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*Recent progress in the synthesis of
oxepanes and medium ring ethers*

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Recent Advances in the Preparation of Medium Ring Ethers

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1. Introduction

Molecules containing medium-sized rings continue to attract considerable attention from synthesis chemists.¹ Less stable than 6-membered rings as a result of transannular (Prelog),² bond (Baeyer) and torsional (Pitzer) strains,³ the synthesis of medium-sized rings remains a significant challenge, primarily because both entropic and enthalpic barriers hamper cyclization strategies.⁴ Of particular interest is the medium-sized cyclic ether,⁵ a structural feature that is abundant in both naturally occurring (Figure 1) and designed target molecules.

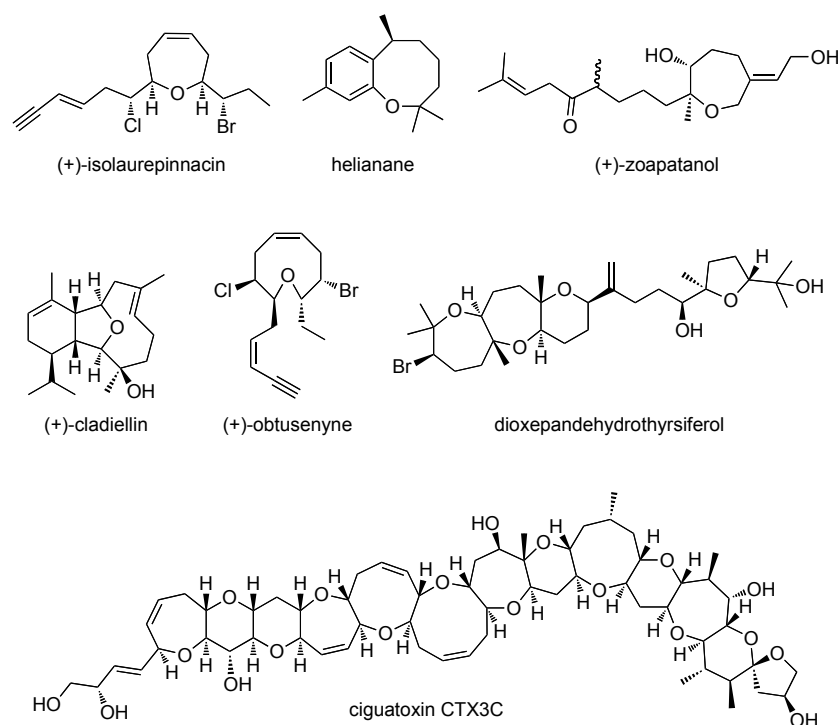


Figure 1

In this report we highlight some of the more recent (2000–present) and innovative approaches to prepare medium ring oxacycles, including oxepanes, oxocanes, oxonanes and oxecanes, as well as ring systems with varying degrees of unsaturation about the parent ring.⁶ Our discussion is arranged such that the syntheses and methods are classified into five general categories: (1) ring expansion and rearrangement processes; (2) epoxide rearrangement and opening; (3) carbon–carbon bond forming events; (4) carbon–oxygen bond forming events; (5) selected ring-closing metathesis (RCM) processes representing unique advances in, or applications of, RCM. Excluded from this report are methods based on lactonization⁷ as these approaches have been the subject of recent reviews. Where relevant, we have included mechanistic details with the aim that this report will stimulate the development of new methods for the synthesis of this important class of oxacycles.

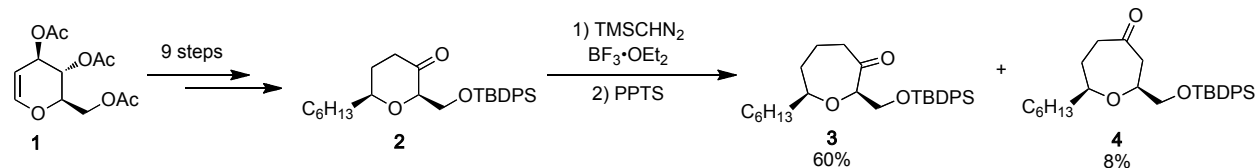
2. Formation via Ring Expansion and Rearrangement

The synthesis of medium ring ethers by ring expansion or rearrangement processes has several advantages over methods that involve the cyclization of acyclic substrates. Most notably, the ring expansion of smaller rings circumvents many of the entropic penalties accrued for formation of a medium ring and overcomes the need for high-dilution conditions. These processes often occur from a preformed

bicyclic system, or through the transient formation of a bicyclic intermediate, which templates the formation of the desired ring.

2.1 Single-Carbon Ring Expansion

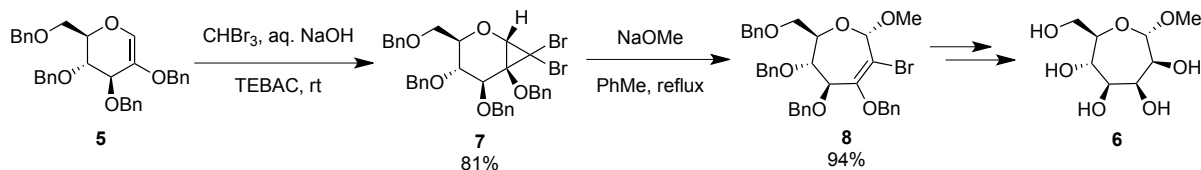
The expansion of 6-membered rings to 7-membered rings with a single carbon atom has been widely employed.⁸ For example, Fall and co-workers recently reported a synthesis of (+)-isolaurepan employing such a strategy.⁹ Commercially available tri-*O*-acetyl-D-glucal **1** was elaborated to ketone **2** in nine steps (Scheme 1). Treatment of ketone **2** with trimethylsilyldiazomethane and $\text{BF}_3 \cdot \text{OEt}_2$, followed by protodesilylation of the intermediate α -trimethylsilylketone, afforded 7-membered ring ether **3** in 60% yield, in addition to 8% of the isomeric ketone **4**. Oxacycle **3** was then elaborated into (+)-isolaurepan.



Scheme 1

2.2 Ring Expansion of Bicyclic Substrates

The expansion of cyclopropane-fused carbohydrates to oxepines has long been employed for the generation of a diverse range of septanoside carbohydrate mimics.¹⁰ Several recent efforts have employed gem-dihalocyclopropanated intermediates for rapid access to a variety of highly functionalized halogenated-septanosides.¹¹

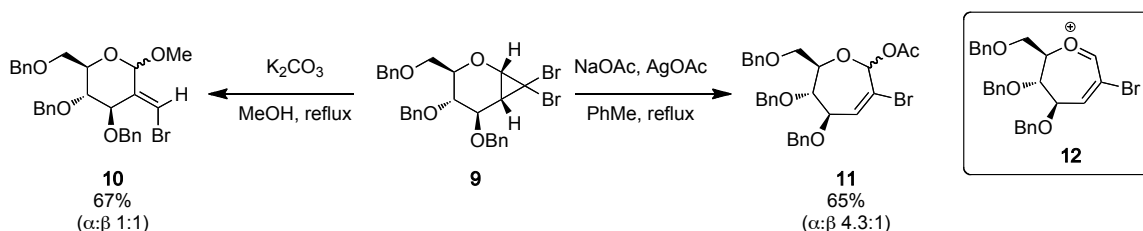


Scheme 2

Jayaraman and Ganesh disclosed the conversion of dehydrocarbohydrate **5** into *D*-glycero-*D*-talo-septanoside **6** (Scheme 2).¹² Treatment of **5** with bromoform and base under phase transfer conditions provided dibromocyclopropane cycloaddition product **7** as a single diastereoisomer. The steric course of the transformation is presumably governed by the bulky C4 benzyloxy group of **5**, which directs the cycloaddition to occur from the opposing face. Ring expansion was achieved through treatment of gem-

dihalocyclopropane **7** with sodium methoxide in refluxing toluene, yielding highly functionalized oxepine **8** as a single anomer. Oxepine **8** was transformed further into the desired septanoside **6** and this general method was employed for the preparation of several related targets.¹³

In a closely related study, Harvey and Hewitt found that *D*-glucal-derived *gem*-dibromocyclopropane **9**, lacking an ether substituent at the ring fusion, exhibits divergent reactivity under similar ring expansion conditions (**Scheme 3**).¹⁴



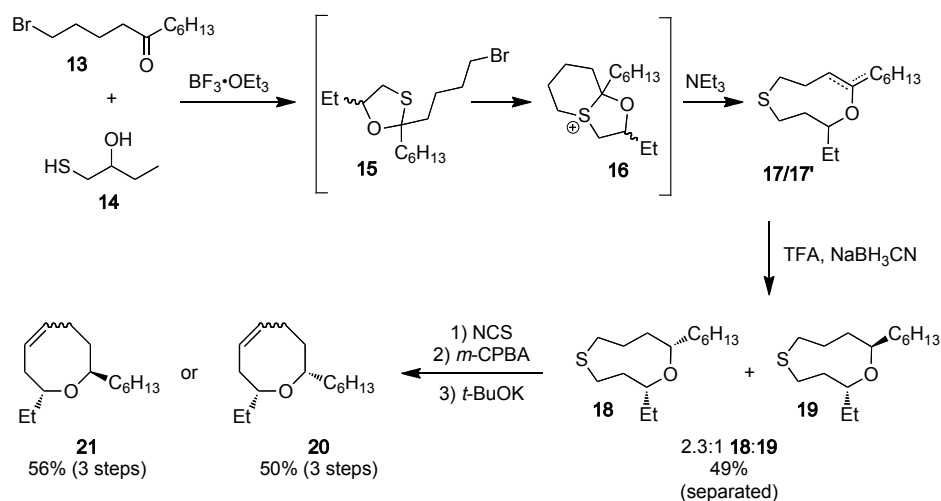
Scheme 3

Treatment of **9** with K_2CO_3 in refluxing methanol provided 2-*C*-branched pyranoside **10** as a 1:1 mixture of anomers. Interestingly, when **9** was heated with the less nucleophilic bases silver acetate and sodium acetate, oxepine **11** was formed as a 4.3:1 mixture of anomers, presumably arising through intermediate oxonium **12**.

Taken together, the studies of Jayaraman and Harvey (**Scheme 2** and **Scheme 3**, respectively) demonstrate how electronic structure and nucleophile strength can affect the course of glucal-derived *gem*-dihalocyclopropane ring expansions. For instance, while Jayaraman observed the formation of the oxepine product upon treatment of **7** with NaOMe, Harvey's analogous substrate **9**, lacking the oxygen at the 6,3-ring fusion, gave branched pyranoside **10**.

