar catalysts.[307]



Scheme 137

Schmidt and co-workers have reported various metathesis reactions, in particular those involving closure of a chiral precursor with two diastereotopic double bonds. While substrate **263** gave good selectivity in the formation of **264** (Scheme 138),[308] substrates with more remote stereogenic centres naturally led to lower diastereomeric excesses.[309] The presence of a quaternary centre adjacent to the site of metathesis is no impediment to reaction.[310]

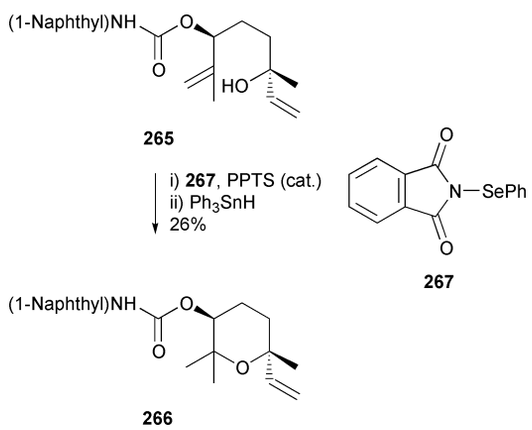
Other variations on this theme include the preparation of single enantiomer 2-(furan-3-yl)-3,6-dihydro-2*H*-pyrans by asymmetric allylation of furan-3-carboxaldehyde followed by allylation and metathesis.[311] Fluorinated dihydropyrans have also been prepared by ring-closing metathesis.[312]



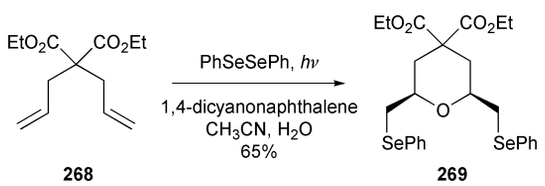
263 **264**

Scheme 138

While halocyclisations are more commonly associated with tetrahydrofuran rings as discussed in the preceding section, this method has also been used to prepare tetrahydropyrans in a 6-*exo* manner.[313] Related 6-*endo* cyclisations of alkynols, mediated by metal carbonyls, have been reviewed by McDonald.[314] Selenocyclisation of **265** (and stereoisomers thereof) provided access to all four stereoisomers of the linalool oxides (*e.g.* **266**, Scheme 139).[315] A related route was described starting from geraniol, also leading to all possible stereoisomers by way of Sharpless asymmetric oxidation chemistry.[316] A further related method involves generation of an electrophilic selenium reagent by photosensitised electron-transfer from diphenyl diselenide to 1,4-dicyanonaphthalene (DCN). Compound **269** was prepared from **268** using water as oxygen source (Scheme 140).[317]



Scheme 139

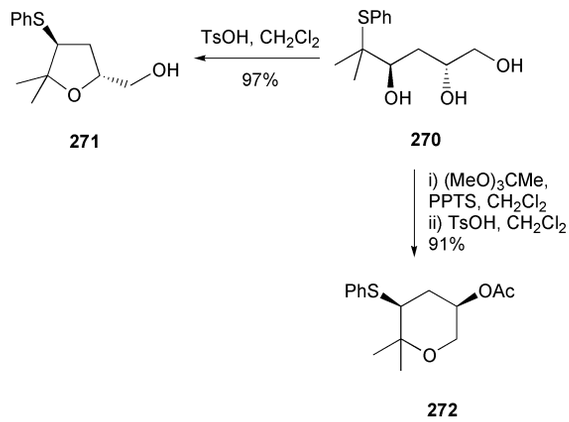


Scheme 140

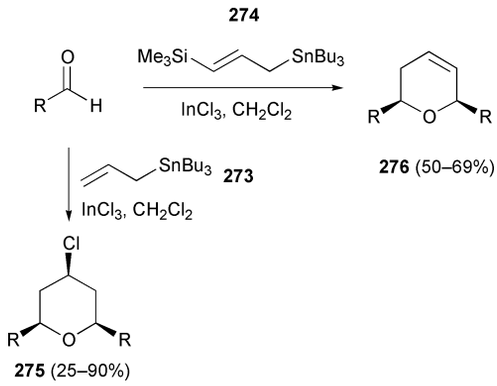
In related work, Warren and co-workers have shown interesting complementarity in the cyclisation reactions of **270**. Treatment with toluenesulfonic acid gave the thermodynamically favoured tetrahydrofuran **271**, while the kinetically favoured cyclisation products could be equilibrated to the thermodynamically more stable tetrahydropyran **272** (Scheme 141).[318]

Prins methodology is particularly valuable for the preparation of tetrahydropyrans. A number of reactions which can be generally classified as the intramolecular attack of alkenes onto oxacarbenium ions will be considered together. Reaction of allylstannanes **273** and **274** with aldehydes leads to the formation of tetrahydropyrans **275** and dihydropyrans **276** respectively, although the latter case failed for aromatic aldehydes (Scheme 142).[319] The intermediate in the latter case would be a compound such as **277**, so that reaction of such a compound with aldehydes in the presence of a Lewis acid leads to the controlled formation of unsymmetrical dihydropyrans (Scheme 143). Use of the *anti* isomer of **277** gives rise to the 2,6-*trans* product.[320]

