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Synthesis of Seven-Membered Oxacycles

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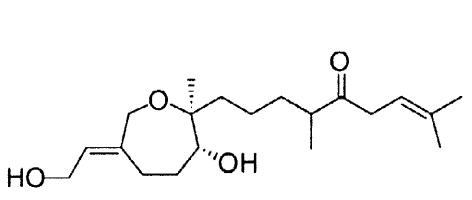
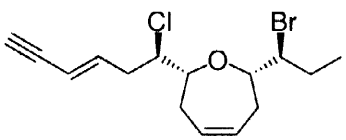
I. Introduction

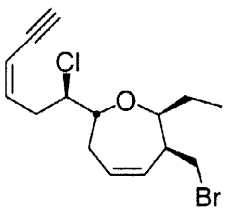
Interest in the synthesis of seven-membered oxacycles has steadily increased in recent years because of their occurrence in natural products,[1] use in polymers,[2] and pharmacological applications.[3] Examples of their occurrence in nature range from the monocyclic zoapatanol,[4] isolaurepinnacin,[5] and rogiolenyne[6] to the highly complex ciguatoxin (Scheme 1).[7] In view of the interest and challenges these molecules present as potential synthetic targets, the number of methods available for the construction of seven-membered oxacycles has steadily increased. The purpose of this review will be to highlight some of the approaches taken in the last four years in assembling new routes to oxepanes and oxepenes. The application of these methods to natural product synthesis will also be presented.



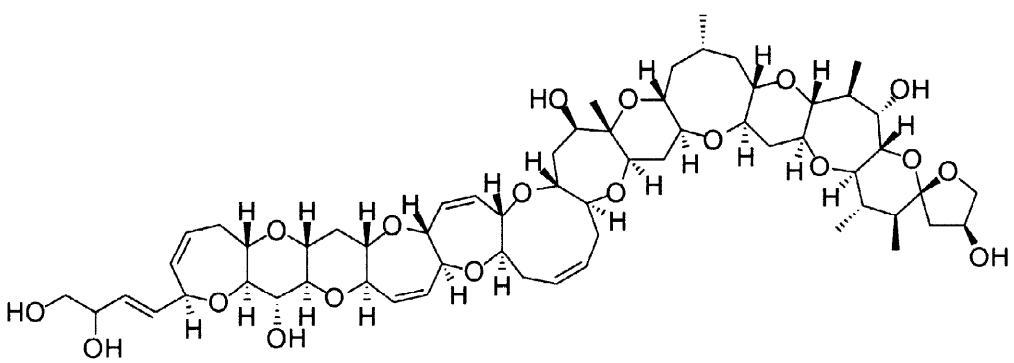
Zoapatanol



Isolaurepinnacin



Rogiolenyne

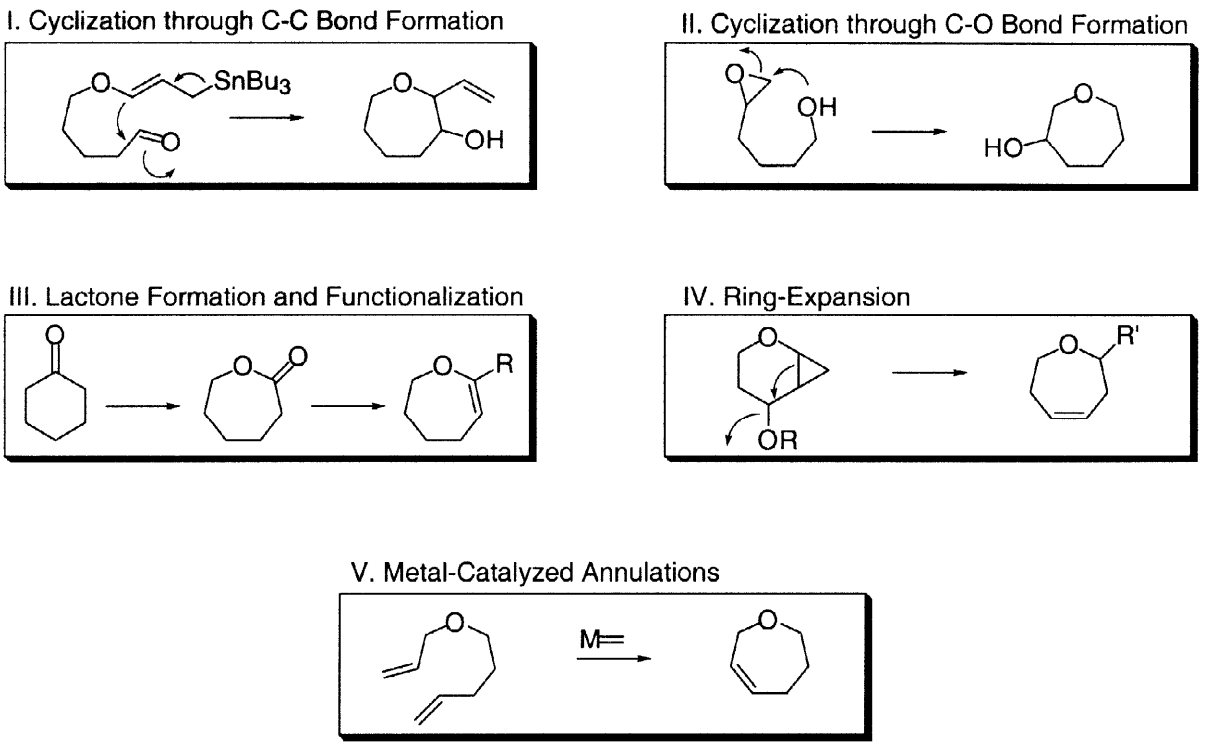


Ciguatoxin

Scheme 1

In this review the syntheses of oxepanes and oxepenes are classified into five general strategies (Scheme 2). The first and second strategies involve cyclization of acyclic precursors through either a carbon-carbon (C-C) bond formation or a carbon-oxygen (C-O) bond formation. Both have received considerable attention during the past few years. In the second strategy, C-O bonds are formed via intramolecular attack of alcohols on epoxides, carbonyls and acetals. This has been the more developed route and offers highly efficient methods for oxepane and oxepene formation. The third section discusses lactone formation by Baeyer-Villiger oxidation and lactonization of hydroxy acids, followed by conversion of the lactone into oxepenes. This approach has also been frequently described in the literature. This section is arranged

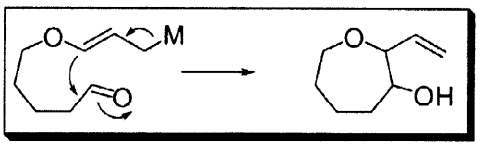
beginning with formation of the lactone followed by conversion into substituted oxepenes. The fourth section involves the ring-expansion of three-, four-, five- and six-membered rings. Finally, the fifth section details the use of transition metal cyclizations including olefin metathesis, diazo cyclizations, and palladium π-allyls. These last two sections provide new and unique solutions to oxepane synthesis. Although the fifth section involves the cyclization of C-C and C-O bonds, it has been split into a separate section because of its recent attention and novelty.



Scheme 2

This review will focus on the literature published from 1994 through mid 1998. For reviews on earlier work that highlight only oxepane derivatives, the reader is referred to Boyd in (1984)[8] and Belen'kll in (1982 through 1993).[9] For reviews on the synthesis of medium-sized rings see Hassenruck and Martin (1988),[10] Moody and Davies (1992),[11] Elliott (1994),[12] Burns (1994),[13] and Martin et al.[14] Nicolaou has also recently published a review on the synthesis of brevetoxin B, which highlights methods discovered by his group in the synthesis of this oxepane-containing marine toxin.[15] Finally, included in the Belen'kll review are theoretical and experimental structural methods, thermodynamic aspects and synthesis, and reactions of fully conjugated and nonconjugated oxepines. Additionally, Espinosa and co-workers have recently published work on conformational analysis of oxepanes.[16]

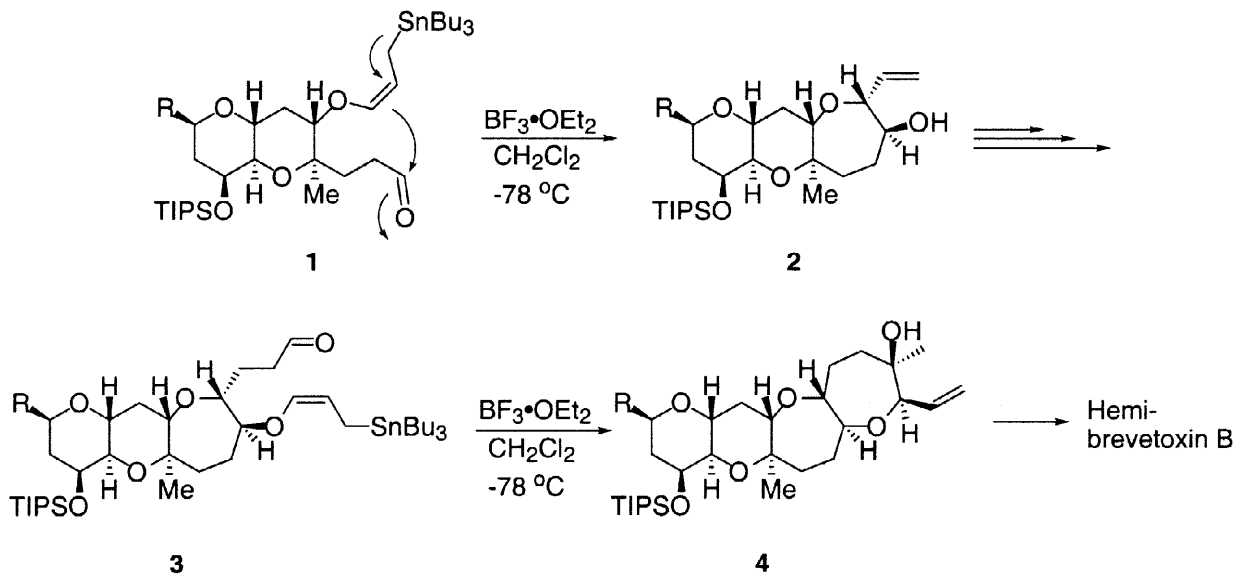
II. Cyclization Through C-C Bond Formation



Several widely used methods exist for the formation of oxepanes and oxepenes through carbon-carbon bond formation. This section outlines the latest developments and applications of these methods. Several of the following methods were developed earlier this decade and have since been modified and applied to the synthesis of natural products.

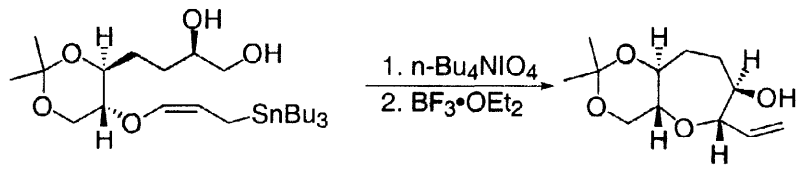
II.1 Intramolecular attack of alkoxyallylstannanes on aldehydes

A general method for preparing cyclic ethers that has been applied to the synthesis of oxepanes was developed by Yamamoto and co-workers and subsequently applied to the synthesis of hemibrevetoxin B (Scheme 3).[17] The method, which involves an intramolecular attack of an alkoxyallylstannane on an aldehyde, generates oxepanes in excellent yield and selectivity. In the synthesis of hemibrevetoxin B, **1** was converted to **2** in 94% yield and produced only 1 diastereoisomer. The allylstannane and aldehyde groups in **3** are reformed in several steps, thus enabling iterative cyclizations. Subsequent conversion of **3** to **4** also produced only 1 diastereoisomer in 98% yield.



Scheme 3

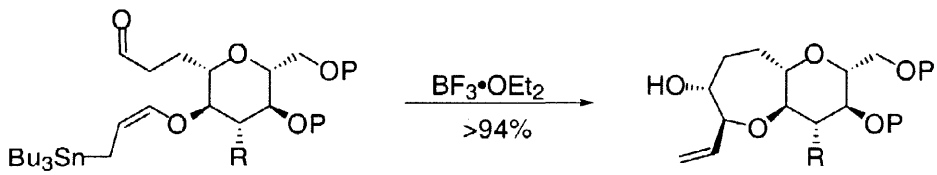
In studies directed toward the synthesis of ciguatoxin, Martin's group introduced a modification of this strategy (Scheme 4).[18] Cyclization of **5** to **6** was accomplished by an initial *vic*-diol fragmentation using n-Bu_4NIO_4. *In situ* cyclization of the resulting aldehyde with BF_3•OEt_2 gave **6** in 95% overall yield.



5 6

Scheme 4

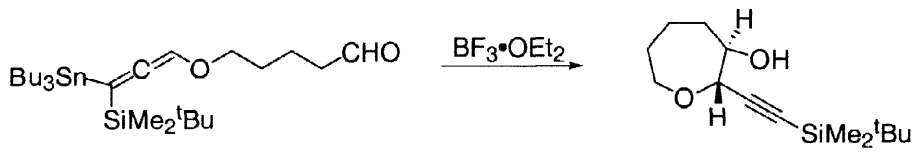
Other uses of Yamamoto's method in synthetic studies of ciguatoxin have also been reported (Scheme 5). Hirama and co-workers used an intramolecular attack in the synthesis of the AB ring.[19] Additionally, the G ring was synthesized by Sasaki and Tachibana co-workers.[20] Both studies reported excellent yields in the cyclization. These high yields are believed to be due to the presence of the tetrahydropyran ring, which is proposed to increase the conformational rigidity of the precursor. Cyclizations without the affixed rings generally result in lower yields.



