REVIEW

# Saturated oxygen heterocycles

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***Received (in Cambridge, UK) 14th May 1999***

Covering: 1 April 1998 to 30 June 1999. Previous review: *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 4175.[1]



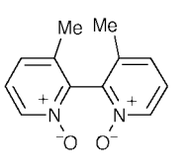
## 1 Introduction

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

## 2 Three-membered rings

Epoxidations can be divided into reactions involving oxygen transfer to alkenes, those involving formal carbene transfer to carbonyls, and cyclisation reactions. The latter two categories are often blurred by the fact that most epoxidations by carbene transfer involve a nucleophilic attack on the carbonyl followed by ring closure (*e.g.* Darzens reactions). However, the formation of epoxides will be broadly treated within these categories.

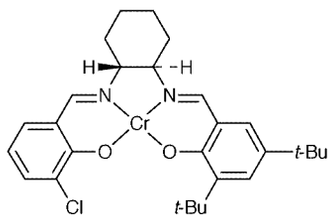
The mechanism of the Jacobsen–Katsuki epoxidation continues to stimulate discussion[2] and computational studies.[3] Miura and Katsuki have improved upon the chemical yields and enantioselectivity in the use of achiral Mn(salen) complexes in conjunction with external chiral modifiers. (+)-3,3′-Dimethyl-2,2′-bipyridine *N*,*N*′-dioxide **1** provided epoxides in up to 90% yield and with 83% ee.[4]




**1**

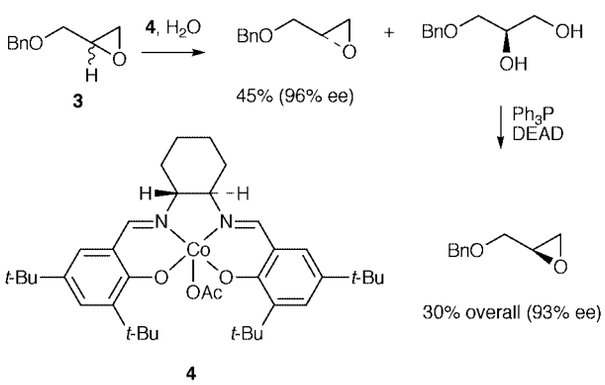
Cr(salen) complexes are complementary to Mn(salen) complexes in that they give higher enantioselectivity for *E*-alkenes. Almost any substituent at the 3 and 3′ positions leads to high enantioselectivity, although halogen substituents gave higher yields.[5] The enantiomeric excess using unsymmetrical salen ligands, *e.g.*, **2**, shows a dramatic sensitivity to added triphenylphosphine oxide. This has been ascribed to *pseudo* $C_2$ symmetry in which there are two diastereomeric oxidants. Selective binding of triphenylphosphine oxide to one of these diastereoisomers would explain this observation.[6]

Jacobsen and co-workers' use of Co(salen) complexes in the enantioselective ring opening of epoxides[7] (to leave behind




**2**

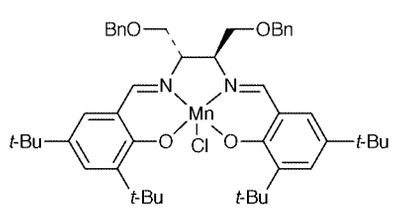
enantiomerically enriched unreacted epoxide) has been used by Gurjar and co-workers in the resolution of benzylglycidol **3**. The advantage of this approach is that the ring-opened product can be readily closed back to the epoxide, so that both enantiomers can be accessed (Scheme 1).[8] This type of reaction is second order in Co(salen) complex **4**, and so Jacobsen and co-workers have been able to design dimeric catalysts which are able to catalyse the azide ring-opening of epoxides at catalytic concentrations an order of magnitude lower than with monomeric catalysts.[9]




**Scheme 1**

This approach has been used to prepare a key intermediate for the synthesis of the annonaceous acetogenin corossilin,[10] and to prepare long chain alkyl epoxides.[11] More conventional enzymic epoxide resolutions have also been reported.[12]

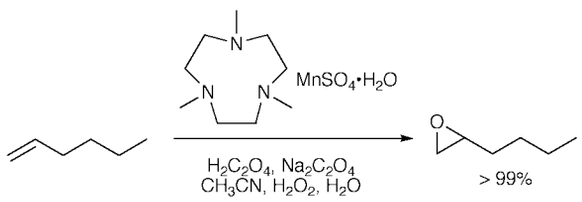
The new manganese complex **5** with oxygen functionality on the backbone gives moderate enantiocontrol in epoxidation reactions, but in all cases gives the opposite major enantiomer to that obtained using the more common Jacobsen ligands.[13]




**5**

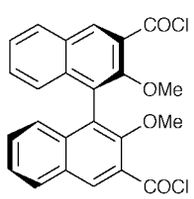
DOI: 10.1039/a903885j

A new procedure involving manganese complexes in epoxidation reactions utilises 1,4,7-trimethyl-1,4,7-triazacyclononane as a ligand. While this complex has been previously used to decompose peroxides, it was found not to be suitable for epoxidation. De Vos *et al*. made the key observation that conducting the reaction in an oxalate buffer suppresses peroxide disproportionation resulting in high yields for the epoxidation of terminal olefins (Scheme 2).[14] Similar results have been obtained by Pietikäinen using manganese–salen complexes (up to 96% ee with hydrogen peroxide as terminal oxidant).[15] Tetrabutylammonium monopersulfate also serves as oxidant with *N*-methylmorpholine *N*-oxide as additive.[16] A further approach uses dimethyldioxirane as terminal oxidant with more conventional salen ligands.[17]




**Scheme 2**

Collman *et al*. have used a novel chiral iron porphyrin with 2-aminophenyl substituents linked with biaryl diacid chloride **6**. This catalyst showed highest enantioselectivity for terminal olefins (*e.g.* styrene, 83% ee). The enantioselectivity increases to a plateau during the course of the reaction, with mass spectrometric and kinetic data supporting modification of the biaryl moiety by oxidation to a more selective catalyst.[18] Chiral ruthenium porphyrin catalysts have been used in alkene epoxidation with fair (<77%) enantioselectivity.[19]



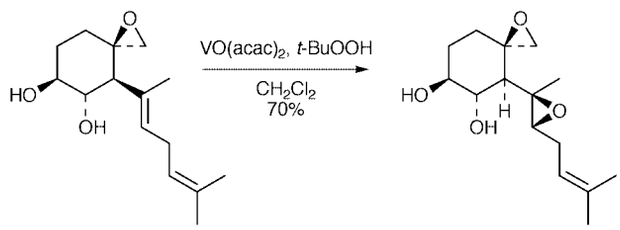

**6**

Espenson has reviewed atom transfer reactions catalysed by methyltrioxorhenium.[20] A recent report shows that epoxidations using this catalyst are particularly efficient in 2,2,2-trifluoroethanol.[21] Various additives have been studied in this reaction,[22] with pyrazole and 3-cyanopyridine proving optimal.[23] The stereoselectivity of epoxidations using this catalyst have also been investigated,[24] and the reaction has also been studied computationally.[25]

Epoxidation of cyclic alkenes using $TiO_2$–$SiO_2$ aerogels gives low yields of epoxides as a result of acid-catalysed side reactions. However, treatment of the aerogel with amines suppressed these reactions to give excellent selectivity in the epoxidation of 3-methylcyclohex-2-en-1-ol with *tert*-butyl hydroperoxide.[26] A ruthenium porphyrin immobilised in mesoporous molecular sieves shows high activity and selectivity, even for relatively sensitive epoxides.[27]

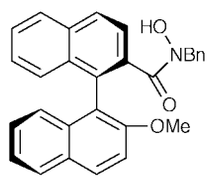
While supercritical $CO_2$ is becoming increasingly popular as a solvent, for the epoxidation of allylic alcohols with *tert*-butyl hydroperoxide–$VO(O^iPr)_3$ there is no need to go above the critical point to achieve good selectivity.[28] Manganese complexes have also been used in supercritical $CO_2$. However, since alkyl hydroperoxides homolytically decompose in the presence of Mn(III) salts, Haas and Kolis used a vanadium–salen complex to catalyse the epoxidation of allylic alcohols.[29]

FR65814 is a novel immunosuppressant containing two oxirane rings. The spiro epoxide was prepared as a single diastereoisomer using the Corey–Chaykovsky reaction. Completion of the synthesis required chemo- and diastereoselective epoxidation as shown in Scheme 3.[30] The Corey–Chaykovsky reaction has been investigated computationally, with pathways involving *anti* addition or torsional rotation calculated to be more favourable than a concerted mechanism.[31]



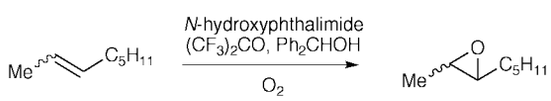

**Scheme 3**

It is largely due to the pioneering work of Sharpless that titanium is most commonly associated with the asymmetric epoxidation of allylic alcohols. Sherrington and co-workers have reported a modified Sharpless procedure using branched/crosslinked polytartrate ester ligands. Enantioselectivities of up to 98% ee were obtained.[32] In other work, Yamamoto and co-workers have shown that ligand **7** gives modest to good selectivity (38–94% ee) using vanadium(v) triisopropoxide and trityl hydroperoxide.[33] Francis and Jacobsen have demonstrated a combinatorial approach to the discovery of metal complexes for asymmetric epoxidation.[34]



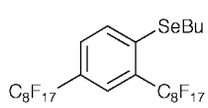

**7**

The use of highly fluorinated catalysts in organic synthesis is attractive since these compounds tend to be only sparingly soluble in common organic solvents. In the case of epoxidation of alkenes with hydrogen peroxide catalysed by perfluoroheptadecan-9-one, the catalyst can be recovered at the end of the reaction simply by filtration of the cooled reaction mixture.[35] This system is about four times as active as hexafluoroacetone as an epoxidation catalyst. However, this latter system has been shown to be advantageous in the epoxidation of oct-2-ene using oxygen as terminal oxidant. The combination of benzhydrol, *N*-hydroxyphthalimide and hexafluoroacetone leads to high yields of the epoxide at only one atmosphere pressure of oxygen (Scheme 4).[36]



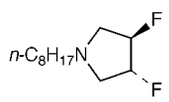

**Scheme 4**

The toxicity of selenium compounds often limits their industrial use. Knochel and co-workers have recently demonstrated a fluorous selenium compound **8** which is an efficient catalyst for alkene epoxidation in a fluorous biphasic system with hydrogen peroxide as terminal oxidant.[37]




**8**

Modified Mn(salen) ligands with fluorous side-chains have also been used in epoxidation reactions. Carrying out the epoxidations in a fluorous biphasic system allowed the use of molecular oxygen as terminal oxidant.[38] In another epoxidation reaction involving fluorinated species, compound **9** was found to be an effective source of chirality in a Sharpless-type epoxidation of geraniol (66% ee).[39] Manganese(III) acetate has also been used as a catalyst in fluorinated solvents with molecular oxygen/pivalaldehyde as oxidant.[40] Square planar nickel(II) complexes have also been used with the same terminal oxidant.[41]



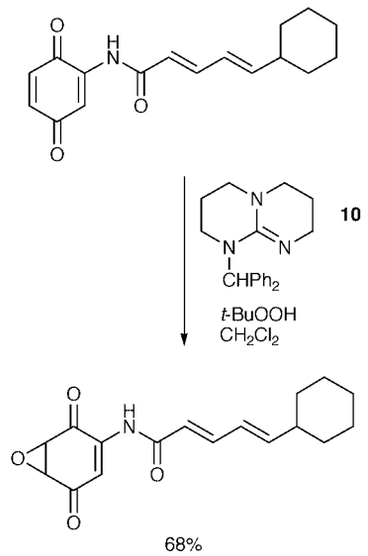
**9**

The Juliá-Colonna reaction is rapidly becoming the *de facto* method for the asymmetric epoxidation of electron-deficient alkenes.[42] Roberts and co-workers have recently reported a variation which allows this reaction to be carried out under continuous flow in a fixed-bed reactor.[43] The same group have used PEG-supported polymers of defined length to offer mechanistic insight into the reaction. Using polymers consisting of both D and L-leucine supported at the C-terminus, they suggest that a C-terminus of 5–15 amino acids is necessary to correctly define the shape of the N-terminus to permit good asymmetric induction.[44] This method has been applied to furyl styryl ketone, leading to the synthesis of (+)-goniofufurone and related compounds,[45] and also to the synthesis of 1,2,3,4-tetrahydro-4-quinolones.[46]

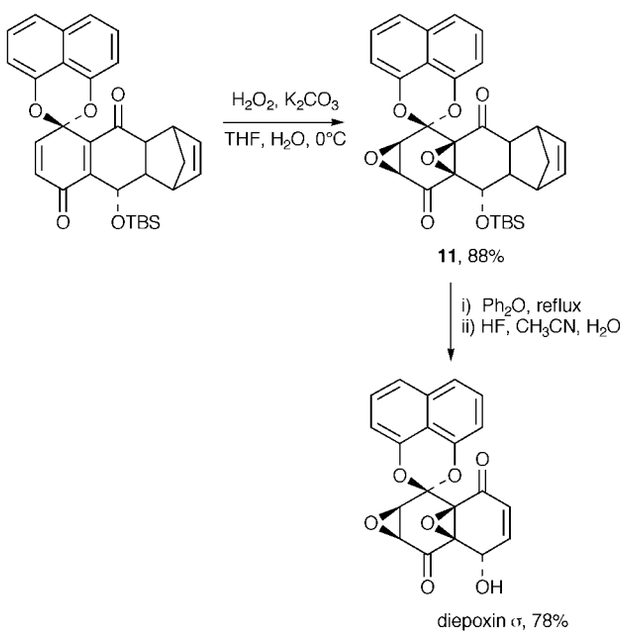
Building on earlier work by Lygo's group,[47] Arai and co-workers have used cinchonidinium salts as phase transfer catalysts for the asymmetric epoxidation of chalcones (up to 92% ee)[48] and naphthoquinone derivatives (up to 76% ee).[49] The same catalysts have been used in asymmetric Darzens reactions with up to 86% ee.[50] The work of Taylor and co-workers have shown epoxyquinones to be particularly sensitive to base, and so mild methods for the epoxidation of electron-deficient alkenes were required. They found the use of 1,5,7-triazabicyclo[4.4.0]dec-5-ene **10** in conjunction with *tert*-butyl hydroperoxide to be particularly efficient. One example of this reaction is shown in Scheme 5. Preliminary results towards an asymmetric version of this reaction (≤35% ee) were also reported.[51] In the synthesis of the highly oxygenated diepoxin σ, Wipf and Jung used hydrogen peroxide–potassium carbonate to prepare an advanced intermediate **11** which was converted into the natural product by retro-Diels–Alder elimination of cyclopentadiene (Scheme 6).[52]

Unsaturated sulfoxides, sulfones and related compounds have also been targets for epoxidation. In the work of Jackson and co-workers, the epoxidation of **12** and **14** was found to be sensitive to both the alkyl group and metal in the metal alkyl peroxide used as oxidant. While the results are not easily rationalised, use of lithium triphenylmethyl peroxide gave identical selectivity with either stereoisomer at sulfur, potassium *tert*-butyl peroxide gave the expected double asymmetric induction (Scheme 7). The corresponding sulfone gave a 5:4 mixture of isomers with $Ph_3COOLi$ and 4:1 with *t*-BuOOK.[53] Others have used similar oxidants with (*Z*)- and (*E*)-vinylsulfoxides.[54] Ray and Roberts have shown that poly-L-leucine and poly-D-leucine can be used to overcome the intrinsic diastereoselectivity of epoxidation of the analogous glyceraldehyde-derived enone.[55]

Incorporation of *tert*-butoxide between the layers of hydrotalcite by anion exchange results in an efficient catalyst for the epoxidation of electron deficient and unfunctionalised alkenes, in most cases within 30 minutes. Extended reaction times led to some loss of yield.[56] Addition of isobutyramide and sodium dodecyl sulfate to hydrotalcites also leads to an effective epoxidation catalyst.[57]



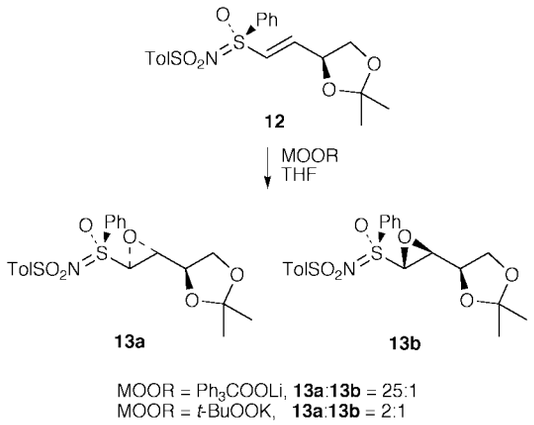

**Scheme 5**

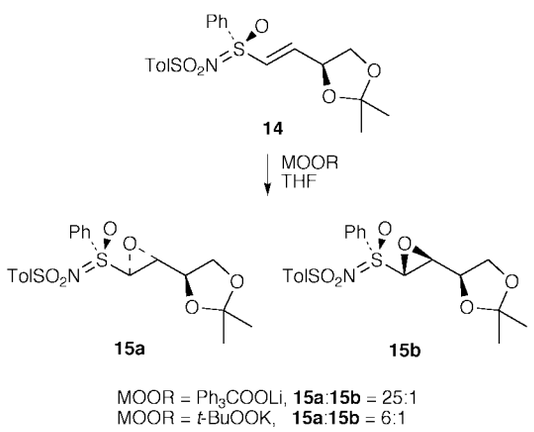



**Scheme 6**

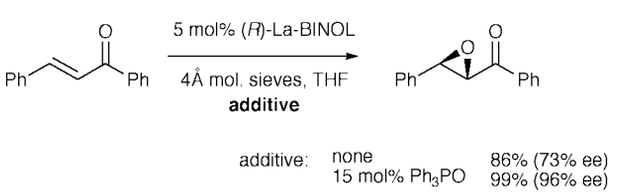
Lanthanoid–BINOL complexes have been pioneered in asymmetric synthesis by Shibasaki and co-workers. Even though the reaction is conducted in the presence of 4 Å molecular sieves, Shibasaki has found that addition of water (4.5 equivalents relative to ytterbium) improved both the yield and enantioselectivity of this process.[58] Others have noted the effect of triphenylphosphine oxide on the reaction (Scheme 8).[59] The epoxidation of (*Z*)-enones is complicated by the tendency of these compounds to form *trans*-epoxides. An ytterbium–BINOL complex proved effective for the formation of *cis* epoxides with high enantioselectivity (>99% ee). Formation of the *trans* epoxides (20–30%) was still a problem with aromatic (*Z*)-enones.[60] Chloroperoxidase has also been used for the epoxidation of functionalised (*Z*)-alkenes, *e.g.* **16** (Scheme 9). While the stereoselectivity was almost uniformly high, yields were variable (28–95%).[61]