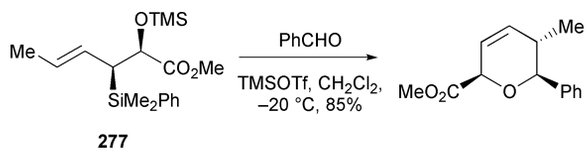
Reaction of aldehydes with homoallyl alcohol in the presence of scandium triflate also gives tetrahydropyrans in an essentially identical reaction.[321]



Scheme 141

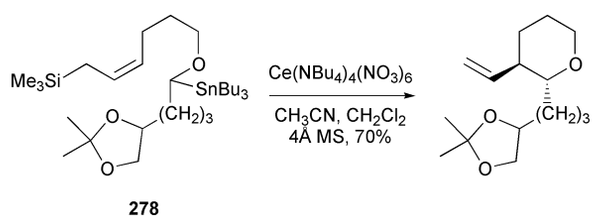


Scheme 142



Scheme 143

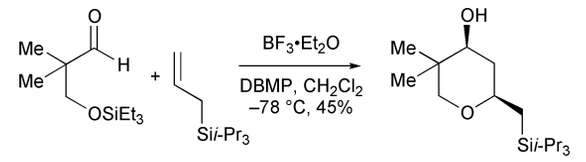
In a modification to this approach, generation of the oxacarbenium ion oxidatively from a precursor such as **278** allows the cyclisation to take place efficiently on a substrate containing acid-sensitive functionality (Scheme 144).[322]



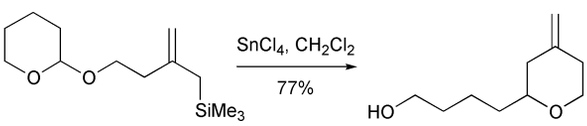
Scheme 144

These reactions are often enhanced by increased nucleophilicity of the double bond as a result of the ability of silicon to stabilise a β-carbenium ion. In related reactions, this intermediate has been trapped intramolecularly giving a further alternative tetrahydropyran synthesis (Scheme 145).[323] The reaction shown in Scheme 146 is taken from a broad study into the rearrangement reactions of tetrahydropyranyl homoallyl ethers under Lewis and protic acid conditions. For such a widely used protecting group, these reactions are surprisingly general.[324]

A further example of this type of reaction is found in the silyl-modified Sakurai reaction. Recent work in this area has shown that ene reaction of **279** with trioxane gives **280** in good yield. Reaction with **281** then provides **282** as a single diastereoisomer (Scheme 147).[325] These studies, like those of

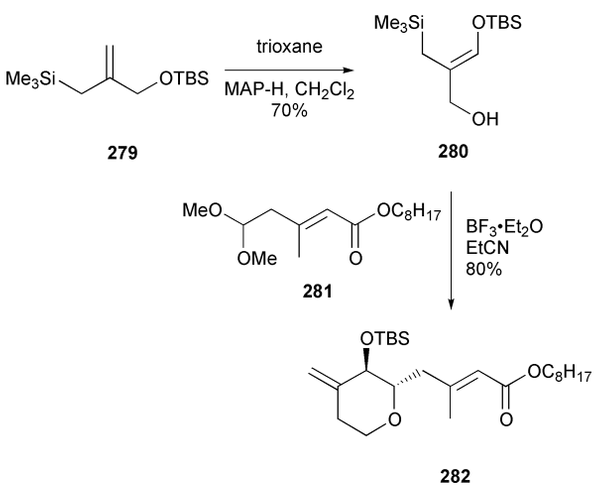


Scheme 145

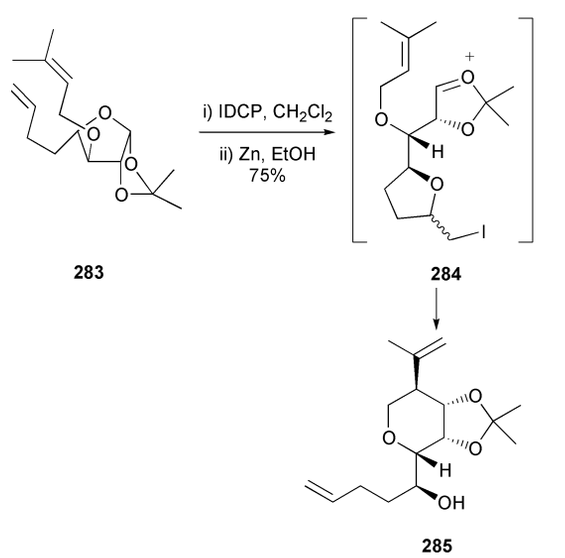


Scheme 146

Khan *et al.* were directed towards the pseudomonic acids. In this latter case, iodocyclisation of **283** provides an oxacarbenium ion intermediate **284** which can then be intercepted by a double bond to give **285** (Scheme 148).[326]



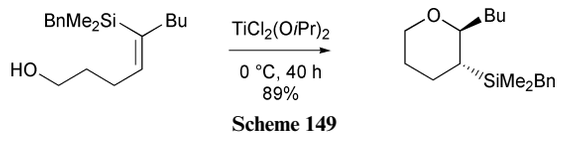
Scheme 147



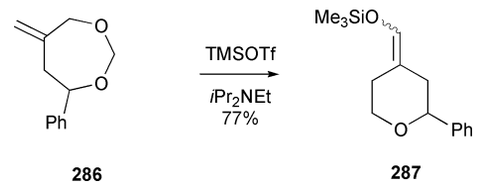
Scheme 148

A slightly more unusual reaction which makes use of the electronic properties of silicon is shown in Scheme 149. In this case, protonation of the double bond is followed by a 1,2-silyl shift and finally cyclisation.[327]