7 8

Scheme 5

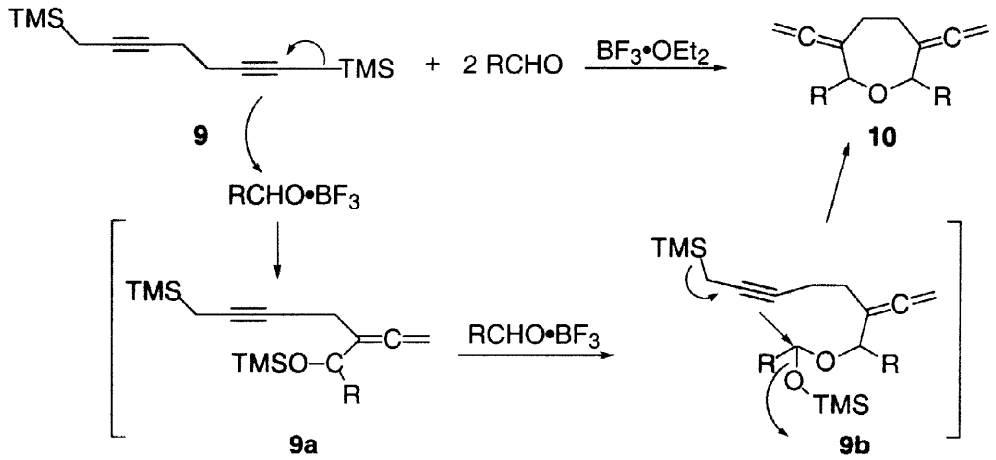
A modification of this reaction was recently developed by Yamamoto's group and involves the use of allenylstannanes (Scheme 6).[21] Treatment of **9** with BF_3•OEt_2 produces **10** in 51% yield as a single isomer.



9 10

Scheme 6

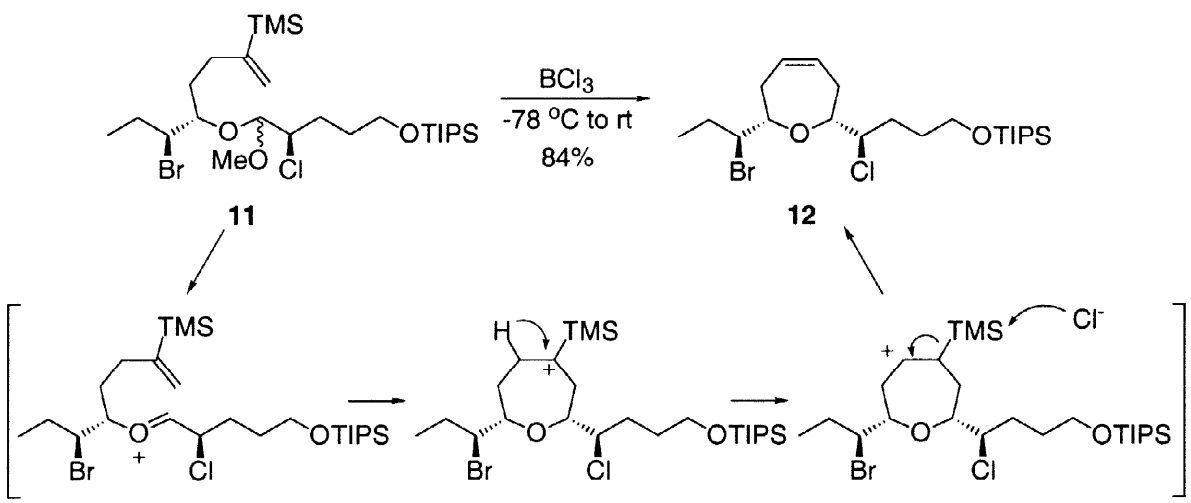
Lewis acid initiated intermolecular attack has also been developed as a general method of oxepane synthesis. Recently, Aubert and Pornet reported on the formation of vinylidene oxepanes using bis-silanes, leading to the formation of the bis(vinylidene) oxepanes **10** (Scheme 7).[22] The yields of the reaction depend on the size of the R group. For example, an ethyl group gave an 85% yield, and a *tert*-butyl group resulted in only 41% yield. The proposed mechanism involves an initial attack of the propargyl silane group on the aldehyde BF_3 complex to produce intermediate **9a**, which undergoes insertion of a second aldehyde resulting in formation of the mixed acetal **9b**. Subsequent intramolecular attack of the mixed acetal results in formation of **10**.



Scheme 7

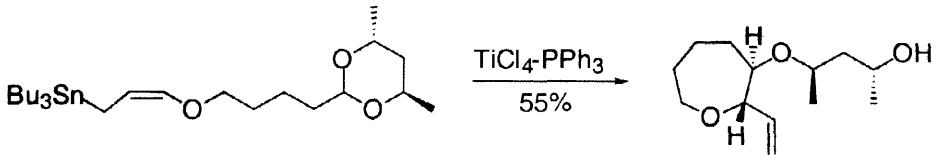
II.2 Intramolecular attack on acetals

Intramolecular attack on acetals has also received considerable attention and has been applied to the synthesis of several natural products. Overman and co-workers investigated a Prins cyclization of mixed acetals, which led to the synthesis of (+)-isolaurepinnacin (Scheme 8).[23] Treatment of **11** with BCl_3 selectively cleaves the methoxy moiety to generate an α-chloro ether. Continued warming to room temperature generates the oxonium ion intermediate, which undergoes cyclization and olefin formation. A single isomer was obtained in the cyclization due to the formation of the more stable *E*-oxonium ion.[24] Also key to the success of this reaction was the use of the TIPS protecting group, as benzoyl or TBDMS groups were cleaved during the reaction.



Scheme 8

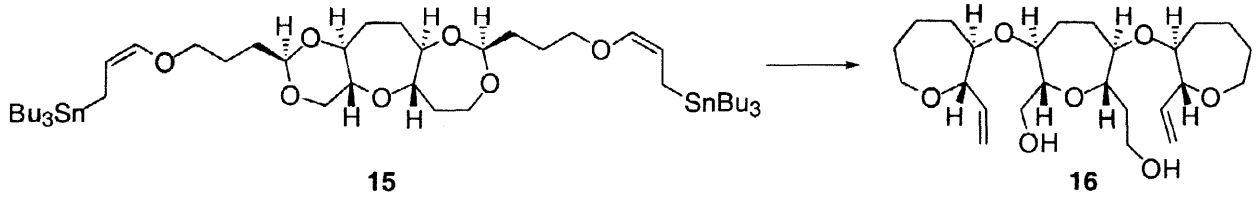
Intramolecular allylstannane-acetal cyclizations using chiral acetals have also been investigated by Yamamoto and co-workers (Scheme 9).[25] Although a moderate yield of **14** is achieved, a 91:9 ratio of (2*S*, 3*R*) to (2*R*, 3*S*) was obtained without any cis isomers being produced.



13 14

Scheme 9

Martin's group recently reported an elegant two-directional synthesis of oxepanes for application to the synthesis of marine toxins (Scheme 10).[26] Cyclization of **15** with $TiCl_3(O^iPr)$ to produce **16** was successful, but, in only 15% yield. Although this specific cyclization resulted in a low yield, the strategy might offer a highly efficient route to oxepane-containing marine toxins.



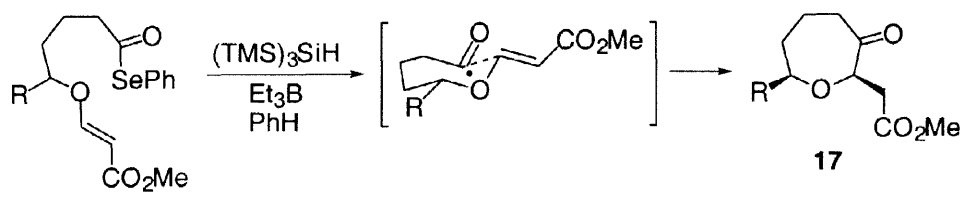
15 16

Scheme 10

II.3 Radical, cycloaddition and ring-contraction Carbon-carbon bond-forming reactions

Carbon-carbon bond-forming cyclizations complementing the use of aldehydes and acetals have also been developed as a general method for cyclic ether formation. These include radical cyclizations, nitrile oxide cycloaddition and the use of an oxathiane cyclization/sulfur dioxide extrusion reaction. Several of these have been developed as new methods while others were developed previously and applied to natural product synthesis.

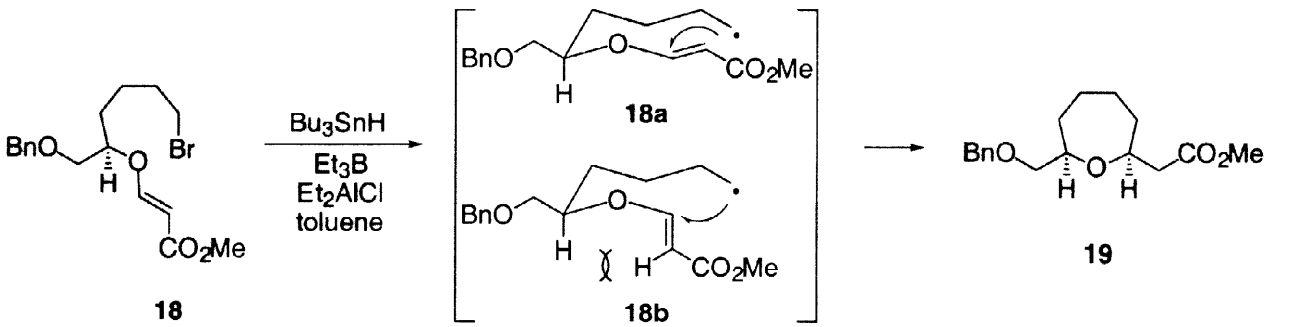
Evans and co-workers introduced a new method that uses an intramolecular acyl radical cyclization of acyl selenides (Scheme 11).[27] Yields for **17** ranged from 80 to 90% (R = Me, *i*-Pr, Ph) and diastereoselectivities of >19:1 were achieved for all three oxepanones, with the cis configuration being preferred. The high selectivities were expected based on the Beckwith transition state model, in which a transition state with a chair like conformation, pseudo equatorial R group and an s-trans configuration of the vinyl ether occurs.[28] This transition state alleviates any 1,3-allylic strain. Additionally, the acyl selenide of **17** is easily generated; thus, additional cyclizations via the acyl radical can be accomplished. This iterative strategy allows for a general method for constructing fused polycyclic ethers.



17

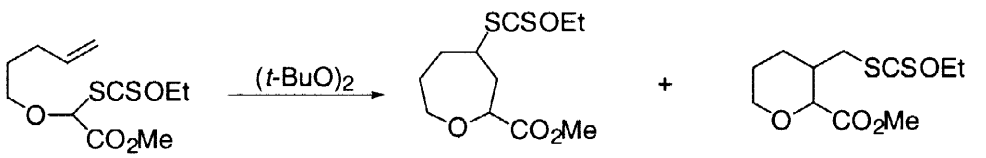
Scheme 11

A similar radical cyclization involving alkoxyacrylates has also been accomplished by the Shibuya group (Scheme 12).[29] Treatment of **18** with Et_3B as the radical initiator in the absence of a Lewis acid gave only a 43% yield of oxepane **19**. However, the Lewis acid Et_2AlCl, which lowered the LUMO energy, gave a 61% yield and 3.6:1 diastereoselectivity. The selectivity favored the cis isomer, which can be rationalized by preference of transition state **18a** over **18b**.



Scheme 12

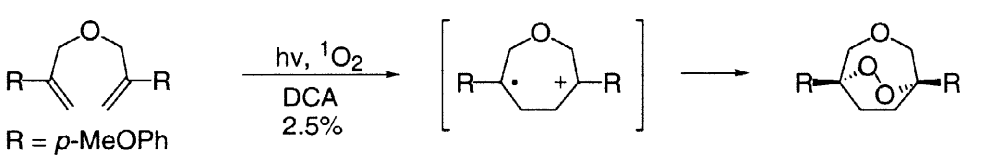
Radical group-transfer cyclizations have also been used in oxepane formation with limited success (Scheme 13). During studies directed at the formation of tetrahydropyran rings, Hiemstra, Speckamp and co-workers found that cyclization of **20** using DTBP as the initiator results in equal amounts of the oxepane **21** and pyran **22** with a total yield of 84%.[30] Similar results have been obtained using Bu_3SnH as the initiator.[31]



20 **21** **22**

Scheme 13

During studies of the synthesis of artemisinin derivatives, Posner's group used a photo-oxygenative cyclization of the diene **23** to produce the endoperoxide **24** (Scheme 14).[32] Subsequent opening of the peroxide moiety of **24** was envisioned to produce highly substituted oxepanes; however, the low yield of the cyclization prohibited further chemistry. However subsequently, both the Posner and d'Angelo groups have reported yields for the peroxide ranging from 10% to 42%.[33]

