Saturated oxygen heterocycles

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Reviewing the literature published between 1 October 1995 and 30 September 1996 (3–6 membered rings), and between 1 July 1994 and 30 September 1996 (7 membered rings and larger) Continuing the coverage in *Contemporary Organic Synthesis*, 1996, **3**, 229 (3–6 membered rings) and 1994, **1**, 457 (7 membered rings and larger).

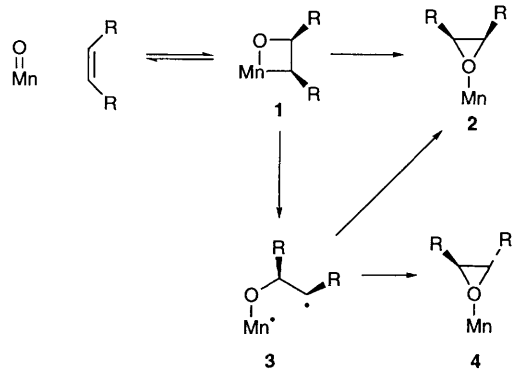
1 Introduction

The synthesis of cyclic ethers of all sizes has continued unabated during the last 12 months. Owing to the large amount of material published, this review makes no effort to cover the area comprehensively. Instead, appropriate examples have been selected in order to demonstrate general trends in the area. In many cases, a single method has been used for the preparation of a number of different ring sizes. In these cases, the method has been included in the section which appeared to be most appropriate according to the slightly arbitrary considerations of efficiency and applications of the methodology. All sizes of ring are included in this article; in previous reviews small and medium rings were considered separately.[1,2]

2 Three membered rings

Epoxides are versatile synthetic building blocks which are constantly finding new applications. For example, a recent report of oxiranyl peptides was prompted by the discovery that such compounds function as protease inhibitors by irreversible covalent binding to the active site of the enzyme.[3]

Undoubtedly one of the highlights of recent years is the development of efficient catalysts for asymmetric epoxidation.[4] Two groups have postulated likely mechanisms for the enantioselection in Mn(salen)-catalysed epoxidations. Norrby, Linde and Åkermark have taken into account conformational changes in the ligand during the reaction, and propose that a metallaoxetane **1** is initially (and reversibly) formed, which then rearranges to a metal-bound epoxide **2** either directly or *via* a diradical **3** (which explains the formation of *trans*-epoxides **4** from *cis*-olefins) (**Scheme 1**). Molecular mechanics calculations show considerable distortion of the ligand in the metallaoxetane intermediate.[5]



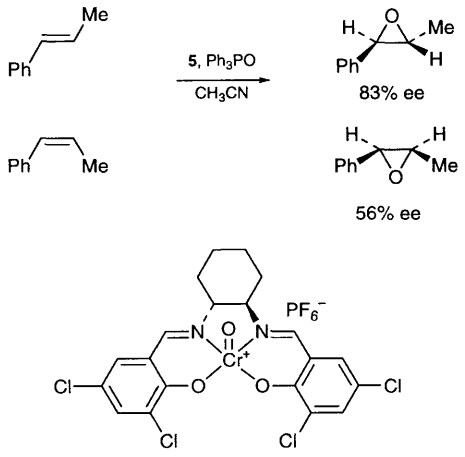
Scheme 1

Non-linear temperature effects observed by Katsuki also point to a mechanism whereby reversible formation of diastereoisomeric intermediates is followed by irreversible conversion to product. Although radicals have been implicated in manganese(salen)-catalysed epoxidation reactions, the reversible formation of a radical in this case seems unlikely, and the results seem to be better explained by a mechanism involving a metallaoxetane.[6] Katsuki considers the approaches of the olefin to the metal, and the steric interactions involved in the rotation of the olefin to achieve a geometry suitable for metallaoxetane formation, as the driving force for the observed enantioselectivity.

Mn–salen catalysts are normally more efficient for the epoxidation of *Z*-alkenes. It is therefore interesting to note that Cr–salen complexes **5** give higher selectivities for *E*-alkenes (**Scheme 2**).[7]

Similar catalysts have been used by Jacobsen for the kinetic resolution of terminal epoxides by azide ring opening.[8] In the case of styrene oxide **6**, allowing the reaction to proceed to 76% conversion permits recovery of epoxide (*R*)-**6** of 98% ee (**Scheme 3**).[9]

A novel catalytic cycle for the generation of epoxides from sulfur ylides and aldehydes was



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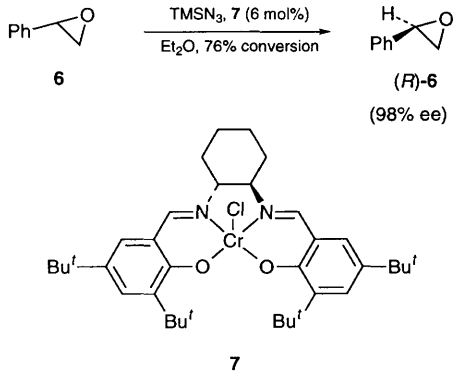
Scheme 2



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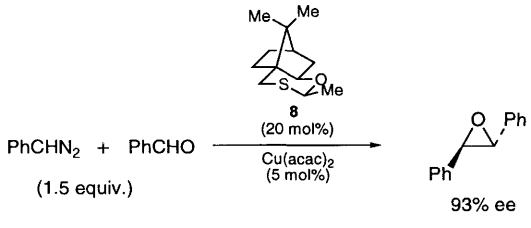
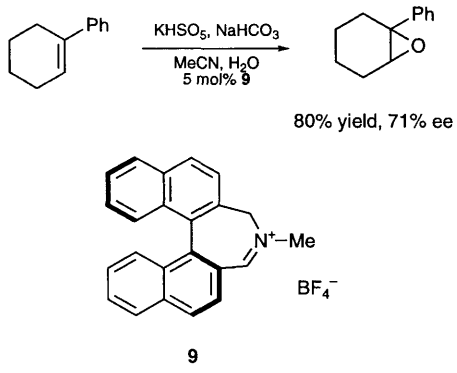
Scheme 3

reported by Aggarwal and co-workers in 1994. The same group now report that the use of a chiral nonracemic sulfide **8** in this reaction can give rise to epoxides of up to 93% ee. This is the highest reported selectivity for the epoxidation of stilbene (**Scheme 4**).[10]



Scheme 4

Aggarwal has also recently reported a new catalytic asymmetric system for epoxidation reactions based on the *in situ* generation of oxaziridines.[11] Using Oxone as a nucleophilic terminal oxidant, and iminium salt **9** as an oxygen transfer reagent, epoxides were produced in up to 71% ee (**Scheme 5**). This method is environmentally and industrially attractive, since cheap reagents are used, and no transition metal waste is produced.



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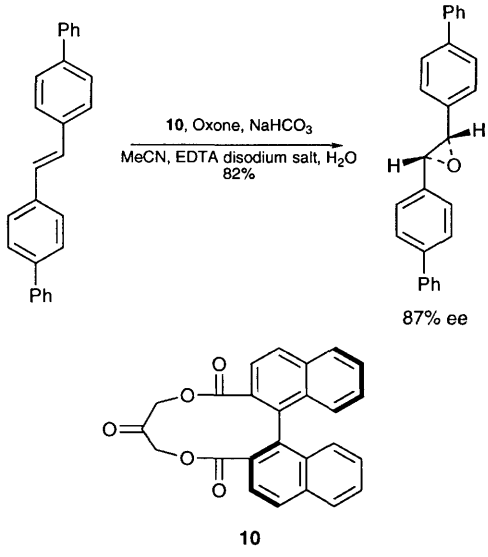
Scheme 5

Olefins are epoxidised with moderate to good ee by reaction with ketone **10** in the presence of Oxone (**Scheme 6**).[12] The reaction presumably proceeds *via* a dioxirane, although a recent report casts doubt on the intermediacy of dioxiranes in some reactions in which they had previously been implicated.[13]



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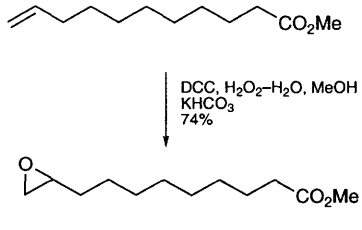
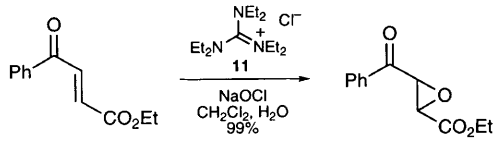
Scheme 6

Dicyclohexylcarbodiimide (DCC) acts as an oxygen-relay in the epoxidation of simple olefins by dilute aqueous hydrogen peroxide (**Scheme 7**). The presumed intermediate, a peroxyurea, is isoelectronic with a peracid.[14]



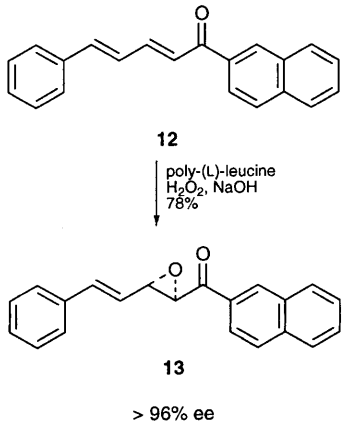
Scheme 7

Electron-deficient olefins are efficiently epoxidised by sodium hypochlorite in dichloromethane–water using guanidinium salt **11** as phase transfer catalyst (**Scheme 8**).[15]



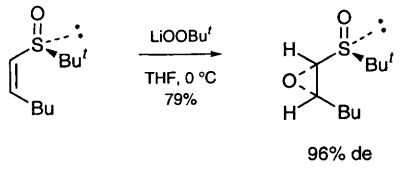
Scheme 8

The Juliá asymmetric epoxidation of substituted chalcones using poly(amino acids) as catalysts has received little attention compared to other methods of asymmetric epoxidation. The reaction will no doubt gain popularity following the recent report that a wide range of unsaturated ketones can be epoxidised selectively using this method (*e.g.* **12** to **13**) (**Scheme 9**).[16]



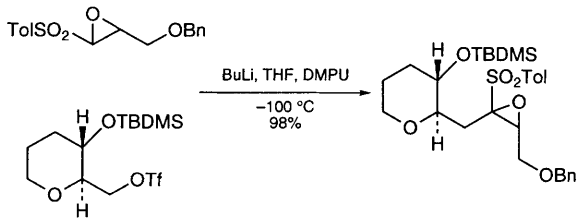
Scheme 9

The directing effect of an adjacent chiral sulfur atom has been used in the diastereoselective epoxidation of vinyl sulfoxides. In favourable cases (*e.g.* **Scheme 10**), extremely high diastereoselectivities were observed.[17]



Scheme 10

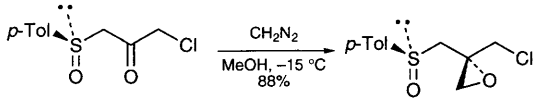
Since epoxidation is faster than oxidation to the sulfone, this approach can be used to prepare oxiranyl sulfones in enantiomerically enriched form. These compounds can then be deprotonated and the resulting anions subjected to electrophilic quench as shown in **Scheme 11** (also see **Scheme 60**).[18,19]



DMPU = 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one

Scheme 11

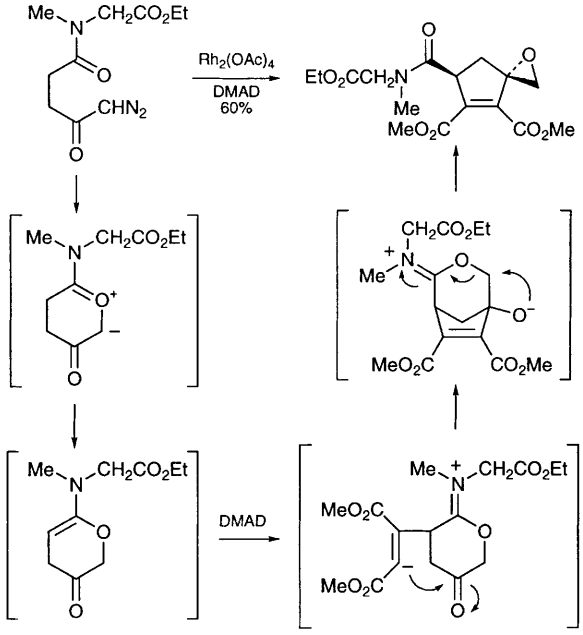
Another report on the diastereoselective epoxidation of sulfoxides utilises the addition of diazomethane to ketones (**Scheme 12**). The products are useful as precursors to chiral nonracemic amino alcohols, chloro alcohols and related compounds.[20]



