Saturated oxygen heterocycles

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REVIEW PERKIN 1

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1 Introduction

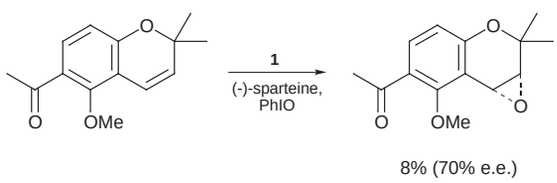
This review covers the literature on three to nine-membered oxygen heterocycles containing one oxygen. With the large amount of published material, no attempt at comprehensive coverage has been made. The distinction between a sugar derivative and a pyran is becoming increasingly blurred as sugar derivatives are being used to a greater extent in total synthesis, and in general sugars are not discussed. However, a number of *C*-glycosidation procedures are likely to have general utility in the synthesis of tetrahydropyrans, and so have been mentioned. Acetals and ketals, including spiroketals, are not discussed.

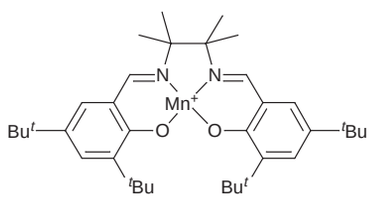
As usual, three and five membered rings form the bulk of the material, with six membered rings coming a close third. This mainly reflects the synthetic use of the first and the widespread occurence in natural products of the latter two.

One very clear message to come from the writing (and hopefully reading!) of this review is the widespread use of Sharpless' oxidation chemistry in the synthesis of a whole range of oxygenated compounds with high enantioselectivity.

2 Three membered rings

The Jacobsen–Katsuki epoxidation is rapidly becoming one of the mainstays of catalytic asymmetric synthesis. The chirality usually present on the backbone of the ligand is considered to induce a chiral twist in the manganese-salen complex. Since external ligands are known to affect the selectivity of this process, it should come as no surprise that external *chiral* ligands are able to exert an effect in cases where the salen ligand itself is achiral. Up to 70% enantiomeric excess was obtained in this way (Scheme 1). Higher yields were obtained in some cases, but at higher temperatures and at the expense of enantioselectivity.[2]





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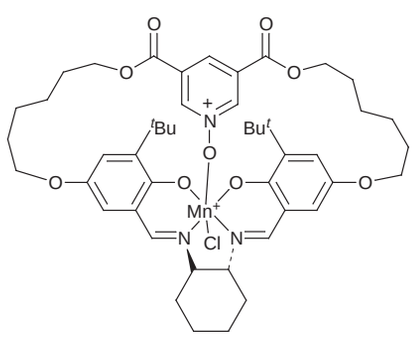
Scheme 1



2

Meanwhile, the mechanism of this reaction is still a cause of contention. Feichtinger and Plattner have demonstrated evidence for the existence of the long-postulated (and generally accepted) oxomanganese–salen complexes by electrospray mass spectrometry,[3] while Jacobsen has discussed the implications of metallaoxetane involvement in the epoxidation reaction and reached the conclusion that they are unlikely intermediates. Results from catalyst **2**, in which the pyridine *N*-oxide often used as an additive is built into the ligand and is therefore *definitely* an axial ligand, suggest that the distortion of the ligand required for formation of the metallaoxetane is unlikely.[4] However, Norrby *et al.* have used radical trapping and stereoselectivity arguments to suggest that a metallaoxetane *is* the first intermediate, which may subsequently undergo homolytic cleavage to give radicals with the observed loss of stereochemical integrity in the epoxidation.[5]

Hughes *et al.* have studied the role of the pyridine *N*-oxide in detail, and reach the conclusion that as well as stabilising the catalyst and accelerating the epoxidation, it also plays a part in transporting the HOCl oxidant into the organic phase in biphasic systems.[6] Others have observed significant uncatalysed background reactions at high substrate : catalyst ratios, and concur with Jacobsen that the addition of *N*-oxides may shift the catalyst equilibrium away from an inactive μ-oxo dimer.[7] These observations have been discussed by Linker.[8] Jacobsen has outlined the importance of electronic effects on selectivity, suggesting that modification of the electronic properties of the ligand affects the position of the transition state.[9] Two groups have almost simultaneously reported the heterogeneous asymmetric epoxidation of olefins by manganese-salen complexes encapsulated within a zeolite [10] while a third group has reported a dimeric manganese-salen complex which shows improved retention in a polydimethylsiloxane membrane.[11]

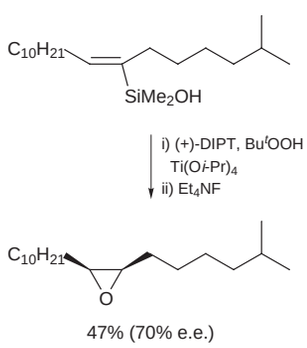
Manganese complexes of chiral 1,4,7-triazacyclononanes can also be used as catalysts for asymmetric epoxidation, although in the preliminary report the enantioselectivities were relatively low.[12]

While the regioselective *asymmetric* epoxidation of the 2,3-

double bond of geraniol is relatively straightforward, the epoxidation of the 6,7-double bond is less so. Promising results have now been reported using the Jacobsen–Katsuki epoxidation under neutral conditions with hydrogen peroxide as terminal oxidant (Scheme 2).[13] Using dimethyldioxirane or methyltrioxorhenium in conjunction with urea–hydrogen peroxide complex also leads to similar selectivity in the epoxidation of 1-methylgeraniol, a potentially useful mechanistic probe, although solvent effects can be quite pronounced.[14]

Scheme 2

The epoxidation of nearly-symmetrical alkenes is still a challenge for direct epoxidation strategies. In this case, temporary introduction of a silanol followed by Sharpless epoxidation is effective (Scheme 3). The silanol can then be removed with retention of stereochemistry.[15]

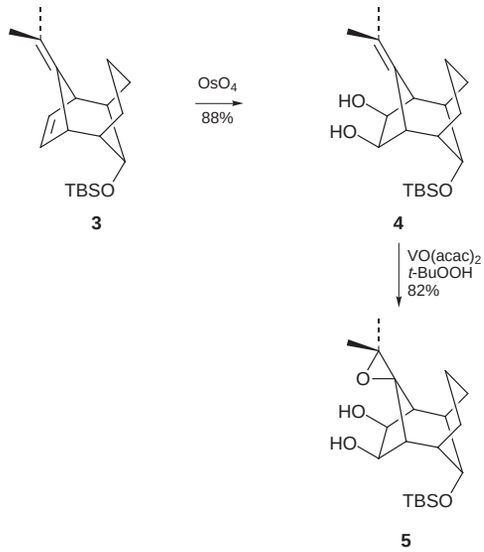


Scheme 3

The Sharpless asymmetric epoxidation of cyclopropylidene alcohols followed by rearrangement to chiral non-racemic cyclobutanones has provided access to a number of natural products. This process has been reviewed recently.[16] A modified Sharpless protocol using poly(tartrate esters) has also been reported,[17] and a further variation uses an achiral diol and a chiral hydroperoxide. Allylic alcohols were epoxidised with up to 50% ee in this manner.[18]

The interplay of functional groups within a molecule is a central theme in organic chemistry. While the exocyclic double bond in **3** is relatively unreactive, it was found that attempted dihydroxylation of the less hindered double bond using triethylbenzylammonium permanganate gave appreciable amounts of epoxide **5**. Epoxidation of the diol **4** using VO(acac)$_2$/*t*-BuOOH gave the epoxide **5** in 82% yield. Presumably the diol directs the epoxidation (Scheme 4).[19]

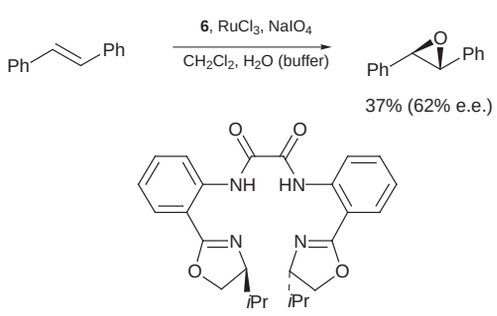
Other transition-metal catalysed epoxidations include the use of methyltrioxorhenium as catalyst, either for the epoxidation of alkenes with hydrogen peroxide as terminal oxidant[20] or the conversion of aldehydes into epoxides using ethyl diazoacetate.[21] Sharpless has extended the utility of the former process by using bis(trimethylsilyl) peroxide as terminal oxidant. These anhydrous conditions (in fact a catalytic amount of water is advantageous) allow the use of less expensive catalysts such as Re_2O_7 or ReO_3.[22] A silica-supported variation has also been reported.[23] Thiel has studied ligand effects in the use of pyrazolylpyridine complexes of oxodiperoxomolybdenum(VI). No doubt these results will lead to the design of new, superior, ligands.[24] The cobalt(II) porphyrin[25] and polyaniline-supported



Scheme 4

cobalt(II)-catalysed[26] epoxidations are applicable to both electron-rich and electron-deficient alkenes while a large scale epoxidation catalysed by sodium tungstate in the absence of organic solvents is of industrial importance.[27]

Pfaltz has reported new bis-oxazoline ligands **6** for the asymmetric epoxidation of stilbene in up to 62% ee. Benzaldehyde is a significant by-product in this process (Scheme 5).[28] Nishiyama has shown that [bis(acetoxy)iodo]benzene is a superior oxidant for this process, with yields of up to 80% and selectivities of up to 74% ee, although unfortunately not simultaneously, with the well established pybox ligand.[29]



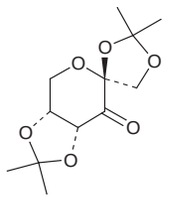
Scheme 5

Chiral ruthenium porphyrins catalyse the asymmetric epoxidation of alkenes, with the best selectivities being obtained for cycloalkenes.[30] The use of an achiral bis-oxazoline has also been reported, using molecular oxygen as terminal oxidant. This protocol is particularly efficient for the selective epoxidation of the β-face of cholest-5-ene.[31] Bimetallic iron complexes have also been used.[32]

Sugar-derived hydroperoxides have also been used for the asymmetric epoxidation of allylic alcohols with low ee.[33]

Three membered rings containing oxygen and a second heteroatom are popular as oxygen-transfer agents. Perfluorinated oxaziridines have recently been used.[34] Oxaziridinium ions, derived from iminium ions, can also be used to epoxidise alkenes. Armstrong has reported new iminium ions which act as epoxidation catalysts.[35] The most common reagents of this class are dioxiranes, where the second heteroatom is also oxygen. Denmark has disclosed results of a study which point strongly to the intermediacy of dioxiranes in ketone-catalysed epoxidations.[36]

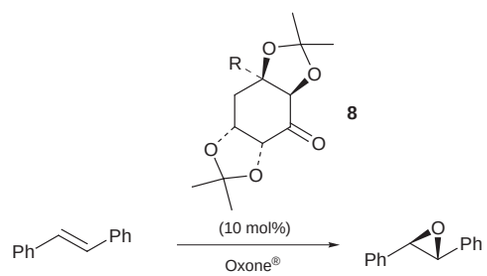
Shi recently reported a fructose-derived ketone **7** for use in asymmetric epoxidations,[37] and noted that the efficiency could



7

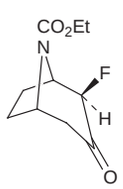
be increased if the epoxidation was carried out at pH 10.5, unusually high for such systems. This result was interpreted as suppression of a competing Baeyer–Villiger pathway leading to decomposition of the ketone.[38]

Wang and Shi have now reported a new group of chiral ketones **8** which give high enantioselectivities in the epoxidation of stilbene (<96% ee), styrene (<68% ee) and other alkenes (Scheme 6).[39]



Scheme 6

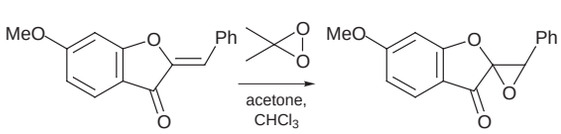
Armstrong has reported a tropinone-derived ketone catalyst **9** for the epoxidation of ketones. (*E*)-Stilbene was epoxidised in 88% yield and with 76% ee.[40]



9

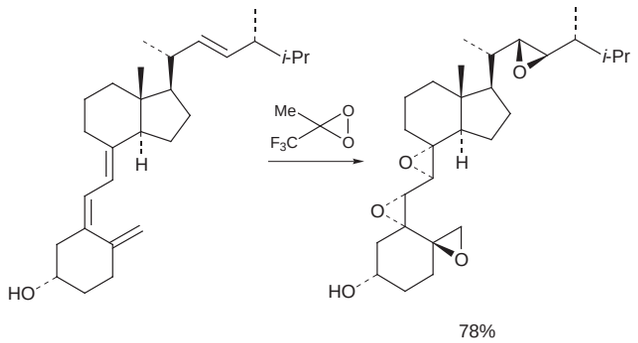
Yang and co-workers have further refined their earlier-described C_2 symmetric binaphthyl-derived ketone which epoxidises (*E*)-stilbene in up to 84% ee *via* the corresponding dioxirane.[41]

Dimethyldioxirane is often the oxidant of choice where sensitive substrates or epoxides are involved. For example, (*Z*)-6-methoxyaurone epoxide can be isolated in quantitative yield (Scheme 7).[42] Similar results have also been obtained by Adam and co-workers.[43] Other examples of sensitive epoxides prepared in this manner include the trioxide of chrysene, a polycyclic aromatic hydrocarbon (PAH)[44] and the tetraepoxide of vitamin D_2 (Scheme 8).[45]



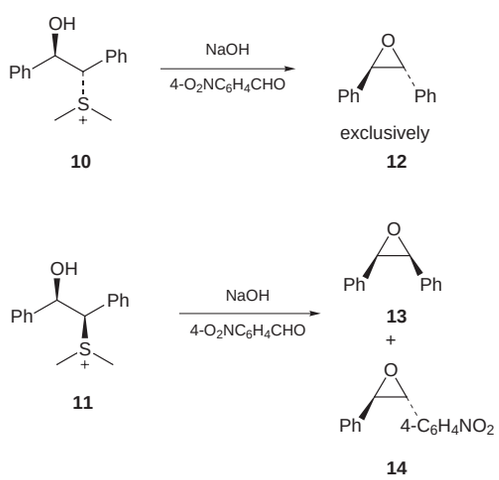
Scheme 7

Adam and co-workers have used radical clocks and strained alkenes in order to assess claims that a free-radical pathway is involved in the oxidation of some substrates by dimethyldioxirane. At this point, all evidence points to a concerted mechanism for epoxidations, although an oxygen rebound mechanism cannot be ruled out for oxidation of C–H bonds.[46] Minisci and co-workers continue to support a free-radical mechanism for some oxidations, although they admit that the evidence for a free-radical pathway in alkene epoxidation is circumstantial.[47] Recent DFT calculations also point to a concerted mechanism.[48]



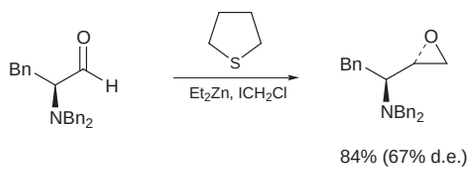
Scheme 8

Sulfur ylides (and more recently iodonium ylides[49]) have long been known to convert aldehydes into epoxides. A detailed understanding of the reaction mechanism is important for the development of efficient asymmetric variants. Aggarwal has now presented evidence that *anti*-betaines **10** (which lead to *trans*-epoxides **12**) are generated irreversibly while *syn*-betaines **11** are generated reversibly, and so can lead to a mixture of *cis*- and *trans*-epoxides **13** and **12** in addition to crossover products **14** (Scheme 9).[50]



Scheme 9

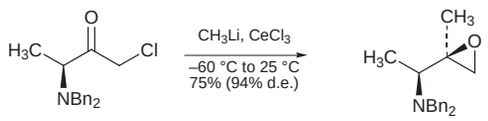
This reaction can also be carried out with moderate (<58% ee) asymmetric induction using dimethylsulfonium methylide in chiral micelles derived from ephedrine.[51] Sulfur ylides generated *in situ* from diethylzinc, chloroiodomethane and tetrahydrothiophene also undergo this reaction. This result is slightly surprising in that sensitive epoxides are generated in the presence of a Lewis acid (Scheme 10).[52]