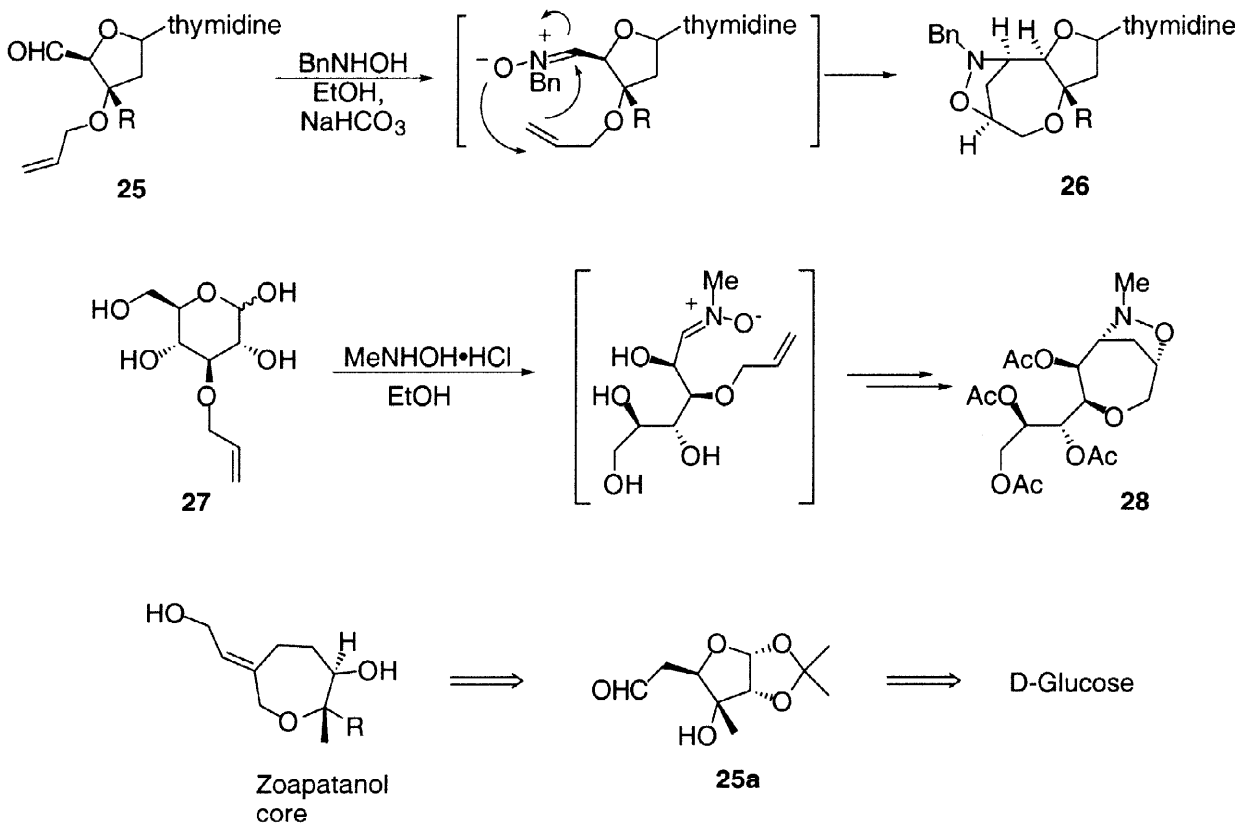


23 **24**

Scheme 14

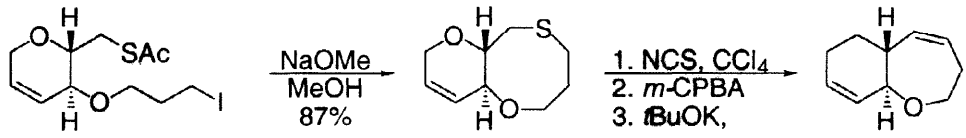
Intramolecular nitrile oxide cyclizations are also effective in oxepane synthesis. Conversion of **25** to **26** via a 1,3-dipolar cyclization occurs in yields from 61 to 96% (Scheme 15).[34] Several variations of this method have been developed. For example, treatment of **25** (R = H) with BnNHOH provides the intermediate oxime, which undergoes cyclization to produce **26**. During studies of this transformation, Shing and co-workers discovered that steric congestion was detrimental to the formation of oxepane rings. For instance, cyclization where R = Me produced only tetrahydropyrans. This situation can be resolved by extending the aldehyde unit by one methylene group.

An alternative approach is to use 3-*O*-allyl-D-glucose **27**. Treatment with *N*-methylhydroxylamine in boiling ethanol followed by acetylation provides the oxepane **28** in an overall 53% yield.[35] These methodologies have been applied to the synthesis of Zoapatanol derivatives. The retrosynthesis involved the conversion of D-glucose to **25a**, conversion to the oxepane using the nitrile oxide cyclization, and subsequent functionalization. This strategy has the advantage of using the optically active carbohydrate precursor.



Scheme 15

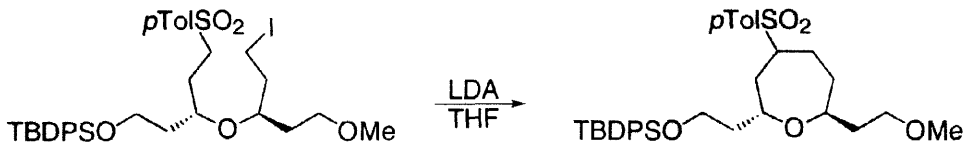
As part of their program for the construction of fused polycyclic ethers, Martin and co-workers recently disclosed a new strategy for the synthesis of oxepenes of type **31** (Scheme 16).[36] The approach involves thioannulation of **29** in 87% yield followed by a Ramberg-Backlund olefination of the thioether **30** in 41% yield. The precursor **29** is readily available in a minimum of steps from the diol of the pyran.



29 30 31

Scheme 16

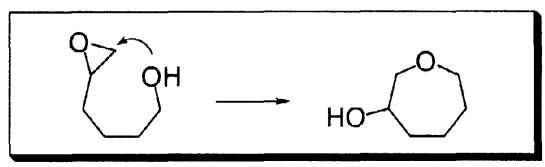
Oxepanes have also been prepared by Palenzuela and co-workers via nucleophilic displacement of iodides of type **32** (Scheme 17).[37] Although cyclization produced a single isomer, the yield was only 21%. Use of a tosylate as the leaving group did not produce any cyclization.



32 **33**

Scheme 17

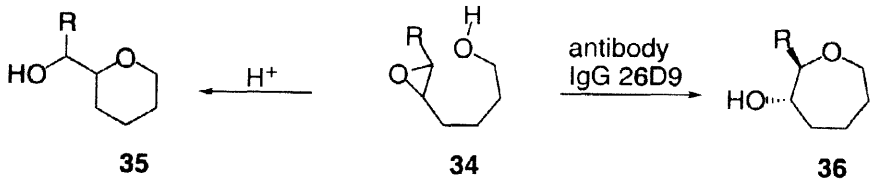
III. Cyclization Through C-O Bond Formation



III.1 Intramolecular cyclization of hydroxy epoxides and epoxy ketones

Cyclization of hydroxy epoxides, as discussed earlier, has generated a great deal of interest and has been utilized in several natural product syntheses. Conceptually, the transformation has many benefits because the epoxide can be formed enantiospecifically from an olefin and the resulting ring opening provides a new chiral hydroxy unit for further cyclizations. In practice, however, the cyclization suffers from competing pyran formation according to Baldwin's rules resulting in mixtures of products.[38] Recent methods to direct cyclization toward oxepane formation involve the use of enzymes and other catalysts.

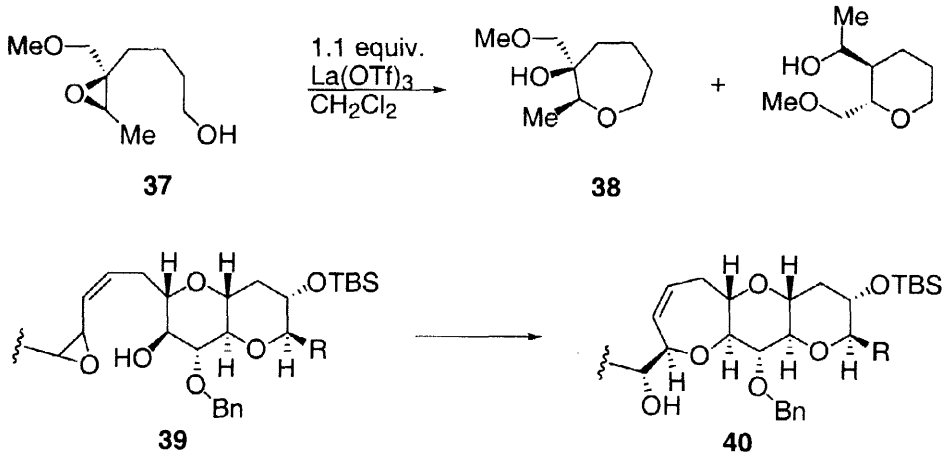
An exciting new reagent for these cyclizations is a catalytic antibody, which results in complete formation of oxepanes over the preferred pyran (Scheme 18).[39] Consistent with normal 6-*exo* ring closure, epoxide **34** produces the pyran **35** under acid conditions (R = *p*-MeOBn). However, in the presence of an antibody, 7-*endo* cyclization occurs, resulting in the formation of oxepane **36** in >98% yield. The antibody preferred the *R,R* epoxide over its *S,S* antipode with the absolute configuration of the major oxepane (78%) having the *S, R* configuration.



35 34 36

Scheme 18

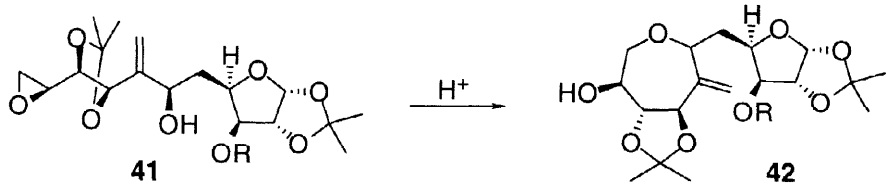
The development of lanthanide Lewis acid catalyzed ring closures has also been successful. Murai and co-workers recently disclosed the use of Lewis acids in oxepane synthesis and applied this to the synthesis of the A, B and C-rings of ciguatoxin.[40] Use of $La(OTf)_3$ in the cyclization of epoxides **37** produced high selectivities with moderate to good yields (Scheme 19). Yields ranged from 46 to 74%, and selectivities as high as 92:8 were obtained in favor of oxepane **38** over the pyran. Nevertheless, use of this method to the partial synthesis of ciguatoxin met with limited success. A series of Lewis acids were examined for the cyclization of **39**; however, only a 38% yield of the oxepene **40** was obtained using $Eu(fod)_3$.



37 38 39 40

Scheme 19

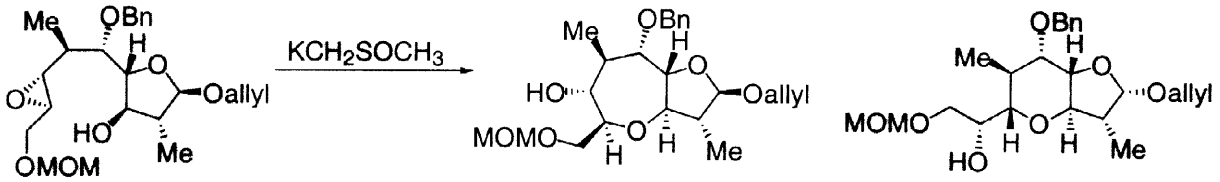
Often, the desired oxepane can be formed via sterically hindered systems as displayed in Scheme 20.[41] Treatment of **41** with camphorsulfonic acid resulted in formation of **42** with no pyran formation.



41 42

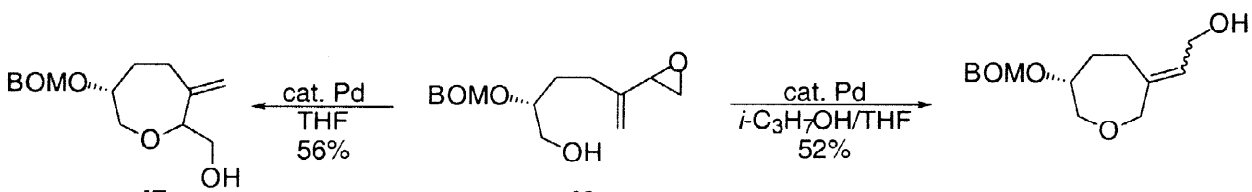
Scheme 20

An additional consequence of steric effects is the cyclization of the β-diastereomer **43**, which produced only the β-oxepane **44**. However, cyclization of the α-diastereomer of **43** gave a 1.7:1 mixture of α-**44** and **45**.[42]



43 44 45

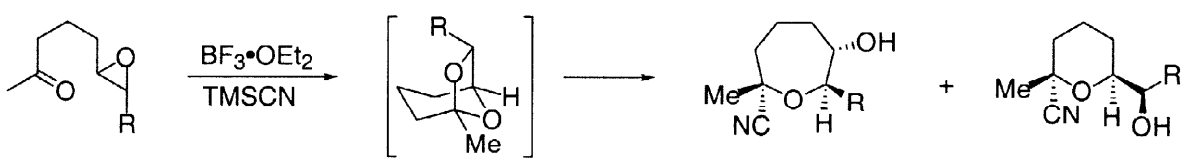
An interesting dichotomy in terms of the regioselective attack on vinyl epoxides has been reported by Trost's group (Scheme 21).[43] Palladium-catalyzed cyclization of **46** in THF produced only oxepane **47**, generated by a proximal attack of the hydroxy moiety on the epoxide. The observed selectivity can be rationalized by hydrogen bonding of the hydroxyl group with the departing oxygen of the epoxide. To reverse the regioselectivity, an alcohol solvent was used. Reaction in a 4:1 mixture of isopropanol/THF produced regioisomerically pure **48** as a 3:1 mixture of *E/Z* isomers.



47 46 48

Scheme 21

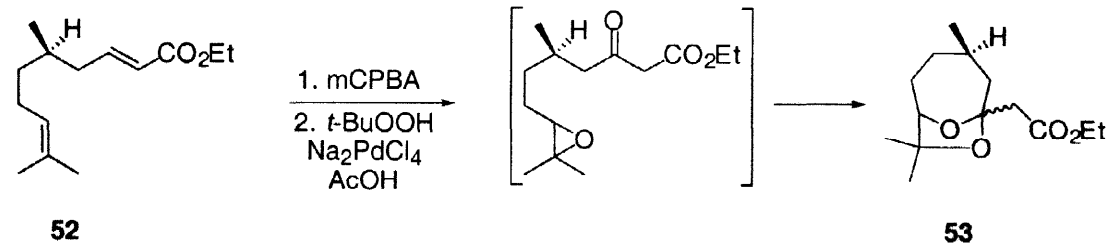
Cyclization and cleavage of epoxy ketones leading to oxepanes has also been studied (Scheme 22).[44] Treatment of several derivatives of **49** with TMSCN and BF_3•OEt_2 induces cyclization to the bicyclic acetal, which cleaves to produce mixtures of **50** and **51**. The combined yields of the oxepane and pyran ranged from 63% to 96%; however, ratios of only 2.2:1 of **50**:**51** were obtained. Additionally, TMSCN was unique among the nucleophiles surveyed in producing an oxepane. Nucleophiles such as Ph_3SiH, allyltrimethylsilane or DIBAL all produced exclusively pyrans. Additional openings of bicyclic acetals in the formation of oxepanes will be presented in Section V.5.



