Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 62 (2006) 9301–9320

Tetrahedron report number 769

Recent developments in the synthesis of oxepines

Nicole L. Snyder,[a] Heather M. Haines[a] and Mark W. Peczuh[b,*]

[a]*Department of Chemistry, Wellesley College, 106 Central Street, Wellesley, MA 02481, USA*
[b]*Department of Chemistry, The University of Connecticut, 55 North Eagleville Road, Storrs, CT 06269-3060, USA*

Received 25 June 2006
Available online 9 August 2006

Contents

1. Introduction

A remarkable diversity of natural products contains a seven-membered oxacycle in their molecular architecture (Fig. 1). Structures range from the ladder polyether neurotoxins ciguatoxin, brevetoxin, and gambierol (**1**–**3**) to the functionalized monocycles such as isolaurepinnacin (**6**) and rogioloxepane (**7**), to the spirocyclic crambescidin (**5**) and fused aryloxepine structures janoxepin, oxepinamide C, and bauhiniastatin (**10**–**12**). Notably, a majority of the natural products in Figure 1 are from marine sources. Reported pharmacological investigations on these structures showed that they have ion-channel blocking (**1**,**2**),[1] antiviral (**5**),[2] and antifungal (**8**)[3] activities.

Abbreviations: CAN, ceric ammonium nitrate; Cy, cyclohexyl; dba, dibenzylideneacetone; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DEAD, diethyl azodicarboxylate; DMAP, *N*,*N*-4-dimethylaminopyridine; DMDO, dimethyldioxirane; Eu(fod)$_3$, europium 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedione; EVE, ethyl vinyl ether; IDCP, bis(2,4,6-collidine)-iodonium perchlorate; Imid, imidazole; MEM, (2-methoxyethoxy)methyl; Mes, mesityl; MPM, methoxy(phenylthio)methyl; Ms, methanesulfonyl; NaHMDS, sodium 1,1,1,3,3,3-hexamethyldisilazane; Ns, 2-nitrobenzenesulfonyl; Piv, pivaloyl; PPTS, pyridinium *p*-toluenesulfonate; TBDPS, (also BPS) *tert*-butyldiphenylsilyl; TBS, (also TBDMS) *tert*-butyldimethylsilyl; TEA, triethyl amine; TES, triethylsilyl; TFP, tris(2-furyl)phosphine; TMEDA, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; TMS, trimethylsilyl.

* Corresponding author. Fax: +1 860 486 2981; e-mail: mark.peczuh@uconn.edu

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.07.021

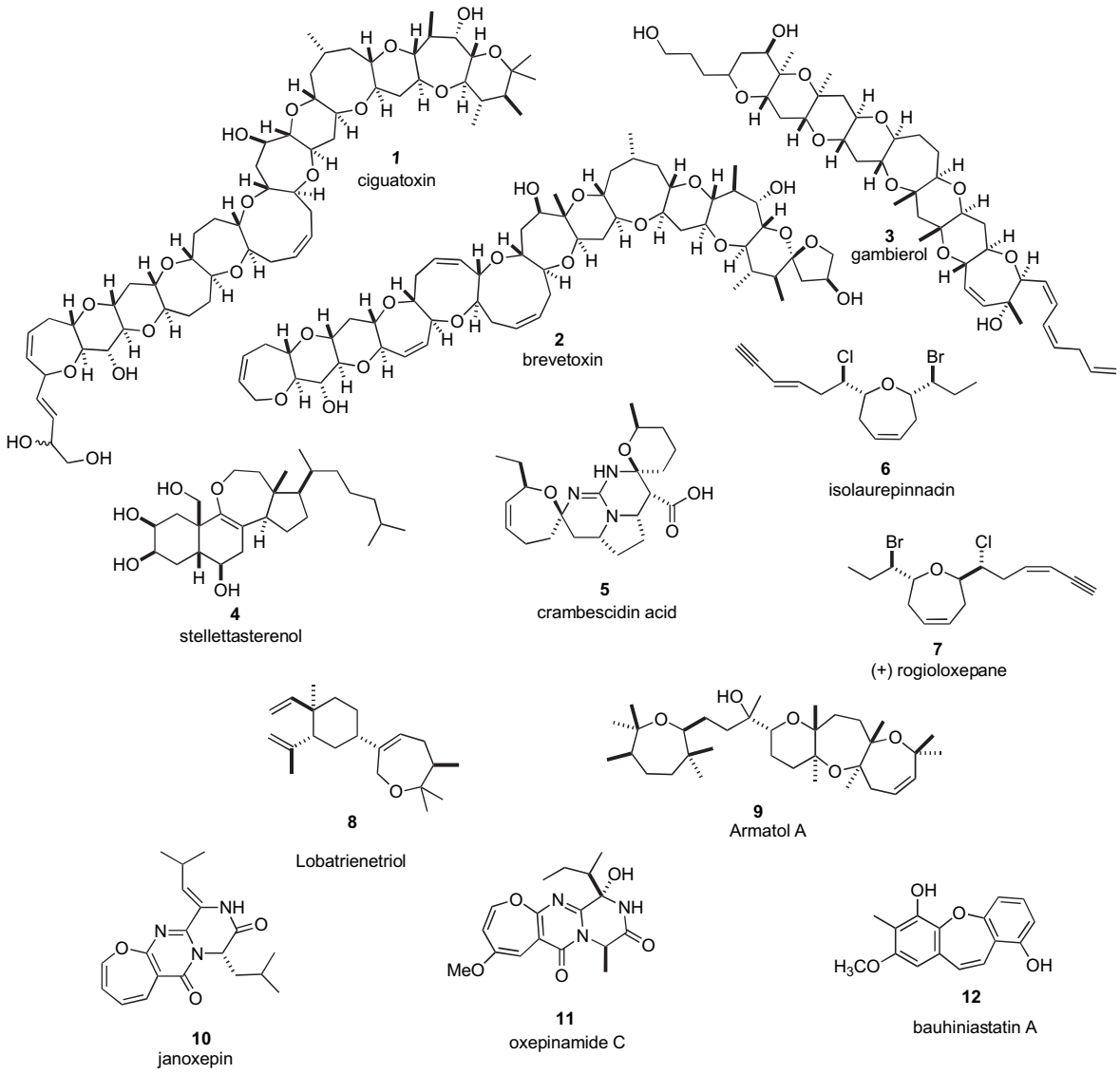
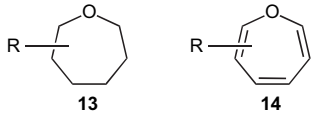


Figure 1.

From a chemical perspective, the intricacy of the structures in Figure 1 has made them the target of increased attention by synthetic chemists. The synthesis of medium ring oxacycles has been treated previously in reviews by Elliot[4] and Hoberg.[5] Here we review significant advances made in the synthesis of unsaturated seven-membered ring oxacycles. Strategies defined in the earlier reviews will be updated and new methods that have been recently reported will also be introduced. Dibenz[*b*,*f*]oxepines, which occur in natural products and synthetic pharmaceuticals will not be presented here; strategies for their synthesis have recently been reviewed.[6]

The key structural feature shared by the examples in Figure 1 is that the seven-membered oxacycle in each contains at least one carbon–carbon double bond. Following IUPAC nomenclature,[7] saturated seven-membered oxacycles are termed as oxepanes (**13**) and if the ring contains 'the maximum number of double bonds' it is an oxepine (**14**). The names of oxepine containing natural products like janoxepin (**10**) and oxepinamide (**11**) evoke the direct connection to this definition. Structures that have one double bond in the ring have been referred to as oxepanes, di-dehydro-oxepanes, oxepenes, and oxepines in the literature. Based on the prevalence of its usage, it is suggested that, in addition to **14**, the general structures in Figure 2 also be called oxepines for convenience here. Oxepines of type **15** and **16** are present in the widest variety of natural products (Fig. 1). The cyclic enol ether motif **17**, on the other hand, has only recently been identified in the unusual steroid ether stellettasterenol (**4**).[8]



13 **14**

The objective of this report is to review synthetic strategies for preparing the three classes of oxepines **15**–**17** as outlined in Figure 2. For each of the oxepine subtypes, a dashed line designates a key bond to be formed in a cyclization reaction that gives rise to that oxepine structure. Adjacent to the dashed line are listed the specific reaction types that effect

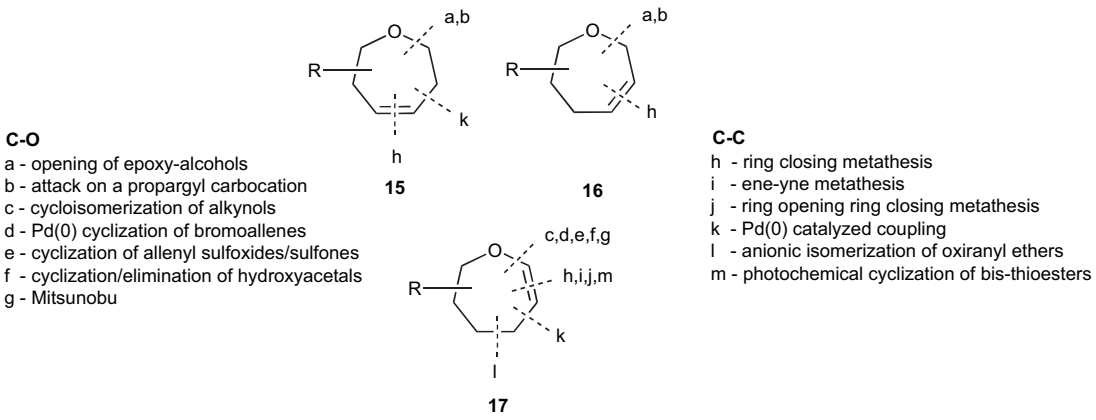


Figure 2.

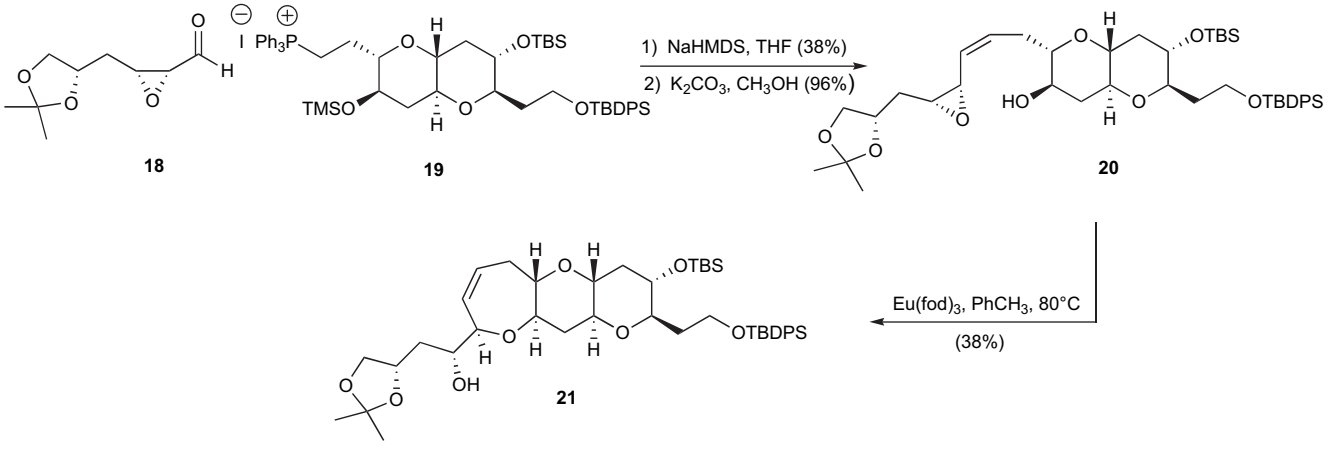
the cyclization. Reactions are broken into two classes: C–O bond forming reactions and C–C bond forming reactions. As evidenced by considering the strategies in Figure 2, the variety of new cyclization reactions that have been introduced recently for the preparation of oxepines is noteworthy. Among them, the growing focus on cyclic enol ether **17** as synthetic targets is especially interesting. Syntheses of this class of oxepine have, by and large, been characterized by the development of methods rather than being motivated by specific natural product targets. In fact, they have become attractive as intermediates en route to more complex structures. Their utility in these applications derives from the ability to functionalize the cyclic enol ether functionality (via epoxidation and nucleophilic attack, for example) under mild conditions. This strategy has been implemented in an iterative fashion for the overall synthesis of fused polycyclic ethers such as brevetoxin (**2**) and gambierol (**3**).[9–11] In total, progress in the synthesis of the oxepines reviewed here should provide a perspective on the breadth of current methods and the opportunities for development that they represent.

2. Cyclization via C–O bond formation

Formation of oxepines via C–O bond formation takes advantage of the inherent nucleophilicity of oxygen onto an electrophilic carbon species. Strategies such as cyclization of diols,[12] iodoetherification,[13] and lactonization followed by derivatization to oxepines[14] are all noteworthy, but have been discussed in previous reviews without significant new developments. Advancements on two established approaches, the intramolecular attack by a hydroxyl group on an epoxide or on a propargyl cation, are discussed first. The remainder of the methods for oxepine synthesis in this section has been introduced recently. Transformations involving cyclizations through attack at the central carbon of various allenes (metal, bromo, sulfuryl/sulfonyl) constitute the major focus. The cyclization–elimination of hydroxy-acetals and a novel Mitsunobu approach to aryl-oxepines will also be presented.

2.1. Lewis acid-mediated opening of epoxy-alcohols

Cyclization by the intramolecular attack of a hydroxyl group onto a Lewis acid-coordinated epoxide is an established method for the formation of tetrahydropyrans and oxepanes.[15] Epoxy-alcohols containing a double bond can give oxepines such as **15** or **16**. This strategy is attractive because the epoxide can often be formed enantioselectively and gives rise to a new chiral hydroxy group upon ring opening. An illustrative example comes from the synthesis of the ABC ring system of ciguatoxin (**1**) (Scheme 1).[16] Aldehyde **18** was derived from Sharpless epoxidation of the corresponding allylic alcohol followed by oxidation. Wittig coupling of **18** with phosphonium salt **19** and removal of TMS group gives the cyclization precursor **20**. After evaluating a variety



Scheme 1.

of conditions (base, protic acid, Lewis acid), the cyclization was found to be of only modest efficiency, giving oxepine **21** in 38% yield using $Eu(fod)_3$ as a Lewis acid promoter of cyclization. An alternative set of conditions where treatment of the starting material with $(Bu_3Sn)_2O$ followed by $Eu(fod)_3$ gave a similar yield for the cyclization (36%).