Scheme 10

α-Amino epoxides are in much demand as building blocks for the synthesis of HIV-protease inhibitors. Another approach to

these epoxides uses the addition of organolithium reagents to suitable α-chloro ketones **15** in the presence of cerium chloride. High diastereoselectivities were observed, with no racemisation at the amino group (Scheme 11).[53] Similar routes have been used by others.[54]

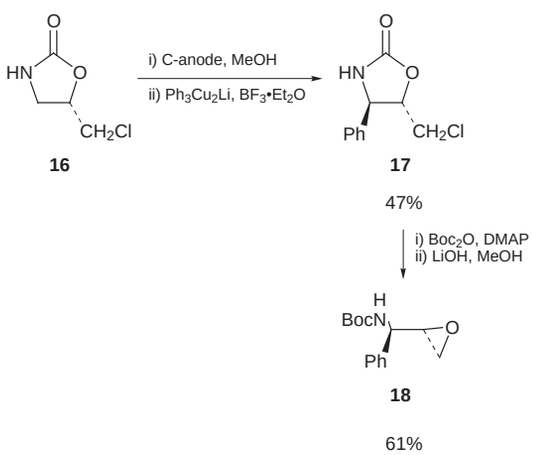


15

Scheme 11

Ghosh's approach to the same compounds relies on asymmetric aldol methodology to introduce the required stereogenic centres, and a Curtius rearrangement to transform a chiral carboxylic acid into a chiral amine. The actual epoxidation is by ring closure of a 1,2-diol.[55]

A further, more general, approach starts with oxazolidinone **16** derived from malic acid. Oxidation followed by acyliminium ion generation and reaction leads to the *trans*-isomer **17** with good selectivity. Protection of the nitrogen followed by oxazolidinone cleavage with concomitant cyclisation gave the epoxide **18** (Scheme 12).[56]



16 **17**

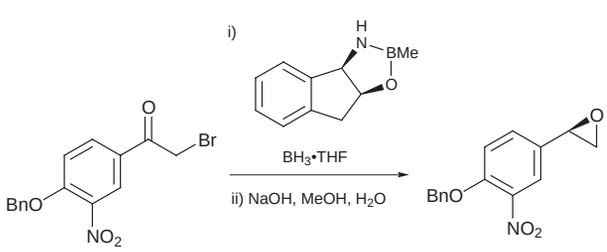
47%

18

61%

Scheme 12

Epoxide **20**, required for the asymmetric synthesis of the β_2-agonist formoterol, was prepared by oxazaborolidine reduction of **19** followed by cyclisation (Scheme 13).[57]



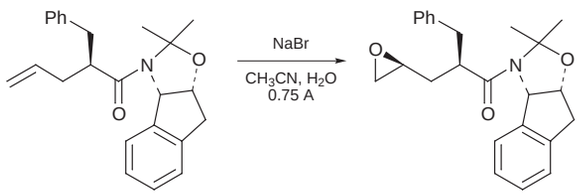
19 **20**

96% (96% e.e.)

Scheme 13

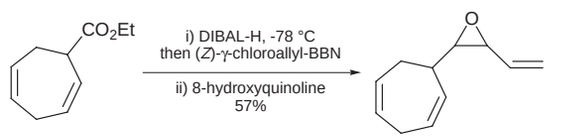
The diastereoselective electrochemical epoxidation shown in Scheme 14 is a particularly attractive process since the product crystallises from the reaction mixture. HOBr adds to the double bond at the anode, while hydroxide generated at the cathode effects ring closure.[58]

Lamoxirene **22**, the gamete-releasing and gamete-attracting pheromone of Laminariales, has been synthesised by a diastereoselective allylation related to the Darzens condensation. (*Z*)-γ-Chloroallylborabicyclononane [(*Z*)-γ-chloroallyl-BBN] reacts with the aldehyde derived from **21**, followed by cyclisation (Scheme 15).[59]



86% (88% d.e.)

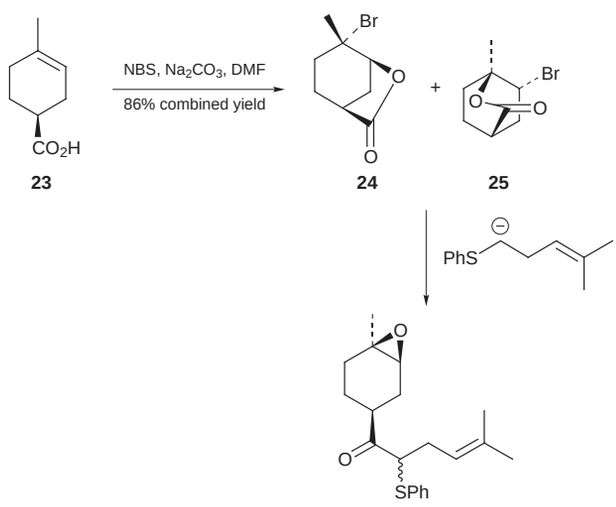
Scheme 14



21 **22**

Scheme 15

Another epoxide-containing pheromone, that of the southern green stink bug, has been prepared using a tandem lactone opening epoxide formation as shown in Scheme 16. Bromolactonisation of **23** gave a mixture of regioisomeric lactones **24** and **25** which were treated with the anion of 2-methyl-5-phenylthiopent-2-ene to give a single epoxide isomer **26**.[60]



23 **24** **25**

26

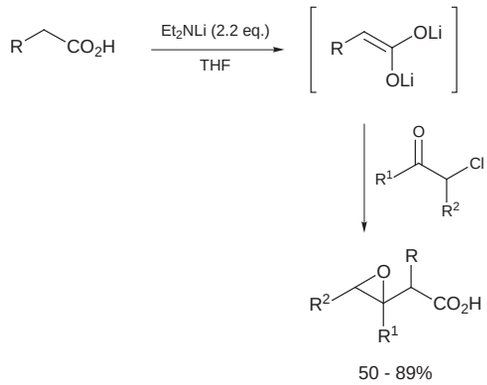
81%

Scheme 16

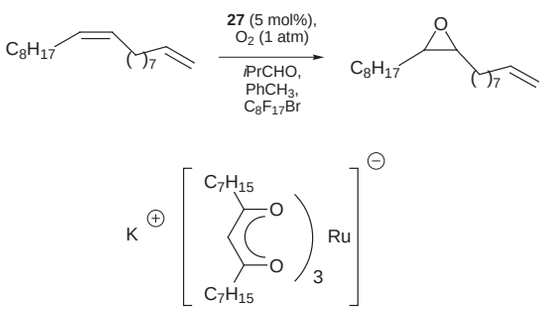
Addition of enediolates to α-chloro ketones provides β,γ-epoxy acids (Scheme 17).[61]

The chemoselective epoxidation of disubstituted alkenes in the presence of monosubstituted alkenes can be effected by the use of a perfluorinated ruthenium catalyst **27** in a fluorinated solvent (Scheme 18).[62]

The asymmetric epoxidation of electron-deficient double bonds has lagged behind that of electron-rich bonds. Jackson *et al.* have now reported that diethyl tartrate–dibutylmagnesium can be used as a chiral catalyst for the epoxidation of chalcone and related compounds with high selectivity (Scheme 19)[63] while Enders *et al.* have reported the use of oxygen as terminal oxidant in conjunction with diethylzinc and (1*R*,2*R*)-*N*-methylpseudonorephedrine **28** as source of asymmetry. In one case essentially complete enantiocontrol was observed (Scheme 20) although selectivities were generally in the range 60–90%.[64]



Scheme 17



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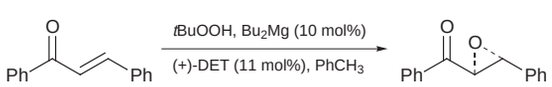
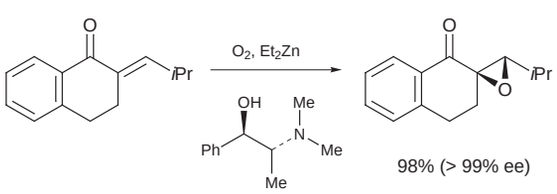
Scheme 18



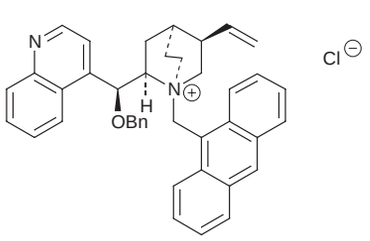
Scheme 19



28

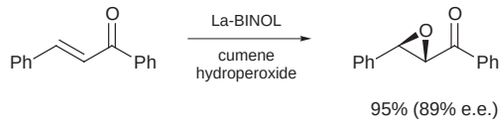
Scheme 20

Efficient asymmetric epoxidation of electron-deficient alkenes can be carried out using aqueous sodium perchlorate as oxidant in a biphasic system with a cinchodinium phase transfer catalyst. Using **29** as catalyst, chalcone was epoxidised with 81% ee (90% yield).[65]



29

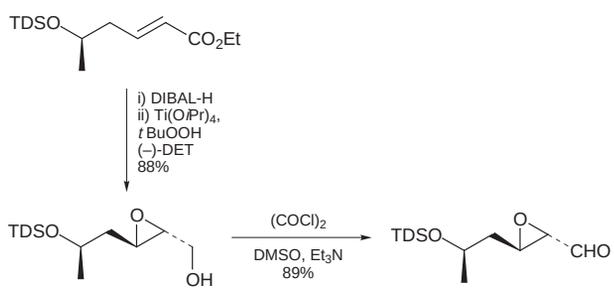
Lanthanum and ytterbium BINOL complexes are also efficient catalysts for this process. As little as 1 mol% can be used with excellent yield and selectivity (Scheme 21). Although the exact structure of the catalyst is unknown, a ratio of 1:1 BINOL:La(O*i*Pr)$_3$ proved optimal.[66]



Scheme 21

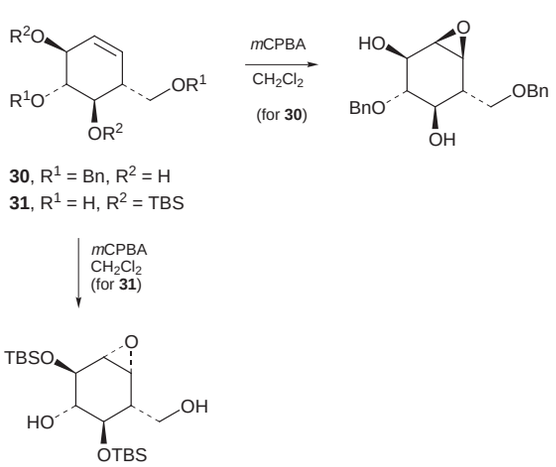
Roberts *et al.* have continued to extend the scope of the poly-L-leucine catalysed epoxidation to include alkyl enones, enediones, dienones and unsaturated keto esters.[67] This process has been reviewed by Ebrahim and Wills.[68]

The alternative approach to epoxidation of electron-deficient alkenes is reduction to the allylic alcohol, which can be epoxidised enantioselectively by the Sharpless method and re-oxidised, for example, to the aldehyde (Scheme 22).[69] Of course this approach lacks the generality and convenience of direct epoxidation.



Scheme 22

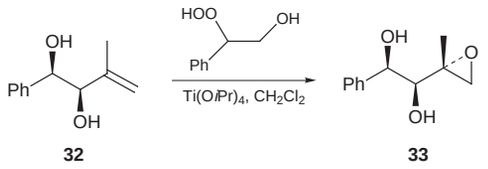
A model has been proposed to explain the diastereoselectivity of the Payne epoxidation (PhCN–H_2O_2) of allylic ethers. This method usually gives good *syn*-selectivity whereas *m*CPBA favours the *anti*-diastereoisomer.[70] Control of selectivity using protecting groups has been demonstrated in the synthesis of the glycosidase inhibitor cyclophellitol and its diastereoisomer (Scheme 23). As expected, epoxidation of the alcohol **31** gave *syn*-selectivity, whereas use of the benzyl ether **30** gave complete selectivity for the *anti*-isomer.[71] A further example is found in a total synthesis of (+)-eutypoxide B.[72]



Scheme 23

A related procedure is the diastereoselective epoxidation of ene diols using β-hydroperoxy alcohols as oxygen donors. Thus, epoxidation of **32** gave good selectivity for the *erythro*-isomer **33** and with good chemical yield (Scheme 24).[73] These compounds are similar to the portion of the azinomycin natural products prepared by Shipman *et al.*[74] and Coleman *et al.*[75]

However, in many cases the diastereoselectivity is dependant on the conformation of the substrate[76] or the pH at which the reaction is carried out.[77]



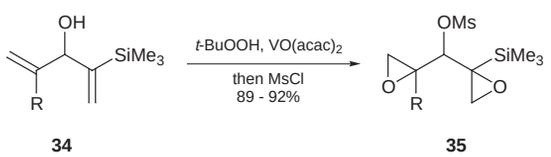
Scheme 24

The diastereoselective epoxidation of cyclic *t*-butyl allyl peroxides, generated under modified Kharasch–Sosnovsky conditions, has been described using a number of oxidising agents.[78]

The diastereoselective epoxidation of allylic alcohols by titanium-containing zeolites has been studied by Adam and co-workers, who provide evidence that the oxidising species is a hydrogen-bonded peroxy complex.[79] A range of alkenes have also been epoxidised using hydrotalcite catalysts.[80]

The use of molecular oxygen and isobutyraldehyde in 1,2-dichloroethane is an efficient method for the introduction of ^{18}O labelled epoxides. This method will doubtless prove valuable in studies on lipid metabolism.[81]

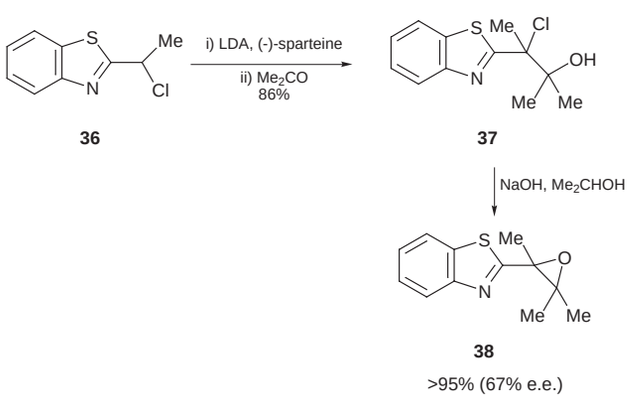
Allene oxides are versatile synthetic intermediates which can be generated from silyloxiranes with a suitably disposed leaving group. Kabat reports that the precursors **35** can be prepared by vanadium-catalysed epoxidation of **34** (Scheme 25). Generation of the allene oxide and subsequent rearrangement gave 4-alkylfurans including steroid furans.[82]



Scheme 25

Carbonyl ylides are versatile intermediates which can be formed by the thermolysis or photolysis of epoxides. A recent study has probed the effect of orbital symmetry in these reactions.[83]

An asymmetric Darzens condensation mediated by (−)-sparteine allows access to enantiomerically enriched benzothiazolyloxiranes. Lithiation of **36** in the presence of sparteine followed by addition of acetone gave chlorohydrin **37** in 86% yield. This was then treated with sodium hydroxide in propan-2-ol to give the epoxide **38** with 67% ee in essentially quantitative yield (Scheme 26).[84]



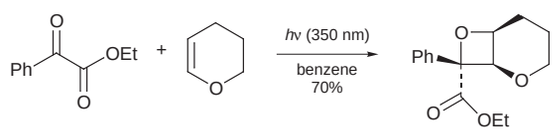
Scheme 26

A theoretical study by Bach *et al.* outlines the importance of acid catalysis in the epoxidation of simple alkenes with peroxy acids.[85] Further studies by the same group centre on the epoxidation of allylic alcohols with peroxyformic acid[86] and of simple alkenes (and other substrates) with peroxynitrous acid.[87,88]

In other work, Colombani and Maillard discuss the stereochemical features of epoxide formation by addition of radicals to hydroperoxy-substituted acrylates.[89]

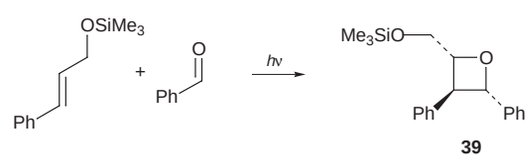
3 Four membered rings

Once again the Paternò–Büchi reaction takes pride of place as far as methods for the formation of oxetanes are concerned. Bach has reviewed his own work in this area[90] as well as presenting a full account of work suggesting that 1,3-allylic strain is the major source of stereocontrol in the photochemical reaction of chiral silyl enol ethers with aromatic aldehydes.[91] One example from a recent study of the photochemical reactions of ethyl phenylglyoxylate is shown in Scheme 27.[92]



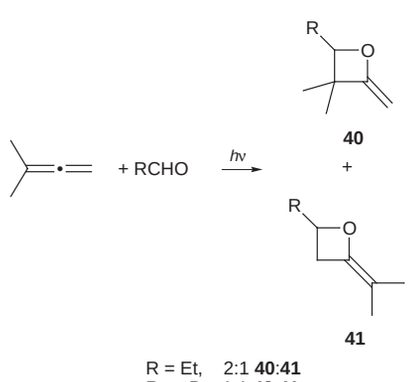
Scheme 27

Fleming and Gao have studied the Paternò–Büchi reaction of the trimethylsilyl ether of cinnamyl alcohol, and reached the conclusion that non-covalent tethering is involved since this reaction gives only the all-*trans* isomer **39** whereas the reaction of β-methylstyrene gives a mixture of products (Scheme 28).[93]



Scheme 28

Another study of the Paternò–Büchi reaction centres on the reaction of allenes with selected aliphatic aldehydes. The regioselectivity as shown in Scheme 29 is clearly dependent on steric and electronic effects.[94] Excess allene was required to prevent the formation of by-products (presumably including spirocyclic bis-oxetanes as previously reported[95]).