49 50 51

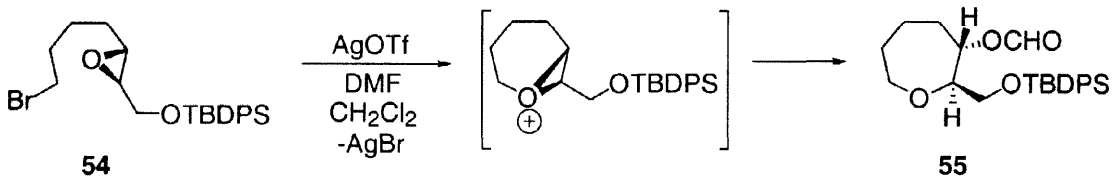
Scheme 22

Similar types of bicyclic acetals were formed by oxidizing unsaturated esters to β-keto esters.[45] The intermediate epoxide is formed by treating **52** with *m*-CPBA, followed by rearrangement of the crude product with catalytic palladium salt and peroxide. Acetal **53** was formed in 68% yield as a mixture of isomers.



52 53

An additional use of epoxides in the formation of oxepanes was recently developed by Murai and co-workers (Scheme 23).[46] Using the epoxy moiety as the nucleophile, **54** was treated with silver triflate in the presence of dimethylformamide to obtain oxepane **55** in 25% yield. The formation of **55** can be viewed as a reaction proceeding in an endo fashion, producing the kinetic product.

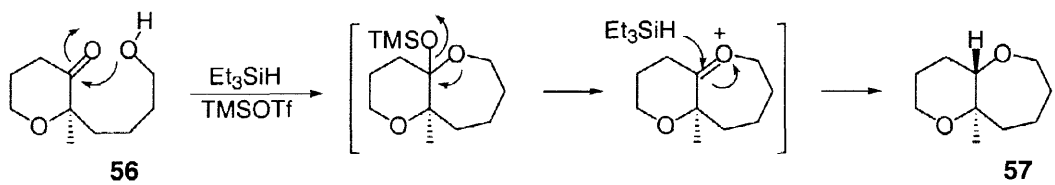


54 55

Scheme 23

III.2 Intramolecular cyclization of hydroxy carbonyls

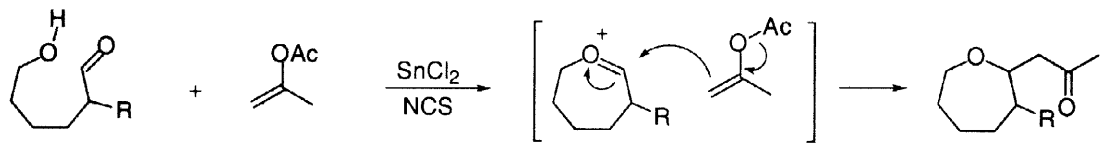
Several novel methods using the attack of an oxygen nucleophile on carbonyls have also been developed. As part of their synthesis of Brevetoxin B, Nicolaou and co-workers modified the work of Olah for the synthesis of oxepanes from hydroxy ketones (Scheme 24).[47] Using one equivalent of TMSOTf, the activation of the carbonyl oxygen in **56** is followed by an intramolecular attack of the hydroxyl moiety producing the trimethylsilyl lactol. Displacement of the TMSO moiety leads to the oxonium ion, which undergoes hydride attack to produce **57**. Yields of this process ranged from 50% to 90% and the selectivity varied from 1:1 to 4:1, with the trans stereochemistry predominating. Extensions of this method have also been reported by Moody and co-workers.[48]



56 57

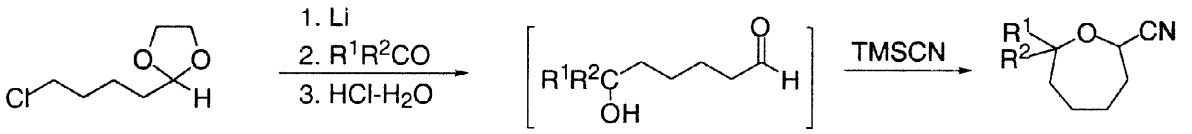
Scheme 24

A similar cyclization has been developed by Masuyama's group using an aldol reaction of isopropenyl acetate with the intermediate oxonium ion of **58**.[49] In the presence of *N*-chlorosuccinimide and tin chloride, hydroxy aldehyde **58** cyclizes to produce a tin alkoxide lactol which leads to an intermediate oxonium ion. Aldol reaction with enol acetate provides the oxepanes **59** in 49% (R = H) and 59% (R = C_5H_{11}) yields. A 95:5 anti:syn-diastereoselectivity was observed for the pentyl derivative.



58 59

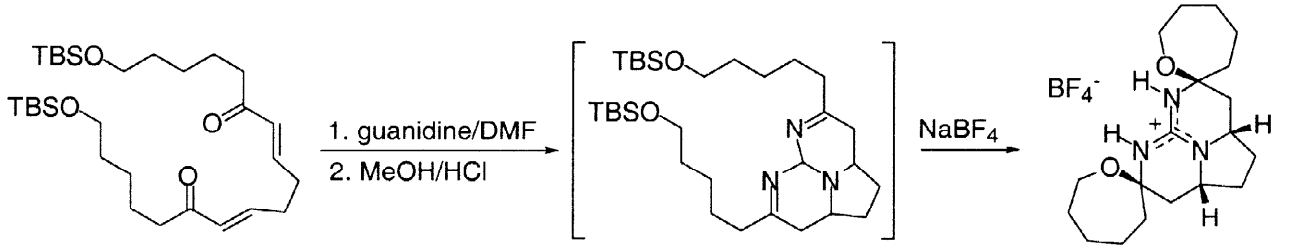
Related examples of cyclization of masked hydroxycarbonyls, imines, and an oxo-acetal have also been reported. Yus and co-workers have applied functionalized organolithium compounds to the synthesis of oxepanes (Scheme 25).[50] In this strategy, the reaction of chlorodioxolane **60** with lithium generates a masked alkyllithium that is quenched with aldehydes or ketones to produce intermediate hydroxy aldehydes. Addition of the cyano group to the hydroxy aldehyde produces the corresponding cyanohydrin, which after intramolecular dehydration leads to oxepanes **61**.



60 61

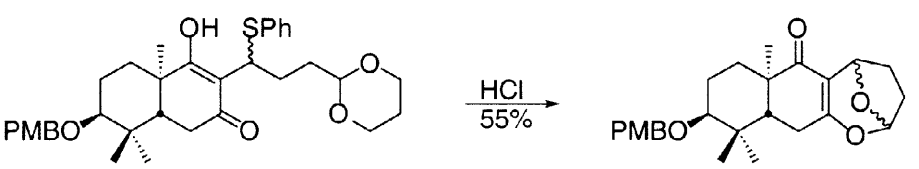
Scheme 25

In biomimetic studies of ptilomycalin A, Murphy and co-workers used a double Michael addition of guanidine to enone **62**.[51] The resulting pyrrolidine was subsequently cyclized to generate the spirooxepanes **63**. However, yields for this process were only 20%.



62 63

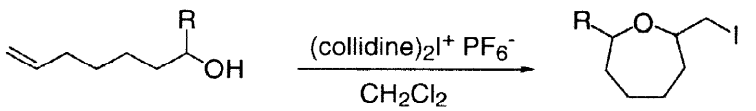
During studies directed toward the synthesis of the diterpenoids methylshikoccin and methylepoxyshikoccin, Paquette's group observed the formation of the diastereomeric oxepane-acetals **65** from the oxo-acetal **64**.[52] Presumably, these arise from deprotection of the acetal upon treatment with HCl.



64 65

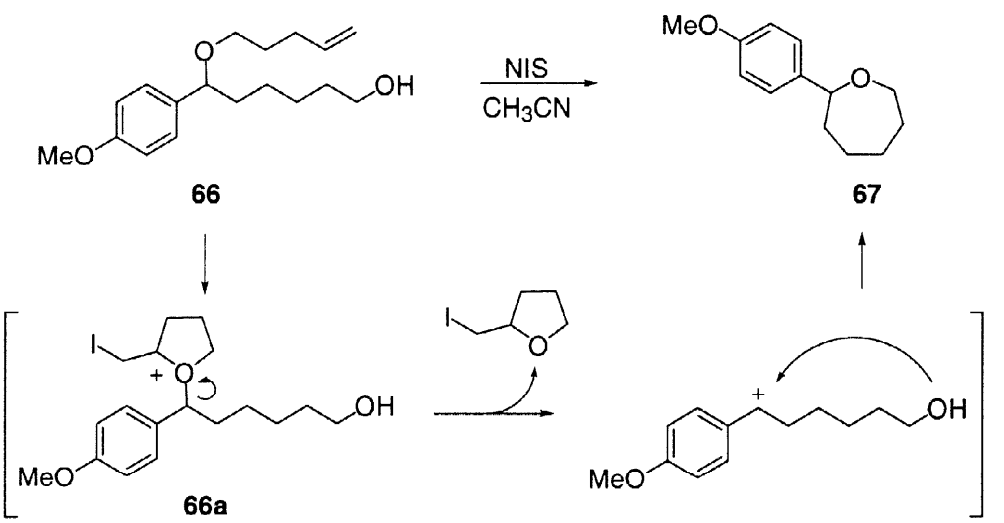
III.3 Intramolecular cyclization by etherification of hydroxy olefins

Although haloetherification has been investigated intensively for the preparation of furans and pyrans, the preparation of oxepanes via this method has only recently been shown to be reliable. For example, reactions that were successful in the preparation of furans and pyrans produced oxepanes in yields from 0 to 30%. Rousseau's group has investigated this divergence in the formation of oxepanes and has shown that the use of bis(collidine) iodine hexafluorophosphate produces oxepanes in good to excellent yields (Scheme 26).[53] Yields for the formation of oxepanes ranged from 65 to 95%, although diastereomeric ratios were only 1:1. Examples of oxepene formations were also accomplished in yields of 18 to 70%.



Scheme 26

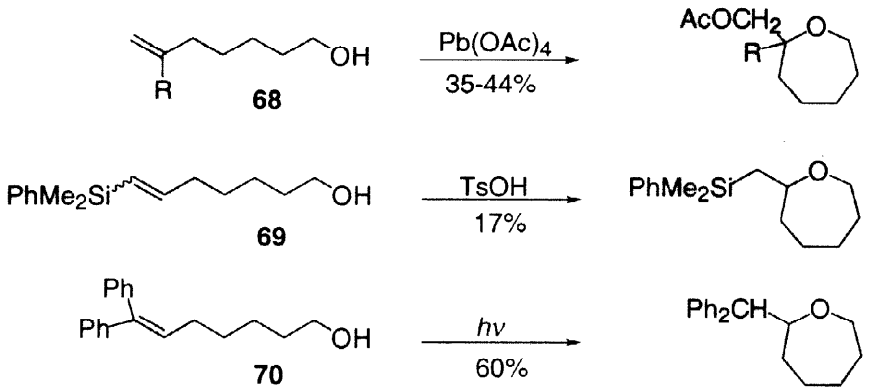
An interesting modification of this concept was reported by Taguchi's group (Scheme 27).[54] During studies on the iodoetherification of pentenyl ether derivatives, they observed that the incorporation of a terminal hydroxy group such as in **66** generated the oxepane **67** in 41% yield. The proposed mechanism involves the *N*-iodosuccinimide (NIS) generation of the oxonium furan intermediate **66a**. Loss of the furan moiety produces the p-methoxybenzyl cation, which undergoes cyclization.



Scheme 27

Other methods used in the cyclization of hydroxy olefins include lead tetraacetate-mediated, photochemically-initiated, and acid catalyzed procedures (Scheme 28). In the reaction of **68**, stoichiometric lead tetraacetate produced mixtures of seven- and eight-membered rings; the isolated yields of the oxepanes ranged from 35 to 44% (R = H and Me).[55] The formation of non-oxepane ring sizes can be avoided by the use of a silicon-directed addition of the hydroxy group; however, conversion of **69** produced the desired product in

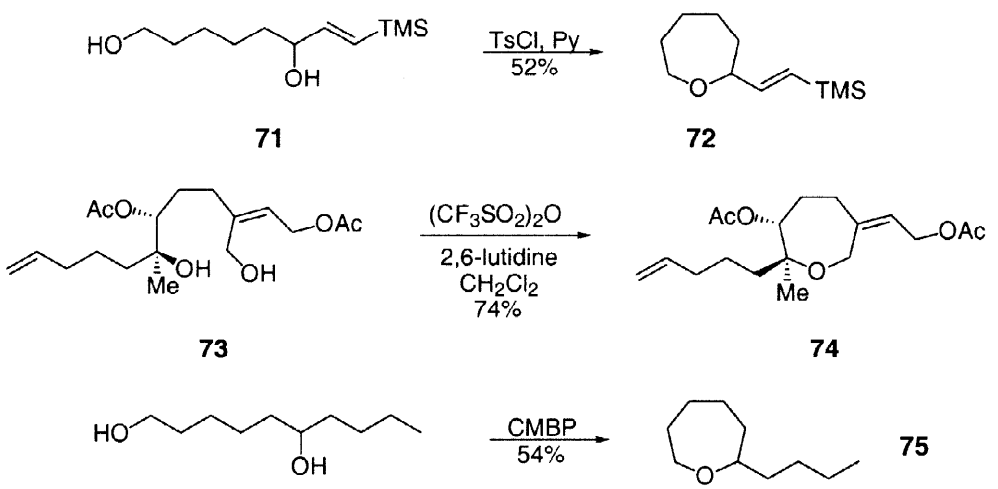
only 17% yield.[56] Finally, photochemical cyclization of **70** has been accomplished in moderate yield with the use of 9,10-anthracenedicarbonitrile.[57]



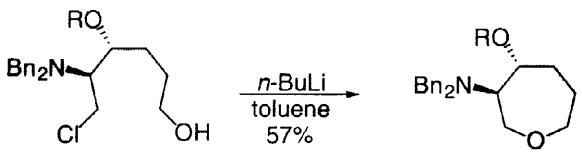
Scheme 28

III.4 Intramolecular cyclization of diols and hydroxy halides

There are numerous reports on the formation of cyclic ethers via cyclization of diols. Often these are applied to medicinal or natural product synthesis. Typically these dehydrocyclizations are accomplished by converting a single hydroxy group into a tosylate or triflate group followed by spontaneous cyclization. For example, in studies of the formation and conversion of allysilanes, diol **71** was converted to oxepane **72** via a monotosylate.[58] For the synthesis of (+)-zoapatanol, Trost and co-workers converted **73** into the triflate, which spontaneously cyclized to the oxepane **74** in 74% yield.[43] Finally, using cyanomethylenetributylphosphorane (CMBP) in a Mitsunobu reaction, Tsunoda and co-workers obtained a 58% yield of **75**.[59] Use of the traditional DEAD-triphenylphosphine reagent produced no oxepane.



