Recent developments in the synthesis of medium-ring ethers

MARK C. ELLIOTT

Department of Chemistry, Loughborough University of Technology, Loughborough, Leicestershire, LE11 3TU, UK

Reviewing the literature published between 1 October 1990 and 30 June 1994[1]

1 Introduction

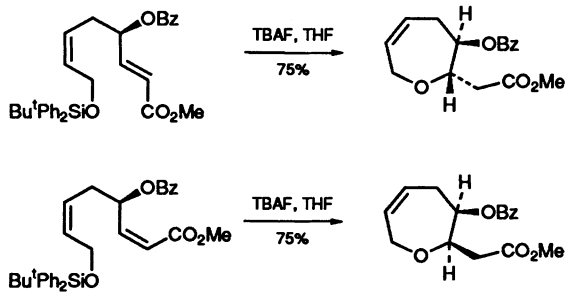
Medium-sized rings, both carbocyclic and heterocyclic, are widely recognized as being difficult to prepare,[2] and methods which work well for five- and six-membered rings are often unsatisfactory when applied to seven-membered rings and larger. The synthesis of cyclic ethers is no exception, and although the subject has been reviewed in general,[3] the special problems posed by medium rings, together with the discovery of an ever increasing array of natural products containing such rings, merits a separate article.

Many syntheses of seven- to nine-membered cyclic ethers have been reported since this subject was last reviewed.[1] Much of the impetus behind this work has been influenced by the structures of the monocyclic (*Laurencia* derived, *etc.*) and polycyclic (brevetoxin,[4,5] ciguatoxin) natural products containing these functionalities. This review covers the literature on medium-ring ether synthesis from 1 October 1990 to 30 June 1994, with emphasis on methods specifically designed for the synthesis of such compounds rather than extensions of tetrahydropyran synthesis to larger ring sizes. Examples of six-membered ring formation have, however, been included in some cases in order to explain mechanistic points.

The reactions have been classified into those involving C–O bond formation, C–C bond formation, rearrangement and ring expansion as the cyclic ether forming step. Also a number of groups have developed general methods for the conversion of lactones into cyclic ethers, and a section on these reactions has been included. However, in cases where the lactone has been formed using novel chemistry these reactions have been included elsewhere in the appropriate section.

2 Cyclization by C–O bond formation

V. S. Martin *et al.* have shown[6] that oxepanes can be formed in good yield by an intramolecular hetero-Michael reaction (**Scheme 1**), although the *cis*-double bond in the substrate proved necessary for cyclization to occur.



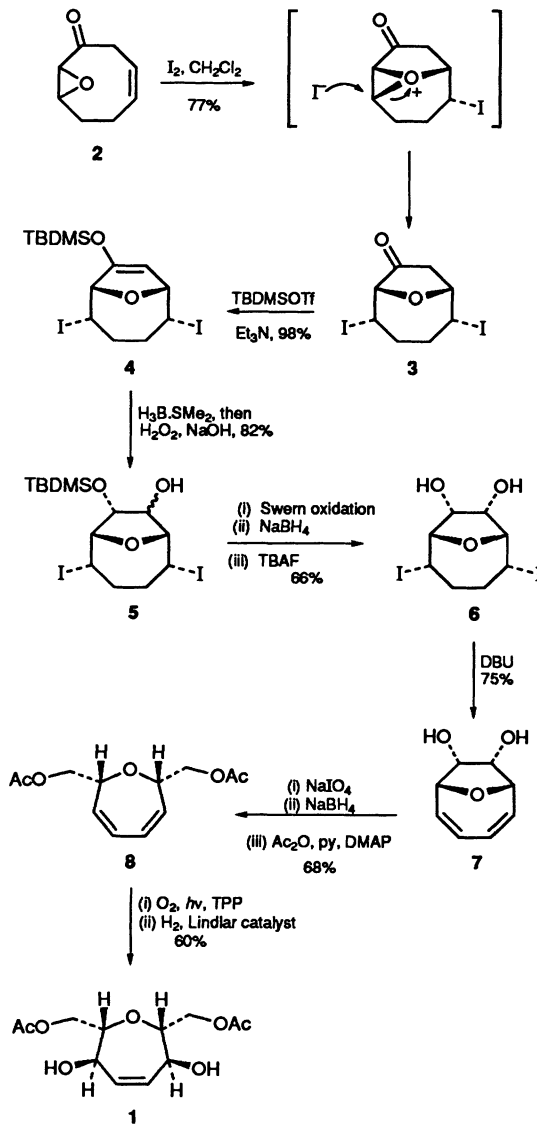
Scheme 1

Nevertheless since the oxepane ring in natural products is often unsaturated, any methodology which permits the inclusion of a double bond is valuable. The stereochemistry of the cyclization can be controlled by the double bond geometry of the Michael acceptor, and therefore either diastereomer of the oxepane can be readily accessed.

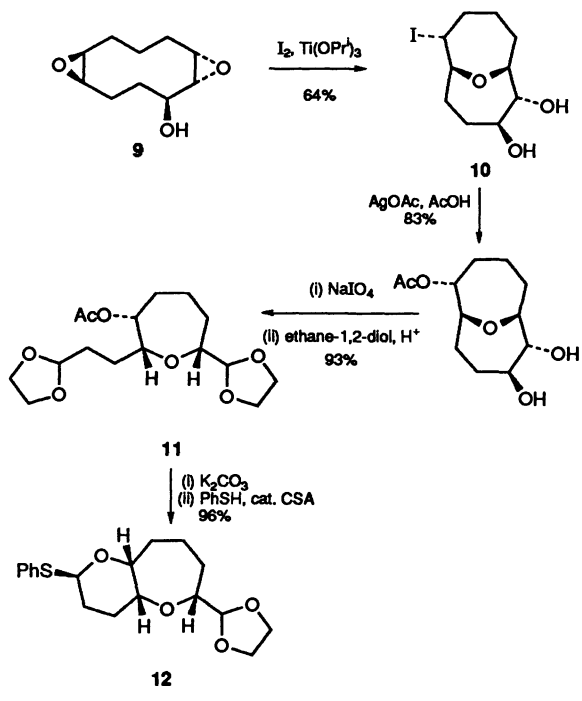
This methodology is versatile, and has also been applied to the preparation of tetrahydropyrans and tetrahydrofurans. As expected, in these cases no *cis*-double bond was required for cyclization to occur.[7,8]

J. D. Martin and colleagues have embarked upon an ambitious program towards the development of methodology for the synthesis of polycyclic medium-ring ethers.[9] The symmetrical unsaturated oxepane **1** has been prepared by the route shown in **Scheme 2**.[10]

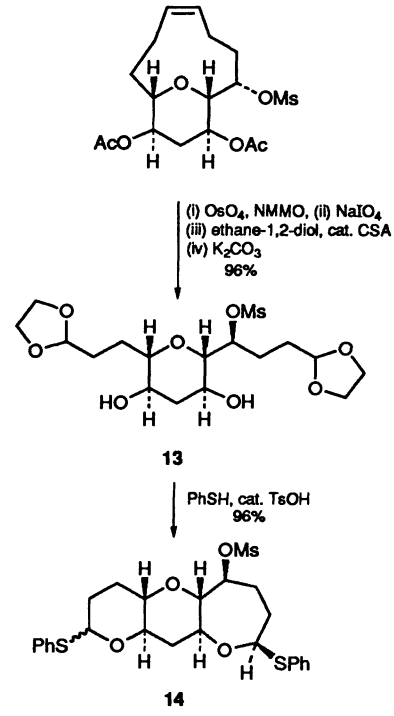
The bicyclic ketone **3** was prepared[11] by iodination of the cyclooct-3-enone-7,8-epoxide **2**. Its silyl enol ether **4** was hydroborated and oxidized to give **5**. Further oxidation followed by a diastereocontrolled reduction and deprotection gave the *cis*-diol **6**. Treatment with DBU led to the formation of diene **7**, the diol moiety of which was cleaved with periodate to



Scheme 2



Scheme 3



Scheme 4

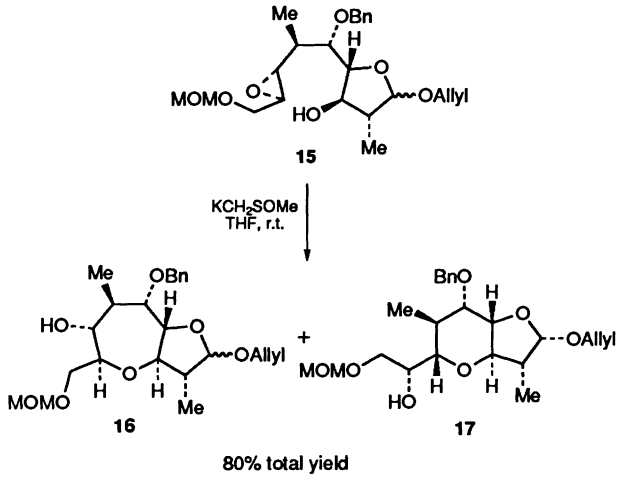
give, after reduction and protection, the oxepane **8**. Reaction with singlet oxygen followed by reduction gave the desired oxepane **1**, containing the functionality and stereochemistry of the oxepane rings found in polycyclic natural products such as ciguatoxin and the brevetoxins.

A similar transannular iodine mediated epoxide opening of the diepoxide **9** provided the oxacycle **10**. Acetolysis was followed by oxidative cleavage of the diol as above to give, after aldehyde protection, the oxepane **11**. Further manipulation provided the 6-7 fused system **12** as a single stereoisomer (**Scheme 3**).[12]

This method, involving acid catalysed treatment of a hydroxy-aldehyde in the presence of thiophenol, can also be used to prepare seven-membered rings (**Scheme 4**).[13] The tetrahydropyran precursor **13** was prepared in a similar manner to the above oxepane. Treatment with thiophenol in the presence of catalytic *p*-toluenesulfonic acid led to the formation of the 6-6-7 fused system **14** in excellent yield.

Oxidation of the thioacetal to the sulfone would presumably allow further carbon–carbon bond formation, a process which Martin has described in similar systems.[14]

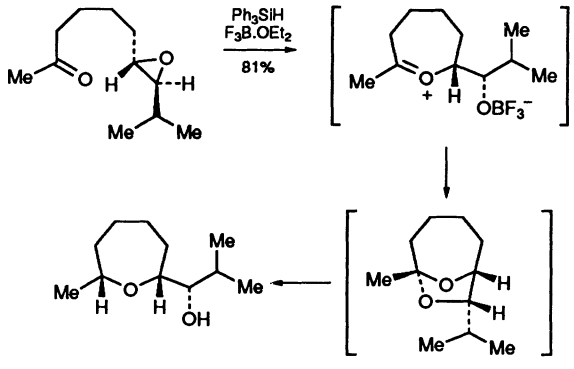
Recent studies towards ciguatoxin have shown that treatment of a 3:2 anomeric mixture of epoxy alcohols **15** with base produces a mixture of oxepane **16** and tetrahydropyran **17**. It was further shown that the β-anomer produced only the oxepane whereas the



Scheme 5

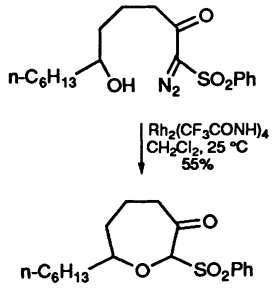
α-anomer produced a 1.7:1 mixture of oxepane and tetrahydropyran (**Scheme 5**).[15]

Kotsuki has previously described the use of bicyclic ketals in medium-ring ether synthesis.[16] Fotsch and Chamberlin[17] have described a novel variant of this method which involves the intramolecular opening of an epoxide by a carbonyl oxygen (**Scheme 6**).