Cationic rearrangement also features in the ring contraction of dioxepanes reported by Okuma *et al.* Treatment of **286** with trimethylsilyl trifluoromethanesulfonate in the presence of Hünig's base gave **287** in good yield (Scheme 150).[328]



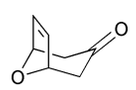
Scheme 149



Scheme 150

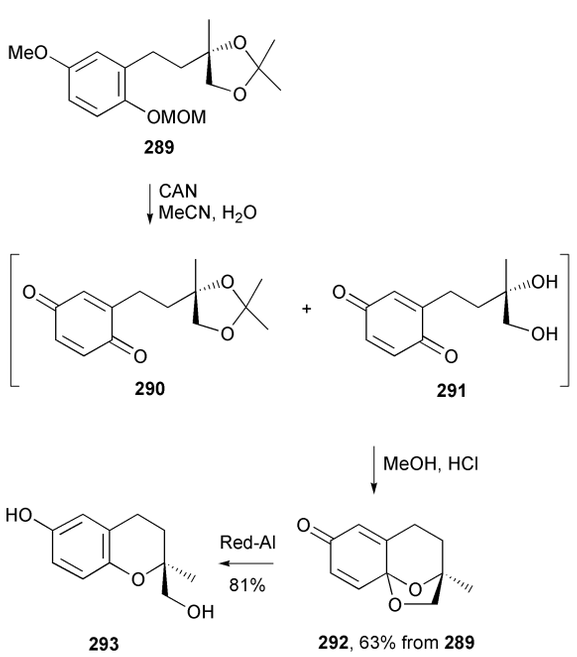
Ring opening reactions of bicyclic compounds can be efficiently used to provide monocyclic products. Hoffmann *et al.* have demonstrated a wide range of synthetic applications of compound **288** based on stereoselective reduction of the ketone and asymmetric hydroboration of the double bond leading to eventual cleavage by ozonolysis or Baeyer–Villiger oxidation.[329]

Benzopyrans occur in a wide range of natural products and pharmaceutical compounds. Nicolaou and co-workers have demonstrated a combinatorial approach to this ring system based on selenocyclisation methodology.[330]



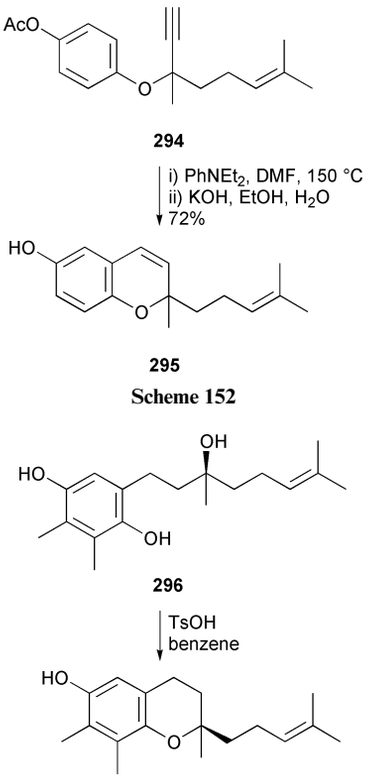
288

Cordiachromene **295** is a simple chromene with interesting biological activity. Oxidative demethylation of **289** gave a mixture of **290** and **291** which were treated with methanolic HCl to give **292** in 63% overall yield (Scheme 151). Reduction with Red-Al® then provided **293** as a key intermediate *en route* to a total synthesis.[331] A second synthesis is shorter, but only provides access to racemic material. Thermolysis of **294** followed by removal of the acetate ester gave the natural product, **295**, directly (Scheme 152).[332]



Scheme 151

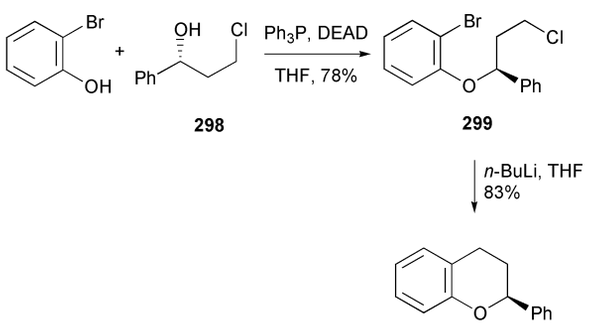
In addition to the cyclisation onto a quinone shown in Scheme 151, cyclisation onto hydroquinones is possible. For instance, treatment of single enantiomer **296** with acid results in the formation of **297** with retention of stereochemistry (Scheme 153). The yield over 4 steps, including this one, was 55%.[333]



Scheme 152

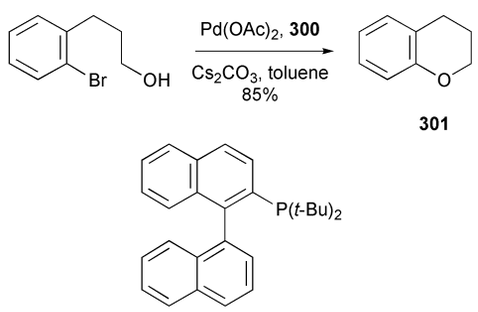
Scheme 153

An efficient stereocontrolled route in which C–O bond formation precedes C–C bond formation is shown in Scheme 154. Mitsunobu reaction of **298** with 2-bromophenol gave **299** which cyclised smoothly upon treatment with butyllithium.[334]