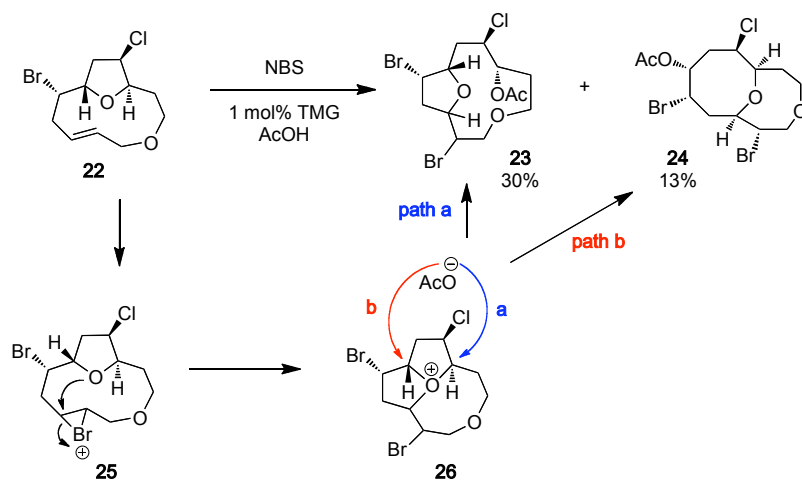
2.3 Ring Expansion via Transient Bicycle Formation

The synthesis of medium ring ethers using methods that involve the ring expansion of a transiently formed smaller ring have also been developed. De Voss and Coster reported the use of a halo-*O,S*-acetal ring expansion, followed by a Ramburg–Bäcklund ring contraction, for the formation of Δ^4 -oxocenes (**Scheme 4**).¹⁵



Scheme 4

Condensation of ketone **13** with α -hydroxythiol **14** initially gave *O,S*-acetal **15**, which spontaneously cyclized in situ to afford bicyclic sulfonium **16**. Upon addition of base, the sulfonium species fragmented to provide isomeric enols ethers **17/17'**. Subsequent reduction of **17/17'** provided the *cis* and *trans* 1,5-oxathianes **18** and **19**. The extrusion of the sulfur atoms in **18** and **19** was then accomplished via a three-step Ramburg–Bäcklund then rearrangement sequence. Independently, **18** and **19** were treated successively with *N*-chlorosuccinimide (NCS), *meta*-chloroperoxybenzoic acid (*m*-CPBA) and finally potassium *tert*-butoxide to afford the desired Δ^4 -oxocenes **21** and **20** respectively, each as a mixture of alkene isomers.

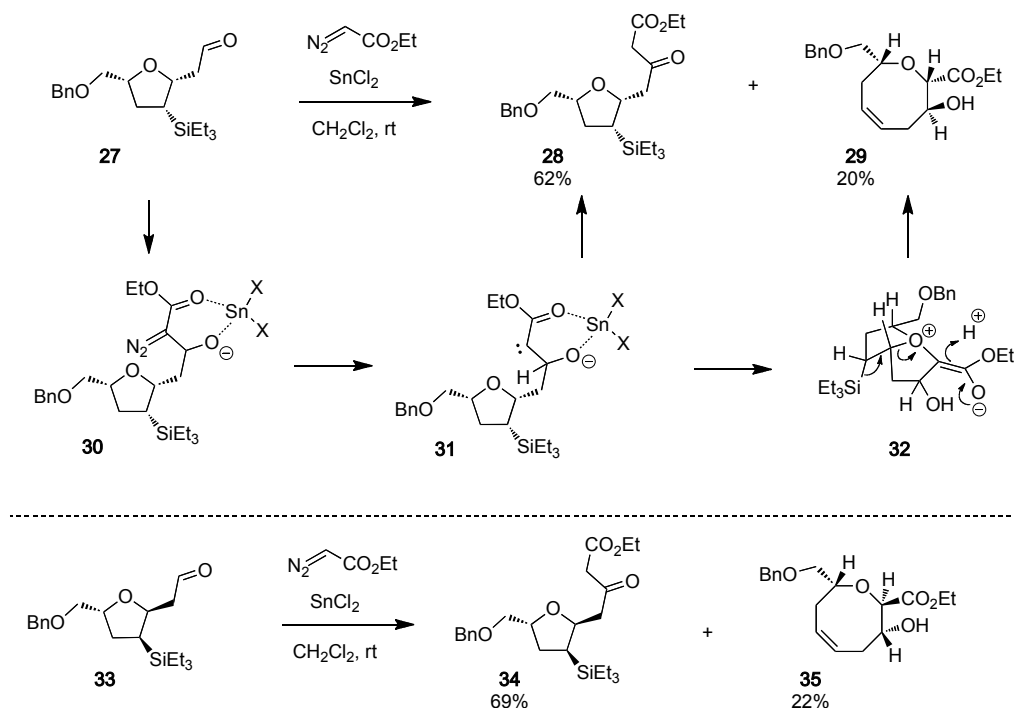


Scheme 5

Conceptually related to the De Voss *O,S*-acetal fragmentation, Braddock reported a transannular oxonium ion formation–fragmentation during their work towards the obtusallene family of natural products (Scheme 5).¹⁶ Treatment of an acetic acid solution of macrocycle **22** with *N*-bromosuccinimide

(NBS) and a catalytic amount of tetramethylguanidine (TMG) resulted in the formation of the desired rearranged macrocycle **23** and [5.5.1]bicyclotridecane **24**. The proposed mechanism involves initial formation of bromonium ion **25** followed by transannular oxonium ion formation to afford **26**. The incoming acetate may then react via **path a** to afford the desired macrocycle **23**, or via **path b** to form **24**. While **23** embodies the core framework of the obtusallene natural products, the authors speculate that **24** may represent an undiscovered natural product core from the *Luarencia* species.

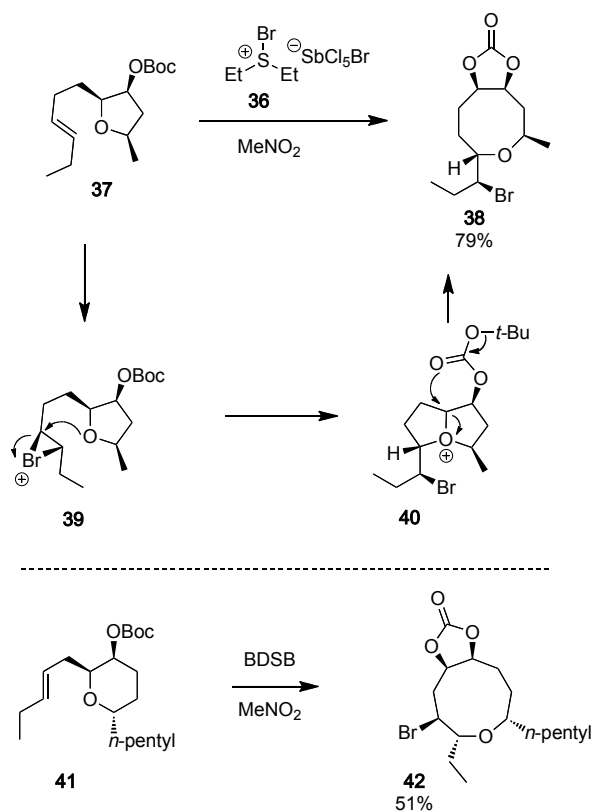
In a similar example, Li and co-workers disclosed an enantioselective synthesis of the Δ^4 -oxocene core of the laurencin family of natural products via an oxo-carbenoid tetrahydrofuran fragmentation process (**Scheme 6**).¹⁷



Scheme 6

Tetrahydrofuran **27** was prepared in seven steps from commercially available starting materials. Treatment of **27** with ethyl diazoacetate and a catalytic amount of Sn(II) chloride resulted in the formation of β -ketoester **28** as the major product, with Δ^4 -oxocene **29** as the minor product. The authors propose that the formation of these two products arises from divergence of a shared mechanistic pathway. Namely, initial aldol condensation of ethyl diazoacetate and **27** provides intermediate diazo **30**, which subsequently loses N_2 to form carbene **31**. The β -ketoester **28** then likely arises from a hydride shift within **31**, while oxo-carbenoid insertion transiently generates hydrindane-ylide intermediate **32**. Protonation of **32** occurs from the pseudo-convex face, whilst ring expansion of the fused-bicycle occurs via β -elimination-fragmentation of the triethylsilyl group. The *cis*-relationship of the triethylsilyl and the

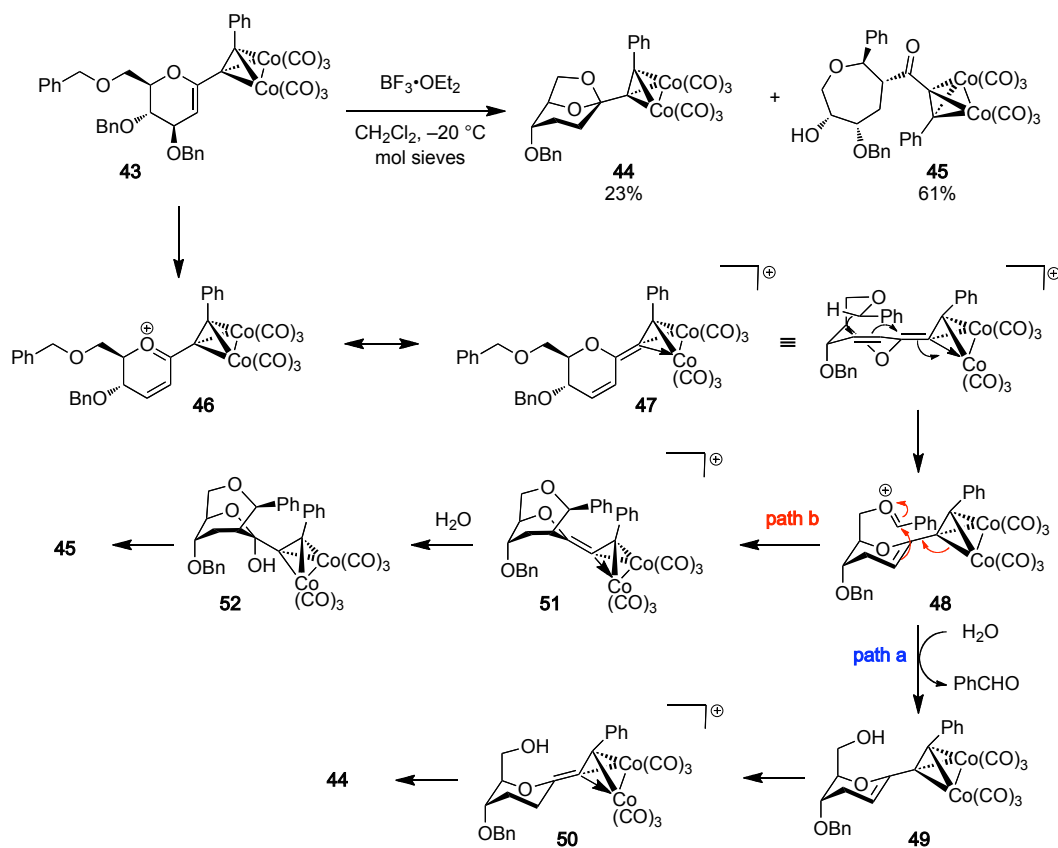
ethylaldehyde substituents of the tetrahydrofuran ring system appear to govern the diastereoselectivity of this process as when diastereoismer **33** is treated under otherwise identical reaction conditions, β -ketoester **34** and Δ^4 -oxocene **35** are formed.