Recent examples of the epoxy-alcohol cyclization are taken from the formal total synthesis of (+)-isolaurepinnacin A (**6**)[17] and the total synthesis of (+)-rogioloxepane A (**7**).[18] The key difference between these two natural products, aside from the difference in the olefin geometry of the C8–C9 bond (*E* vs *Z*), is the disposition of the substituents adjacent to the ring oxygen of the oxepine. For **6** they are cis and for **7** they are trans.

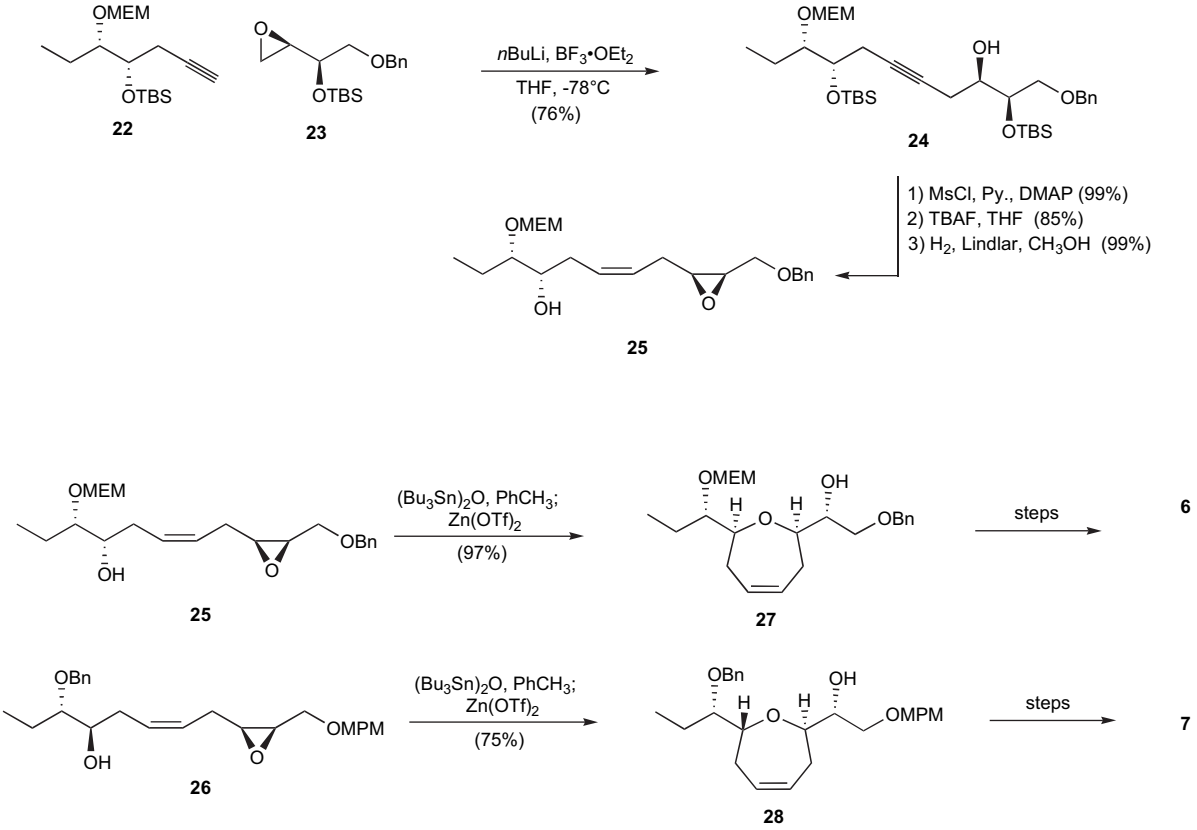
In the following examples (Scheme 2), the stereocenter of the nucleophilic oxygen determines the cis/trans stereochemistry.[19] Epoxy-alcohol precursors **25** and **26** were prepared in a similar fashion; the route is illustrated here for **25**. The anion derived from alkyne **22** is coupled with epoxide **23** to give homo-propargyl alcohol **24**. Reduction of the triple bond followed by epoxidation and nucleophilic displacement gives **25**. In the cyclization reactions the acyclic epoxy-alcohols **25** and **26** are first treated with $(Bu_3Sn)_2O$ followed by the Lewis acid $Zn(OTf)_2$ to form oxepines **27** and **28** in 97 and 75% yields, respectively.[20] The $(Bu_3Sn)_2O$ in the reactions allows the pre-formation of alkyl tin-ethers, which are argued to increase the nucleophilicity of the oxygen, presumably due to the longer Sn–O bond length relative to H–O.

Despite nearly identical reaction conditions, the cyclization of **25** and **26** to form **27** and **28** appears to be significantly more efficient than in the ciguatoxin A-ring (**20** to **21**, Scheme 1). According to the authors, the poor yield for cyclization of **20** was based on inefficient formation of the tin-ether and a ground state conformation where the nucleophilic hydroxyl group was in closer proximity to the alkene rather than the epoxide functionality. In contrast, the acyclic precursors **25** and **26** were presumably efficient in the formation of tin ethers and subsequently cyclized using $Zn(OTf)_2$ as Lewis acid.

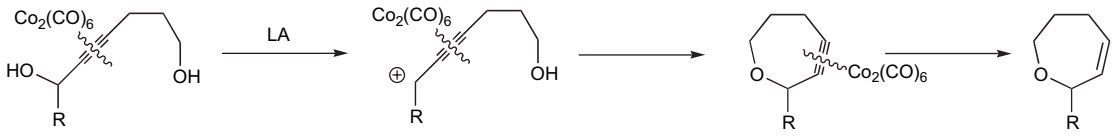
2.2. Attack on a propargyl cation

Carbocations adjacent to an alkynyl-dicobalt unit are relatively stable species that can be attacked by nucleophiles (Nicholas reaction).[21] If the propargyl carbocation is linked covalently to an alcohol, intramolecular attack will provide an oxepine. The position of the carbocation relative to the oxygen nucleophile can be on the opposite side of the $Co_2(CO)_6$ complexed alkyne (Scheme 3) or on the same side (Scheme 4). This relationship determines whether the alkyne complex is included in the developing ring or is on its periphery. Decomplexation of $Co_2(CO)_6$ using reducing conditions (H_2/$RhCl(PPh_3)_3$ or Bu_3SnH) is most common when the complex is part of the ring. Ceric ammonium nitrate (CAN) as a decomplexing agent regenerates the alkyne.

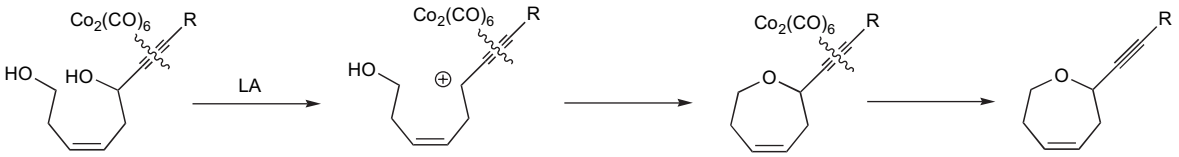
Isobe and co-workers originally reported the intracyclic approach (Scheme 5) in the synthesis of the AB ring system of ciguatoxin (**1**).[22] Cobalt complex **29** is cyclized using



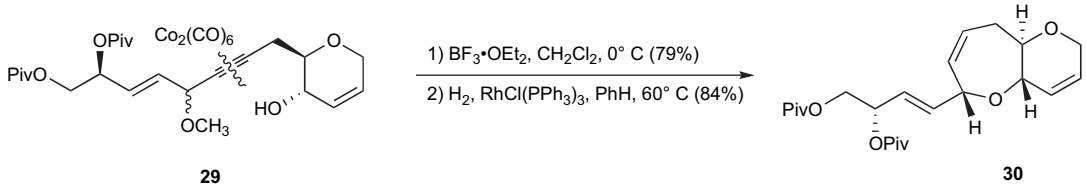
Scheme 2.



Scheme 3.



Scheme 4.

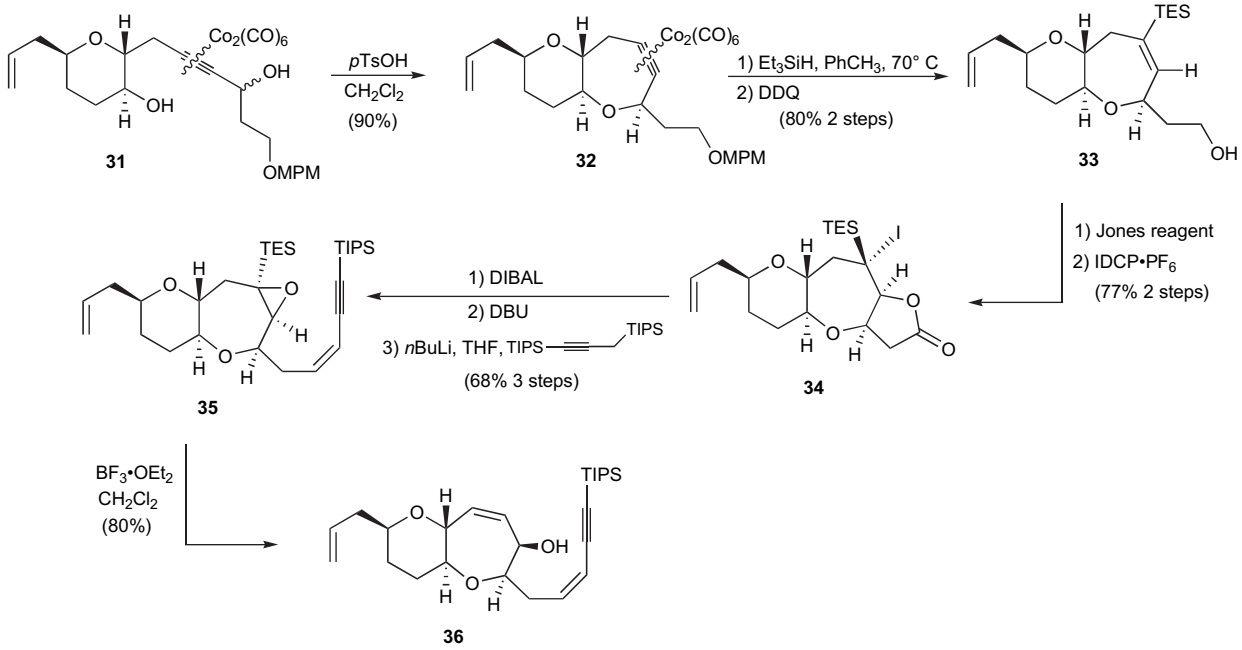


Scheme 5.

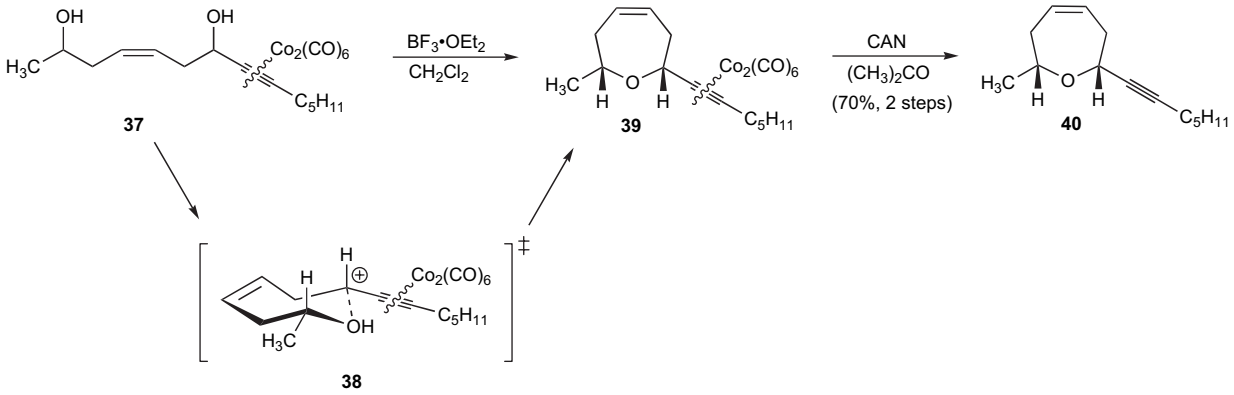
$BF_3 \cdot OEt_2$ as a Lewis acid promoter to give, after reductive decomplexation, oxepine **30** in good yield (66%, two steps). Albeit it is a different precursor, the efficiency of cyclization of the ciguatoxin A ring by this method is markedly better than in the case of the epoxy-alcohol **20** mentioned earlier. An illustration of the combination of the cyclization of a propargyl cation followed by transposition of the double bond after cyclization via a multi-step sequence is given in Scheme 6. Isobe and co-workers have made significant progress on the application of this strategy to cyclizations of the other oxepanes in the ciguatoxin (**1**) structure.[23–25]

In addition to the A ring, synthesis of the D, E, and the nine-membered F ring have also been possible using this approach.

An interesting innovation that has been added in these later treatments is that in place of the usual reductive decomplexation conditions. A reductive hydrosilylation was developed to generate a vinyl silane **33**.[26] The resulting vinyl silane serves two purposes: first, it allows further functionalization of the fused-ring system; second, it promotes migration of the double bond within the ring to its desired position.



Scheme 6.



Scheme 7.

The process is nicely illustrated in the synthesis of the (D)EF rings of ciguatoxin shown in Scheme 6.[23] Lewis acid-promoted cyclization of cobalt complex **31** cleanly provides **32**. Reductive decomplexation of the Co_2CO_6 using triethylsilane and deprotection of the MPM group gives vinyl silane **33**. Oxidation of the alcohol in **33** then sets up an iodolactonization to give **34**. Reduction of the lactone, epoxidation, and addition to the aldehyde gives epoxide **35**. Lewis acid-mediated epoxide opening and elimination provided oxepine **36** where the double bond has migrated to the adjacent carbons relative to the original (vinyl silane) oxepine.