60% de

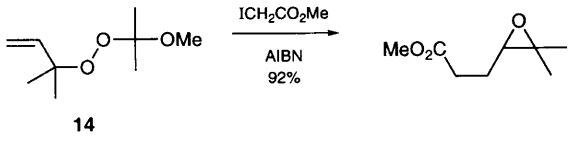
Scheme 12

Spirocyclic epoxides are formed from diazo compounds by a novel cascade process shown in **Scheme 13**. In all cases the epoxide was spirocyclic to a five-membered ring, and the reaction is not limited to the use of dimethyl acetylenedicarboxylate.[21]



Scheme 13

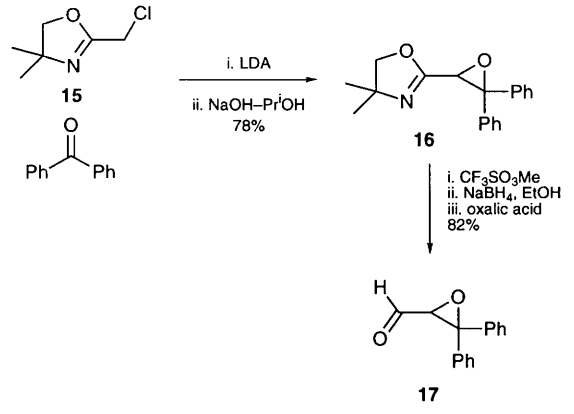
Radical addition to unsaturated peroxyketals **14** followed by fragmentation provides a high yielding synthesis of epoxides (**Scheme 14**). This reaction is less efficient with simple alkyl halides, since the



Scheme 14

methyl radicals formed by the eventual fragmentation of **14** can enter into the cycle leading to the production of ethyloxiranes at the expense of the desired products.[22]

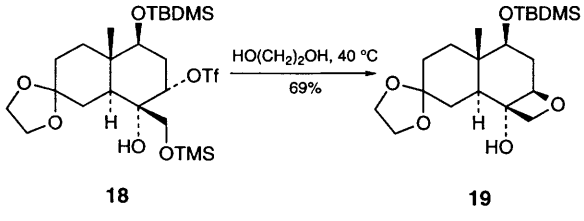
(Chloromethyl)oxazoline **15** participates in a Darzens-type condensation to give epoxides such as **16**. This was then reduced to the corresponding epoxyaldehyde **17** (**Scheme 15**).[22]



Scheme 15

3 Four membered rings

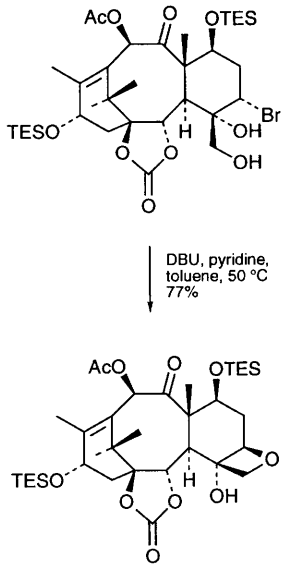
Taxol is probably the most illustrious natural product which contains an oxetane ring. Three total syntheses have been published to date, along with numerous partial syntheses. The Danishefsky synthesis features the direct and somewhat surprising conversion of **18** into **19** to establish the four membered ring (**Scheme 16**).[24]



Scheme 16

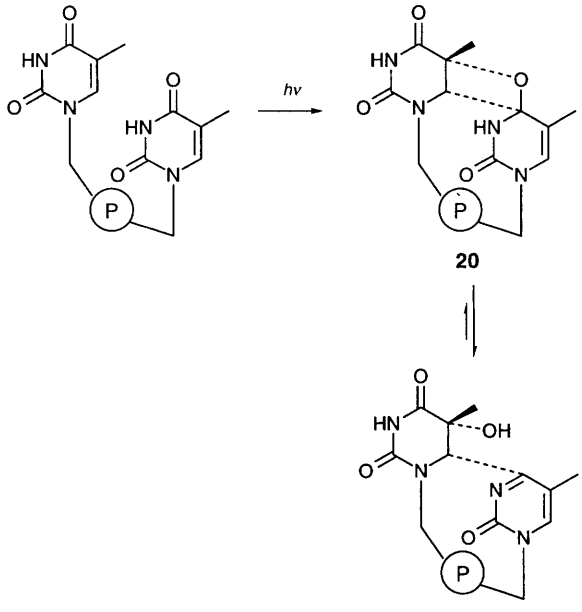
In a relay-based approach, Mukaiyama elected to introduce the oxetane at a later stage as shown in **Scheme 17**.[25]

Oxetanes have been implicated in photochemical DNA damage. In the biological systems these oxetanes are rapidly opened, and it has been suggested that the mode of action of DNA

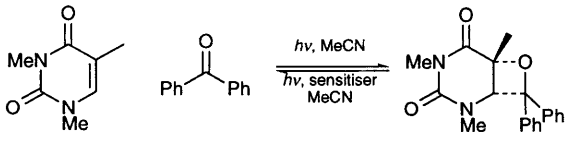


Scheme 17

photolyases (enzymes which repair this damage) is due to the ability of the enzyme to favour the oxetane form **20** (**Scheme 18**). Model studies by Prakash and Falvey have demonstrated the photochemical formation and sensitised photochemical splitting of related oxetanes as shown in **Scheme 19**.[26]

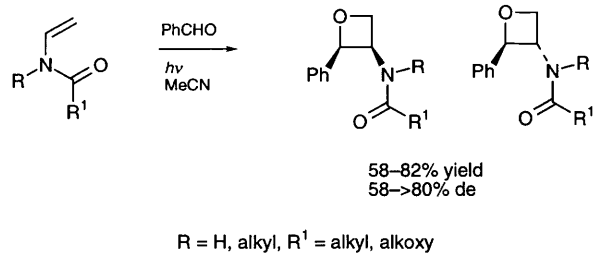


Scheme 18



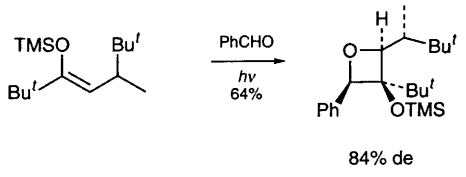
Scheme 19

The Paternò–Büchi reaction is the classical method for the preparation of oxetanes. Bach has reported such reactions of *N*-acylenamines to give 2-substituted 3-aminooxetanes with good regio- and diastereo-selectivity (**Scheme 20**).[27]



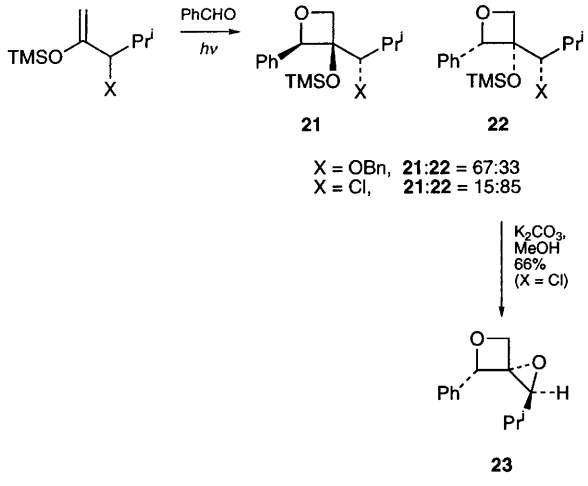
Scheme 20

Diastereofacially selective Paternò–Büchi reactions of β-chiral silyl enol ethers were also reported to provide useful highly functionalised oxetanes (**Scheme 21**).[28]



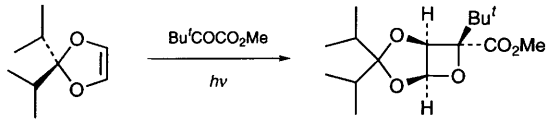
Scheme 21

Silyl enol ethers with chiral substituents at the α-position have been less successfully used in Paternò–Büchi reactions. Bach has now shown that some selectivity can be obtained in these reactions, and that this can be reversed by replacing a benzyloxy group on the stereogenic centre with a chlorine atom (**Scheme 22**). The major diastereoisomer in this case was converted into the novel spiro oxetane **23**. The origin of this selectivity is, as yet, unclear.[29]



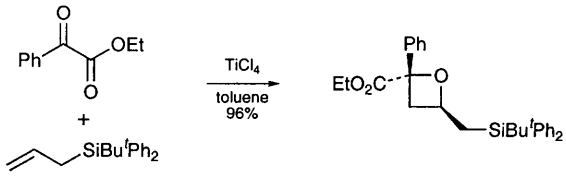
Scheme 22

The Paternò–Büchi reaction shown in **Scheme 23** gives extremely high selectivity for the *endo* Bu^t diastereoisomer, despite the *exo* isomer being significantly more stable. This result has been rationalised in terms of spin–orbit coupling.[30]



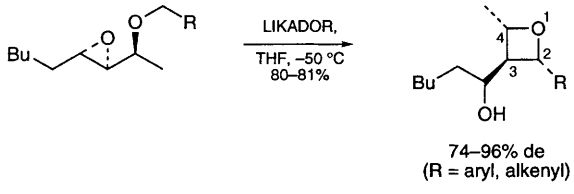
Scheme 23

A stepwise Lewis acid-promoted cycloaddition related to the Paternò–Büchi reaction has also been reported (**Scheme 24**). The presence of bulky groups on silicon is essential in order to realise a high yield of the oxetane.[31]



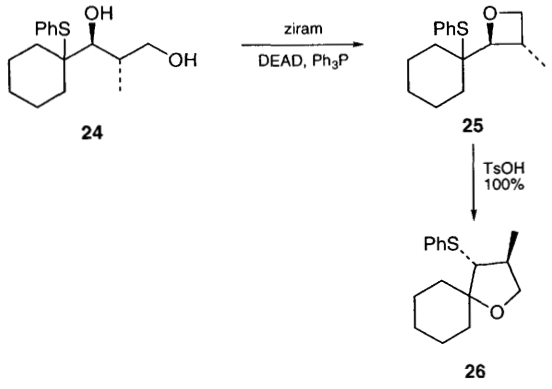
Scheme 24

Oxetanes are produced stereoselectively by LIKADOR (BuLi–Pr$^i_2$NH–Bu^{t}OK) promoted 4-*exo* cyclisation of oxiranyl ethers (**Scheme 25**). Since the requisite epoxides can be prepared by Sharpless kinetic resolution, the oxetanes were accessed in enantiomerically enriched form.[32] The 3,4-substituents were always *anti* as a result of the *trans* geometry of the epoxides. When R = aryl or alkenyl the 2,3-*anti* isomer was predominant; however, when R = PhS the selectivity was reversed (56% de in favour of the 2,3-*syn* isomer). A number of different pathways are open to epoxides of this type, so that the mode of reaction is dependent on the acidity of the various sites, and on the reactivity of the metallated species formed.[33]



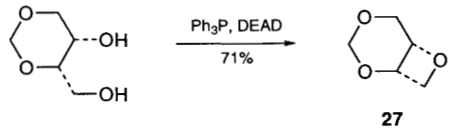
Scheme 25

Eames and Warren serendipitously noted the formation of oxetanes **25** while attempting a Mitsunobu reaction of **24** with ziram as sulfur nucleophile.[34] Tetrahydrofurans **26** were produced from these compounds by acid catalysed thiiranium ion cyclisations (**Scheme 26**; see also **Scheme 45**).