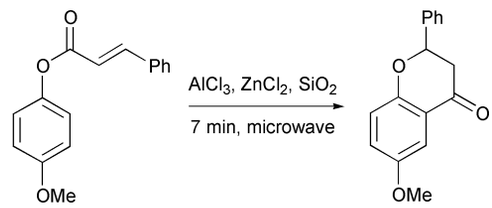
Scheme 154

Buchwald has previously reported the palladium-catalysed C–O bond formation from tertiary alcohols to give a range of benzo-fused oxygen heterocycles. This process, which was inefficient for cyclisation of primary and secondary alcohols, has been improved with the use of phosphine **300**, so that formation of **301** proceeded in good yield (Scheme 155).[335]



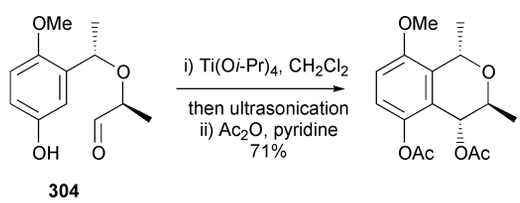
Scheme 155

A novel route involving conjugate addition is shown in Scheme 156, where substrates such as **302** undergo Fries rearrangement followed by cyclisation to give flavone **303**. In this example, a mixture of aluminium chloride and zinc chloride supported on silica was used as catalyst under solvent free conditions with microwave irradiation.[336]



Scheme 156

Intramolecular diastereoselective arylation of aldehyde **304** can be accomplished upon ultrasonication in the presence of titanium tetraisopropoxide (Scheme 157). Cyclisation of the diastereoisomer of **304** proved to be less selective (3 : 1 ratio of stereoisomers).[337]



Scheme 157

Knight and co-workers have previously described the interception of benzynes with alcohols to give chromans and chromenes. A full account of this work has now been presented.[338]

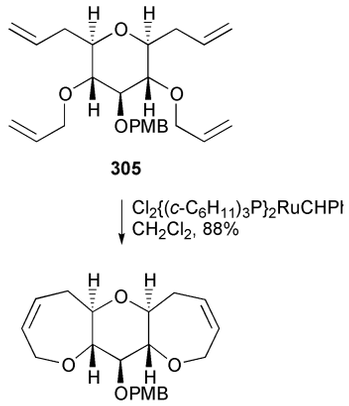
In addition to the methods discussed, there are a number of approaches to tetrahydropyrans which centre around the reduction and *C*-glycosidation of lactone and lactol derivatives. Some have already been mentioned in the context of total synthesis, and while a detailed description of related methods has been omitted due to space constraints, references are included for the interested reader.[339]

6 Medium sized rings

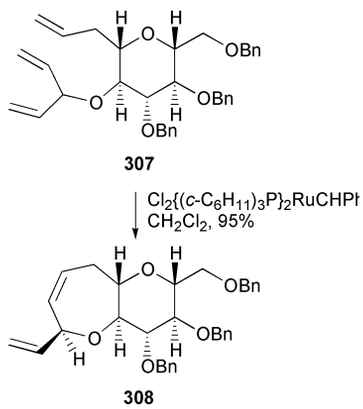
The last five years have seen the emergence of ring-closing metathesis as the method of choice for the formation of medium sized rings.[340] Clark has reported the use of this reaction for cyclic ether formation,[341] and more recently has demonstrated a bidirectional approach to polyether natural products. For instance, RCM of **305**, prepared from tri-*O*-acetyl-D-glucal, gave **306** in excellent yield (Scheme 158). Six-, eight- and nine-membered rings were also formed by this method.[342] A similar approach was previously reported by Leeuwenburgh *et al.*, although in this case only a 6–6–7 fused system was prepared.[343]

An interesting system, **307**, has also been elaborated from a glucal derivative in which two diastereotopic double bonds can undergo metathesis. In this case ring closure was totally diastereoselective, giving **308** (Scheme 159), although elaboration of the side chain by a subsequent metathesis reaction led to some scrambling of this stereochemistry, presumably by ring-opening and ring closing prior to the cross-metathesis.[344] A related approach, although without the potential for a diastereoselective metathesis, has also been reported.[345]

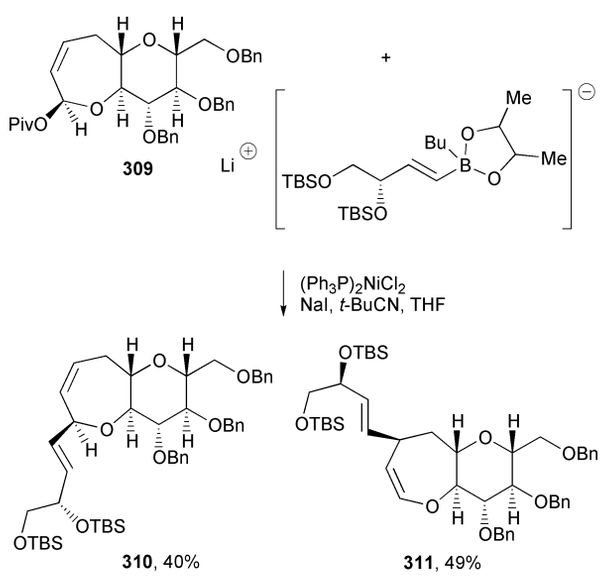
Since the introduction of the side chain by this approach was inefficient, approaches relying on cross-coupling reactions were also explored. Compound **309**, prepared by ring-closing metathesis, underwent nickel-catalysed cross-coupling to give