Scheme 7

Using a related tetrahydrofuran ring expansion approach, Snyder recently described a novel method for bromonium ion-induced ring expansion to afford 8- and 9-membered oxacycles related to the *Laurencia* family of natural products (**Scheme 7**).¹⁸ Employing the recently introduced brominating agent bromodiethylsulfonium bromopentachloroantimonate (BDSB, **36**),¹⁹ it was found that tetrahydrofuran **37** could be regio- and stereo- selectively transformed into oxocane **38** in high yield. This reaction is likely initiated *via* reversible formation of bromonium ion **39**. Ring opening of the more reactive bromonium diastereoisomer by a 5-exo attack of the tetrahydrofuran oxygen generates intermediate bicyclic oxonium ion **40**. Bicycle **40** may then undergo a regioselective ring opening through nucleophilic addition of the neighboring carbonate moiety to yield the observed oxocane **38**. The researchers also found that this method was suitable for the formation of 9-membered oxacycles from the corresponding pyrans. For example, treatment of **41** with BDSB gave a reasonable yield of the medium ring ether **42**.

In a unique example of a skeletal rearrangement, Gómez and co-workers²⁰ found that Nicholas-Ferrier pyranosidic cation **43**, upon treatment with a Lewis acid, rearranged to give **44** and oxepane **45** (**Scheme 8**).



Scheme 8

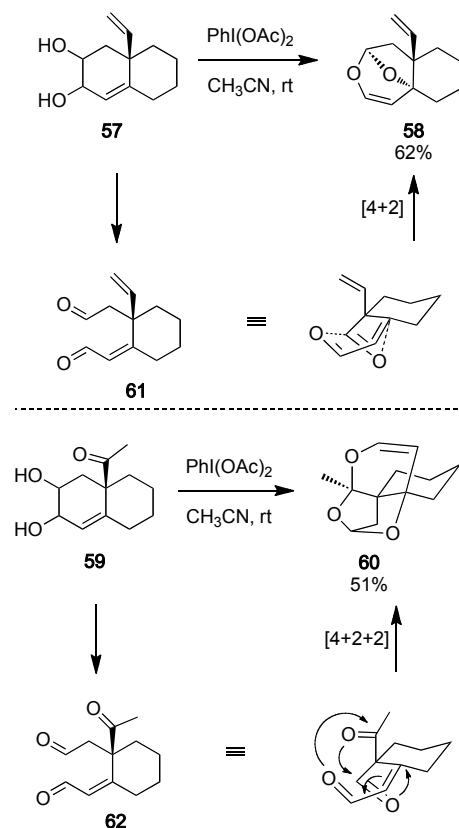
The author’s rationale for the formation of **44** and **45** involves divergence from a common reaction pathway. Lewis acid induced ionization of the C4 benzyl ether in **43** results in the formation of pyranosidic allylic cation **46** (‘Ferrier’ cation), which has resonance contributor **47**. A 1,6-hydride shift from the benzylic position of **47** generates oxocarbenium ion **48**. Hydrolysis of **48** (**path a**) may then lead to alcohol **49** that, upon protonation of the enol ether, generates **50** (only one resonance contributor shown), which through intramolecular cyclization forms ketal **44**. Alternatively, oxocarbenium **48** may be quenched via intramolecular cyclization of the enol ether to give **51** (**path b**). Hydration of bicyclic intermediate **51** affords hemi-ketal **52**, a cyclized form of the observed oxepane **45**.

2.4 Pericyclic Cyclizations and Cycloaddition Reactions

Boeckman and co-workers have reported the use of a retro-Claisen transformation for the formation of dihydrooxocine **53** during their synthesis of (+)-laurenyne (**Scheme 9**).²¹



Arseniyadis and co-workers have studied an intriguing domino reaction that exhibits differential chemical reactivity as a result of subtle substrate variation (**Scheme 10**).²²

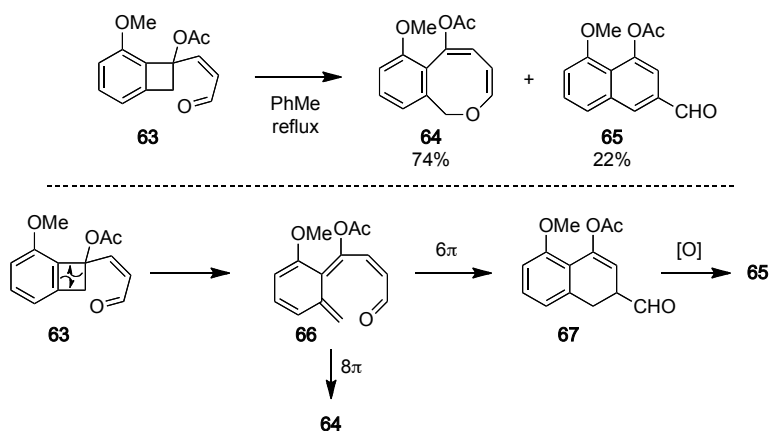


Scheme 10

Namely, treatment of vicinal-diol **57** with iodobenzene diacetate resulted in the formation of the complex tricyclic oxepine containing ene-acetal **58**. Subjecting the related vicinal diol **59** to identical reaction conditions afforded tetracyclic bis-acetal **60**. It is proposed that tricyclic acetal **58** arises from iodobenzene diacetate mediated diol cleavage to dialdehyde **61**, followed by hetero[4+2] cycloaddition to afford the observed oxepine product. Changing the angular substituent from a terminal alkene (**57**) to a methyl ketone (**59**) results in complete suppression of the [4+2] pathway in favor of a rare formal [4+2+2] pathway. Specifically, initial diol cleavage of **59** affords dialdehyde **62** in which the oxygen of the methyl ketone can engage the carbon of the aldehyde, effectively shunting the reaction through a formal [4+2+2] pathway and yielding **60**. The precise mechanistic rationale underpinning these contrasting pericyclic pathways is still under investigation.²³

In a rare example of the use of an electrocyclization for the formation of a medium ring, Suzuki and co-workers reported an electrocyclic ring-opening/ring-closing cascade for the generation of 2-benzoxocin derivatives (Scheme 11).²⁴ The group reported that heating a toluene solution of 1-acyloxybenzocyclobutene **63** resulted in a mixture of 2-benzoxocin **64** and naphthalene **65**, with **64** being the major product observed. This reaction presumably proceeds via initial retro-4 π -electrocyclization of

63 to give quinodimethane intermediate **66**. Direct oxo-8 π -electrocyclization of **66** yields **64**, whilst competing 6 π -electrocyclization affords dihydronaphthalene **67** as a precursor to the isolated naphthalene **65**.



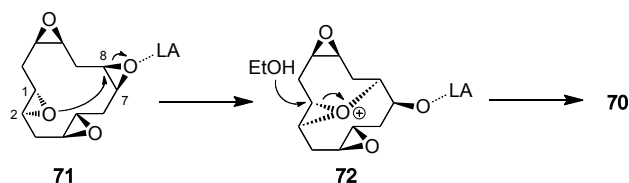
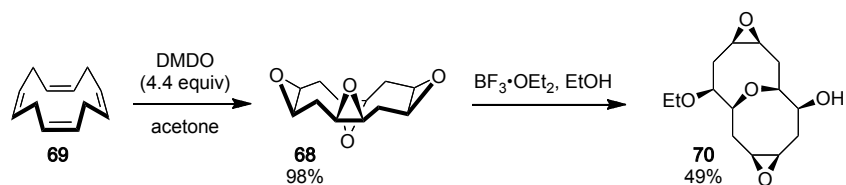
Scheme 11

3. Formation via Epoxide Rearrangement and Opening

Epoxides are highly versatile building blocks for the preparation of oxygen-containing heterocycles and have long been employed for the preparation of medium ring ethers. The opening of epoxides with oxygen nucleophiles (*vide infra*), with the notable exception of polyepoxide opening cascades,²⁵ results in the oxygen of the epoxide as an alcohol substituent of the resulting ring. Additionally, there have been several reported rearrangements of epoxide-containing substrates resulting in a medium ring oxacycle in which the epoxide oxygen becomes the ethereal oxygen. Less commonly employed is the use of carbon nucleophiles for epoxide opening, as this approach requires that the ethereal bond is prepared in a separate step.

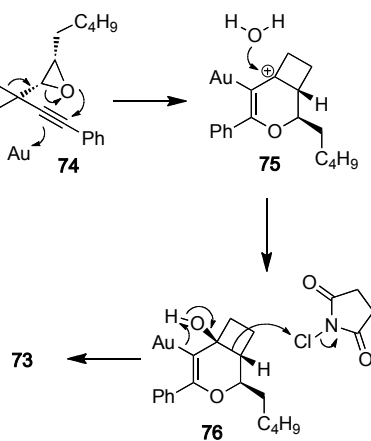
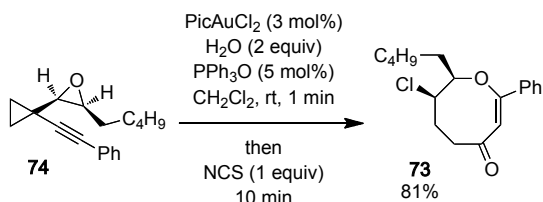
3.1 Epoxide Rearrangement

Reminiscent of the pioneering studies of Simmons²⁶ and Paquette²⁷ who reported the use of epoxide-opening cascades for the preparation of topologically non-planar molecules, and related to the early reports of Martin,²⁸ Parrain and co-workers disclosed the preparation of bridged bis-oxocanes from macrocyclic polyepoxides.²⁹ Namely, tetraepoxide **68**, derived from an exhaustive epoxidation of all-(*Z*)-1,4,7,10-cyclododecatetraene **69**, rearranges to form bridged bis-oxocane **70** (Scheme 12).



Scheme 12

Treatment of tetraepoxide **68** with boron trifluoride and ethanol yielded the diepoxy-oxabicyclo[5.5.1]tridecane **70**. The reaction proceeds with complete regiochemical control in that only the product of the C1–C2 epoxide opening the C7–C8 epoxide was reported in all examples. The reaction likely occurs via formation of Lewis acid-base complex **71**, followed by transannular nucleophilic attack by the C1–C2 epoxide to give epoxonium ion intermediate **72**. Regioselective epoxide ethanolysis then accounts for the observed bicyclic product.