Dioxiranes are becoming increasingly popular as oxidising agents,[62] especially with the recent discovery of several homochiral dioxiranes which exhibit high enantioselectivity towards alkenes. Shi and co-workers have prepared a range of ketones as

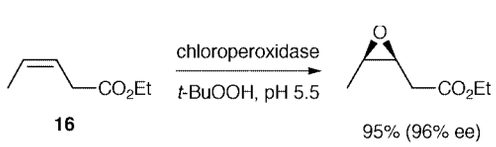


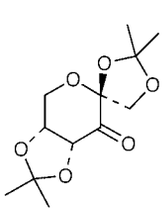

**Scheme 7**




**Scheme 8**

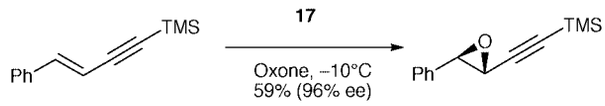



**Scheme 9**



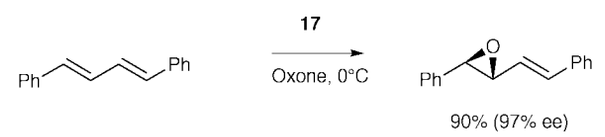

modified versions of the highly effective dioxirane precursor **17** with the reaction proving tolerant to a wide range of ketals.[63]

Although such epoxidation reactions are normally carried out under extremely mild basic conditions, Shi and co-workers have shown that more strongly basic conditions can be advantageous. This has been attributed to competition of direct epoxidation by Oxone at lower pH.[64] Chemoselective epoxidations are always of interest, and Shi and co-workers have reported the selective epoxidation of enynes shown in Scheme 10.[65] The same catalyst has been used for epoxidation of enol ethers and enol esters *en route* to α-hydroxyketones (up to 95%




**Scheme 10**

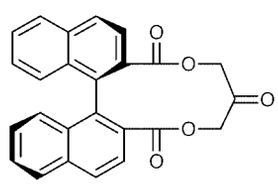
ee).[66] Epoxidation of dienes generally takes place with high chemoselectivity for the more nucleophilic double bond, and even with symmetrical dienes the mono-epoxide can be obtained in high yield (*e.g.* Scheme 11).[67]



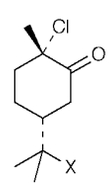

**Scheme 11**

Yang *et al.* have described in detail the development of ketone **18** and related compounds as dioxirane precursors.[68]

The same group have produced surprisingly linear Hammett plots for the enantioselectivity of epoxidation of (*E*)-stilbene by dioxiranes derived from ketones **19** (X = F, Cl, OH, OEt, H).[69]

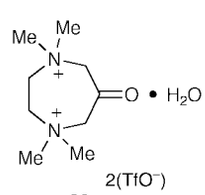


**18**

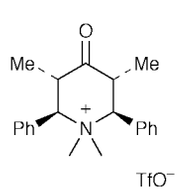


**19**

The use of 4-oxopiperidinium salts as dioxirane precursors has been extensively investigated by Denmark and Wu. The recently reported diazepanediium salt **20** is a particularly efficient catalyst for alkene epoxidations by Oxone, being resistant to Baeyer–Villiger oxidation, and catalyses the decomposition of Oxone at a dramatic rate.[70] One of the problems with such catalysts is the non-productive decomposition of Oxone, so that large excesses of Oxone are often needed. Yang and co-workers have reported new ketones such as **21** which efficiently catalyse the epoxidation of alkenes with only 1.5 equivalents of Oxone.[71]



**20**

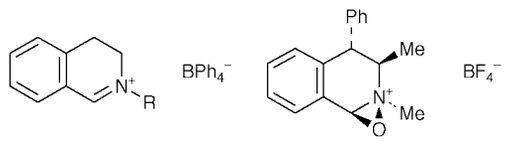


**21**

The mild conditions and simple work-up procedures associated with dimethyldioxirane allow the isolation of sensitive epoxides, including two diastereoisomers of cyclooctatetraene tetraepoxide.[72] Computational evidence continues to accumulate for dimethyldioxirane epoxidation, suggesting that for 1,1-disubstituted alkenes (as well as other alkene types) the epoxidation takes place *via* a concerted pathway rather than a biradical pathway.[73] While the "butterfly" transition state seems almost universally accepted, with monosubstituted and *trans* alkenes the C–O bond formation appears to be asynchronous.[74]

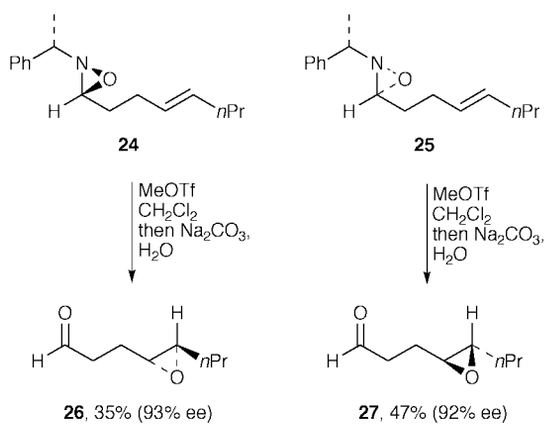
The synchronicity of epoxidations using peroxyformic acid has also been investigated computationally.[75]

Page *et al*. have used chiral iminium salts of general structure **22** as catalysts for asymmetric epoxidation. The optimum enantioselectivity (73% ee for the formation of stilbene oxide) was found for R = isocamphenyl.[76] Bohé *et al*. chose to isolate the oxaziridinium salt **23** prior to using it in epoxidation reactions (up to 61% ee for stilbene oxide).[77]




**22** **23**

Armstrong *et al*. have shown that exocyclic iminium salts are efficient catalysts for alkene epoxidation, although preliminary attempts to render the process asymmetric were fraught with problems.[78] In related work, Armstrong and co-workers have demonstrated intramolecular oxygen transfer from an oxaziridinium ion. Thus, **24** and **25** were formed by Oxone oxidation of the corresponding imine and separation of diastereoisomers. Upon quaternisation of the nitrogen with methyl triflate, oxygen transfer took place to give, after hydrolysis, **26** and **27**, both with good enantiomeric excess (Scheme 12).[79]

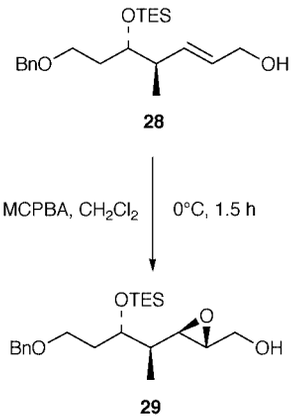



**Scheme 12**

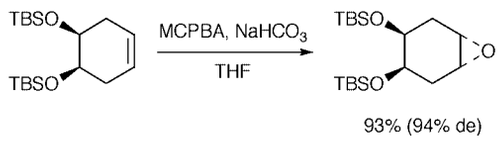
Diastereoselective epoxidations can be particularly sensitive to protecting groups. For instance, while the MOM-protected secondary alcohol gave only 18% de, use of the TES protecting group in **28** gave the epoxide **29** in 82% yield and 90% de (Scheme 13). A number of related substrates, both *syn* and *anti*, were examined with similar success.[80] Hexafluoroacetone perhydrate offers superior diastereoselectivity to MCPBA or dimethyldioxirane in some cases.[81] While allylic alcohols can usually be epoxidised with high diastereoselectivity, some alcohols show poor reactivity and/or selectivity. Allylic strain has been used to explain some of these reactions.[82] Adam and co-workers have compared a range of catalysts, including manganese–salen complexes, iron porphyrins, titanium and vanadium salts, peracids and dioxiranes, for the epoxidation of allylic alcohols. In general, alcohols with 1,3-allylic strain gave *threo* epoxides, although as expected from such a structurally diverse range of catalysts, the results were extremely catalyst-dependent.[83]

Solvent effects play a significant role in epoxidation reactions. For example, the reaction shown in Scheme 14 showed almost no diastereoselectivity in dichloromethane.[84] Epoxidation of a number of similar compounds was investigated with MCPBA and Oxone–1,1,1-trifluoroacetone as oxidant.[85]

Frank required a non-acidic diastereoselective epoxidation of **30** so that the acid-catalysed rearrangement of this sensitive

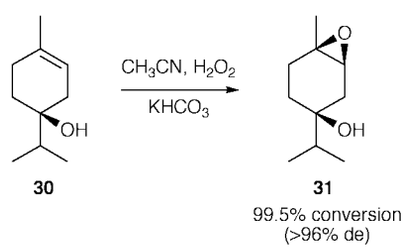



**Scheme 13**




**Scheme 14**

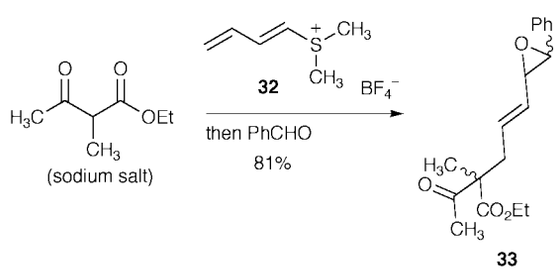
epoxide **31** could be studied (Scheme 15). The Payne epoxidation served admirably in this case.[86]




**Scheme 15**

Peroxyisoureas are isoelectronic with peracids, the classic reagents for epoxidation. Since these can be generated from carbodiimides, it has recently been shown that the epoxidation of alkenes by aqueous hydrogen peroxide promoted by carbodiimides can be an efficient process. A large excess (5 equivalents) of hydrogen peroxide was required for optimal yields.[87]

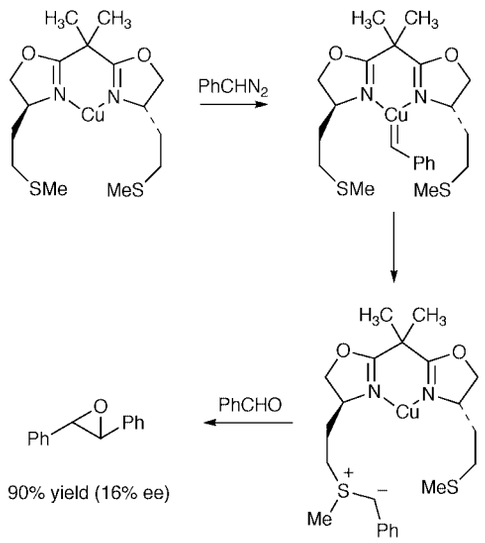
Moving on to carbene transfer reactions, those involving sulfur ylides are among the most common. A three component coupling, as shown in Scheme 16, involves *in situ* generation of the sulfur ylide by nucleophilic attack on buta-1,3-dienyldimethylsulfonium tetrafluoroborate **32**. Unfortunately the product **33** was a mixture of the four possible diastereoisomers.[88]



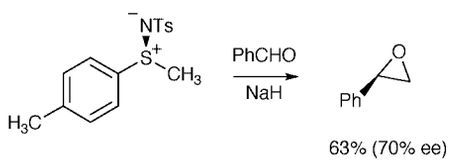

**Scheme 16**

Meanwhile Aggarwal and co-workers continue their work on the use of chiral sulfides for asymmetric epoxidation of carbonyl compounds with diazo compounds. A detailed discussion of the optimisation of reaction conditions and origin of asymmetric induction has recently been published.[89,90] The same group have also reported a conceptually elegant approach

which involves a bisoxazoline ligand with pendant sulfide groups. Decomposition of phenyldiazomethane at the metal centre is followed by immediate sulfur ylide formation and subsequent trapping to give the epoxide. Unfortunately while the yields are excellent, the enantioselectivity at present is modest (Scheme 17).[91] Baird and Taylor have reported a similar approach in which the methylidene is converted from a sulfimide. In this way, styrene oxide was formed with 70% ee (Scheme 18).[92] A further related report centres on the use of the

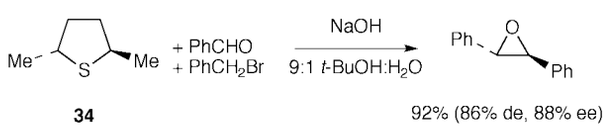



**Scheme 17**



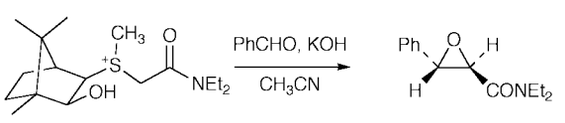

**Scheme 18**

$C_2$ symmetric thiolane **34** for the preparation of enantiomerically enriched stilbene oxide (Scheme 19).[93]



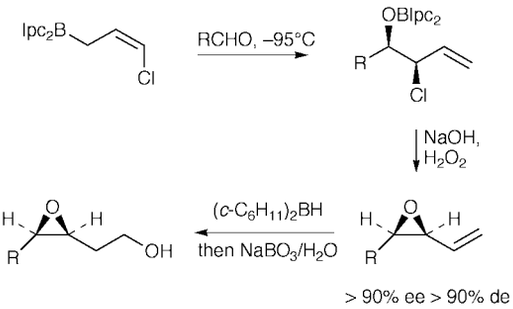

**Scheme 19**

All of these approaches are formally Darzens reactions. In an approach using an isolated sulfonium salt, it has been shown that **35** leads to enantiomerically enriched epoxides (Scheme 20).[94] 1,2-Epoxyalkylphosphonates can also be prepared using the Darzens reaction.[95]



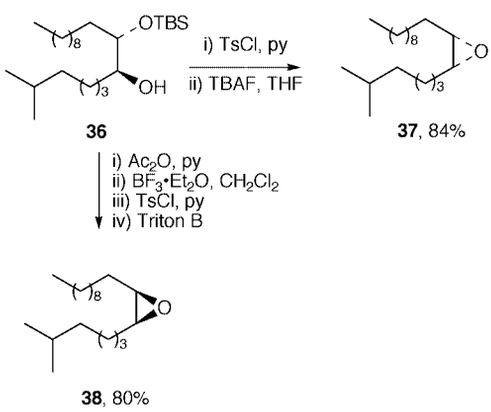

**Scheme 20**

Cyclisation reactions giving epoxides are often overlooked compared to oxygen transfer reactions. Maillard and coworkers have previously reported the addition of free-radicals to unsaturated peroxides leading to epoxides. The same group have now reported an anionic version of this reaction.[96] Use of chloroallylboranes in asymmetric aldol reactions allows the formation of *cis*-vinylepoxides and hence, by hydroboration,



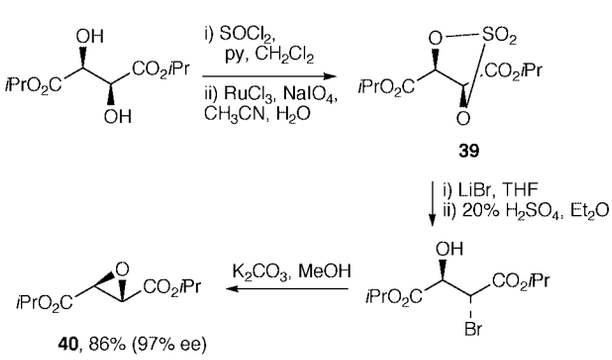

**Scheme 21**

*cis*-3,4-epoxyalcohols (Scheme 21).[97] This approach has been used to prepare the gypsy moth pheromone (+)-disparlure.[98] An essentially identical approach has been used to prepare sphingoid bases by chloroallylation of the Garner aldehyde.[99] In this case epoxide formation was followed by allylic epoxide opening with organometallic reagents. A related approach uses chloropropargylation of aldehydes *en route* to alkynyloxiranes.[100] Marshall *et al*. have also prepared disparlure by a conceptually similar but more versatile route allowing preparation of both enantiomers from a common intermediate. Compound **36**, prepared by addition of a homochiral allylstannane to an aldehyde followed by hydrogenation, was tosylated and then treated with tetra-*n*-butylammonium fluoride to give (+)-disparlure **37** (Scheme 22). Alternatively, acetylation of **36** followed by removal of the silicon protecting group, tosylation of the liberated secondary alcohol and subsequent acetate hydrolysis afforded (−)-disparlure **38** (Scheme 22).[101] Similar approaches have been applied to other insect pheromones.[102]



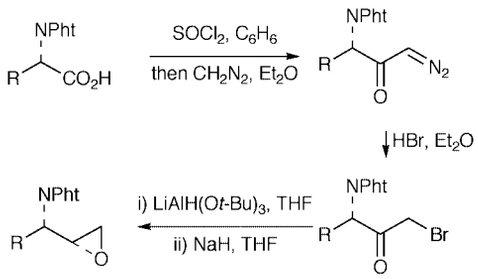

**Scheme 22**

A further cyclisation strategy makes use of the fact that homochiral 1,2-diols are readily available either from natural sources or by Sharpless asymmetric dihydroxylation. Treatment of the corresponding cyclic sulfate **39** with lithium bromide was followed by ring closure to the epoxide **40** (Scheme 23).[103]



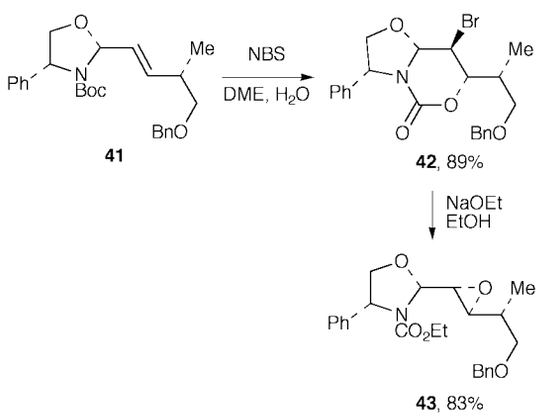

**Scheme 23**

Amino epoxides are useful chiral building blocks. While these have been previously prepared by diastereoselective reduction of α-aminoketones, a new method uses the conversion of a diazo group into a bromomethyl as a direct method for the formation of amino epoxides from α-amino acids (Scheme 24).[104] Hydroxyepoxides were prepared in a similar way, with either diastereoisomer being accessible by judicious choice of reducing agent.[105]




**Scheme 24**

A two step diastereoselective epoxidation of alkenyloxazolidines proceeds as shown in Scheme 25. Cyclisation of **41** with NBS gave **42** as a single diastereoisomer. Treatment with sodium ethoxide then gave **43**.[106]