Scheme 26

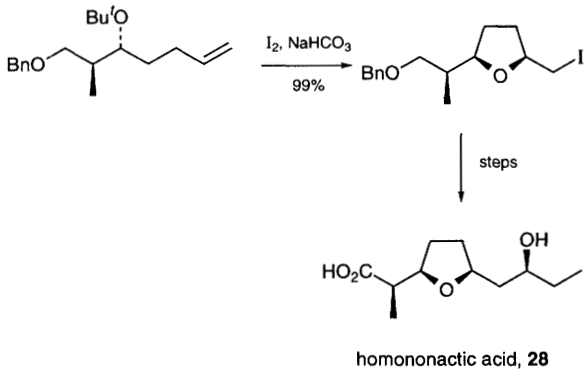
A number of tartrate-derived chiral building blocks have been prepared by Gras *et al.*, including oxetanes **27** (**Scheme 27**) and tetrahydrofurans (see also ref. 63).[35]



Scheme 27

4 Five membered rings

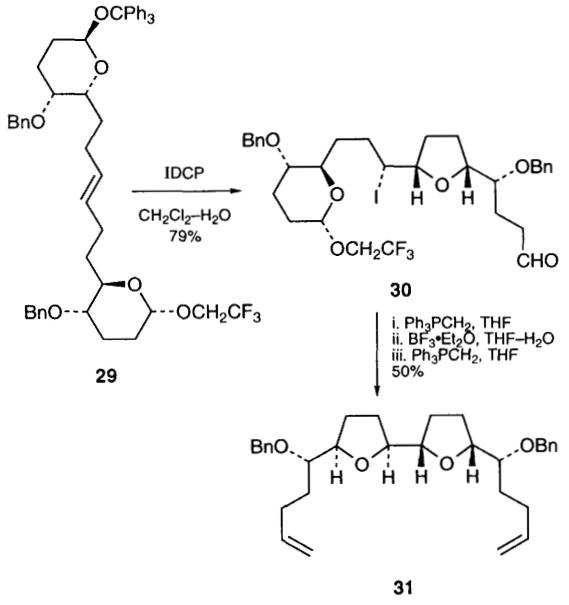
Cyclisation of alcohols onto alkenes provides one of the more direct entries into tetrahydrofuran derivatives. It has been known for many years that 5-*exo* cyclisations are particularly favoured. It is therefore not surprising that a recent study of competitive iodoetherification has shown that 5-*exo* cyclisation predominates over 6-*exo*.[36] This method has been used for the preparation of homononactic acid **28**, of which the natural product tetranactin is a tetramer (**Scheme 28**).[37]



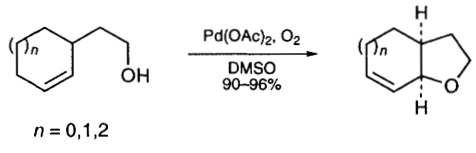
Scheme 28

A similar reaction involving bis-pyranoside alkenes has given rise to an elegant new synthesis of adjacently linked tetrahydrofurans. Thus, reaction of **29** with iodonium dicollidine perchlorate (IDCP) in wet dichloromethane gave the tetrahydrofuran **30**. Wittig olefination followed by cyclisation and a second olefination gave **31** which is structurally related to the bis-tetrahydrofuran portion of rolliniastatin (**Scheme 29**).[38]

Palladium(II)-catalysed alcohol–alkene cyclisations allow tetrahydrofurans to be fused on to five to seven membered rings in excellent yield (**Scheme 30**).[39]



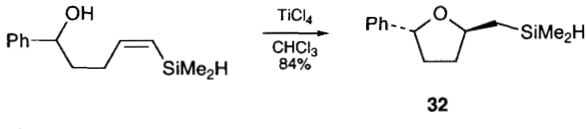
Scheme 29



n = 0,1,2

Scheme 30

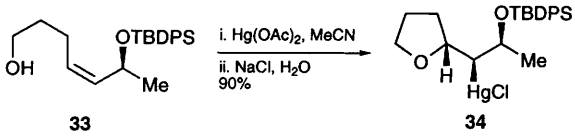
Titanium tetrachloride catalysed cyclisation of 5-silylpent-4-en-1-ols provides a stereoselective entry into 2,5-disubstituted tetrahydrofurans.[40] Thus **32** was obtained in 84% yield and 92% de (**Scheme 31**).



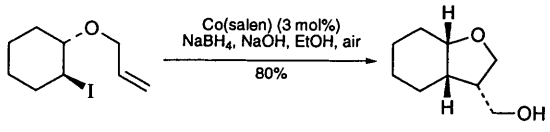
Scheme 31

Perlmutter's group have reported diastereoselective oxymercurations of γ-hydroxyalkenes. Protection of the allylic alcohol as a silyl ether **33** gave the best selectivities in the formation of **34** (up to 90% de) (**Scheme 32**).[40] This reaction has subsequently been used to prepare a subunit of pamamycin 607.[42]

Radical cyclisations are among the more efficient methods for the formation of five membered rings, and preparation of oxacycles by this method is no exception. Bamhaoud and Prandi now report the



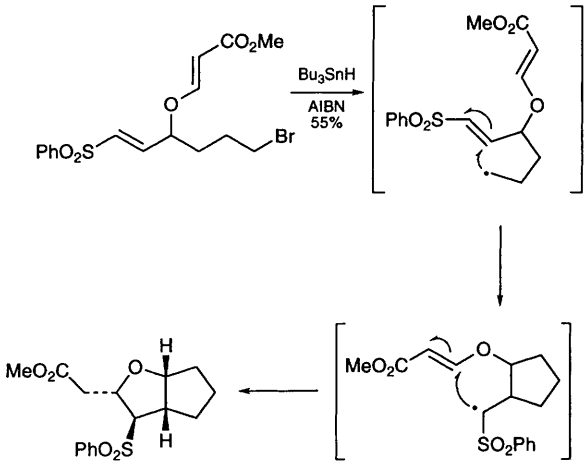
Scheme 32



Scheme 33

cobalt-catalysed oxygenation of primary and secondary radicals to give an efficient route to 3-hydroxymethyl tetrahydrofurans **35** (**Scheme 33**).[43]

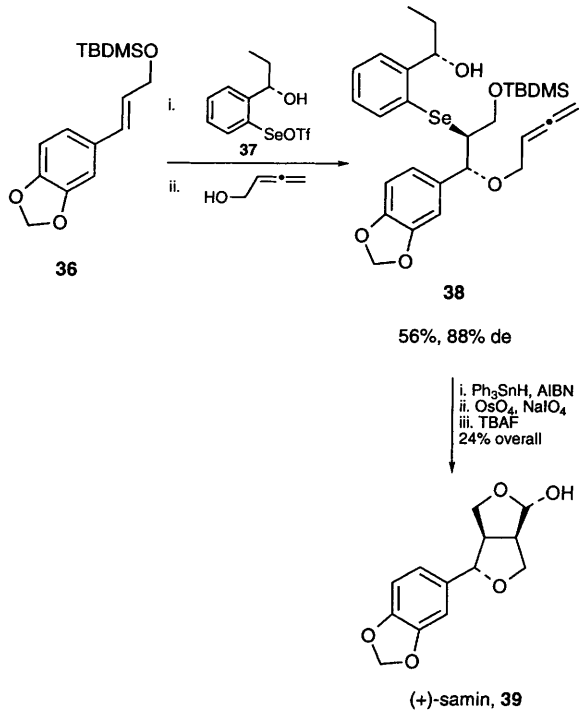
A cascade process involving addition of a radical to an unsaturated sulfone followed by trapping of the intermediate radical with an acrylate also provides fused tetrahydrofurans as shown in **Scheme 34**.[44]



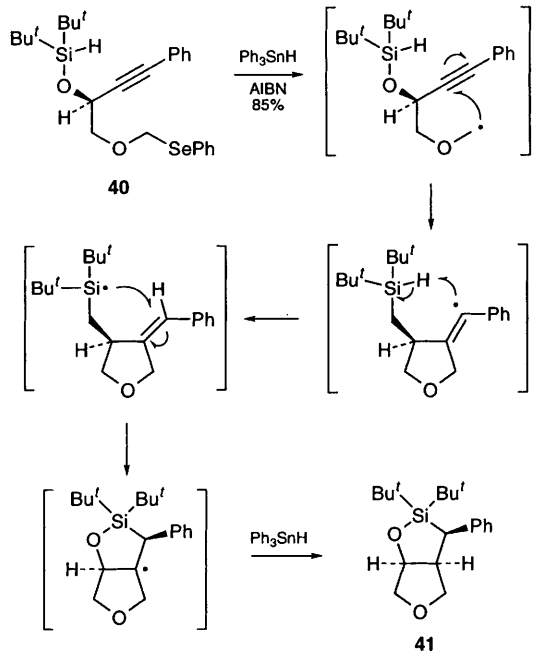
Scheme 34

Wirth has reported a short asymmetric synthesis of the lignan (+)-samin **39** using organoselenium chemistry.[45] Reaction of the protected allylic alcohol **36** with the chiral selenium trifluoromethanesulfonate **37** (this compound was prepared by organozinc addition to an aldehyde in the presence of an aminoselenide) followed by addition of buta-2,3-dien-1-ol gave **38** with 88% de. Radical cyclisation followed by oxidation and deprotection completed the synthesis (**Scheme 35**).

Clive and Yang have reported an effective sequence of radical reactions of substrates such as **40**. Cyclisation of the initial radical in a 5-*exo*-dig manner is followed by hydrogen transfer from silicon and finally a 5-*endo*-trig cyclisation to give **41** (**Scheme 36**). This process was used for the



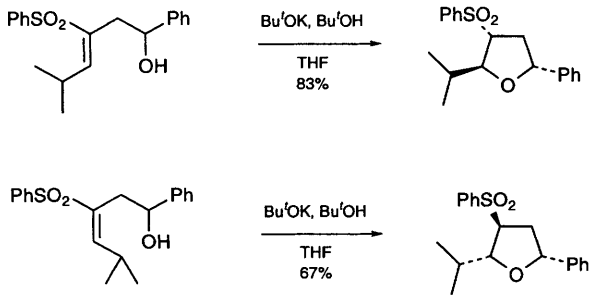
Scheme 35



Scheme 36

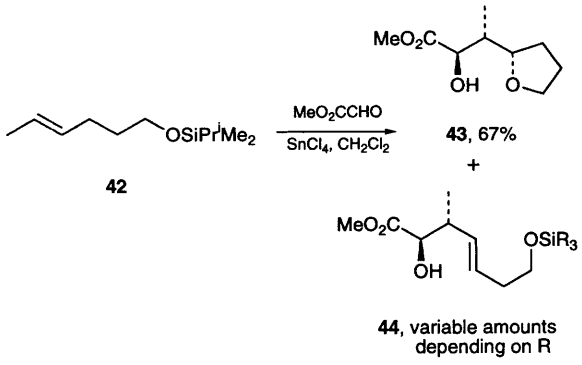
formation of tetrahydrofurans, γ-lactones and pyrrolidines; a similar reaction was used to prepare tetrahydropyrans.[46]

Cyclisation of sulfonyl-substituted homoallylic alcohols by a 5-*endo* process can give rise to tetrahydrofurans with good selectivity (10:1 for both the examples shown in **Scheme 37**). The relative stereochemistry is dependent on the double bond geometry, although in some cases isomerisation processes led to lower selectivity.[47]



Scheme 37

In the course of their investigations into the carbonyl ene reaction, Mikami and Shimizu observed an unexpected Prins-type reaction to form tetrahydrofurans. Silyl-protected hydroxy alkenes **42** form the tetrahydrofurans **43** at the expense of the carbonyl ene product **44** (**Scheme 38**).[48]



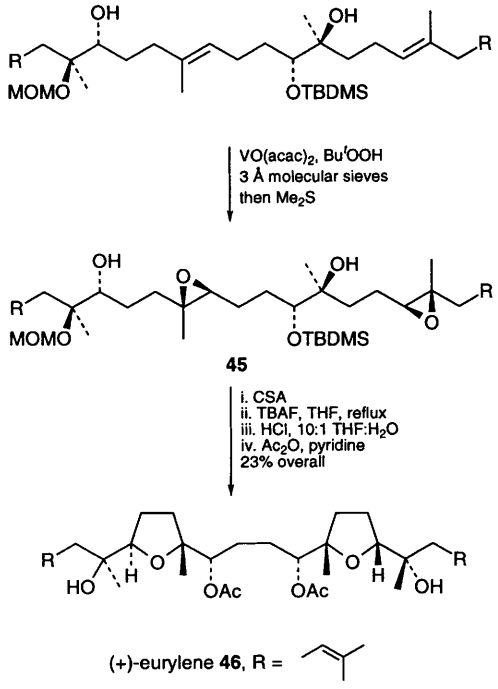
Scheme 38

Hydroxyepoxide cyclisations also provide efficient access to functionalised tetrahydrofurans. Ujihara and Shirahama have reported a total synthesis of (+)-eurylene **46** by a double epoxide cyclisation of **45**. The stereogenic centre at the alcohol directs the epoxidation, and hence controls the stereochemistry of the tetrahydrofuran rings as shown in **Scheme 39**.[49]

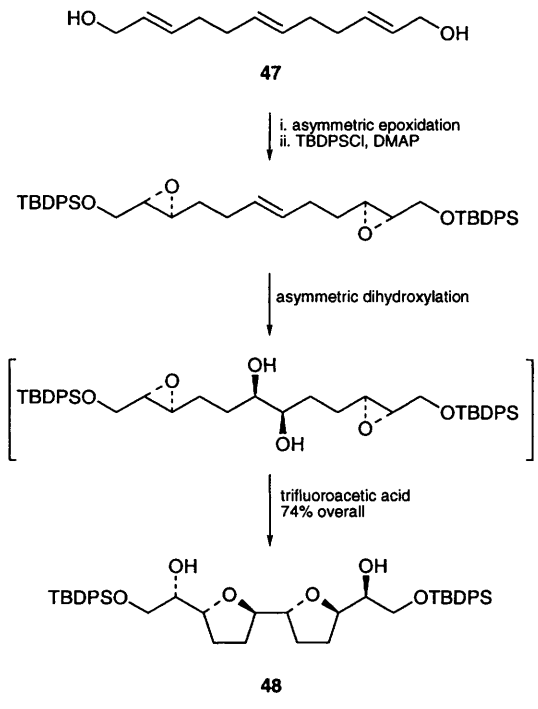
Hoye and Ye have used similar hydroxyepoxide cyclisations in a particularly elegant synthesis of the cytotoxic annonaceous acetogenin (+)-parviflorin (**Scheme 40**). Sharpless asymmetric epoxidation of **47** was followed by Sharpless asymmetric dihydroxylation; acid-promoted cyclisation then led to **48**.[50] A further eight steps were required for conversion of **48** into the natural product (not shown).