Scheme 6

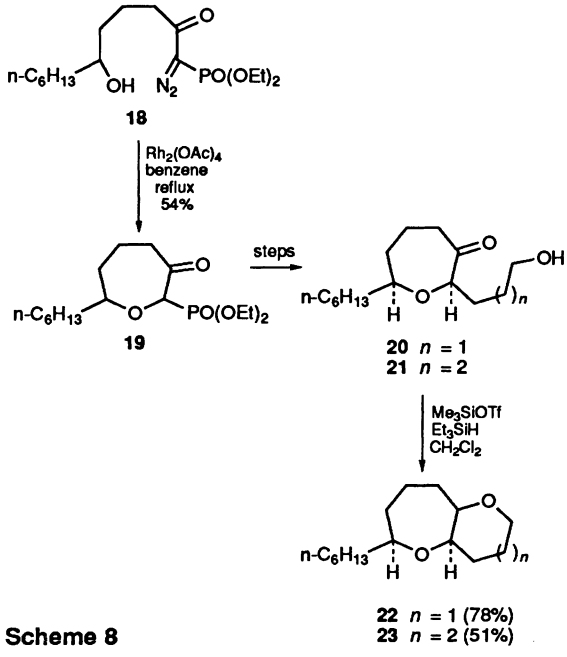
Moody *et al.* have shown that some of the earlier described rhodium(II) acetate catalysed cyclizations leading to oxepanes can be carried out under milder conditions using the more active catalyst rhodium(II) trifluoroacetamide.[18] The reaction shown (**Scheme 7**) can be carried out at room temperature in



Scheme 7

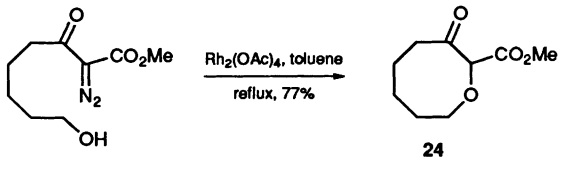
dichloromethane, whereas using rhodium(II) acetate as catalyst, heating under reflux in benzene was required to effect conversion.[19]

In related work,[20] the cyclization of the diazophosphonate **18** resulted in the formation of the corresponding oxepane-2-phosphonate **19**, which was transformed into the *cis*-2,7-disubstituted oxepanes **20** and **21** using standard chemistry. Cyclization to the 7-6 and 7-7 bicyclic systems **22** and **23** was effected by treatment with TMSOTf and triethylsilane, conditions originally developed by Olah[21] and used to great effect by Nicolaou (see later). Although the reaction predominantly gave the *trans*-ring fused ethers, the stereoselectivity was at best 3:1 (**Scheme 8**).



Scheme 8

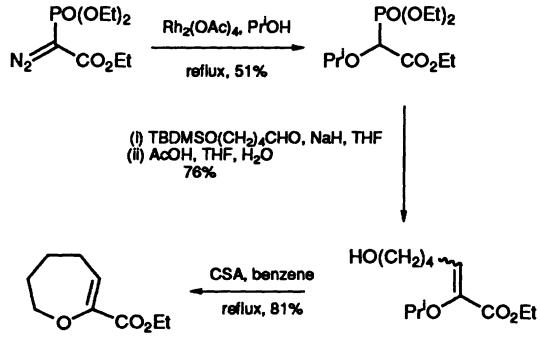
The rhodium carbenoid cyclization can also be used for the formation of eight-membered rings. Meier *et al.* have improved on the earlier reported yield[22] for the synthesis of the oxocane **24** by the use of high dilution techniques and slow addition.[23] A fivefold increase in dilution led to an increase in yield from 31% to 77% (**Scheme 9**).



Scheme 9

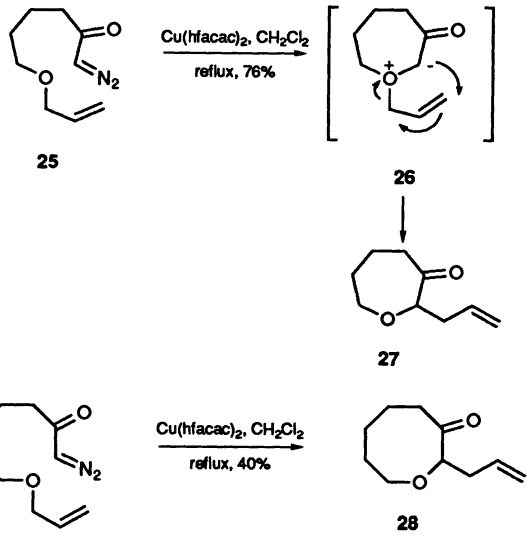
In an alternative procedure, intermolecular rhodium(II) catalysed O–H insertion reactions were used; these were followed by a Wadsworth–Emmons reaction and simple acid catalysed cyclization (**Scheme 10**).[24]

A further carbenoid-based approach to medium-ring ether synthesis has been described by



Scheme 10

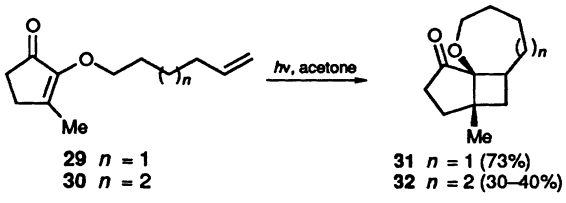
Clark and co-workers (**Scheme 11**).[25] The oxonium ylide **26** formed by transition metal catalysed decomposition of the diazo compound **25** rearranges by a [2,3]-sigmatropic shift to give the oxepane **27**. This process also gives, albeit in lower yield, the oxocane **28**.



Scheme 11

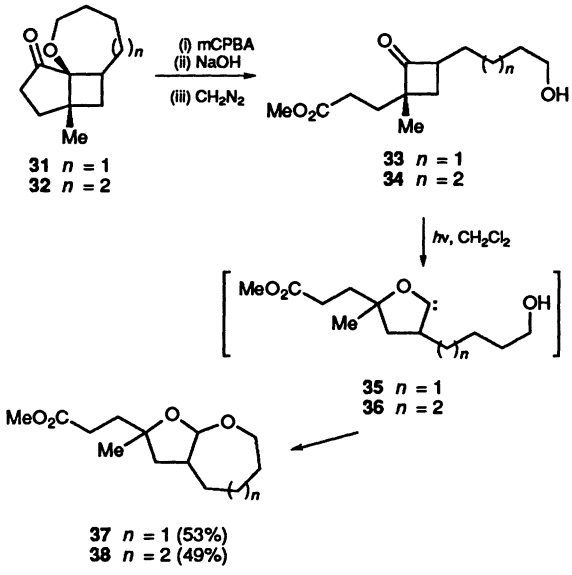
Copper(II) hexafluoroacetylacetonate is the catalyst of choice since, rhodium(II) acetate, the more commonly used catalyst for such reactions, is less selective in that C–H insertion products are also obtained, resulting in a lower yield of the desired cyclic ethers.

Pirrung has described a sequence of photochemical reactions which involve medium-ring ethers at two stages.[26] Irradiation of cyclopentanone enol ethers **29** and **30** gave the fused cyclobutanes **31** and **32** containing oxepane and oxocane rings respectively (**Scheme 12**).



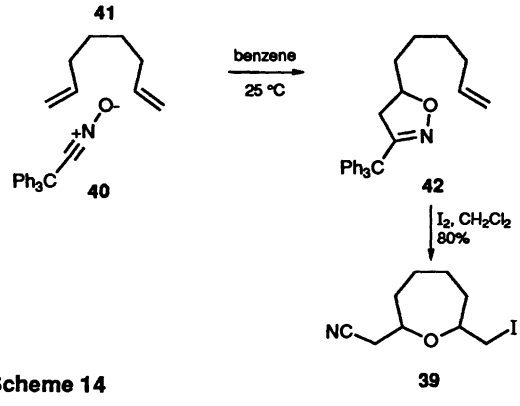
Scheme 12

Baeyer–Villiger oxidation of **31** and **32** followed by hydrolysis and esterification gave the cyclobutanones **33** and **34** respectively. Photolysis of cyclobutanones is believed to proceed *via* a 2-tetrahydrofuranylidene, *e.g.* **35** and **36**. This oxacarbene then inserts into O–H bonds to give moderate yields of the oxepane **37** and oxocane **38** acetals as shown in **Scheme 13**.



Scheme 13

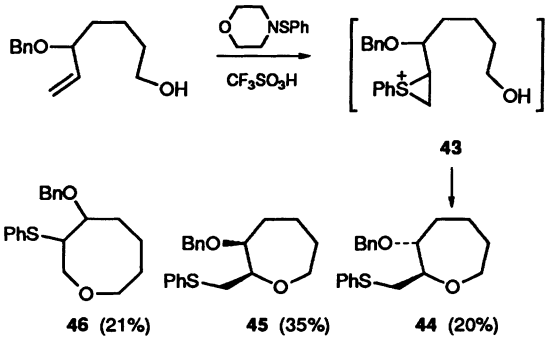
A simple two step procedure has been used to prepare the functionalized oxepane **39** from 1,7-octadiene.[27] Cycloaddition of triphenylacetonitrile oxide **40** with 1,7-octadiene **41** gave the isoxazoline **42** in almost quantitative yield. Treatment with iodine then gave the oxepane **39** in 80% overall yield (**Scheme 14**). However, following the same protocol using 1,8-nonadiene resulted in none of the corresponding oxocane.



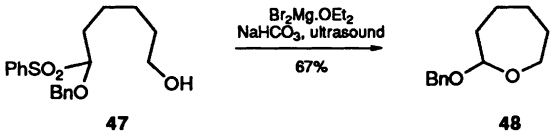
Scheme 14

Intramolecular 7-*exo* cyclization of an alcohol onto an thiiranium ion **43** gave a mixture of diastereomeric oxepanes **44** and **45** along with a single isomer of the oxocane **46**. As expected, oxepane formation was the predominant process (**Scheme 15**).[28]

Five- to eight-membered ring lactol ethers, *e.g.* **48**, are formed in good yield by the intramolecular cyclization of ω-hydroxy-α-sulfonylmethanoethers **47** (**Scheme 16**).[29]

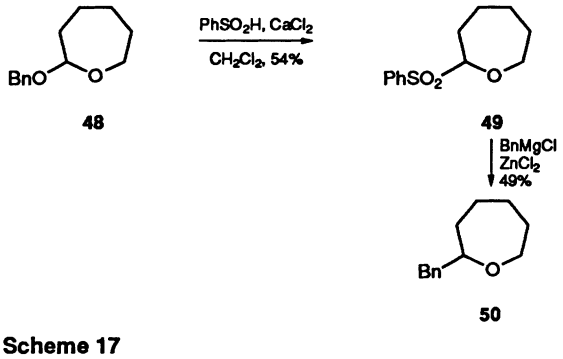


Scheme 15



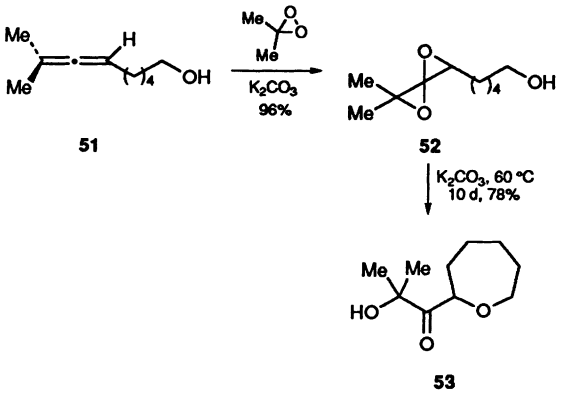
Scheme 16

Exchange with benzenesulfinic acid gave the 2-phenylsulfonyloxepane **49** which was allowed to react with benzylmagnesium chloride to give 2-benzyloxepane **50** (**Scheme 17**).[29]



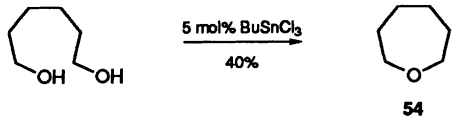
Scheme 17

Dimethyldioxirane oxidation of the ω-hydroxyallene **51** gave the isolable bis-epoxide **52**. Simply heating this compound at 60°C for 10 days in the presence of potassium carbonate gave a 78% yield of the oxepane **53** (**Scheme 18**).[30]



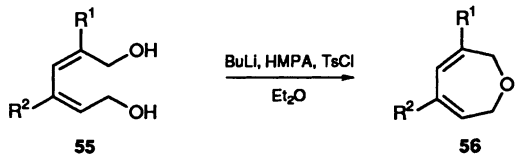
Scheme 18

Although direct cyclization of 1,6-diols is not generally an efficient method for the production of oxepanes, Tagliavini *et al.* have shown[31] that a catalytic amount of butyltin trichloride promotes this cyclization by way of an organotin alkoxide. Water and the product oxepane **54** are co-distilled out of the reaction (**Scheme 19**).



