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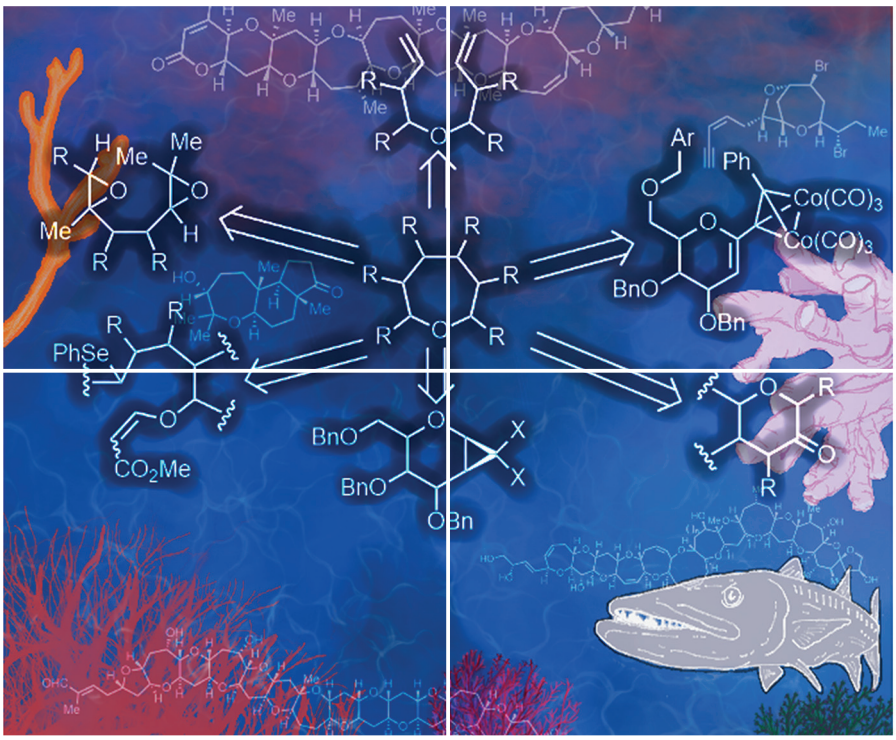

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Advancements in the synthesis of polyoxygenated oxepanes and thiepanes for applications to natural products

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Oxepanes are central motifs and tenants of many biologically important molecules, and their synthetic construction often presents a challenge to chemists due to consequential entropic and enthalpic barriers that have limited the synthetic toolbox to access these seven-membered oxacycles. This review covers the breadth of synthetic methods to afford the oxepane/thiepane moiety, with a focus on polyoxygenated oxepanes and includes radical cyclizations, Lewis acid-mediated cyclizations, ring closing-metathesis, Nicholas–Ferrier rearrangement, homologations, and ring-expansion strategies. Implementation of these tactics towards sugar-based and non-sugar based (*de novo*) approaches is presented alongside their extensive application to the total synthesis of several complex polyoxygenated oxepane-containing natural products, which are also highlighted.

1. Introduction

Oxepanes are seven-membered cyclic ethers that are important motifs found within physiologically relevant small molecules and exhibit complementary, as well as differing biological activities to their six-membered counterparts.[1] Oxepanes can vary in structural or stereochemical complexity and are often found as core structures embedded within biologically active