Marshall has also reported on the synthesis of bis-tetrahydrofurans related to the annonaceous acetogenins. Addition of chiral allylic stannane **50** to the tartrate-derived dialdehyde **49** followed by cyclisation of the resulting diol provides **51** (**Scheme 41**). Modification of the reaction conditions allows similar preparation of a number of stereoisomers.[51]

Cyclisation of chiral diols has also been used in the preparation of novel chiral ferrocenyl tetrahydrofuran derivatives.[52]

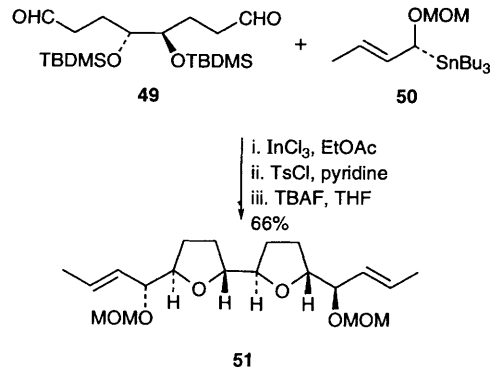


Scheme 39

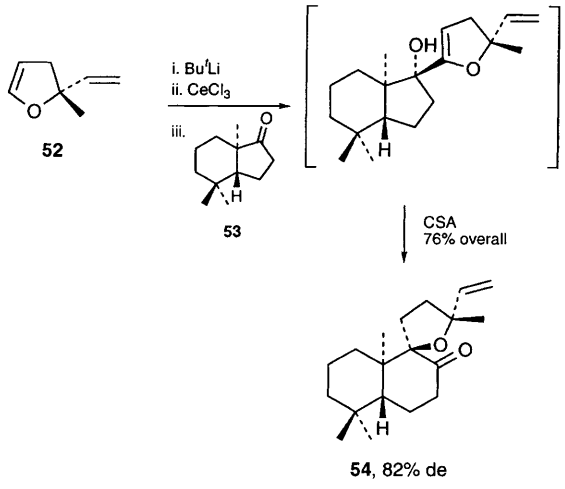


Scheme 40

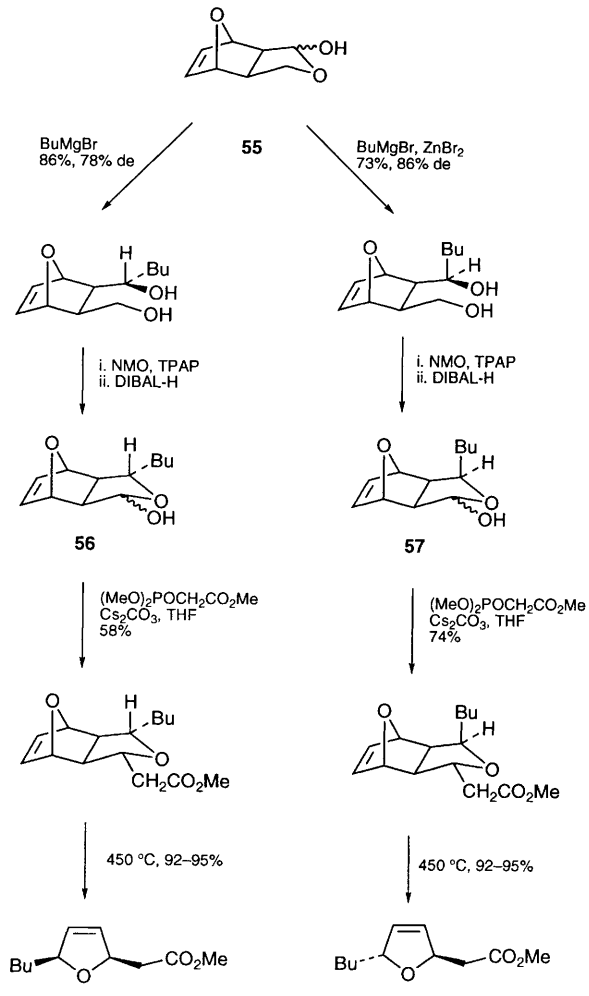
Paquette has now applied the pinacolic ring expansion method to grindelic acid, and resolved a long-standing debate about the absolute configuration (and hence biosynthetic origin) of this natural product. The key step (**52** to **54**) is shown in **Scheme 42**, whereby the cerium derivative of **52** was treated with ketone **53**, followed by a pinacolic ring



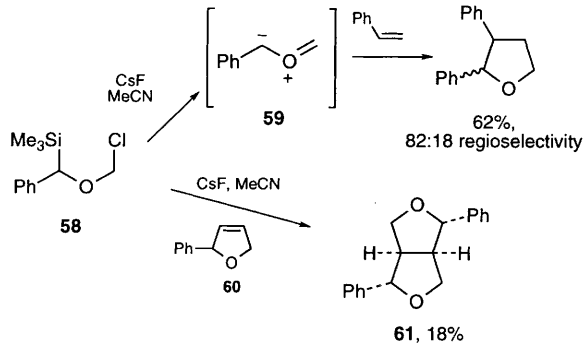
Scheme 41



Scheme 42



Scheme 43



Scheme 44

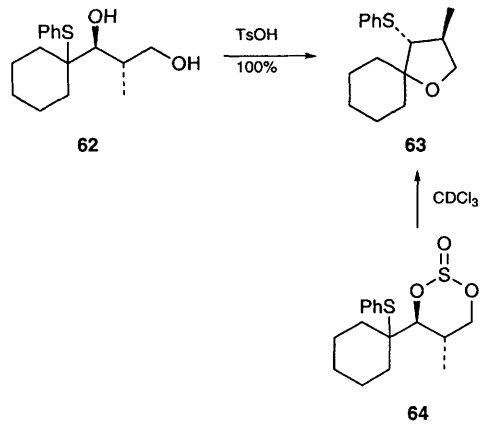
expansion upon acidic work-up to give **54** with good stereocontrol.[53]

Bloch *et al.* have described a route to dihydrofurans based on a retro-Diels–Alder approach.[54] Lactol **55**, which is available in enantiomerically pure form, reacts with organometallic reagents under appropriate conditions to afford either diastereoisomer of the diol preferentially. Selective tetrapropylammonium perruthenate (TPAP) oxidation of the primary alcohol followed by DIBAL-H reduction generates the lactols **56** and **57**. The sequence was then completed by a tandem Wittig–Horner–intramolecular conjugate addition and finally flash thermolysis (**Scheme 43**).

Azomethine ylides normally only react with electron deficient dipolarophiles. In contrast, the analogous carbonyl ylides **59**, generated *in situ* from chloromethyl silylmethyl ethers such as **58**, react well with styrenes and other electron-rich alkenes (as well as electron-deficient and hetero-dipolarophiles) to provide tetrahydrofuran derivatives in moderate to good yields. Regio-selectivities of up to 9:1 were observed (**Scheme 44**). Reaction of **58** with **60** provided rapid, albeit low-yielding, entry into bis-tetrahydrofuran lignans **61**.[55]

Nitrone cycloadditions of sugar derivatives have also been used for the preparation of tetra-hydrofurans.[56]

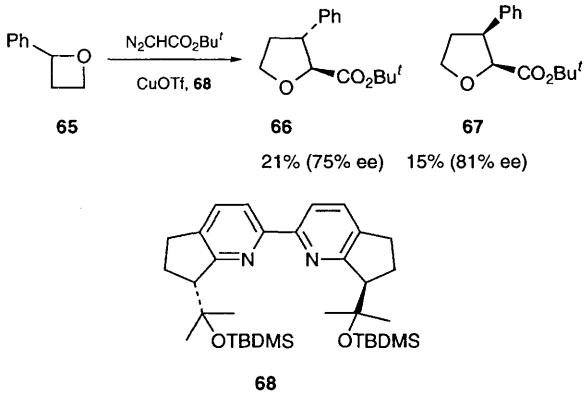
As noted in the previous section (**Scheme 26**), suitably functionalised oxetanes rearrange to tetrahydrofurans. In fact, the precursors to these oxetanes undergo direct cyclisation to tetra-hydrofurans (*e.g.* **62** to **63**). Cyclic sulfates can be used as precursors to the thiiranium ions, so that



Scheme 45

the reaction can be carried out in the absence of acid (**64** to **63**, **Scheme 45**).[34] Secondary and tertiary alcohols are also able to act as the nucleophiles.[57]

A catalytic asymmetric ring expansion of oxetanes **65** to tetrahydrofurans **66** and **67** has been reported by Katsuki.[58] In this case, each enantiomer of the oxetane gives rise to a single diastereoisomer of the tetrahydrofuran. Competing metal-free ring expansions were invoked to account for the less than perfect enantioselectivity. Although the yields are low, significant quantities of oxetanes (30–43%) were recovered (**Scheme 46**).



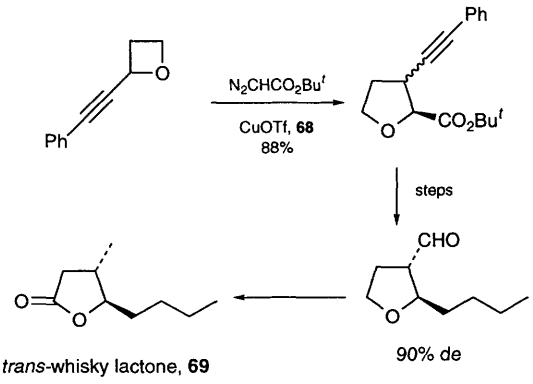
Scheme 46

This method has since been used to prepare *trans*-whisky lactone **69**. In this case both diastereoisomers of the initial product were used *via* epimerisation of a late intermediate (**Scheme 47**).[59]

The parent compounds, tetrahydrofuran and tetrahydropyran can be directly functionalised *via* the corresponding radicals.[60] Buchwald has reported a nickel(0)-catalysed process similar to the Pauson–Khand reaction,[61] and Schinzer has disclosed a new allylsilane annulation to tetrahydrofurans.[62] A report on the kinetic resolution of five-membered oxacycles is also of note.[63]

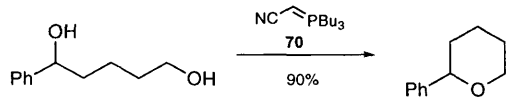
5 Six membered rings

Cyclodehydration of diols is conceptually the most simple method for the preparation of cyclic ethers.



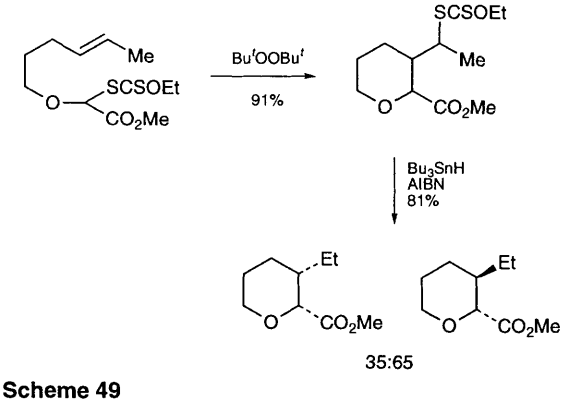
Scheme 47

In practice this reaction is not always so straightforward, since strong acids and high temperatures are often required. The Mitsunobu reaction is an attractive possibility, which has been made viable by the development of modified Mitsunobu reagents by Tsunoda and co-workers.[64] Cyanomethylene(tributyl)phosphorane (CMBP, **70**) is the most effective for the formation of tetrahydropyrans (**Scheme 48**). This method is less effective for seven-membered ring formation, and was completely unsuccessful in forming a ten-membered ring (although 12-crown-4 was formed in 30% yield by this method).



Scheme 48

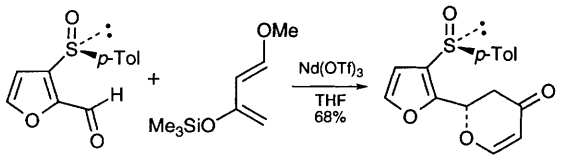
A radical cyclisation involving transfer of a xanthate group has provided a range of ring sizes.[65] Application of this method to tetrahydropyran synthesis is shown in **Scheme 49**.



Scheme 49

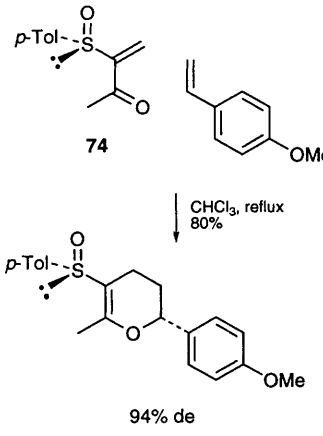
Hetero-Diels–Alder reactions involving both oxa-dienes and oxa-dienophiles have been very successfully used in dihydropyran synthesis and recently much emphasis has been placed on asymmetric variants of these reactions.