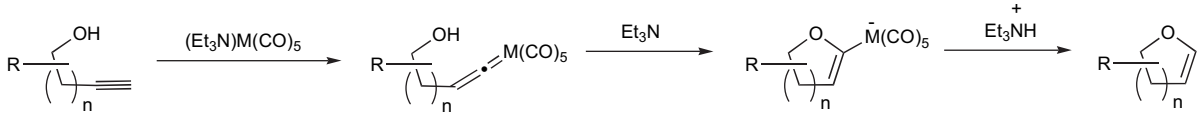
Cyclization where the cobalt complex is exocyclic to the oxepine ring formed has been utilized by Martín in the synthesis of 2,7-disubstituted oxepines similar to isolaurepinnacin (**6**).[27,28] Diol cobalt complex **37** was cyclized in the usual fashion using $BF_3 \cdot OEt_2$ as Lewis acid to give oxepine **39** as shown in Scheme 7. This was followed by removal of the Co_2CO_6 moiety using CAN to deliver the 2,7-disubstituted oxepine **40**. The diol precursor **37** in the sequence was racemic and leads to racemic mixture of oxepines **40**. There was, however, high cis diastereoselectivity in the cyclization step. This selectivity is argued to arise from the reduced transannular interactions experienced when the 2 and 7 substituents are placed in a pseudo-equatorial orientation in the transition state (**38**) to cyclization of the propargyl carbocation.[29]

2.3. Metal-mediated cyclizations by C–O bond formation

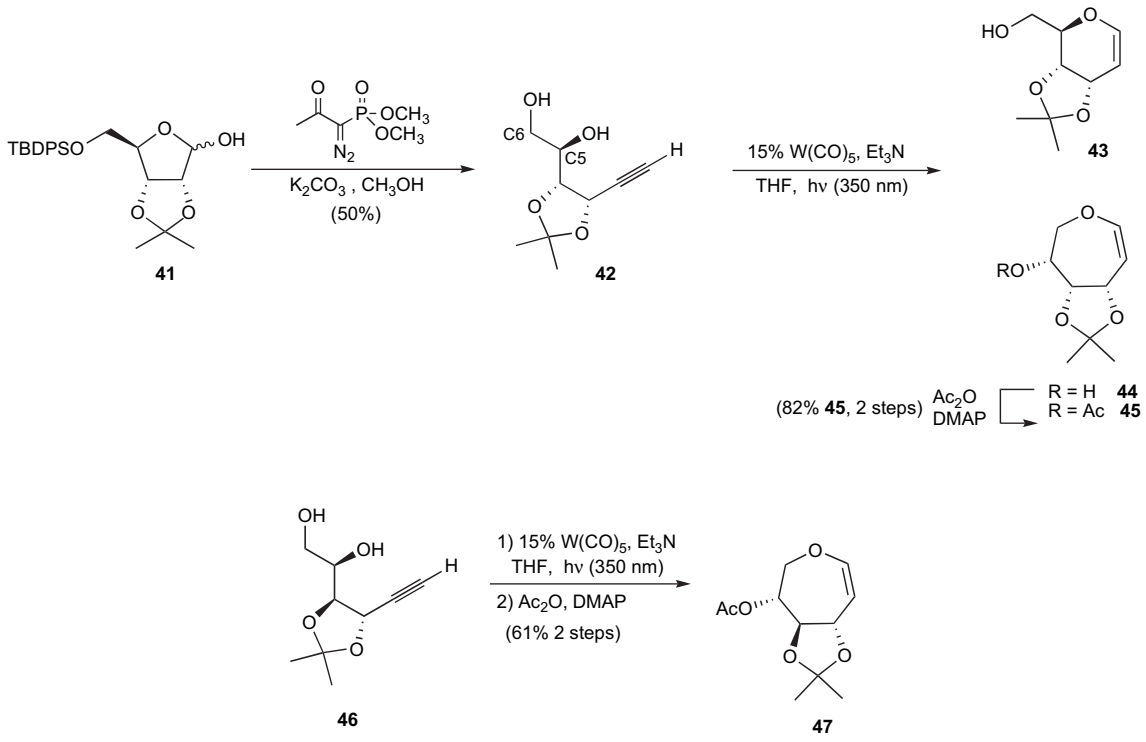
2.3.1. Cycloisomerization of alkynols. The transition metal-mediated isomerization of alkynols in the formation of five- and six-membered ring cyclic enol ethers has proven to be a rapid and effective way for preparing these useful materials.[30–32] The initial step in these reactions is the formation of a metal (ruthenium, rhodium, molybdenum, tungsten) vinylidene species[33] that undergoes intramolecular cyclization by an oxygen nucleophile. Under anaerobic conditions, formation of the metal vinylidene ensures *endo* attack on the erstwhile alkyne in forming a metal oxacarbene, which reductively eliminates to form the corresponding cyclic enol ether (Scheme 8).

This cycloisomerization strategy was recently extended to the preparation of oxepines from furanose-derived alkynols.[34] The synthesis of the alkynol precursor and the cyclization are shown in Scheme 9. Furanose lactol **41** was converted to the alkynol **42** via a modified Seyferth–Gilbert homologation;[35] the TBDPS group was removed under these reaction conditions. Cycloisomerization of **42** was originally expected to deliver a glycal such as **43** based on the rationale that 6-*endo* attack (at C5) would be preferred. However, a preference for the 7-*endo* (at C6) product **44** was observed. The hydroxy-oxepine was routinely acetylated in this study as it was found to be more stable and amenable to purification. The yield for the two-step sequence of cycloisomerization and acetylation was 82%. The acetonide protecting group on the C3 and C4 hydroxyls was shown to be necessary for cyclization to be observed. It likely contributes to the preorganization of the starting alkynol in a way that is favorable to cyclization. A subtle dependence on the orientation of the C3/C4 acetonide where the trans disposition leads to slightly lower yield (61% for conversion of **46** to **47**, Scheme 9) relative to the *cis*-oriented acetonides was noted.

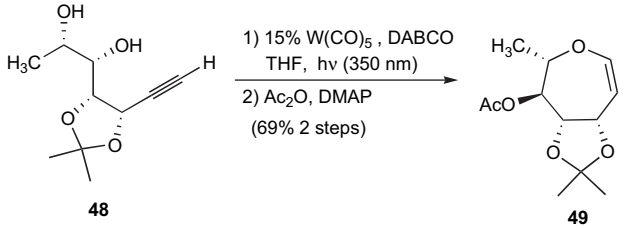
Additionally, the authors demonstrated that oxepine formation was not merely due to the greater nucleophilicity of the primary hydroxyl group (C6) over the secondary hydroxyl group (C5). This was shown by efficiently converting **48** to **49** under essentially the same reaction conditions (Scheme 10). For cyclization precursor **48**, both the hydroxyls giving rise to the 6-*endo* product and the 7-*endo* product were secondary alcohols, but cyclization occurred to preferentially form the oxepine **49** (61%).



Scheme 8.



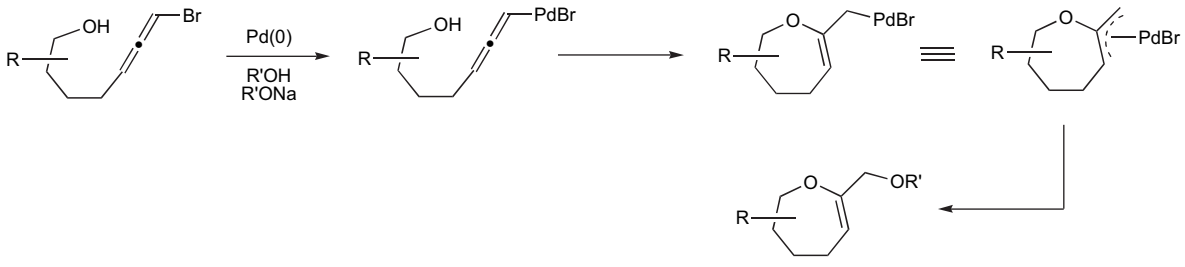
Scheme 9.



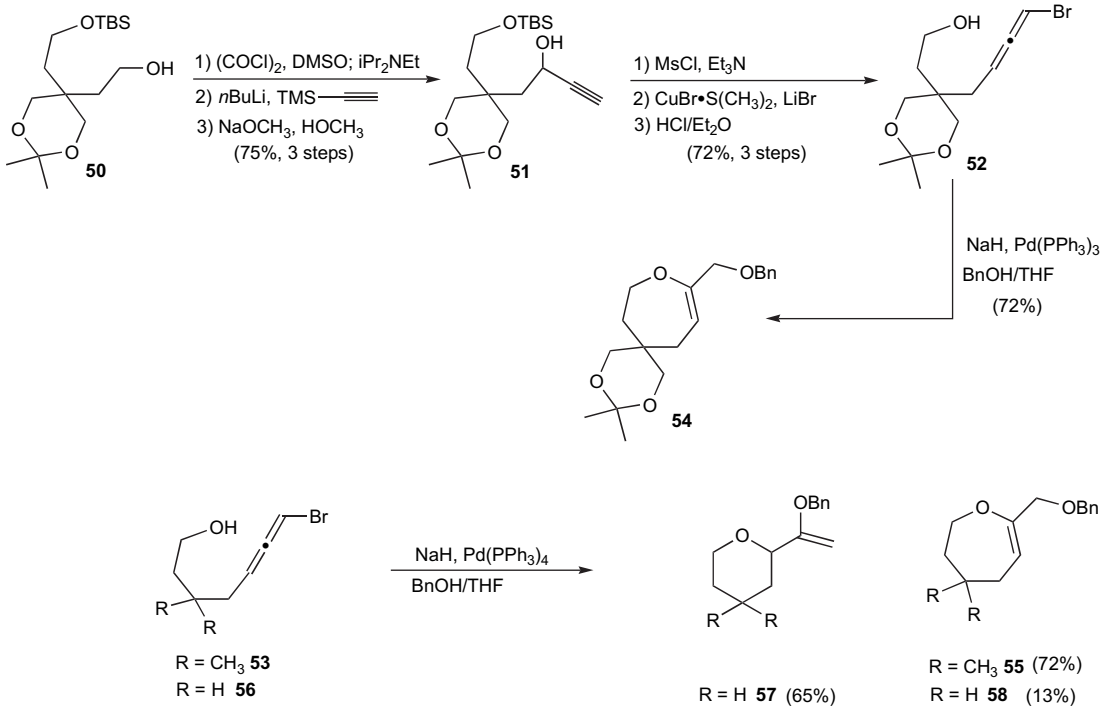
Scheme 10.

2.3.2. Pd(0) cyclization of bromoallenes. The palladium(0)-mediated allylic substitution reaction (Tsuji–Trost) is a versatile method for the formation of carbon–carbon and carbon–heteroatom bonds. Formation of a cationic π-allyl palladium complex is a key intermediate in these reactions; the π-allyl palladium species, therefore, can be considered to be functionally equivalent to an allyl cation because it is susceptible to nucleophilic attack. Palladium(0)-mediated reactions of bromoallenes[36,37] have been shown to have reactivity that is equivalent to allyl dications (Scheme 11). That is, they can be attacked sequentially by two nucleophiles to give a substituted allylic product rather than by one nucleophile as is the case in the allylic systems. Attack on the central carbon of the allene moiety occurs first to give a π-allyl palladium complex, which is then attacked by the second nucleophile to give the substituted allylic system. As shown in Scheme 11, the inclusion of an intramolecular nucleophile (the first nucleophile in this case) allows for cyclization to occur.

Bromoallene **52** (Scheme 12) was accessed through a five-step sequence from alcohol **50**. Swern oxidation of **50** followed by trimethylsilyl acetylene addition and removal of the TMS group gave propargyl alcohol **51**. Sulfonation, formation of the bromoallene functionality, and TBS deprotection gave cyclization precursor **52**. Using the same sequence, the related bromoallene **53** was also prepared. Treating **52** or **53** to reaction conditions of NaH and benzyl alcohol in the presence of $Pd(PPh_3)_4$ gave the substituted methyleneoxy oxepines **54** and **55** in 72% yield in both cases.[38] The ordering of nucleophiles in this reaction follows that outlined in Scheme 11. That is, intramolecular attack of the hydroxyl group is first, which forms the intermediate cyclic π-allyl palladium complex. Subsequent intermolecular attack by benzyl oxide on the π-allyl palladium complex provides the benzyloxymethyl substituted oxepine products.



Scheme 11.



Scheme 12.

The product distribution in this reaction depended on the substitution of the tether between the nucleophile and the bromoallene. In contrast to substituted bromoallenes **52** and **53**, precursor **56** preferentially formed dihydropyran **57** (65%) over the oxepine **58** (13%). The dihydropyran arises because intermolecular attack by benzyl oxide to form an acyclic π-allyl palladium complex predominates over intramolecular attack by the internal hydroxyl group. While a rationale to explain these results is currently incomplete, preorganization of the acyclic bromoallene precursors is presumably a key factor for oxepine formation by this route. Nonetheless, the potential for application of this strategy in the preparation of related oxepines is apparent.

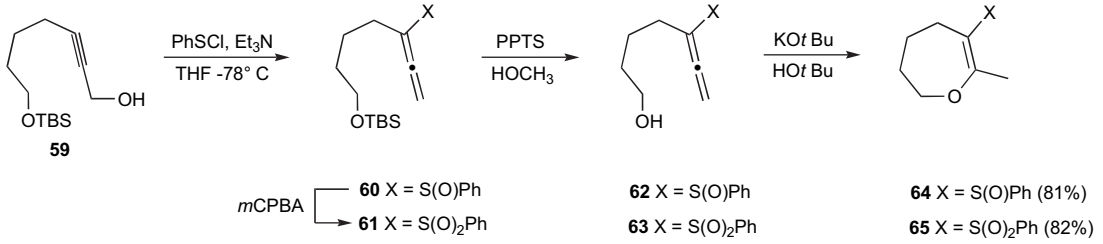
2.4. Cyclization of allenyl sulfoxides and sulfones

The reported cyclization of allenyl sulfoxides **62** and sulfones **63** shown in Scheme 13 is a cycloisomerization that is mechanistically related to the palladium-mediated cyclization of bromoallenes just discussed.[39] A [2,3]-sigmatropic rearrangement of the phenylsulfenyl ether derived from TBS protected 2-octyn-diol (**59**) and phenylsulfenyl chloride gave allenyl sulfoxide **60**. Removal of the TBS group under acidic conditions gave **62**. The allenyl sulfone precursor **63** for cyclization was prepared from sulfoxide **60** via oxidation with *m*CPBA to give **61** followed by desilylation. Under basic conditions, intramolecular attack on the central carbon of activated allenes **62** and **63** cleanly delivered the 1-methyl-2-sulfinyl oxepine **64** (81%) or 1-methyl-2-sulfonyl oxepine **65** (85%) in good yields. Formation of the related five-, six-, and eight-membered cyclic enol ethers using this strategy were also presented in the report.