**Scheme 25**

Harada *et al*. have taken the strategy a step further with an extension of a deracemisation process. The enantiomeric mixture of acetals **44** were treated with **45** and oxazaborolidine catalyst **46** to give **47** and **48**, both by selective C–$O_{PRO-R}$ bond cleavage. Formation of the mesylate and cyclisation gave **49** from both *pseudo* enantiomeric intermediates (Scheme 26).[107]

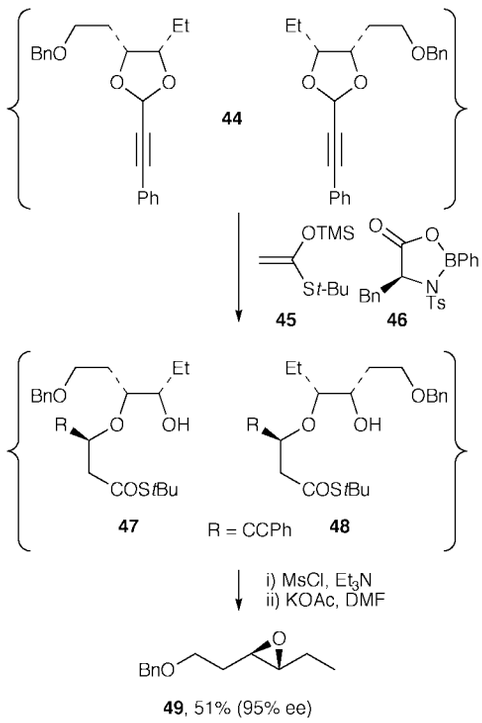
The Jocic reaction is the seldom-used cyclisation of trichloromethylmethanols to dichlorooxiranes, followed by nucleophilic ring-opening and hydrolysis. Oliver and Schmidt have reported a variation on this reaction where the nucleophile is an internal hydroxy group to give 2,3-epoxyacids (Scheme 27).[108]

Palladium catalysed arylation of allenes is well known to produce π-allylpalladium complexes which can undergo further chemistry. With a suitably disposed alcohol this complex can lead to epoxides (Scheme 28). Where R = alkyl, use of caesium carbonate was necessary, potassium carbonate leading instead to the formation of cyclic carbonates. However, R = aryl or heteroaryl gave epoxides in both cases.[109]

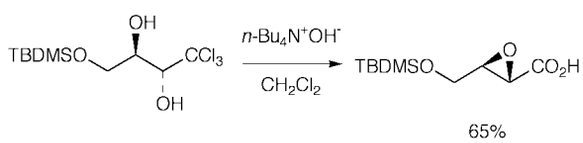
Epoxide **50**, required for a synthesis of the azinomycins, has caused some confusion in the literature. Coleman and McKinley have summarised the issue after reports by Shipman highlighting the discrepancy. The error has been attributed to inaccuracies in the measurement of optical rotation on dilute samples.[110]

## 3 Four-membered rings

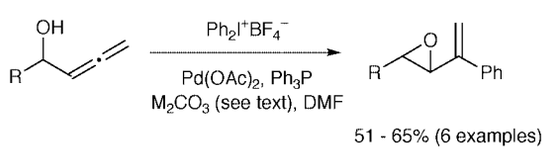
The relative dearth of literature on oxetanes is no doubt due to the relative scarcity of this ring system in natural products and



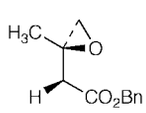

**Scheme 26**




**Scheme 27**



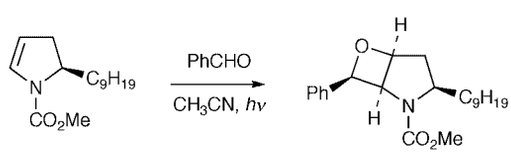

**Scheme 28**




**50**

the lack of general synthetic utility compared to epoxides. Bach has reviewed [2+2] cycloadditions, including a detailed account of his own work on the stereochemistry of the Paternò–Büchi reaction.[111] More recent work utilises chiral enamines in this process with modest to good selectivity.[112] With enecarbamates this reaction provides efficient entry into 2-amino-1,3-diols by intramolecular oxetane opening.[113]

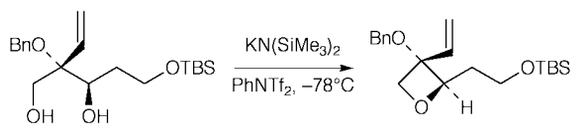
Bach and Brummerhop have demonstrated impressive diastereoselectivity in the Paternò–Büchi reaction of **51** giving **52** as the major diastereoisomer (63% de) (Scheme 29). Hydrogenolysis of the benzylic C–O bond and reduction of the methyl carbamate gave the antifungal alkaloid preussin.[114]




**51** **52**

**Scheme 29**

Paquette *et al*. have cyclised **53** to **54** *via* the triflate to prepare a precursor to the C and D rings of Taxol (Scheme 30). This approach is intended to avoid generating the strained ring late in the synthesis.[115]

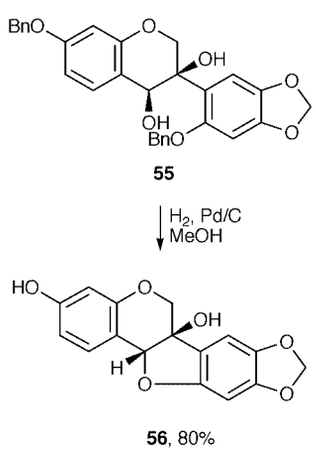



**53** **54**, 73%

**Scheme 30**

## 4 Five-membered rings

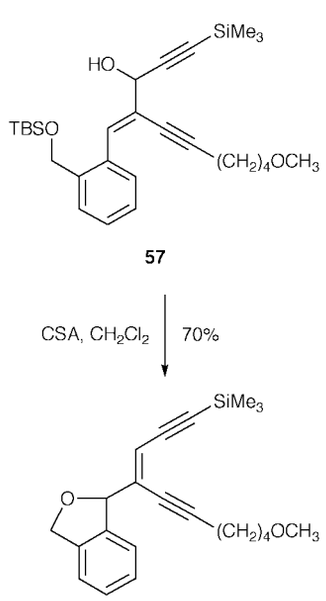
Cyclisation of diols is conceptually the simplest way to prepare any oxygen heterocycle. A number of such reactions are discussed later in this section as applied to the synthesis of acetogenin natural products. The final stages in Pinard's synthesis of (+)-pisatin were shortened by the fortuitous observation that hydrogenolysis of **55** led directly to **56** (Scheme 31). Methylation of the phenol completed the synthesis.[116]




**56**, 80%

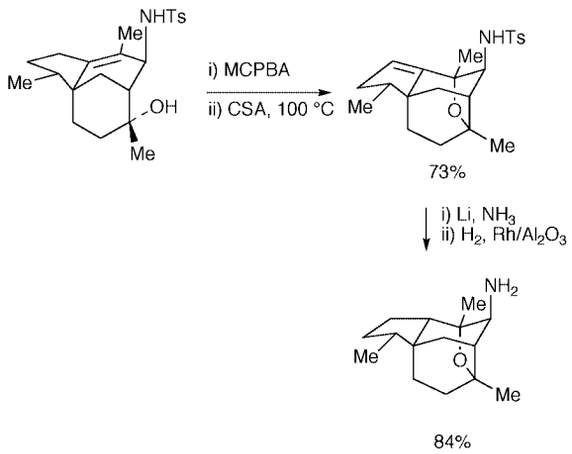
**Scheme 31**

In other work, the stability of the cation derived from **57** means that no activating group is necessary (Scheme 32). Simple treatment with camphorsulfonic acid is sufficient to deprotect the silyl ether and effect cyclisation with allylic rearrangement.[117]



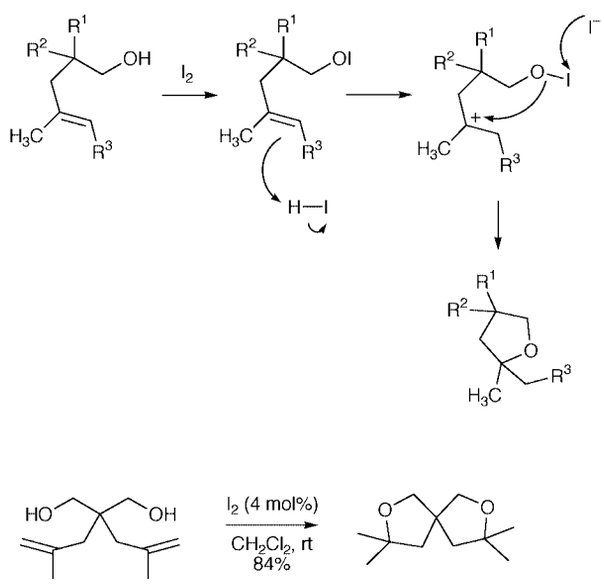

**Scheme 32**

Overman and Tomasi's synthesis of hispidospermidin highlights unexpected difficulties in tetrahydrofuran formation, and the solution to the problem is shown in Scheme 33. The use of either protic acids or oxymercuration to form the THF ring were unsuccessful, and so the double bond was instead epoxidised stereoselectively from the β-face using MCPBA. Epoxide opening was then followed by elimination, and finally removal of the tosyl group from nitrogen allowed stereoselective hydrogenation to give the desired tetracyclic core.[118]




**Scheme 33**

Halocyclisation of hydroxyalkenes normally results in the incorporation of the halogen into the product. However, a recent report details modified conditions involving only catalytic quantities of iodine. The proposed mechanism is shown in Scheme 34, along with an example of spirocyclic bis-THF synthesis by this method.[119]

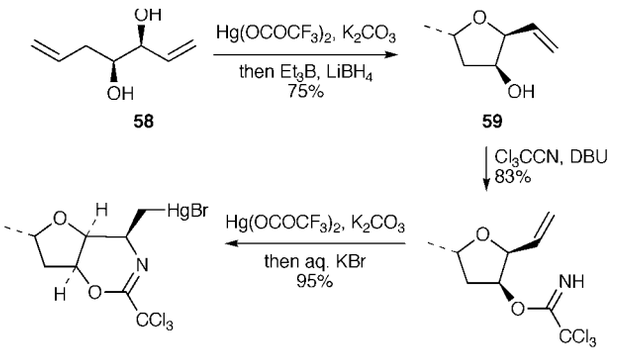



**Scheme 34**

More conventional iodocyclisations were carried out on a carbohydrate template by Gesson and co-workers.[120] Benzyl protected alcohols may also be used, debenzylation occurring under the reaction conditions.[121] Jung *et al*. have used 5-*endo* bromocyclisations to protect a double bond and effect the conversion of a homoallylic alcohol to the corresponding methyl ketone.[122]

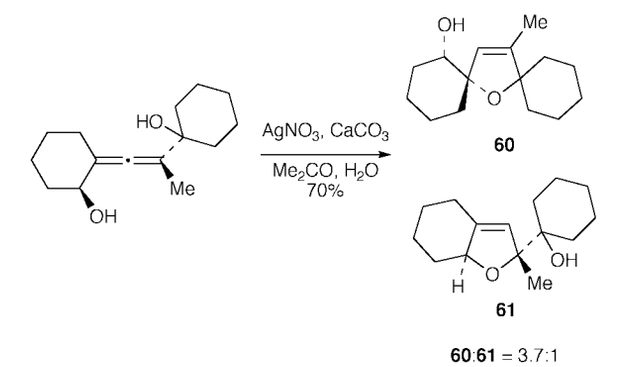
Oxymercuration was used by Kang and Lee in the synthesis of (+)-furanomycin. Cyclisation of tartrate-derived **58** gave **59** as the major diastereoisomer of a 9:1 mixture. Protection of the alcohol as the trichloroacetimidate allowed intramolecular

aminomercuration to install the stereogenic centre at nitrogen (Scheme 35). A further six steps were required to complete the total synthesis.[123]



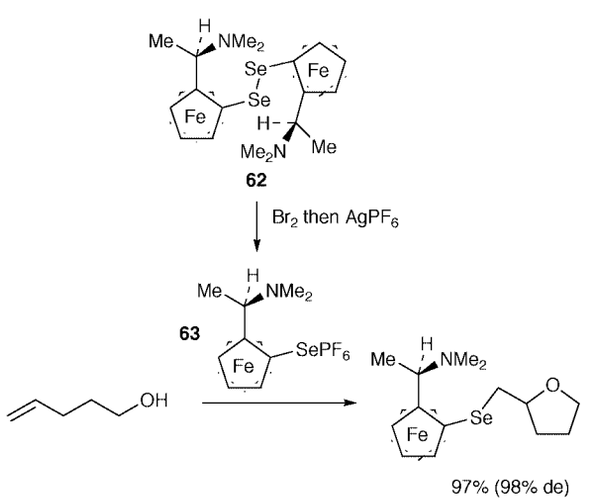

**Scheme 35**

Dihydrofurans can be formed by silver mediated cyclisation of allenic alcohols. When allenic diols are used in this reaction, cyclisation of the more hindered hydroxy group generally occurs (Scheme 36).[124]



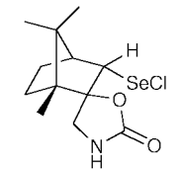

**Scheme 36**

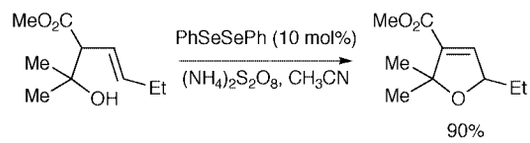
Spectacular diastereoselectivities were obtained in the selenocyclisation of alkenols using a chiral diferrocenyl diselenide **62**. Bromination of **62** and counter-ion exchange provided **63** which cleanly cyclised pent-4-en-1-ol (Scheme 37).[125] Back *et al.* have reported the diastereoselective synthesis (≤90% de) of tetrahydropyrans (6-*exo*-*trig*) and tetrahydrofurans (5-*exo*-*trig* and 5-*endo*-*trig*) using the camphor-derived chiral selenyl chloride **64**.[126] Wirth has reviewed this area of chemistry[127] and presented a full account of his own work.[128]




**Scheme 37**

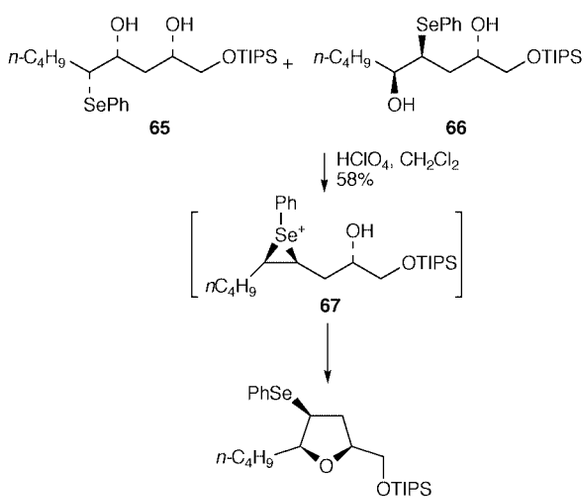
In the case of 5-*endo* cyclisations, conducting the reaction in the presence of ammonium persulfate has two effects. Firstly the oxidant cleaves the selenium–selenium bond to produce the highly reactive phenylselenyl sulfate, and secondly the oxidant promotes elimination of selenium from the product. Since this regenerates phenylselenyl sulfate, sub-stoichiometric amounts of selenium are required (Scheme 38).[129] Oxidative elimination of selenium can also take place to generate the enol ether.[130]




**Scheme 38**

A further selenium-based approach is shown in Scheme 39. A mixture of **65** and **66** were formed from ring opening of an epoxide with sodium phenyl selenide. When this mixture was treated with perchloric acid in dichloromethane, a single tetrahydrofuran **68** was formed *via* the intermediacy of a selenonium ion **67**. If the primary alcohol was not protected, a *ca.* 1:1 mixture of products was obtained arising from 5-*endo* and 5-*exo* attack. With sulfur in place of selenium, only 5-*exo* attack was observed.[131]

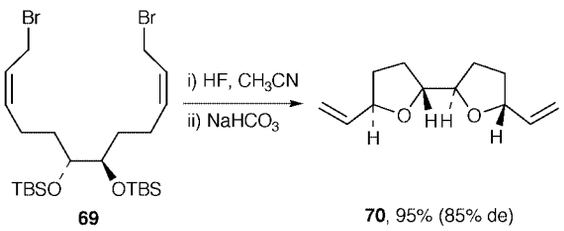



**Scheme 39**

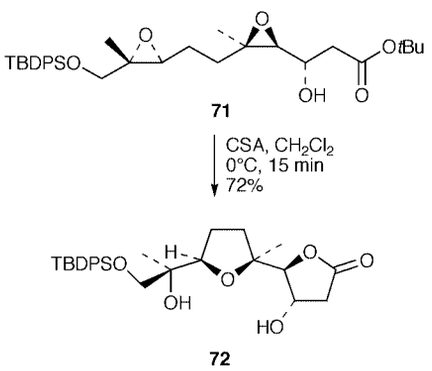
An interesting tandem reaction to produce 2,4- and 2,5-disubstituted and 2,3,5-trisubstituted tetrahydrofurans is shown in Scheme 40. Addition of an organometallic reagent (including DIBAL-H) to 6-bromohexen-4-al derivatives gave an intermediate alkoxide, which then underwent $S_N'$ cyclisation to give the oxacycle. Although the stereochemical details remain unclear (in some cases the double bond geometry of the precursor is critical, in other cases less so) this approach is versatile, tolerating a wide range of organometallics (alkyl, allyl, aryl derivatives of Li, Mg, Ce).[132] A similar approach has been applied to the bis-tetrahydrofuran portion of annonaceous acetogenins. Thus, **69** was deprotected with HF in acetonitrile to give **70** with 85% de (Scheme 41). Lower diastereoselectivity was obtained using the precursor with (*E*)-double bonds.[133]

An alternative tandem process involves the hydrolysis of ester **71** leading directly to **72** (Scheme 42).[134]