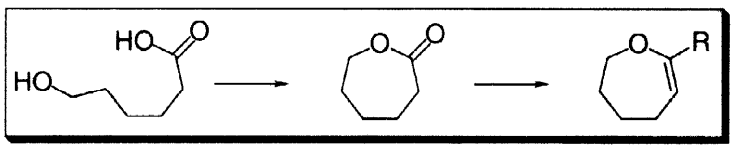
Cyclizations of 6-chloro alcohols have also been used in the synthesis of analogs of the protein kinase C inhibitor balanol (Scheme 29).[60] Deprotonation of the chloro alcohol **76** in boiling toluene gave oxepane **77** in 57% yield. Further transformations of the protected amine and ether groups gave balanol analogs.



76 77

Scheme 29

IV. Formation and Conversion of Lactones

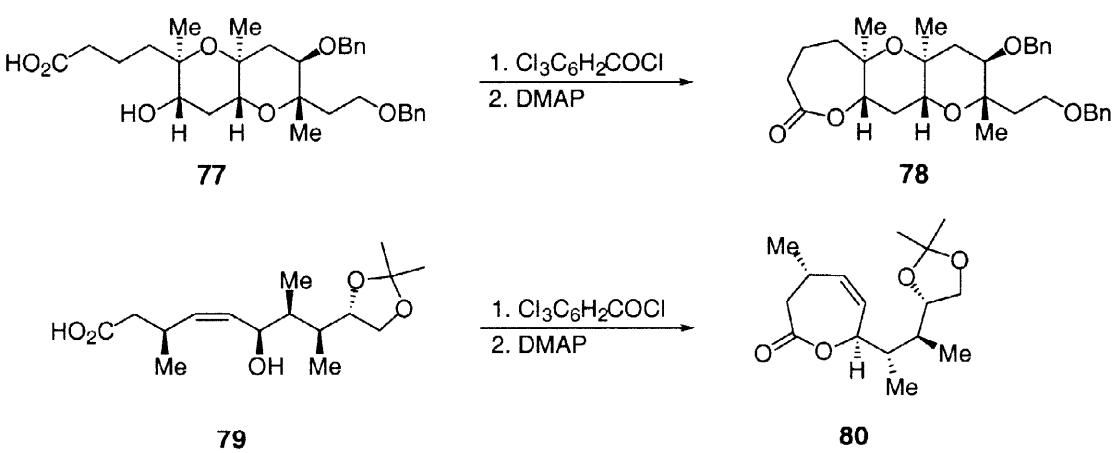


The conversion of caprolactone derivatives into oxepanes and oxepenes has played an important role in the synthesis and application of oxepane-containing natural products. This section will present methods for the lactonization of hydroxy acids and the oxidation of cyclohexanones to caprolactone derivatives. The final section will involve the latest strategies for converting these lactones into substituted oxepenes.

The formation and subsequent functionalization of lactones provide substituted oxepenes, typically in high yields. This type of method has been employed extensively in the synthesis of natural products. Several representative examples will be presented.

IV.1 Intramolecular lactonization of hydroxy acids

One of the well-known lactonizations of hydroxy acids, developed by Yamaguchi, involves conversion of the acid to the acid chloride using trichlorobenzoyl chloride followed by cyclization with DMAP.[61] Numerous uses of this procedure have been reported in the synthesis of natural products. For example, in the synthesis of brevetoxin B, Nicolaou and co-workers used this procedure for the cyclization of hydroxy acid **77** to lactone **78** in 90% yield (Scheme 30).[62] Murai's group has also applied this methodology in the partial synthesis of ciguatoxin, where lactonization of **79** to **80** was accomplished in 81% yield.[63]

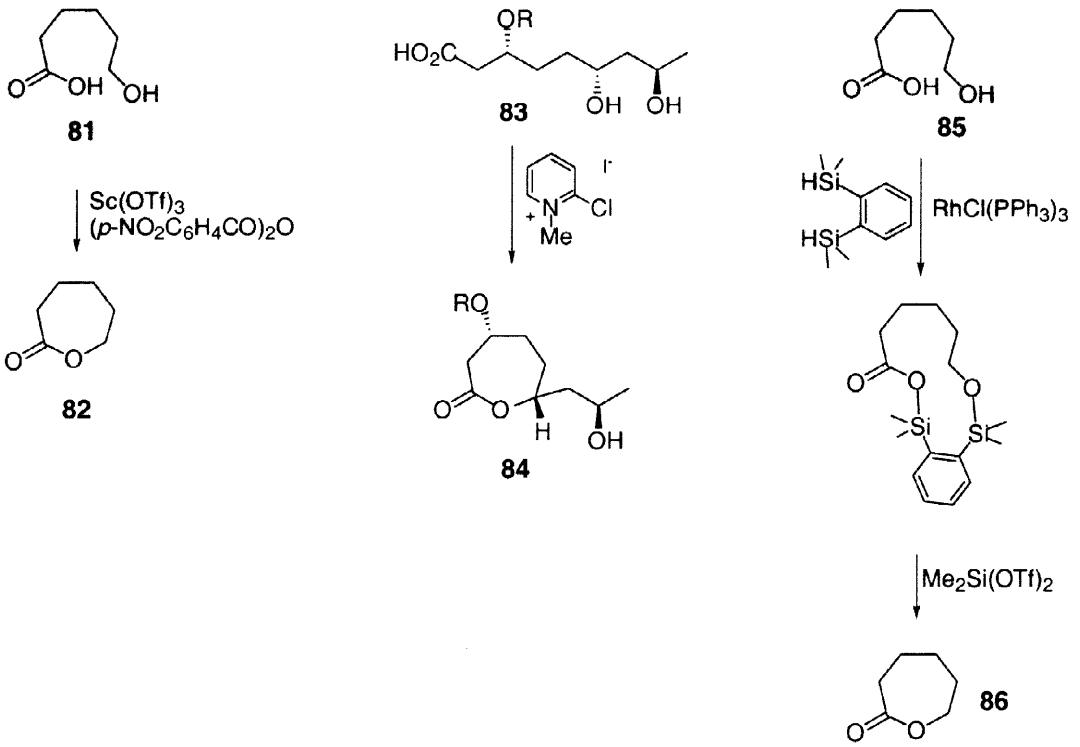


77 78

79 80

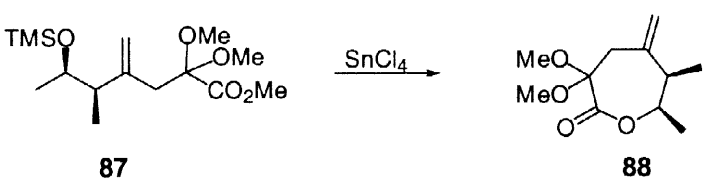
Scheme 30

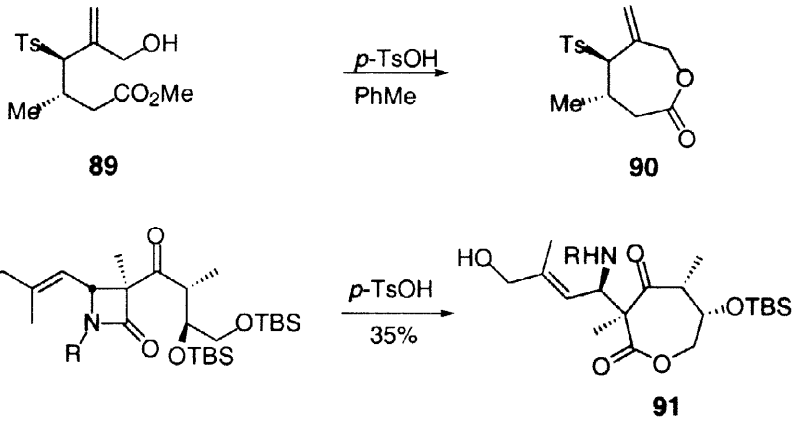
Other methods for the lactonization of hydroxy acids include the use of catalytic scandium triflate developed by Yamamoto and co-workers (Scheme 31).[64] Activation of **81** by $Sc(OTf)_3$ and two equivalents of *p*-nitrobenzoic anhydride yields lactone **82** in 99% yield. Alternatively, Fleming and co-workers used Mukaiyama's reagent, chloro-*N*-methylpyridinium iodide, to convert derivatives of **83** to **84** in yields greater than 80%.[65] Finally, an optional method for forming medium-sized lactones involves catalytic $RhCl(PPh_3)_3$ and bisdimethylsilylbenzenes.[66] Using a bisdimethylsilylbenzene as a bridging agent, **85** was converted to lactone **86** in 35% yield.



Scheme 31

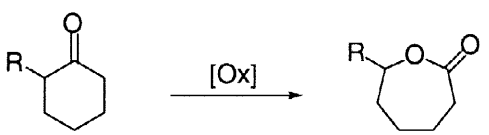
There are also numerous examples of the lactonization of hydroxy esters and hydroxy amides. For example, prolonged treatment of **87** with $SnCl_4$ in dichloromethane resulted in formation of lactone **88** in 65% yield.[67] Alternatively, **89** was converted to the caprolactone **90** in 70% yield using toluenesulfonic acid.[68] Thomas's group also used an acid catalyzed lactonization in studies for the synthesis of the lankacidins **91**.[69]





IV.2 Baeyer-Villiger oxidation of cyclohexanones

The well known Baeyer-Villiger oxidation of cyclohexanones using *m*-CPBA as the oxidant is a common method for the formation of caprolactones (Scheme 32).[70] This oxidation has been optimized with the use of additives such as sodium and potassium bicarbonates, or catalytic hydrotalcite. Yields of greater than 90% have been attained using these procedures.[71] Additionally, silicon-directed *m*-CPBA oxidations have also been developed and used, producing regioselectivities greater than 99:1 in 80-99% yields.[72] Resolution of these racemic caprolactones has also been investigated using pig liver esterase.[73] The yield of the optically active lactones ranged from 30 to 35% with ee's of 60 to 98%, where R was an alkyl group ranging from methyl to octyl.



Scheme 32

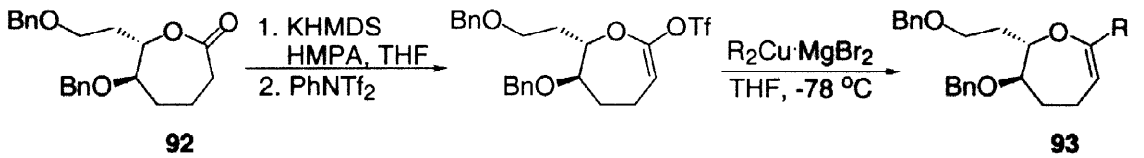
Alternative reagents for *m*-CPBA oxidations that have been applied to cyclohexanone derivatives are shown in Table 1. Most permit the use of water-free conditions and, in the case of entries 5, 6 and 7, asymmetric versions have been developed. In addition, the enzymatic oxidations have produced ee's greater than 98%.

Table 1. Baeyer-Villiger oxidation of cyclohexanones

Entry	Reagent	Yields	Reference
1	magnesium monoperphthalate hexahydrate (MMPP)	55-97%	74
2	Cyclohexaneperoxycarboxylic acid (CHPCA)	89-96%	75
3	CF_3CO_3H	81-98%	76
4	TMSOOTMS/catalyst	61-91%	77
5	O_2, PhCHO, catalyst	40-100%	78
6	H_2O_2/ catalyst	45-92%	79
7	Enzyme	20-86%	80

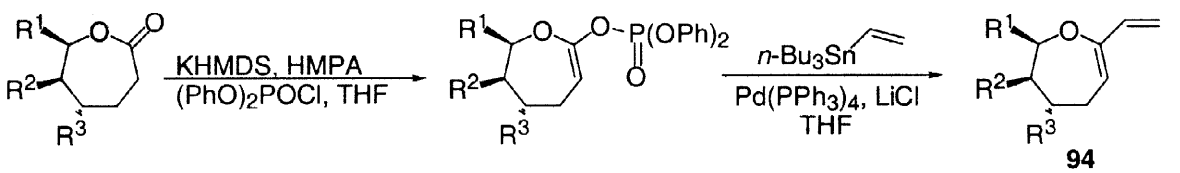
IV.3 Conversion of lactones to oxepenes

The conversion of lactones to substituted oxepanes via their triflate enolates has been well developed. Recently, Murai and co-workers applied this to the synthesis of the G ring in ciguatoxin.[81] Formation of **92** was achieved using a *m*-CPBA oxidation from the corresponding ketone in 85% yield. Treatment of **92** with base and $PhNTf_2$ followed by cuprate coupling produced oxepene **93** [R = $(CH_2)_3OEE$]. A 60% overall yield from **92** to **93** was achieved.



92 **93**

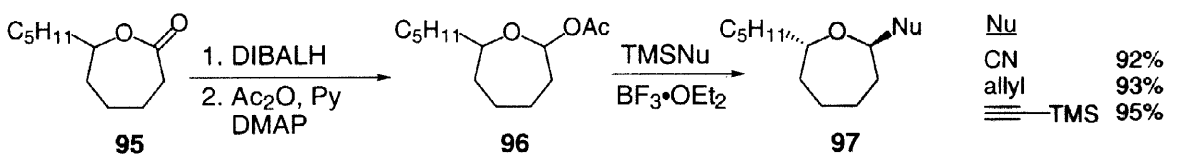
Nicolaou and co-workers improved on this procedure by introducing a ketene acetal phosphate (Scheme 33).[82] Several phosphates were generated at -78 °C in 80-92% yields that were stable at ambient temperatures and toward silica gel chromatography. Stille coupling with vinylstannane produced **94** in 58-97% yields. This method is also applicable to a wide variety of ring sizes.