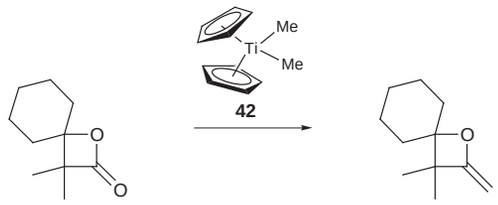


Scheme 29

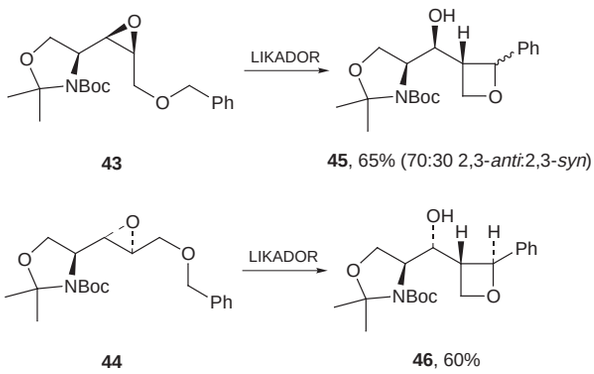
A more selective approach to these compounds is the direct methylenation of β-lactones using Petasis' dimethyltitanocene reagent **42** (Scheme 30).[96]

Mordini and co-workers have continued their previous work on the rearrangement of oxiranyl ethers. The stereoselectivity is dependent on the stereochemistry of the starting epoxide; for example **43** gave a 70:30 *anti*:*syn* mixture **45** while **44** gave exclusively the *anti*-isomer **46** (Scheme 31).[97]

Intramolecular glycosidation provides access to some

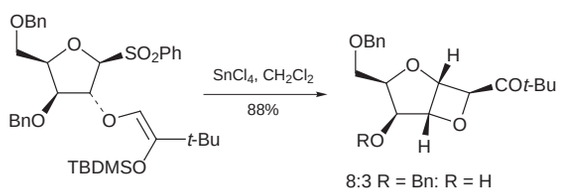


Scheme 30



Scheme 31

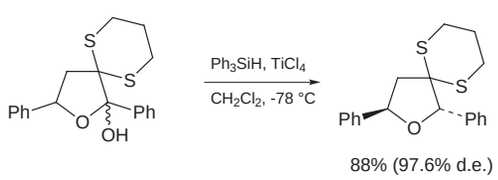
unusual fused oxetanes (Scheme 32).[98] Similar reactions have also been used to prepare tetrahydrofurans.[99]



Scheme 32

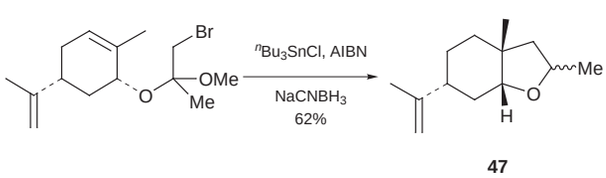
4 Five membered rings

Reduction of lactols and derivatives is a common strategy for the synthesis of oxacycles of all sizes. Nishiyama *et al.* report that the reduction of hemiketals with Ph_3SiH–$TiCl_4$ gives tetrahydrofurans with high stereoselection (Scheme 33).[100]



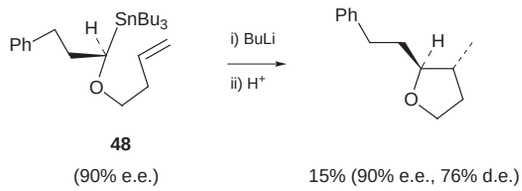
Scheme 33

Srikrishna and co-workers have combined this with the classic 5-*exo*-*trig* radical cyclisation in a one pot procedure. Although **47** (Scheme 34) was formed as a 1 : 1 epimeric mixture, stereochemical studies on related compounds suggest strongly that cyclisation preceeds reduction.[101]



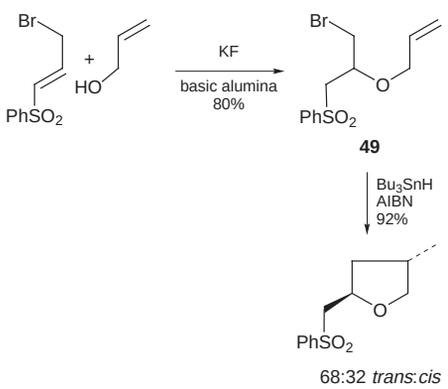
Scheme 34

Similar ionic cyclisations are also possible. In line with work by Coldham *et al.*[102] on the corresponding nitrogen heterocycles, Nakai *et al.* have shown that cyclisation of the organolithium species derived from **48** proceeds with retention of configuration at the metal centre (Scheme 35).[103]

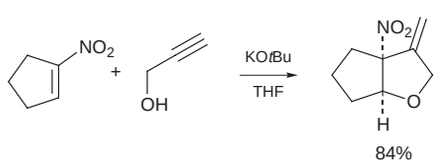


Scheme 35

Two new approaches are based on intermolecular conjugate addition followed by cyclisation. In the first method, halogenated unsaturated sulfones react with allylic and prop-2-ynylic alcohols to give compounds such as **49**. Radical cyclisation then gives the five-membered ring (Scheme 36).[104] The second approach uses a similar conjugate addition onto unsaturated nitro compounds, after which the resulting nitronate cyclises onto the triple bond (Scheme 37).[105] Palladium-catalysed carbocyclisation was also used to close the ring in a related process.[106]

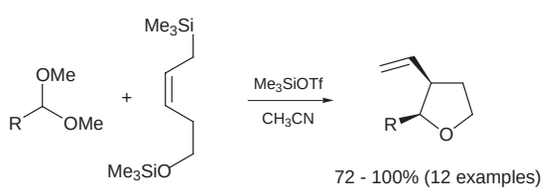


Scheme 36



Scheme 37

The condensation of allylsilane **50** with dimethyl acetals of aromatic and aliphatic aldehydes gives rise to 2-substituted-3-vinyltetrahydrofurans with almost complete diastereocontrol (Scheme 38).[107] The reaction also works for ketals.

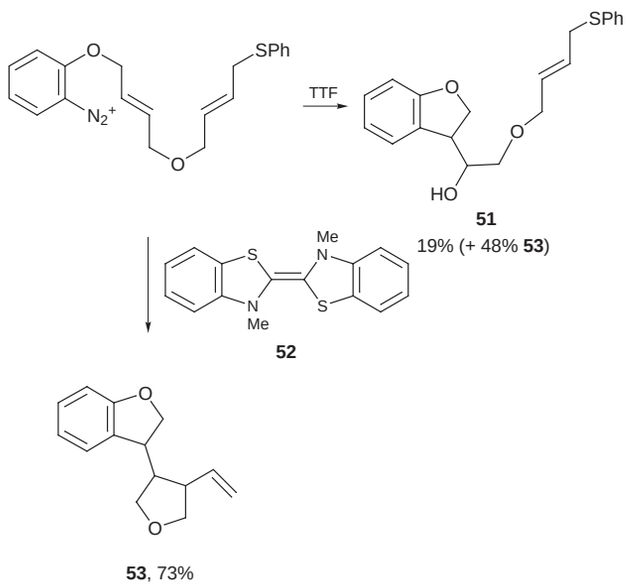


Scheme 38

Hosomi *et al.* have independently reported the use of a manganese–lead system for generation of carbonyl ylides which undergo cycloaddition reactions to give tetrahydrofurans.[108] Cycloadditions of allylgermanes have also been reported.[109]

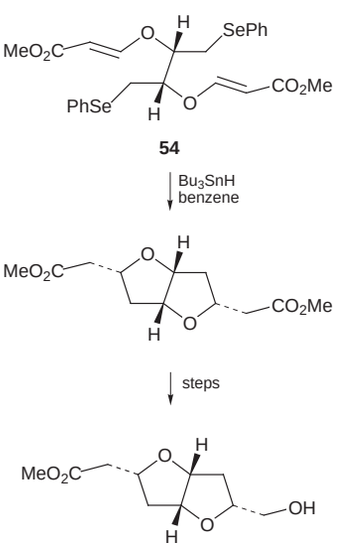
Murphy continues to provide evidence for a radical–polar crossover mechanism in reactions of arenediazonium salts with tetrathiafulvalene (TTF).[110] It was previously reported that reaction of the cyclised radical with the radical cation formed in

the first step from TTF (leading ultimately to **51**) was competitive with a possible second cyclisation. New, more hindered, electron donors such as **52** have now been developed which favour the second cyclisation to give **53** (Scheme 39).[111]



Scheme 39

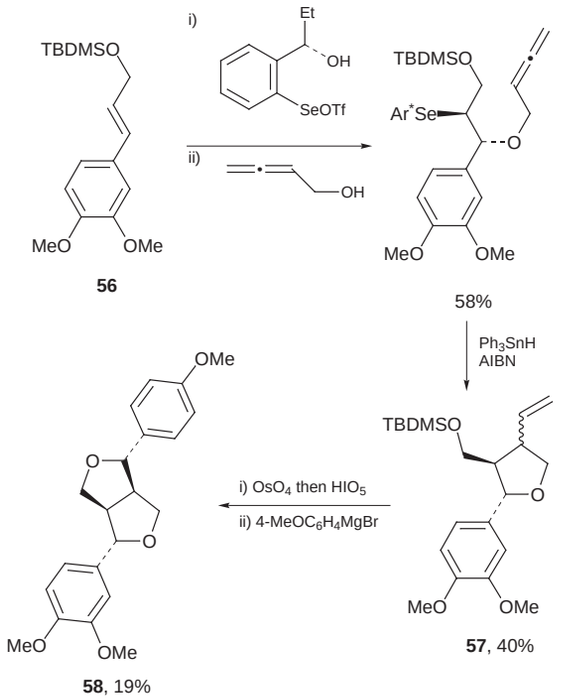
A formal total synthesis of kumausallene has been reported[112] which uses a double radical cyclisation of **54**, derived from diethyl tartrate (Scheme 40). Enzymic partial hydrolysis was followed by routine transformations to give **55**, used by Overman in his total synthesis.



Scheme 40

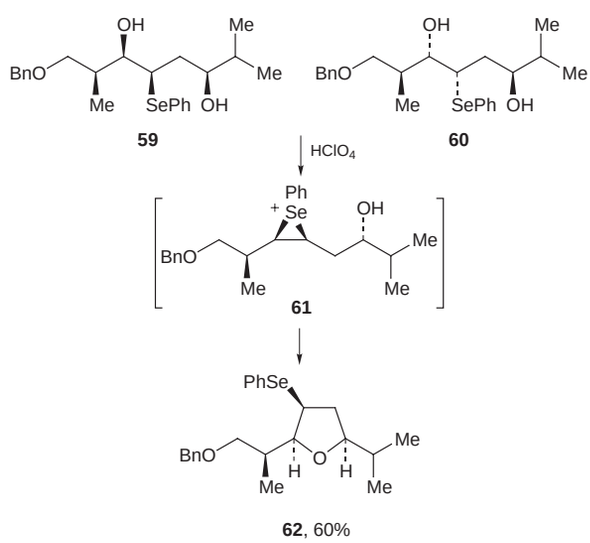
Wirth continues his elegant studies on chiral selenium reagents with a particularly short synthesis of the furofuran lignan (+)-membrine. Oxyselenation of **56** gave a separable 92:8 mixture of diastereoisomers of which the major isomer was obtained in 58% isolated yield. Radical cyclisation to **57** was followed by oxidation of the double bond and addition of a Grignard reagent to give the natural product **58** (Scheme 41).[113] An umpolung of this strategy involves the ring opening of epoxides with organoselenium and organotellurium reagents.[114]

A further related approach proceeds *via* the intermediacy of a seleniranium ion **61**. Treatment of a mixture of **59** and **60**,



Scheme 41

prepared using allyltin chemistry, with perchloric acid gave the tetrahydrofuran **62** in 60% yield (Scheme 42).[115]



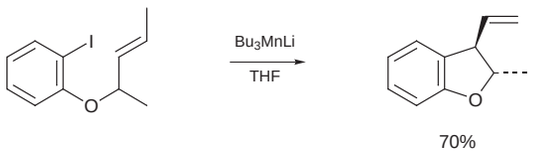
Scheme 42

Full details of the tandem radical cyclisation onto unsaturated sulfones reported by Adrio and Carretero have also appeared.[116]

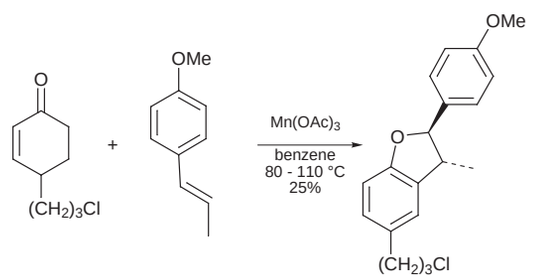
Trialkylmanganates promote the cyclisation of 2-iodophenyl ethers to give 2,3-dihydrobenzo[*b*]furans. While this process appears to be free radical in nature, it offers advantages over more traditional radical approaches in that the product may be unsaturated (Scheme 43), or that electrophilic trapping of the manganese species is possible.[117] Related reactions (although leading to unsaturated products) have been carried out on a solid support.[118]

A more conventional generation of α-keto radicals using manganese(III) acetate was used by Snider and co-workers in a synthesis of racemic conocarpan (Scheme 44).[119]

A number of other approaches based on free radical chemistry have been reported[120] including one on a solid



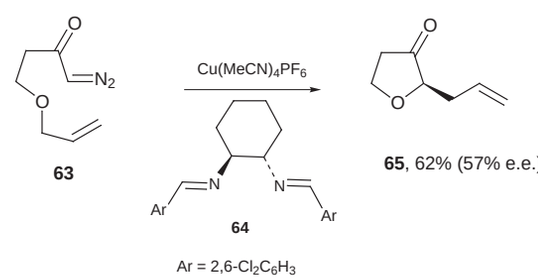
Scheme 43



Scheme 44

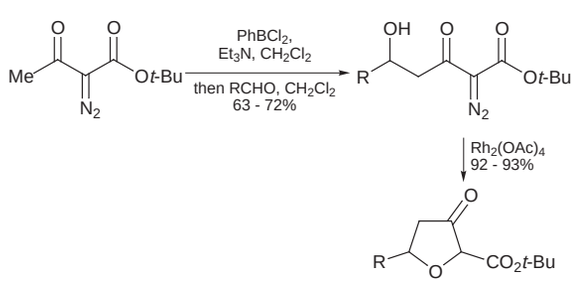
support.[121] Free radical chemistry has also been used to deoxygenate a lactol derivative.[122]