Scheme 40

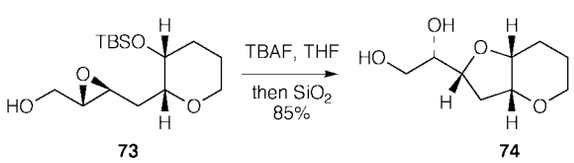


Scheme 41



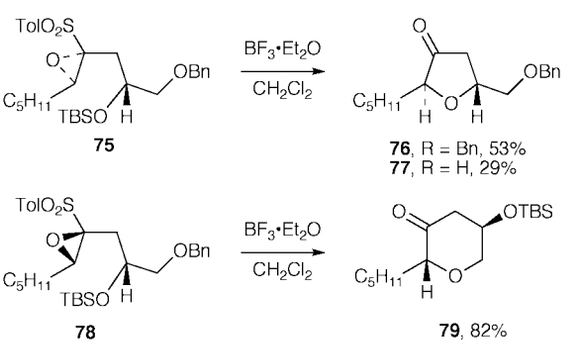
Scheme 42

Epoxide opening has also been used to prepare a model compound for dysiherbaine, a novel amino acid with neurological properties. Desilylation of **73** was followed by cyclisation on silica gel to give **74** (Scheme 43).[135]



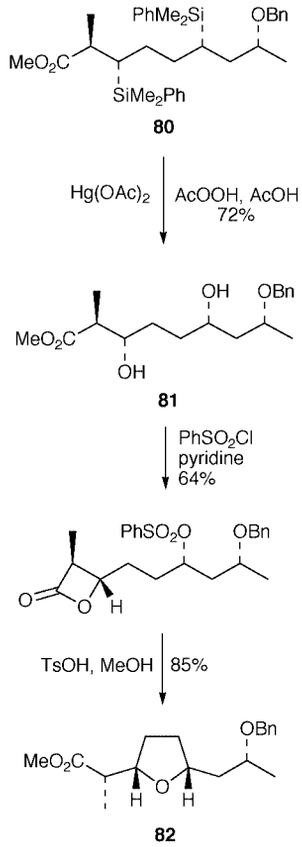
Scheme 43

Endocyclic epoxide opening was used to prepare a marine epoxy lipid. Cyclisation of **75** gave a mixture of **76** and **77**, while the diastereoisomer **78** cyclised *via* the protected primary alcohol to give only the tetrahydropyran **79** (Scheme 44).[136]



Scheme 44

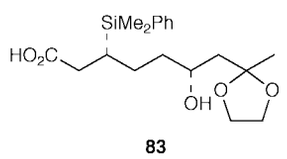
Fleming and Ghosh's synthesis of methyl (+)-nonactate also features the opening of a strained ring, this time a β-lactone, to prepare a tetrahydrofuran. Selected steps are shown in Scheme 45. Oxidative removal of silicon from **80** gave **81** with retention of configuration. β-Lactonisation with simultaneous activation of the remaining free hydroxy group was followed



Scheme 45

by acidic hydrolysis with concomitant THF formation to give **82**.[137]

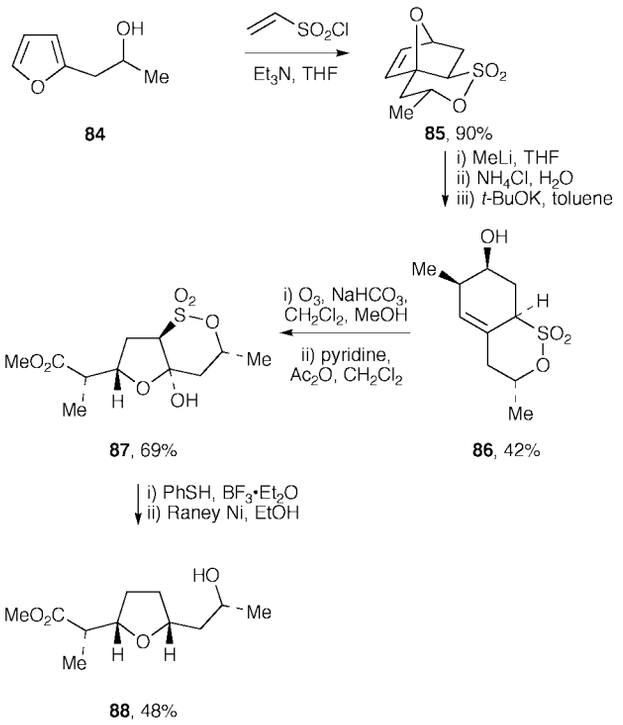
Since nonactin is a tetramer consisting of two molecules of each enantiomer of nonactic acid, a total synthesis requires preparation of both enantiomers. This was accomplished from the key intermediate **83** using a simple sequence of protecting group chemistry and oxidative desilylation to invert the appropriate stereogenic centre during the THF ring formation.[138]



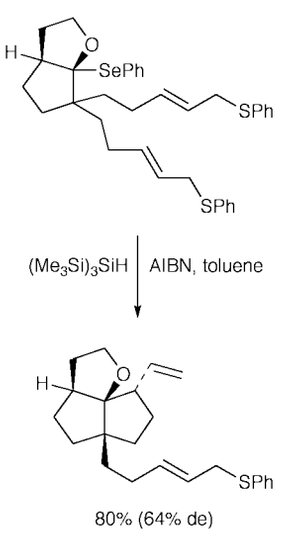
Metz and co-workers have reported a novel route to the same compounds based on intramolecular furan Diels–Alder chemistry. Reaction of **84** with vinylsulfonyl chloride gave **85** in 90% yield (Scheme 46). Reaction with methyllithium and subsequent equilibration gave **86**. Ozonolysis followed by work-up with pyridine–acetic anhydride gave the lactol **87** in good yield. Treatment with thiophenol was followed by Raney nickel reduction to give methyl nonactate **88**.[139] A similar lactol modification was used by Usui and Paquette in the synthesis of modified diquinanes. In this case free radical chemistry was used to form a cyclopentane ring (Scheme 47).[140]

Benzofuran **89** inhibits lipid peroxidation and dopamine release. A double epoxide opening strategy was used to prepare this compound (Scheme 48).[141]

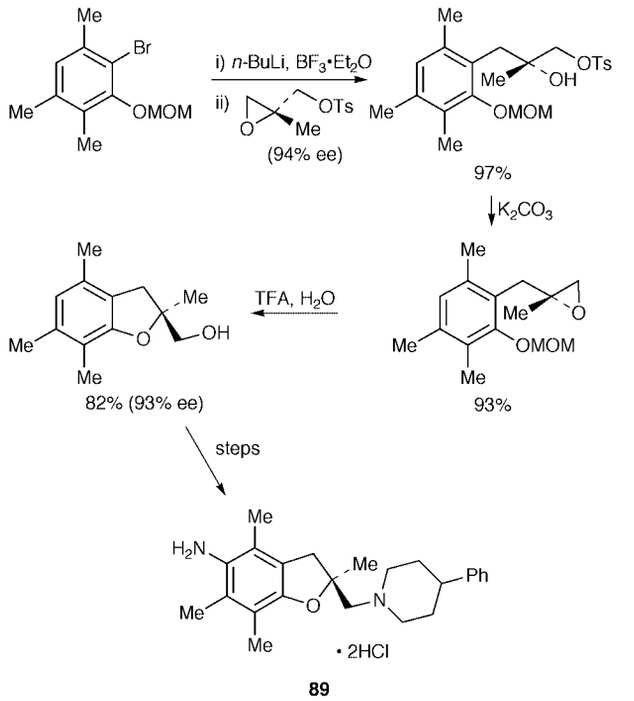
A cascade process involving epoxide opening followed by conjugate addition to an unsaturated sulfone has been used as an entry into isosorbide analogues. Sharpless epoxidation of **90** provided the bis-THF **91** in 50% yield (Scheme 49).[142] A similar procedure under nucleophilic epoxidation conditions resulted in epoxidation of the dihydrofuran since the allylic alcohol required for further cyclisation was not present.[143] Cyclisation



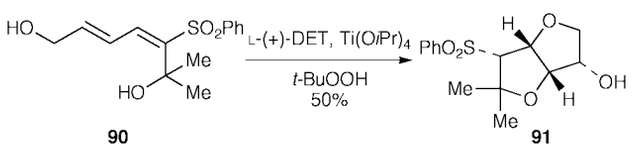

**Scheme 46**



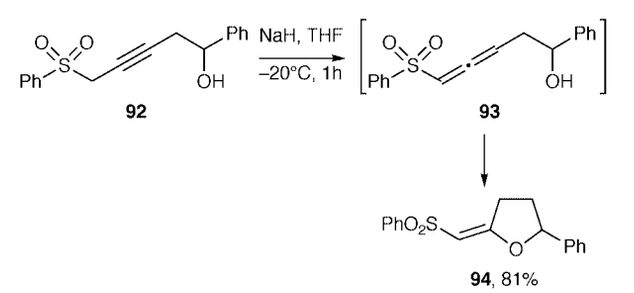

**Scheme 47**



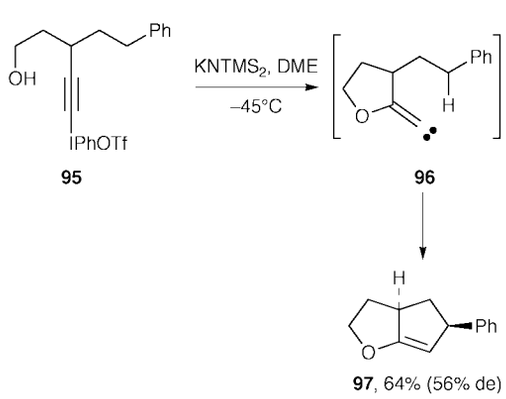

**Scheme 48**




**Scheme 49**




**Scheme 50**




**Scheme 51**

reactions of allenic sulfones **93** (derived *in situ* from propargylic sulfones **92**) give *exo*-methylenetetrahydrofurans **94** with high (*E*)-selectivity (Scheme 50).[144]

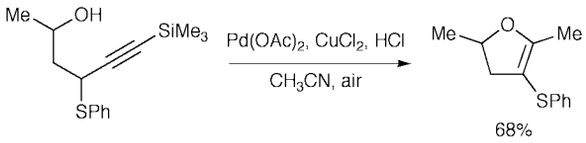
Another route to *exo*-methylenetetrahydrofurans centres on the cyclisation of hydroxypentynyliodonium triflate **95** resulting in an alkylidene carbene **96** which undergoes insertion into a C–H bond to give a diastereomeric mixture in which **97** predominated (Scheme 51).[145]

A further hydroxyalkyne cyclisation is shown in Scheme 52.[146]

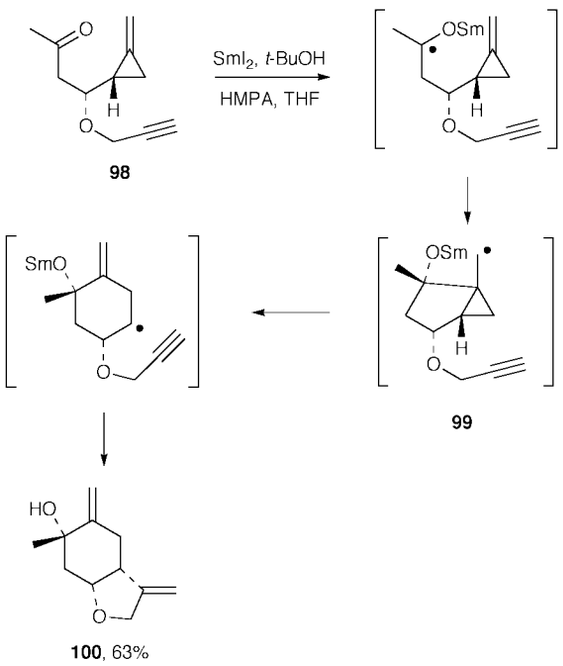
Kilburn and co-workers have reported a concise synthesis of paeonilactone B using an elegant radical cascade process. Generation of the ketyl from **98** was followed by cyclisation to the cyclopropylmethyl radical **99**. Fragmentation was then followed by cyclisation to the fused furan derivative **100** (Scheme 53).[147]

Active manganese also initiates a free-radical pathway as shown below (**101** to **102**), although in this case no stereocontrol was observed (Scheme 54).[148]

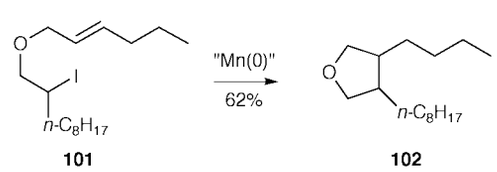
Another approach to spirocyclic bis-THFs has been reported by Murphy *et al*. Treatment of **103** with nitrosonium tetrafluoroborate followed by tetrathiafulvalene gave **104** by a radical–polar crossover mechanism (Scheme 55).[149] Radical to anionic crossover reactions are also possible, both in solution and on solid support (Scheme 56).[150] Alternatively, more conventional radical formation (allyltributyltin, AIBN) allows the



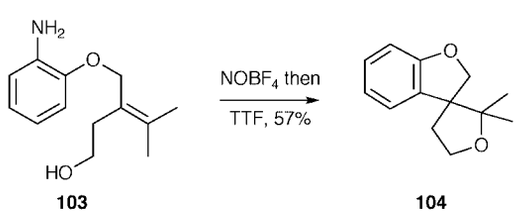

**Scheme 52**



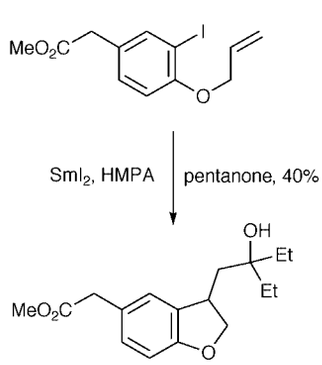

**Scheme 53**




**Scheme 54**

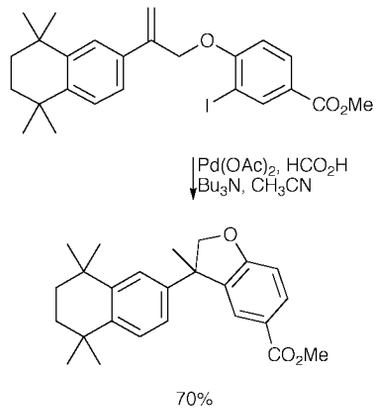



**Scheme 55**




**Scheme 56**

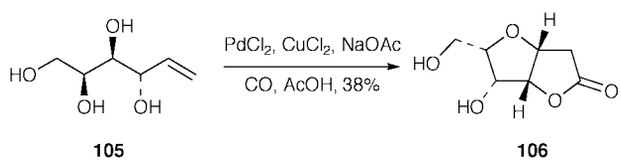
cyclised radical to be trapped with allyltributyltin.[151] Similar cyclisation reactions can be catalysed by palladium acetate (Scheme 57) (see also the following section).[152] A further new




**Scheme 57**

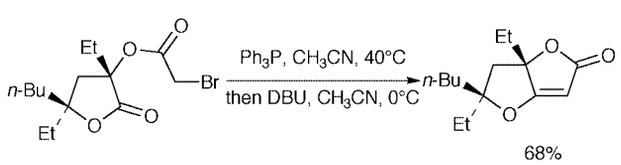
advance in free radical chemistry is an environmentally benign approach to free radical generation using 1-ethylpiperidinium hypophosphite.[153]

Transition metal chemistry often allows the preparation of complex compounds from simple building blocks, with a number of transformations occurring in a single step. Compound **106** was prepared by alkoxycarbonylation/lactonisation of **105**, and used in the total synthesis of erythroskyrine (Scheme 58).[154]



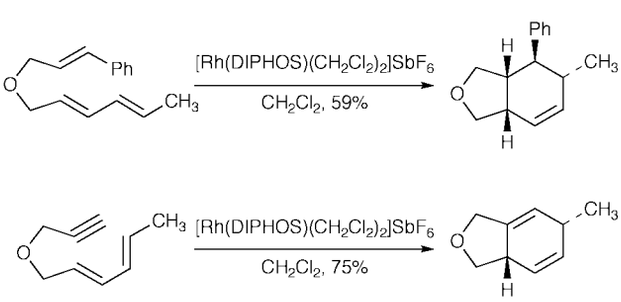

**Scheme 58**

Related compounds have been prepared by Wittig cyclisation onto lactones (Scheme 59).[155]



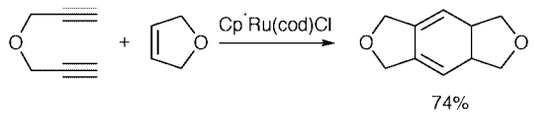

**Scheme 59**

Two groups have independently reported transition metal catalysed formal intramolecular Diels–Alder reactions as a route to fused furan derivatives. While the rhodium(I) complex catalysed the reactions of alkenes and alkynes as "dienophiles" (Scheme 60),[156] palladium(II) acetate only catalysed the latter process.[157] Thermal intramolecular Diels–Alder reactions resulting in tetrahydrofuran formation are also known.[158]



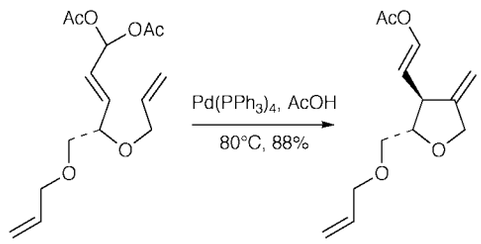

**Scheme 60**

A related ruthenium-catalysed cycloaddition of 1,6-diynes has been shown to lead to effective annulation onto 2,5-dihydrofuran (Scheme 61).[159]



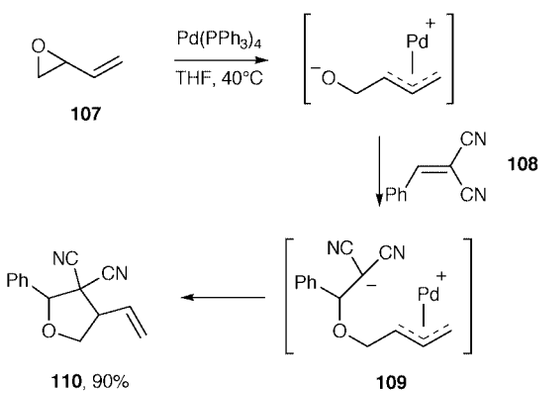

**Scheme 61**

π-Allylpalladium species can be intercepted by alkenes and alkynes (Scheme 62). In some cases the organopalladium species was able to undergo further reaction.[160]



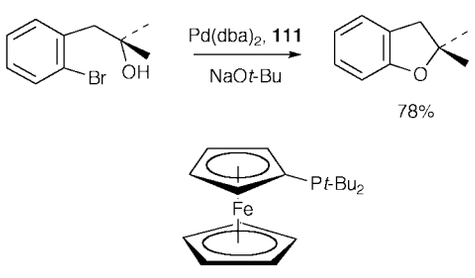

**Scheme 62**

A slightly unusual example of π-allylpalladium chemistry is shown below. Generation of the π-allyl complex from a vinyloxirane **107** is followed by nucleophilic attack on a Michael acceptor **108**. This generates a nucleophile which can attack the π-allyl complex **109** in the usual way to generate tetrahydrofuran **110** (Scheme 63).[161]