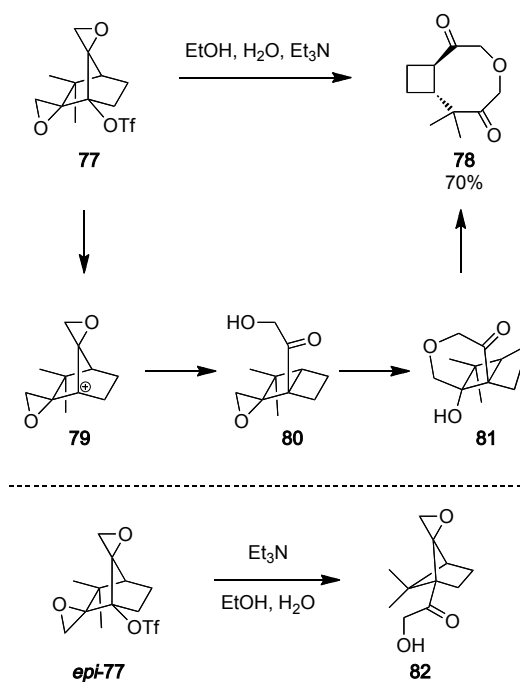


Scheme 13

The use of noble metals as catalysts in synthetic organic chemistry has advanced rapidly in recent years. Particularly noteworthy is the use of gold complexes to selectively activate π -bonds, which has allowed for the development of unique rearrangement processes.³⁰ In this regard, Liu and Liao reported the formation of 8-membered cyclic enol-ether **73** via a gold catalyzed isomerization of cyclopropane-epoxide **74** (Scheme 13).³¹

Treatment of epoxide **74** with a catalytic quantity of Au(III) picolate chloride (PicAuCl₂), water and triphenylphosphine oxide afforded 8-membered oxacycle **73**. Product **73** is proposed to arise from an initial gold mediated ring-expansion/isomerization of *cis*-1-oxiranyl-1-alkynylcyclopropane **74** to hypothetical cation **75**. Trapping of cation **75** with water gives cyclobutanol **76**, which upon treatment with NCS furnishes **73**.

In an unexpected result, Martínez and co-workers found that camphor-derived di(spiroepoxide)-triflate **77** rearranges to give trans-fused oxa-bicyclo[6.2.0]decane **78** (Scheme 14).³²



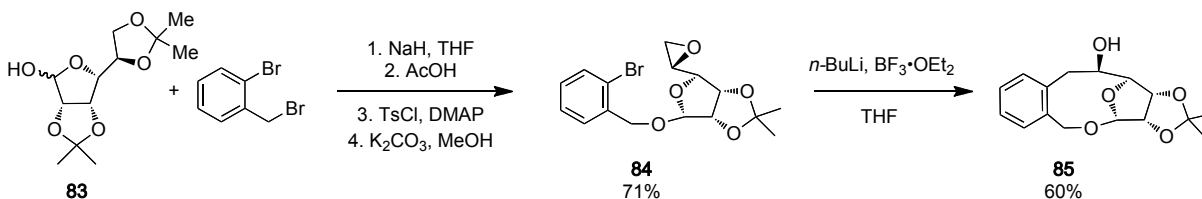
Scheme 14

Mechanistically, the formation of the oxocane-containing product **78** is likely the result of an initial triflate solvolysis that generates bridgehead cation **79**. This can then undergo an epoxide-based Pinacol-type rearrangement to yield α -hydroxy ketone **80**. A 6-*exo*-tet cyclization-epoxide opening may then afford tricyclic **81**, which upon undergoing a retro-aldol transformation would yield the observed fused bicycle **78**. The researchers also found that *epi*-**77** did not rearrange to **78** but underwent an

epoxide-based Pinacol-type rearrangement to furnish bicyclo[2.1.1]heptane **82**, a result that is likely a consequence of the stereoelectronic requirement of the Pinacol-type rearrangement.

3.2 Epoxide Opening with Carbon Nucleophiles

Whilst the opening of epoxides with oxygen-based nucleophiles has long been exploited for the generation of medium ring oxacycles, the use of carbon nucleophiles is relatively rare. However, during studies on eleutherobin analogs, Chandrasekhar and co-workers employed such a strategy (**Scheme 15**).³³

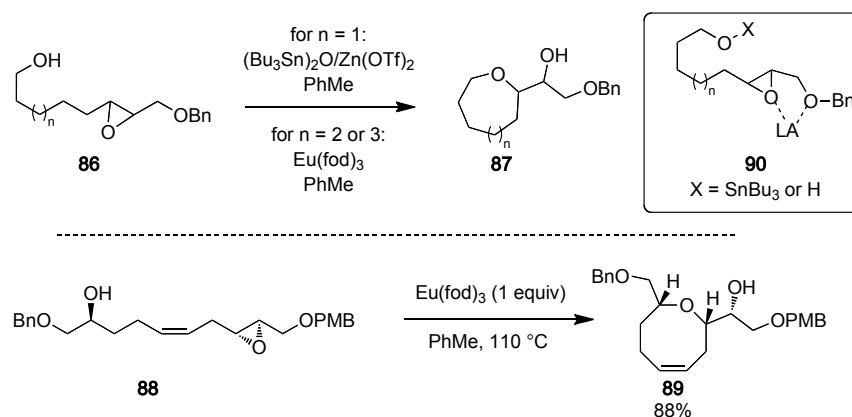


Scheme 15

Anomeric alkylation of protected D-mannose **83** with *ortho*-bromobenzyl bromide, followed by selective ketal deprotection and a two-step epoxide installation, afforded **84**. Generation of an intermediate arylanion, through a lithium–halogen exchange of **84** and then treatment with a Lewis acid afforded the oxecine product **85**.

3.3 Epoxide Opening with Oxygen Nucleophiles

Intramolecular cyclization of linear epoxy-alcohols is a well-established method for the preparation of five and six membered rings.³⁴ The use of this strategy for the preparation of larger ring oxacycles has been the subject of investigation but has generally been limited to oxepane preparation. Suzuki has extensively investigated Lewis acid-mediated epoxide openings for the generation of a variety of medium ring ethers (**86**→**87**, **Scheme 16**).

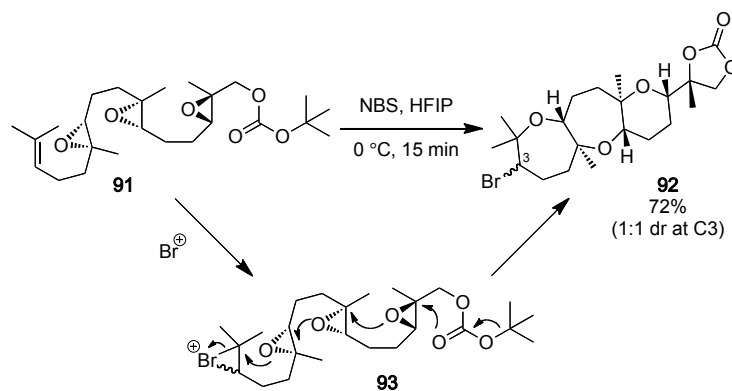


Scheme 16

Initially, the group investigated the use of $(\text{Bu}_3\text{Sn})_2\text{O}$ and $\text{Zn}(\text{OTf})_2$ for the formation of oxepanes,³⁵ but these conditions were deemed unsuitable for the formation of larger ring sizes.³⁶ Evaluation of a variety of Lewis acid catalysts revealed that $\text{Eu}(\text{fod})_3$ was suitable for cyclization to larger ring sizes and the Suzuki group has successfully applied this method for the preparation of several natural product targets, including examples of cyclization of highly functionalized linear precursors.³⁷ In one instance, linear precursor **88** was cyclized in high yield to the desired α, α' -cis-oxonene **89**. It is presumed that these cyclizations are regioselective for the proximal carbon of the epoxide (carbon closest to the nucleophilic hydroxyl group) due to a chelation effect with the terminal benzylether, as depicted in **90**.

Epoxide-opening processes³⁸ have found extensive application in polycyclic ether natural product total synthesis.³⁹ In this vein, a relatively recent development in the preparation of polycyclic medium ring oxacycles has been the introduction of polyepoxide-opening cascades, particularly for the formation of trans-syn-trans-fused polyoxepanes.⁴¹

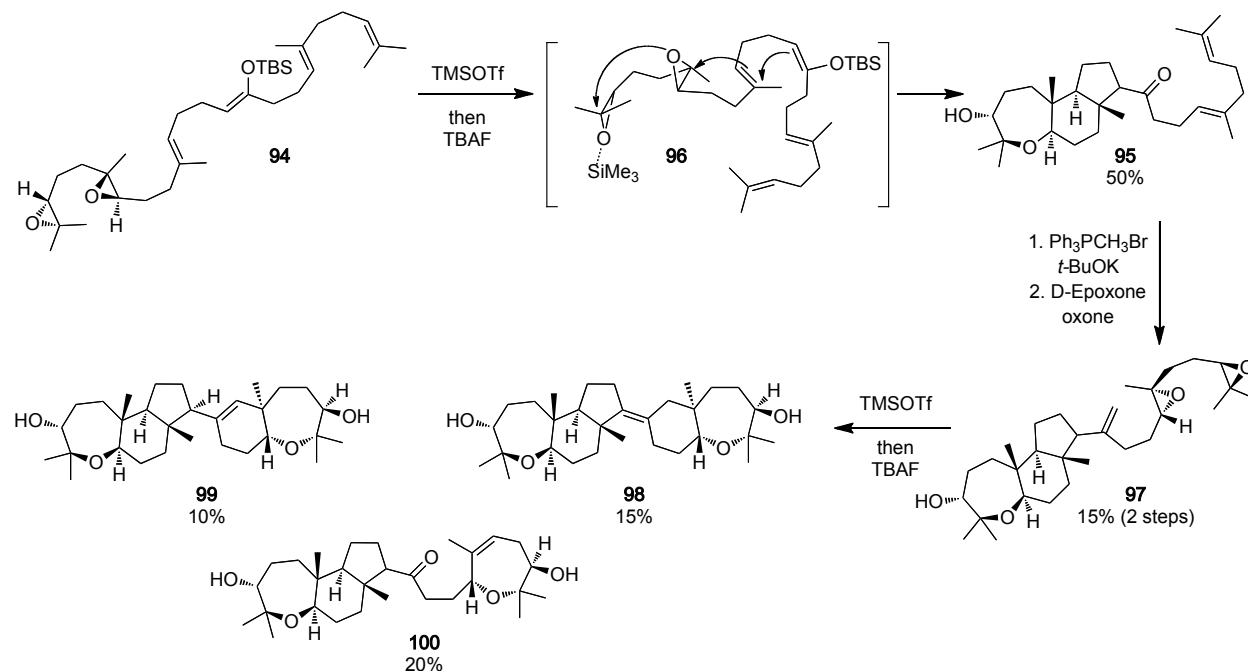
Jamison and co-workers reported the first example of a halonium-initiated polyepoxide-opening cascade for the formation of a 7,7,6-trans-anti-trans fused tricyclic subunit during their synthesis of the *ent*-dioxepandehydrothysiferol (Scheme 17).⁴²



Scheme 17

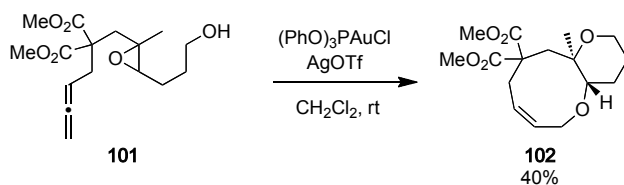
Treatment of triepoxide **91** with NBS in 1,1,1,3,3,3-hexafluoro-*iso*-propanol (HFIP) resulted in the formation of 7,7,6-trans-anti-trans-fused tricycle **92**, as a 1:1 mixture of C3 diastereoisomers, presumably via bromonium ion **93**.