Scheme 19

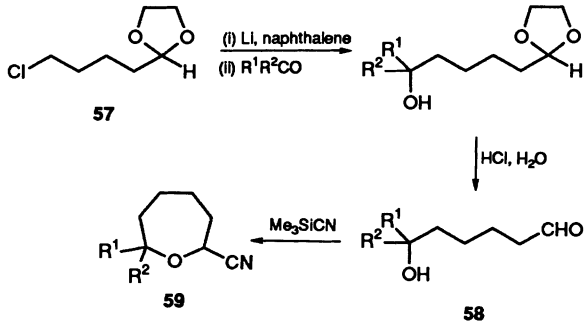
Cyclization of diols can, however, be efficient if the conformational mobility of the substrate is reduced. The presence of two *cis*-alkene moieties in the diols **55** facilitates the cyclization to the dihydrooxepins **56** (**Scheme 20**).[32]



$R^1 = Bu^t$, $R^2 = H$ 85%
$R^1 = H$, $R^2 = Bu^t$ 87%

Scheme 20

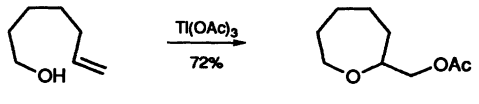
The hydroxyaldehydes **58**, prepared as shown in **Scheme 21**, cyclize efficiently to the oxepanes **59** upon treatment with trimethylsilyl cyanide. The yields shown are for the three step process from **57**.[33]



$R^1 = H$, $R^2 = Ph$ 36%
$R^1 = R^2 = Me$ 22%
$R^1 = R^2 = Et$ 39%
$R^1R^2 = -(CH_2)_5-$ 34%

Scheme 21

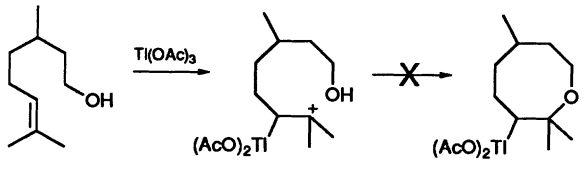
Thallium(III) acetate has been found to promote the intramolecular cyclization of hydroxyalkenes **60**. This reaction works best for the formation of tetrahydropyrans, but is still efficient for the preparation of tetrahydrofurans and oxepanes, *e.g.* **61** (**Scheme 22**).[34]



60 61

Scheme 22

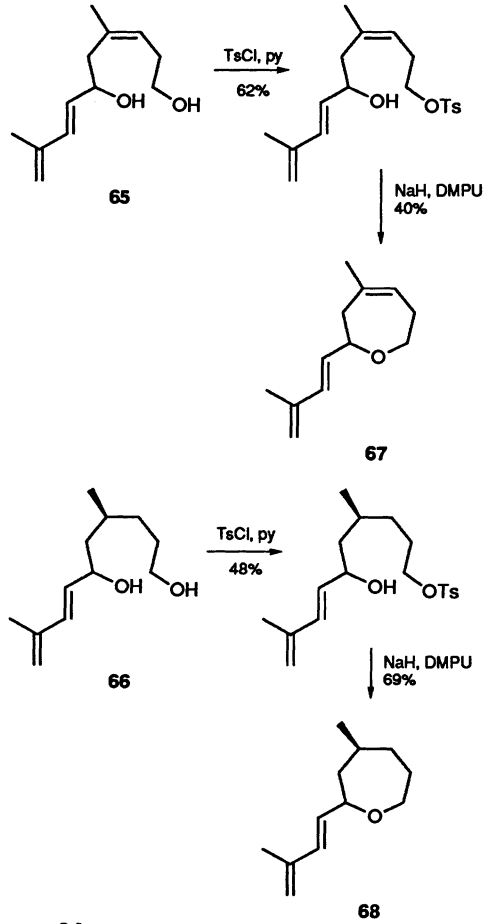
However, oxocane formation was unsuccessful, as was oxepane formation from citronellol **62**. These observations suggest that the reaction proceeds *via* Markovnikov addition of thallium(III) acetate to give the more stable carbenium ion **63**. Thus, in the case of citronellol, cyclization would give the oxocane **64**, which is presumably disfavoured on entropic grounds (**Scheme 23**).



62 63 64

Scheme 23

Terpenoid oxepanes **67** and **68**, isolated from quince fruit, have been synthesized from the corresponding diols **65** and **66**. The primary alcohol was selectively tosylated and cyclization was effected using sodium hydride in DMPU (**Scheme 24**).[35]

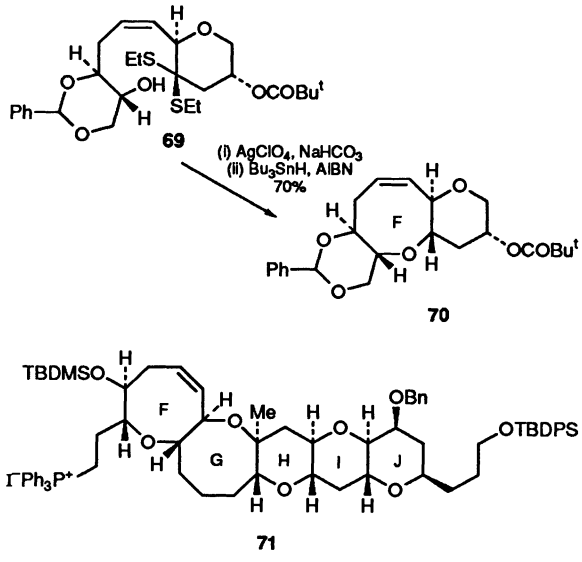


65 67 66 68

Scheme 24

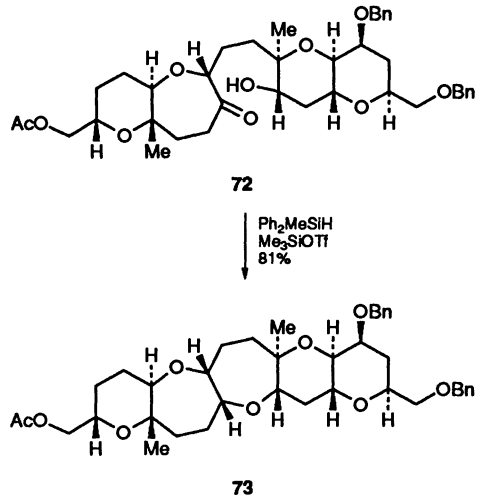
Surprisingly, in this case the inclusion of a double bond in the acyclic precursor **65** actually resulted in a lower yield of the cyclized product **67**.

The 8-8-6-6-6 fused system **71** which corresponds to the FGHI and J rings of brevetoxin A has been synthesized by the Nicolaou group. Both oxocanes were formed by cyclization of an alcohol onto a dithioketal. One of the cyclizations (**69** to **70**) is shown in **Scheme 25**.[36]



Scheme 25

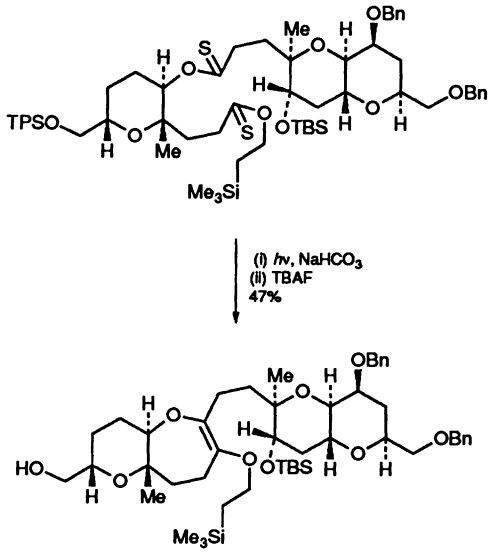
The same workers have prepared hemibrevetoxin B (see later) and its epimer, (7aα)-*epi*-hemibrevetoxin B using a range of cyclization chemistry developed for this purpose. The C-ring was prepared by the simple but effective reductive cyclization of a hydroxyketone (**72** to **73**) as shown in **Scheme 26**.[37]



Scheme 26

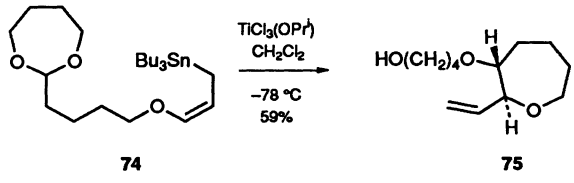
3 Cyclization by C-C bond formation

The B-ring of (7aα)-*epi*-hemibrevetoxin B was prepared using the photochemical cyclization of a bis-thioester (**Scheme 27**).[37]



Scheme 27

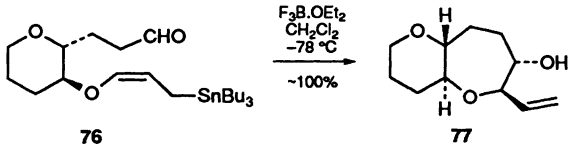
Yamamoto's group have developed an efficient route to β-alkoxy substituted cyclic ethers related to the brevetoxin natural products. Lewis acid treatment of the stannane **74** gave a 59% yield of **75** as a single *trans*-diastereoisomer (**Scheme 28**).[38]



74 **75**

Scheme 28

A similar cyclization was used to prepare the AB-ring fragment of gambiertoxin 4B. Treatment of chiral non-racemic **76** with boron trifluoride etherate gave an essentially quantitative yield of the fused oxepane **77**.[39] An earlier report[38] suggested that the fusion of a cyclohexyl ring makes cyclization more favourable by reducing the conformational mobility of the acyclic precursor. Presumably the tetrahydropyran ring exerts the same effect in this case (**Scheme 29**).