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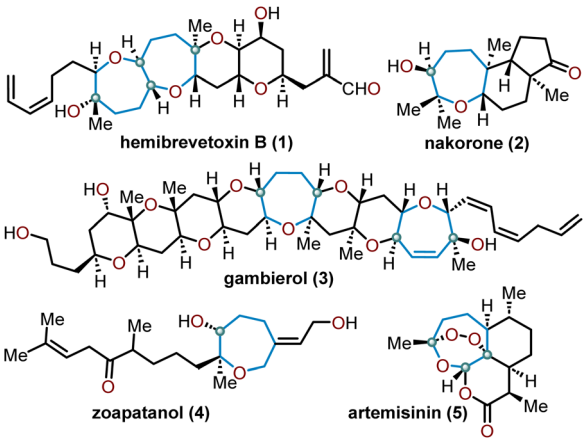
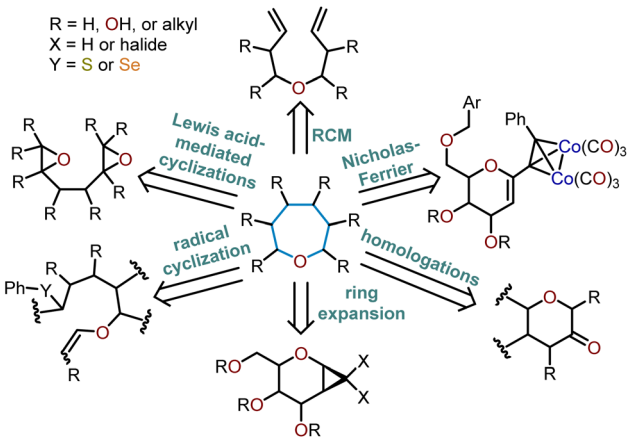


Fig. 1 Biologically relevant natural products containing an oxepane.



Scheme 1 General strategies to access seven-membered oxacycles.

natural product targets such as hemibrevetoxin B (**1**), nakorone (**2**), gambierol (**3**), zoapatanol (**4**), as well as pharmaceuticals such as artemisinin (**5**) (Fig. 1).[1–3] Given the prevalence of this cyclic ether motif in these synthetically challenging targets combined with the unfavorable entropic and enthalpic barriers that preclude formation of such ring-expanded oxacycles, efficient methods for their preparation are of high interest to synthetic and medicinal chemists.[4]

There is a plethora of developed methodologies that have been utilized to construct the oxepane moiety (Scheme 1). Various strategies such as radical cyclizations, Lewis acid-mediated cyclizations, and ring-closing metathesis are widely accepted cyclization strategies to access oxepanes from acyclic precursors. Additionally, ring-expansion of cyclopropanated glycals, homologations, and the Nicholas–Ferrier rearrangement are commonly used synthetic tactics to derive oxepanes from their pyranyl analogs. The routes taken to prepare these seven-membered oxacycles arise from either sugar-based or non-sugar-based starting materials. Advancements in the preparation of these seven-membered cyclic ethers have substantially impacted the synthesis of complex natural products laden with oxepane units within their scaffolds.

The oxepane motif is common within the core structures of various biologically relevant molecules of marine origin. Amongst the array of oxepane-containing natural products, the biological effects range from extremely lethal to potential therapeutic agents. Additionally, the total synthesis of these target molecules has been a daunting task due to the extensive structural and stereochemical complexity of these seven-membered polycyclic ethers. To this point, the total synthesis of these complex molecules has been a highly sought-after area of research.

Other implications of deriving the seven-membered oxacycles come from their close resemblance to their six-membered analogs. In terms of physiochemical properties as well

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Dr Kyle M. Lambert is an Assistant Professor in the Department of Chemistry and Biochemistry at Old Dominion University. Dr Lambert received his PhD in Chemistry in 2017 from the University of Connecticut under the supervision of Prof. Bill Bailey where his dissertation research focused on developing selective oxidations using oxoammonium salts. He was a NIH Ruth L. Kirschstein postdoctoral fellow in Prof. John Wood's group at Baylor University from 2017–2020 until starting his independent career at Old Dominion University. His group's research is focused on the synthesis of natural products, transition metal catalysis, computational chemistry, and developing new oxidative transformations.

as activity towards biological targets (*i.e.*, serving as ligands for lectins and substrates for glycosidases)[5,6] the synthesis of polyoxygenated oxepanes has medicinal importance.

Current synthetic routes to access oxepanes are outlined in the present work, which covers the synthesis of functionalized oxacycles with an emphasis on methods to prepare polyoxygenated oxepanes *via* cyclizations, ring-closing metathesis (RCM), rearrangement, ring expansion, and homologation strategies (Scheme 1). Applications of these synthetic advancements to the construction of bioactive oxepane-containing natural products and synthetic analogs is also covered.