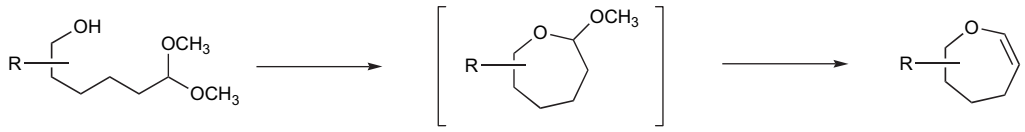
2.5. Cyclization and elimination of hydroxy-acetals

Formation of a mixed, seven-membered ring acetal from an acyclic hydroxy-acetal followed by elimination of a second equivalent of alcohol gives rise to a cyclic enol ether oxepine (Scheme 14).[40] As mentioned previously, a sequence of cyclic enol ether formation, epoxidation, and nucleophilic attack has been successfully utilized by Rainier and coworkers in the synthesis of fused polycyclic ethers.[9] The sequence is especially attractive because it can be conducted in an iterative fashion to construct ladder toxin structures.

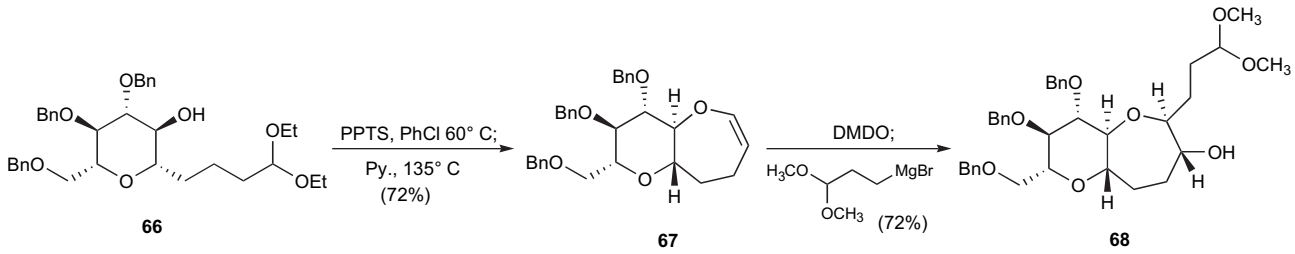
Both the cyclization–elimination strategy for oxepine formation and the iterative assembly of fused polycyclic ethers are illustrated using the model system depicted in Scheme 15.[10]



Scheme 13.



Scheme 14.



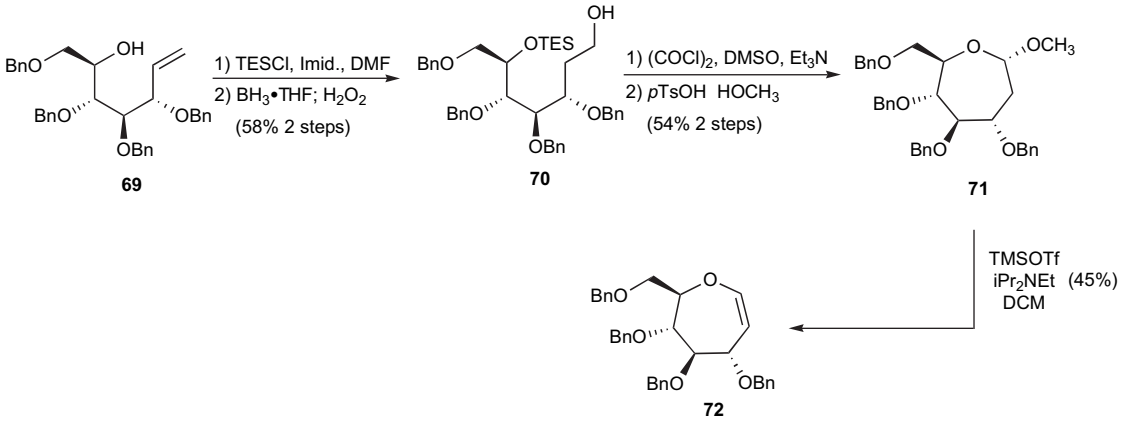
Scheme 15.

Diethyl-acetal **66** was prepared by cuprate addition to the 1,2-anhydro-sugar derivative from benzyl glucal. Cyclization of **66** occurred using PPTS in chlorobenzene; the product of this reaction is a cyclic mixed acetal analogous to the intermediate structure shown in Scheme 14. Elimination of this mixed acetal is accomplished by addition of pyridine and by increasing the temperature of the reaction. Oxepine **67** is formed in 72% yield over this two-step, one pot sequence. The product oxepine can then be functionalized in a similar manner giving rise to the iterative nature of the approach. Treatment of **67** with dimethyldioxirane (DMDO) followed by the attack of Grignard reagent delivers another hydroxy-acetal **68**, which can then undergo subsequent cyclization.

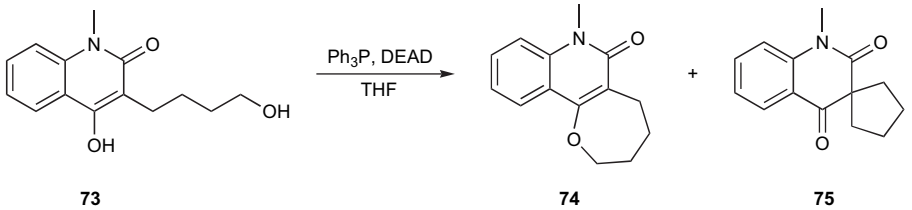
Peczuh and Castro have utilized the same strategy but in a stepwise approach for the formation of carbohydrate-based oxepines (Scheme 16).[41] Heptenitol **69**, prepared from tetra-benzyl glucose via Wittig olefination, was used to prepare glucose-based oxepine **72** in a five-step process. The C6 hydroxyl group of **69** was protected as the TES ether, and then the alkene was converted to alcohol **70** by hydroboration and oxidation. This alcohol was then oxidized to the aldehyde and treated to tosic acid in methanol. The sequence provided the cyclic mixed acetal **71** directly (54%, two steps) along with the acyclic hydroxy-acetal (11%). Mixed acetal was then converted to oxepine **72** by elimination under Gassman conditions in modest (45%) yield. The sequence is of somewhat limited scope based on the nature of the starting heptenitol (or the corresponding pyranose), but it has the advantage of being easily scalable.

2.6. Mitsunobu approach to aryl-oxepines

A Mitsunobu based cyclization has recently been reported in the synthesis of a quinolinone-fused oxepine (Scheme 17).[42]



Scheme 16.



Scheme 17.

Starting from the substituted quinolinone **73**, oxepine **74** formation (23%) competed with a spirocyclization through the α-carbon to form **75** (31%). It is unclear whether this result is from the pK_as of the respective oxygen and carbon moieties, the size of the ring formed, or a combination of these factors. The route may be applicable to other β-keto fused oxepines, making it an attractive disconnection in the preparation of aryl-oxepines such as janoxepin (**10**) and oxepinamide (**11**).

3. Cyclization via C–C bond formation

As may be expected, ring closing metathesis dominates the C–C bond forming annulation strategies to be presented. Included in this treatment will be the recent advances with ene–yne and ring rearrangement metatheses reactions. New approaches for the preparation of oxepines such as palladium-catalyzed inter- and intramolecular couplings and the anionic cyclization of glycidyl ethers will also be presented. A number of important strategies that include intramolecular Wittig[43] and Horner–Wadsworth–Emmons olefinations,[44] acetal–alkene (Prins),[45] and alkyne[46] cyclizations, and sigmatropic rearrangements[47] have been discussed in previous reviews without significant new developments.

3.1. Metal-mediated cyclizations

3.1.1. Ring closing metathesis (RCM). Recent progress in the development of organometallic catalysts for ring closing metathesis (RCM) has provided researchers with a new and convenient tool for the synthesis of medium-sized rings. The power of the RCM approach for the synthesis of oxepines, or rings containing a double bond generally, is that the disconnection is simple. It quickly defines an acyclic target structure that will provide the desired oxepine. On top of this strategic facility is the proven reactivity of a number of RCM catalysts in systems with complex functionality. These factors weigh heavily in the continued utilization of RCM as a method for the preparation of all rings including oxepines. It is worth noting that RCM is the only method that has been used to generate all three types of oxepines **15**–**17**.

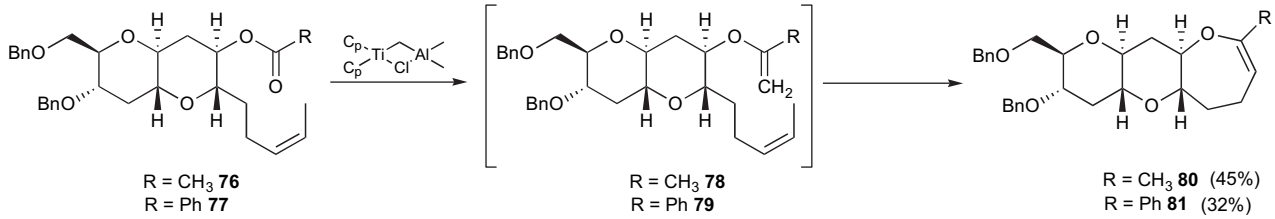
One of the first preparations of substituted oxepines of type **17** (Fig. 2) was reported by Nicolaou and co-workers.[48] These structures were inspired by the complex polyether frameworks of ciguatoxin (**1**) and brevetoxin (**2**). Olefinic esters such as **76** and **77** were subjected to methylenation using Tebbe reagent ($(Cp)_2TiCH_2ClAl(CH_3)_2$) (Scheme 18) to produce the corresponding vinyl ethers **78** and **79**. The vinyl ether intermediates were not isolated, but reacted with a second equivalent of Tebbe reagent in situ to provide oxepines **80** and **81** in 45 and 32% yields, respectively. The titanium-mediated metathesis is a key for this tandem transformation. The approach is attractive because of the ability to vary the alkyl group attached at C1 of the oxepine in the acylation step. A number of different substrates with various substituents were employed to construct six- and seven-membered ring cyclic enol ethers showing the utility of this methodology.

As presented previously, the formation of cyclic enol ethers (including oxepines) followed by epoxidation and nucleophilic attack sets up a sequence for the building of polycyclic ethers such as **1**–**3** in an iterative fashion.[11] Access to cyclic enol ether oxepines **17** in Section 2.5 was through the cyclization and elimination of hydroxy-acetals. Rainier and co-workers[10,49] have also developed an RCM approach for the synthesis of substituted cyclic enol ethers that could be used to prepare the fused polycyclic ethers. This methodology was used to prepare *C*-glycosides that could serve as the asymmetric ring junctures of the ladder polyether structures of brevetoxin (**2**) and gambierol (**3**).

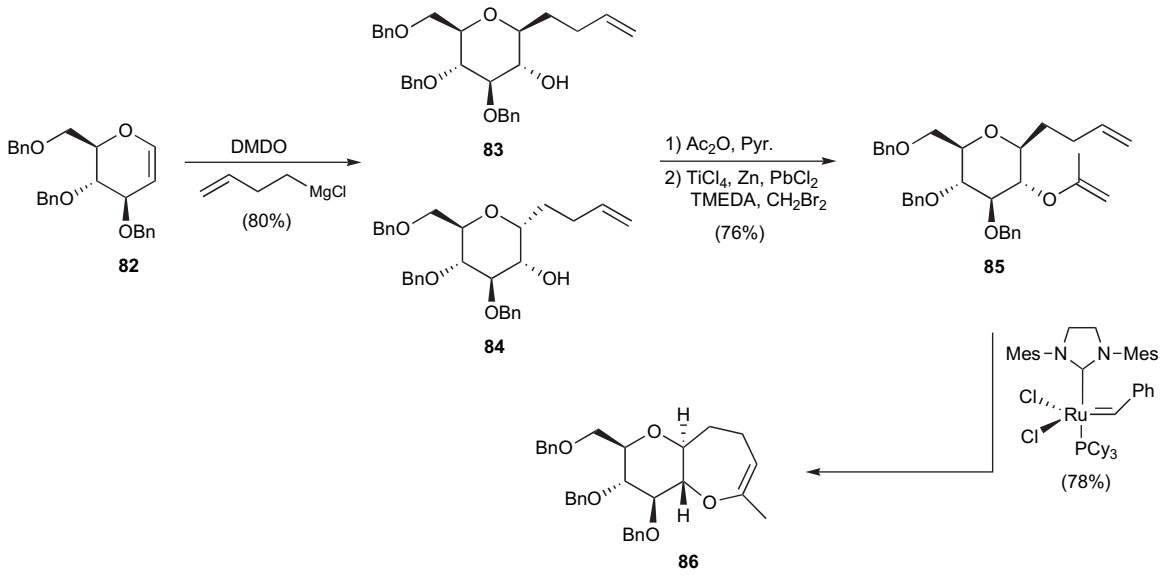
An example of this strategy is outlined in Scheme 19. Epoxidation of tri-*O*-benzyl-D-glucal (**82**) with DMDO, followed by subsequent addition of homoallylmagnesium chloride provided a 1:1 ratio of *C*-glycosides **83** and **84** in 80% yield. Acetylation of the free hydroxyl group of **83**, followed by methylenation using the Takai protocol provided metathesis precursor **85**. Ring closing metathesis of **85** using Grubbs' second generation catalyst gave the corresponding oxepine **86** in 78% yield. Note that the bicyclic oxepine **86** is now prepared for a subsequent iteration of epoxidation, nucleophilic attack, and cyclization to continue the growth of the fused polycyclic ether.