Scheme 158



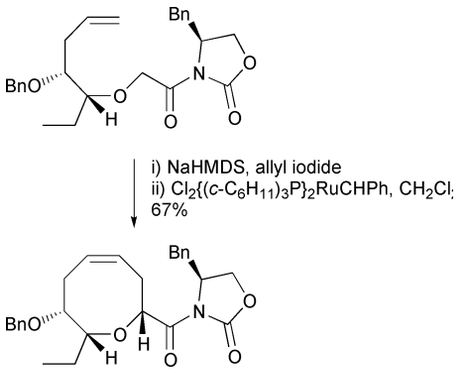
Scheme 159



Scheme 160

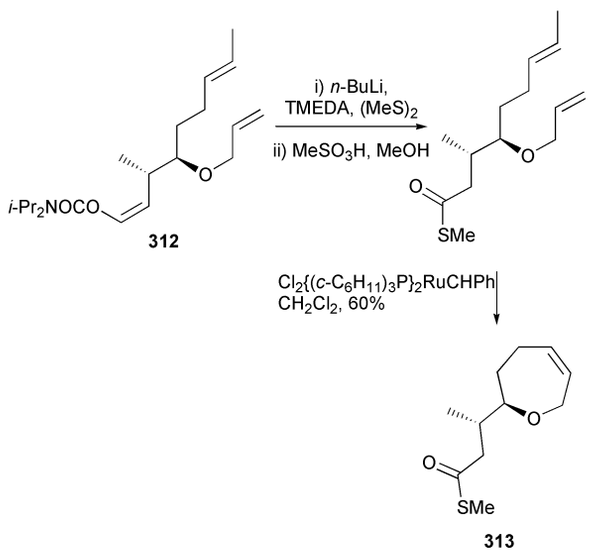
the mixture of regioisomers **310** and **311** in high yield (Scheme 160).[346]

In early 1999, Crimmins reported a formal total synthesis of Laurencin using a combination of Evans aldol methodology and ring-closing metathesis. This synthesis has now been further refined, using the Evans auxiliary no less than three times, the fourth stereogenic centre being installed in a chelation controlled Grignard addition. The key ring-forming step is shown in Scheme 161.[347] Further work from Crimmins and Emmitte showed how the stereochemical scope of the reaction can be broadened by a suitable combination of substrate and oxazolidinone enantiomers.[348] Enantioselective total syntheses of prelaureatin and laurallene make use of the same chemistry.[349]



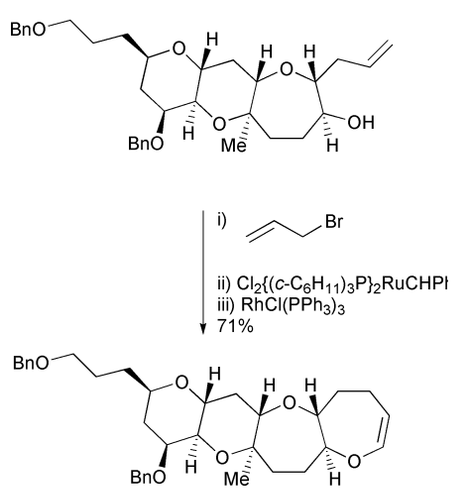
Scheme 161

Hoppe has used a sparteine-mediated asymmetric homoaldol reaction to prepare dienes such as **312** with high ee. Elaboration and ring-closing metathesis then gave cyclic ethers such as **313**, although nine-membered ring formation failed in this instance (Scheme 162).[350]



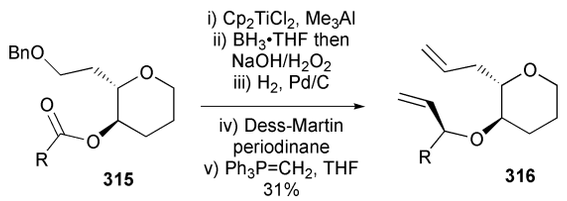
Scheme 162

A new synthesis of the hemibrevetoxin B ring system also makes extensive use of ring-closing metathesis, along with enol-ether oxidation to provide **314** in only 14 steps from the Danishefsky–Kitahara diene (Scheme 163).[351]



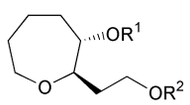
Scheme 163

Clearly many of these reactions are essentially identical, with the variations being the method of preparation of the metathesis substrates. For instance, **316** was prepared from ester **315** (Scheme 164) by olefination, hydroboration and Wittig olefination prior to the metathesis reaction (not shown). The diastereoselectivity of the hydroboration was modest to good as controlled by an adjacent stereogenic centre (R = protected diol).[352]



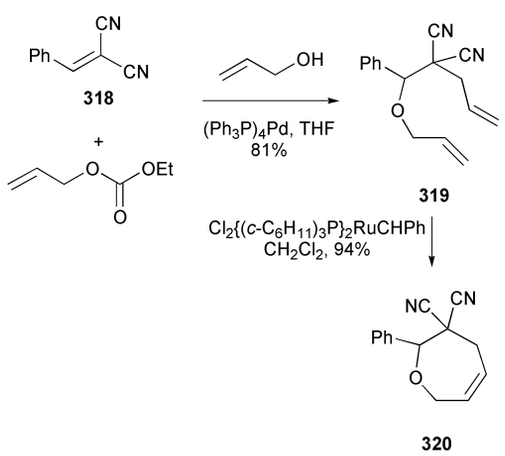
Scheme 164

A further route from the same group makes efficient use of epoxide chemistry to prepare both enantiomers of the differentially protected oxepane diol **317**. These were subsequently elaborated to provide a 7-6-6-7 fused tetracycle using lactol reduction to provide the inner pyran rings.[353]