Of the chiral auxiliary-based approaches, the use of chiral sulfoxides has proved efficient in both classes of Diels–Alder reaction. Reaction of the chiral aldehyde **71** with Danishefsky's diene **72** in the presence of lanthanide trifluoromethanesulfonate Lewis acids gave excellent diastereoselectivities of the dihydropyran-4-one **73** after hydrolysis (**Scheme 50**).[66]



Scheme 50

The sulfoxide-substituted unsaturated ketone **74** gives impressive diastereoselectivity in the reaction with styrene derivatives (**Scheme 51**). However, with enol ethers the selectivity was much lower; this was attributed to this reaction proceeding *via* a non-concerted pathway.[67]



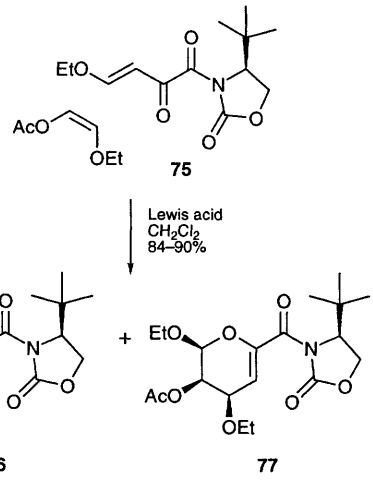
Scheme 51

Oxa-dienes **75** derived from chiral oxazolidinones have also been successfully used in hetero-Diels–Alder reactions (**Scheme 52**).[68]

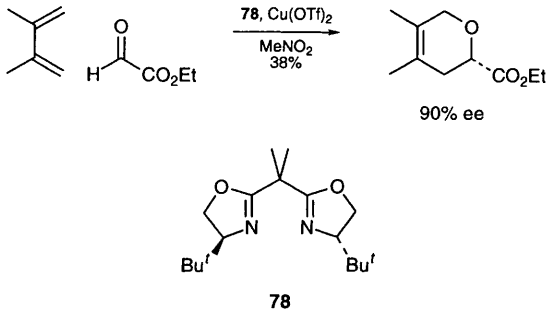
In this case, changing the Lewis acid promoter used gives rise to a reversal of the π-facial diastereoselectivity. With Me_2AlCl, **76** and **77** were produced in a ratio of 60:1, whereas with TMSOTf the ratio was 1:7.9, with the *endo* isomers (shown) predominating (>50:1). These results have been explained by considering the conformation of the oxazolidinone in the presence of the different Lewis acids.

Asymmetric catalysis of hetero-Diels–Alder reactions has been reported using the copper trifluoromethanesulfonate complex of bis-oxazoline **78**, although the yields were low due to a competing (asymmetric) ene reaction (**Scheme 53**).[69]

1,3-Dioxan-4-ones, which are readily available from β-hydroxy acids, have been converted in two



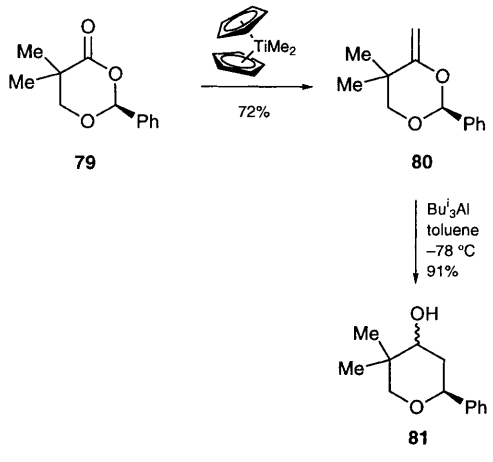
Scheme 52



Scheme 53

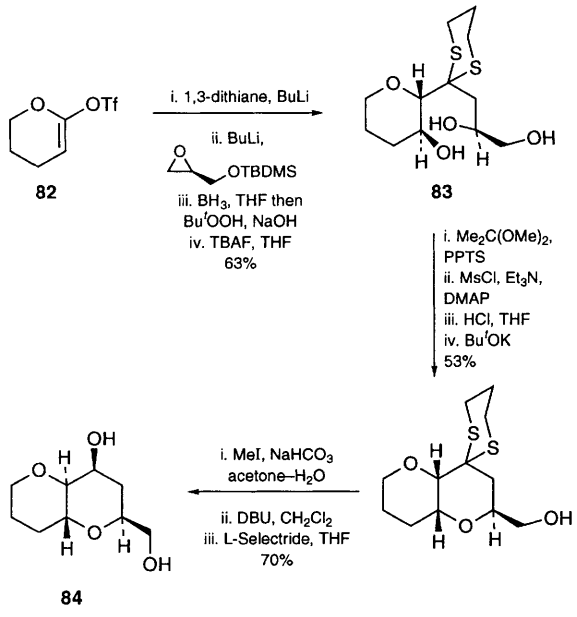
steps into tetrahydropyrans **81**. Methylenation of **79** with dimethyltitanocene gave **80** which underwent aluminium-mediated rearrangement to **81** in toluene at low temperature (**Scheme 54**).[70]

Murai and co-workers have contributed significantly to the development of methodology applicable to the synthesis of large marine polyether natural products. Recent reports include the synthesis of the AB ring systems of hemibrevetoxin B.[71] Thus, lithiated 1,3-dithiane was reacted first with the enol trifluoromethanesulfonate **82** derived



Scheme 54

from δ-valerolactone, then with protected (*R*)-glycidol. Hydroboration and oxidation gave a 1:1 mixture of diastereoisomers, the more polar of which (**83**) was converted into **84** as shown in **Scheme 55**.



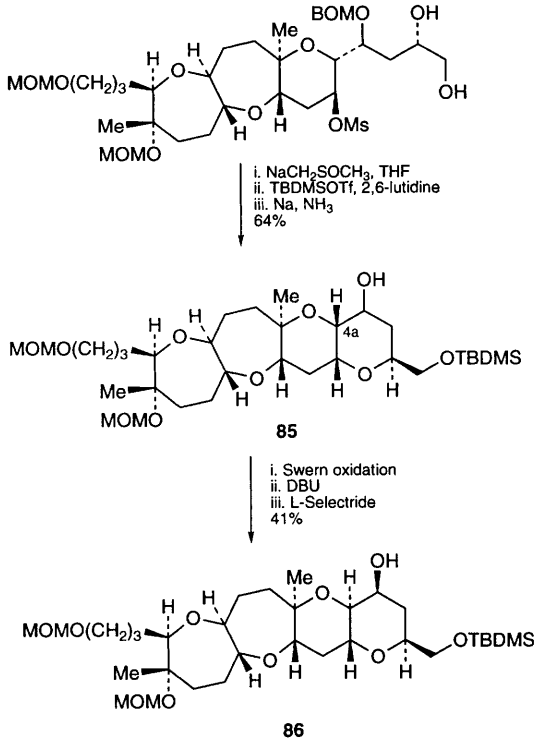
Scheme 55

A combination of this method and their earlier reported ring expansion of decalin-1,5-dione and enol trifluoromethanesulfonate methodology led to the construction of the hemibrevetoxin ring system (see also **Scheme 67**, **Scheme 86** and **Scheme 87**), albeit with the incorrect stereochemistry at C-4a.[72] Difficulties associated with the removal of the dithiane protecting group prompted a modification of the original strategy to give compound **85** in which C-4a has the incorrect stereochemistry. Oxidation, epimerisation and finally reduction gave **86** with the ring system and all stereocentres of hemibrevetoxin in place (**Scheme 56**).[73]

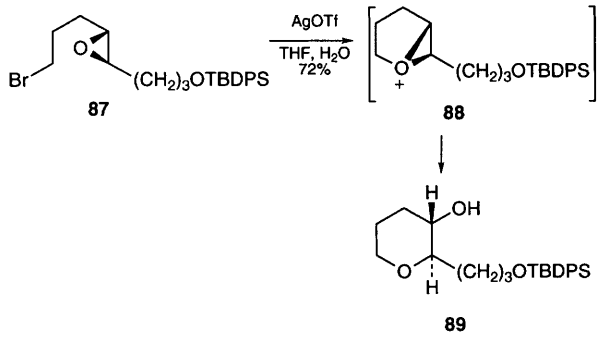
The same group has also reported the silver-promoted conversion of 1-bromo-4,5-epoxyalkanes **87** into tetrahydropyrans **89**. The reaction presumably proceeds through the intermediacy of an oxiranium ion **88** (**Scheme 57**).[74] A double application of this method has also been reported, although the yield in this case was lower (**Scheme 58**).[75]

Other reports from this group are concerned with the synthesis of ciguatoxin fragments.[76] This marine natural product contains thirteen oxacyclic rings ranging from five to nine membered.

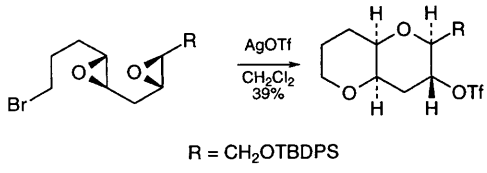
Martín and co-workers have also continued their earlier work towards the synthesis of marine polyethers. Compound **92**, which was prepared in six straightforward steps from the stannane **90** and aldehyde **91**, was deprotected and reductively cyclised to give **93**. Epimerisation then led to **94** with the *trans* ring junctions characteristic of the target natural products (**Scheme 59**).[77]



Scheme 56

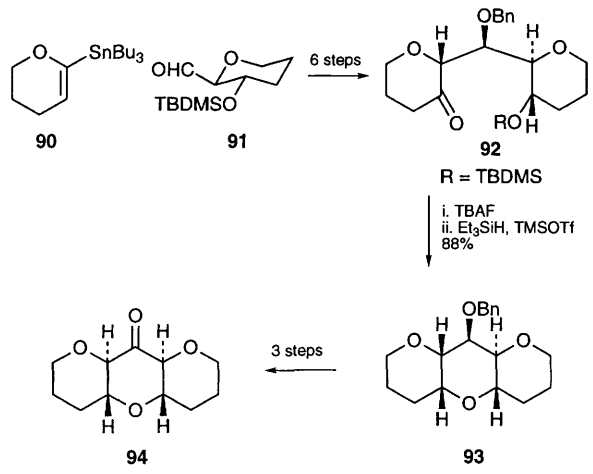


Scheme 57

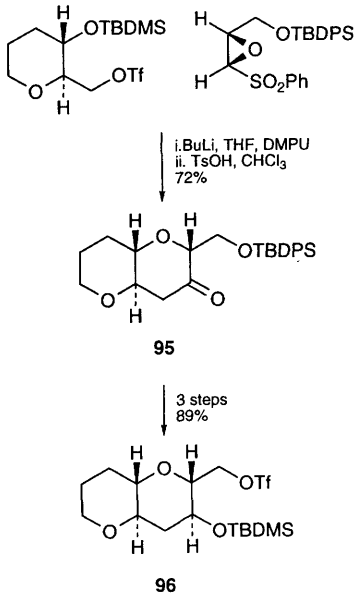


Scheme 58

A high yielding iterative synthesis of *trans*-fused tetrahydropyrans has recently been reported by Mori. The displacement of a trifluoromethanesulfonate by an oxiranyl anion (see also **Scheme 11**) was followed by oxirane ring opening to give the ketone **95**. Three further steps were required to give **96** which is ready for a second annulation (**Scheme 60**). Four tetrahydropyran rings were fused in this manner.[19]

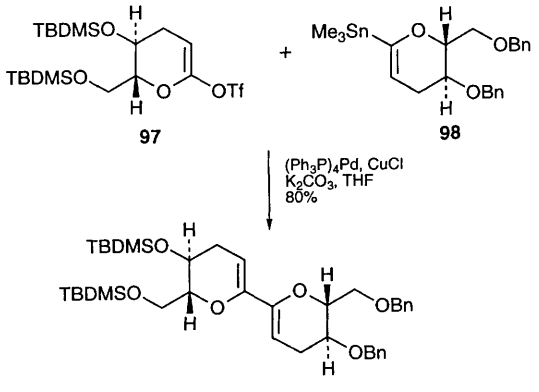


Scheme 59



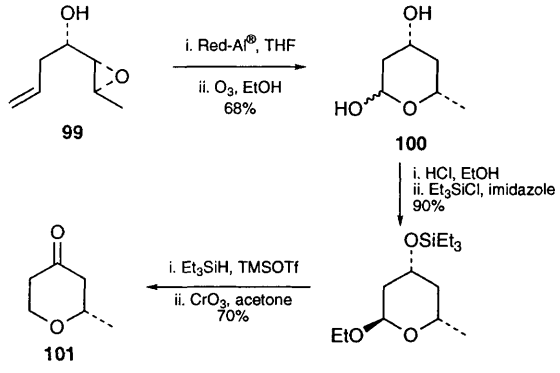
Scheme 60

The Nicolaou group have disclosed an efficient cross-coupling method for linking dihydropyrans **97** and **98**.[78] Fragments related to maitotoxin were prepared in this way (**Scheme 61**).