A route to unsubstituted cyclic enol ether **88** using Grubbs' first generation catalyst was recently reported by Cossy and co-workers.[44c] The authors first described the synthesis of diene **87** from 1,4-butane diol in 15 steps. Diene **87** was then subjected to ring closing metathesis using Grubbs' first generation catalyst to afford the enol ether oxepine **88** in 70% yield (Scheme 20). A related oxepine bearing a THP group in place of the TBDPS group of **88** was a key intermediate in an earlier synthesis of zoapatanol (**90**).[50] Attempts of hydroboration–oxidation followed by oxidation of the resulting alcohol under conditions that were reported in the earlier system failed to produce oxepanone **89**. The utility of oxepines as intermediates in the synthesis of complex natural (and unnatural) products is still apparent, however, from this strategy.

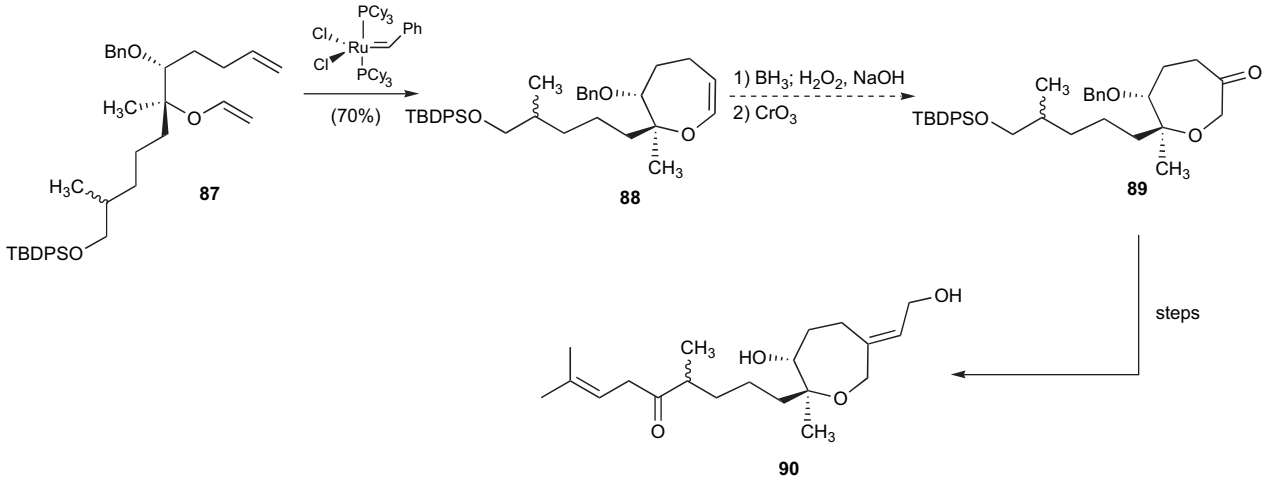
Peczuh[51] reported a ring closing metathesis method for synthesizing carbohydrate-based oxepines with functional equivalence to glycals. Glycals are unsubstituted cyclic enol ethers that are known to serve as glycosyl donors in



Scheme 18.

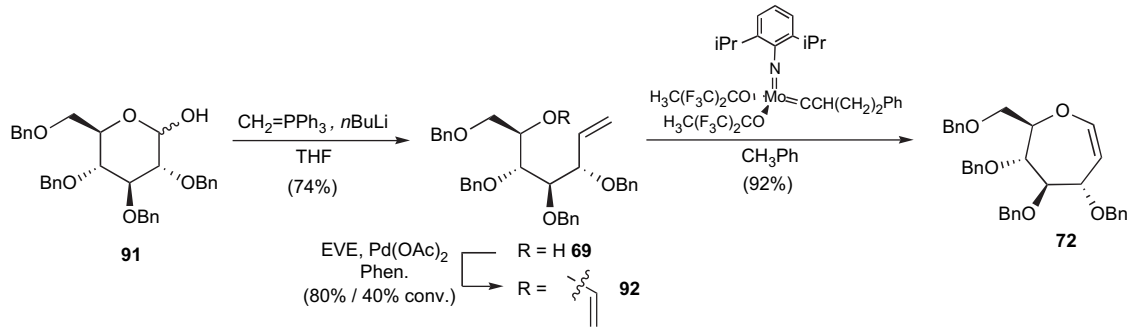


Scheme 19.



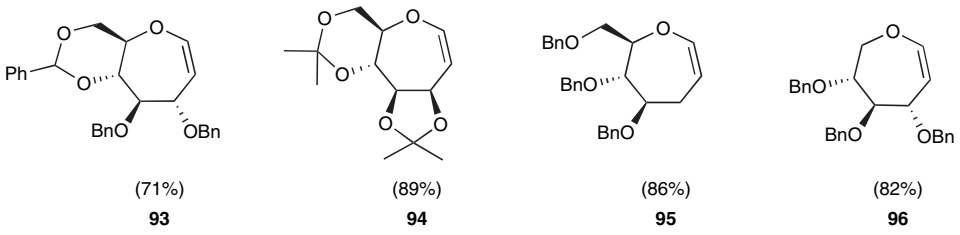
Scheme 20.

a number of glycosylation reactions[52] and can be selectively substituted through a number of processes to afford 2-oxo, 2-amino, and 2-iodo sugars with various groups positioned at the anomeric carbon C-1. Scheme 21 illustrates the three-step synthesis using readily available 2,3,4,5-tetra-*O*-benzyl-D-glucose (**91**). Wittig olefination of **91** revealed the C5 hydroxyl group of **69** and made it available for further functionalization. Vinyl ether formation using conditions involving Pd(II) in the presence of phenanthroline and ethyl vinyl ether provided enol ether **92**. Enol ether **92** was then subjected to ring closing metathesis conditions using Schrock catalyst to give oxepine **72** in 92% yield.



Scheme 21.

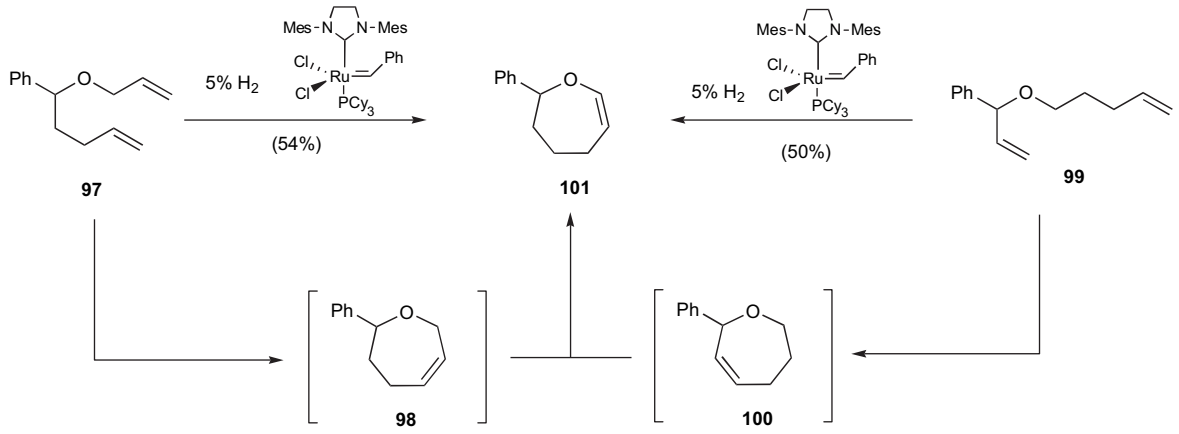
A number of carbohydrate-based oxepines with various protecting groups and sites of deoxygenation proved amenable to this approach, giving RCM yields using Schrock catalyst of 71–92%. These seven-membered ring cyclic enol ethers were derived from readily available 4,6-*O*-benzylidiene-2,3-di-*O*-benzyl-D-glucose **93**, 2,3:4,6 diacetonide-D-mannose **94**, 3,4,6-tri-*O*-benzyl-2-deoxy-D-glucose **95**, and 2,3,4-tri-*O*-benzyl-D-xylose **96** pyranosides and have been used to access a number of important septanosides.[53] Unlike the previous examples (Schemes 19 and 20), oxepine formation using either of the Grubbs' catalysts from the carbohydrate-based dienes gave consistently poor results (yields ranged from 0 to 25% for **72**, **93**–**96**). The low yields were explained based on steric and electronic arguments.[51,54,55] Reaction of the ruthenium catalysts with the enol ether forms a relatively unreactive ruthenium alkylidene. For dienes such as **85** and **87**, the alkene double bond is sterically accessible; this allows loading of the ruthenium on the alkene carbon followed by subsequent cyclization to form the enol ether oxepines. Rigidified diene precursors, afforded by benzylidene or acetonide protecting groups, showed improved RCM yields using ruthenium catalysts.



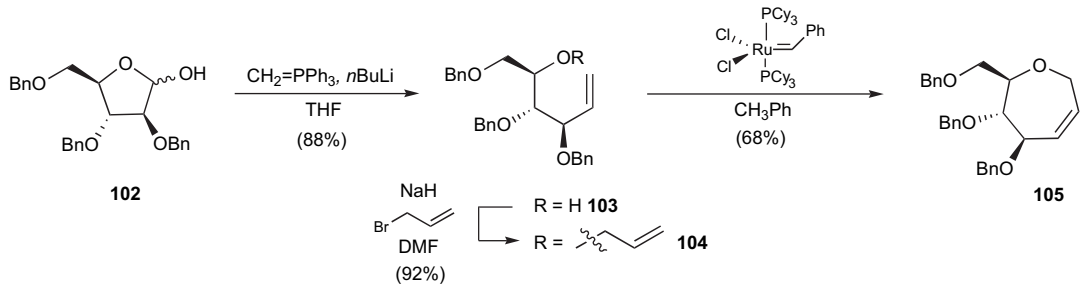
In the previous examples of enol ether oxepine (**17**) synthesis, the diene precursor consisted of an alkene and a vinyl ether. An alternative approach toward the synthesis of cyclic enol ethers has been reported by Snapper and co-workers. It entails a tandem reaction where RCM of two alkenes followed by ruthenium hydride-mediated double bond migration forms the cyclic enol ether.[56] Scheme 22 outlines the preparation of oxepine **101** via two different dienes, **97** and **99**. The reaction utilized Grubbs' second generation catalyst in the presence of 5% H_2. The H_2 facilitated the formation of a ruthenium hydride species, which is essential for double bond migration. Diene **97** initially formed oxepine **98** while **99** formed oxepine **100**. Both **98** and **100** isomerized to form the less substituted oxepine **101** under the reaction conditions in 54 and 50% overall yields, respectively. The trisubstituted oxepine (with C1 having the phenyl substituent) was not observed; the authors suggested that this product was disfavored based on sterics.

van Boom and co-workers[57] utilized one of the first ring closing metathesis routes to access carbohydrate-based oxepines of type **16** (Fig. 2). Wittig olefination of 2,3,5-tri-*O*-benzyl-D-arabinofuranose (**102**) produced the corresponding olefin **103** and revealed C4 for further functionalization (Scheme 23). Allylation of the free hydroxyl using allyl bromide to give **104** followed by ring closing metathesis using Grubbs' first generation catalyst produced oxepine **105** in 68% yield. In order to show the utility of this technique, furanose derivatives were designed that varied both the stereochemistry and electronics of the functional groups. These molecules were subjected to similar reaction conditions to obtain oxepines derived from 2,3,5,6-di-*O*-isopropylidene-D-mannofuranoside and 5-*O*-trityl-2,3-*O*-isopropylidene-D-ribofuranose in 99 and 85% RCM yields, respectively. The authors planned to apply the methodology toward the synthesis of oxepane-containing natural products and higher carbon sugars.[58] Sturino and co-workers[59] were also able to prepare a number of carbohydrate-based oxepines using this approach.

Jenkins and Ghosh[60] used a ring closing metathesis approach to produce enantiomerically pure annulated carbohydrate derivatives that could be used as templates to prepare a number of complex natural products via the chiron approach.



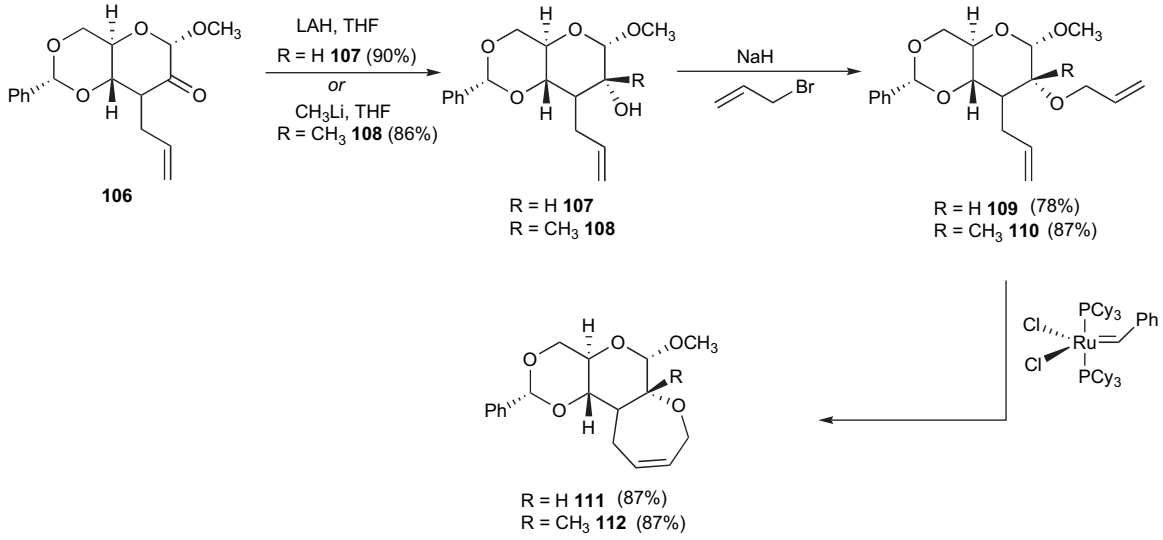
Scheme 22.