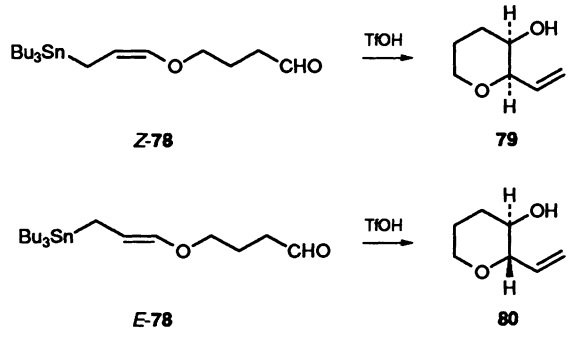


76 **77**

Scheme 29

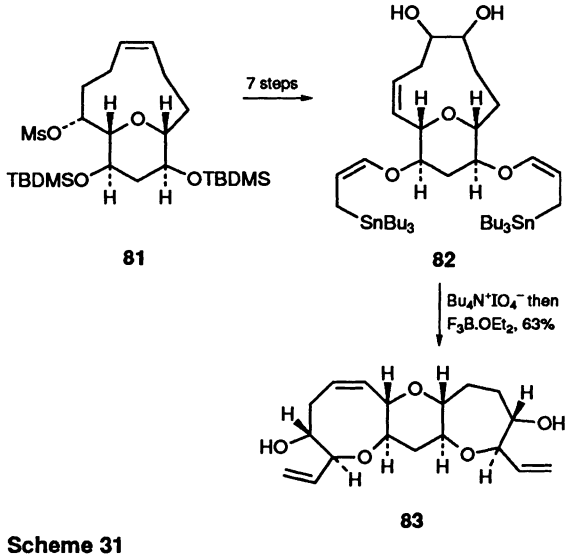
The cyclization onto aldehydes is generally accompanied by higher stereocontrol than the acetal cyclizations. In cases where diastereoselectivity is low, the use of titanium(IV) chloride in conjunction with triphenylphosphine can be advantageous.[40] The aldehyde cyclizations have been used to prepare 6-7-7-6 and 7-7-6-6 fused systems related to brevetoxin B and hemibrevetoxin respectively.[41,42]

This methodology is equally applicable to the synthesis of tetrahydropyrans. In this case the reaction has been studied under a wide range of conditions.[43] It has been found that if a protic acid is used, the sense of diastereocontrol is determined by the double bond geometry (**Scheme 30**). However Lewis acid promoted cyclization of *E* or *Z* **78** produced the same *trans*-isomer **80**.



Scheme 30

Martin has shown that this type of cyclization can be applied to the preparation of the heavily functionalized 8-6-7 fused system **83**. The protected diol **81** (the diacetate analogue of which was earlier used in the preparation of the 6-6-7 fused system **14**, see **Scheme 4**) was converted into the bis-stannane **82**. This was then oxidized and cyclized to **83** in a one-pot process (**Scheme 31**).[44]

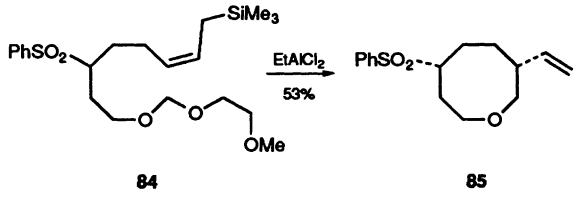


81 **82** **83**

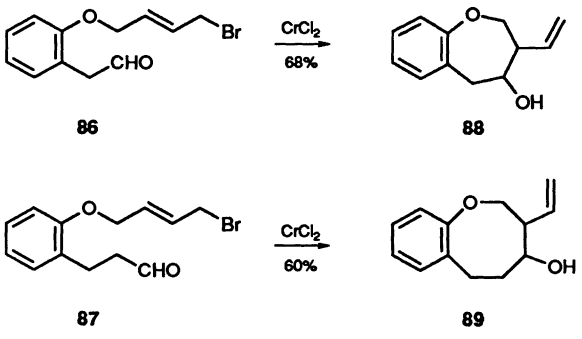
Scheme 31

Cyclization of allylsilanes onto acetals proceeds similarly to the analogous allylstannane cyclizations (**Scheme 32**).[45] In this case an acyclic acetal **84** was used, such that one of the acetal oxygen atoms is retained in the oxacyclic ring **85**. This is therefore an *endo* cyclization rather than an *exo* acetal cyclization as described by Yamamoto.

A further, similar example is provided by the chromium-mediated cyclization of bromo aldehydes **86** and **87** to give fused oxepanes **88** and oxocanes **89** (**Scheme 33**).[46] Attempted production of a benzopyran



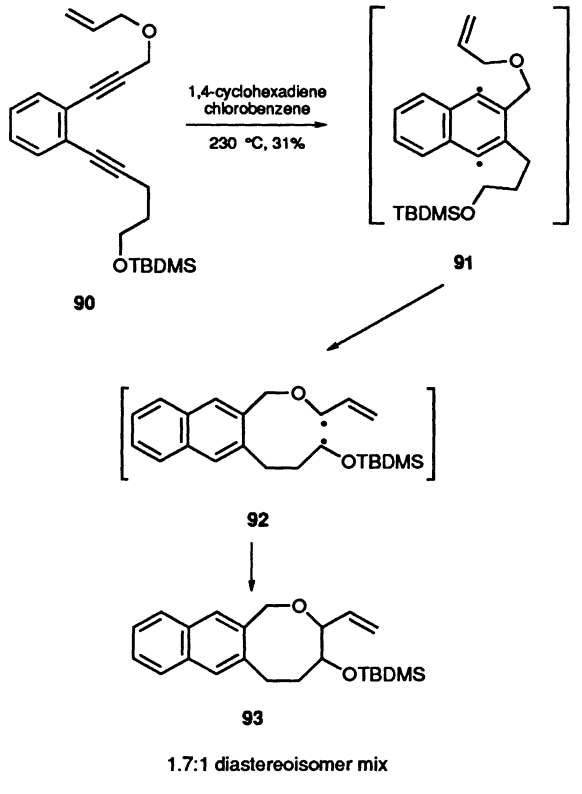
Scheme 32



Scheme 33

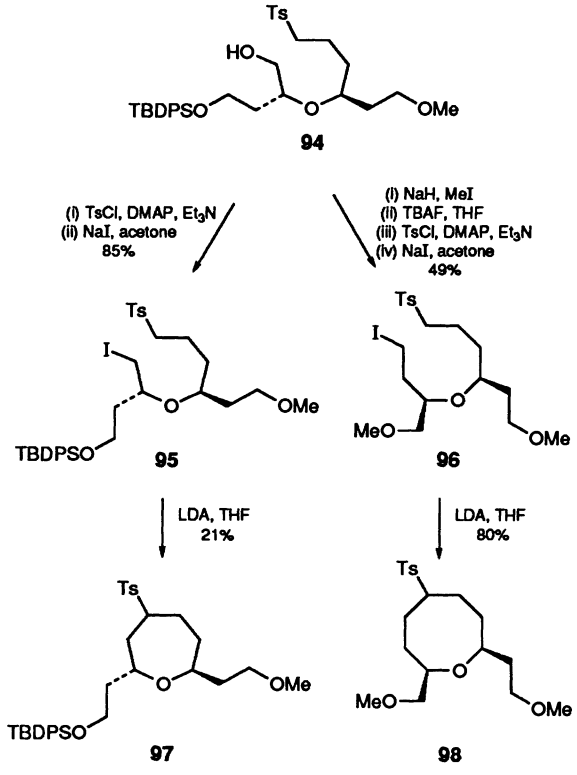
by this method failed as elimination gives predominately the phenol (salicylaldehyde).

A similar oxocane **93** is formed, albeit in low yield, by the process shown in **Scheme 34**.[47] Bergman cyclization of the enediyne **90** gives the diradical **91** which rearranges by two [1,5] shifts to the diradical **92**. Recombination then gives the oxocane **93**.



Scheme 34

An elegant approach to oxepanes and oxocanes from a common precursor has recently been reported by Mujica *et al.*[48] whereby the alcohol **94** was transformed into the halides **95** and **96**. These were then cyclized to the oxepane **97** and oxocane **98** in 21% and 80% yields respectively (**Scheme 35**). The lower yield in the oxepane cyclization was rationalized in terms of the known difficulty in displacing halides with β-alkoxy substituents.

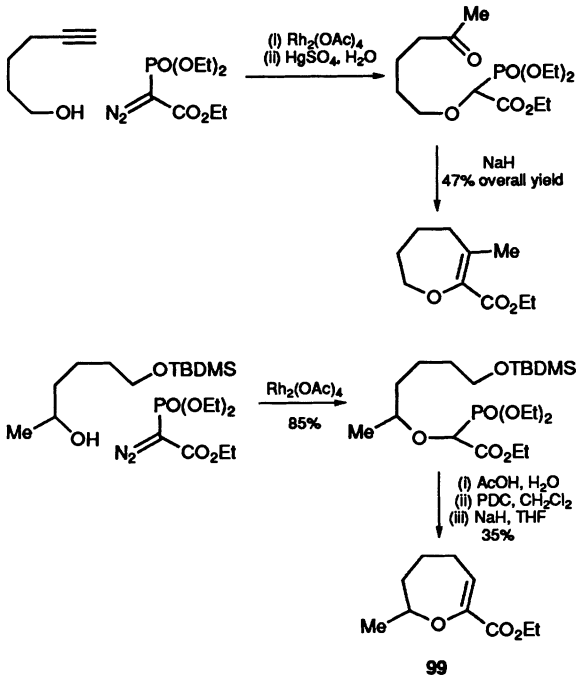


Scheme 35

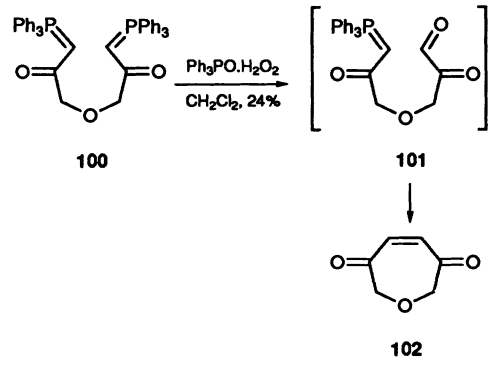
In connection with the rhodium(II) acetate catalysed cyclizations of diazo alcohols, it has been shown that it is also possible to use an intermolecular O–H insertion of a rhodium carbenoid, followed by an intramolecular Wadsworth–Emmons reaction as the cyclization step.[24,49] The reaction is quite general, and works with both aldehydes and ketones as the carbonyl component, and for phosphonyl-ketones, -sulfones, and bis-phosphonates, as well as phosphonoacetates (as shown in **Scheme 36**). Rhodium(II) acetate catalysed insertion into a secondary alcohol led to the 2,7-disubstituted oxepane **99**.

A similar intramolecular Wittig reaction has been used by Bestmann *et al.* to prepare the oxepane **102**. Oxidation of the bis-phosphonium ylide **100** gave a 24% yield of the oxepane **102**, presumably *via* the aldehyde **101** (**Scheme 37**).[50]

Overman *et al.* have demonstrated the power of their acetal-alkene cyclizations[51] with an elegant first total synthesis of the marine natural product isolaurepinnacin. The precursor **103**, with most of the required functionality in place, was cyclized to the oxepane **104** in 90% yield (**Scheme 38**). This



Scheme 36



Scheme 37

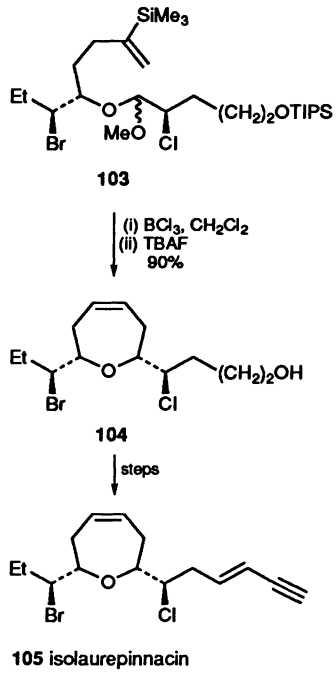
intermediate was converted into isolaurepinnacin (**105**) in five simple steps.[52]

An acetal-alkyne cyclization has recently been used by Speckamp and co-workers[53] to provide the unsaturated oxepane shown in **Scheme 39**.