94

Scheme 33

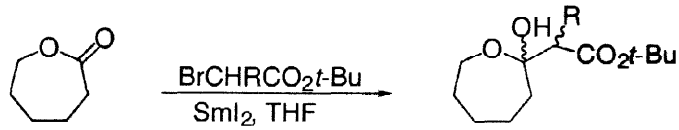
A complementary method was developed by Rychnovsky and Dahanukar that utilized the acetylated lactol **96** (Scheme 34).[83] Reduction of lactone **95** with DIBALH,[84] followed by *in situ* acetylation of the unstable lactol, produces **96** in 65% yield. Lactol **96** was then coupled with carbon nucleophiles via the intermediate oxonium ion producing **97** with 16:1 trans selectivity for the allyl and alkyne products. Additional studies using unsaturated oxepenes were also reported.



95 **96** **97**

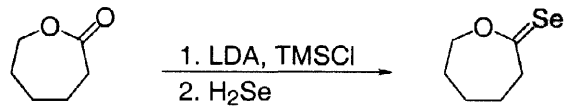
Scheme 34

Reformatsky-type reactions are also useful in the synthesis of functionalized oxepanes. Using a SmI_2 mediated reaction, Hanessian and Girard generated lactols **98** in 75 and 65% yields with R = H and Me, respectively. [85]



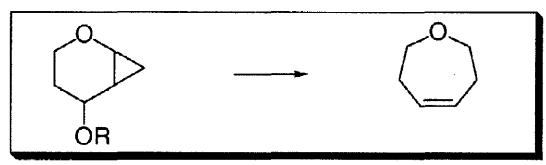
98

Finally, conversion to the selenoester has been accomplished in 85% yield by reacting the trimethylsilyl ketene acetal with hydrogen selenide (Scheme 35).[86] The chemistry of selenocarbonyl compounds has been developed extensively during the past few years, this intermediate could prove useful in subsequent conversions.[87]



Scheme 35

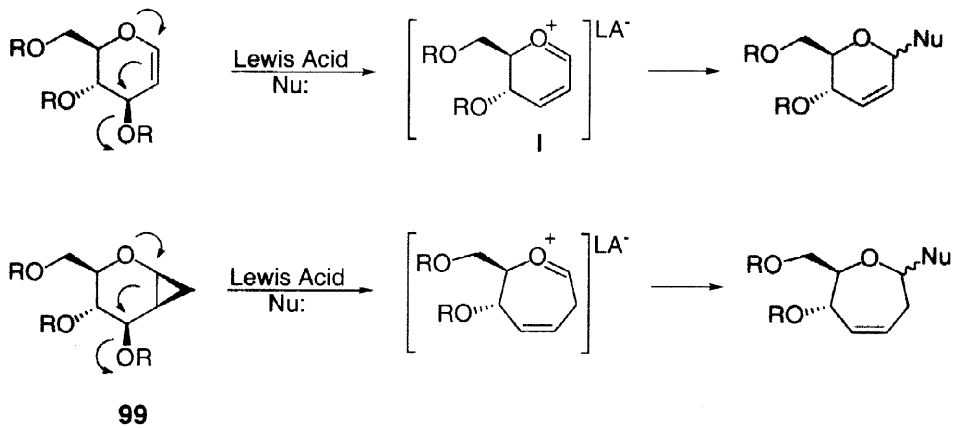
V. Ring Expansions



A relatively new and exciting method for the formation of oxepanes and oxepenes involves the ring-expansion of smaller rings. These methods have proven to be highly efficient and their applications to the synthesis of natural products have already proven successful. Some advantages of these transformations are optically active starting materials, simultaneous formation of multiple oxepane rings and formation of oxepanes with multiple functional groups.

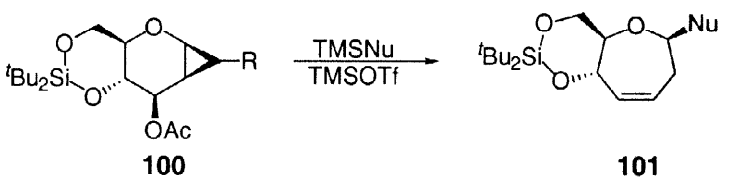
V.1 Ring expansions of cyclopropanes

The formation of medium-sized rings from the ring expansion of cyclopropanes is a well-developed method. However, the application of this process to the formation of oxepanes and oxepenes has been limited until lately. In view of this our group recently attempted to transform cyclopropanes into oxepenes. Our strategy was based on the well-known Ferrier rearrangement of glycals (Scheme 36).[88] These reactions proceed via a Lewis acid-induced removal of the allylic group to form oxonium ion **I**, followed by nucleophilic attack at the anomeric center. In view of the similarity of cyclopropane rings to olefinic bonds,[89] we speculated that upon treatment with a Lewis acid and nucleophile the cyclopropanated sugar **99** would undergo ring opening and provide ring-expanded oxepenes.[90]



Scheme 36

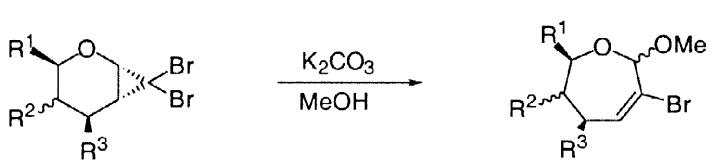
Ring expansion using cyclopropane **100** (R = H) provided oxepenes **101** in good to excellent yields with a diverse range of nucleophiles (Scheme 37).[91] Generally, yields ranged from 82 to 93% using silylated nucleophiles such as N_3, SPh, CN and allyl. Although syn stereochemistry for the nucleophilic attack was obtained, the selectivity was only 2:1. The poor selectivity was thought to be due to a planar geometry in the intermediate oxonium ion. Molecular modeling studies of the intermediate oxonium ion supported this assumption.



Scheme 37

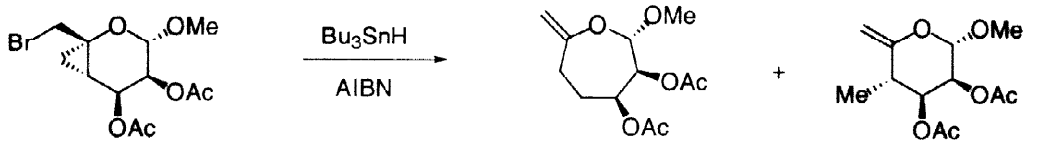
Formation of ester-substituted cyclopropanes (R = CO_2Et), followed by attempted ring-expansion, did not produce the desired oxepenes.[92] This was attributed to a deactivation of the cyclopropane by the ester group.

Nagarajan and co-workers have also reported the synthesis of oxepenes from dibromo cyclopropanated sugars via a solvolytic ring expansion (Scheme 38).[93] Initial attempts at solvolysis of the dibromocyclopropanes with silver or Lewis acid catalysis produced only decomposition at high temperatures. At room temperature the substrates remained inactive. However, in the presence of K_2CO_3 and boiling methanol, anomeric mixtures of oxepenes were obtained in 55 to 67% yields.



Scheme 38

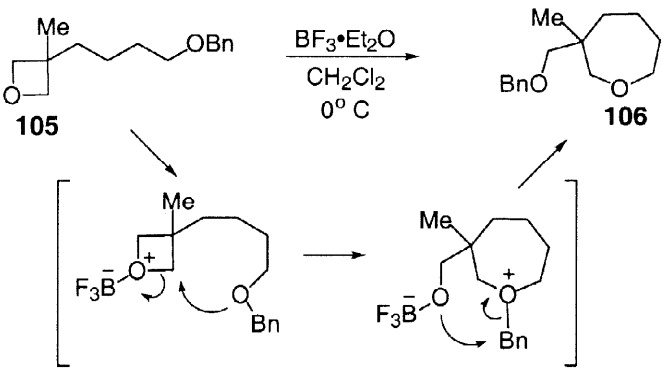
Using similar cyclopropanated sugars, Gurjar and co-workers observed radical ring expansion.[94] Treatment of **102** with Bu_3SnH and AIBN in boiling toluene produced a 2:3 mixture of **103** and **104**. Separation by preparative tlc gave **103** in 37% yield.



102 **103** **104**

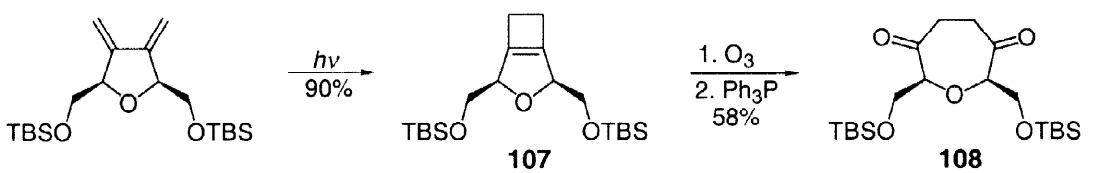
V.2 Ring expansions of four- and five-membered rings

Several interesting methods for the ring expansion of four- and five-membered rings have recently been reported. An intriguing method for converting oxetanes to oxepanes was described by Masaki and co-workers (Scheme 39).[95] The conversion of **105** involves the transposition of the ether side chain during the ring opening of the oxetane to produce medium-sized cyclic ethers such as **106**. In a single example of oxepane formation, the Lewis acid-promoted conversion of the oxetane was achieved in 49% yield under mild conditions. Using crossover experiments, the reaction appears to involve an intra- and intermolecular rearrangement via an oxonium ion intermediate.



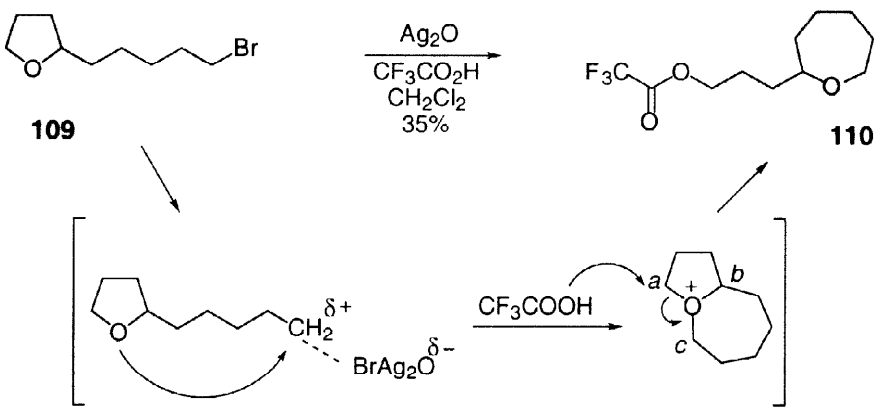
Scheme 39

In studies directed toward the synthesis of ciguatoxin, Hirama and co-workers reported the ring expansion of the bicyclic system **107**.[96] Formation of **107** was achieved photochemically, then ring-expanded by ozonolysis and reduction to provide the diketooxepane **108** in modest yield. Further functionalization of **108** produced dihydroxyoxepanes and dihydroxyoxepenes, both of which are useful precursors in natural product synthesis.



107 **108**

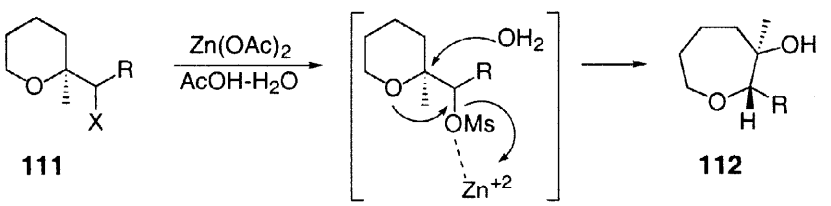
An additional method for an intramolecular transposition using pyrans was reported by Oku's group.[97] Expanding on their previous work, the present study generated oxonium ions by treating **109** with silver(I) oxide in the presence of trifluoroacetic acid (Scheme 40). Attack of the intermediate oxonium ion by trifluoroacetic acid can occur at three locations - *a*, *b* or *c*. Preference for attack at carbon *a* is postulated to be due to a release of steric strain, because the vicinal hydrogen atoms on the furan ring lie in a nearly eclipsed conformation. Thus, elongating or reducing the side chain in **109** modifies the steric strain and causes disappearance of **110**.



Scheme 40

V.3 Ring expansions of six-membered rings

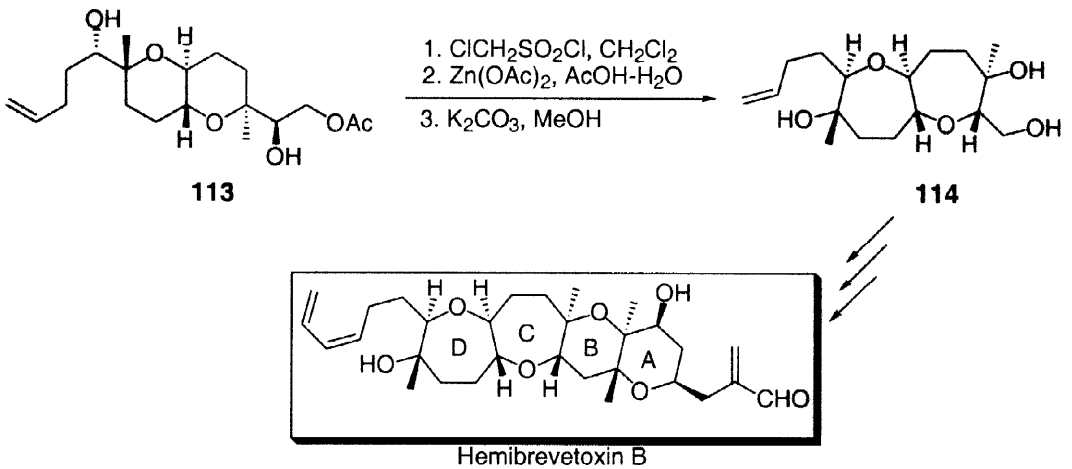
Several methods for transforming tetrahydropyrans into oxepanes have recently been reported. Nakata and co-workers have developed an efficient method for this conversion using a rearrangement ring expansion strategy and have applied it to the total and partial synthesis of marine natural products. For the rearrangement of **111**, the use of a leaving group positioned on the side chain of the anomeric carbon is used (Scheme 41).[98] Treatment with a metal salt in an acid/water medium produces **112** in good to excellent yields. Conditions that have been investigated involve the use of bromo and mesylate leaving groups and the use of various zinc and silver metal salts. Zinc acetate and a mesylate leaving group in boiling acid/water have proven to be the most effective combination, producing yields from 82 to 95%.