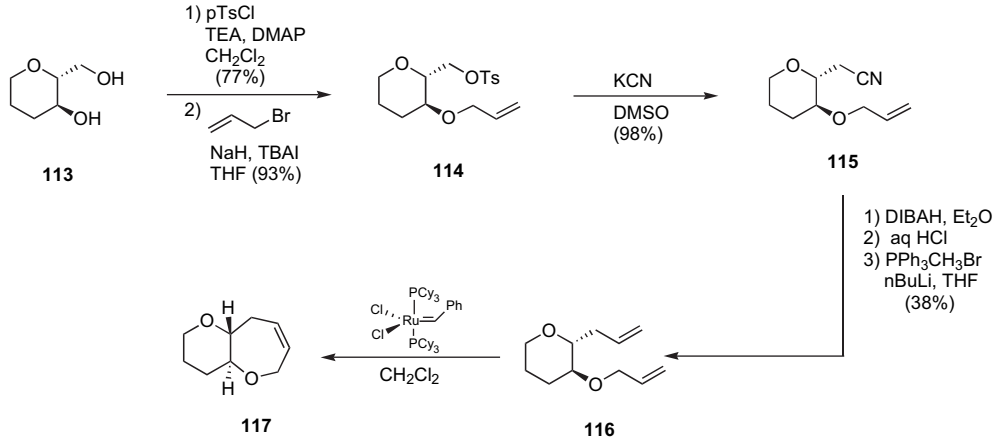
Scheme 23.

The chiron approach employs carbohydrates as chiral starting materials in the stereoselective synthesis of target molecules.[61] Their synthesis involved the addition of lithium aluminum hydride or methyl lithium to ketone **106**, which produced alcohols **107** and **108** in 90 and 86% yield, respectively (Scheme 24). Deprotonation of the alcohols using sodium hydride followed by addition of allyl bromide afforded dienes **109** and **110** in 78 and 87% yield. Upon exposure to Grubbs' first generation catalyst, dienes **109** and **110** readily cyclized to afford oxepines **111** and **112** in 87% yield. The route exemplifies the rapid access to complex 'natural product-like' structures that are afforded by RCM. Additional reactions on **111** and **112** could lead to other distinct carbon skeletons.

Martin and Delgado[62] reported the ring closing metathesis of medium-sized oxacycles in the preparation of trans-fused polyoxygenated macrocycles such as those found in ciguatoxin (**1**) and brevetoxin (**2**). As shown in Scheme 25, treatment of **116**, prepared in five steps from (2*R*,3*S*)-2-(hydroxymethyl)-tetrahydropyran-3-ol (**113**), with a catalytic amount of Grubbs' first generation catalyst resulted in the formation



Scheme 24.



Scheme 25.

of oxepine **117** in greater than 95% yield. The authors' attempts to assay the scope and limitations of this methodology revealed that the ruthenium-catalyzed ring closing metathesis was more efficient for the preparation of seven- and eight-membered ring oxacycles in comparison to larger ring systems. This observation is presumably related to the increased energy required for preorganization of larger diene species prior to ring closing metathesis. The authors also noted that the cyclization for seven- and eight-membered ring oxacycles was highly effective regardless of the position of the reacting olefin. Treatment of **120**, prepared in six steps from (2*R*,3*S*)-2-(hydroxymethyl)-tetrahydropyran-3-ol (**113**), with a catalytic amount of Grubbs' first generation catalyst resulted in the formation of oxepine **121** in greater than 95% yield (Scheme 26). It is important to note that the preparation of cyclic enol ethers, where the position of the olefin is adjacent to the oxygen in the ring, was not attempted using this methodology.

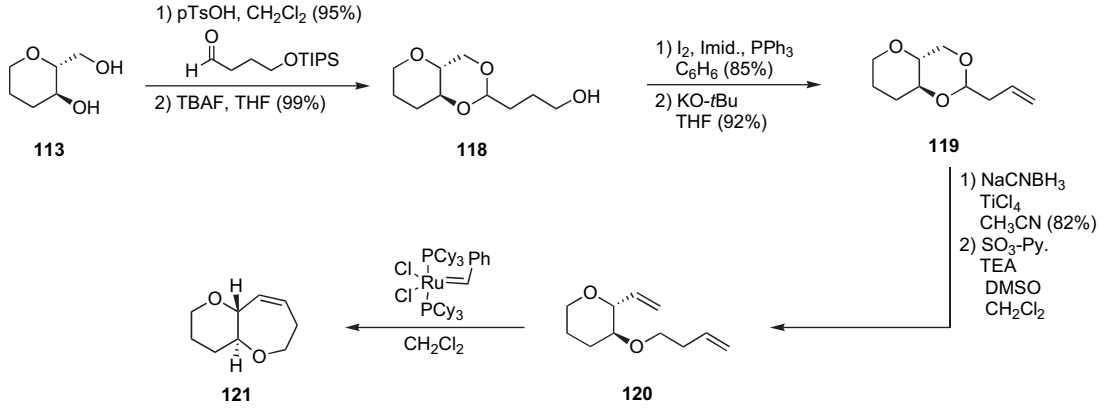
Ring closing metathesis reactions have also been used to produce oxepines of type **15**. Recently, Crimmins and DeBaillie reported the successful enantioselective total synthesis of rogioloxepane.[63] One of the key steps in their total synthesis required the cyclization of diene **123** via ruthenium-catalyzed RCM to produce the desired oxacyclic skeleton **124**. As shown in Scheme 27, production of diene **123** from racemic 1,5-hexadien-3-ol (**122**) over eight steps followed by ring closing metathesis using Grubbs' first generation catalyst gave the desired oxepine **124** in 95% yield. Rogioloxepane (**7**) was prepared from **124** in 12 additional steps.

3.1.2. Ene–yne metathesis. Clark and co-workers[64] reported one of the first successful ring closing ene–yne metathesis reactions of alkynyl ethers to form oxepines in an effort toward the preparation of gambieric acid and gambierol (**3**). Deprotonation of alcohol **125**, prepared from (*R*)-2,3-*O*-isopropylidene glyceraldehyde, followed by nucleophilic addition of the corresponding alkoxide onto 1,1,2-trichloroethene provided the corresponding enol ether **126** (Scheme 28). Base-catalyzed elimination of **126** gave the corresponding alkynyl ether **127** in good yield. Ring closing ene–yne metathesis of the alkynyl ether **127** using Grubbs' second generation catalyst provided the corresponding vinyl substituted cyclic enol ether oxepine **128** in 70% yield.

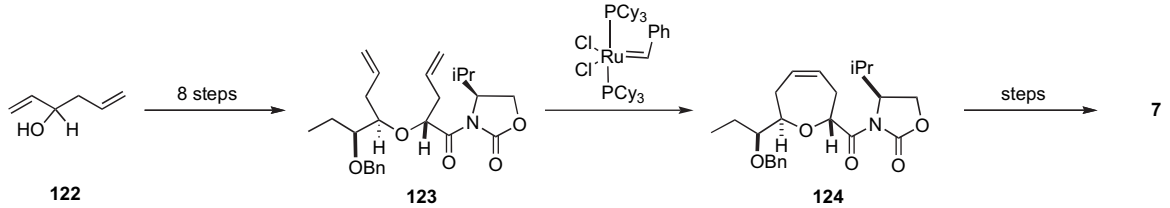
The authors also noted that the success of the ene–yne metathesis depended on the size of the group at the terminus of the alkyne. Cyclization precursor **129** showed efficient conversion to the product oxepine **131** (72%). The larger TMS substituted precursor **130**, however, failed to undergo ring closing metathesis to produce oxepine **132** using either catalyst (Grubbs' first generation or second generation catalyst) due to the inaccessibility of the alkynyl ether.

The ene–yne methodology was recently utilized by Majumdar and co-workers[65] to prepare a number of tricyclic 1,8-naphthyridinones. Examples of their synthesis are shown in Scheme 29. 3-Allyl-4-hydroxy-1,8-naphthyridinone **133**, prepared from readily available 4-allyloxy-1,8-naphthyridinone in two steps, was alkylated using propargyl bromide/chloride derivatives to provide the corresponding ene–ynes **134** and **135** (50–55%). Ring closing metathesis of **134** and **135** using Grubbs' first generation catalyst gave oxepine derivatives **135** and **136** in yields equal to or above 90%. The CH_2-*O*-aryl substitution on the alkyne in **135** in this system apparently does not inhibit cyclization; in comparison to the examples in Scheme 28, this observation suggests that the substitution on the alkyne in **135** is more like the methyl (**129**) rather than the TMS (**130**) group.

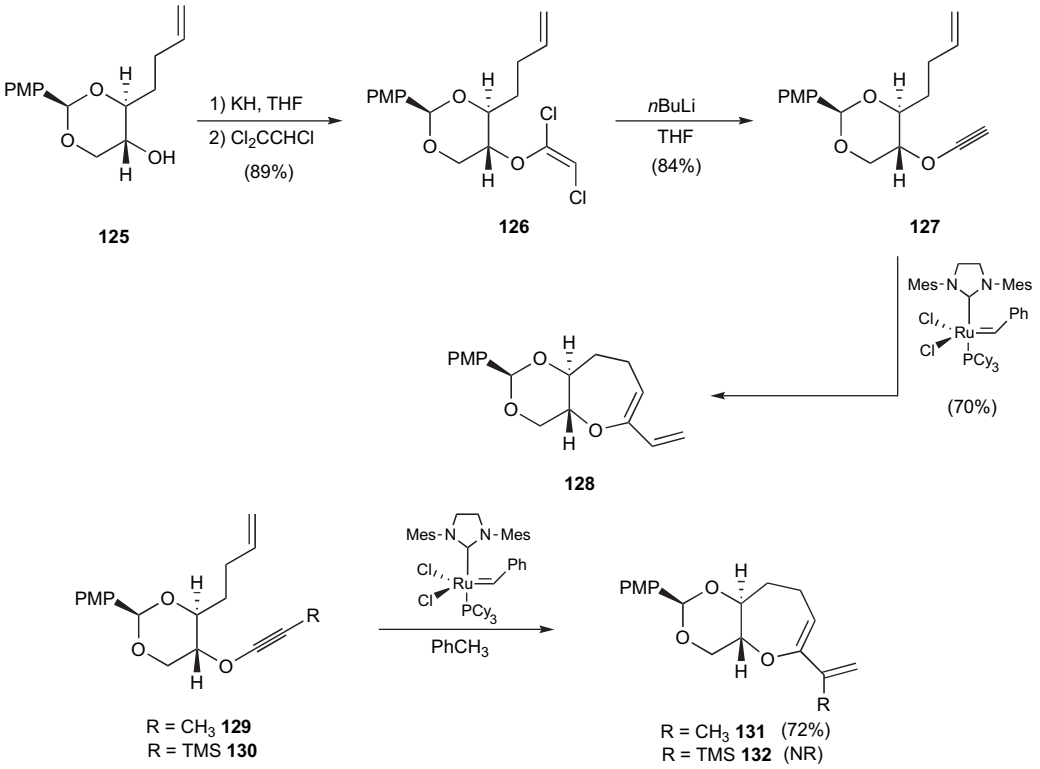
3.1.3. Ring rearrangement (ring opening–ring closing) metathesis. The first ruthenium-mediated ring rearrangement metathesis route (RRM) used to prepare oxepines



Scheme 26.



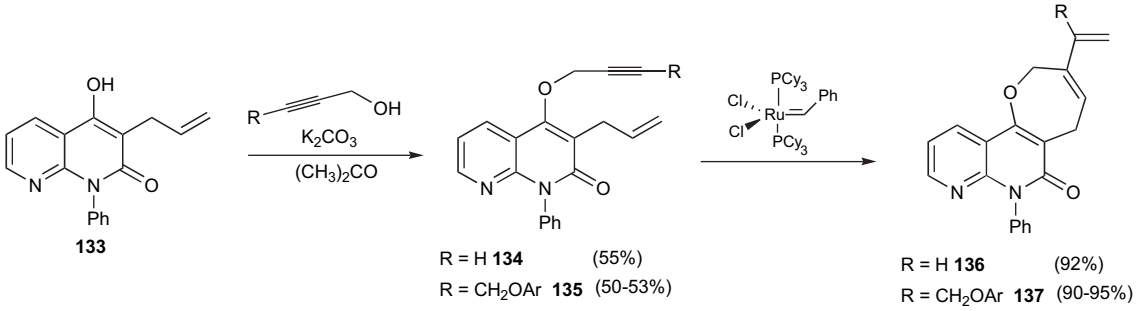
Scheme 27.



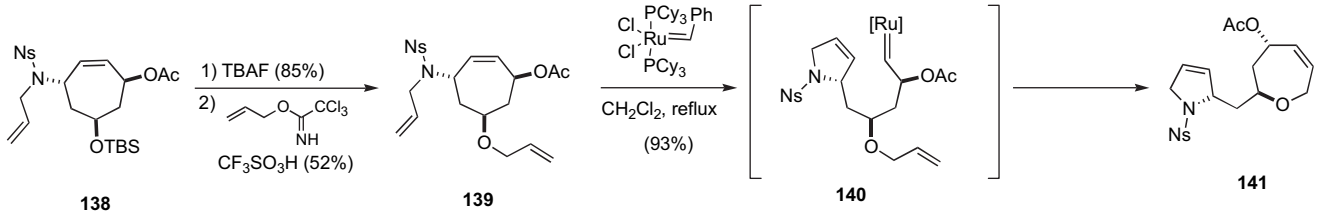
Scheme 28.

was reported by van Boom and co-workers (Scheme 30).[66] Removal of TBS protecting group of **138** with TBAF and allylation using allyl trichloroacetimidate gave the cyclization precursor **139**. The initial coordination of Grubbs' first generation catalyst to the more activated *N*-allyl alkene was followed by ring opening metathesis to give the substituted 2,5-dihydro-1*H*-pyrrole **140**. This set up the molecule for subsequent ring closing metathesis to produce the desired oxepine ring **141**. The two-step RCM process gave a yield of 93%. The authors theorized that the combined ring rearrangement metathesis reaction, which involves the liberation of ethylene as part of the reaction process, provides an additional thermodynamic sink shifting the equilibrium toward formation of the desired oxepine.