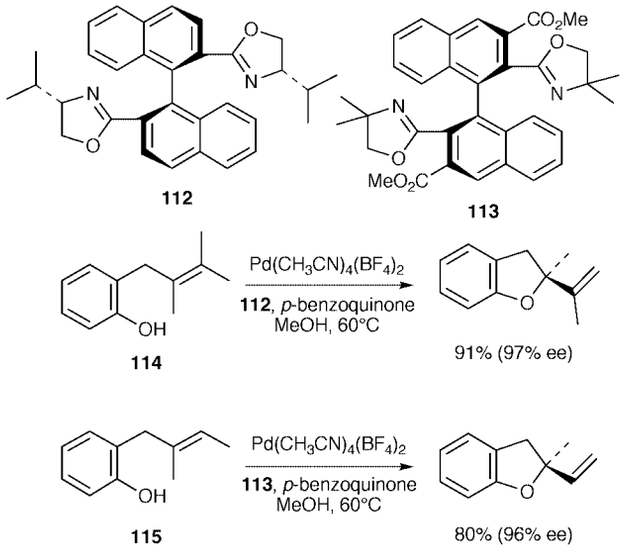

**Scheme 63**

Direct formation of aryl–carbon to oxygen bonds under palladium catalysis is less common. However, the reaction shown in Scheme 64 is particularly effective for the production of hindered ethers.[162]



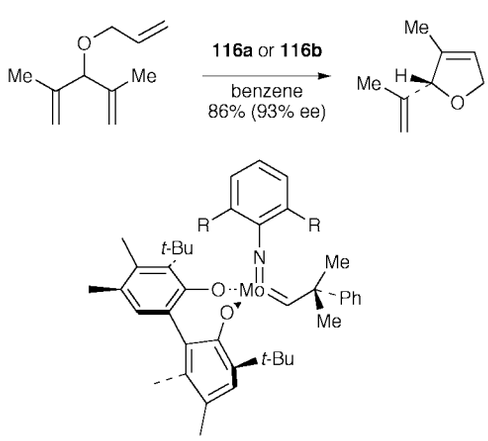

**Scheme 64**

Uozumi *et al.* have further probed the ligand requirements for Wacker oxidation of 2-allylphenols. While ligand **112** proved optimal for substrate **114** (97% ee, 91% yield), it was ineffective for **115** (9% ee) (Scheme 65). Conversely ligand **113**, with only axial chirality, gave only 4% ee with **114** but up to 96% ee with **115**.[163] Benzofurans have also been prepared by palladium catalysed reaction of 2-iodophenols with dienes.[164]




**Scheme 65**

The explosion of work on ring-closing metathesis shows no sign of slowing down.[165] Chiral molybdenum complexes **116a** and **116b** have been used for ring-closing desymmetrisation of allylic ethers (Scheme 66), and also for kinetic resolution of unsymmetrical chiral allylic amines.[166]



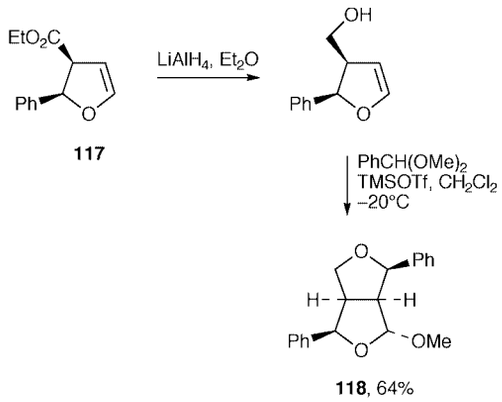

**Scheme 66**

Furofuran lignans are popular synthetic targets due to their wide range of biological properties. Steel and co-workers have recently reported an efficient new preparation of these compounds as shown in Scheme 67. Compound **117** was prepared by thermolysis of a vinyloxirane. Reduction to the alcohol was followed by Lewis acid promoted reaction with aldehyde dimethyl acetals to give products such as **118**. The reaction works best with the dimethyl acetals from aromatic aldehydes, but does give some of the desired product with the dimethyl acetal of ethanal.[167]

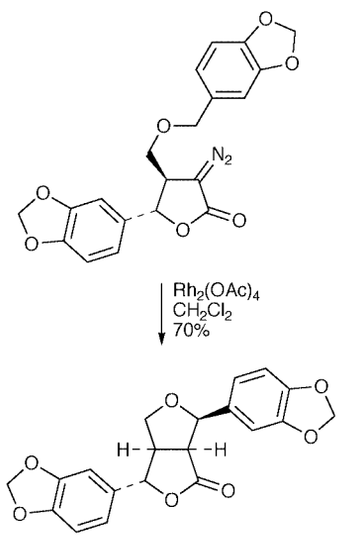
Rhodium-catalysed decomposition of diazo compounds provides a particularly efficient route to furofuran lignans, especially since the C–H bond into which the carbenoid inserts is doubly activated due to its benzylic nature and being adjacent to oxygen (Scheme 68).[168]

Insertion of rhodium carbenoids into O–H bonds is also a common strategy. This approach has been used to prepare *cis*-2,5-disubstituted tetrahydrofurans as *C*-nucleosides.[169]

Another interesting diazo decomposition reaction leading to tetrahydrofurans has been further investigated. Thus, reaction of benzyl diazoacetate with silyl-protected β-hydroxyaldehydes gave **119**, the *gem*-dimethyl group proving advantageous for

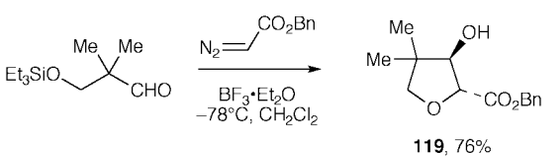



**Scheme 67**

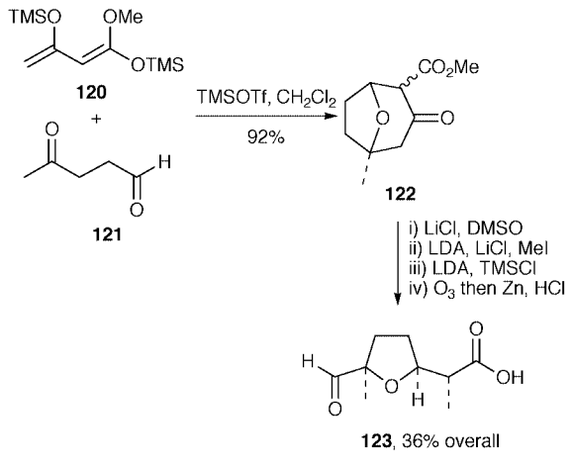



**Scheme 68**

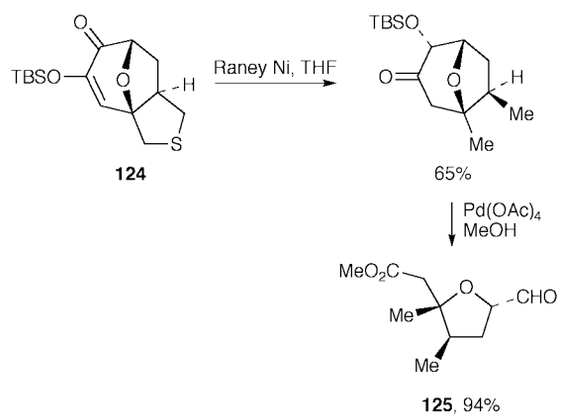
high yield (Scheme 69). With no methyl groups the yields were extremely low,[170] but only a single alkyl group in this position provided moderate to good yields of the tetrahydrofurans with good stereocontrol.[171]



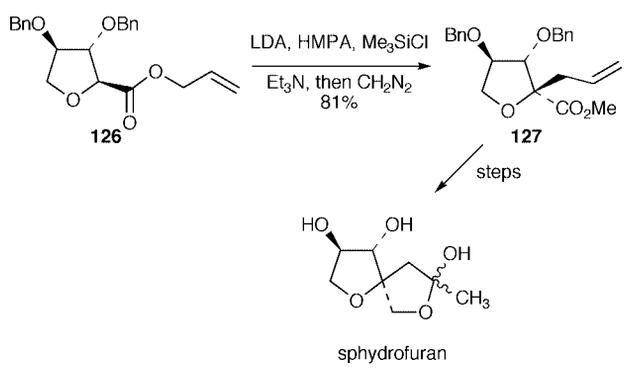

**Scheme 69**




**Scheme 70**




**Scheme 71**




**Scheme 72**

Molander and Haas have used a combination of [3 + 4] annulation and ozonolysis to prepare racemic davanone. Treatment of a mixture of **120** and **121** with trimethylsilyl triflate gave **122** in excellent yield. Decarboxylation, regio- and stereoselective methylation followed by enol ether formation and ozonolysis revealed the monocyclic tetrahydrofuran **123**. A further three steps were required to complete the synthesis (Scheme 70).[172]

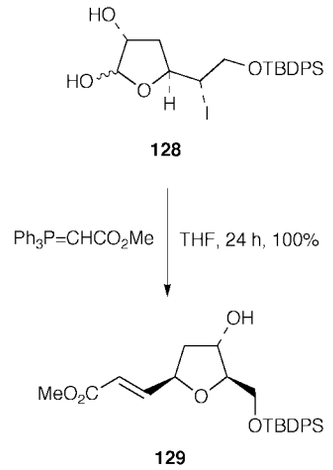
A similar approach has been used to prepare racemic nemorensic acid. Compound **124** was prepared by [5 + 2] cycloaddition of a pyrone. Removal of the sulfur tether with Raney nickel was accompanied by ketone reduction and transposition of the silyl group. Lead tetraacetate cleavage of the siloxyketone revealed the tetrahydrofuran **125** (Scheme 71).[173]

Sphydrofuran has been synthesised again, this time starting with the tetrahydrofuran ring intact and installing the spiro-stereogenic centre using an Ireland–Claisen rearrangement (**126** to **127**) (Scheme 72).[174] A group of related natural products, the secosyrins, have been approached using intramolecular displacement of a tosylate.[175]

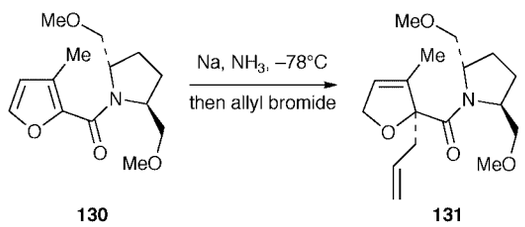
In the synthesis of a sugar-derived tetrahydrofuran, it was found that during Wittig olefination of **128**, extended heating led to the direct formation of **129** (Scheme 73).[176]

2,5-Dihydrofurans can be prepared by Birch reduction of furoic acid derivatives. Reduction of the amide **130** followed by electrophilic quench gave **131** with almost complete diastereocontrol (Scheme 74).[177]

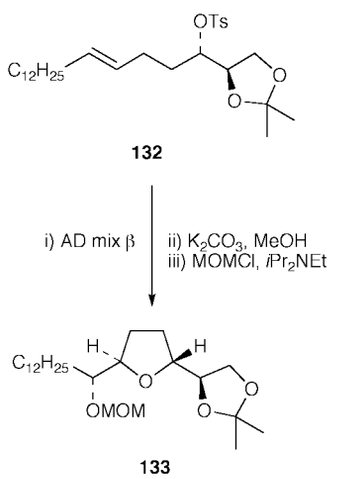
Acetogenins remain popular targets, and despite the wide range of strategies used to prepare these compounds, all the methods will be discussed together. Displacement of a sulfonate ester has been used in the first total synthesis of the cytotoxin acetogenin 4-deoxyannomontacin. Sharpless asymmetric dihydroxylation of **132** was followed by cyclisation to give **133** in 90% overall yield after protection of the secondary alcohol (Scheme 75).[178] A similar approach was used by Makabe *et al.* in the total synthesis of (+)-4-deoxygigantecin.[179] Cobalt-




**Scheme 73**



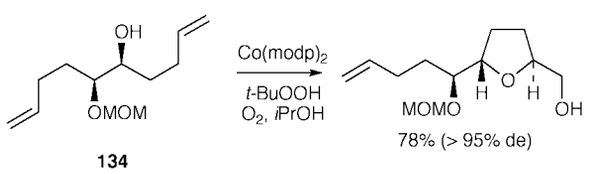

**Scheme 74**




**Scheme 75**

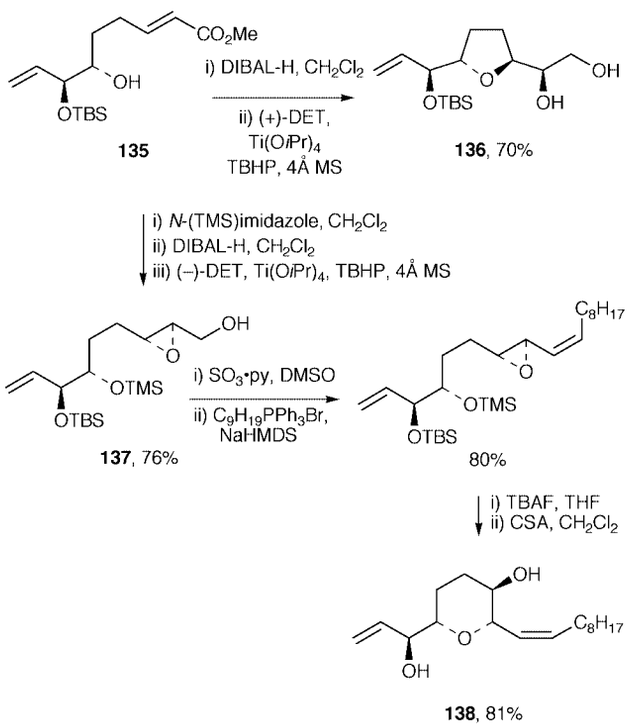
mediated oxidative cyclisation was used to prepare the tetrahydrofuran ring of the related gigantetrocin A (Scheme 76), providing the first total synthesis of this particular acetogenin.[180] The same approach has been used to prepare another acetogenin, asimilobin using a double cyclisation of the diol corresponding to **134**.[181] Marshall and Jiang have continued their work in this area with a total synthesis of trilobin and squamostatin D, using a combination of allylstannane chemistry to introduce the requisite stereochemistry and cyclisation of hydroxy groups onto tosylate esters to form the tetrahydrofuran rings.[182]

Mucocin and muconin are two structurally related acetogenins with antitumour properties. These compounds are




**Scheme 76**

unusual in that they contain tetrahydrofuran and tetrahydropyran rings. The formation of both rings will be discussed in this section. Evans and Murthy make effective use of the hidden symmetry in mucocin to prepare both rings from a common intermediate, showing interesting facets of epoxide opening along the way. In order to prepare the tetrahydrofuran ring, **135** was reduced with DIBAL-H and subjected to Sharpless asymmetric epoxidation to give **136** directly (Scheme 77). The same compound was converted into epoxide **137** using standard transformations. Oxidation and olefination was followed by removal of both silicon protecting groups and acid-catalysed cyclisation to give the tetrahydropyran **138**. Clearly the double bond stabilises the build-up of positive charge along the 6-*endo* pathway.[183] An essentially identical approach to the tetrahydropyran ring has been reported by Bäurle *et al.* who used asymmetric organozinc addition and tosylate displacement to form the five-membered ring in their total synthesis of mucocin.[184] Takahashi and Nakata's total synthesis of the same compound uses a protected galactonolactone as precursor to the tetrahydropyran and the $C_2$-symmetric 2,5-anhydro-D-mannitol for the tetrahydrofuran.[185]

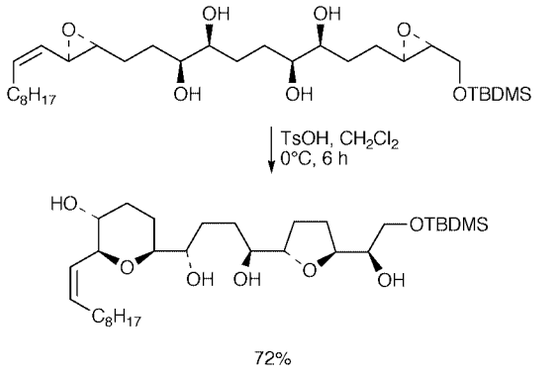



**Scheme 77**

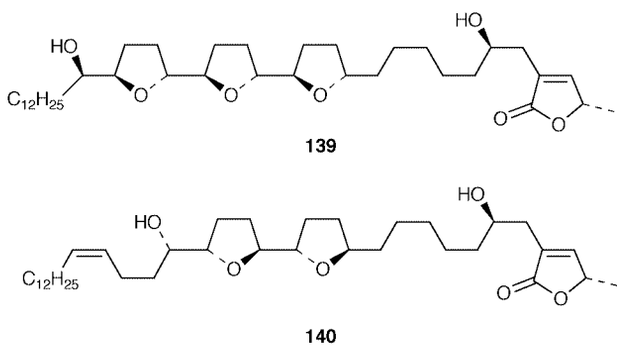
A further synthesis again uses epoxide opening and the directing effect of an alkene to determine the ring size formed. In this case the selectivity is even more impressive since both rings are formed in a single step (Scheme 78). All eight stereogenic centres were introduced using Sharpless chemistry.[186] The same group have prepared trilobin, also using Sharpless chemistry to introduce the stereogenic centres, and epoxide opening and mesylate displacement to form the rings.[187]

Almost all acetogenins have (*R*)-configuration at C10. Goniocin, **139**, is an exception to this, and it is therefore remarkable that the organism which produces this acetogenin also produces goniodenin, **140**, which is almost identical except for the configuration at C10 and the lack of the third tetrahydrofuran ring. The configuration of these compounds has been confirmed by total synthesis.[188]

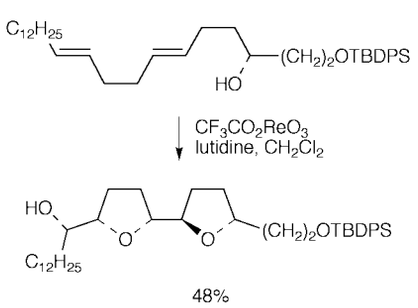
Two groups had previously reported contrasting stereochemical outcomes in the oxidative cyclisation of hydroxytrienes with trifluoroacetylperrhennate. Sinha *et al.* have presented work in support of their previous assignment, and a




**Scheme 78**




comparison with data supplied by McDonald show that both groups did in fact prepare the same stereoisomer. All four double bond isomers of a hydroxydiene were subjected to double cyclisation with stereochemical results which can be readily rationalised. One such cyclisation is shown in Scheme 79.[189]