Asymmetric oxonium ylide rearrangement provides a route to enantiomerically enriched tetrahydrofurans. Decomposition of **63** by $Cu(MeCN)_4PF_6$ in the presence of ligand **64** gave **65** with 57% ee (Scheme 45).[123] Similar compounds and selectivities have been reported by McKervey *et al.* using a catalyst derived from *tert*-leucine[124] while Hodgson reports that the ylides can undergo intramolecular cycloaddition with up to 53% ee if hydrocarbon solvents are used.[125] Katsuki *et al.* have also reported further examples of the asymmetric ring expansion of oxetane ylides.[126]



Scheme 45

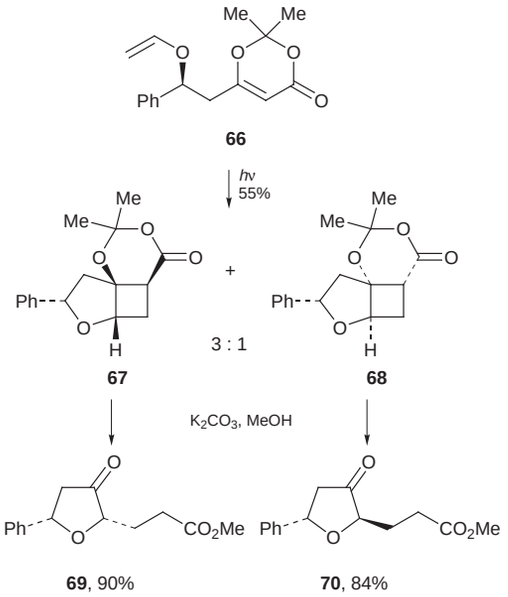
A related approach is the aldol reaction of *t*-butyl 2-diazoacetoacetate followed by rhodium(II) acetate catalysed cyclisation (Scheme 46).[127]



Scheme 46

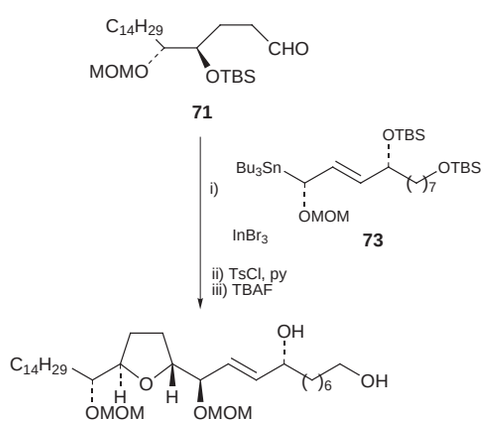
In another route to five-membered rings based on aldol chemistry, Dritz and Carreira have reported that enol ethers **66** derived from the products of their dienolate chemistry undergo a cycloaddition–fragmentation as shown in Scheme 47. Photolysis of **66** gave a separable 3 : 1 mixture of diastereoisomers **67** and **68** which gave, upon deprotection and fragmentation, **69** and **70**.[128]

The annonaceous acetogenins remain popular synthetic



Scheme 47

targets, with Marshall completing total syntheses of a number of compounds in this class. Addition of the indium reagent derived from stannane **73** to **71** was followed by standard cyclisation to give **72** (Scheme 48) in the lead up to longifolicin.[129]

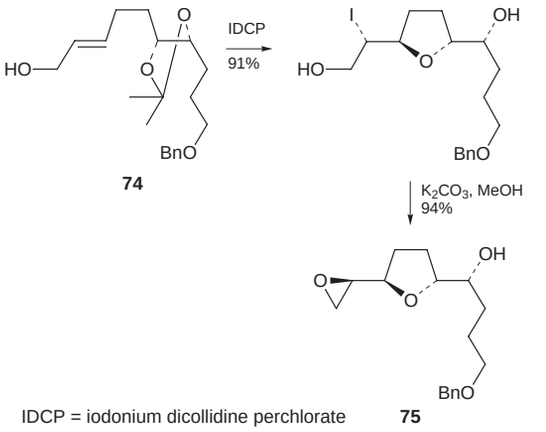


Scheme 48

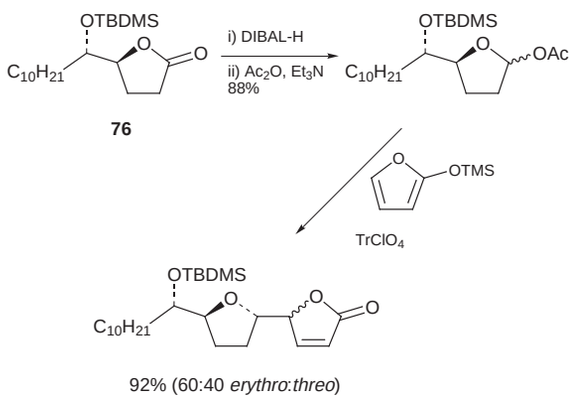
A similar approach was used for the bis-tetrahydrofurans bullanin,[130] asimicin[131] and asiminocin,[132] although the latter synthesis has the advantage of introduction of the butenolide in a single step. Bradley and Thomas have also reported the combination of allyltin chemistry followed by cyclisation as an approach to tetrahydrofurans.[133]

Mootoo *et al.* have described a new building block for acetogenin synthesis. Iodoetherification of **74** followed by cyclisation to the epoxide gave **75** (Scheme 49). The epoxide could then be opened by a Grignard reagent as an approach to the natural products.[134]

Another efficient route to these compounds uses the Lewis-acid catalysed addition of 2-trimethylsiloxyfuran to lactols. Hanessian and Grillo have used this chemistry to prepare a stereoisomer of the proposed structure of annonacin A.[135] In other work, reduction of **76** and acetylation was followed by treatment with 2-trimethylsiloxyfuran in the presence of trityl perchlorate to give a separable mixture of only two of the possible diasteroisomers which could be hydrogenated and subjected to a similar sequence of reactions (Scheme 50).[136] This



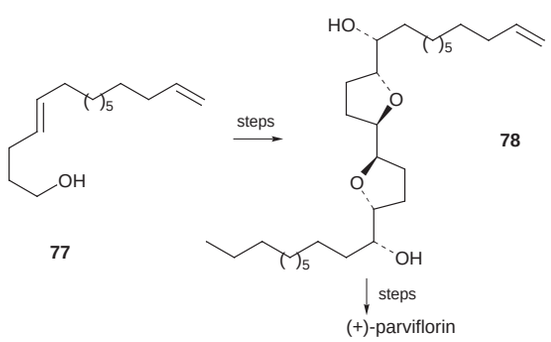
Scheme 49



Scheme 50

procedure has been extended to the corresponding thiophene and pyrrole.[137]

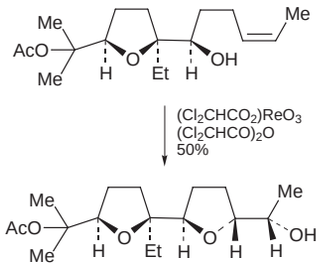
Trost's synthesis of (+)-parviflorin uses the asymmetric dihydroxylation of **77** to provide two fragments which were then coupled and further dihydroxylated. Conventional ring closure provided the almost-symmetrical intermediate **78** which was further elaborated into the natural product (Scheme 51).[138]



Scheme 51

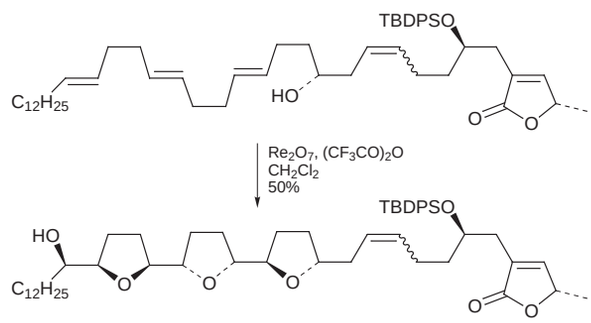
The intramolecular opening of epoxides by alcohols to give tetrahydrofurans leads to an *anti* relationship between the oxygen functionalities. Although yet unproven, it seems possible that polyether antibiotics such as monensin are formed by a *syn*-selective oxidation of a hydroxyalkene. This transformation can be accomplished chemically using pyridinium chlorochromate or dichloroacetylperrhenate (Scheme 52).[139] Such cyclisations may be under steric or chelation control, giving rise to diastereoisomers at the newly formed tetrahydrofuran ring.[140] The example shown in Scheme 52 is under steric control.

In work by Sinha *et al.*, three adjacent tetrahydrofuran rings



Scheme 52

have been generated in a single step using the more reactive trifluoroacetylperrhenate in a synthesis of a diastereoisomer of goniocin (Scheme 53),[141] while in similar model studies Towne and McDonald have shown that, in line with their previous work, the correct natural product stereochemistry is obtained.[142]

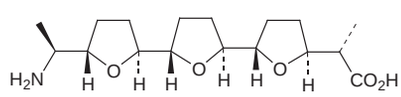


Scheme 53

Sinha and co-workers have used this reaction, along with asymmetric dihydroxylation and Mitsunobu inversion to prepare eight of the possible bis-THF isomers in a controlled manner.[143] McDonald has also reported tetrahydropyran synthesis by this method.[144]

A number of other approaches to acetogenins have been reported.[145]

A number of other structurally interesting poly-tetrahydrofurans have been prepared recently, including a novel peptide consisting of amino acid **79** containing a tris-THF. Such peptides are of interest as ion-channel models.[146]



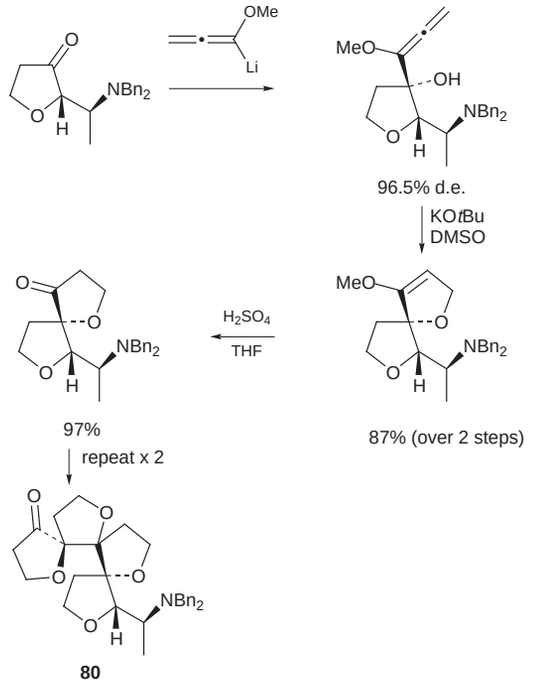
79

The related spirocyclic compounds have a helical structure. Reißig[147] has built on earlier work by Magnus[148] to prepare non-racemic helices such as **80** by the iterative procedure shown in Scheme 54.

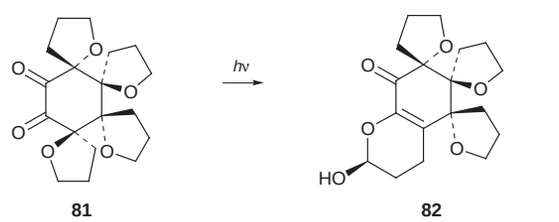
These compounds bear some resemblance to Paquette's belted spirocyclic tetrahydrofurans. In recent work, the diketone **81** was shown to undergo rapid photochemical isomerisation into **82** (Scheme 55).[149]

An enzymatically desymmetrised precursor **83** was elaborated in a number of steps to compound **84** (Scheme 56). Fluoride ion-catalysed Michael addition was then followed by flash thermolysis to give **85** related to pamamycin 607.[150]

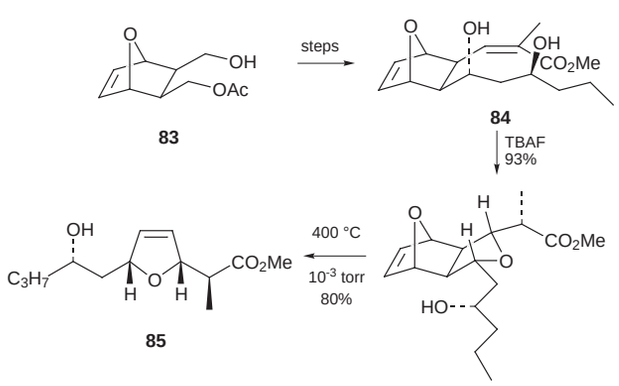
The same workers used a similar approach to (+)-methyl nonactate.[151] Since nonactin is a cyclic tetramer consisting of two molecules of (+)-nonactic acid and two molecules of (−)-nonactic acid, approaches which rely on a late separation of the two enantiomers are attractive. Kajiwara has shown that **86**, prepared by iodoetherification, undergoes highly selective



Scheme 54



Scheme 55

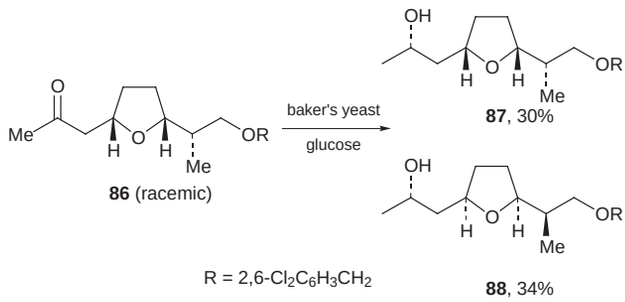


Scheme 56

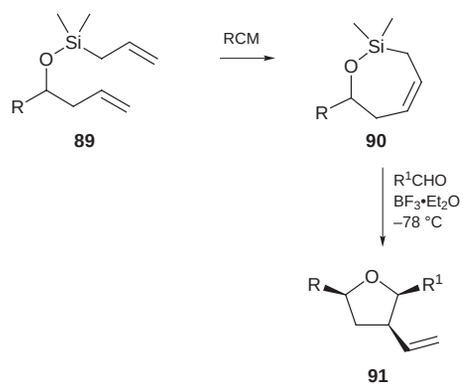
baker's yeast reduction to give **87** and **88** each with >97% ee (Scheme 57).[152]

Marsden[153] and Cossy[154] have independently reported that allyldimethylsilyl-protected homoallylic alcohols **89** undergo ring-closing metathesis (RCM) to give seven-membered ring compounds **90**. These then react with aldehydes under Lewis acid catalysis to give tetrahydrofurans **91** (Scheme 58). Yields are high, even for hindered aldehydes, and with good to excellent diastereoselectivity for the isomer shown. A similar 2,3,5-trisubstituted tetrahydrofuran was prepared by allylation of a lactol in synthetic studies towards gymnodimine,[155] while a reversal of polarity from the same group sees α-lithiated tetrahydrofurans reacting with aldehydes in an approach to pectenotoxin 1.[156]

The palladium-catalysed reactions of 1,3-dienes have been

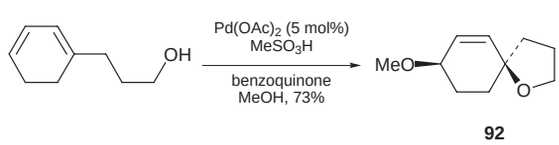


Scheme 57



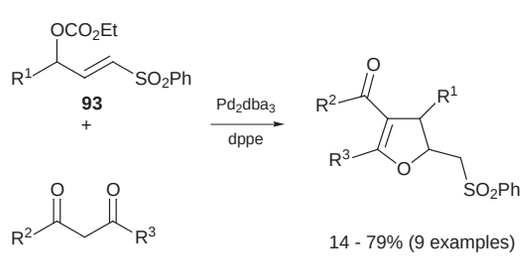
Scheme 58

used by Bäckvall *et al.* to prepare a range of oxygen heterocycles. The same group have now extended their 1,4-dialkoxylation of dienes to give spirocycles such as **92** (Scheme 59).[157] A similar approach was used in the synthesis of fused pyrans.