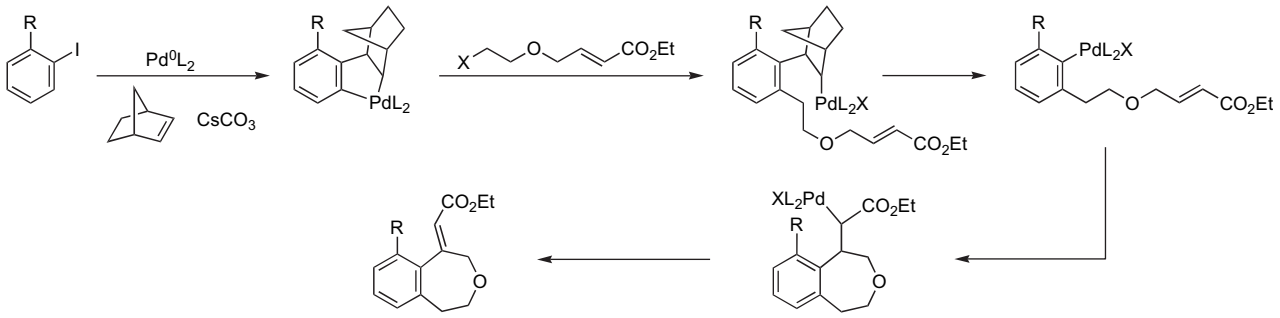
3.1.4. Palladium-catalyzed couplings. Benzoxepines have been prepared by palladium-mediated coupling of the aryl halides with activated allylic species. Although this method



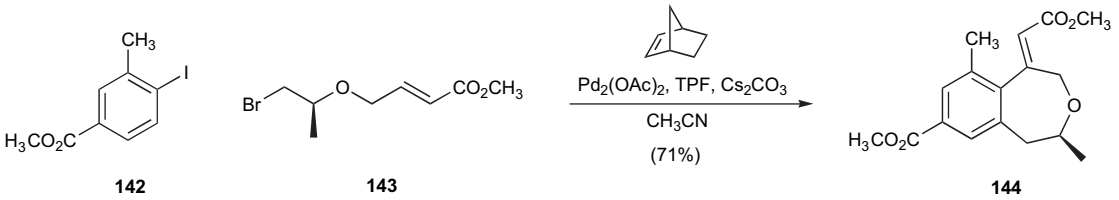
Scheme 29.



Scheme 30.



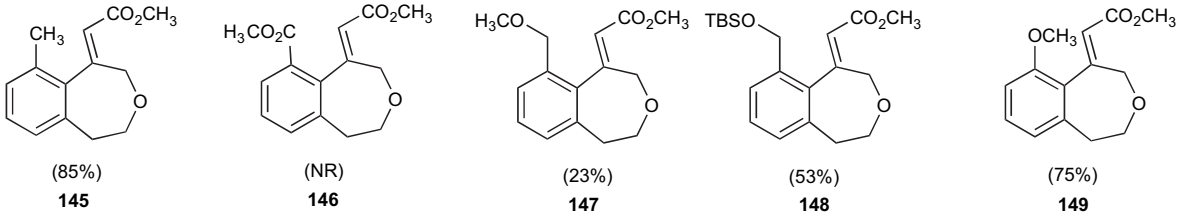
Scheme 31.



Scheme 32.

is for the preparation of 4-benzoxepines, it is added here because of its novelty and with the appreciation that the strategy could be extended to form oxepines such as **15**. The process is a palladium-mediated alkylation followed by an intramolecular alkenylation, which also constitutes the cyclization step. Scheme 31 outlines the mechanism for the transformation.[67] Oxidative addition to the aryl halide, carbopalladation of norbornene, and aryl C–H activation gives the palladacyclic species as shown. A second oxidative addition to an allyl-substituted haloethanol is followed by expulsion of norbornene to give an aryl palladium species. 1,4-Attack on the α,β-unsaturated ester and reductive elimination gives the product benzoxepine.

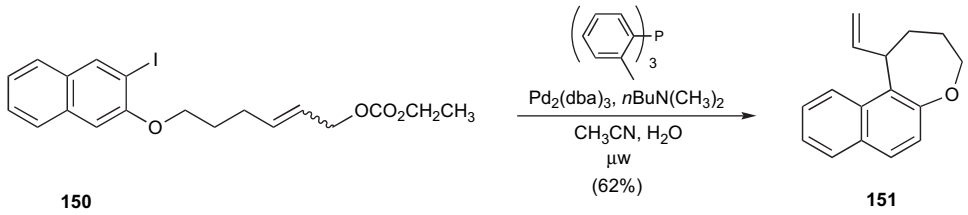
Palladium-catalyzed one pot sequential alkylation–alkenylation reactions were first reported by Lautens and co-workers in their synthesis of 2-substituted-4-benzoxepines.[68] An example of their synthesis is shown in Scheme 32. Palladium(II) acetate, trifurylphosphine, norbornene, and cesium carbonate were combined with aryl iodide **142** and ethyl bromoenoate **143** to give benzoxepine **144** in 71% yield. The effect of the 2-substituent (substituent *ortho* to iodide) in the aryl ring of the starting material was examined to evaluate the scope and limitation of this reaction. The authors noted a dramatic reduction in benzoxepine formation when the corresponding starting material was substituted with a group that could complex palladium in the intermediate aryl palladium species. This complexation inhibits further reaction through the catalytic cycle. Product benzoxepine **145**, where the 2-substituent is a methyl group serves as a reference, was formed in 85% yield. Formation of the acyl benzoxepine **146** was not observed; similarly the alkoxymethyl-substituted **147** was produced in only 23% yield. This effect was attenuated by changing the methyl group of the alkoxy group to a sterically bulkier TBS group, which disfavored complexation and gave a higher yield (53%) of the corresponding benzoxepine product **148**. The methoxy-substituted material was formed with efficiency similar to that of the original system.



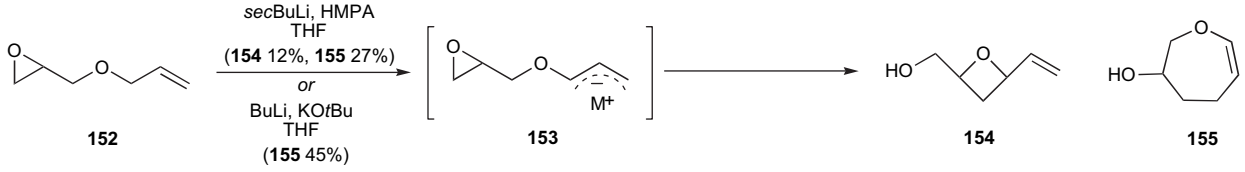
More recently, Lautens and co-workers[69] used a related palladium-catalyzed intramolecular coupling approach, coupling of aryl iodides with allyl carbonates to form five-, six-, and seven-membered ring unsaturated oxacycles with the unit of unsaturation adjacent to the ring oxygen. Seven-membered ring precursor **150** (Scheme 33) was subjected to either refluxing conditions or microwave irradiation in the presence of $Pd_2(dba)_3$, tri-*ortho*-toluyl phosphine, and *N*,*N*-dibutylmethylamine in an acetonitrile–water mixture (10:1). The resulting product **151** was prepared in 72% yield when microwave conditions were used. Refluxing provided only a 49% yield of the desired product. The authors also studied the formation of five- and six-membered ring substrates using the same reaction conditions, noting interestingly that the yields increased as the size of the ring formation increased from five- to seven-membered ring oxacycles.

3.2. Anionic isomerization of oxiranyl ethers

The base (*sec*-butyl lithium) mediated isomerization of glycidyl ether **152** to form oxetane **154** and oxepine **155** in 12

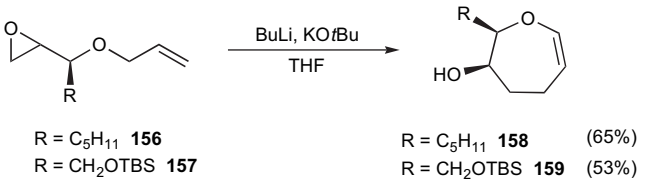


Scheme 33.



Scheme 34.

and 27% yields was reported by Ichikawa and co-workers (Scheme 34).[70] The reaction illustrates the ability of the tethered allyl anion intermediate **153**, generated via deprotonation of the allylic proton, to react at either ends of the epoxide. Attack by the interior carbon of the allylic anion on the more substituted carbon gives oxetane **154** while attack of the terminal allylic carbon on the less substituted epoxide carbon gives oxepine **155**. By switching the base in the reaction to BuLi–KO*t*Bu mixture (Schlosser's base) the formation of oxepine **155** can become the dominant mode of reaction.[71] This was attributed to the preference of the allyl potassium species (**153** where M^+ is K^+) to react at the terminal position.

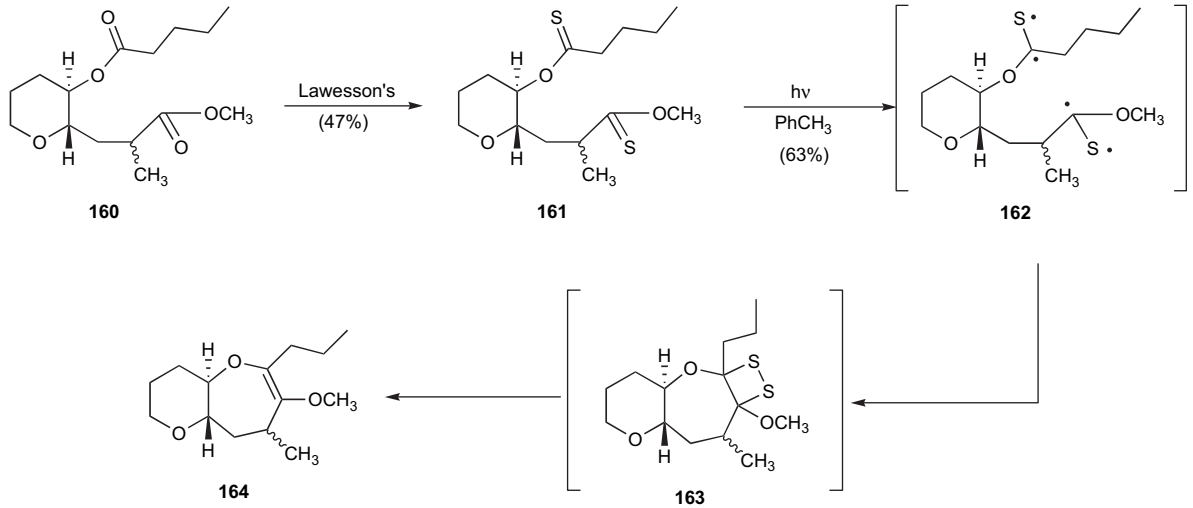


Scheme 35.

Improved yields for oxepine formation under Schlosser's base conditions from the substituted glycidyl ethers **156** and **157** were also noted. As shown in Scheme 35, cyclizations gave the corresponding oxepines **158** and **159** as the major products of the reaction in yields ranging from 53 to 65%. Glycidyl ethers **156** and **157** are homochiral and give rise to *cis*-isomers upon cyclization. However, the authors noted that the oxepines were not configurationally stable and produced a mixture of *cis*- and *trans*-isomers in deuterated chloroform.

3.3. Photochemical cyclization of bis-thioesters

Nicolaou and co-workers[72] have used the photochemical coupling of bis-thioesters to prepare oxepine intermediates in the synthesis of brevetoxin **2**. The strategy was especially attractive because one could envision it being used as a late stage connection of two complex fragments in the synthesis of the natural product. Linkage of fragments through facile ester linkages could be followed by functionalization of the thioesters and subsequent cyclization. For example, oxepine **164**, shown in Scheme 36, was prepared as a model of the D ring of brevetoxin. Diester **160** was thionated using



Scheme 36.

Lawesson's reagent to produce the dithiono system **161**. Upon exposure to UV light (450 W), **161** presumably generated the diradical **162**, which coupled to form the dithietane **163**. The dithietane expels S_2 under the reaction conditions to provide oxepine **164** in 47% yield.

4. Conclusions

The number and variety of new strategies for oxepine synthesis collected here demonstrate an increased interest in this motif as an intermediate to other oxepane or oxepine targets by synthetic chemists. The majority of these new methods give access to enol ether oxepines such as **17**. Among these, the reactions involving allenes (metal, bromo, sulfonyl) and the anionic isomerization of oxiranyl ethers provide specific examples to general themes. First, the transformations are validated by the examples given. Second, while the generality of the strategies in terms of functional group compatibility and molecular architecture has been demonstrated, careful consideration of the reaction conditions and their mechanisms may give insight into their optimization and application in a more complex setting. With increased examples of biologically active oxepines and oxepanes, and the challenge to synthesize these novel structures, it should be anticipated that the field should be active for the foreseeable future.