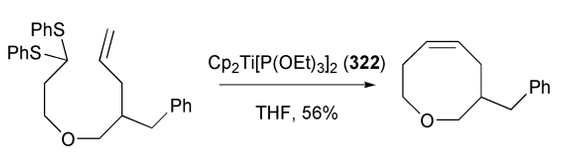
317

Alkoxyallylation of electron-deficient double bonds provides a particularly rapid entry into the metathesis substrates. For instance, reaction of **318** with allyl alcohol and ethyl allylcarbonate provides **319** which underwent cyclisation to **320** (Scheme 165).[354]



Scheme 165

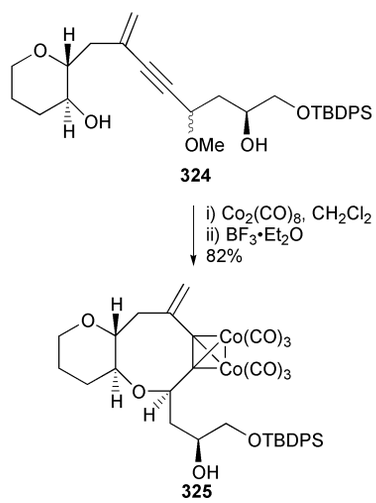
One final example of ring-closing metathesis features the novel use of a dithioacetal as precursor to a titanium alkylidene. Thus treatment of **321** with **322** led to the formation of **323** in 56% yield (Scheme 166), although in some cases double bond migration was observed.[355]



Scheme 166

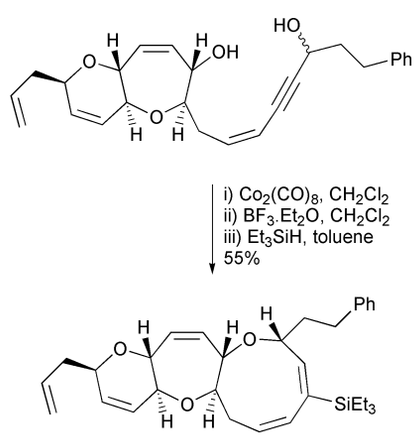
A number of other approaches use metathesis in the preparation of polycyclic ethers and related compounds.[356]

The groups of Isobe and Mukai have independently investigated aspects of the Nicholas reaction as applied to medium ring ether synthesis. Treatment of **324** with octacarbonyldicobalt led to the formation of **325** as a model to the HI rings of ciguatoxin in excellent yield (Scheme 167).[357] Elaboration of the right hand side of this compound to the δ-lactone was followed by acetylide addition and Et_3SiH–BF_3·Et_2O reduction of the resulting lactol to set the stage for a conjugate addition followed by a further Nicholas reaction to form the 7-membered K ring.[358,359]



Scheme 167

The 9-membered F ring of ciguatoxin arguably provides the greatest synthetic challenge in this natural product. Once again, the Nicholas reaction provides access to a fragment containing this ring (Scheme 168). No doubt the *Z*-double bond assists the cyclisation.[360] In 1997 and 1998 Inoue, Sasaki and Tachibana demonstrated the use of an intramolecular Reformatsky reaction for the preparation of this particular oxonane. A full paper describing this work has now appeared.[361]

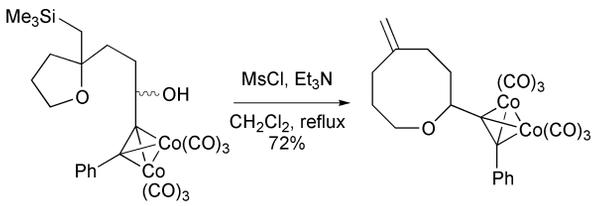


Scheme 168

A further use of hexacarbonyldicobalt complexes features a tetrahydrofuran oxygen as nucleophile in a novel fragmentation process. Reaction of **326** with methanesulfonyl chloride gave **327** in good yield (Scheme 169), although the reaction was less regioselective at room temperature. Nine-membered rings were also formed by this method.[362]

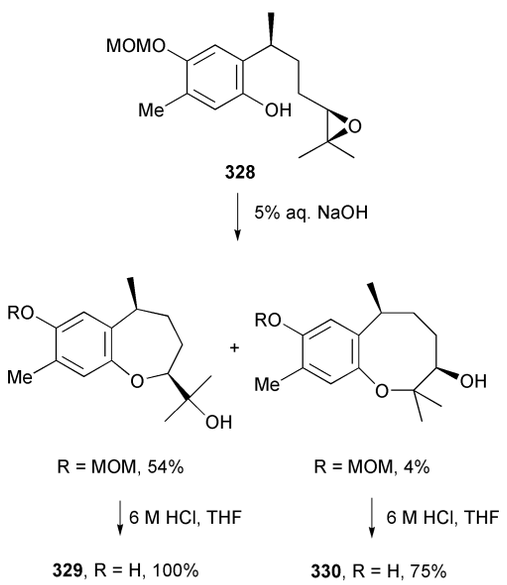
Heliannuols A (**329**) and D (**330**) were synthesised by straightforward epoxide opening from **328**, with enzymic desymmetrisation and Sharpless asymmetric dihydroxylation providing the necessary stereochemistry (Scheme 170).[363] A similar earlier route only provided Heliannuol D, this

being obtained in racemic form.[364] Related benzoxepins were prepared by intramolecular Mitsunobu reaction of hydroxyphenols.[365]