McDonald has reported a Lewis acid promoted polyepoxide-opening cascade for the synthesis of the triterpene *ent*-abudinol and related natural products (**Scheme 18**).⁴³ Treatment of diepoxide **94** with TMSOTf initiated the biomimetic tricyclization to afford 7,6,5-trans-anti-trans tricyclic ketone **95**, following the addition of TBAF. This transformation likely occurs via a concerted antiparallel addition through chair-like conformer **96**. Conversion of the resulting ketone to a terminal alkene, followed by epoxidation of the trisubstituted alkenes, afforded diepoxide **97**. Subjecting diepoxide **97** to TMSOTf induced an epoxide-opening cascade that afforded a mixture of desired *ent*-abudinol B **98**, alkene regioisomer **99** and oxepine **100**.



Scheme 18

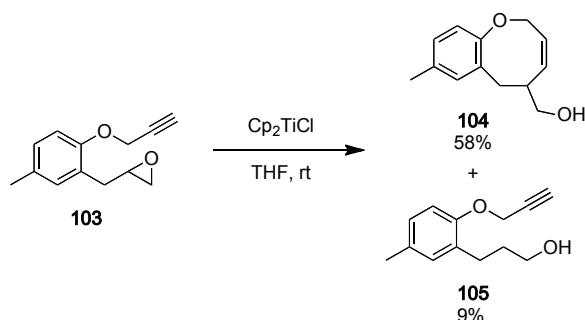
Gagné disclosed a Au(I)-promoted cascade cyclization of allenyl epoxides that resulted in the formation of various fused and linked ring systems.⁴⁴ In one example, allenyl epoxide **101** was treated with $(\text{PhO})_3\text{PAuCl}$ and AgOTf, to unexpectedly provide the fused 9,6-membered ring product **102** as a single diastereoisomer (**Scheme 19**). In this example the methyl group positioning on the epoxide controlled the ring-opening regiochemistry.



Scheme 19

3.4 Radical Cyclization

Radical-based C–C bond forming cyclizations are powerful synthetic transformations that have been extensively employed by the synthesis community. Roy and Mandal reported a Ti(III)-mediated 8-*endo* radical cyclization for the formation of benzooxocine derivatives (Scheme 20).⁴⁵ Treatment of epoxide **103** with Cp_2TiCl at room temperature resulted in the formation of benzooxocine **104** and epoxide opening product **105**.



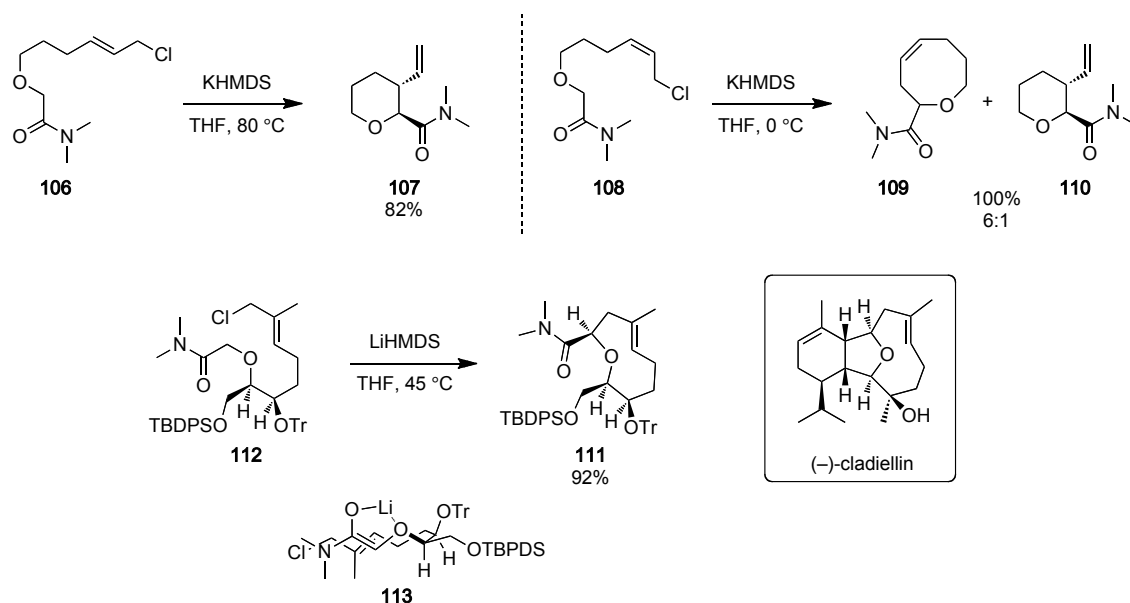
Scheme 20

4. Cyclization Via C–C Bond Formation

A plethora of methods for the preparation of medium ring ethers through C–C bond forming reactions have been reported, including: anion alkylations, allylmetal additions to aldehydes, radical cyclizations, and cycloadditions.^{5,46} Despite this, inventive and novel applications continue to be developed.

4.1 Anion Alkylation

While intramolecular enolate alkylation has not found widespread use for the preparation of medium ring ethers, Kim has extensively developed an intramolecular amide enolate alkylation as a key macrocyclization strategy for the syntheses of several cladiellin diterpene^{47,48} and laurencin⁴⁹ natural products.

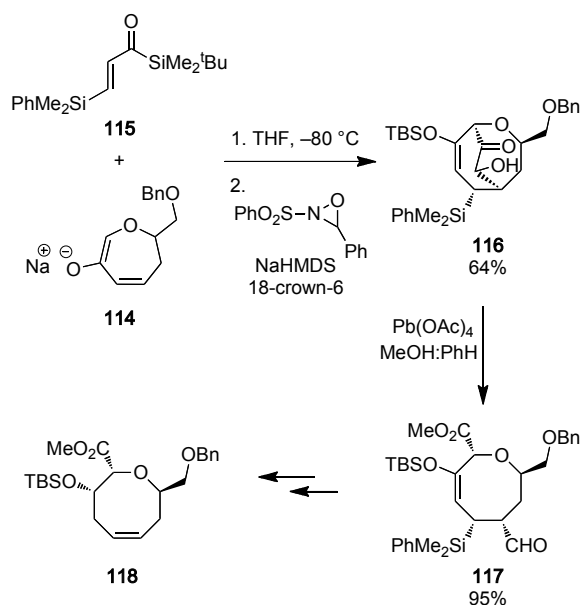


Scheme 21

The group originally investigated cyclizations of trans-allylic chloride amides through an S_N2' pathway to furnish tetrahydropyrans, such as the conversion of **106** to **107** (Scheme 21). However, when the corresponding cis-allylic chloride **108** was employed, Δ^4 -oxocine **109** was found to be the major product, the result of an S_N2 pathway, with only a minor amount of the expected S_N2' product **110** recovered. This result highlighted the importance the alkene geometry plays in directing the course of the cyclization.⁵⁰

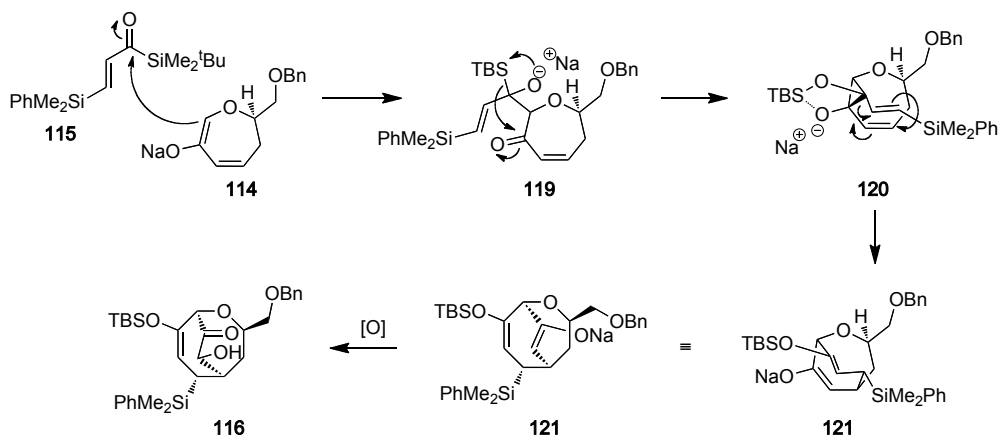
The Kim group has demonstrated the powerful nature of this strategy in the context of total synthesis on several occasions. A striking example came during their preparation of the complex macrocyclic intermediate **111** in their synthesis of (-)-cladiellin and related natural products. Enolization of highly functionalized amide **112** with LiHMDS cleanly afforded 9-membered ring ether **111**, presumably through chelated *E*-enolate **113**. The researchers note that employing KHMDS or starting with the C6/C7 *Z*-alkene lead to decomposition and a reduced yield respectively, thereby supporting **113** as an intermediate in the formation of **111**.

Takeda and co-workers have developed a Brook rearrangement-mediated [3+4] annulation for the preparation of 7-membered carbocycles,⁵¹ a method which was later extended to the preparation of 8-membered carbo- and oxacycles.^{52,53} This method was then employed in a formal synthesis of (+)-laurallene⁵⁴ and later (+)-prelaureatin.⁵⁵ As an illustration of this strategy, the group's approach to (+)-laurallene is shown in Scheme 22.



Scheme 22

Sodium enolate **114** was treated with acryloylsilane **115** and then Davis' oxaziridine to afford α-hydroxyketone bicycle[3.3.2]decene **116**. Oxidative cleavage of the α-hydroxyketone bridge afforded 8-membered ring ether **117**, which was further elaborated to **118**, an intermediate in Crimmins' synthesis of (+)-laurallene. A proposed mechanism for the Brook rearrangement-mediated [3+4] annulation is shown in Scheme 23.

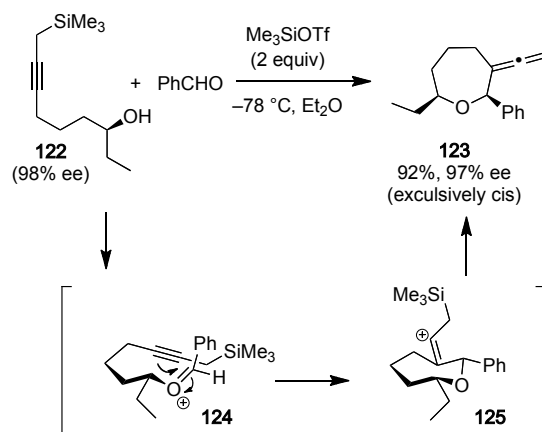


Scheme 23

A 1,2-addition of enolate **114** to acryloylsilane **115** generates alkoxide **119**, which then undergoes a Brook rearrangement and condensation of the resulting vinyl-anion to give cyclopropane **120**. A [3,3]-sigmatropic rearrangement of bicycle **120** generates enolate **121**, the product of a formal [4+3] reaction. In situ oxidation of **121** yields the desired α-hydroxy ketone **116**.