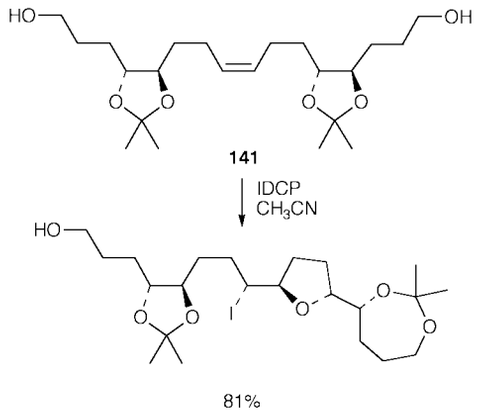

**Scheme 79**

Ruan and Mootoo have reported a novel desymmetrisation process as part of a formal total synthesis of trilobacin and asimicin. Treatment of **141** with IDCP resulted in iodocyclisation with transposition of the acetal (Scheme 80).[190]

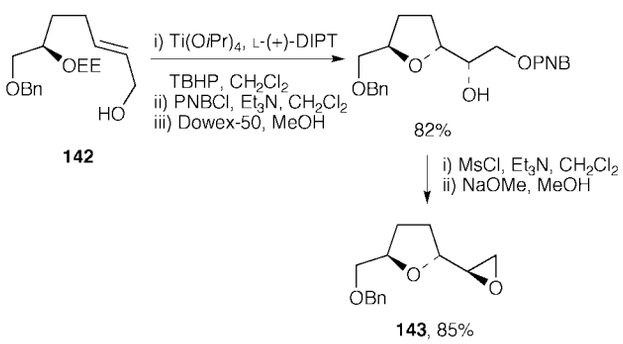
A particularly versatile building block for these natural products has been prepared making efficient use of the epoxide functionality. Sharpless epoxidation of **142** was followed by protection of the primary alcohol and acid catalysed cyclisation. Routine transformations provided the epoxide **143** (Scheme 81).[191]

Both diastereoisomers of 2,2′-bi(tetrahydrofuran) were prepared as shown in Scheme 82. Bromocyclisation of **144** was followed by base-promoted ring closure to give the *meso* isomer **145**. Alternatively ozonolysis of **146** followed by reduction gave **147** by spontaneous cyclisation onto the epoxide. This was then followed by cyclisation *via* the triflate to give the DL-isomer **148**.[192]

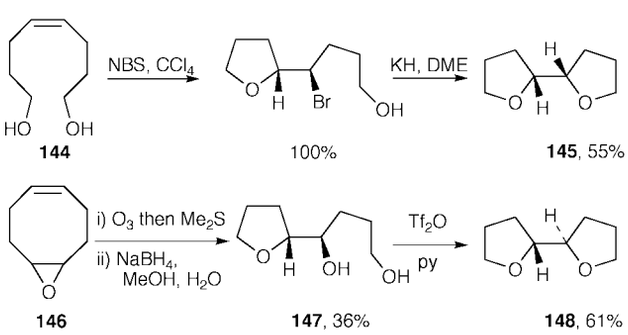
Gesson and co-workers have used a variation on a reaction reported by Defaye to prepare a hydroxylated acetogenin sub-




**Scheme 80**




**Scheme 81**




**Scheme 82**

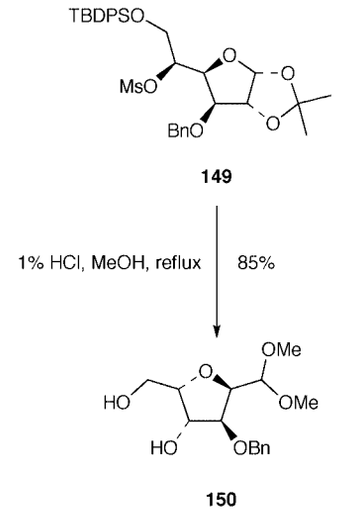
unit **150** by treatment of **149** with acid in methanolic solution (Scheme 83).[193] Unfortunately these conditions also resulted in deprotection of the primary alcohol.

## 5 Six-membered rings

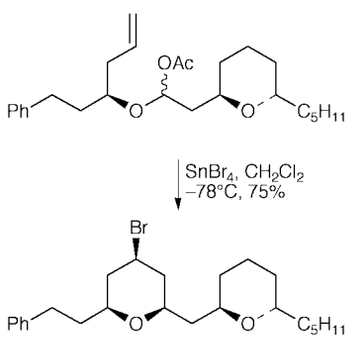
Forsyth *et al.*'s approach to phorboxazole A was mentioned in the previous review in this series. Three subunits were prepared which have now culminated in a convergent total synthesis.[194] A full account of Paterson *et al.*'s synthesis of scytophycin C has also been published.[195]

Rychnovsky *et al.* have used a Prins reaction to form a bis-tetrahydropyran related to the phorboxazoles (Scheme 84).[196] The complex starting material was prepared by DIBAL-H reduction and acetylation of the corresponding ester. Wolbers and Hoffmann's approach to this fragment relies upon the allylation of a lactol ether.[197]

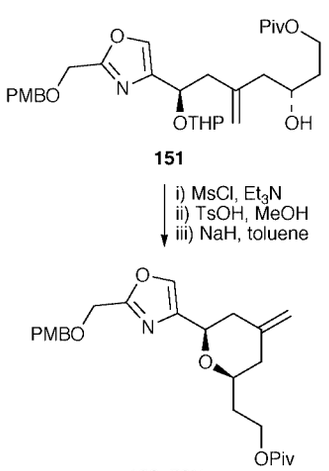
Williams *et al.* used an iterative approach to the same bis-tetrahydropyran. Compound **151**, prepared by asymmetric addition to the corresponding oxazole-4-carbaldehyde, was subjected to an activation–cyclisation sequence shown in Scheme 85. After hydrolysis of the pivaloate ester **152** and oxidation of the primary alcohol, a repeat of the same sequence formed the second tetrahydropyran. The isolated tetrahydro-




**Scheme 83**




**Scheme 84**

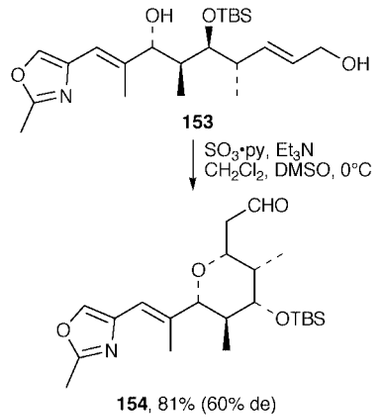



**Scheme 85**

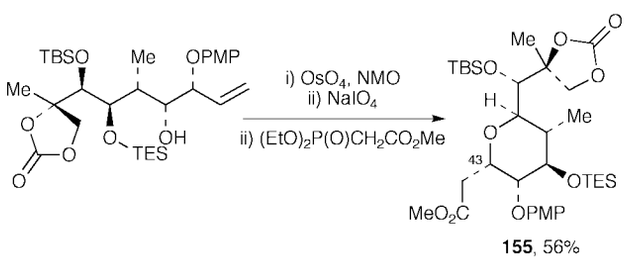
pyran ring present in the same natural product was prepared by a similar method.[198]

Paterson and Arnott's approach to the same natural products relies upon stereoselective aldol chemistry to prepare the precursor **153**. Selective oxidation of the primary alcohol was accompanied by intramolecular Michael addition to give **154** (Scheme 86).[199] An intramolecular Michael addition was also used by Yamamoto and co-workers to prepare the AB ring fragment of gambierol.[200]

A similar method (Scheme 87) was applied by Micalizio and Roush to the synthesis of one of the pyran rings of spongistatin. After removal of the triethylsilyl group (which migrated during cyclisation) it was possible to equilibrate **155** to a mixture favouring (9 : 1) the isomer with the correct configuration at C43.[201]

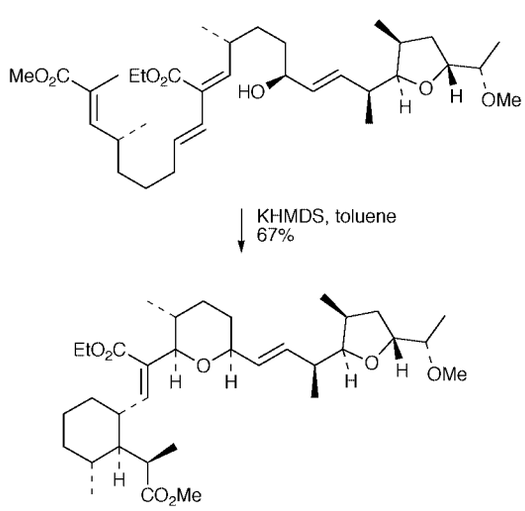



**Scheme 86**



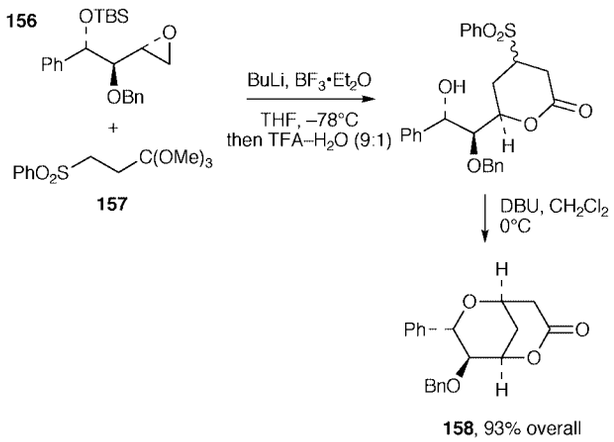

**Scheme 87**

Dankwardt *et al.* have reported a new approach to okadaic acid. In a recent series of publications, four fragments were prepared which between them contain the entire carbon skeleton of the natural product with all necessary functionality.[202] The non-spiroketal pyran ring was formed by intramolecular hydroxymercuration. A third total synthesis of this natural product has been reported by the Ley group, relying on the elaboration of a sulfone to form the aforementioned ring.[203] The same group's total synthesis of tetronasin features a spectacular double cyclisation, installing a tetrahydropyran and cyclohexane in a single step (Scheme 88).[204]

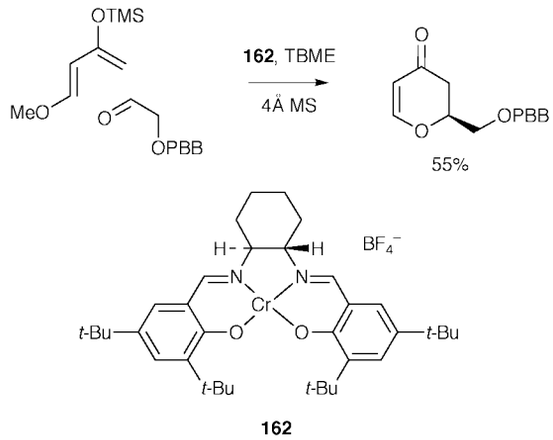



**Scheme 88**

A further conjugate addition approach provides a synthesis of the naturally occurring 8-*epi*-9-deoxygoniopypyrone. Opening of the epoxide **156** with the anion derived from **157** was followed by deprotection of the ortho ester and silyl ether with concomitant lactone formation. Elimination of benzenesulfinic acid was followed by intramolecular conjugate addition to give **158** which was debenzylated to give the natural product (Scheme 89).[205]

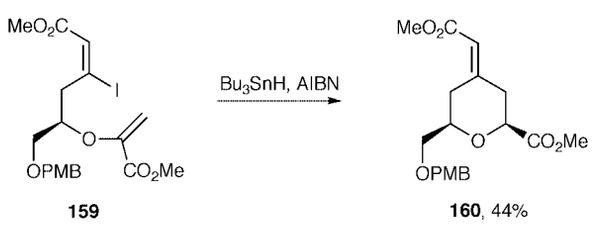



**Scheme 89**

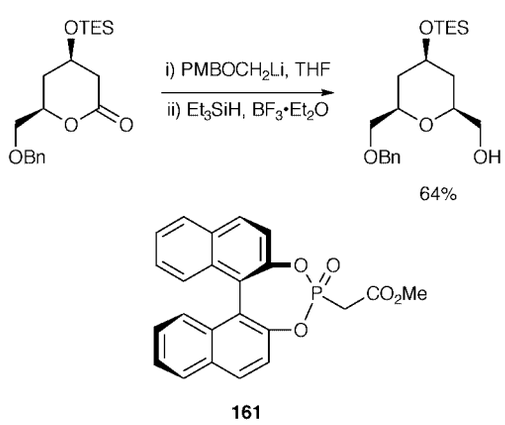



**Scheme 92**

The bryostatins are a group of macrolides with anti-cancer activity. In a new approach to these compounds, Thomas and co-workers have used a vinyl radical cyclisation (**159** to **160** (Scheme 90)) to prepare the key 2,6-*cis*-disubstituted tetrahydropyran.[206] Evans (and now distinguished co-workers!) has reported the first total synthesis of bryostatin 2, using lactone alkylation–reduction to prepare this ring (Scheme 91). The double bond was introduced after macrocycle formation by stereoselective olefination using chiral phosphonate **161**.[207]



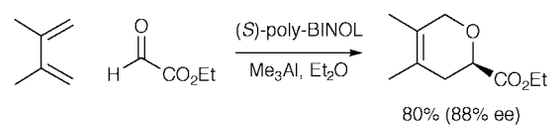

**Scheme 90**




**Scheme 91**

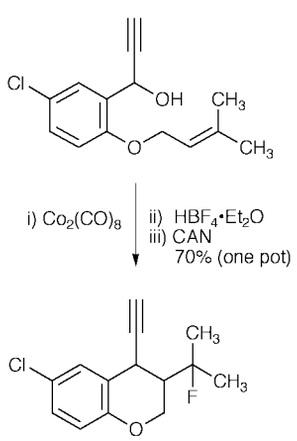
Some synthetic approaches to the tetrahydropyran rings of mucocin and muconin were discussed in the previous section.[183–186] Jacobsen and co-workers' synthesis of muconin relies heavily on epoxide building blocks, and uses an asymmetric hetero-Diels–Alder reaction to prepare the pyran ring (Scheme 92). Esterification and Ireland–Claisen rearrangement was then followed by ring-closing metathesis to form the tetrahydrofuran.[208]

Intermolecular oxa-Diels–Alder reactions of *o*-quinomethanes have also been used to prepare chromanes. In this case, the reactions were best carried out in nitromethane with $LiClO_4$ as additive and wet Montmorrilonite clay as catalyst.[209] BINOL and related ligands have previously been used in asymmetric oxa-Diels–Alder reactions. Aluminium complexes of BINOL polymers have now been used, and give high enantioselectivity (Scheme 93).[210] Cobaloxime-substituted dienes have been used to provide *exo* selectivity in oxa-Diels–Alder reactions.[211] Jørgensen and co-workers have used copper–bisoxazoline complexes as catalysts with both oxadienes (β,γ-unsaturated-α-ketoesters)[212] and with oxadienophiles (ketones).[213] Evans *et al.* obtained similar results in the former process.[214]




**Scheme 93**

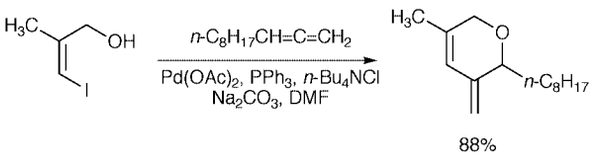
A further method involves an intramolecular Nicholas reaction as shown in Scheme 94. Leaving the reaction longer prior to oxidative decomplexation results in proton loss from the intermediate carbenium ion being the major reaction pathway.[215]



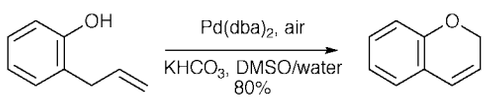

**Scheme 94**

A palladium-catalysed annulation reaction from Larock *et al.* provides access to *exo*-methylenedihydropyrans (Scheme 95).[216] Oxidative addition of the initial organopalladium species to the allene to form a π-allyl palladium intermediate is followed by nucleophilic attack. A second method from the same group provides a general approach to chromenes (Scheme 96).[217] Incorporation of vinyl halides or triflates into the reaction medium results in a Heck-type coupling prior to cyclisation (Scheme 97).[218]

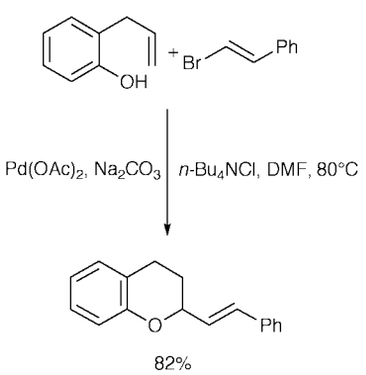
A further palladium-catalysed method involves the preparation of caparrapi oxide **163** and its epimer **164** by allylic




**Scheme 95**

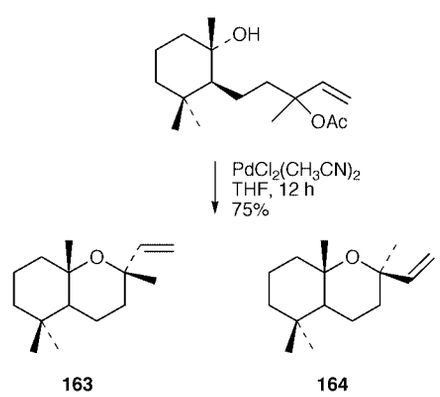



**Scheme 96**




**Scheme 97**

substitution (Scheme 98).[219] A related method involves generation of the π-allyl species by hydropalladation of an allene.[220]



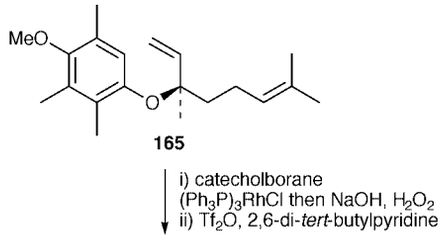

**Scheme 98**

Trost and Toste's asymmetric synthesis of chromanes relies on palladium catalysed allylic alkylation to form the carbon–oxygen bond in **165** followed by electrophilic substitution to form the ring (Scheme 99).[221]

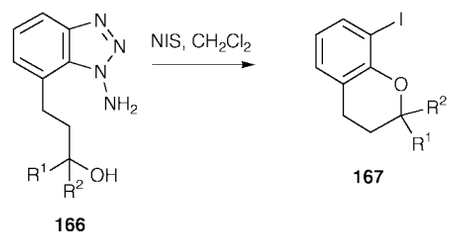
Knight and Little have reported a new approach to chromanes and chromenes based on intramolecular benzyne-trapping chemistry. Compounds **166**, prepared *via* Sonogashira coupling followed by hydrogenation, were treated with *N*-iodosuccinimide in dichloromethane to give the chromanes **167** in excellent yields (Scheme 100). Partial hydrogenation of the Sonogashira product led to chromenes.[222] An analogous method led to xanthene formation.[223]