326 **327**

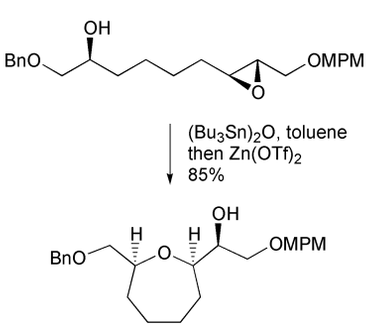
Scheme 169



328

329, R = H, 100% **330**, R = H, 75%

Scheme 170

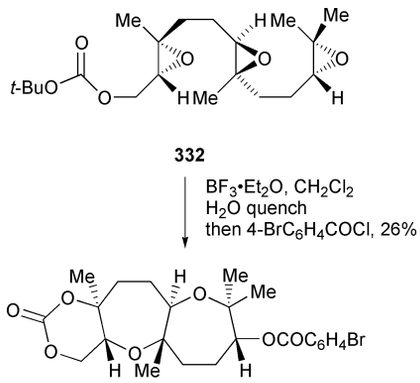


331

Scheme 171

Efficient conditions for intramolecular epoxide opening to give seven-membered rings have been developed using bis(tributyltin) oxide in conjunction with zinc triflate. The product **331** (and various diastereoisomers thereof) prepared by this method will no doubt be useful in the synthesis of oxepane-containing *Laurencia* metabolites (Scheme 171).[366]

The brevetoxins and related natural products are believed to be biosynthesised by a cascade epoxide opening process. However, this has proven difficult to realise synthetically since oxepane formation by this method requires a 7-*endo* process in preference to the more favoured 6-*exo*. Recently it has been shown that these reactions are feasible if one considers the stability of bicyclic oxiranium ion. Compound **333** was the major product formed from **332** in this way as shown in Scheme 172.[367] The factors which affect the relative proportions of tetrahydrofurans and tetrahydropyrans produced in similar reactions have been studied in detail.[368]

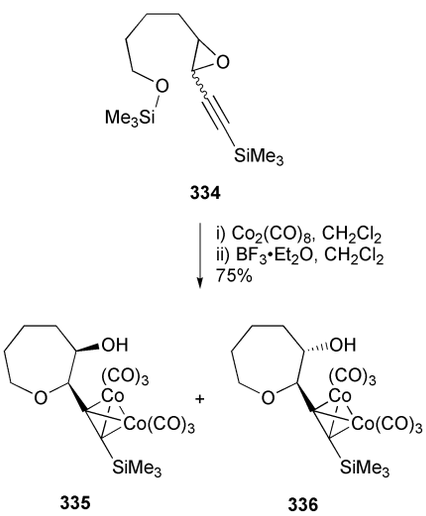


332

333

Scheme 172

The use of cobalt–alkyne complexes has already been discussed. One further example shows the directing effect of this substituent in epoxide opening reactions. However, in this case the stereospecificity usually observed in epoxide opening reactions is lost due to the formation of a stabilised carbenium ion intermediate. Thus, both stereoisomers of epoxide **334** gave the same mixture of diastereomeric oxepanes **335** and **336**, and in identical yields (Scheme 173).[369]



334

335 **336**

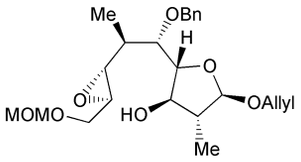
335: **336** = 70:30

Scheme 173

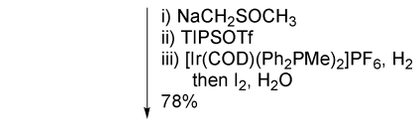
Sasaki and co-workers have demonstrated the regioselective opening of epoxide **337** to give, after elaboration, **338** (Scheme 174). In this case the stereochemistry at the anomeric position proved critical to the regioselectivity of the epoxide opening. While **337** gave a near-quantitative yield of the oxepane in the ring opening step (83% pure by NMR), its anomer gave a 63 : 37 mixture of oxepane and the tetrahydropyran formed by 6-*exo* epoxide opening.[370] Preparation of a model compound containing eight of the thirteen rings of ciguatoxin was reported by the same group in 1998. More recent work following the same methodology has provided a decacyclic compound.[371]

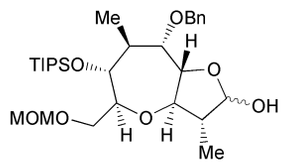
Nakata has also demonstrated the synthetic utility of oxiranium ion intermediates in the ring expansion of **339** to **340** (Scheme 175), leading to a synthesis of the EFG ring system of brevetoxin B.[372]

The same group have developed a reductive cyclisation approach to cyclic ethers which can be used in an iterative manner as shown in Scheme 176. Reaction of **341** with samarium(II) iodide with concomitant lactonisation gave **342**. This was then elaborated as shown to permit a second (and eventually third) such cyclisation.[373]