4.2 Cyclization via Prins-Type Reactions

The intramolecular Prins reaction has long been recognized as a powerful method for the preparation of 2,6-disubstituted tetrahydropyrans and 2,7-disubstituted oxepanes.⁵⁶ A challenge in employing secondary homoallylic alcohols for the Prins reaction in enantioselective synthesis is the competing Cope rearrangement, which leads to racemization.⁵⁷ Increasing the nucleophilicity of the alkene component has proven to be a successful means by which to suppress this undesired reaction pathway.⁵⁶ Furman and co-workers have reported employing propargylsilanes as nucleophiles in a Prins reaction for the preparation of nonracemic 2,6-disubstituted-3-vinylidene tetrahydropyrans and 2,7-disubstituted-3-vinylidene oxepanes (**Scheme 24**).⁵⁸

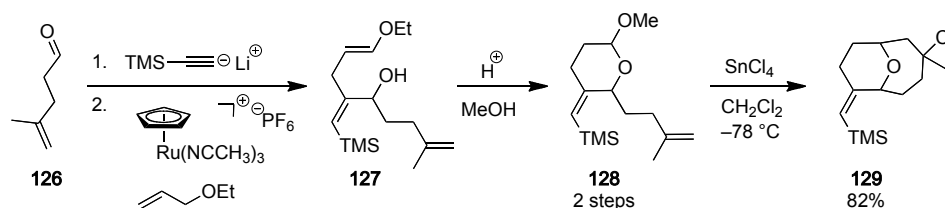


Scheme 24

Treatment of enantiomerically enriched alcohol **122** with benzaldehyde and a Lewis acid provided Prins cyclization product **123** with retention of enantioenrichment. Mechanistically this transformation likely proceeds through initial formation of oxocarbenium ion **124** and then cyclization of the alkyne to generate vinyl cation **125**. Subsequent loss of the trimethylsilyl cation affords observed allene **123**. Although the present method is limited in scope to arylaldehydes as the reaction partners in the Prins sequence, if the scope can be expanded further, the facile preparation of the starting materials will undoubtedly make this an attractive method for the preparation of cyclic ethers.

In a related report, Mascareñas and co-workers reported the formation of 1,5-oxygen-bridged medium ring systems via a Prins type cyclization (**Scheme 25**).⁵⁹ The precursor to the cyclization substrate was rapidly prepared through addition of the anion of TMS-acetylene to aldehyde **126** and a ruthenium-catalyzed alkyne-alkene isomerization of the product to afford enol ether **127**. Treatment with acidic methanol then generated acetal **128**. Subsequent Lewis acid mediated oxonium ion formation induced a Prins-like cyclization to give 10-oxabicyclo[4.3.1]decane **129**. It is noteworthy that this method

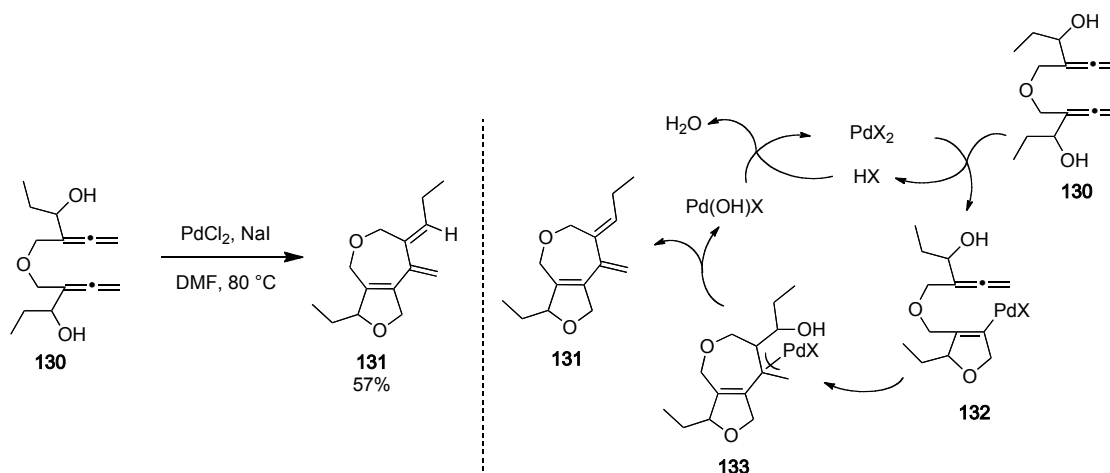
was developed for the preparation of medium ring carbocycles, after reductive ring opening of the bridging oxacycle, rather than the bridging medium ring oxacycle shown. By passing through medium ring bridged oxacycle intermediates, such as **129**, the researchers template the formation of the desired carbocyclic ring system; a general approach that has emerged as a powerful strategy for the preparation of medium ring carbocycles.⁶⁰



Scheme 25

4.3 Metal-Mediated Cyclizations

Studies by Ma and co-workers on tethered 1,5-bisallenols resulted in the development of a Pd(II)-mediated cyclization for the generation of fused 5,7- and 5,8-membered ring systems. These cyclization reactions include examples in which the tethering group contains a heteroatom, thereby generating fused heterocycles (Scheme 26).⁶¹

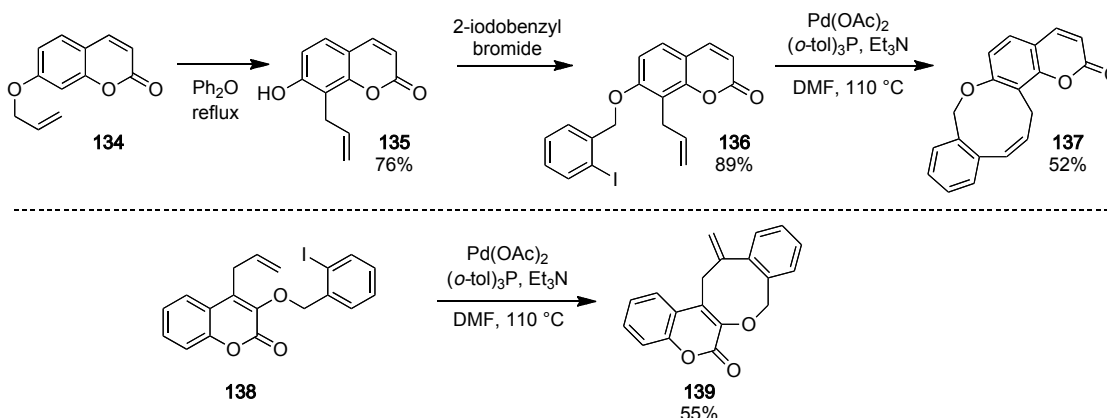


Scheme 26

Several examples of medium ring ether synthesis were presented. For example, treatment of 1,5-bisallenol **130** with in situ generated PdI₂ at an elevated temperature resulted in the formation of fused bicyclic[5.3.0] **131**. This reaction is postulated to proceed through an initial electrophilic oxypalladation to afford dihydrofuran **132** and an equivalent of acid. Regioselective carbopalladation of the remaining allene forms the medium ring and π -allyl-palladium **133**. Finally, trans- β -hydroxide elimination affords the

observed bicycle **132** and generates a palladium hydroxide intermediate which may then be converted to the initial Pd(II) catalyst through ligand exchange with exogenous acid. The researchers have very recently expanded the scope of this process for the preparation of furan-fused ring systems, starting from 1,5-bis(1,2-allenylketones).⁶²

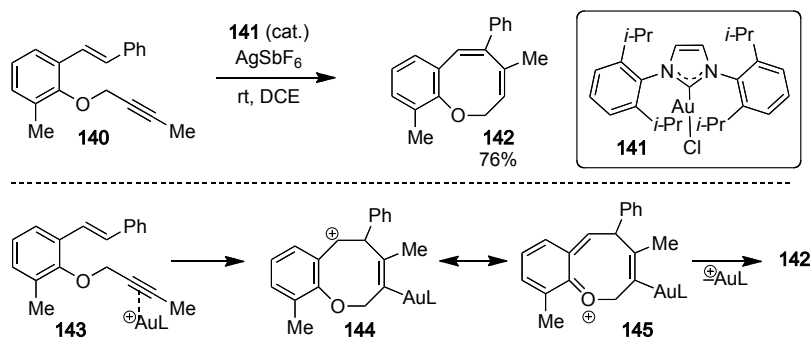
Chattopadhyay reported a sequential Claisen rearrangement then intramolecular Heck cyclization for the formation of benzoxocine- and benzoxonine-fused coumarin and quinolone derivatives, previously unknown chemical structures (**Scheme 27**).⁶³



Scheme 27

Thermally induced Claisen rearrangement of 7-allyloxycoumarin **134** gave **135**, which upon alkylation with 2-iodobenzyl bromide gave Heck precursor **136**. Subjecting **136** to standard Heck conditions gave 9-endo cyclization product **137** in reasonable yield. Intriguingly, changing the substitution pattern of the linear precursor changed the mode of cyclization. Namely, treatment of 4-allylcoumarin **138** under identical reaction conditions gave 8-exo cyclization product **139**, a result that has yet to be accounted for mechanistically.

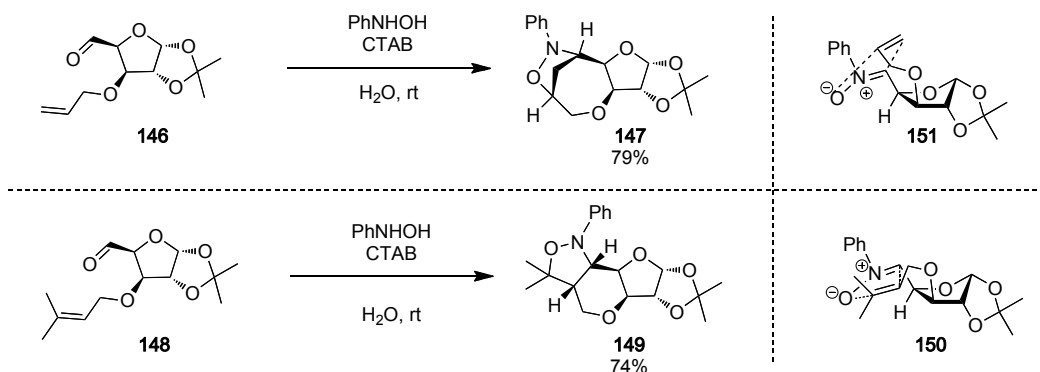
In a recent report, Kumar and Waldmann disclosed the preparation of benzoxocines via a Au(I) catalyzed 8-endo-dig cyclization (**Scheme 28**).⁶⁴



Treatment of propargyl ether **140** with an in situ generated cationic Au(I) species derived from **141**, yielded benzoxocine **142**. This reaction presumably proceeds through initial formation of gold–alkyne complex **143**, followed by 8-endo-dig cyclization to generate **144** that has resonance contributor **145**. Cation **145** may then collapse to give the observed product **142**, whilst regenerating the gold catalyst.