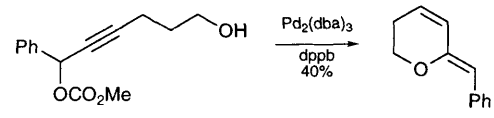
Scheme 61

In their search for efficient inhibitors of 5-lipoxygenase, chemists at Zeneca Pharmaceuticals required various chiral nonracemic tetrahydropyran-4-ones. (*S*)-2-Methyl-3,4,5,6-tetrahydro-2*H*-pyran-4-one **101** was prepared by the route shown in **Scheme 62**.[79] Epoxide **99**, prepared by a Sharpless kinetic resolution, was reduced with Red-Al and ozonised to give the lactol **100**. Conversion into the acetal and protection of the secondary alcohol was followed by silane reduction and oxidation to give **101**.



Scheme 62

Dihydropyrans have also been prepared by palladium-catalysed cyclisations. In the example shown in **Scheme 63**, the reaction presumably occurs *via* the intermediacy of a palladium allene complex.[80]

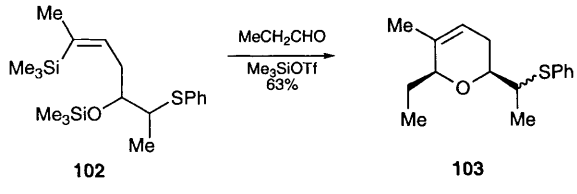


dppb = 1,4-bis(diphenylphosphino)butane

Scheme 63

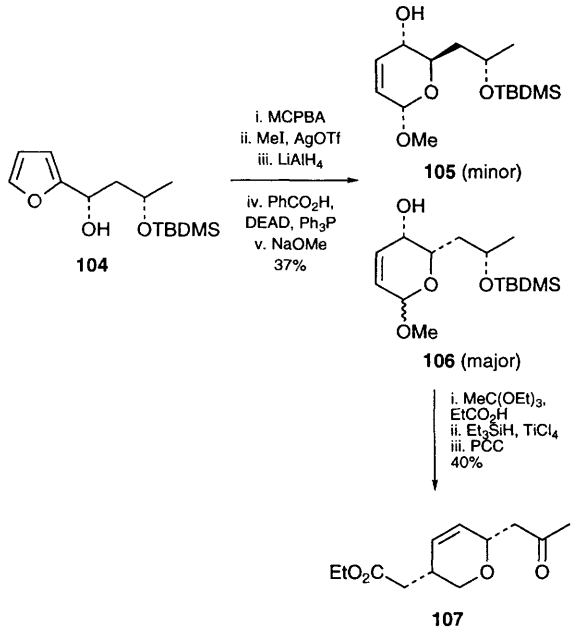
The silyl-modified Sakurai reaction has been used by Markó to prepare the dihydropyran portion of the antifungal antibiotic ambruticin. Condensation of **102** with propionaldehyde gave the 2,6-*cis* dihydropyran **103** as a 1:1 mixture of epimers as the PhS-bearing carbon atom (**Scheme 64**).[81]

Oxidation of the furan **104** followed by methylation, reduction and Mitsunobu inversion



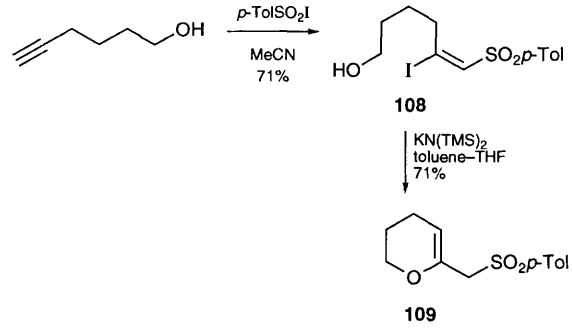
Scheme 64

gave a 2:1 *cis*:*trans* mixture of **105** and **106** (the major isomer is a mixture of anomers). Routine manipulations then provided **107**, which has previously been converted into the antibiotic pseudomonic acid A (**Scheme 65**).[82]



Scheme 65

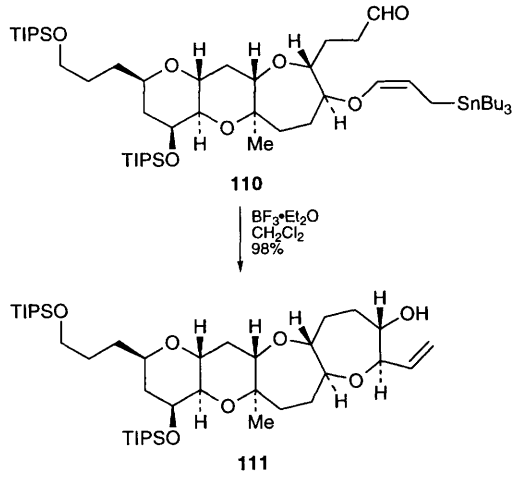
Finally for this section, addition of arenesulfonyl iodide to alkynes can be followed by intramolecular attack of oxygen with concomitant loss of HI to give the five and six membered cyclic enol ethers. For example, addition of tosyl iodide to hex-5-yn-1-ol gave **108** in good yield. Treatment with potassium hexamethyldisilazide then gave **109** (**Scheme 66**).[83]



Scheme 66

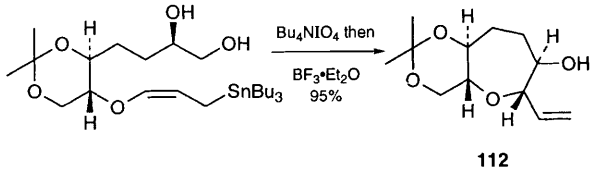
6 Medium sized rings

Once again, much of the development in this area has been spurred on by the fascinating structures of the polycyclic ethers derived from marine sources. An entertaining review of Nicolaou's synthesis of brevetoxin B has appeared in print.[84] A number of other groups have also made significant progress towards the synthesis of this compound, most notable being the total synthesis of hemibrevetoxin B by the Yamamoto group.[85] Both seven membered rings were formed by allylstannane cyclisations, the latter of which (**110** to **111**) is shown in **Scheme 67** (for other approaches to this natural product, see **Scheme 56**, **Scheme 86** and **Scheme 87**). More recently these cyclisations have been extended to the the use of allenyl and prop-2-ynyl-stannanes,[86] and to cyclisations onto hydrazones (although in this case only five and six membered rings were reported).[87]



Scheme 67

Martín and co-workers have also expanded on their previously reported acetal stannane cyclisations as shown in **Scheme 68** for the preparation of **112**.[88]



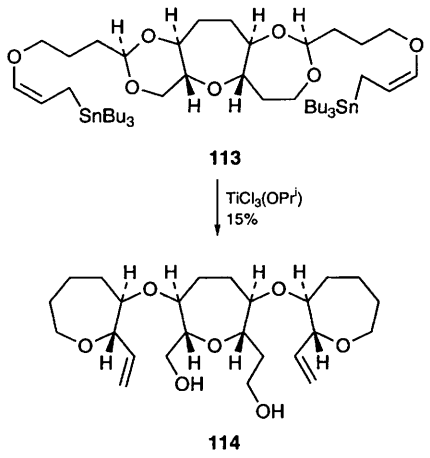
Scheme 68

Compound **112** was converted into **113** in straightforward manner, which then underwent a double cyclisation to **114** (**Scheme 69**).

Their strategy for joining the remaining two rings in **114** is based on Ramberg–Bäcklund chemistry. A model reaction is shown in **Scheme 70**,[89] while the preparation of the more complex oxocane **115** is shown in **Scheme 71**.[90]

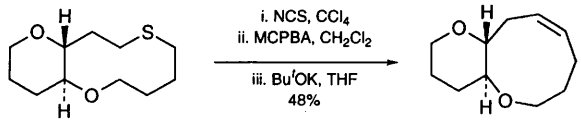
The same group have reviewed the synthesis of marine polyether toxins,[91] and have presented a detailed account of their own earlier work in the area.[92]

Although direct cyclodehydration reactions are not often used for the preparation of medium sized rings, benzo-fused oxepanes **116** are efficiently prepared by this method (**Scheme 72**).[93]

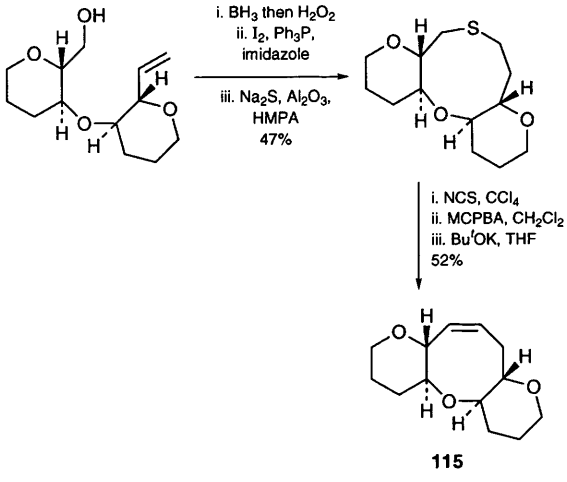


113 114

Scheme 69



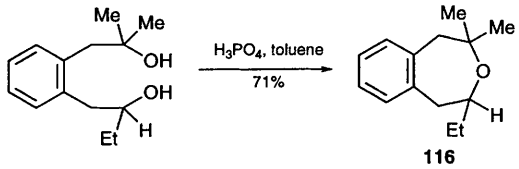
Scheme 70



115

Scheme 71

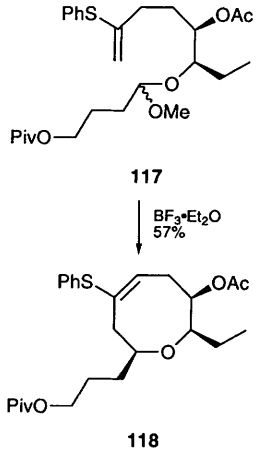
The precursors in **Scheme 72** were prepared by lithiation of phthalan. Full details of another route from phthalan to medium ring oxacycles have also appeared.[94]



116

Scheme 72

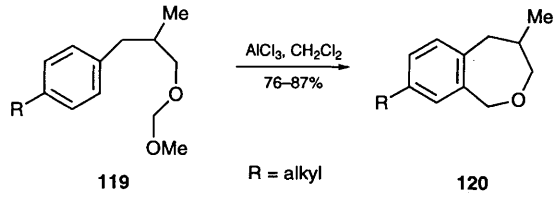
The Overman synthesis of (+)-laurencin uses an acetal–alkene cyclisation (**117** to **118**) to form the key eight membered ring (**Scheme 73**).[95]



117 118

Scheme 73

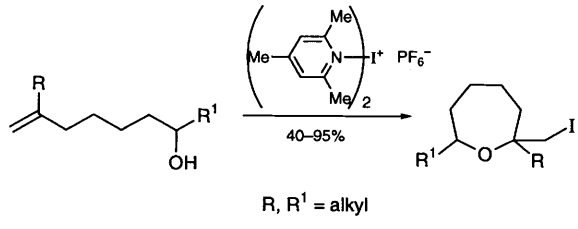
Oxonium ion–arene cyclisations are also known. Methoxymethyl ethers such as **119** were smoothly cyclised in the presence of a Lewis acid to afford the benzoxepins **120** in an intramolecular Friedel–Crafts reaction (**Scheme 74**).[96]



119 120

Scheme 74

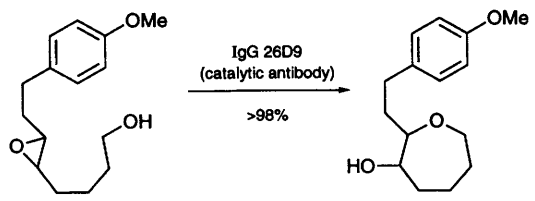
Oxepanes are formed efficiently by a 7-*exo* iodoetherification of unsaturated alcohols (**Scheme 75**), although the yields for oxocane formation by this method were much lower.[97]



R, R[1] = alkyl

Scheme 75

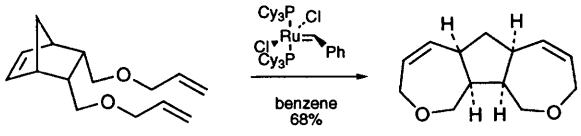
Cyclisation of epoxy alcohol **121** would be expected to (and indeed does) lead to a tetrahydropyran, in accordance with Baldwin's rules. However, a catalytic antibody promoted reaction can be made to favour the oxepane **122** (**Scheme 76**).[98]



121 122

Scheme 76

It is largely due to the pioneering work of Grubbs and co-workers that olefin metathesis is a viable tool for synthetic organic chemists. The same group now report a ring opening–ring closing metathesis approach to bis-dihydrofurans, bis-dihydropyrans and bis-oxepanes.[99] Possibly the most elegant example from this paper is shown in **Scheme 77**. The reaction most probably occurs by initial metathesis of the terminal alkene.