Scheme 59

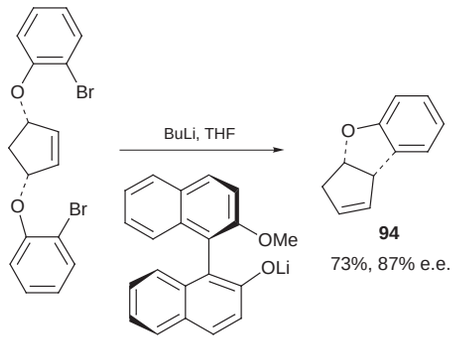
Another palladium-catalysed reaction, allylic alkylation, has been used to prepare dihydrofurans. While malonate esters are among the more common nucleophiles, the use of β-keto esters and β-diketones in conjunction with substrates **93** containing a sulfone leads directly to the dihydrofuran with good to excellent selectivity in favour of the *trans*-isomer (Scheme 60).[158] Other palladium,[159] silver[160] and base[161] promoted variations on this reaction have been reported. Intramolecular palladium-catalysed allylic alkylation with an oxygen nucleophile has also been reported.[162]



Scheme 60

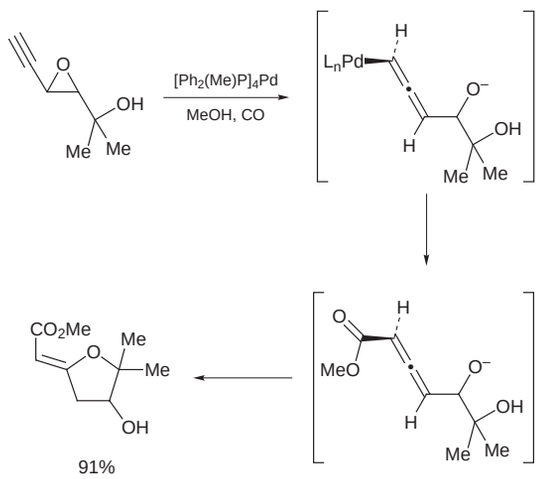
A further allylic substitution route, the symmetry-breaking cyclisation of *meso*-diethers mediated by a chiral lithium alkoxide, has been used to provide benzofuran **94** with good enantiomeric excess (Scheme 61).[163]

Piotti and Alper have shown that alkynyl epoxides can under-



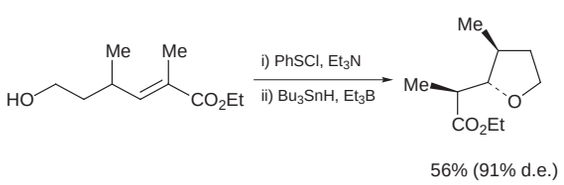
Scheme 61

go carbonylation followed by cyclisation as shown in Scheme 62.[164]



Scheme 62

Significant selectivity has been demonstrated in the cyclisation of oxygen radicals and the subsequent hydrogen transfer to generate two new contiguous stereogenic centres (Scheme 63).[165]

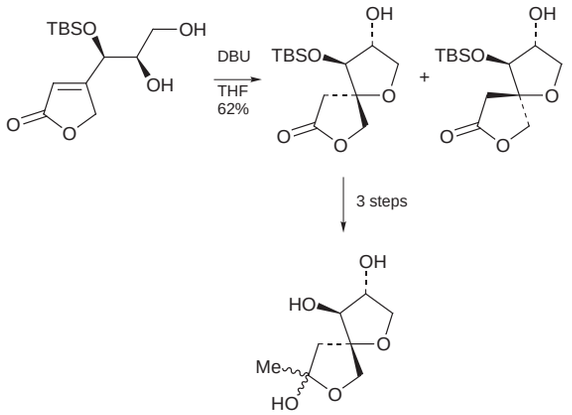


Scheme 63

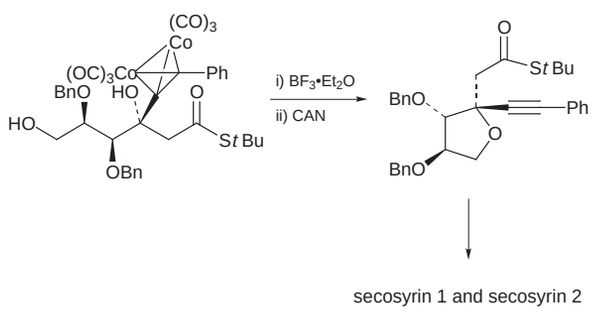
This reaction is analogous to an intramolecular Michael addition. A similar (non-radical) reaction has been used to prepare the spirocyclic tetrahydrofuran sphydrofuran **95** as shown in Scheme 64.[166]

An intramolecular Nicholas reaction was used to prepare related natural products (Scheme 65).[167] Six-membered rings have been prepared in a similar way by intramolecular addition of alkenes to the intermediate carbenium ion in a manner reminiscent of the ene reaction.[168] Cobaloxime-stabilised cations have also been used in tetrahydrofuran synthesis.[169]

Paquette's pinacol rearrangements provide another method for the preparation of spirocyclic tetrahydrofurans (and tetrahydropyrans). Since the spirocyclic carbon is stereogenic, the possibility of simple asymmetric induction is an attractive one which has been recently investigated. Deprotonation of **96** and addition of cyclopentanone followed by CSA (camphorsulfonic acid)-mediated rearrangement produced a 4.5:1 mixture of diastereoisomers favouring **97** (Scheme 66).[170] This method-

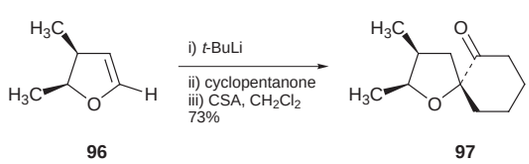


Scheme 64



Scheme 65

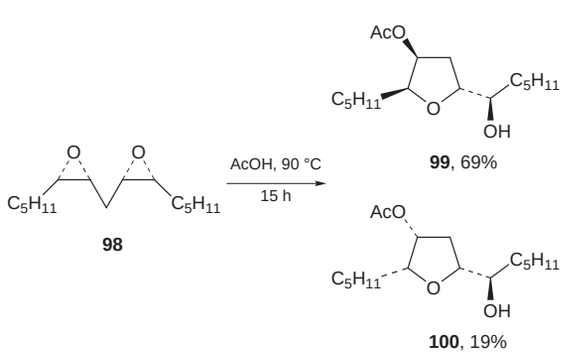
ology has been applied to the synthesis of spirocyclic bis-C,C-glycosides.[171]



Scheme 66

Allylsilane–oxonium ion cyclisations have also been used to prepare (six membered) spirocyclic ethers.[172]

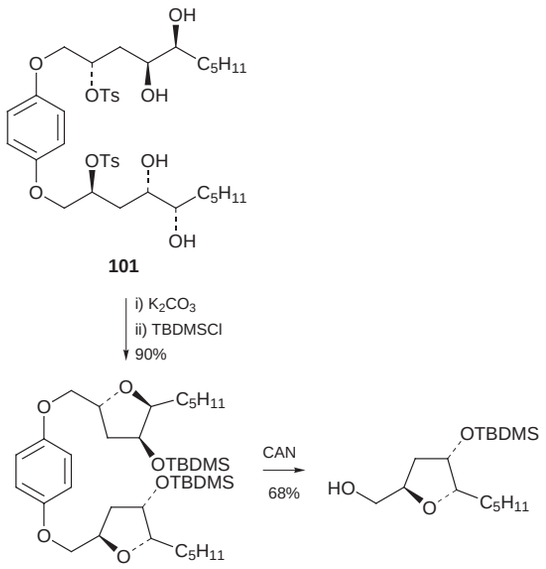
Methylene-interrupted bis-epoxides are likely biosynthetic precursors to tetrahydrofurans isolated from marine algae. Capon and Barrow have prepared a number of the proposed bis-epoxides and subjected them to acid-promoted rearrangement. For example, **98** gives a mixture of **99** and **100** in 88% yield (Scheme 67).[173]



Scheme 67

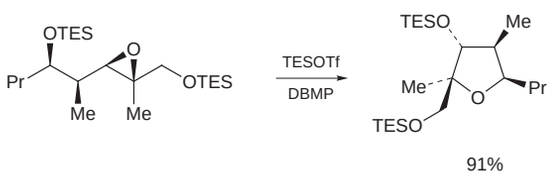
Similar compounds were prepared by the cyclisation shown in Scheme 68.[174] The precursor **101** was prepared from a bis-epoxide previously used by Hoye and Ye in a synthesis of

parviflorin,[175] with the Sharpless asymmetric dihydroxylation being the source of all three stereogenic centres.



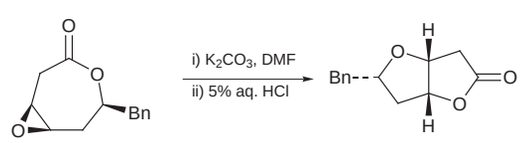
Scheme 68

Highly substituted tetrahydrofurans are accessible by a 5-*endo*-*tet* cyclisation of β-siloxy epoxides as shown in Scheme 69. Since both diastereoisomers of the epoxides can be prepared selectively from both double bond isomers, this approach allows access to all four stereoisomers at the centres generated during the epoxidation–rearrangement sequence.[176]



Scheme 69

Epoxide **102**, formed by the deconjugation and epoxidation of the corresponding α,β-unsaturated lactone, undergoes a base-promoted rearrangement to give **103**. It seems likely that this compound is formed by α-deprotonation with concomitant epoxide opening, followed by rearrangement of the ε-lactone to the γ-lactone followed by intramolecular conjugate addition of the pendant alcohol (Scheme 70).[177]

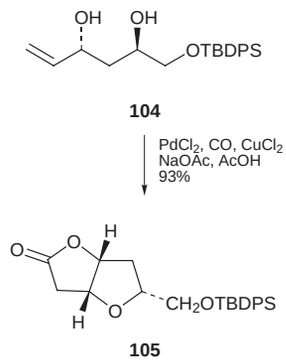


102 **103**, 96%

Scheme 70

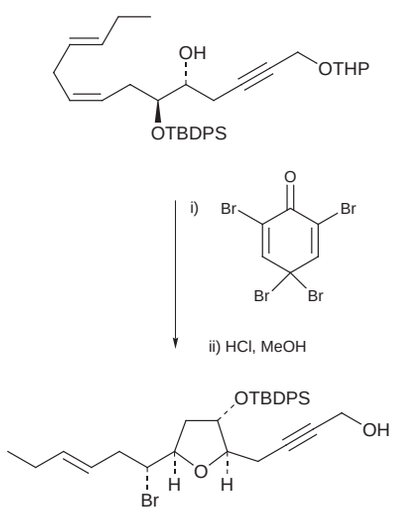
Laurencia-derived tetrahydrofurans continue to attract interest. A compound related to the one above was prepared by a mechanistically similar pathway. Tandem alkoxycarbonylation–lactonisation of **104**, derived from dimethyl (*R*)-malate, gave **105** in 93% yield (Scheme 71). A further six steps were required to convert this intermediate into (−)-*trans*-kumausyne.[178] A radical cyclisation of a β-alkoxyacrylate derived from D-(+)-xylose has provided a further synthesis of this natural product.[179]

The above lactone is similar to those isolated from the Hagen's gland of certain species of wasp; these lactones have been synthesised by an essentially identical method.[180]



Scheme 71

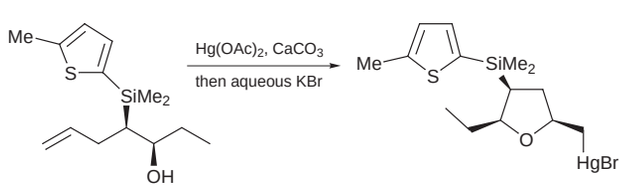
A recent biomimetic approach from Martín *et al.* culminates in a total synthesis of *trans*-(+)-deacetylkumausyne. Although the stereochemistry of the OTBDPS group in **106** is inverted with respect to the natural product, it was found that using the precursor with the correct stereochemistry in the cyclisation led to an unacceptable mixture of diastereoisomers at the tetrahydrofuran ring, so that the correct stereochemistry was introduced later in the sequence by oxidation–reduction (Scheme 72).[181]



106, 79%

Scheme 72

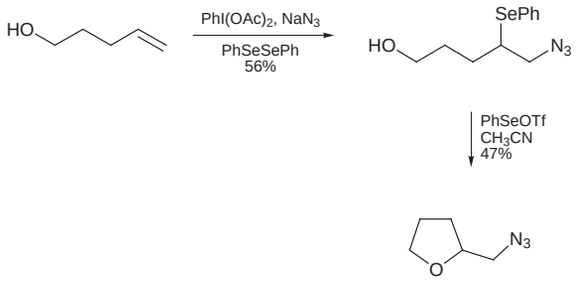
A similar approach has been used by Landais *et al*. Intramolecular oxymercuration of **107** gave **108** with 90% de (Scheme 73). Cyclisation of a related compound using NBS led to incorporation of the side-chain bromine with correct stereochemistry.[182] Related 5-*endo* cyclisations have also been reported.[183] An improved method for the work-up of intramolecular oxymercuration involves the use of triethylborane and sodium borohydride.[184] This method was applied to the synthesis of tetrahydrofurans and tetrahydropyrans as well as lactones and nitrogen heterocycles.



107 **108**, 90% (90% d.e.)

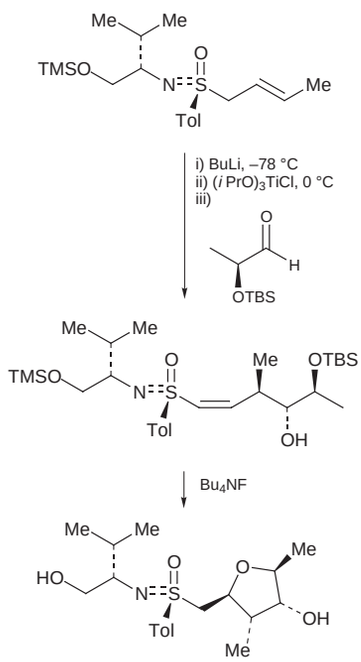
Scheme 73

The azidoselenation of alkenes offers another approach to tetrahydrofuran synthesis (Scheme 74).[185]



Scheme 74

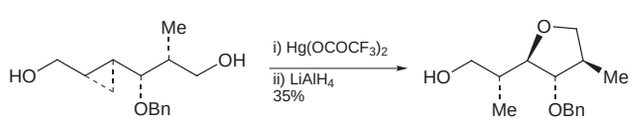
A further example of stereocontrol using group six elements is the metallation of unsaturated sulfoximines and addition to aldehydes, followed by intramolecular conjugate addition as shown in Scheme 75. Using the epimeric (at sulfur) sulfoximine and enantiomeric aldehyde four diastereoisomers of **109** were accessible.[186]



109, 61% (>97% d.e.)