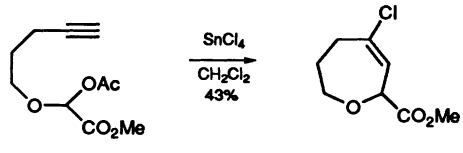
The Lewis acid catalysed carbonyl-ene reaction has been shown to provide oxepanes **106** in moderate yields (**Scheme 40**). Use of a chiral titanium BINOL complex led to high levels of asymmetric induction.[54]

Oxocanes **107** can also be formed by this process although the yields are lower, reflecting the greater difficulty of eight-membered ring formation. Addition of silver perchlorate led to a slight increase in enantioselectivity, although the yields were again decreased.

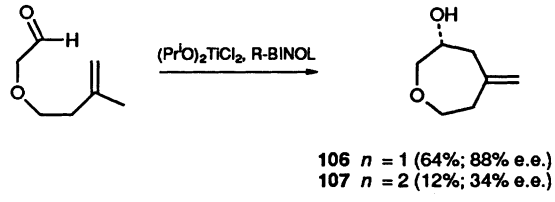
When the organozinc compound **108** is heated under forcing conditions a similar intramolecular ene reaction takes place to give the oxepane **109** as a mixture of geometrical isomers (**Scheme 41**).[55] A small amount of an oxocane, produced by *endo* cyclization, was also obtained.



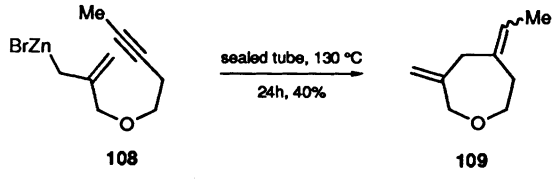
Scheme 38



Scheme 39

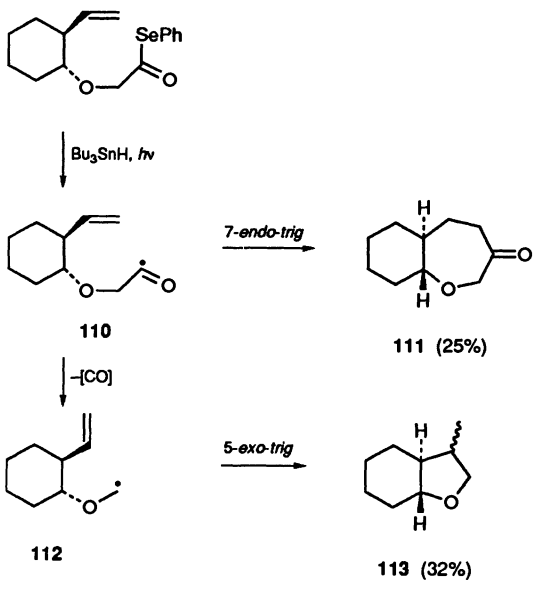


Scheme 40



Scheme 41

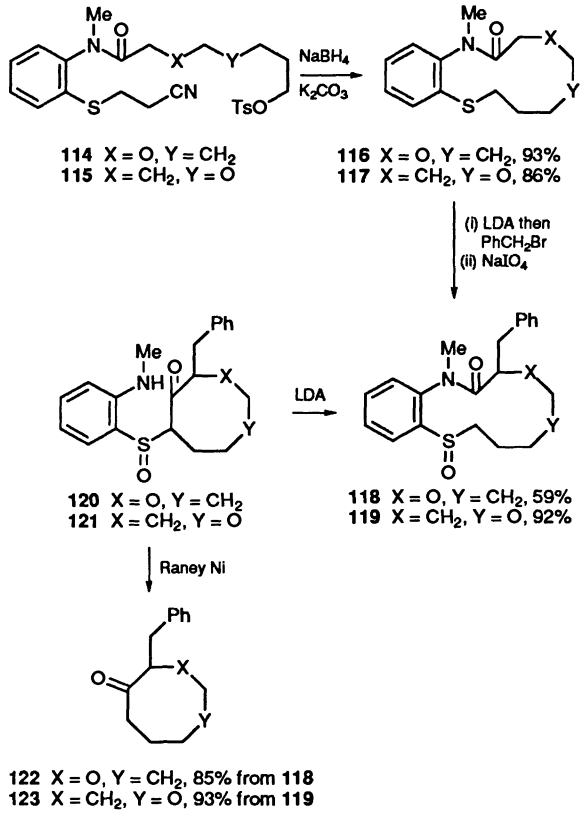
Radical reactions to form medium-sized rings are often accompanied by hydrogen abstraction processes which lead to overall reduction of the radical. Crich has shown that in the case of the cyclization of the acyl radical **110** the favoured process is a 7-*endo*-cyclization, to give the fused oxepane **111**. The yield is low due to the rapidity of decarbonylation of **110** to give the stabilized radical **112** which cyclizes to the tetrahydrofuran **113** (**Scheme 42**).



Scheme 42

Although a tetrahydropyran would be produced by *exo*-cyclization of the acyl radical **110**, one was not observed.[56]

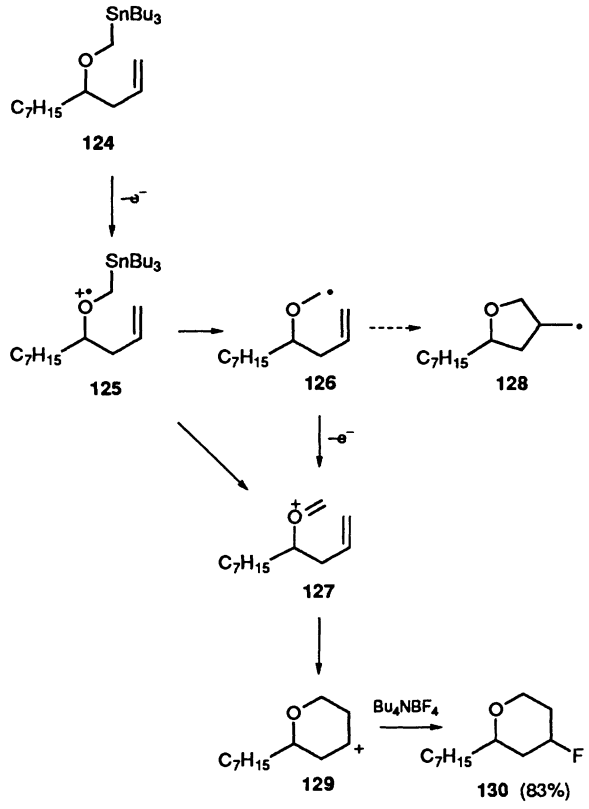
Cyclizations to give rings larger than ten-membered become easier because of the lack of transannular strain present in these molecules. Ohtsuka *et al.* have used this to good effect in their preparation of oxocanes and azocanes (**Scheme 43**).



Scheme 43

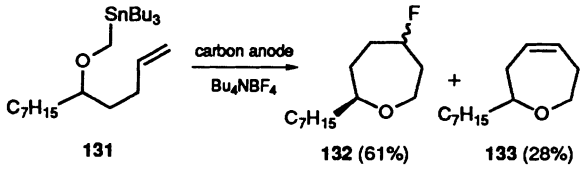
Macrocyclization of **114** and **115** gave the 12-membered ring amides **116** and **117** in good yields. This functionality then 'holds' the reacting sites together so that the actual cyclization steps (**118** to **120**, **119** to **121**) proceeded in almost quantitative yield. Having served its purpose, the temporary connection was then reductively removed to give the oxocanes **122** and **123**.[57]

Electrochemical synthesis has recently been enjoying increased popularity.[58] Anodic oxidation of α-stannylethers has been demonstrated to be effective in the synthesis of tetrahydropyrans and oxepanes. The proposed mechanism is illustrated for the formation of a tetrahydropyran **130** (**Scheme 44**). Single electron oxidation of the substrate **124** leads to the formation of the radical cation **125**. Loss of tin can be heterolytic, leading to the oxygen stabilized radical **126**, or homolytic leading to the oxonium ion **127**. Since the radical **126** would be expected to cyclize onto the double bond in a 5-*exo-trig* manner, to give a tetrahydrofuran **128**, then it is proposed that if this intermediate is formed, it must be rapidly oxidized to the oxonium ion **127**. This ion undergoes a 6-*endo-trig* cyclization to give the more stable (as opposed to the primary carbenium ion which would be formed by 5-*exo* cyclization) carbenium ion **129** which is quenched by the tetra-n-butylammonium tetrafluoroborate present in the reaction mixture.[59]



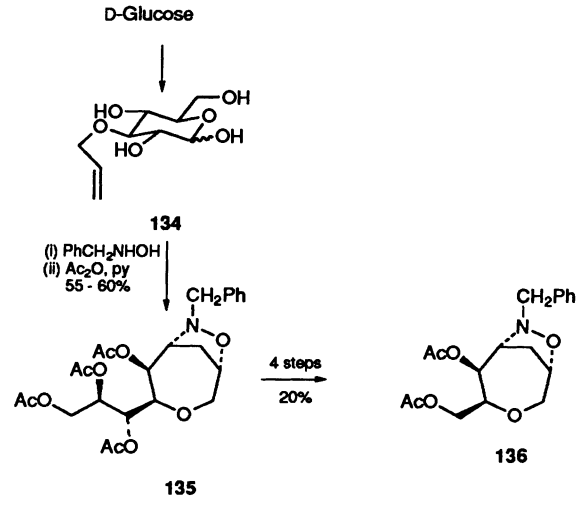
Scheme 44

The carbenium ion **129** can also lose a proton to give an alkene. Thus in the case of **131**, the fluorinated oxepane **132** and the tetrahydrooxepin **133** are obtained in a combined yield of 89% (**Scheme 45**).



Scheme 45

A nitrone cycloaddition of a glucose derivative provides access to either enantiomer of the chiral oxepane derivative **136**.[60,61] Treatment of 3-*O*-allyl-D-(+)-glucose **134** with *N*-benzylhydroxylamine, followed by acetylation gave a 55–60% yield of oxepane **135**, oxidative cleavage of the side chain of which gave **136** which contains two of the original chiral centres of the glucose (**Scheme 46**).