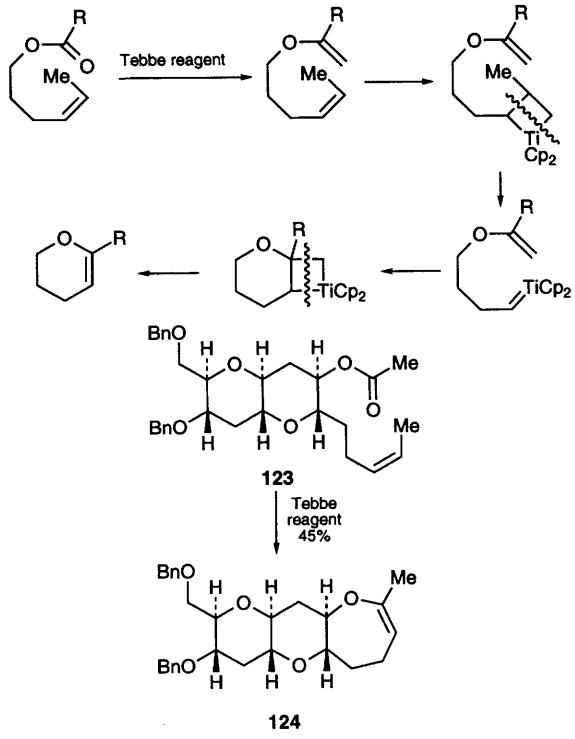
Scheme 77

In a similar vein, the Nicolaou group report the tandem methylenation–metathesis of olefinic esters to give six and seven membered rings.[100] Methylenation of the esters is followed by a metathesis to generate a titanium alkylidene which then undergoes ring closing–metathesis as shown in **Scheme 78**. This method was applied to the synthesis of six and seven membered rings (*e.g.* **123** to **124**).

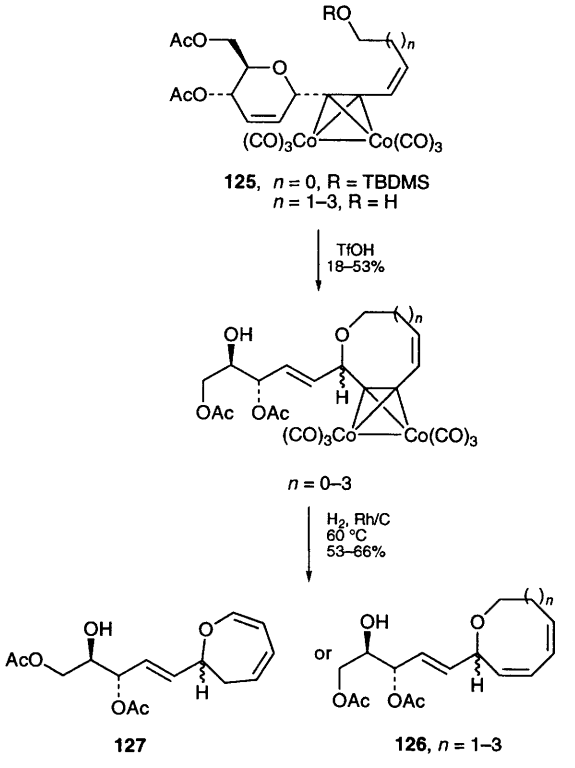
The intramolecular Nicholas reaction has been shown to be effective in the construction of seven to ten membered rings. Isobe and co-workers report the cyclisation of dicobalt hexacarbonyl–alkyne complexes **125** under acidic conditions (**Scheme 79**).[101] Oxidative decomplexation was not successful due to the high strain energy of the cycloalkynes which would have been formed, so that decomplexation was effected under reducing conditions to give **126**. In the seven membered ring compound, double bond migration occurred to give the more stable cyclic enol ether **127**.

This method was applied to the synthesis of an AB ring fragment of ciguatoxin[102] and also to a fragment corresponding to the ABC rings of ciguatoxin.[103] A related cyclisation of a bis-alkyne complex is shown in **Scheme 80**.[104] The unusually high yield for nine membered ring formation is due in part to the use of high dilution techniques.

Similar methodology was reported by Palazón and Martín, although in their case the cobalt–alkyne complex did not form part of the ring (**Scheme 81**).[105]

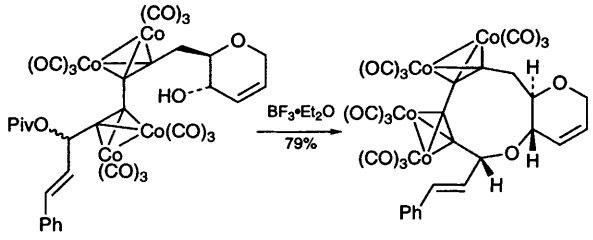


Scheme 78

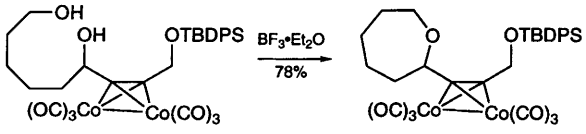


Scheme 79

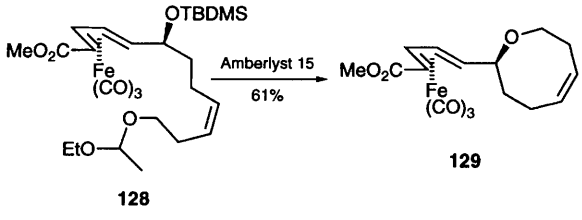
Stabilisation of carbenium ions by transition metal complexation to a neighbouring π-system was also used by Grée and co-workers. In their case, iron–diene complex **128** was an effective precursor to the oxocane **129** (**Scheme 82**).[106]



Scheme 80

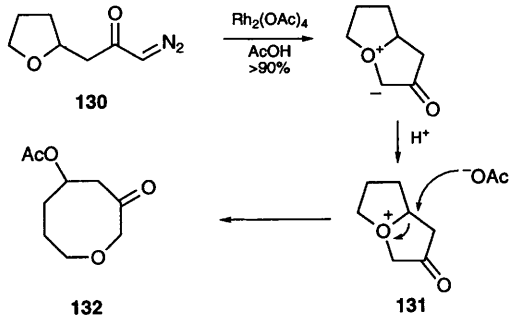


Scheme 81



Scheme 82

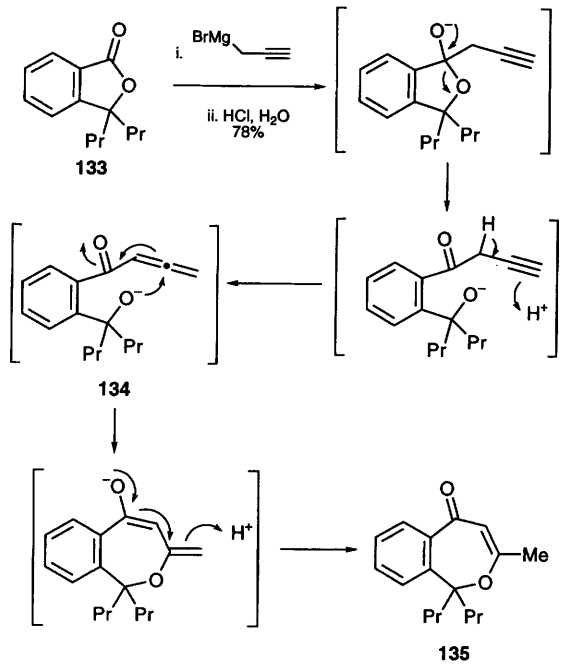
Nucleophilic attack on bicyclic oxonium ions **131** results in ring expansion to **132** (**Scheme 83**), although the position of attack is dependent on ring size. The oxonium ions were generated by protonation of oxonium ylides from diazo compounds **130**.[107]



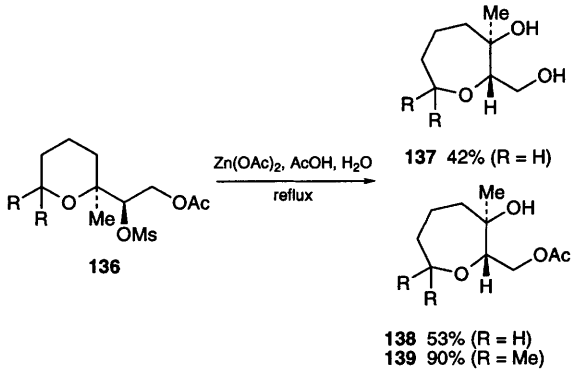
Scheme 83

Cyclisation of an ω-hydroxy allenyl ketone (shown here in its deprotonated form **134**) led to the benzo-fused oxepin **135**. The allenyl ketone was generated *in situ* from the attack of prop-2-ynylmagnesium bromide on the corresponding phthalide **133**, so that this method constitutes a two-carbon ring expansion (**Scheme 84**).[108]

Nakata has reported the ring expansion of tetrahydropyran derivatives **136** to give oxepanes **137–139** (**Scheme 85**) (similarly the ring expansion



Scheme 84

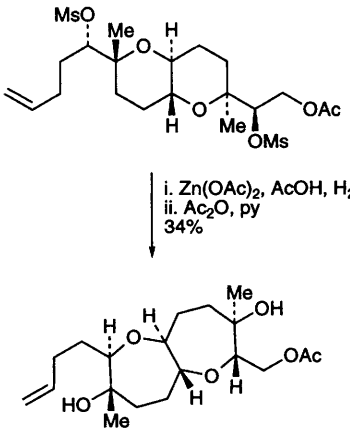


Scheme 85

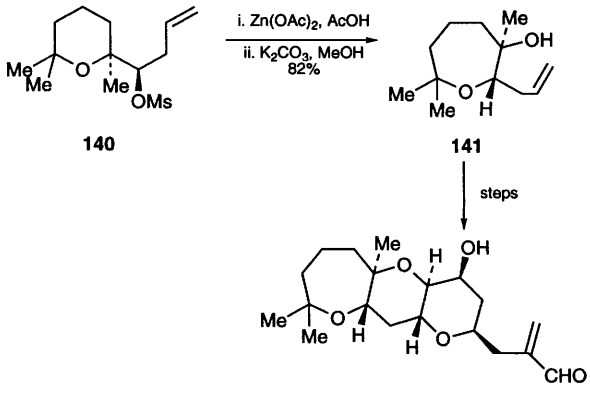
of tetrahydrofurans led to tetrahydropyrans). In the case where R = Me, the reaction was significantly accelerated, presumably as a result of 1,3-diaxial interactions in the starting material. One consequence of this is the lack of cleavage of the acetate ester in **139**.[109]

An elegant double application of this method led to a fragment corresponding to the C and D rings of hemibrevetoxin B (**Scheme 86**),[110] whereas combination of this method (**140** to **141**) with others has led to a synthesis of rings A, B and C of hemibrevetoxin B (**Scheme 87**).[111] For other approaches to this natural product, see **Scheme 56** and **Scheme 67**.