Scheme 75

Following seminal work on the total synthesis of cyclopropane-containing natural products, Barrett *et al.* have investigated the opening of bi- and tercyclopropanes using mercury(II) salts. For example, treatment of **110**, derived from a biscyclopropane, with mercury(II) trifluoroacetate followed by reduction led to **111** (Scheme 76).[187]

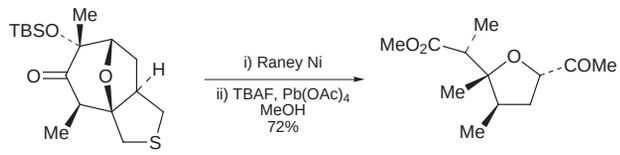


110 **111**

Scheme 76

Compounds such as **112** are easily accessible by intramolecular [5 + 2] cycloaddition reactions. Desulfurisation followed by oxidation then leads to the tetrahydrofuran **113** as a single stereoisomer (Scheme 77).[188]

Other syntheses of note include that of sesaminone, which confirms the structure and stereochemistry of the natural product.[189] Kiyota and co-workers have further refined their earlier



112 **113**

Scheme 77

synthesis of homononactic acid,[190] and a large scale synthesis of both enantiomers of 3-hydroxytetrahydrofuran has been reported.[191]

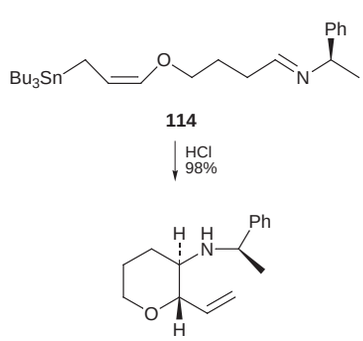
Miscellaneous other tetrahydrofuran preparations include the simple acid-catalysed cyclisation of hydroxyalkenes,[192] a tandem Claisen rearrangement-cyclisation catalysed by molybdenum[193] and an unusual reductive cleavage of a 7-oxabicyclo[2.2.1]heptane system.[194] An intramolecular Diels–Alder reaction of a furan has been used to prepare benzo[*c*]furans.[195] The reaction of a benzyl anion with a carbonyl group without competing Wittig rearrangement has been observed.[196]

5 Six membered rings

Recent highlights in total synthesis of pyrans include the synthesis of altohyrtins C and A by the Harvard groups of Evans[197] and Kishi[198] respectively.[199] These complex macrolides contain six pyran rings, although five of them are incorporated as ketals or hemiketals. Paterson has also completed a synthesis of scytophycin C[200*a*] while Kocienski's group have synthesised salinomycin.[200*b*] Kishi *et al.* have addressed some earlier limitations in their synthesis of halichondrin B with an improved synthesis of one of the tetrahydropyrans based on a Ni(II)/Cr(II) mediated coupling followed by intramolecular conjugate addition.[201] Forsyth's synthesis of okadaic acid uses a carbohydrate precursor to the pyran ring.[202]

A pentasubstituted tetrahydropyran related to phorboxazole A has been synthesised using highly diastereoselective allylations and a Sharpless epoxidation followed by a hydroxy-epoxide cyclisation[203] whereas another portion of this natural product has been prepared using a diastereoselective oxa-Diels–Alder reaction.[204]

Mori has reviewed a number of iterative approaches to fused tetrahydropyrans, including his own approach based on oxiranyl anions (see the following section) and the iterative allylstannane cyclisations of Yamamoto.[205] Yamamoto has extended his earlier work in this area with the reaction of chiral imine **114**. Optimal conditions were simply 36% aqueous HCl, which led to the formation of **115** in 98% yield, and with 92% de. Only the *trans*-isomer was obtained under these conditions (Scheme 78).[206]

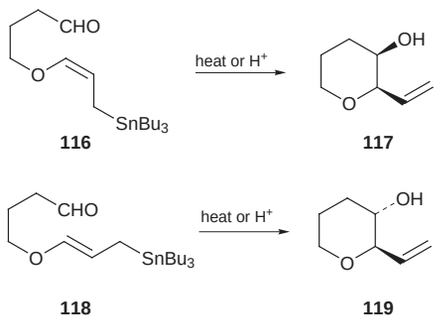


114 **115**

Scheme 78

The related cyclisations onto aldehydes occur under thermal conditions (5- and 6-membered rings) and both Lewis and pro-

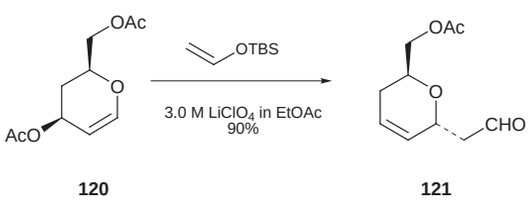
tic acid catalysis (5-, 6- and 7-membered rings). The stereochemical outcome is dependent on the reaction conditions as well as the double bond geometry of the substrate. While Lewis acid promoted reactions give *trans*-products in all cases, the (*Z*)-substrate **116** led to the *cis*-product **117** and the (*E*)-substrate **118** to the *trans*-product **119** under both thermal and protic acid conditions (Scheme 79). In the case of 5-membered ring formation, the outcome was dependent on the conditions rather than the substrate geometry.[207]



Scheme 79

Similar reactions were used in a synthesis of 1,5-dioxa-*cis*-decalin and 1,8,10-trioxa-*cis*-*syn*-*cis*-perhydroanthracene, the conformations of which were studied by NMR spectroscopy.[208]

Ferrier reaction of **120** in ethyl acetate containing 3.0 M $LiClO_4$ gave the dihydropyran **121** used in a synthesis of the C(1)–C(18) fragment of scytophycin C (Scheme 80).[209] A similar method was used in a new approach to forskolin.[210]



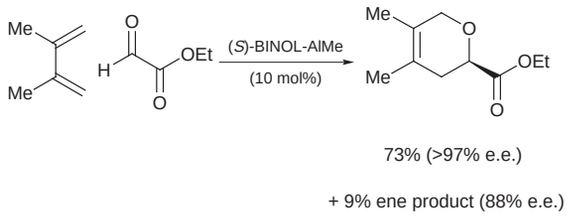
Scheme 80

The hetero Diels–Alder reaction using a carbonyl compound as dienophile is a prime candidate for Lewis acid catalysis. Bismuth(III) chloride has recently been used as a catalyst, with an ene reaction being a significant (up to 35%) competing pathway.[211] In the asymmetric ytterbium binaphthylphosphonate-catalysed process, 2,6-lutidine was shown to be an effective additive, increasing the ee from 70 to 89% in the reaction of benzaldehyde with the Danishefsky diene.[212]

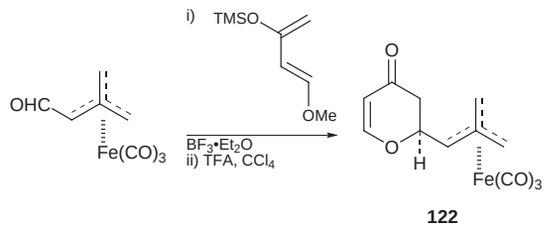
Jørgensen *et al.* have addressed the problem of competing ene reactions in carbonyl hetero Diels–Alder reactions. Using a BINOL-AlMe catalyst the ene reaction was reduced to the minor pathway, with high enantioselectivity observed for both products (Scheme 81).[213] The same group have used the copper-bis-oxazoline variation of this reaction in an asymmetric synthesis of (*R*)-dihydroactinidiolide and (*R*)-actinidiolide.[214] Zinc-bis-oxazoline complexes also catalyse this process.[215] An auxiliary-based approach to the same hetero-Diels–Alder reaction has also been reported.[216]

Dihydropyranone **122** with a pendant (trimethylene-methane)iron moiety was prepared as a single diastereoisomer in a hetero-Diels–Alder reaction with the Danishefsky diene (Scheme 82).[217]

Jacobsen *et al.* have previously demonstrated the usefulness of chromium–salen complexes in asymmetric epoxide opening, and now report that these catalysts also promote the asymmetric hetero-Diels–Alder reaction of aldehydes with the Dan-

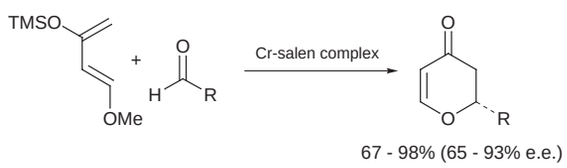


Scheme 81



Scheme 82

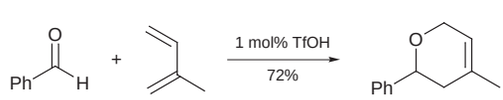
ishefsky diene (Scheme 83). This method is successful for alkyl, aryl, heteroaryl and α,β-unsaturated aldehydes.[218]



Scheme 83

Evans has reported another hetero-Diels–Alder approach to the same compounds, involving the isolation and dehydrogenation of a silyl enol ether,[219] while a further report shows that with perfluorinated aldehydes a Lewis acid is not necessary.[220] Ghosh *et al.* have prepared a C_3–C_{14} fragment of laulimalide by combination of a copper(II) bis-oxazoline-catalysed hetero-Diels–Alder reaction and Ferrier rearrangement.[221]

Aggarwal *et al.* have shown that hetero-Diels–Alder reactions of "simple" dienes such as isoprene are possible with trifluoromethanesulfonic acid as catalyst. The high regioselectivity and the fact that a Prins reaction is sometimes observed suggests that this reaction probably proceeds by a stepwise mechanism rather than a concerted one (Scheme 84).[222]



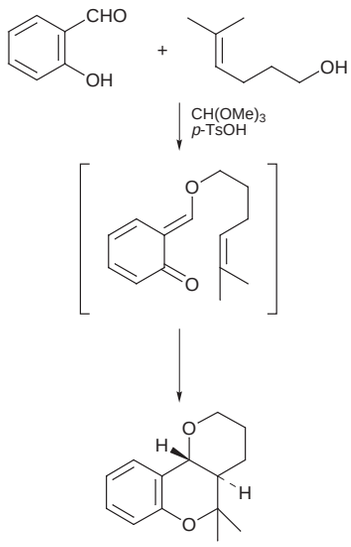
Scheme 84

Hetero Diels–Alder reactions of oxadienes are less common, although certainly not unknown. *o*-Quinomethanes are particularly strained examples, and undergo smooth cycloaddition to give fused pyrans as shown in Scheme 85 *via* an *exo*-transition state.[223]

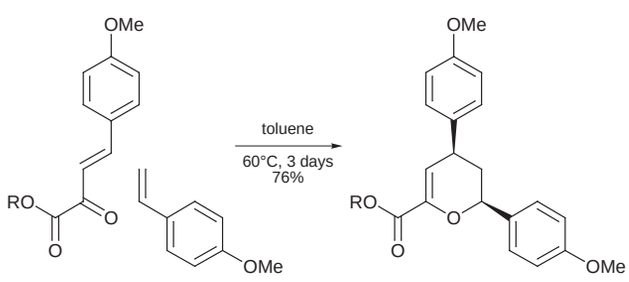
An asymmetric cycloaddition of a 1-oxadiene uses an erythronolactone ester **123**. Reaction with 4-methoxystyrene gave **124** in 76% yield with high *endo*-selectivity and 90% diastereomeric excess (Scheme 86).[224]

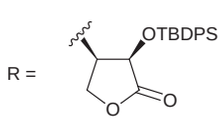
Lithiation of a sulfone such as **125** bearing a pendant hydroxy group can be followed by addition of an aldehyde or ketone. Simple cyclisation of the resulting diol then leads to functionalised unsaturated pyrans such as **126** (Scheme 87).[225]

Electrophile-initiated cyclisations have been discussed in the previous section. Greeves and co-workers have subjected hydroxy alkenes, prepared by a tandem [2,3]-Wittig rearrangement followed by anionic oxy-Cope rearrangement and subsequent reduction, to such a process leading to a stereoselective synthesis of tetrahydropyrans.[226]

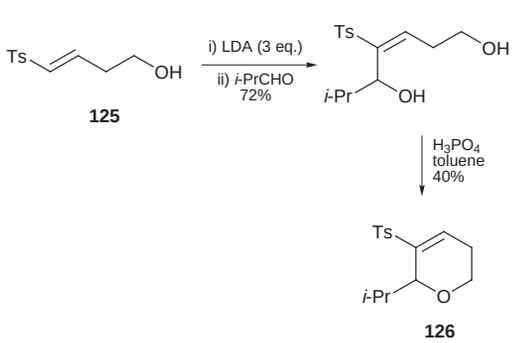


Scheme 85





Scheme 86

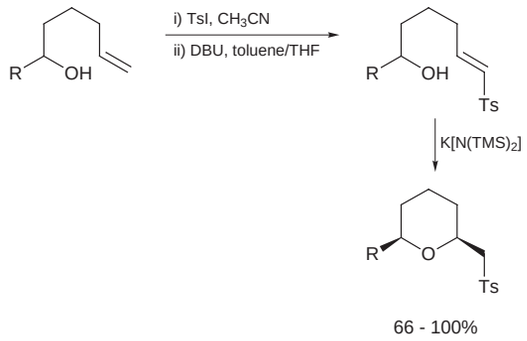


Scheme 87

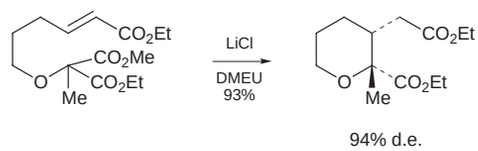
Edwards and co-workers have reported a convenient preparation of vinyl sulfones by addition/elimination of tosyl iodide to alkenes. Intramolecular conjugate addition then leads to the tetrahydropyrans in high yield and, with two exceptions, good selectivity (Scheme 88).[227]

A related reaction using a carbon nucleophile is possible by using the tandem decarboxylation/Michael addition shown in Scheme 89. As expected only the methyl ester is decarboxylated.[228]

However, the most thorough study of intramolecular conjugate addition approaches to substituted tetrahydrofurans is that of the Martín group. Starting with 1,4-diene **127**, standard transformations, including a double application of the Sharpless epoxidation, led to compounds **128** as all combinations of stereochemistry at the double bond and benzoyloxy group.



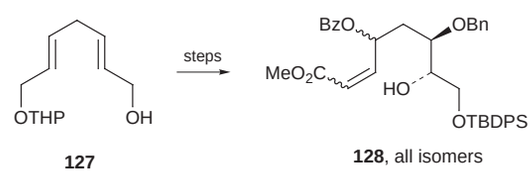
Scheme 88

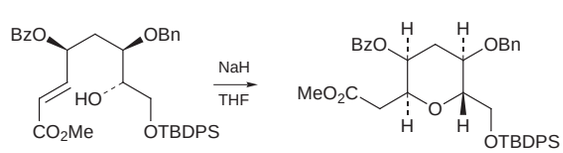


DMEU = 1,3-dimethylimidazolidin-2-one

Scheme 89

Cyclisation of the precursor with a *trans*-double bond leads to a *cis*-relationship between the new stereocentre and that adjacent (*e.g.* **129** to **130**) and *vice versa*. An almost staggering number of mono- and bicyclic compounds testify to the generality of the method (Scheme 90).[229]

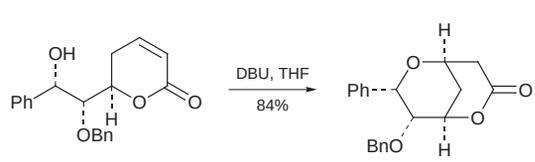




Scheme 90

A computational study complements these results,[230] and a similar approach has been used in a synthesis of the perfume component of the civet cat.[231]

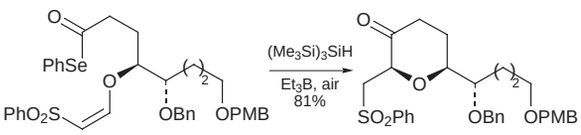
A number of members of the styryllactone natural products have been prepared. The cyclisation of **131** into benzyl-protected (+)-9-deoxygoniopypyrone **132** is shown in Scheme 91.[232,233]



Scheme 91

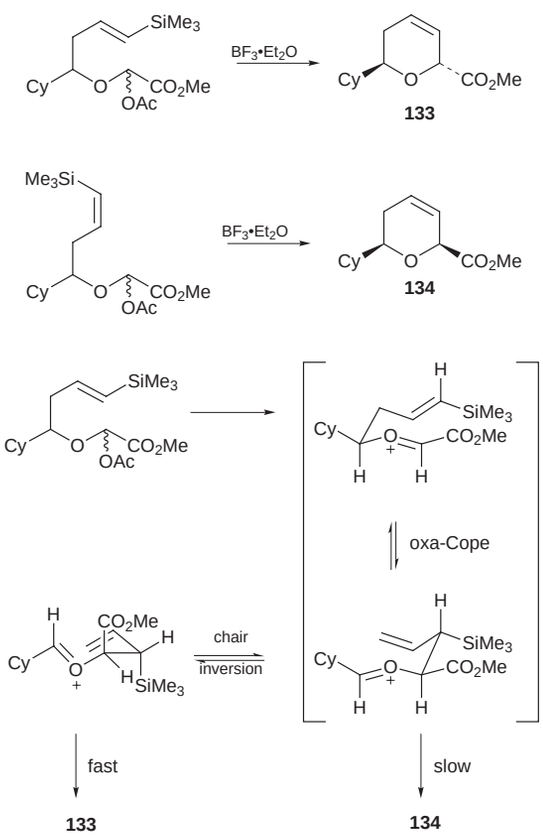
An acyl radical cyclisation (Scheme 92) has been used by Evans and Roseman in the synthesis of the hydroxylated tetrahydropyran ring of mucocin, the first acetogenin to contain such a ring. The precursor is a single enantiomer by way of Sharpless asymmetric dihydroxylation.[234]

The cyclisation of vinylsilanes onto oxycarbenium ions has been used to great effect in total synthesis by Overman and others. Markó has used this reaction in the synthesis of the bis-



Scheme 92

pyran subunit of okadaic acid.[235] Hiemstra and Speckamp *et al.* now report a dramatic effect of the double bond geometry of the vinylsilane on the stereochemistry of the product (Scheme 93). These results have been rationalised as follows (only the (*E*)-isomer is shown). The initial oxycarbenium ion is assumed to undergo an oxa-Cope rearrangement to give an allylic silane. This is then only able to undergo cyclisation if the silyl group is axial to give **133**.[236]



(Cy = cyclohexyl)

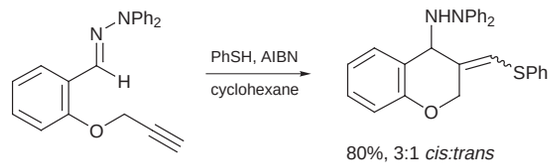
Scheme 93

Similar compounds have been prepared using an Ireland–Claisen rearrangement.[237] Others have investigated the cyclisation of alcohols onto vinylsilanes.[238] Selenoetherification has been used to form a pyranoid ring in an approach to the chrysomycins.[239]

Mead *et al.* have explored the competition between acyl and β-ring cleavage in β-lactones. For example, when **135** was treated with Me_3SiOTf–Et_3SiH, exclusive β-cleavage occurred. The observed mechanism was found to depend on a number of factors including size of ring formed (Scheme 94).[240]

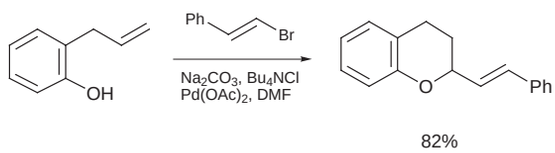
Scheme 94

While radical cyclisations are generally more efficient for five-membered rings, addition of alkenyl radicals onto hydrazones provides a route to amino substituted benzopyrans (Scheme 95).[241] A number of examples of the formation of five-membered rings by this method were also reported, only one of which was a tetrahydrofuran.