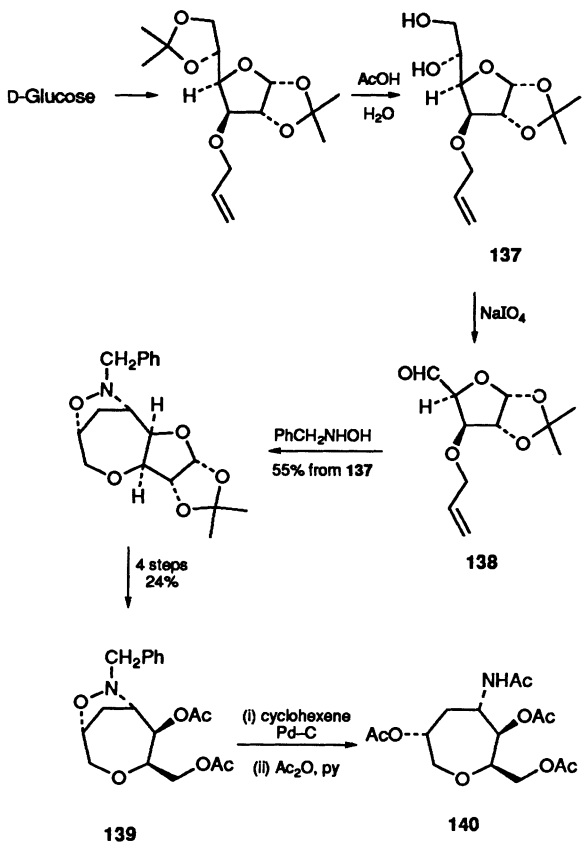
Scheme 46

Alternatively,[61] a one-carbon degradation of glucose provided the aldehyde **138** (*via* **137**) in which the two chiral centres to be retained have the opposite stereochemistry to those in the original glucose derivative **134**. Thus, formation of the nitrone followed by cycloaddition and modification gave the oxepane **139**, the enantiomer of **136**. Finally, the isoxazolidine ring was reductively cleaved to give the chiral oxepane **140** (**Scheme 47**).

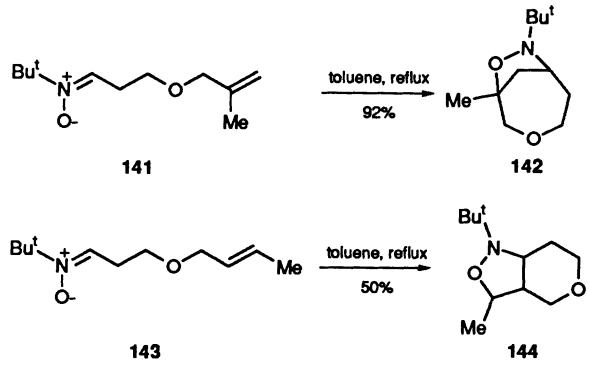
A further example of a nitrone cycloaddition to give oxepanes has been reported by Aurich and co-workers (**Scheme 48**).[62]

This reaction is extremely substrate dependent. Nitrone **141** gives only the oxepane **142** (92% yield) while the isomeric nitrone **143** gives the tetrahydropyran **144** exclusively. This is in agreement with the observations of Shing *et al.* who have noted that for systems related to **138**, minor structural modifications can lead to the formation of tetrahydropyrans at the expense of oxepanes.[63]

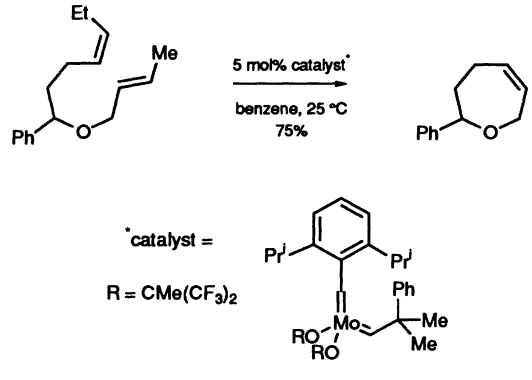
Olefin metathesis has received little attention from synthetic organic chemists. The metathetic ring closure of 1,6- 1,7- and 1,8-dienes has been recently investigated and found to be efficient and mild. Oxepane formation by this method is shown in **Scheme 49**.[64]



Scheme 47



Scheme 48

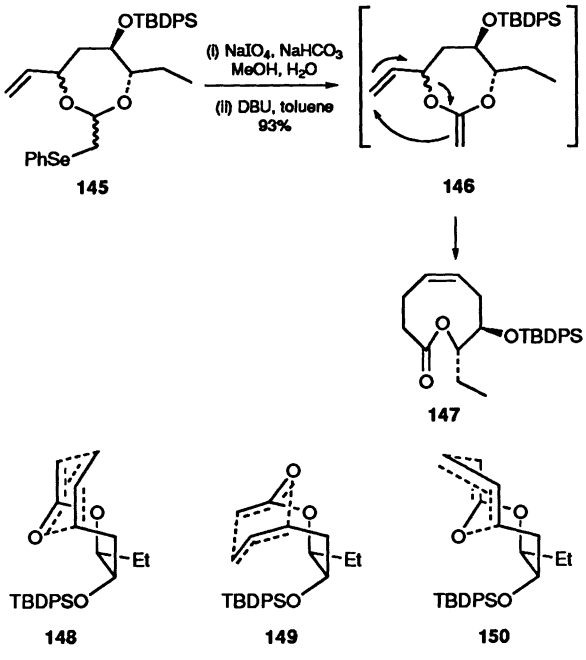


Scheme 49

The same authors have more recently reported a ruthenium-based catalyst which gives comparable yields, with the advantage of being less air sensitive.[69]

4 Rearrangement reactions

Holmes has shown that his earlier described Claisen rearrangement of ketene acetals can be readily extended to the synthesis of nine-membered lactones. The easily prepared (79% over six steps) selenyl ether **145** was isolated as a mixture of three diastereoisomers. These were oxidized to the selenoxide and immediately heated to give the ketene acetal **146** which underwent Claisen rearrangement to give the lactone **147**. The ketene acetal is presumably a mixture of diastereoisomers. However, both isomers react to give the same lactone *via* chair transition states **148** and **149**. Reaction through a boat transition state **150** would give rise to a product containing a *trans*-double bond, and is not observed (**Scheme 50**).[66]

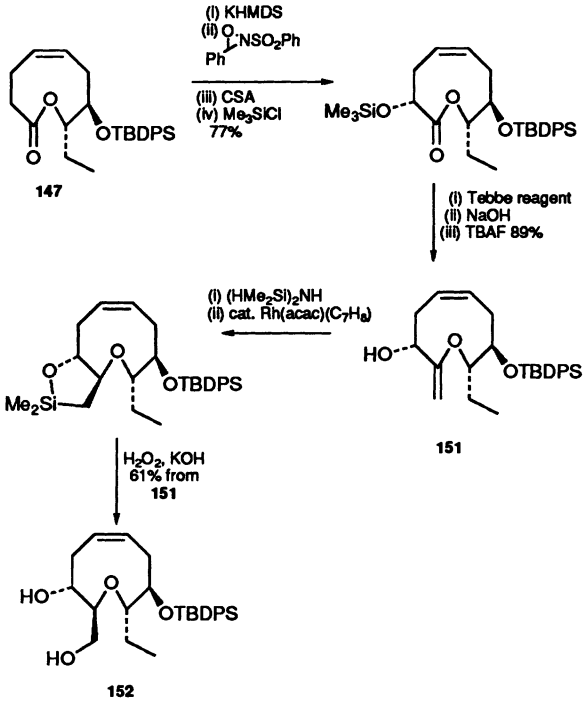


Scheme 50

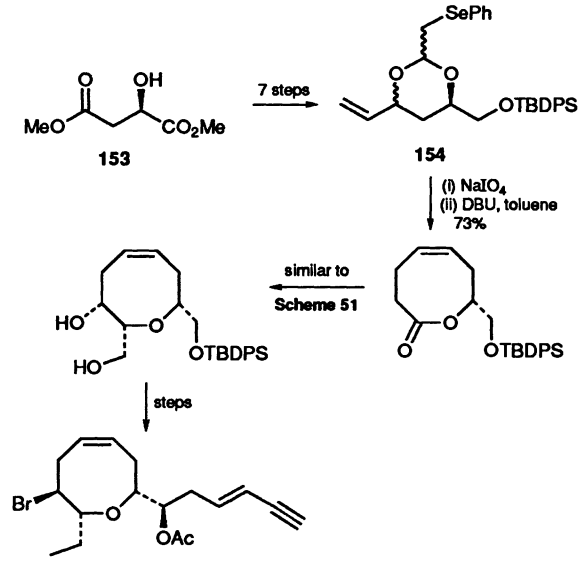
This lactone has been converted into an advanced intermediate for the synthesis of obtusenyne (**Scheme 51**).[67,68] A highly diastereoselective oxidation of the enolate of **147** followed by Tebbe methylenation gave **151**. This was then subjected to intramolecular hydrosilylation followed by oxidation to give **152**.

A similar sequence of reactions starting from dimethyl (*R*)-malate **153** *via* a six-membered cyclic acetal **154** has resulted in an elegant total synthesis of (+)-laurencin **155**, another of the many *Laurencia* metabolites, (**Scheme 52**).[69]

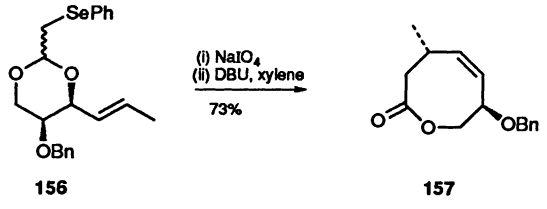
Incorporation of substituents onto the double bond of the selenyl ether precursor can result in a diastereoselective Claisen rearrangement; *e.g.* **156** to **157** (**Scheme 53**).[70]



Scheme 51



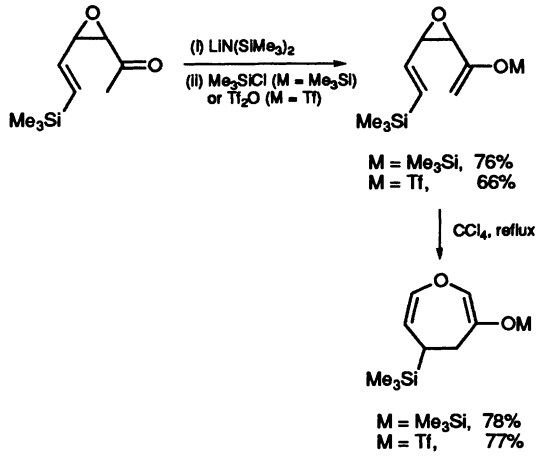
Scheme 52



Scheme 53

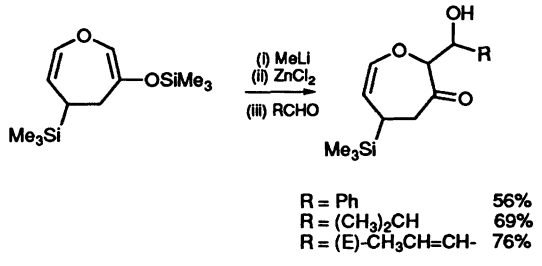
This methodology has also been applied to the synthesis of the proposed nine-membered lactone structure of ascidiatrienolide A, leading to a revision of the structure of this natural product.[71]

Cope rearrangement of *cis*-divinylepoxides gives rise to dihydrooxepins in synthetically useful yields (**Scheme 54**).[72]



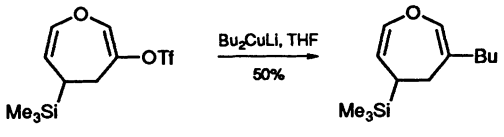
Scheme 54

Where one of the double bonds forms part of a silyl enol ether or an enol triflate the dihydrooxepins formed are amenable to further modification. The silyl enol ether can be converted into the lithium enolate, which then undergoes aldol reactions with aliphatic, aromatic, and α,β-unsaturated aldehydes (**Scheme 55**).[72]