4.4 Pericyclic Cyclizations and Cycloaddition Reactions

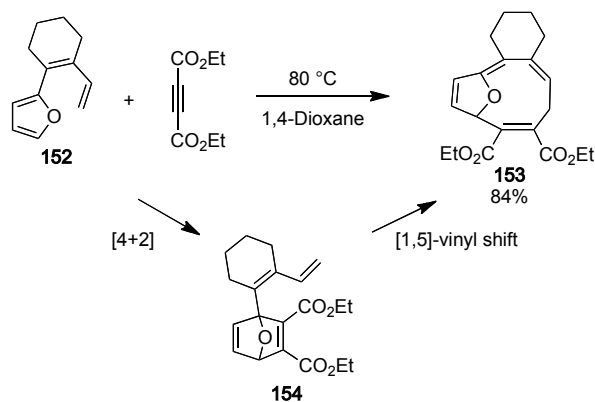
The use of cycloaddition processes for the preparation of fused or bridged ring systems is a powerful tactic in organic synthesis. In this regard, Bhattacharya and Chatterjee found that 3-*O*-allyl-1,2-isopropylidene *N*-phenyl nitrones undergo intramolecular cycloaddition to afford oxepanes (**Scheme 29**).⁶⁵



Treatment of 3-*O*-allyl derived furanoside **146** with *N*-phenylhydroxyamine in water with the surfactant hexadecyltrimethylammonium bromide (CTAB) gave oxepane **147** in good yield. Prenyl derivatives **148** afforded pyrans **149** under identical reaction conditions. This may be due to a steric interaction between the vinylic methyl groups and the *N*-phenyl group of the nitron in the cycloaddition transition state **150**. This interaction is absent in the allyl-cycloaddition transition state **151**. Subsequent reports have

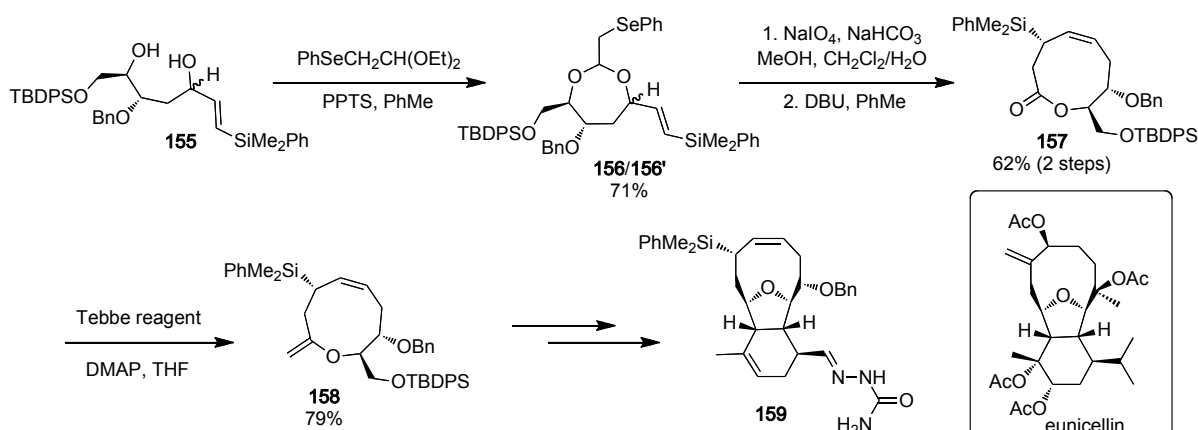
demonstrated that the *N*-phenyl nitron is favorable over alternative *N*-substituents and that this reaction can be efficiently executed in traditional organic solvents if desired.⁶⁶

Employing an [8+2]-cycloaddition is an attractive, yet albeit challenging, approach for the formation of 10-membered ring systems. Although there is a limited number of successful reports of [8+2]-cycloaddition reactions, Herndon and co-workers, have disclosed the successful synthesis of various oxo-bridged 10-membered ring systems using such an approach (**Scheme 30**).⁶⁷ In one example, dienyfuran **152** was heated with diethyl acetylenedicarboxylate to afford furan-bridged 10-membered



oxacycle **153**. In mechanistic studies on related systems, the group found that these reactions likely proceed through initial [4+2]-cycloaddition to afford oxacycle **154**, which then undergoes a [1,5]-vinyl shift, generating the observed product.⁶⁸

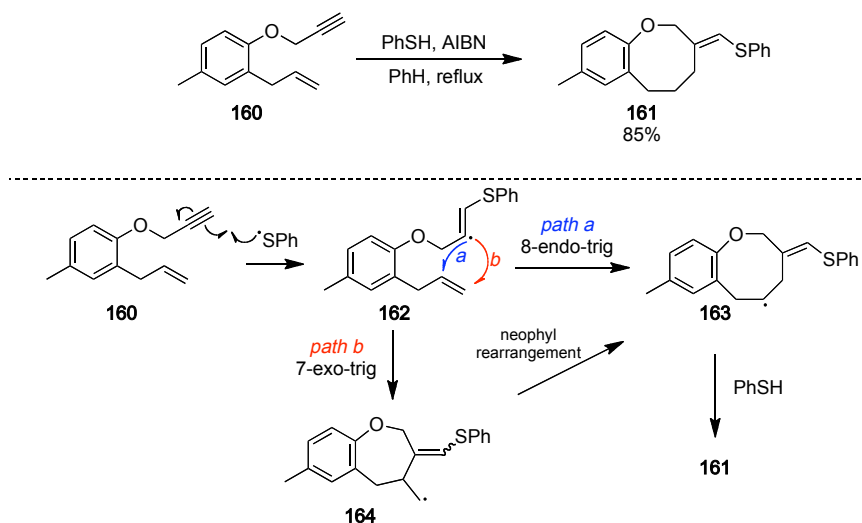
Recently, Holmes and co-workers employed a Claisen rearrangement during their synthesis of (+)-obtusenyne⁶⁹ and the core of eunicellin (**Scheme 31**).⁷⁰



The diastereoisomeric mixture of diols **155** underwent transacetalization with phenylselenenyl acetaldehyde diethyl acetal, yielding selenoacetals **156/156'**. Selenide oxidation with sodium periodate, followed by treatment with DBU and heating gave lactone **157** as a single diastereoisomer. The transformation likely proceeds via elimination of the selenoxide to an intermediate ketene acetal (not shown), which then undergoes a Claisen rearrangement, yielding lactone **157**. Treatment of **157** with the Tebbe reagent afforded enol ether **158**, which was further elaborated to tricycle **159**. While this review generally precludes lactonization strategies, this novel example departs from traditional lactonization methods from acyclic precursors and allows rapid entry into the desired natural product core structures.

4.5 Radical Cyclization

Recently, Majumdar reported the tin-free formation of medium ring oxacycles via an intramolecular 8-*endo*-trig radical cyclization of tethered enynes.⁷¹ In one example, the formation of benzoxocine derivatives was achieved (**Scheme 32**), an important substructure in a number of natural products.⁷²



Scheme 32

Treatment of enyne **160** with two equivalents of both thiophenol and AIBN in refluxing *t*-BuOH afforded benzoxocine derivative **161** as a single alkene isomer. This reaction likely proceeds via initial addition of the thiophenol radical to the alkyne of **160** to generate vinyl radical **162**. Direct 8-*endo*-trig cyclization of **162** would yield secondary radical **163** (**path a**, **Scheme 32**), which may then abstract a hydrogen from thiophenol to yield observed product **161**. Alternatively, vinyl radical **162** may undergo a 7-*exo*-trig cyclization, generating primary radical **164** (**path b**), which upon neophyl rearrangement

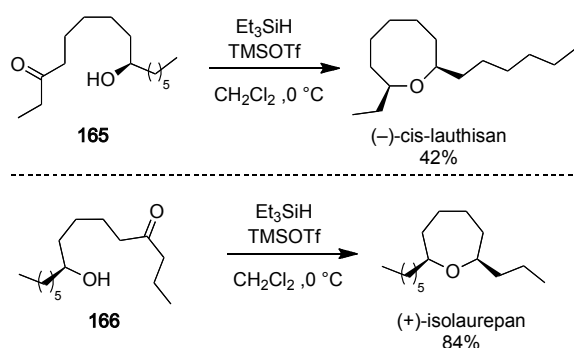
would generate benzoxocine secondary radical **163**. Employing a similar strategy, the research group has also reported the preparation of benzoxepin derivatives via a 7-endo radical cyclization.⁷³

5. Cyclization via C–O Bond Formation

The cyclization of linear precursors is a conceptually appealing strategy for the synthesis of medium ring ethers, particularly when using a C–O bond-forming event. Indeed, the closure of linear alcohols was one of the first methods to be investigated and revealed the difficulties associated with this approach.^{4, 5} Despite these kinetic and thermodynamic challenges, researchers have continued to pursue this strategy owing to the vast strategy level benefits a successful method would provide.

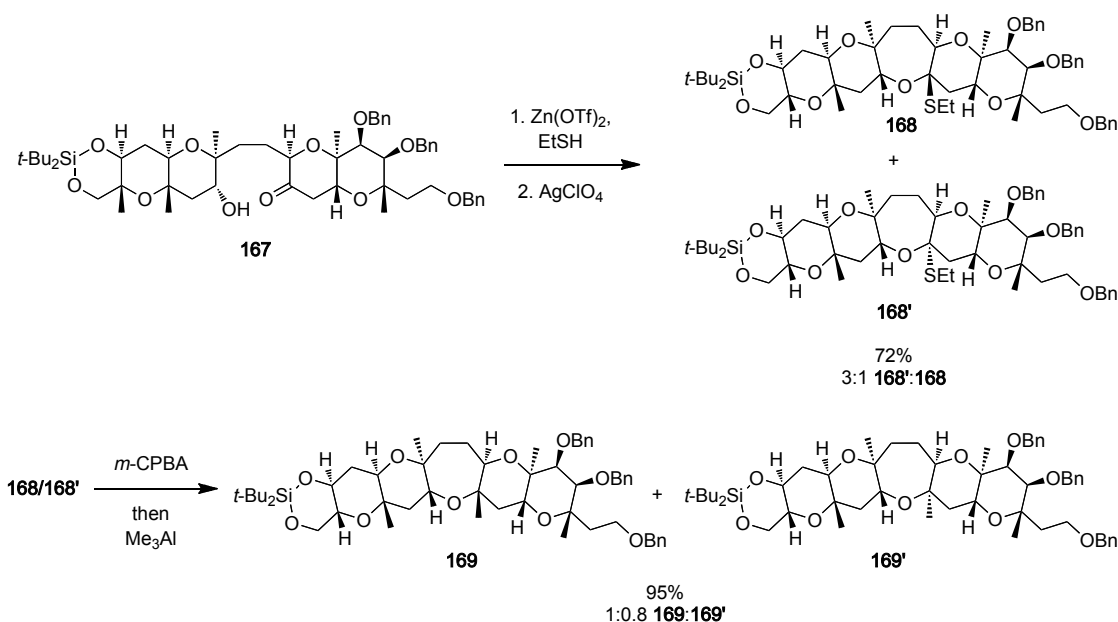
5.1 Intramolecular Alkylation

The use of hydroxy–ketone reductive C–O bond formation for the preparation of oxepanes was originally reported by Nicolaou during his group’s pioneering work on the synthesis of the marine ladder polyethers.⁷⁴ Expanding on this powerful strategy for oxacycle formation, Kumar and co-workers reported the synthesis of (–)-cis-lauthisan and (+)-isolaurepan *via* reductive cyclization (**Scheme 33**).⁷⁵



Scheme 33

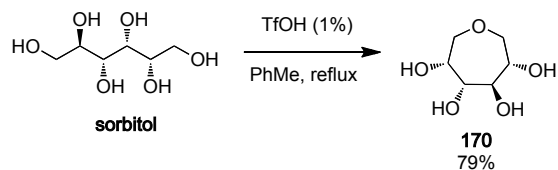
In the event, treatment of linear hydroxy ketone **165** with $\text{Et}_3\text{SiH}/\text{TMSOTf}$ yielded the oxocane containing natural product, while treatment of **166** afforded the corresponding oxopane natural product. This highly diastereoselective reaction afforded the desired natural products from simple hydroxy ketone starting materials, thus enabling rapid procurement of the target molecules.