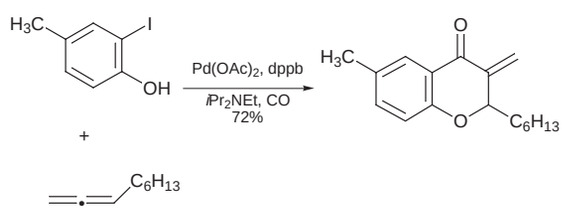
Scheme 95

Palladium catalysis of the reaction between vinylic halides or triflates with alkenyl substituted phenols gives benzopyrans, presumably *via* isomerisation of the initial adduct to a π-allyl–palladium complex (Scheme 96).[242]



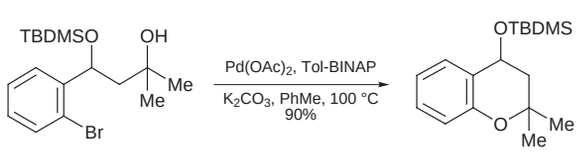
Scheme 96

Carbonylative coupling of 2-iodophenols with allenes provides an alternative route to benzopyrans (Scheme 97).[243]



Scheme 97

Palladium-catalysed C–O bond formation is a much less efficient process. Buchwald and co-workers now report that palladium acetate in conjunction with either DPPF or *p*-tolyl-BINAP and a base such as potassium carbonate or sodium *tert*-butoxide leads to the efficient formation of five, six and seven-membered rings (*e.g.* Scheme 98).[244]



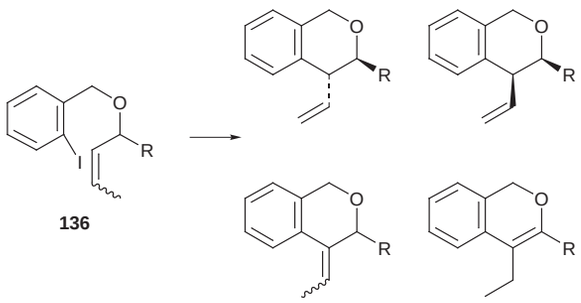
Scheme 98

Control of the regioselectivity of the β-hydride elimination step in the Heck reaction is still a challenge. Tietze *et al.* have shown that the diastereoselectivity and regioselectivity in the reactions of compounds **136** (Scheme 99) are dependent on the size of substituents and double bond geometry, and also on the reaction conditions.[245]

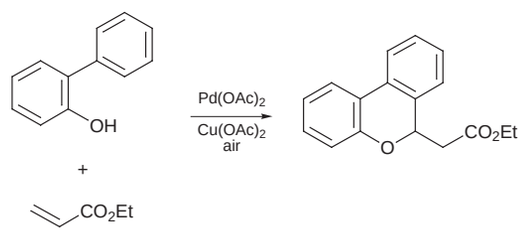
An oxidative variation involves the coupling of 2-phenylphenols with acrylate derivatives (Scheme 100).[246]

Similar heterocycles can be made by zeolite-catalysed condensation of phenols with prop-2-ynyl alcohols. The simple work-up makes this an attractive process (Scheme 101).[247]

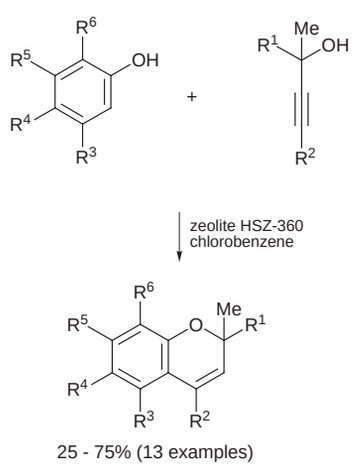
Other approaches to chromans include nitrone cycloadditions,[248] molybdenum-catalysed Claisen rearrangements[249] and an unusual example of the formation and fragmentation of a quinone ketal.[250]



Scheme 99

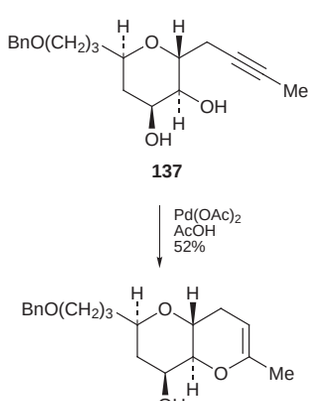


Scheme 100



Scheme 101

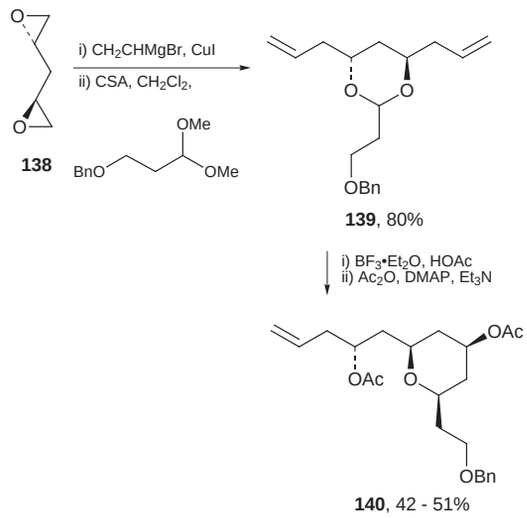
A new approach to the AB-rings of the brevetoxin natural products centres on the palladium-catalysed cyclisation of alkynol **137** (Scheme 102).[251]



Scheme 102

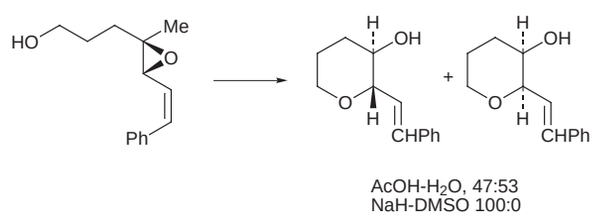
Snider and He have used a palladium-catalysed cyclisation of an alcohol onto an allene in a synthesis of rhopaloic acid A.[252]

The desymmetrisation of a C_2 symmetric diol *via* a Prins reaction has been used in a synthesis of 17-deoxyroflamycoin. Starting from the bis-epoxide **138**, double addition of vinylmagnesium bromide followed by acetal exchange gave **139**. Prins cyclisation then led to tetrahydropyran **140** (Scheme 103).[253]



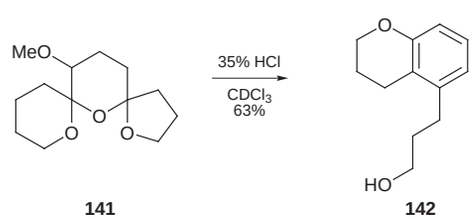
Scheme 103

Nakata *et al.* have improved upon earlier selectivities from the Nicolaou group in the *endo*-selective epoxide opening cyclisations. Exclusive 6-*endo* (and 7-*endo*) attack was observed when a styryl group was used to stabilise the build-up of positive charge in an S_N1 type transition state. Consistent with this mechanism, acid-catalysed cyclisations led to a mixture of diastereoisomers, however sodium hydride in DMSO gave complete *endo*-selectivity *and* clean inversion (Scheme 104).[254]



Scheme 104

Acid-catalysed rearrangements can still provide some surprises. This is the case with the rearrangement of various stereoisomers of **141** into **142** (Scheme 105). A plausible mechanism has been proposed.[255]

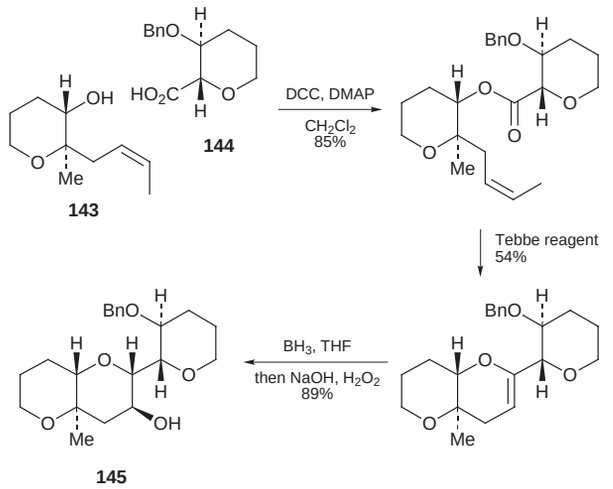


Scheme 105

The stereochemistry of the V–W ring junction of maitotoxin has been established by Kishi *et al.* by synthesis of a model compound. A combination of radical cyclisation and lactol reduction was used.[256]

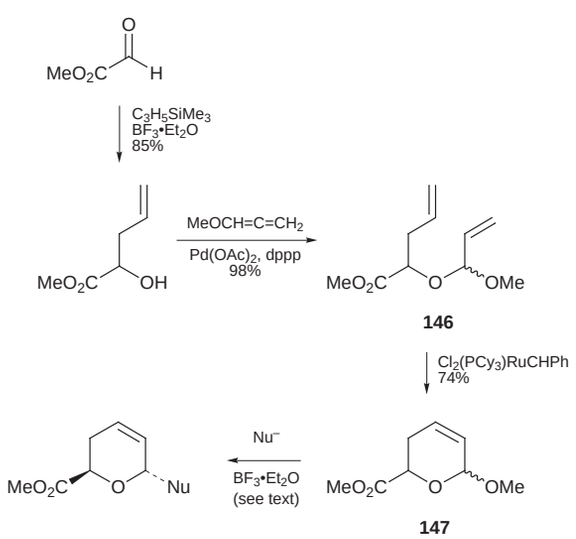
Nicolaou's group continues to pursue maitotoxin, and have applied their ester metathesis strategy to fragments corresponding to the JKL, OPQ and UVW ring systems. For example, ester formation from **143** and **144** was followed by metathesis and hydroboration to give **145** (Scheme 106).[257]

Metathesis is more commonly used for medium and large rings. However, two more examples of the use of this reaction in pyran synthesis are of note. The allylation of methyl glyoxyl-



Scheme 106

ate followed by reaction with 1-methoxypropa-1,2-diene gave substrate **146** which underwent metathesis to give lactol **147**. This was then elaborated by Lewis-acid mediated substitution of the methoxy with allyl (65%), cyano (42%) or benzoylmethyl (59%) (Scheme 107).[258] A resin-supported metathesis is a particularly elegant example of solid-phase synthesis since the ring-formation and detachment occur in a single step.[259]



Scheme 107

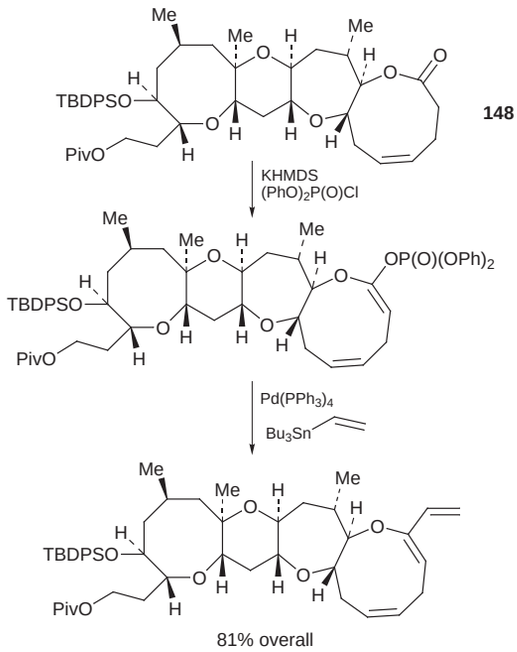
Other groups have also reported improved methods for the synthesis of pyrans from δ-lactols and their derivatives.[260]

6 Medium sized rings

Part of the fascination with medium-sized rings is a result of the difficulty often associated with the preparation of these ring systems. Transannular effects and conformations play a large role in this, and a new classification of the conformations of seven-membered rings based on their endocyclic torsion angles has been proposed.[261]

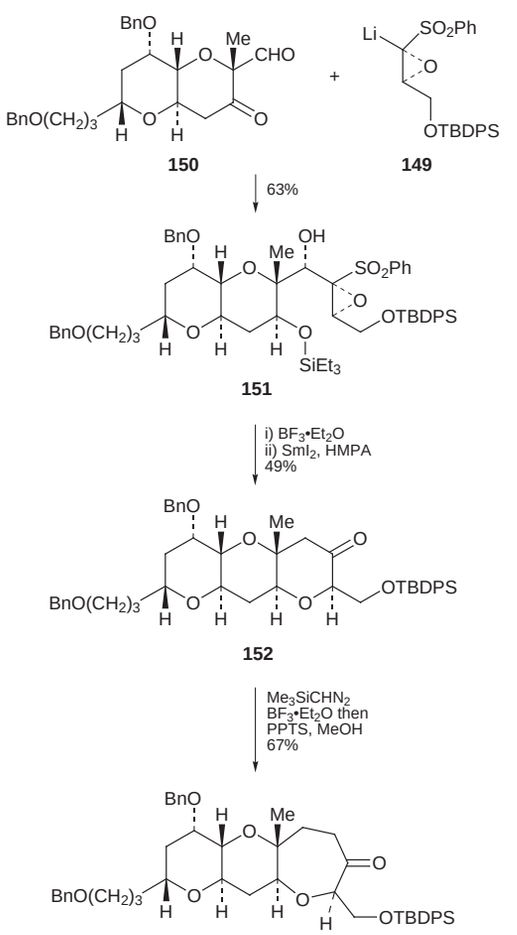
The Nicolaou group has recently completed a total synthesis of brevetoxin A,[262] making much use of the Yamaguchi lactonisation and enol phosphate cross-couplings.[263] For example, the oxonane E ring, probably the most challenging ring in the molecule, was prepared from **148** by reaction with KHMDS and $(PhO)_2P(O)Cl$ followed by cross-coupling with tributylvinyltin (Scheme 108).

Mori *et al.* have accomplished a formal total synthesis of hemibrevetoxin B using oxiranyl anion chemistry and ring expansions. For example, addition of **149** to **150** gave **151**.