Scheme 55

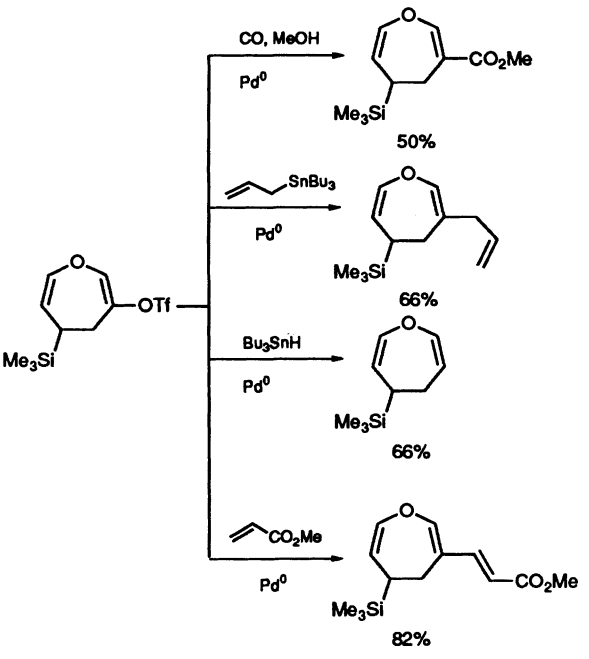
The triflate group can be replaced by an alkyl group *via* a cuprate displacement (**Scheme 56**).[72]



Scheme 56

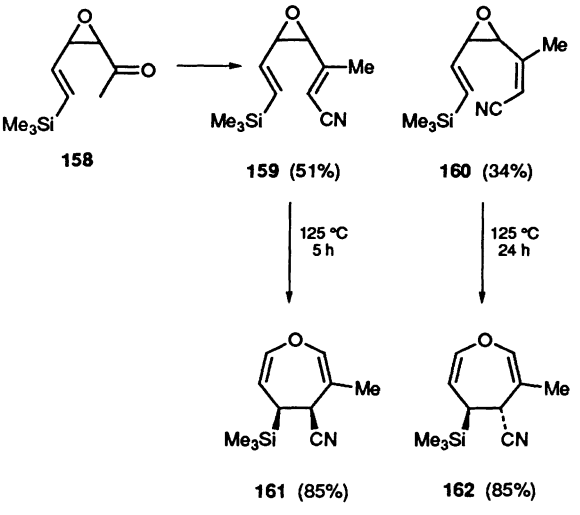
Palladium-catalysed Stille and Heck type couplings can also be carried out on the triflate (**Scheme 57**).[72]

Wadsworth–Emmons olefination of the 2,3-epoxyketone **158** gave a mixture of *cis*- and *trans*-divinylepoxides **159** and **160** which were readily separated and subjected to Cope rearrangement (**Scheme 58**). Assuming a boat-like transition state



Scheme 57

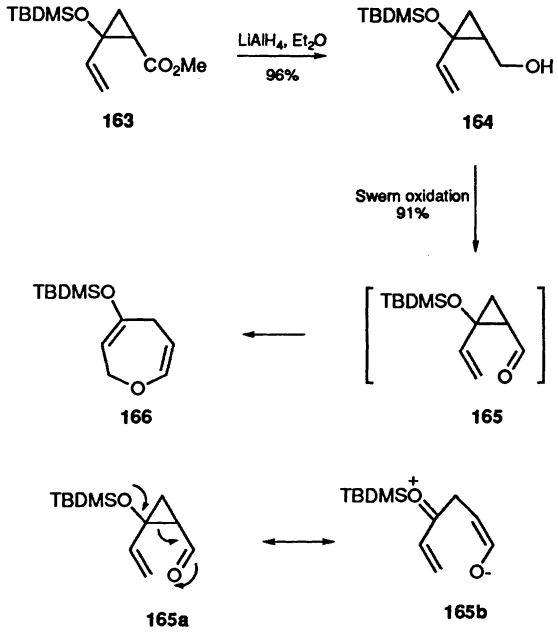
(steric constraints due to the epoxide preclude the normally favoured chair transition state), the *E*-isomer **159** rearranges smoothly to give the 4,5-*cis*-dihydrooxepin **161**, whereas the *Z*-isomer **160** requires a longer reaction time, giving only the 4,5-*trans*-dihydrooxepin **162**.[73]



Scheme 58

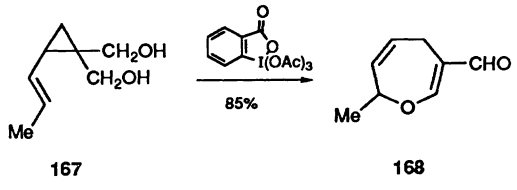
A similar [3,3]-sigmatropic shift has been used by Hofmann and Reissig[74] and by Boeckman *et al.*[75] to prepare 2,5-dihydrooxepins. Since the product is an allyl vinyl ether, this reaction is formally a retro-Claisen rearrangement. The cyclopropane ester **163** (prepared by a selective metal-catalysed cyclopropanation of a 2-siloxy diene with methyl diazoacetate) was reduced to the alcohol **164** in high yield. Partial oxidation under Swern conditions gave only the dihydrooxepin **166**. Since the cyclopropane ring in **165** is substituted by both an electron donor

and an electron-acceptor, one would expect the central C–C bond to be weakened (see resonance structures **165a** and **165b**), thereby favouring dihydrooxepin formation (**Scheme 59**).[74]



Scheme 59

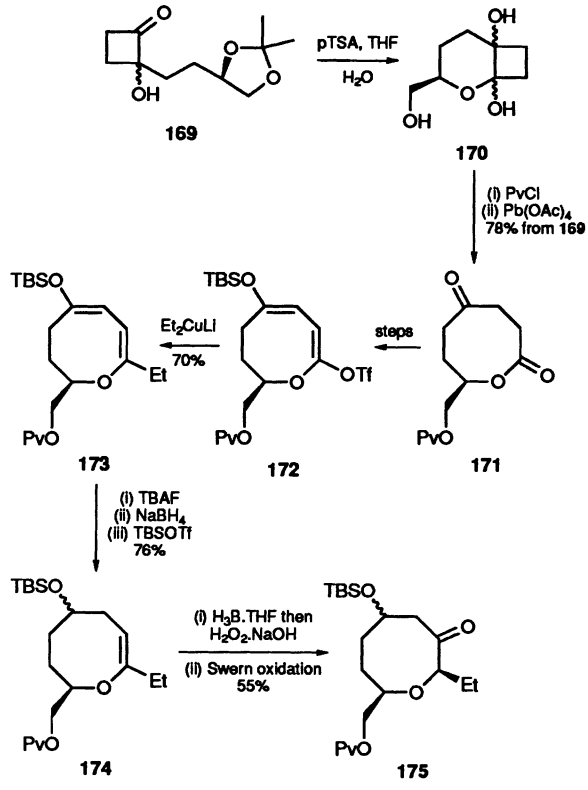
A similar oxidation of cyclopropane derivative **167** gave the 2,5-dihydrooxepin-6-aldehyde **168** (**Scheme 60**). As expected, if the cyclopropane is enantiomerically enriched, then the dihydrooxepin is formed with no loss of stereochemical integrity.[75]



Scheme 60

5 Ring expansions

Another total synthesis of (+)-laurencin **155** shows an interesting approach to oxocane synthesis (**Scheme 61**). Treatment of the cyclobutanone **169** with acid led to the hemi-ketal **170**. Selective protection of the primary alcohol was followed by oxidative cleavage of the diol to give the keto-lactone **171** in high yield. Conversion to the diene-triflate **172** was followed by cuprate displacement to give **173**. Finally, the silyl enol ether **173** was converted into the silyl ether **174** which was hydroborated and oxidized to give the oxocane ketone **175**, obtained as the 2,8-*cis*- isomer after epimerization with triethylamine. Conversion into (+)-laurencin was accomplished in a further 11 steps.[76]



Scheme 61

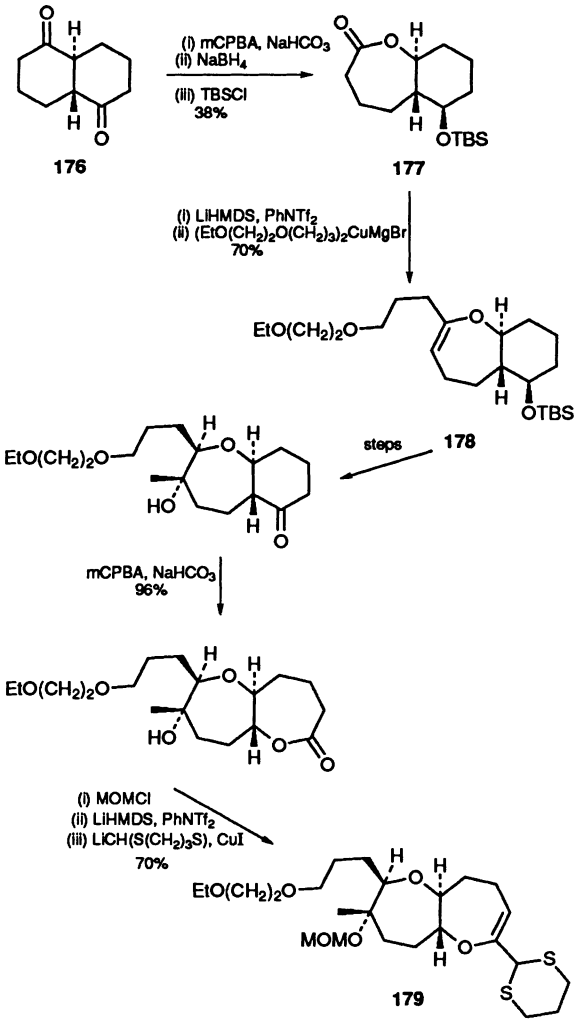
Feng and Murai have also developed a novel approach to the C- and D-rings of hemibrevetoxin B based on a double Baeyer–Villiger oxidation of the decalin-dione **176**. Oxidation of **176** gave the lactone **177** which was converted into the oxepane **178** using a cuprate displacement of a triflate in a similar manner to the above. Almost identical modification of the other ring gave the fused bis-oxepane system **179** (**Scheme 62**).[77]

A recent approach to the anti-fertility agent zoapatanol uses a cyclopropanation-ring expansion strategy to provide the key oxepane ring (**Scheme 63**). Thus the silyl enol ether **181** of the ketone **180** was cyclopropanated using bromoform in the presence of base. Acidic treatment led to the oxepane **182** (65% overall yield) which was further elaborated to provide the advanced intermediate **183**.[78]

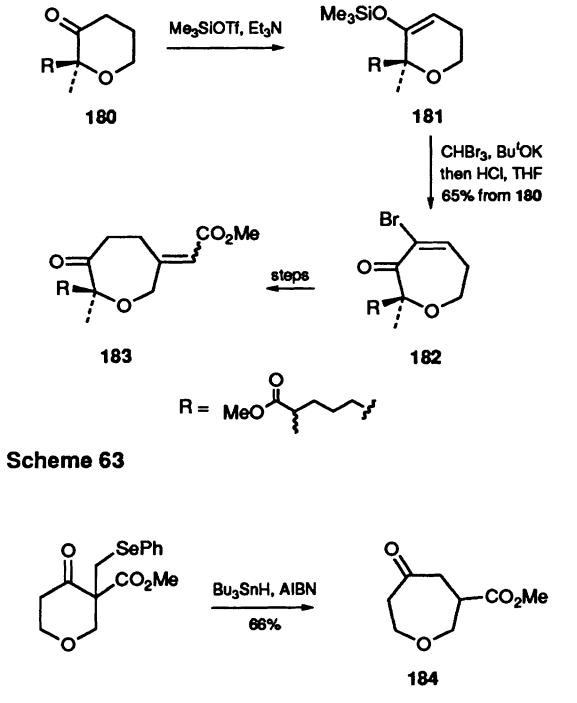
Free radical ring expansions are much more efficient than direct free radical cyclizations where medium-sized rings are desired. Dowd and Choi have used a one-carbon ring expansion to prepare the oxepane **184** in 66% yield. Slow addition of the substrate to tributyltin hydride was required (**Scheme 64**).[79]