Scheme 34

Very recently, the Nicolaou lab applied a milder version of this reductive cyclization, in the form of a hydroxyl–thioether reductive cyclization⁷⁶ during their preparation of the QRSTU ring system of maitotoxin (Scheme 34).⁷⁷ Following conversion of the ketone in **167** to the dithioether, treatment with AgClO_4 provided a mixture of oxepane *O,S*-ketal diastereoisomers **168/168'**, with **168'** being the major product. Oxidation of the mixture of **168/168'** and then subsequent treatment with trimethylaluminum afforded methylated oxepane diastereoisomers **169/169'**. Interestingly, the diastereoisomeric ratio of the starting materials was not maintained in the products, which suggests differential rates of oxonium ion formation and equilibration. The Oishi laboratory made similar observations during their preparation of marine ladder polyether fragments.⁷⁸

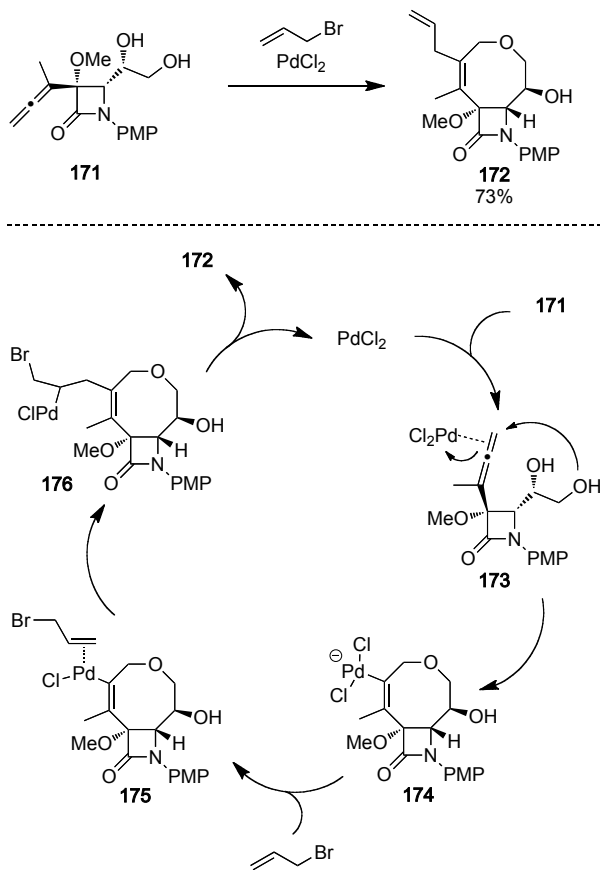
In a rapid preparation of tetrahydroxyoxepanes, Smith and co-workers reported the direct conversion of sorbitol or mannitol into **170** following treatment with triflic or tosic acid.⁷⁹ Treatment of sorbitol with a catalytic amount of triflic acid gave a high yield of tetrahydroxyoxepane **170** (Scheme 35). Although the precise nature of the mechanism of this transformation remains unclear, the observation of retention of the stereochemistry at C3 and C6 suggests that ionization of the secondary hydroxyl groups is not occurring.



Scheme 35

5.2 Metal-Mediated Cyclization

Alcaide and co-workers reported the formation of oxocine fused β -lactams via a Pd(II) mediated cyclization of γ,δ -allendiols (**Scheme 36**).⁸⁰ Treatment of β -lactam **171** with PdCl₂ and allyl bromide yielded azalactam fused oxocine **172**. The formation of **172** presumably arises from initial coordination of the Pd(II) to allene **171**, followed by regioselective 8-*endo*-trig cyclization of the primary hydroxyl to



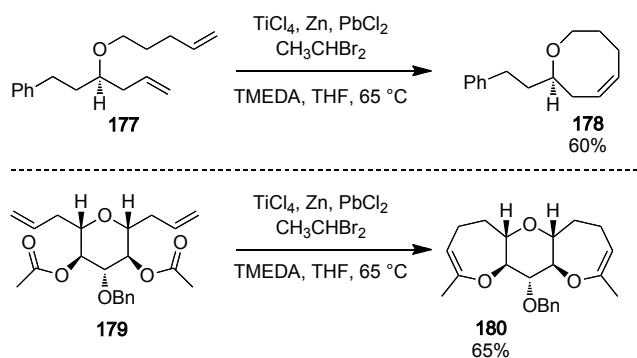
Scheme 36

vinyl palladium intermediate **173**. Ligand exchange of one of the chlorides of vinyl palladium **174** with allyl bromide may generate **175**. Heck-type migratory alkene insertion of **175**, to give **176**, followed by β -halide elimination regenerates the Pd(II) catalyst as well as the observed 8-membered ring product. Intriguing in this process is the regioselective 8-endo-trig cyclization (**173** \rightarrow **174**), which is favored for this substrate over the competing 6-exo-trig cyclization of the secondary alcohol in **173**. Recent reports from this group have elaborated on the factors governing the selectivity in related cyclization reactions.⁸¹

6. Cyclization via Ring-closing Metathesis

Ring-closing metathesis has been the subject of intense investigation and reviewed on numerous occasions, including a recent review specifically pertaining to the formation of medium ring oxacycles.⁸² Therefore, while there have been recent reports employing RCM for the preparation of medium ring oxacycles, we will not review those examples, but direct the reader to several lead references.⁸³ Herein, we will describe two examples that employ RCM but represent interesting departures from traditional RCM methods and substrates.

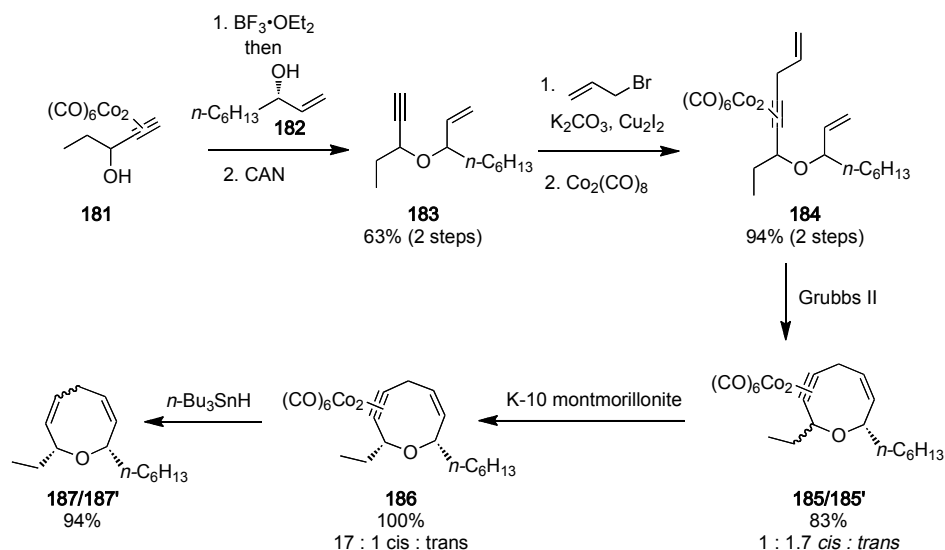
An example that departs from classical RCM methods is Rainier's report on the use of a reduced titanium alkylidene for olefinic ester and diene ring-closing metathesis (**Scheme 37**).⁸⁴



Scheme 37

In situ generation of the reduced titanium alkylidene via titanium tetrachloride, zinc metal, Pb(II) chloride and 1,1-dibromoethane, then addition of tethered diene **177** gave RCM product Δ^4 -oxocine **178**. Demonstrating the applicability of this method toward natural product like scaffolds, the Rainier group reported bidirectional olefinic ester coupling for the preparation of polycyclic ethers.^{84b} In one example, treatment of dienyl diester **179** with an excess of the in situ generated reduced titanium alkylidene yielded 7,6,7-fused triad **180**. This method also played a critical role in the groups' recent synthesis of the natural product brevenal.⁸⁵

Both RCM and the Nicholas reaction have been employed independently for the preparation of medium ring oxacycles. The Martín group has reported an intriguing union of these approaches for the preparation of 8-membered ring oxacycles (**Scheme 38**).⁸⁶



Scheme 38

Nicholas reaction of the cobalt-complex of racemic oct-7-en-4-yn-3-ol **181** with stereochemically pure non-1-en-3-ol **182**, followed by decomplexation, provided linear enyne ether **183**. Alkylation of the alkyne followed by complexation of the alkyne with cobalt gave metathesis precursor **184**. Subjecting **184** to Grubbs' second-generation catalyst gave 8-membered cyclic ether **185/185'** as a mixture of diastereoisomers. Presumably the bent nature of the cobalt-alkyne complex assists in facilitating the RCM while preventing the alkyne from participating in undesired side reactions during the metathetic ring closure. Prior to decomplexation, **185/185'** could be isomerized to essentially a single diastereoisomer **186** through treatment with K-10 montmorillonite clay. A final reductive decomplexation was achieved through treatment of **186** with tributyltin hydride, yielding **187/187'** as a mixture of alkene isomers.

7. Conclusion and Outlook

The challenges associated with the synthesis of medium ring ethers, in conjunction with their interesting properties and functions, have prompted chemists to develop a plethora of elegant methods for their preparation that are ever more efficient and innovative. In this report we hope to have summarized the recently reported methods for the synthesis of these ring systems, while also attempting to include mechanistic explanations and natural product targets where relevant.

It is clear from this report that whilst a number of methods exist, with the notable exception of RCM, there is a relative paucity of catalytic means for formation of these ring sizes. The non-RCM catalytic methods presented herein allude to an emerging trend of employing catalyst control to overcome the kinetic barriers intrinsic to medium ring ether formation, although the substrate scope is presently limited to special cases. To be sure, RCM has been one of the primary enabling technologies in this field; in fact, future catalytic methods must be measured against the high bar set by RCM.

The recent advances in cascade and templated processes demonstrates not only the underpinning desire of synthetic chemists for transformations which rapidly generate molecular complexity, but also the field's continued search for transformations that build these difficult ring systems in a controlled manner.

On the whole, the formation of these ring systems remains a significant challenge during the preparation of any target that contains one. While the lessons of the past clearly present methods by which to prepare nearly any molecule with these subunits, the search for evermore selective and efficient means for their preparation is fertile ground for exciting scientific investigation.

8. Acknowledgements

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