Scheme 108

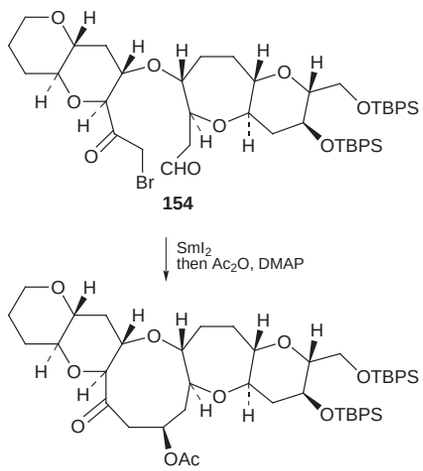
Lewis-acid promoted cyclisation followed by removal of the hydroxy group gave **152** which underwent a one-carbon ring expansion to give **153** (Scheme 109). The fourth and final ring was constructed in a similar way to converge with Yamamoto's earlier synthesis of the same natural product.[264]



Scheme 109

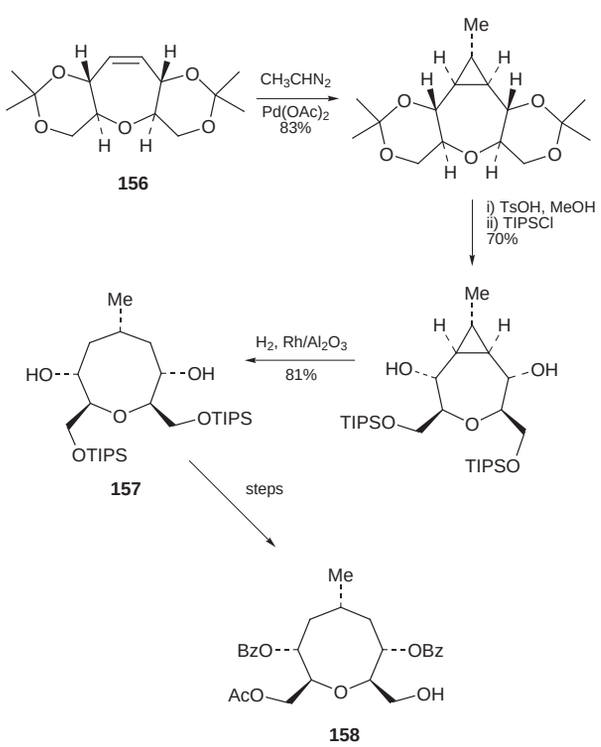
While total syntheses of hemibrevetoxin and brevetoxins A and B have now been reported, no total synthesis of ciguatoxin

has been disclosed at this time. As with brevetoxin A, the nine-membered ring is often considered to be the cause of the problems. Inoue, Sasaki and Tachibana have used an intramolecular Reformatsky reaction of **154** to provide **155** in high yield (the yield over 5 steps including this one was 66%) (Scheme 110). This compound was subsequently elaborated into a target containing eight of the thirteen rings of ciguatoxin almost fully functionalised.[265]



Scheme 110

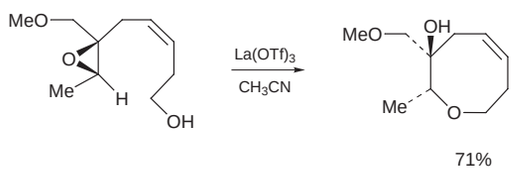
Hirama and co-workers have also reported an approach to the HIJ ring system of ciguatoxin. Palladium-catalysed cyclopropanation of oxepine **156** was followed by protecting group manipulation, and ring expansion gave **157**. Further protecting group manipulation set the stage for an enzymatic desymmetrisation to give **158** with 92% ee (Scheme 111).[266]



Scheme 111

The H and J rings were then fused onto this fragment by hydroxy-epoxide cyclisations, one palladium-catalysed, the other acid-catalysed.[267] The same group have used Yamamoto's allylstannane cyclisation to prepare an AB ring fragment of ciguatoxin in order to determine the absolute stereochemistry of the C2 hydroxy group by the CD exciton chirality method.[268] Murai *et al.* have reported a GH ring fragment of ciguatoxin by Baeyer–Villiger oxidation of a cyclohexanone precursor followed by enol triflate cross coupling similar to that used in Nicolaou's brevetoxin A synthesis[269] and an ABC ring fragment by intramolecular conjugate addition and epoxide opening.[270]

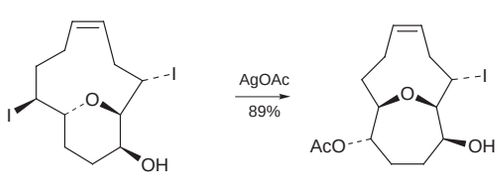
Meanwhile, more related ciguatoxins have been isolated.[271] Since these natural products are believed to arise from epoxide opening on a grand scale, controlling the selectivity of such epoxide openings is a common aim in synthetic studies. Chelation of the epoxide oxygen and a suitably disposed methyl ether with lanthanum triflate leads to a dominance of the 7-*endo* pathway over the 6-*exo*, and even, when the substrate contains a double bond, 8-*endo* over 7-*exo* (Scheme 112).[272] A 7-*exo* cyclisation was also used to prepare an ABC ring fragment of ciguatoxin.[273]



Scheme 112

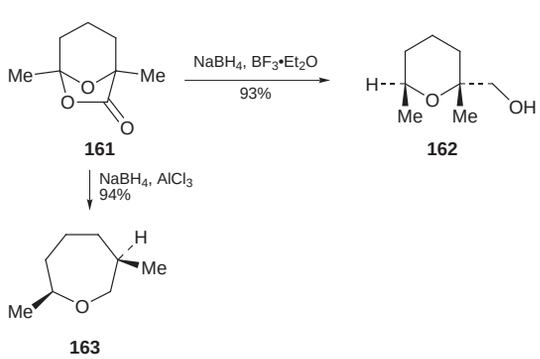
It is possible to use a dicobalt hexacarbonyl–alkyne complex to direct intramolecular epoxide opening towards the "anti-Baldwin" product, although only six-membered rings were formed in work by Mukai *et al.*[274] A full account of Isobe's earlier work on the use of dicobalt hexacarbonyl complexes of glucal derivatives has also appeared.[275]

Compound **159** undergoes ring expansion *via* the oxiranium ion to give **160** upon treatment with silver acetate (Scheme 113).[276] Murai and co-workers have undertaken a detailed study to delineate the factors which affect the ring size formed in a wide range of epoxide-related ring expansions.[277]



Scheme 113

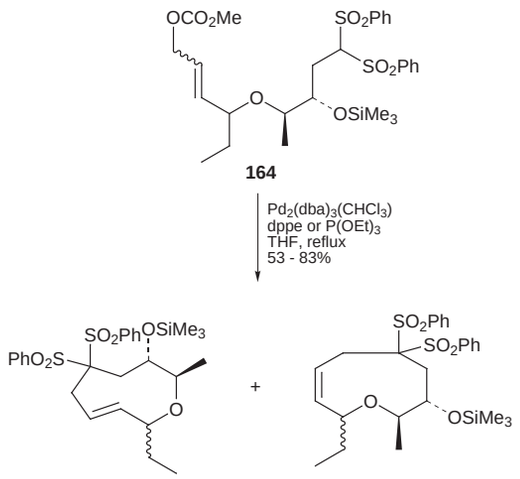
Jun and Lee have observed remarkable selectivity in the ring expansion of lactone ketal **161**. Treatment with $NaBH_4$–$BF_3{\cdot}Et_2O$ gave the pyran **162** while simply changing the Lewis acid to $AlCl_3$ gave exclusively the oxepane **163** (Scheme 114).[278]



Scheme 114

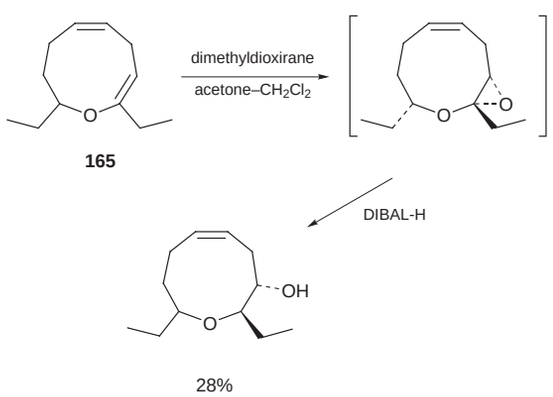
The complexities inherent in π-allylpalladium chemistry are highlighted in work by Hoffmann *et al.* whereby the precursors

164 are subjected to cyclisation. All possible double bond and 2,9-stereoisomers were obtained, the ratios being very sensitive to reaction time and additional ligands as well as the geometry of the double bond in the starting material (Scheme 115).[279]



Scheme 115

An interesting, if low yielding, approach to oxonenes related to the *Laurencia* natural products uses the epoxidation/reduction of enol ether **165**. Essentially pure epoxides were formed in the first step, so presumably the loss in yield occurs during reduction (Scheme 116).[280]



Scheme 116

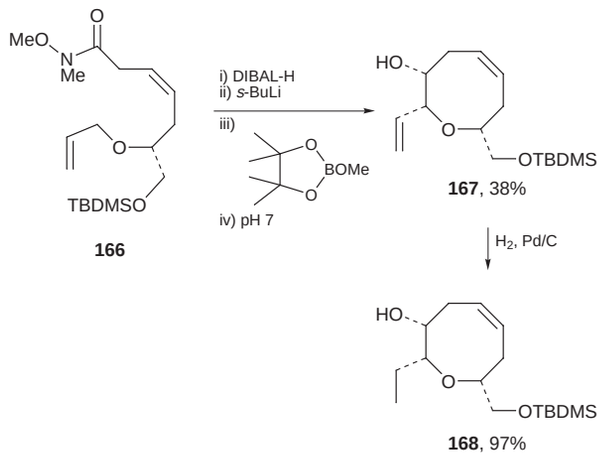
In other work on *Laurencia*-derived natural products, Murai *et al.* has reported both chemical and enzymatic conversions of prelaureatin into laurallene,[281] and full accounts of Overman's synthesis of isolaurepinnacin[282] and Holmes' synthesis of laurencin[283] have appeared.

Hoffmann has reported an approach to laurencin which converges with that of Holmes. Thus **166**, prepared from unnatural diethyl malate, was converted into the oxocine in a one-pot procedure involving reduction of the Weinreb amide to the aldehyde, conversion of the allyl ether into the allylboronate and cyclisation to give **167**. Careful hydrogenation then gave **168**. Replacement of the TBDMS protecting group with TBDPS gave a compound which has been converted into laurencin in only nine steps, so that this constitutes a formal total synthesis of the natural product (Scheme 117).[284]

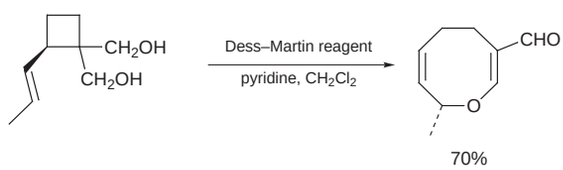
Enantiomerically pure oxocanes are accessible from vinylcyclobutanecarbaldehydes in a retro-Claisen rearrangement (Scheme 118). The precursor was prepared by allylic displacement of an enzymatically resolved alcohol.[285]

A similar rearrangement of divinyloxiranes derived from cycloheptatriene endoperoxides gives dihydrooxepines.[286]

Reaction of lactol acetates **169** with trimethylsilyl cyanide gives rise to cyclic cyanohydrin ethers **170**. These can then be allylated and the cyanide reductively removed. Almost no

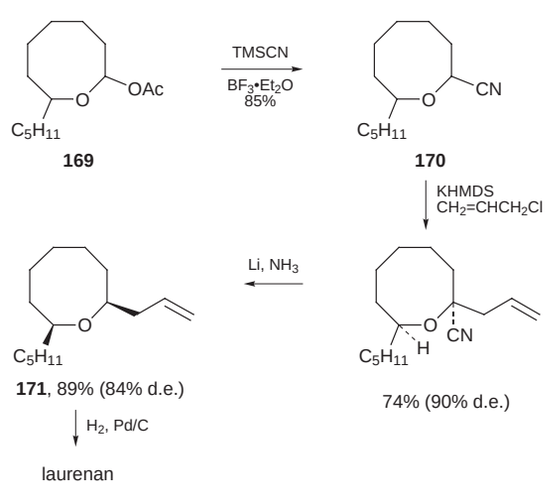


Scheme 117



Scheme 118

diastereoselectivity was observed in the case of five and seven-membered rings, in contrast to six and eight ring oxacycles. Compound **171** was hydrogenated to give laurenan (Scheme 119).[287]

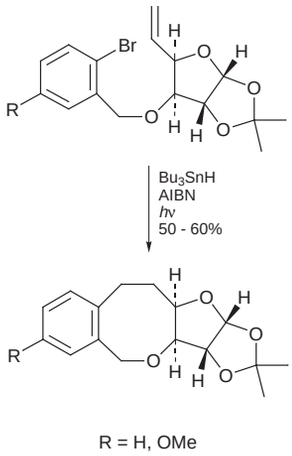


Scheme 119

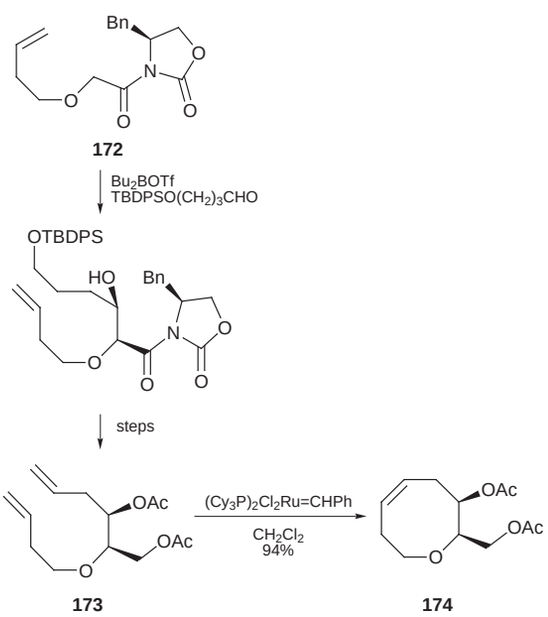
Oxocanes have also been prepared in 50–60% yield by an 8-*endo* radical cyclisation. The rigidity imposed on the precursor by the aromatic and tetrahydrofuran rings presumably assists the cyclisation (Scheme 120).[288]

Both the Evans oxazolidinones and ring-closing metathesis are well established techniques in organic synthesis. Crimmins and Choy now report an elegant combination of these methodologies to prepare six to nine membered cyclic ethers. For example, aldol reaction of **172** was followed by routine transformations to provide **173**, ring-closing metathesis of which gave the oxocane **174** in an impressive 94% yield (Scheme 121).[289]

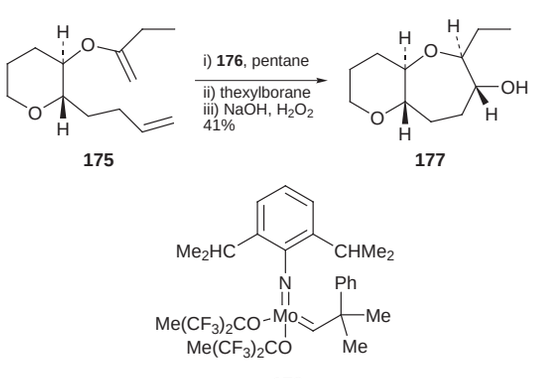
Clark and Kettle have reported examples of ring-closing metathesis of vinyl and allyl ethers in studies related to the brevetoxin natural products. For example, treatment of **175** with catalyst **176** was followed by hydroboration–oxidation to give **177** (Scheme 122).[290] Martín *et al.* have also used metathesis to prepare similar fused oxacycles.[291]



Scheme 120



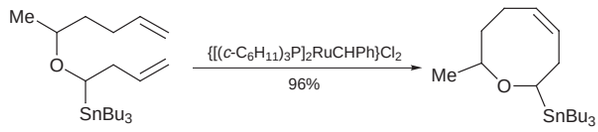
Scheme 121



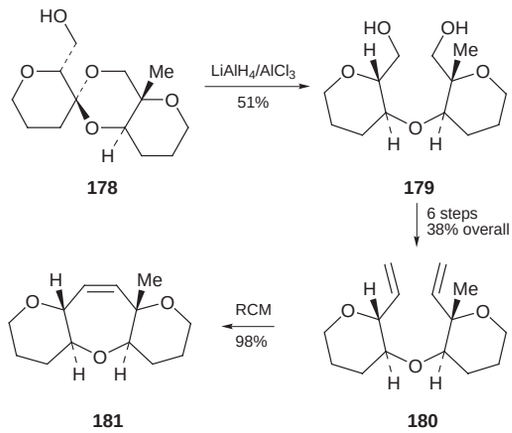
Scheme 122

Linderman and co-workers have used a tributyltin substituent as a conformational bias in metathesis reactions where medium-sized rings are targeted. Eight membered rings were formed in up to 96% yield by this method (Scheme 123).[292]

Another approach using ring-closing metathesis is that of Hirama, in which a diol precursor **179**, formed by $LiAlH_4$–$AlCl_3$ reduction of acetal **178** , is oxidised and methylenated to give **180** (Scheme 124). Metathesis then proceeded as anticipated to give the 6-7-6 fused ring system **181**.[293]



Scheme 123



Scheme 124

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