Directed cleavage of oxiranylcarbinyl radicals, *e.g.* **189**, derived from thiocarbamates **185** and **186** leads to the formation of oxepanes **187** and oxocanes **188** in good yields. The phenyl group is required to stabilize the radical **190**, and so favour C–C bond cleavage over C–O bond cleavage (**Scheme 65**).[80]

Cleavage of bicyclic systems to give ring-enlarged monocyclic systems is a common tactic in organic synthesis. We have recently shown[81] that oxonanes

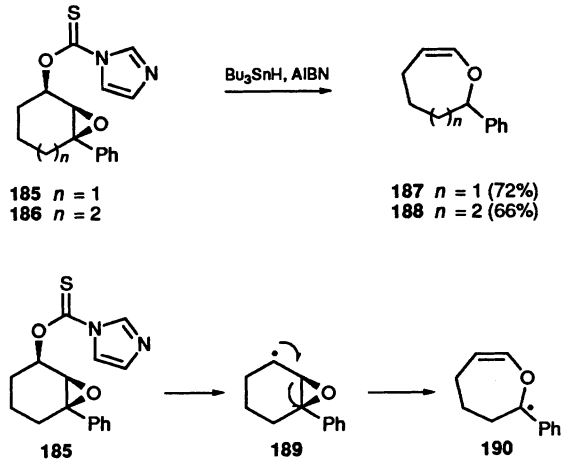


Scheme 62



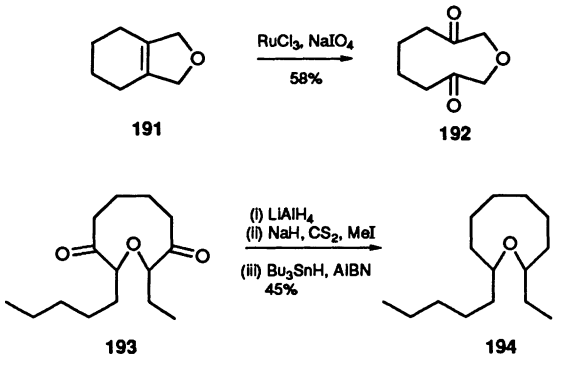
Scheme 63

Scheme 64



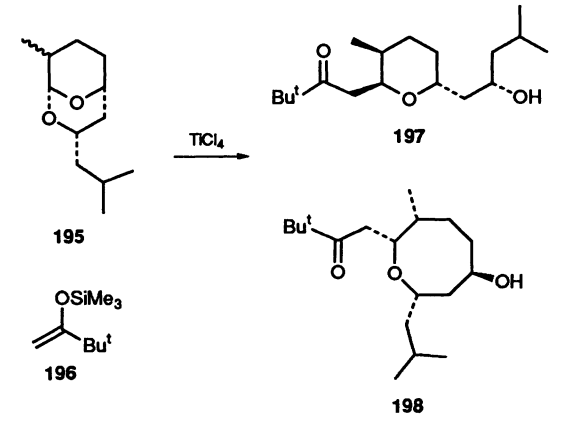
Scheme 65

192 can be readily prepared by the oxidative cleavage of tetrahydrophthalans **191** (**Scheme 66**). The dialkyl oxonane **193**, prepared by this method, was deoxygenated in three steps to give obtusan **194** containing the carbon skeleton of the *Laurencia* metabolite obtusenyne.



Scheme 66

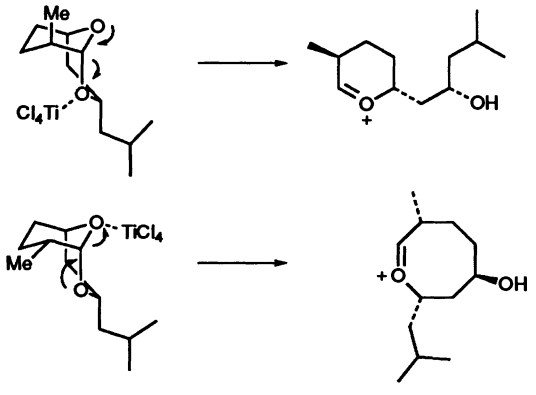
During the course of studies towards nigericin, Holmes and Bartlett discovered that the reaction of silyl enol ether **196** with the cyclic acetal **195** is strongly dependent on the stereochemistry of the substrate (**Scheme 67**). Thus a 78:22 α:β mixture gave



Scheme 67

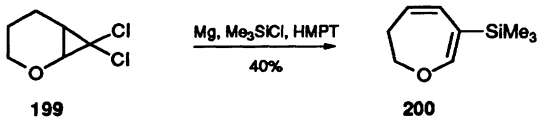
a 23:77 mixture of tetrahydropyran **197** and oxocane **198** (78% total yield), whereas pure (> 95%) α-acetal gave mainly the oxocane **198**, with less than 5% of the tetrahydropyran being formed. Both products were formed as single stereoisomers. This suggests that each isomer of acetal gives rise to the formation of a single product.[82]

It has been suggested that the methyl group directs approach of the titanium tetrachloride to the least hindered acetal oxygen. This dictates the direction of acetal opening and hence the product formed (**Scheme 68**).[82]



Scheme 68

Finally, thermolysis of the cyclopropanated tetrahydropyran **199** in the presence of magnesium and chlorotrimethylsilane led to a one-carbon ring expansion, giving the oxepane **200** in 40% yield (**Scheme 69**).[83]

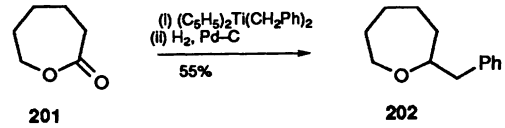


199 **200**

Scheme 69

6 Modification of lactones

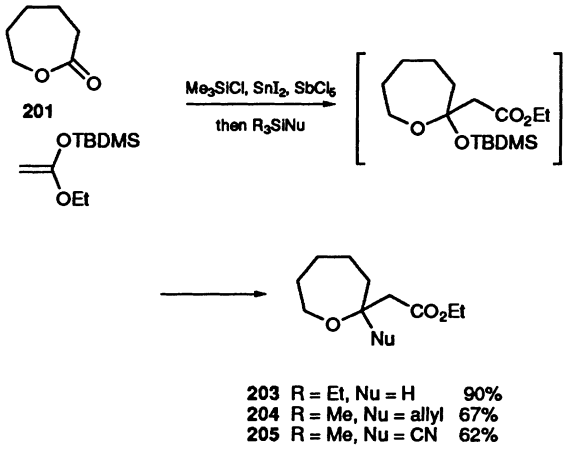
Petasis and Bzowej have reported[84] that dibenzyltitanocene reacts with ketones, esters, and amides in the same way as the Tebbe reagent to give the corresponding benzylidene compounds. In the case of the lactone **201** this was immediately followed by hydrogenation to give the oxepane **202** (**Scheme 70**).



201 **202**

Scheme 70

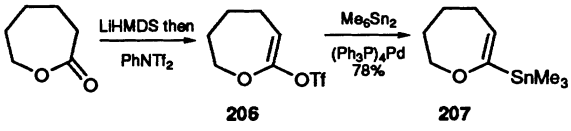
Mukaiyama has described a Lewis acid mediated reaction of lactones with silyl ketene acetals. ε-caprolactone **201** has been converted in this way to **203**, **204**, and **205** in good yields (**Scheme 71**).[85]



203 R = Et, Nu = H 90%
204 R = Me, Nu = allyl 67%
205 R = Me, Nu = CN 62%

Scheme 71

Lactones can also be converted into six- and seven-membered cyclic enol ethers. Palladium(0)-catalysed cross-coupling of the triflate **206**, derived from ε-caprolactone, with hexamethylditin gave the oxepane **207** in 78% overall yield (**Scheme 72**).[86]



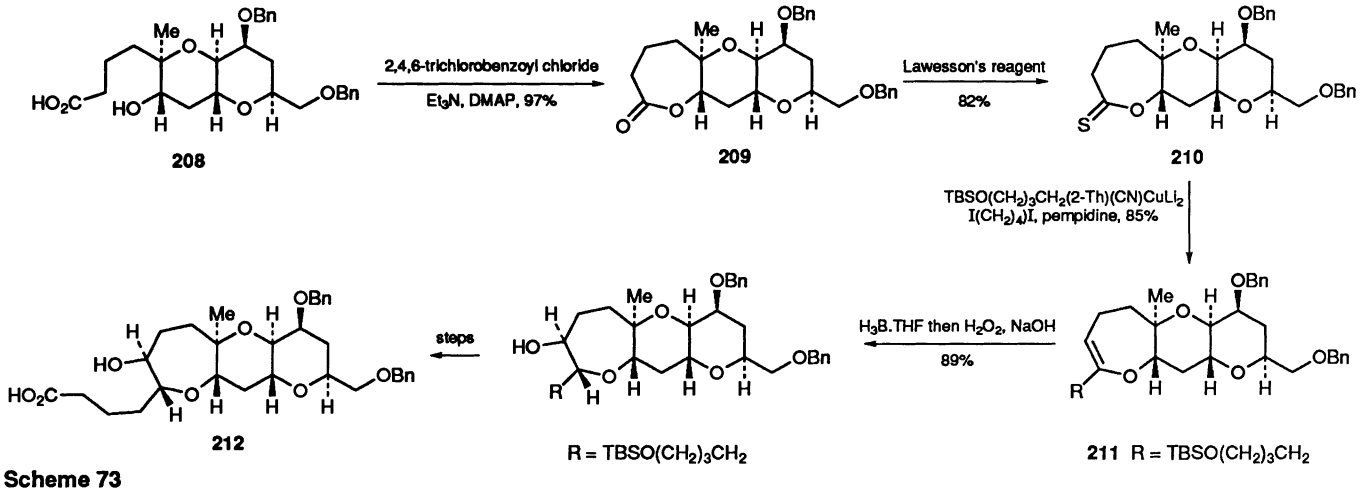
206 **207**

Scheme 72

The final, and most spectacular, example of lactone modification is provided by Nicolaou's synthesis of hemibrevetoxin B (**Scheme 73**). Cyclization of the hydroxy-acid **208** provided the lactone **209** which was first converted into the thiolactone **210**. Cuprate alkylation gave the cyclic enol ether **211**. The required oxygen atom was introduced *via* a hydroboration/oxidation sequence followed by standard chemistry to give the hydroxy-acid **212**. This was then elaborated in a similar manner to provide the tetracyclic 7-7-6-6 ring system of brevetoxin.[37,87]

7 Conclusion

The last four years have seen a wide range of new methods for the synthesis of oxepanes, oxocanes, and oxonanes. These methods are generally mild and tolerant of other functionality in the molecule, as required by the complex natural products which often contain these moieties. A number of total syntheses have been reported, and no doubt more will be achieved in the near future.



Scheme 73

8 References

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