Palladium-catalysed alkoxycarbonylation was discussed in the previous section (Scheme 58). Application of this reaction to **168** gave **169** in acceptable yield (Scheme 101). The reaction proved very sensitive to stereochemical effects.[224]

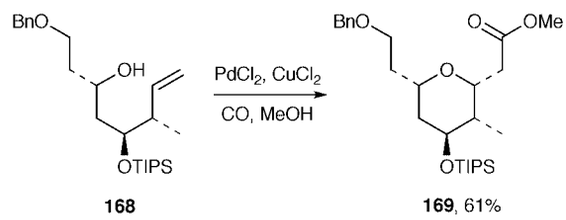
Bowman and McDonald have reported an iterative synthesis of poly-fused tetrahydropyrans using tungsten chemistry. Propargylation of dihydropyran **170** was followed by a two-step




**Scheme 99**

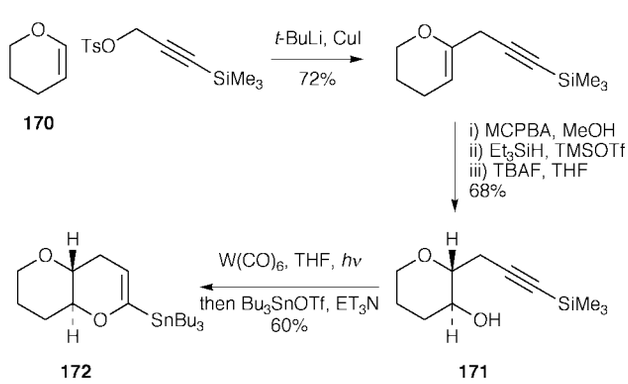



**Scheme 100**




**Scheme 101**

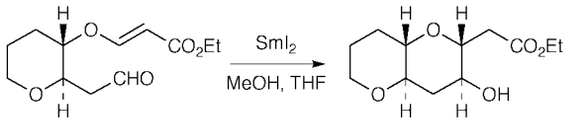
selective oxidation of the enol ether (Scheme 102). Treatment of **171** with tungsten hexacarbonyl followed by tributyltin triflate gave **172**.[225] The same group have reported an approach to similar compounds by *endo* cyclisation of cyclic sulfates.[226]




**Scheme 102**

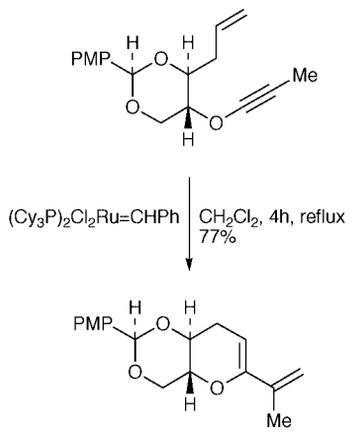
A further iterative approach is shown in Scheme 103. Treatment of **173** with samarium(II) iodide gave **174** in excellent yield. Transformation of the alcohol into a β-alkoxyacrylate and reduction of the ester to the aldehyde allowed repetition of the sequence to give a tetra-fused tetrahydropyran.[227]

The use of olefin metathesis in the preparation of polycyclic medium ring ethers of marine origin is discussed in the following section. Enyne metathesis is a less common strategy which is most efficient for six-membered rings (Scheme 104), seven-membered rings being produced in up to 33% yield.[228]




173 174, 92%

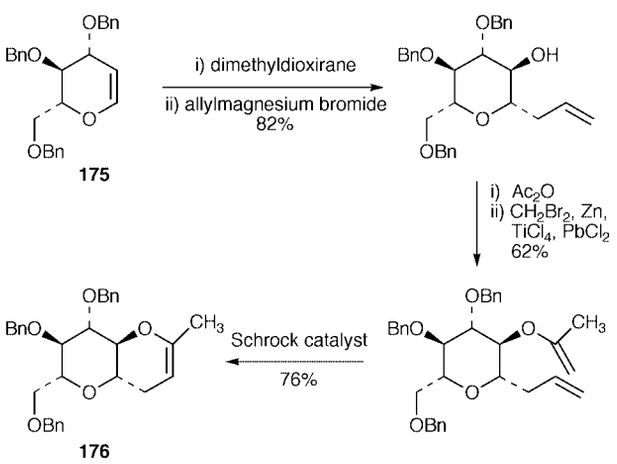
**Scheme 103**




**Scheme 104**

Others have shown that ruthenium allenylidenes catalyse a similar process to give 2,5-dihydro-3-vinylfurans.[229]

Another iterative approach is shown in Scheme 105 in which tribenzyl-D-glucal **175** is epoxidised with dimethyldioxirane, followed by epoxide opening with allylmagnesium bromide. Acetylation and methylenation was followed by ring-closing metathesis to give **176**, which was then subjected to a similar sequence of reactions.[230] An improved sequence introduces the three-carbon fragment with a terminal acetal so that the next ring can be created by simple cyclic enol ether formation.[231]



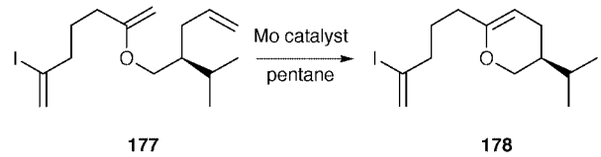

**Scheme 105**

In the above sequence, the Schrock catalyst is generally superior for the metathesis of enol ethers. However, Grubbs' ruthenium catalyst can be used in some cases.[232]

In these reactions, initial metathesis takes place at the least hindered double bond in **177** leading to **178** a step towards a formal total synthesis of (−)-periplanone B (Scheme 106).[233] Spirocyclic pyrans have also been prepared by olefin metathesis.[234]

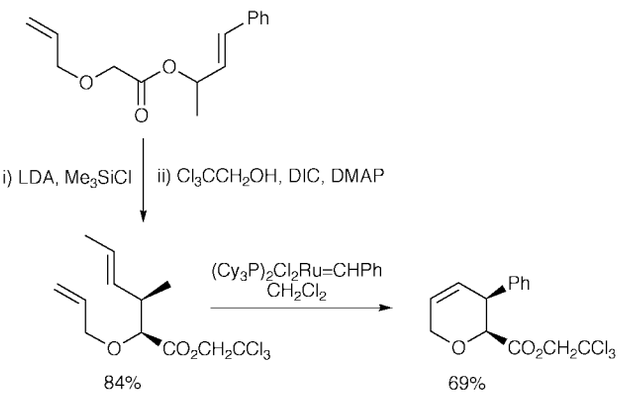
An elegant approach from Burke *et al.* uses a glycolate Claisen rearrangement to prepare the substrate for ring-closing metathesis (Scheme 107).[235]

The same group have used a ring-opening–ring-closing metathesis strategy to prepare a bis-tetrahydropyran as a precursor to halichondrin B (Scheme 108).[236] After zirconium-

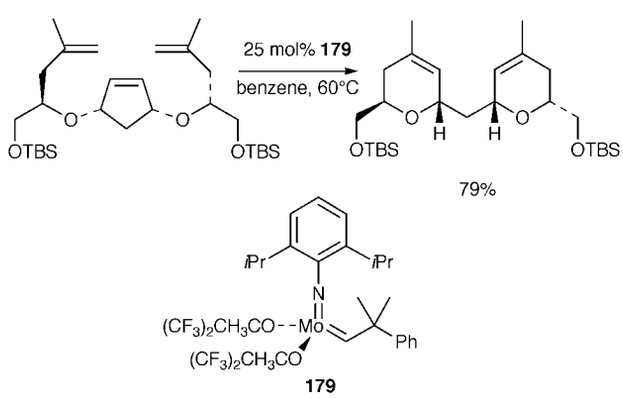



177 178

**Scheme 106**



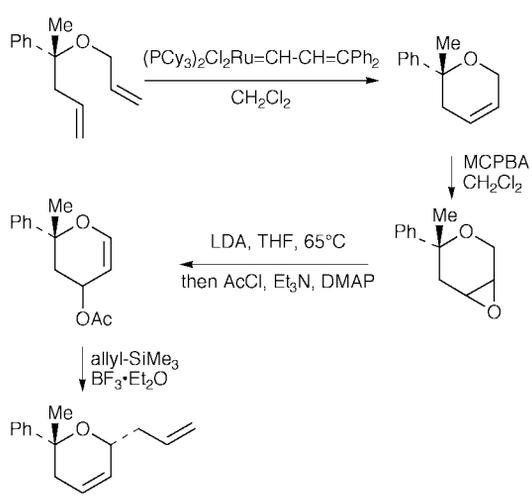

**Scheme 107**



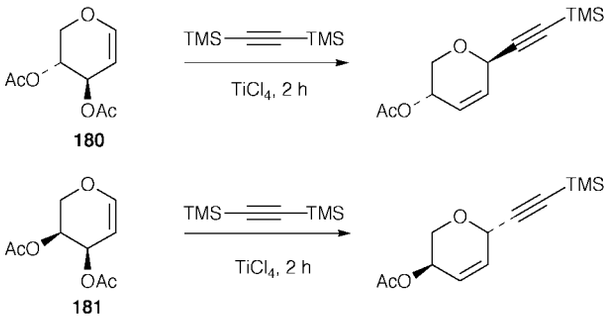

**Scheme 108**

catalysed resolution of an allylic ether precursor, Hoveyda and co-workers have used an essentially identical strategy to prepare chromenes.[237]

Schmidt has combined ring-closing metathesis and Ferrier rearrangement as shown in Scheme 109.[238] Isobe and co-workers have extended earlier work on this rearrangement by showing that compounds **180** and **181** give enantiomeric products in good yield and with high 1,4-*anti* stereocontrol (Scheme 110). This is in direct contrast with the reaction of tri-*O*-acetyl-D-glucal.[239]

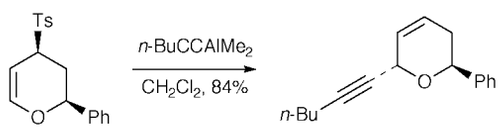



**Scheme 109**



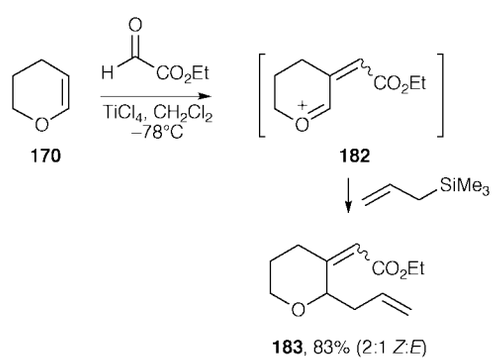

**Scheme 110**

The method of Craig and co-workers is slightly more general in the range of nucleophiles which have been used (alkyl, alkenyl, alkynyl). Stereochemical observations support a dissociative cationic mechanism (Scheme 111).[240] Other examples of the use of enol ethers in *C*-glycosidation have been reported.[241]




**Scheme 111**

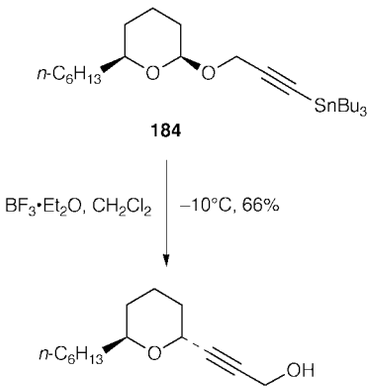
A related three-component coupling has been reported by Ghosh and Kawahama, whereby the dihydropyran **170** reacts first with ethyl glyoxylate under Lewis acidic catalysis (Scheme 112). The intermediate oxonium ion **182** is then trapped by a nucleophile to give the isolated product **183**. Carbon, hydrogen, oxygen and sulfur nucleophiles were demonstrated.[242]



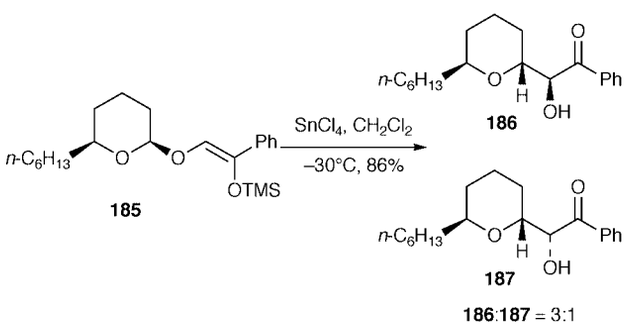

**Scheme 112**

Allylation of sugar derivatives has also been used by Keck and Lundquist to prepare the C19–C32 portion of swinholide A,[243] by Roberts and co-workers to prepare fragments related to altohyrtin A,[244] and by Nakamura *et al.* to prepare the C67–C77 portion of zooxanthellatoxin, establishing the absolute stereochemistry of this portion.[245] A further procedure related to *C*-glycosidation is the anomeric rearrangement reported by Ley and co-workers. Propargyl ethers (prop-2-ynyl ethers) such as **184** undergo efficient rearrangement as shown in Scheme 113.[246] Similarly, silyl enol ethers such as **185** rearrange cleanly to a mixture of diastereoisomers **186** and **187** (Scheme 114).[247] An intermolecular version of the former reaction has been used by Isobe and co-workers in the synthesis of a mannosyl-tryptophan derivative.[248]

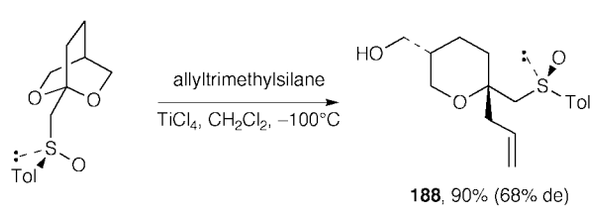
A novel related reaction relies on diastereoselective opening of a bicyclic acetal directed by a chiral sulfoxide. Either C–O bond could be broken, resulting in diastereoisomers at the 5-position, and the allyl group could approach either side of the resulting oxonium ion. In practice, the (2*S*,5*S*) isomer **188** was predominant (up to 84% of the mixture) (Scheme 115).[249]




**Scheme 113**



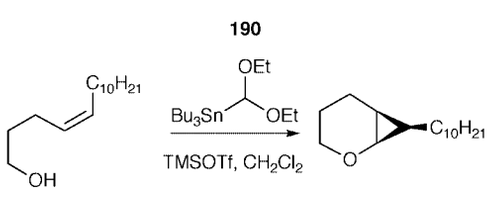

**Scheme 114**




**Scheme 115**

In a similar approach using an unsymmetrical acetal, a five-membered ring was formed at the expense of a six-membered ring in the preparation of an acetogenin fragment.[250]

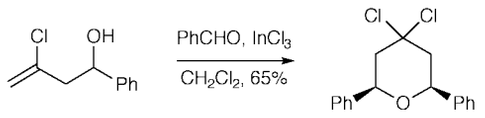
An interesting acetal-based approach leads to cyclopropannulated tetrahydrofurans, tetrahydropyrans and oxepanes. Treatment of **189** with **190** and trimethylsilyl triflate gave **191** in excellent yield (Scheme 116).[251]



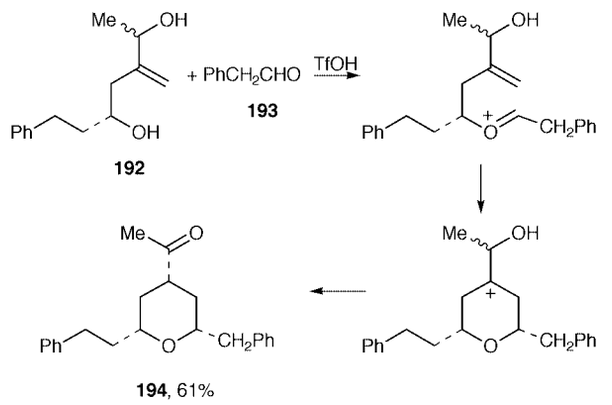

**Scheme 116**

The use of indium reagents has become more prominent in recent years. Yang and co-workers have used indium(III) chloride in the Prins reaction to form 4,4-dichlorotetrahydropyrans (Scheme 117).[252]

A sequence involving Prins cyclisation followed by pinacol rearrangement has been demonstrated by Cloninger and Overman. Treatment of a mixture of **192** and **193** with trifluoromethanesulfonic acid gave **194** *via* oxonium ion formation, cyclisation and hydride shift (Scheme 118).[253] Related allylsilane cyclisations have also been reported.[254]

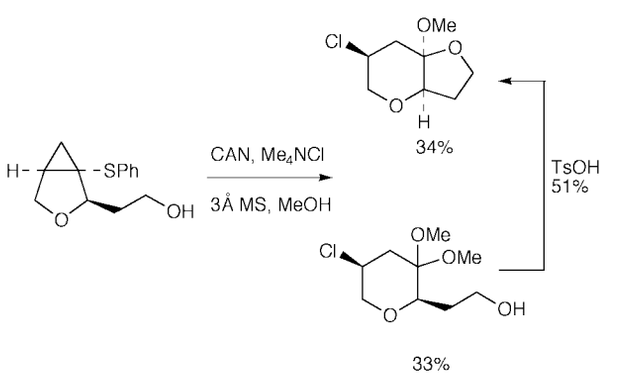



**Scheme 117**

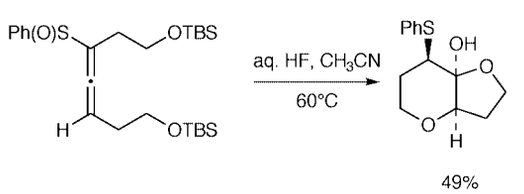



**Scheme 118**

Oxidative ring-opening of appropriately substituted cyclopropyl sulfides provides access to fused and monocyclic pyrans (Scheme 119). The use of methanol as solvent proved central in suppressing sulfoxide formation.[255] Similar compounds were prepared by Parsons and co-workers in a double cyclisation followed by Pummerer rearrangement (Scheme 120).[256]

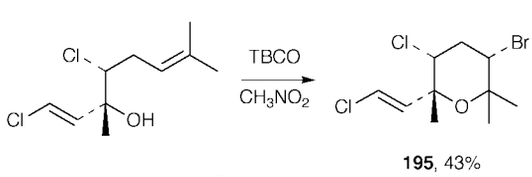



**Scheme 119**




**Scheme 120**

Aplysiapyranoid C **195**, a cytotoxic tetrahydropyran of marine origin, has been prepared by intramolecular bromoetherification using tetrabromocyclohexadienone (TBCO) (Scheme 121).[257]