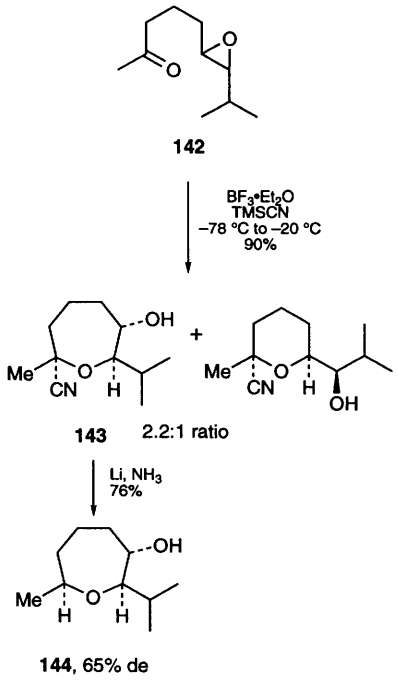
Rychnovsky and Dahanukar[112] have reinvestigated earlier work by Fotsch and Chamberlin.[113] The Lewis acid-mediated reaction of **142** with trimethylsilyl cyanide was reported to give a mixture of diastereomeric tetrahydropyrans. In fact, the major product is the oxepane **143**, which can be



Scheme 86



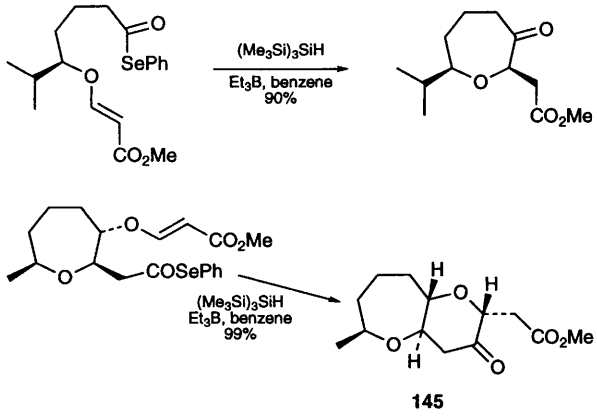
Scheme 87



Scheme 88

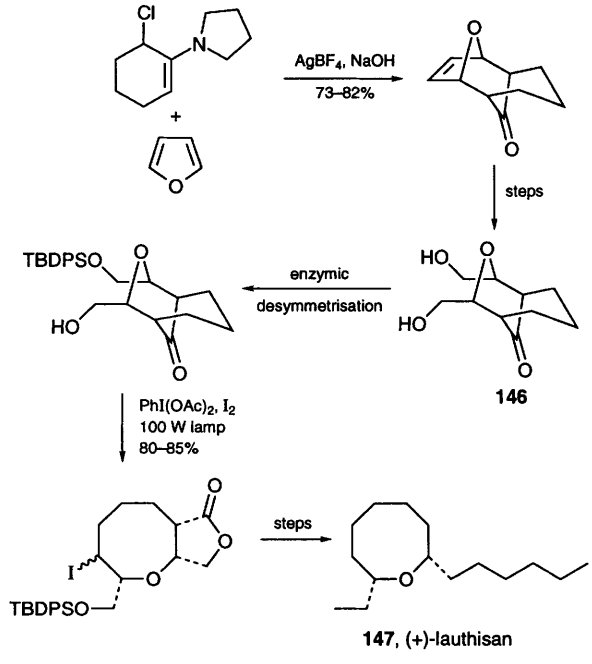
reductively decyanated to **144** (**Scheme 88**). This result is anomalous since, in agreement with the original report, other nucleophiles do give a mixture of tetrahydropyrans.

Five, six and seven membered rings were prepared by acyl radical cyclisations (**Scheme 89**).[114] Bicyclic systems related to the brevetoxins can also be prepared by this method (*e.g.* **145**).[115]



Scheme 89

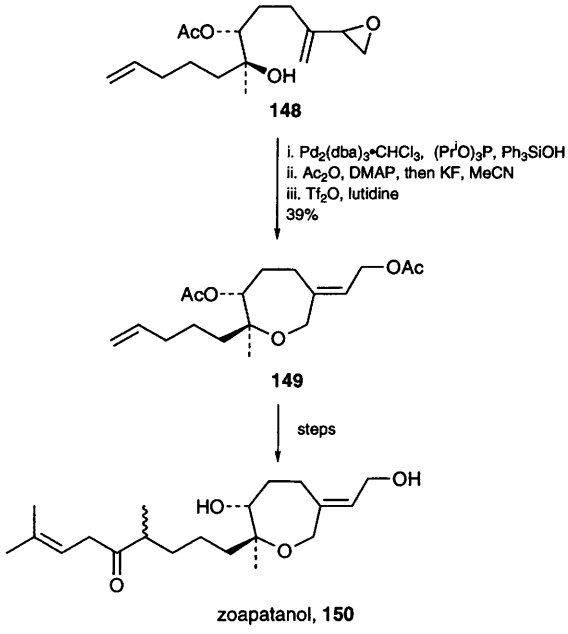
Cycloaddition chemistry has some advantages over standard cyclisations where medium-sized rings are sought. Chemists at Alabama have used the cycloaddition of 3-chloro-2-pyrrolidinocyclohexene with furan (the Schmid cycloaddition) followed by double application of the Suárez cleavage to provide an effective route to lauthisan **147** (**Scheme 90**).[116] In this synthesis, the meso diol **146** was desymmetrised by enzymic methods.



Scheme 90

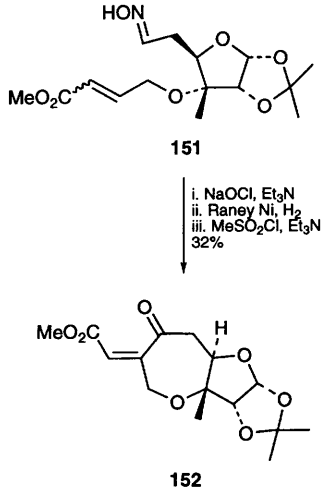
Speckamp and co-workers have also prepared lauthisan, this time using free radical chemistry. Their method is more effective for the formation of six-membered rings, and is discussed in the appropriate section.[65]

The anti-fertility agent zoapatanol has stimulated a great deal of synthetic interest. Trost now reports the first *asymmetric* synthesis of this compound.[117] Epoxide **148** was opened with triphenylsilanol under Pd^0 catalysis. Deprotection and cyclisation of the diol gave the oxepane **149** which was converted into the natural product **150** in a number of routine steps (**Scheme 91**).



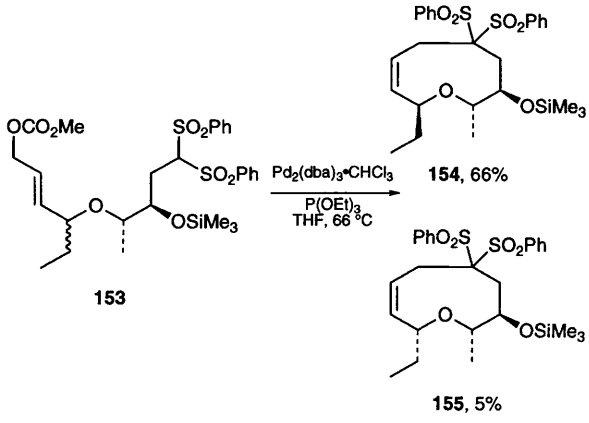
Scheme 91

Shing has also reported a new synthetic approach to zoapatanol. Nitrile oxide cycloaddition from **151** led, after two subsequent steps, to advanced intermediate **152** (**Scheme 92**).[118]



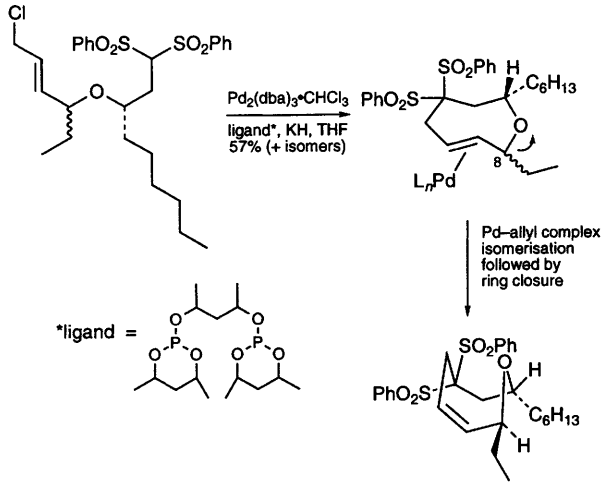
Scheme 92

Nine membered rings are among the most difficult to prepare. Brandes and Hoffmann[119] have expanded on earlier work by Trost in the preparation of compound **154**, related to *Laurencia*-derived medium ring ethers. The optimum conditions for cyclisation of **153** were 5 mol% $Pd_2(dba)_3 \cdot CHCl_3$ and 50 mol% $P(OEt)_3$ as ligand. In this way the 2,9-*trans* isomer **154** was obtained in 66% yield, with only 5% of the (thermodynamically favoured) 2,9-*cis* isomer **155** being formed.



Scheme 93

Compound **153** (and its precursors) was an unspecified mixture of diastereomers. The range of diastereomeric ratios in the products suggests that equilibration is occurring, although the products were found to be stable under the reaction conditions. The authors discuss this point in a following paper related to eight membered ring formation.[120] They propose that the initial product (not isolated) actually contains a *trans*-double bond, and that this can isomerise under the reaction conditions (by C–O bond heterolysis, isomerisation of the resulting π-allyl complex and a second cyclisation) to give the *cis*-double bond isomer with equilibration at C-8 (**Scheme 94**). In the light of this

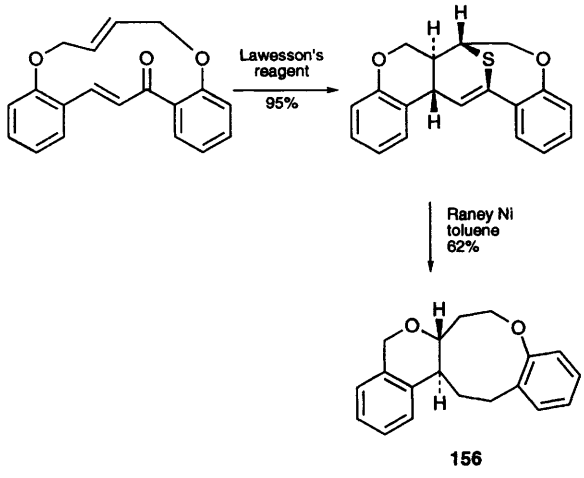


Scheme 94

proposal, the high yielding synthesis of the nine membered ring ether is even more impressive, since not just one but *two* cyclisations to give nine membered rings are in fact occurring.

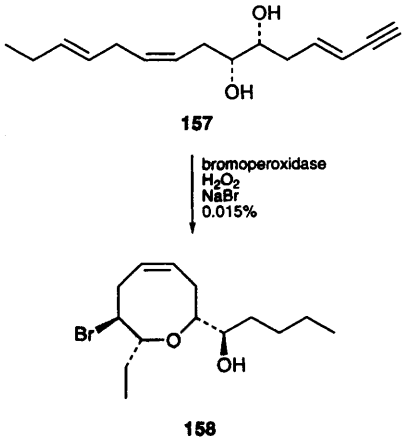
A similar π-allylpalladium cyclisation provided access to both enantiomers of lauthisan. In this case the initial product of the cyclisation was a 1:1 mixture of diastereomers which could be equilibrated to the thermodynamically more stable 2,8-*cis* isomer under basic conditions.[121]

Another approach to nine membered ring ethers makes use of a transannular hetero-Diels–Alder reaction followed by a desulfurisation to reveal the oxonane **156** as shown in **Scheme 95**.[122]



Scheme 95

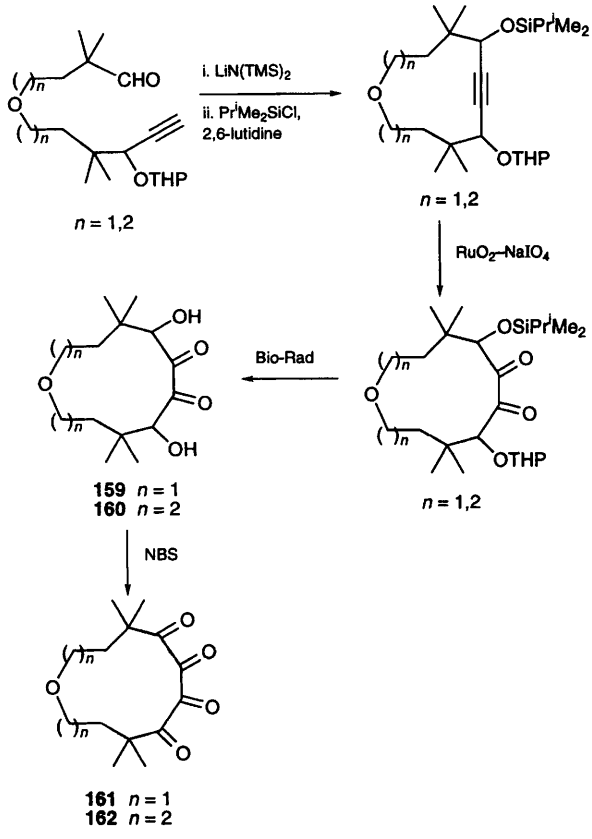
Murai and co-workers have probed the biosynthetic origin of cyclic ethers from *Laurencia* species of red algae. Partially purified bromoperoxidase from these sources was found to catalyse, in the presence of hydrogen peroxide and sodium bromide, the cyclisation of (3*E*,6*R*,7*R*)-laurediol **157** to a number of compounds including deacetyllaurencin **158** (**Scheme 96**).[123]



Scheme 96

7 Ring sizes larger than nine membered

Gleiter *et al.* have recently reported the preparation of eleven and thirteen membered cyclic ethers **161** and **162** (**Scheme 97**).[124] These compounds clearly show the importance of transannular interactions in medium-sized rings. In the eleven-ring compound **161**, a strong attractive transannular interaction was observed between the ether oxygen and the central carbonyl groups of the tetraketone motiety. This was also observed in the diol precursor **159**. No such interactions were observed for the thirteen-membered ring compounds.



Scheme 97

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