References and notes

1. Candenas, M. L.; Pinto, F. M.; Cintado, C. G.; Morales, E. Q.; Brouard, I.; Diaz, M. T.; Rico, M.; Rodriquez, R.; Rodriguez, R. M.; Perez, R.; Perez, R. L.; Martin, J. D. *Tetrahedron* **2002**, *58*, 1921–1924.
2. Venkateswarlu, Y.; Reddy, M. V. R.; Ramesh, P.; Rao, J. V. *Indian J. Chem., Sect. B* **1999**, *38*, 254–256.
3. Edrada, R. A.; Proksch, P.; Wray, V.; Witte, L.; Ofwegen, L. *J. Nat. Prod.* **1998**, *61*, 358–361.
4. (a) Elliott, M. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2301–2323; (b) Elliott, M. C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1291–1318; (c) Elliott, M. C. *Contemp. Org. Synth.* **1994**, 457–474.
5. Hoberg, J. O. *Tetrahedron* **1998**, *54*, 12631–12670.
6. Olivera, R.; San Martin, R.; Churruca, F.; Domínguez, E. *Org. Prep. Proced. Int.* **2004**, *16*, 297–330.
7. (a) Powell, W. H. *Pure Appl. Chem.* **1983**, *55*, 409–416; (b) *Can. J. Chem.* **1989**, *67*, v–viii; (c) For WWW version prepared by Marsh, G. P., see: http://www.chem.qmul.ac.uk/iupac/hetero/HW.html.
8. Van Altena, I. A.; Butler, A. J.; Dunne, S. J. *J. Nat. Prod.* **1999**, *62*, 1154–1157.
9. (a) Rainier, J. D.; Allwein, S. P. *Tetrahedron Lett.* **1998**, *39*, 9601–9604; (b) Rainier, J. D.; Allwein, S. P. *J. Org. Chem.* **1998**, *63*, 5310–5311.
10. Allwein, S. P.; Cox, J. M.; Howard, B. E.; Johnson, H. W. B.; Rainier, J. D. *Tetrahedron* **2002**, *58*, 1997–2009.
11. (a) Majumder, U.; Cox, J. M.; Rainier, J. D. *Org. Lett.* **2003**, *5*, 913–916; (b) Rainier, J. D.; Allwein, S. P.; Cox, J. M. *J. Org. Chem.* **2001**, *66*, 1380–1386; (c) Rainier, J. D.; Allwein, S. P.; Cox, J. M. *Org. Lett.* **2000**, *2*, 231–234.
12. Escher, S.; Niclass, Y. *Helv. Chim. Acta* **1991**, *74*, 179–188.
13. Brunel, Y.; Rousseau, G. *J. Org. Chem.* **1996**, *61*, 5793–5800.
14. Fuwa, H.; Fujikawa, S.; Tachibana, K.; Takakura, H.; Sasaki, M. *Tetrahedron Lett.* **2004**, *45*, 4795–4799.
15. (a) Fujiwara, K.; Mishima, H.; Amano, A.; Tokiwano, T.; Murai, A. *Tetrahedron Lett.* **1998**, *39*, 393–396.
16. Oka, T.; Fujiwara, K.; Murai, A. *Tetrahedron* **1998**, *54*, 21–44.
17. Suzuki, T.; Matsumura, R.; Oku, K.-I.; Taguchi, K.; Hagiwara, H.; Hoshi, T.; Ando, M. *Tetrahedron Lett.* **2001**, *42*, 65–67.
18. Matsumura, R.; Suzuki, T.; Hagiwara, H.; Hoshi, T.; Ando, M. *Tetrahedron Lett.* **2001**, *42*, 1543–1546.
19. Matsumura, R.; Suzuki, T.; Sao, K.; Inotsume, T.; Hagiwara, H.; Hoshi, T.; Kamat, V. P.; Ando, M. *Tetrahedron Lett.* **2000**, *41*, 7697–7700.
20. Matsumura, R.; Suzuki, T.; Sato, K.; Oku, K.-I.; Hagiwara, H.; Hoshi, T.; Ando, M.; Kamat, V. P. *Tetrahedron Lett.* **2000**, *41*, 7701–7704.
21. Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207–214.
22. (a) Saeeng, R.; Isobe, M. *Tetrahedron Lett.* **1999**, *40*, 1911–1914; (b) Hosokawa, S.; Isobe, M. *J. Org. Chem.* **1999**, *64*, 37–48; (c) Hosokawa, S.; Isobe, M. *Synlett* **1995**, 1179–1180; (d) Tanaka, S.; Isobe, M. *Tetrahedron Lett.* **1994**, *35*, 7801–7804.
23. Kira, K.; Isobe, M. *Tetrahedron Lett.* **2000**, *41*, 5951–5955.
24. (a) Kira, K.; Hamajima, A.; Isobe, M. *Tetrahedron* **2002**, *58*, 1875–1888; (b) Kira, K.; Isobe, M. *Tetrahedron Lett.* **2001**, *42*, 2821–2824.
25. Baba, T.; Huang, G.; Isobe, M. *Tetrahedron* **2003**, *59*, 6851–6872.
26. Hosokawa, S.; Isobe, M. *Tetrahedron Lett.* **1998**, *39*, 2609–2612.
27. Palazon, J. M.; Martin, V. S. *Tetrahedron Lett.* **1995**, *36*, 3549–3552.
28. Diaz, D. D.; Betancourt, J. M.; Crisostomo, F. R. P.; Martin, T.; Martin, V. S. *Tetrahedron* **2002**, *58*, 1913–1919.
29. Diaz, D.; Martin, V. S. *Org. Lett.* **2000**, *2*, 335–337.
30. (a) McDonald, F. E.; Reddy, K. S.; Diaz, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4304–4309; (b) McDonald, F. E.; Zhu, H. Y. H. *J. Am. Chem. Soc.* **1998**, *120*, 4246–4247; (c) McDonald, F. E.; Gleason, M. M. *J. Am. Chem. Soc.* **1996**, *118*, 6648–6659; (d) McDonald, F. E.; Bowman, J. L. *Tetrahedron Lett.* **1996**, *37*, 4675–4678.
31. Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 2528–2533.
32. Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **2003**, *125*, 7482–7483.
33. Bruneau, C.; Dixneuf, P. H. *Acc. Chem. Res.* **1999**, *32*, 311–323.
34. Alcazar, E.; Pletcher, J. M.; McDonald, F. E. *Org. Lett.* **2004**, *6*, 3877–3880.
35. Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379–1386.
36. Propargylic carbonates are also equivalent to allyl dications. See: Yoshida, M.; Fujita, M.; Ihara, M. *Org. Lett.* **2003**, *5*, 3325–3327.
37. Ohno, H.; Hamaguchi, H.; Ohata, M.; Tanaka, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 1749–1753.
38. Ohno, H.; Hamaguchi, H.; Ohata, M.; Kosaka, S.; Tanaka, T. *J. Am. Chem. Soc.* **2004**, *126*, 8744–8754.
39. Mukai, C.; Yamashita, H.; Hanaoka, M. *Org. Lett.* **2001**, *3*, 3385–3387.
40. This strategy was originally used to form five-membered cyclic enol ethers rings. See: Corey, E. J.; Kang, M.; Desai, M. C.; Ghosh, A. K.; Houpis, J. N. *J. Am. Chem. Soc.* **1988**, *110*, 649–651.

41. Castro, S.; Peczuh, M. W. *J. Org. Chem.* **2005**, *70*, 3312–3315.
42. Coppola, G. M. *Synth. Commun.* **2004**, *34*, 3381–3387.
43. Bestman, H. J.; Pichl, R.; Zimmerman, R. *Chem. Ber.* **1993**, *115*, 725–731.
44. (a) Moody, C. J.; Sie, E.-R. H. B.; Kulagowski, J. J. *Tetrahedron Lett.* **1991**, *32*, 6947–6948; (b) Moody, C. J.; Sie, E.-R. H. B.; Kulagowski, J. J. *Tetrahedron* **1992**, *48*, 3991–4004; (c) Tallier, C.; Gille, B.; Bellosta, V.; Cossy, J. *J. Org. Chem.* **2005**, *70*, 2097–2108.
45. (a) Berger, D.; Overman, L. E. *Synlett* **1992**, 811–813; (b) Berger, D.; Overman, L. E.; Renhowe, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 9305–9306; (c) Berger, D.; Overman, L. E.; Renhowe, P. A. *J. Am. Chem. Soc.* **1997**, *119*, 2446–2452.
46. Lolkema, L. D. M.; Hiemstra, H.; Semeyn, C.; Speckamn, W. N. *Tetrahedron* **1994**, *50*, 7115–7128.
47. (a) Chou, W.-N.; White, J. B. *Tetrahedron Lett.* **1991**, *32*, 157–160; (b) Hofmann, B.; Reissig, H.-U. *Synlett* **1993**, 27–29; (c) Boeckman, R. K.; Shair, M. D.; Vargas, J. R.; Stoltz, L. A. *J. Org. Chem.* **1993**, *58*, 1295–1297.
48. (a) Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. *J. Am. Chem. Soc.* **1996**, *118*, 1565–1566; (b) For six-membered rings only: Nicolaou, K. C.; Postema, M. H. D.; Yue, E. W.; Nadin, A. *J. Am. Chem. Soc.* **1996**, *118*, 10335–10336.
49. Rainier, J. D.; Cox, J. M.; Allwein, S. P. *Tetrahedron Lett.* **2001**, *42*, 179–181.
50. Kane, V. V.; Doyle, D. L. *Tetrahedron Lett.* **1981**, *22*, 3027–3030.
51. Peczuh, M. W.; Snyder, N. L. *Tetrahedron Lett.* **2003**, *44*, 4057–4061.
52. (a) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661–6666; (b) Honda, E.; Gin, D. Y. *J. Am. Chem. Soc.* **2002**, *124*, 7343–7352; (c) Kim, J. Y.; Di Bussolo, V.; Gin, D. Y. *Org. Lett.* **2001**, *3*, 303–306; (d) Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6656–6660; (e) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 5811–5819; (f) Di Bussolo, V.; Liu, J.; Huffman, L. G., Jr.; Gin, D. Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 204–207; (g) Liu, J.; Gin, D. Y. *J. Am. Chem. Soc.* **2002**, *124*, 9789–9797; (h) Storkey, C. M.; Win, A. L.; Hoberg, J. O. *Carbohydr. Res.* **2004**, *339*, 897–899; (i) Batchelor, R.; Hoberg, J. O. *Tetrahedron Lett.* **2003**, *44*, 9043–9045.
53. (a) Peczuh, M. W.; Snyder, N. L.; Fyvie, W. S. *Carbohydr. Res.* **2004**, *339*, 1163–1171; (b) Fyvie, W. S.; Morton, M.; Peczuh, M. W. *Carbohydr. Res.* **2004**, *339*, 2363–2370.
54. Louie, J.; Grubbs, R. H. *Organometallics* **2002**, *21*, 2153–2164.
55. Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123–1125.
56. Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 13390–13391.
57. Ovaa, H.; Leeuwenburgh, M. A.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *Tetrahdron Lett.* **1998**, *39*, 3025–3028.
58. Jarosz, S. *Pol. J. Chem.* **1996**, *70*, 141–157.
59. Wong, J. C. Y.; Lacombe, P.; Sturino, C. F. *Tetrahedron Lett.* **1999**, *40*, 8751–8754.
60. Holt, D. J.; Barker, W. D.; Jenkins, P. R.; Panda, J. P.; Ghosh, S. *J. Org. Chem.* **2000**, *65*, 482–493.
61. For recent reviews, see: (a) Hanessian, S. *Acc. Chem. Res.* **1979**, 159–165; (b) Fraser-Reid, B.; Sun, K. M.; Tam, T. F. *Bull. Soc. Chim. Fr.* **1981**, 238–246; (c) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon: New York, NY, 1983; (d) Inch, T. D. *Tetrahedron* **1984**, *40*, 3161–3213; (e) Williams, N. R.; Davison, B. E.; Ferrier, R. J.; Furneauz, R. H. *J. Carbohydr. Chem.* **1985**, *17*, 244–255; (f) Hollingsworth, R. I.; Wang, G. *Chem. Rev.* **2000**, *100*, 4267–4282; (g) Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1576–1624; (h) Levy, D. E.; Fugedi, P. *The Organic Chemistry of Sugars*; Taylor and Francis (CRC): New York, NY, 2006.
62. Martin, J. D.; Delgado, M. *J. Org. Chem.* **1999**, *64*, 4798–4816.
63. Crimmins, M. T.; DeBaillie, A. C. *Org. Lett.* **2003**, *5*, 3009–3011.
64. Clark, J. S.; Elustondo, F.; Trevitt, G. P.; Boyall, D.; Robertson, J.; Blake, A. J.; Wilson, C.; Stammen, B. *Tetrahedron* **2002**, *58*, 1973–1982.
65. Majumdar, K. C.; Rahaman, H.; Islam, R.; Roy, B. *Tetrahedron Lett.* **2006**, *47*, 2111–2113.
66. Ovaa, H.; Stapper, C.; van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H.; Blechert, S. *Tetrahedron* **2002**, *58*, 7503–7518.
67. (a) Lautens, M.; Paquin, J.-F.; Piguel, S.; Dahlmann, M. *J. Org. Chem.* **2001**, *66*, 8127–8134; (b) Lautens, M.; Piguel, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 1045–1046.
68. Lautens, M.; Paquin, J.-F.; Piguel, S. *J. Org. Chem.* **2002**, *67*, 3972–3974.
69. Lautens, M.; Tayama, E.; Herse, C. *J. Am. Chem. Soc.* **2005**, *127*, 72–73.
70. Ichikawa, Y.; Niitsuma, S.; Kuniki, K.; Takita, T. *Chem. Commun.* **1998**, 625–626.
71. Mordini, A.; Bindi, S.; Capperucci, A.; Nistri, D.; Reginato, G.; Valacchi, M. *J. Org. Chem.* **2001**, *66*, 3201.
72. Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Nugiel, D. A.; Abe, Y.; Bal Reddy, K.; DeFrees, S. A.; Reddy, D. R.; Awartani, R. A.; Conley, S. R.; Rutjes, F. P. J. T.; Theodorakis, E. A. *J. Am. Chem. Soc.* **1995**, *117*, 10227–10238.

Biographical sketch

Mark W. Peczuh became interested in chemistry while growing up in Carbon County, UT. In 1993, he graduated with a B.S. degree in biochemistry from Boston College. He earned his Ph.D. from Yale University in 1999 under the guidance of Andrew D. Hamilton, investigating the molecular recognition of α-helical peptides by designed receptors. After an NIH post-doctoral stint in the lab of Dan Kahne at Princeton from 1999–2001, Peczuh started his independent career at the University of Connecticut. His research group is interested in the synthesis and characterization of ring-expanded carbohydrate analogs.

Nicole L. Snyder grew up outside of Pittsburgh, PA, and attended Westminster College in New Wilmington, PA where she graduated with B.S. degrees in both chemistry and biology in 2000. While at Westminster College she studied under the direction of Timothy A. Sherwood developing spectroscopic methods for the detection of ergosterol in environmental systems. In 2005, Nicole earned her Ph.D. at the University of Connecticut where she studied under the guidance of Mark W. Peczuh. Her thesis work focused on the synthesis, characterization, and biological evaluation of a number of ring-expanded carbohydrate analogs. Nicole is currently a Visiting Assistant Professor of Chemistry at Wellesley College in Wellesley, MA. Her research interests involve the preparation and characterization of unnatural carbohydrate systems that can be used to study antibiotic resistance and carbohydrate-mediated diseases.

Heather M. Haines grew up outside Chicago, IL and earned her high school diploma in 2004 from the Illinois Mathematics and Science Academy (IMSA) in Aurora, IL. She is currently a junior studying chemistry at Wellesley College in Wellesley, MA where she conducts research in the laboratory of Nicole L. Snyder. Her research primarily focuses on the preparation and evaluation of carbohydrate-based vaccines targeted at galectin-1.