Scheme 41

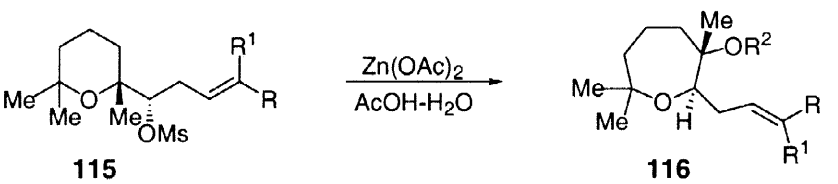
The application of this method to the synthesis of hemibrevetoxin B and maitotoxin has also been reported. In the synthesis of hemibrevetoxin B, a double rearrangement ring expansion was used to construct both the C and D rings (Scheme 42).[99] Expansion of bicyclic ether **113** followed by hydrolysis gave **114** in

60% yield. In this reaction, formation of the bis-chloromethanesulfonate produced significantly higher yields than the bis-mesylates.



Scheme 42

In attempts to modify their method for a more facile synthesis of larger polycyclic ethers, an olefinic side chain was incorporated (Scheme 43).[100] Because epoxidation of the olefin is performed in subsequent steps, the incorporation of the olefin provides a more useful functional group in ensuing reactions. Additionally, complexation of the acetoxyl group with the $Zn(OAc)_2$ in Scheme 42 was thought to impede the reaction. Therefore, substrates with an olefinic moiety on the side chain should produce a more facile expansion. Using **115** as a substrate, the formation of oxepanes **116** was achieved as a mixture of alcohols and acetates at the R^2 position R^2 = H, Ac). These were produced stereoselectively in excellent yields using milder temperatures (50 °C) and shorter reaction times (1-3 h).

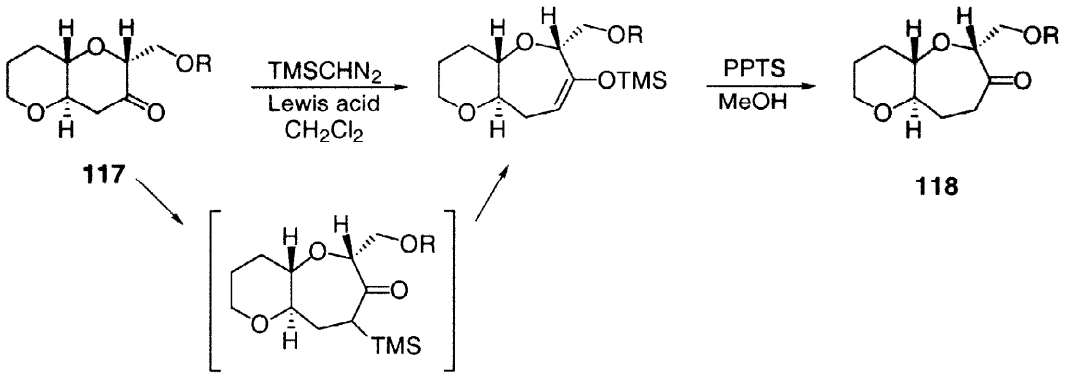


R, R^1 = H	82%
R = Me, R^1 = CO_2Et	93%
R = H, R^1 = CO_2Me	96%
R = Me, R^1 = CH_2OH	94%
R = H, R^1 = CH_2OH	90%

Scheme 43

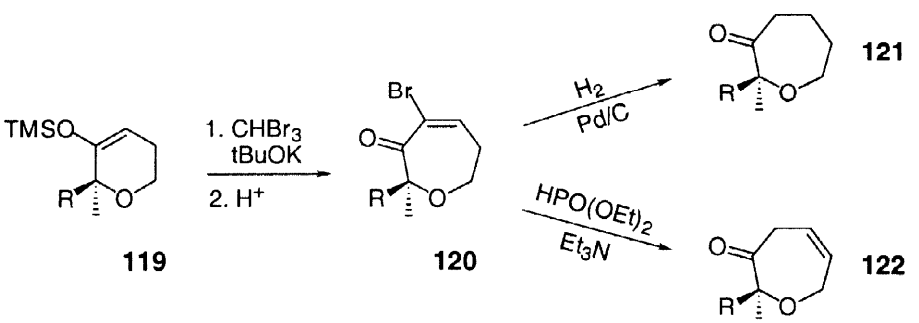
Another strategy for converting pyrans into oxepanes was developed by Mori and co-workers. Their strategy involves the direct insertion of a methylene unit into a pyranone ring. Generally, diazomethane has been used as the methylene unit; however, problems such as low reactivity, oxirane formation or multiple

insertions result. To avoid these problems, trimethylsilyldiazomethane was used as the methylene unit. Treatment of **117** with trimethylsilyldiazomethane in the presence of a Lewis acid and acid hydrolysis resulted in conversion to the oxepanone **118** in good yields (Scheme 44).[101] Yields as high as 76% were obtained with the use of BF_3•OEt_2. Additional Lewis acids that were surveyed included Et_2AlCl and Me_3Al. The presence of the TMS group also serves to direct the diazo group toward the formation of the less crowded α-trimethylsilyl ketone intermediate. Additionally, the formation of the silylenol ether prevents multiple homologations.



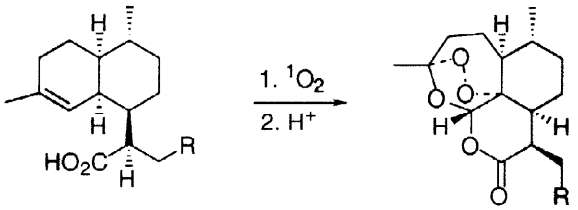
Scheme 44

In synthetic studies toward zoapatanol, Pain, Desmaele and d'Angelo used a similar ring enlargement of a pyranone (Scheme 45).[102] Ring expansions of **119** by addition of dibromocarbene ($CHBr_3$/*t*BuOK) produce oxepenones **120** in 66% and 65% yields. Further conversions of **120** were accomplished using a catalytic reduction, producing **121** in 56% yield. Deconjugative reduction led to enone **122** in 66% yield.



Scheme 45

Ring expansion of cyclohexenes in the formation of oxepane peroxides has also been achieved (Scheme 46).[103] Reaction of **123** with singlet oxygen followed by acid treatment with Amberlyst-15 produced **124** in 40% yield. Further conversions led to analogs of the naturally occurring antimalarial agent artemisinin.

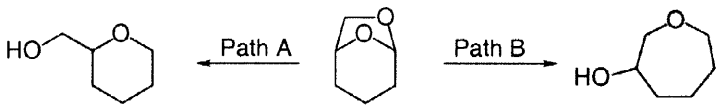


123 **124**

Scheme 46

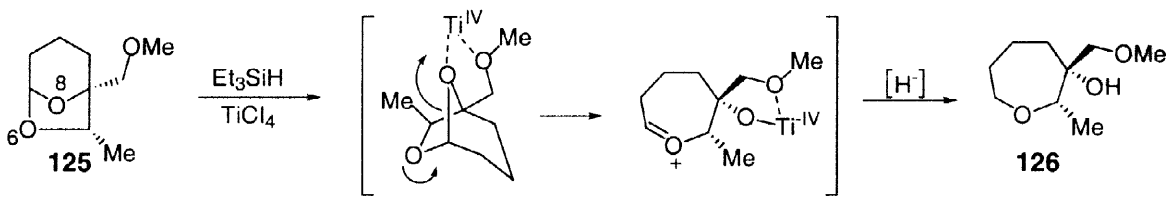
V.4 Ring expansions of bicyclic rings

A final area of ring expansions involves the selective cleavage of 6,9-dioxabicyclo[3.2.1]octane systems with Lewis acids (path B in Scheme 47). Utaka's group initially reported this transformation, and recently others have developed new approaches for the optimization of path B.[104]



Scheme 47

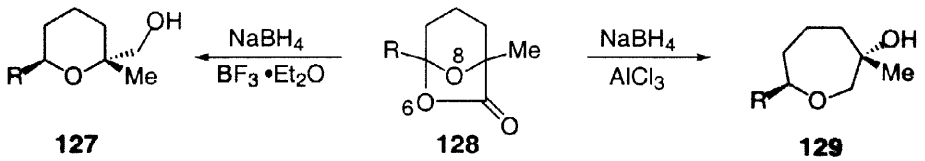
The selectivity of the acetal cleavage appears to depend on the type of Lewis acid and the use of chelation control. For example, ring expansion of acetal **125** with $TiCl_4$ produces oxepane **126** in 98% yield with a selectivity of 99:1 in favor of the oxepane to pyran (Scheme 48).[105] However, if $SnCl_4$ is used as the Lewis acid a 0:100 selectivity is observed. Furthermore, if the methoxy moiety is absent, oxepane formation is interrupted, suggesting that titanium chelation between O-8 and the methoxy oxygen is occurring. The fact that the tin chloride does not form the oxepane is perhaps due to the difference in Lewis strengths.[106]



125 **126**

Scheme 48

Jun and Lee have also reported the regioselective bond cleavage of similar acetals (Scheme 49).[107] Their initial efforts centered on regioselective cleavage of bicyclic acetals without the carbonyl moiety; however, all methods resulted in exclusive formation of pyrans similar to **127**. In contrast, use of the lactone **128** gave excellent stereoselectivity with the use of $AlCl_3$ as the Lewis acid. Treatment with sodium borohydride as the hydride source and 30 equivalents of the Lewis acid produced **129** in 94% and 91% yields as the only products (R = Me and H, respectively). Use of $BF_3{\cdot}Et_2O$ gave 93% and 92% yields of **129** as the only products (R = Me and H, respectively). A possible explanation for this observation is the decreased electron density at O-6; thus, the $AlCl_3$ with its vacant d-orbital would prefer the more electron-rich O-8.



127 128 129

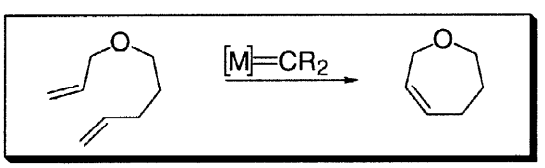
Scheme 49

Finally, an example that uses a phenylthio group as the nucleophile has been reported by Kusumoto and co-workers (Scheme 50).[108] Ring expansion of **130** in 1,2-dichloroethane produced the thioglycoside oxepane **131** in 63% yield. The use of dichloromethane, however, led to the formation of the pyran derivative.

130 131

Scheme 50

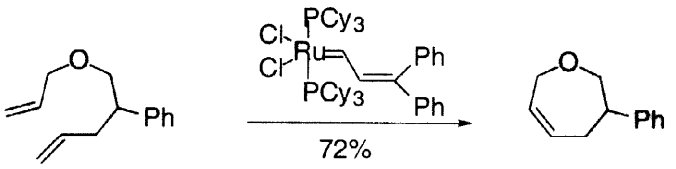
VI. Metal-Promoted Cyclization



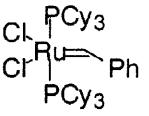
The metal-promoted cyclization of unsaturated ethers, intramolecular insertion of carbenes into C-H bonds, cyclization through alkynyl cobalt complexes, and other organometallic-assisted cyclizations offer another new and exciting method for the formation of oxepanes and oxepenes. During the past few years these methods have attracted considerable attention and have been shown to be highly efficient. Advantages of these transformations are the use of catalytic organometallics, simultaneous formation of multiple oxepane rings, excellent tolerance to a variety of functionalities, and tolerance to atmospheric oxygen.

VI.1 Ring-closing metathesis and metal-catalyzed cyclization

Ring-closing metathesis has rapidly become an important method for the formation of oxygen heterocycles (Scheme 51). Since the original reports by Grubbs and co-workers, numerous accounts have appeared on its use, development, and efficiency.[109] Specific applications to the synthesis of oxepenes and the application in natural products have also appeared. Although initial reports focused on the use of vinylalkylidene complexes, recent reports have been on the use of Grubbs' catalyst **132**, which is commercially available.[110]

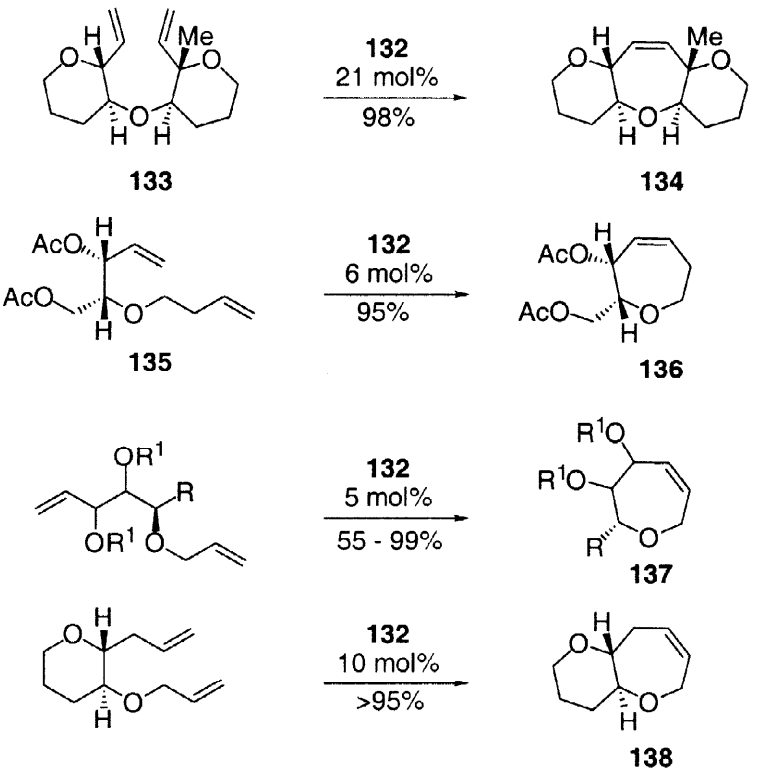


Scheme 51



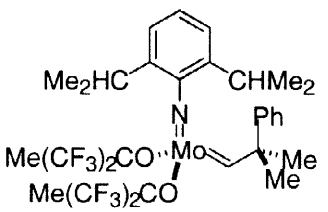
132

This general method for building oxepenes has been used by several groups (Scheme 52). Hirama and co-workers synthesized the *trans*-fused 6-7-6 tricyclic ether **134** from **133** in excellent yields.[111] Crimmins and Choy have reported the metathesis of asymmetric diene **135**,[112] while Van Boom and co-workers have reported on the formation of derivatives of the oxepene **137** from asymmetric dienes.[113] The formation of **136** and **137** demonstrates that incorporating the two stereogenic centers in acyclic systems provides sufficient conformational bias to facilitate ring closure. Previous ring closures of medium- to large rings exhibited the need to incorporate conformational constraints to avoid dimers and oligomers. Finally, Martin's group has further demonstrated the facile nature of this reaction by preparing derivatives of **138** in excellent yields.[114]

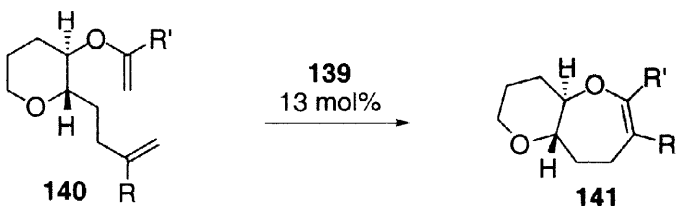


Scheme 52

Although these results demonstrate the synthetic utility of the ruthenium complex, its application to the ring closure of enol ethers of type **140** has proven to be ineffective (Scheme 53). Clark and Kettle therefore used the molybdenum catalyst **139**.[115] Yields of the disubstituted- and trisubstituted oxepenes **141** ranged from 42 to 94%.