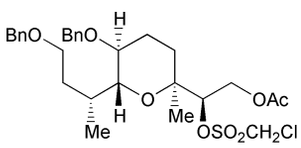
337



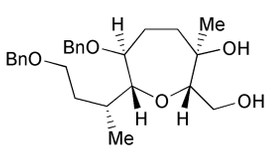


338

Scheme 174



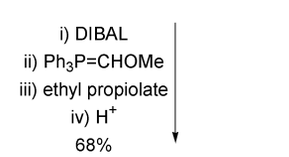
339

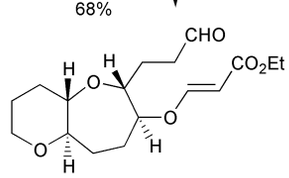


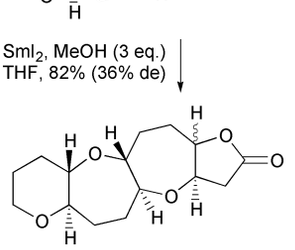
340

Scheme 175

341 342

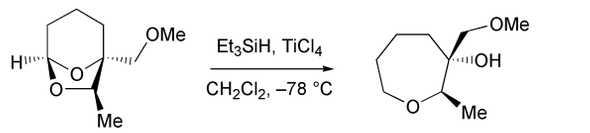






Scheme 176

Chelation is a powerful driving force for regiochemical control. For example, judicious placement of a methoxymethyl group in **343** favours oxepane formation to give **344** rather than the normal mode of cleavage of such compounds giving tetrahydropyrans (Scheme 177). However, the extent of selectivity was very much dependant on the precise structure of the substrate, ranging from 1 : 1 to 99 : 1 in a series of six compounds.[374]

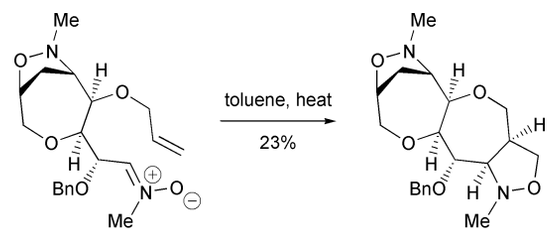


343 **344**, 55% (+ 19% tetrahydropyran)

Scheme 177

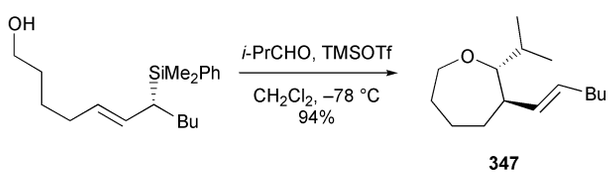
Bhattacharjya and co-workers have previously reported the use of nitrone cycloadditions to prepare oxepanes. New results in this area include the preparation of bis-oxepane **346** from **345**, itself prepared by a nitrone cycloaddition (Scheme 178).[375]

An enantioenriched allylsilane was used by Suginome *et al.* in the acetalisation/cyclisation reaction shown in Scheme 179. In this way, the oxepane **347** was formed in good yield as a single diastereoisomer, and with only 4% loss of enantiomeric purity.[376]



345 346

Scheme 178



347

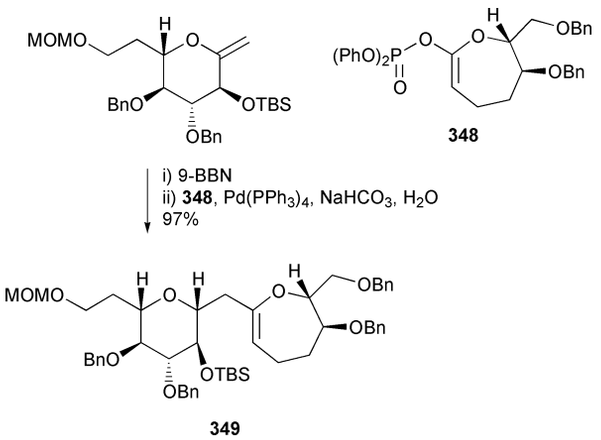
Scheme 179

The use of the Claisen rearrangement to facilitate ring expansions to eight and nine-membered lactones has been extensively investigated by Holmes and co-workers. The same group have now reported the fusion of an eight-membered lactone onto an oxocane by this method.[377]

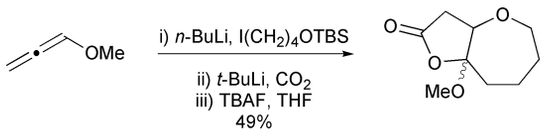
Modification of lactones is a potentially versatile general method for the formation of cyclic ethers, since the corresponding lactones are often easier to prepare. Cross-coupling of alkylboranes, generated *in situ* from exocyclic enol ethers, with enol phosphates provides such a method. Compound **349**, prepared as shown in Scheme 180, was elaborated by stereoselective hydroboration/oxidation of the enol ether to ultimately form a 6-membered ring. Conversion of the left hand side into an allyl ether and ring-closing metathesis gave a 7-membered ring in a manner similar to the examples already described, providing a 7-6-6-7 fused system related to the ABCD rings of ciguatoxin.[378] The same method has been applied to the HIJK rings of the same natural product,[379] and also to the FGH rings of the structurally related gambierol.[380]

Related methods include the methoxycarbonylation of enol phosphates from the same group,[381] and a reversal of the above strategy in the coupling of enol triflates with vinylstannanes.[382]

One final method involves conjugate addition onto a butyrolactone derived from methoxyallene (Scheme 181).[383]



Scheme 180



Scheme 181

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