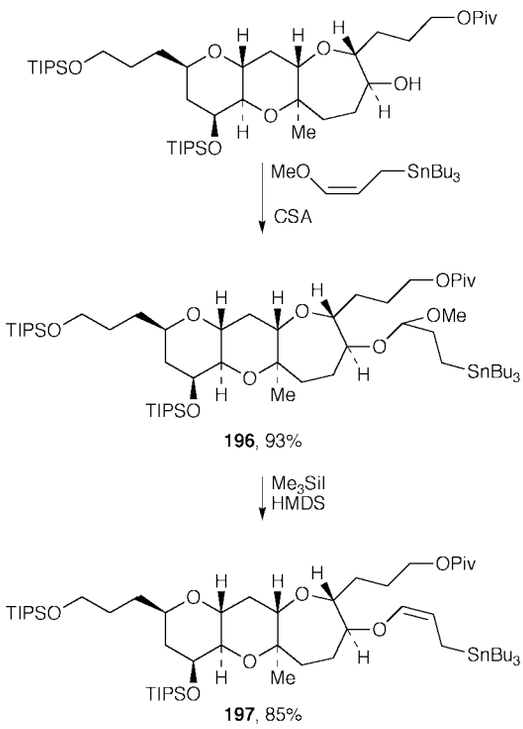



**Scheme 121**

## 6 Medium sized rings

Hoberg has reviewed the formation of oxepanes, covering the literature from 1994 through mid-1998.[258] Some material in this review will also be covered here in keeping with the timeframe of the review. Molander has also presented a short account of his group's work in the area of medium ring synthesis, mainly carbocyclic but with some examples of oxepane formation.[259] A detailed account has been published of Hirama and co-workers' preparation of medium ring ethers using ring expansions.[260]

Kadota and Yamamoto's 1995 synthesis of hemibrevetoxin B is a landmark synthesis slightly marred by the low yielding (16%) formation of the allylstannane **197** prior to formation of the fourth ring. However, this problem has been alleviated by a new method for the preparation of **197** *via* the mixed acetal **196** (Scheme 122).[261] A full account of Mori *et al.*'s formal total synthesis of this natural product, convergent with that of Kadota and Yamamoto, has also been published.[262]

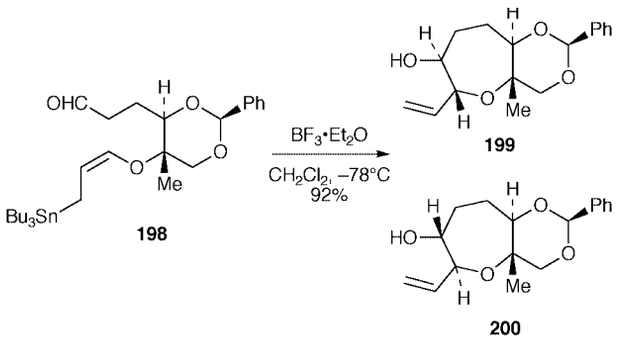



**Scheme 122**

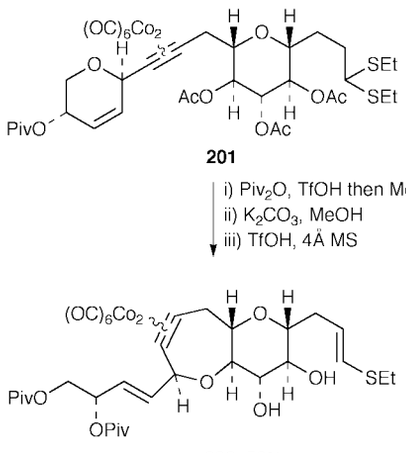
The cyclisation of such a compound is exemplified in Scheme 123 with the preparation of the E ring of gambierol, albeit not in a straightforward manner. Treatment of **198** with boron trifluoride–diethyl ether gave a mixture of desired **199** and undesired **200** stereoisomers in a ratio of 30 : 70. Fortunately it was possible to invert both of the undesired stereocentres of **200** using a high-yielding seven step sequence.[263] A compound analogous to **198** but lacking the methyl group at the ring junction cyclised cleanly (98% yield) giving only the desired stereoisomer, showing the sensitivity of such reactions to small changes.[264] A full account of related cyclisations onto imines has also been published.[265]

Isobe *et al.* have reviewed the use of sugar acetylenes in synthesis, including the application of this chemistry to ciguatoxin subunits.[266] For instance, compound **201**, prepared by a Ferrier-type alkynylation, underwent methanolysis with concomitant pivaloylation of the newly liberated primary alcohol. Removal of the three acetate protecting groups was followed by cyclisation to the oxepane **202** (Scheme 124).[267]

Ciguatoxins[268] have been popular targets in recent years. Hirama's group have reported a synthesis of a 7,6,6,7,7 ring system **203** corresponding to the ABCDE rings of these natural products. Two of the seven-membered rings were formed by ring-closing metathesis, the last of which is shown in Scheme

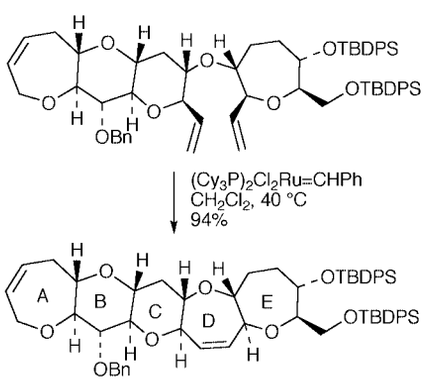



**Scheme 123**




**Scheme 124**

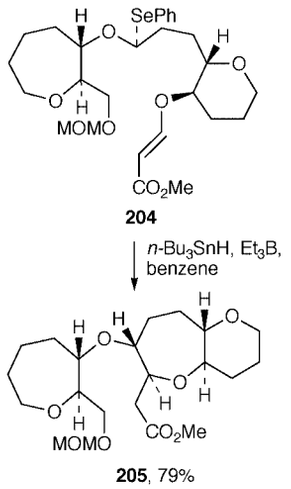
125.[269] The same group have also reported a similar approach to eight-, nine- and ten-membered rings.[270]



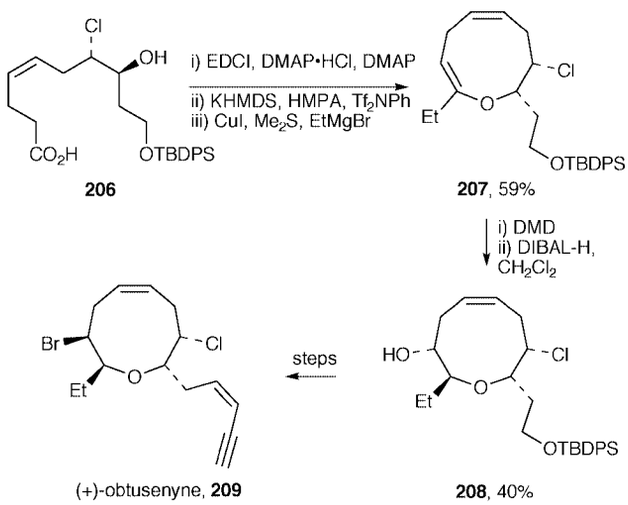

**Scheme 125**

Free radical cyclisations to form seven-membered rings are less common than for other ring sizes. However, the relatively complex precursor **204** underwent clean and stereoselective cyclisation to give **205** in 79% yield along with a small amount of product derived from reduction of the initially formed radical (Scheme 126).[271]

Of the *Laurencia* metabolites, (+)-obtusenyne **209** has arguably proved most difficult to synthesise. Murai's group at Hokkaido University have proved equal to the challenge, preparing the key nine-membered ring by lactonisation followed by enol triflate cross-coupling (**206** to **207**) (Scheme 127). Epoxidation of the enol ether double bond was followed by immediate reduction with DIBAL-H to give 40% of **208**. From this point, introduction of bromine was followed by side-chain elaboration to give the natural product.[272]

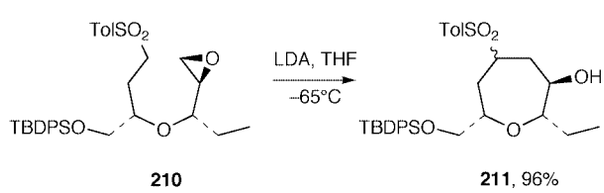



**Scheme 126**




**Scheme 127**

The substrate **210**, prepared by hetero-Diels–Alder reaction of a chiral aldehyde followed by ozonolysis of the double bond and subsequent elaboration, underwent extremely high yielding epoxide opening to give **211** (Scheme 128). Surprisingly no 6-*exo* opening was observed.[273]

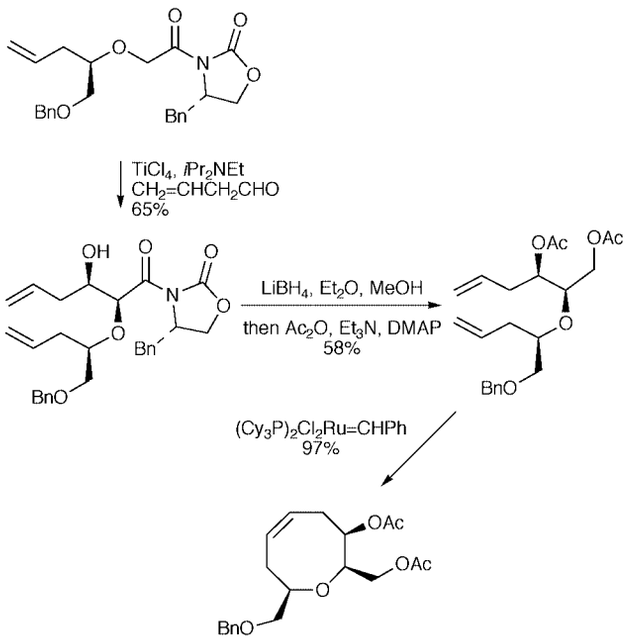



**Scheme 128**

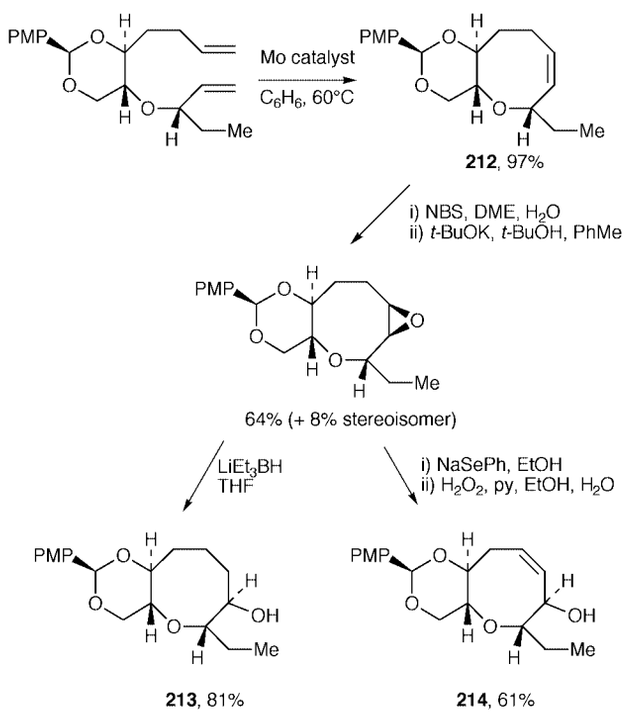
Crimmins and Choy had previously reported the use of the Evans' aldol reaction followed by ring-closing metathesis in the preparation of cyclic ethers. A full account of this work has been recently published, which describes the preparation of seven-, eight- and nine-membered rings by this method, as well as a formal total synthesis of (+)-laurencin (Scheme 129).[274] A similar approach has been reported by Taylor and co-workers making effective use of enzymatic desymmetrisation.[275]

Clark *et al.* have also used ring-closing metathesis to prepare 7- and 8-membered rings. Despite the relative flexibility of the oxocane ring, good stereoselectivity was observed in the epoxidation of **212**. This was then opened either with hydrogen or selenium nucleophiles to provide **213** and **214** (Scheme 130).[276]

Grigg *et al.*'s approach makes use of ring-closing metathesis followed by intramolecular Heck reaction as shown in Scheme




**Scheme 129**



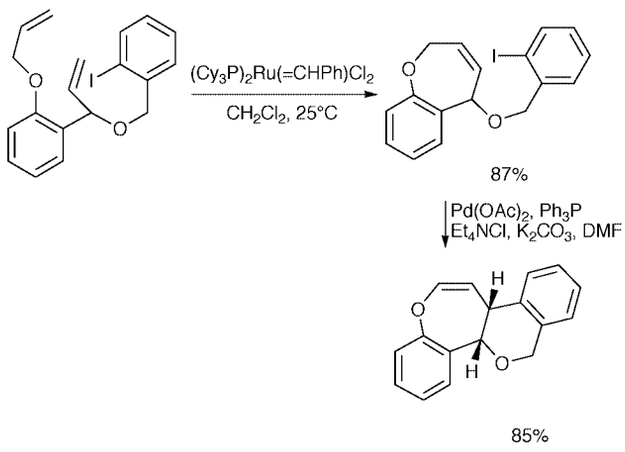

**Scheme 130**

131. This sequence can be carried out as a one-pot process with comparable overall yield.[277]

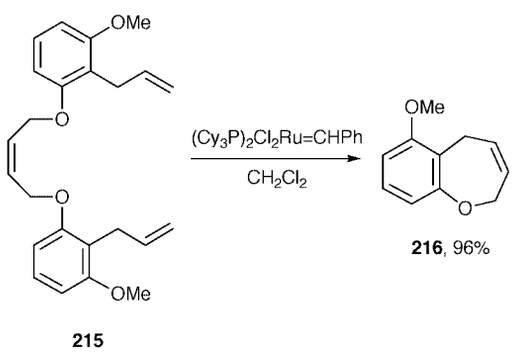
Stefinovic and Snieckus have use directed *ortho* metallation to prepare substrates for metathesis. The formation of **216** from **215** is particularly impressive (Scheme 132).[278]

One final example of olefin metathesis in this context is from the group of Mioskowski, who have shown that it is possible to prepare more than one ring in a single step. Treatment of bis-allylic ether **217** with the usual Grubbs' catalyst gave **218** in good yield (Scheme 133). Five- and six-membered rings were also prepared by this method.[279]

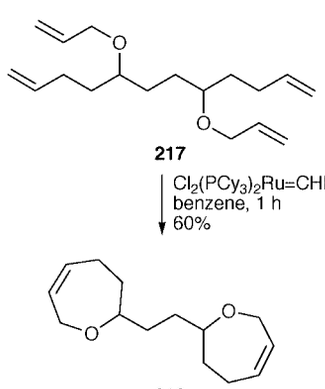
Nakata and co-workers have previously reported ring expansions of tetrahydrofuran and tetrahydropyran mesylates. Not surprisingly the use of chloromethanesulfonates allows these reactions to be conducted at lower temperature. For the reaction shown in Scheme 134 the mesylate required 2 hours at reflux to give similar yields, while 4 days at room temperature



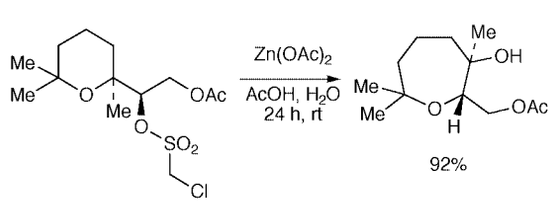

**Scheme 131**




**Scheme 132**



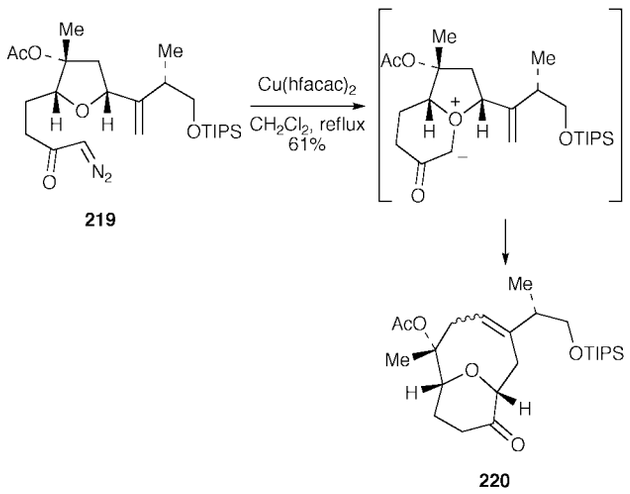

**Scheme 133**




**Scheme 134**

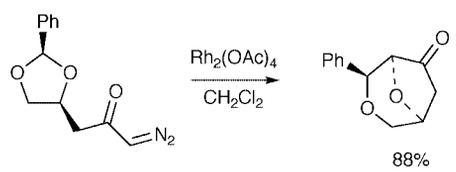
gave little conversion. For the chloromethanesulfonate a similar yield was obtained in 2 hours at 50 °C, although a mixture of alcohol and acetate was formed at the 3-position.[280]

Clark *et al.*'s approach to neoliacinic acid relies heavily on the transition metal-catalysed decomposition of diazo compounds. The precursor **219**, the five-membered ring of which was prepared by rhodium(II) mediated C–H insertion, underwent copper(II) catalysed ylide generation and [2,3] sigmatropic rearrangement to give **220** with the bicyclic core of the target natural product (Scheme 135).[281]



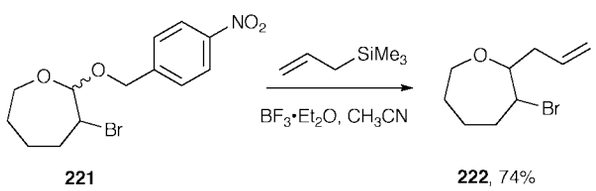

**Scheme 135**

The fate of such ylides can be extremely substrate-dependent. In the work of Tester and West, the ylides formed undergo [1,2] shifts to form bicyclic products (Scheme 136).[282]




**Scheme 136**

As with other ring sizes, conversion of lactones or lactols into the cyclic ether is a common strategy for oxepane formation. Treatment of **221** with allyltrimethylsilane and boron trifluoride–diethyl ether gave a single (unassigned) diastereoisomer of **222** (Scheme 137). When the reaction was carried out in liquid sulfur dioxide at −20 °C, no catalyst was needed, although the iodide corresponding to **221** (methyl acetal) underwent dehalogenation.[283]




**221** **222**, 74%

**Scheme 137**

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