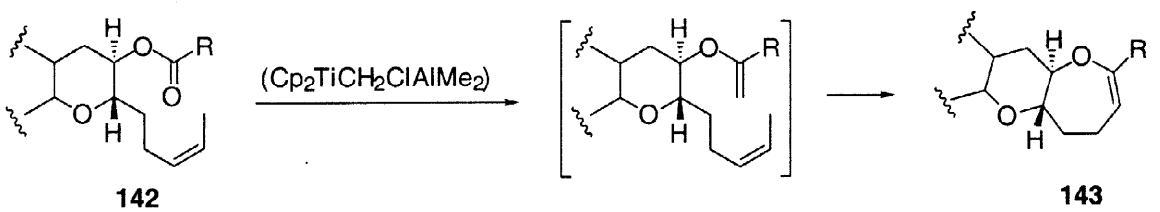


139



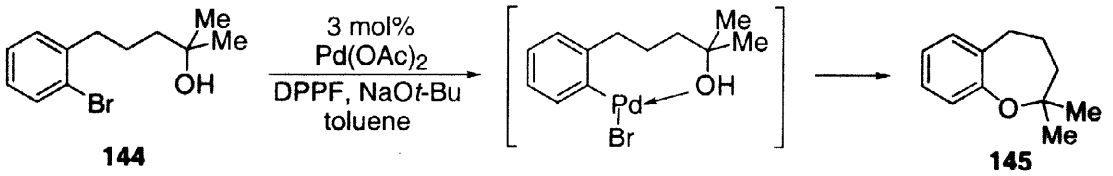
Scheme 53

Another variation of this metathesis method has been reported by Nicolaou and co-workers (Scheme 54).[116] The general concept involves transforming the olefinic ester **142** to the intermediate enol ester with Tebbe's reagent, followed by ring closure to produce **143**. Successful conversions were accomplished using 3-6 equivalents of the Tebbe reagent, resulting in yields from 30 to 45%.



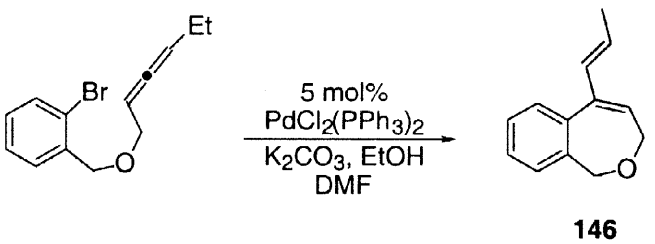
Scheme 54

Although palladium-catalyzed reactions have found wide applications in the synthesis of complex organic molecules, successful extension of these reactions to oxepane and oxepene synthesis has only recently been developed. The palladium-catalyzed C-O bond formation using aryl halide **144** has recently been reported by Buchwald's group (Scheme 55).[117] Mechanistically, this reaction most likely proceeds via the intermediate palladacycle, which upon deprotonation and reductive elimination yields the oxacycle **145** in 64% yield. Attempts to use secondary alcohols resulted in oxidation of the alcohol to the ketone.



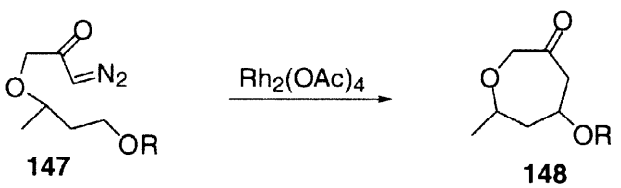
Scheme 55

Negishi also developed a palladium-catalyzed method using allenyl aryl halides (Scheme 56).[118] The cyclization proved to be highly stereoselective, producing only the (*E*)-oxepene **146** in greater than 97% selectivity and 61% yield. Furthermore, in cases were regioisomers could be obtained, excellent selectivity for the formation of oxepenes over pyrans were observed.



Scheme 56

The cyclization of diazo alcohols via rhodium catalysis has been extensively developed by Moody and co-workers.[119] Recently, Lee and co-workers elaborated on this work with the use of silyloxy directing groups.[120] Treatment of the diazo derivatives **147** produced an 80 and 82% yield of the cyclic ethers **148** with 1:1 and 4:1 ratios of isomers (R = TBDMS and TIPS, respectively; (Scheme 57). However, if a benzyl group is used as the R group, the expected furan ring is formed. Thus, the electronic effect of the silicon atom apparently overrides the usual conformational preference for formation of a five-membered ring.

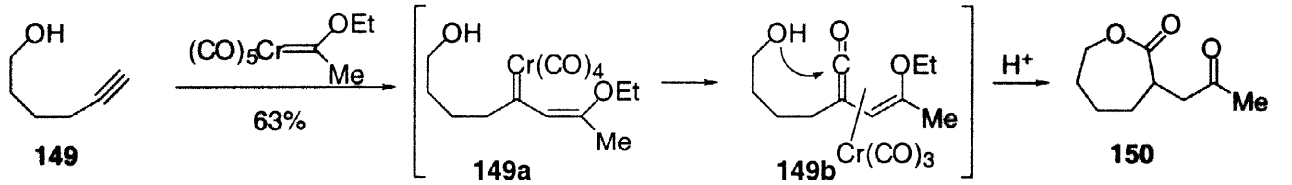


Scheme 57

Additional isolated cyclizations using transition metals that resulted in seven-membered oxacycles have also been reported. Hidai's group used a mixed Pd-Mo cluster for the lactonization of heptynoic acid, resulting in the formation of an enol lactone in 28% yield.[121] Hosomi's group[122] and Okamura's group[123] have both reported on the cyclization of enynes using a zirconium-based system and palladium-catalyzed method, respectively. In each case low to moderate yields were observed in the formation of substituted oxepenes.

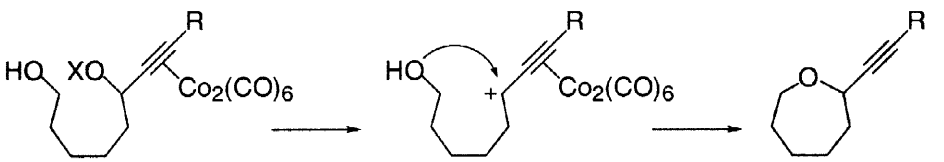
VI.2 Cyclization with stoichiometric metal complexes

Several highly efficient and mild cyclizations using metal complexes have also been reported. A lactone synthesis using a chromium carbene complex was recently developed by the Mori group (Scheme 58).[124] The reaction is believed to proceed through the vinyl carbene complex **149a**, which undergoes CO insertion and reaction with the hydroxyl group at the ketene moiety. Decomplexation and hydrolysis of complex **149b** provides lactone **150**.



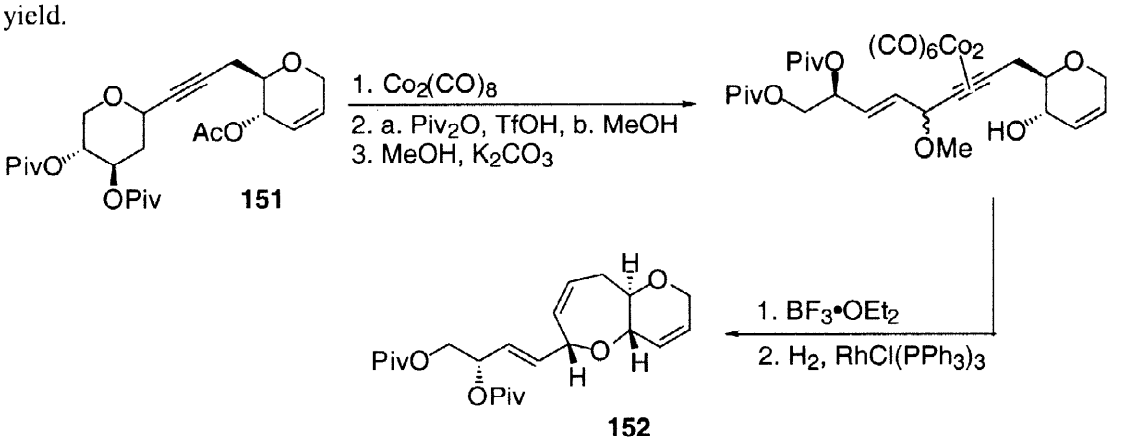
Scheme 58

Cobalt complexes have also been developed in oxepane and oxepene synthesis by both the Isobe and Martin groups (Scheme 59). In this strategy, a suitable hydroxy-substituted propargyl system is complexed with cobalt and then cyclized via a Nicholas-type cation.[125] The acetylene is decomplexed by either a reductive method to afford an olefinic moiety or an oxidative method to reform the alkynyl group.



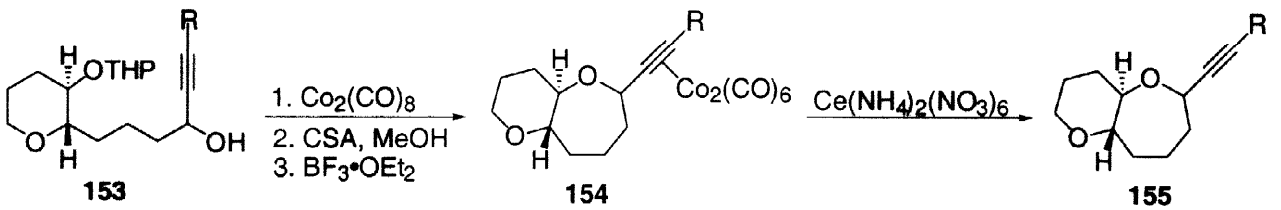
Scheme 59

In Isobe's work, pyran **151** was complexed with cobalt, ring opened, and deacetylated in an overall 72% yield (Scheme 60).[126] Cyclization followed by decomplexation with Wilkinson's catalyst afforded **152** in 51% yield.



Scheme 60

In work by Martin and co-workers, complexation of **153** with $Co_2(CO)_8$, followed by deprotection and cyclization, gave oxepanes of type **154** in 71-78% yield for the cyclization step (Scheme 61).[127] Oxidative treatment with CAN provides acetylene **155** in near quantitative yields.



Scheme 61

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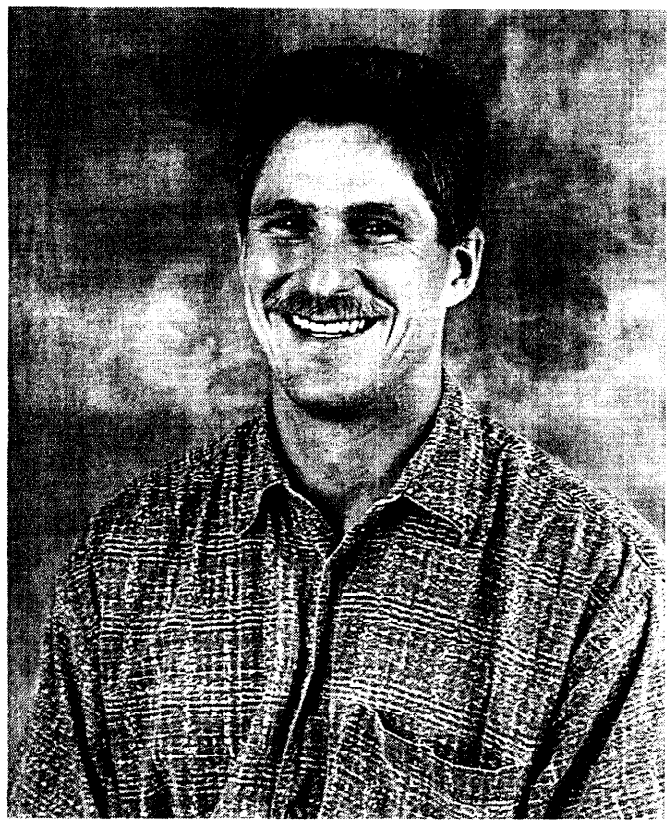
Biographical sketch



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John O. Hoberg was born near Jamestown, ND, USA in 1962. He received his B.A. in chemistry from Jamestown College and his Ph.D. from Montana State University with Professor P. W. Jennings (1990). After two years of postdoctoral work with Gary Molander at the University of Colorado, he joined the National Renewable Energy Laboratory in Golden, CO. In 1998 he moved to Victoria University of Wellington as lecturer of organic chemistry. His research interests lie in the area of carbohydrate and organometallic chemistry.