2. Sugar-based approaches to oxepanes and septanoses

The preparation of oxepanes from pyranose sugars or glycals is among the most commonly used synthetic strategy mainly because it incorporates nearly all of the atoms and sets the stereochemistry at the required stereocenters without any additional effort. Sugar-based approaches to synthesize the oxepanes can be divided into four different sub-categories based on the treatment of the sugar derivatives in order to obtain the appropriate starting material.

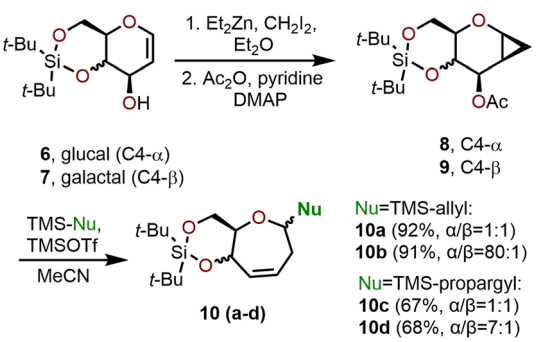
2.1. Ring-expansion of cyclopropanated glycals

Ring-expansion *via* cyclopropanated glycals is among the most widely explored area for the synthesis of polyhydroxylated oxepanes and septanoses. Such a strategy involves the cyclopropanation of carbohydrate-based glucals or galactals followed by an acid or base-mediated ring-opening event to obtain the corresponding seven-membered oxepine (*e.g.*, Scheme 2).[7,8] The resulting oxepine provides a valuable olefin functional handle that allows for further derivatization (*e.g.*, dihydroxylation, halogenation, arylation, *etc.*) to afford a variety of oxepanes and septanose carbohydrates. In the following section, strategies to construct functionalized oxepanes from commercially available glycals through ring-expansion approaches are covered.

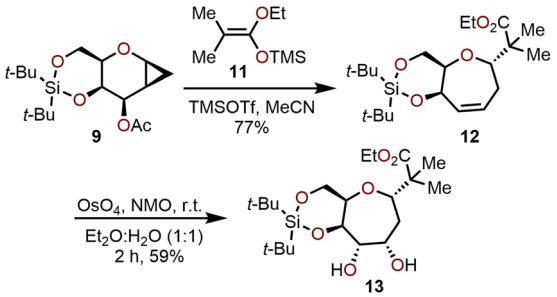
The ring-expansion of cyclopropanated carbohydrates to afford oxepanes has been thoroughly investigated by Hoberg and coworkers, who have demonstrated that the Lewis acid-catalyzed ring expansion of glucal and galactal systems can be executed with trimethylsilyl triflate (TMSOTf) in a process that is compatible with many silylated nucleophiles.[7–11] Hoberg and coworkers' strategy begins with silyl-protected glycals (*e.g.*, **6** or **7**), which are converted to cyclopropanated sugars using the Furukawa modification of the Simmons–Smith reaction as depicted in Scheme 2. The hydroxyl-directed cyclopropanation proceeds from the β-face with a 250 : 1 diastereomeric ratio (dr).[8] To set the stage for the ring expansion event, the C3 hydroxyl group (pyranose numbering) of the glycal is acetylated using acetic anhydride and pyridine as a base. In the event, the acetylated glycal (*e.g.*, **8** or **9**) is treated with a catalytic amount of TMSOTf, which results in the loss of the C3 acetate and enables the ring-opening of the cyclopropane to afford a seven-membered oxonium intermediate that is then intercepted by a nucleophile at C1.[7] The diastereoselectivity of the reaction was found to vary based on the nucleophile and starting material used. Cyclopropanated galactals resulted in higher diastereoselectivity (up to 80 : 1 dr), whereas their glucal counterparts resulted in much lower diastereoselectivity. For example, in the case of silyl-protected glucal **8**, the formation of allylated oxepane **10a** and allenylated oxepane **10c** is observed from treatment with the corresponding TMS-allyl and TMS-propargyl nucleophiles affording the products in 92% and 67% yields, respectively, but the process is not diastereoselective resulting in 1 : 1 α/β selectivity in both cases.[8] In contrast, when silyl-protected galactal **9** is treated with the same two nucleophiles, allylated oxepane **10b** and allenylated oxepane **10d** are in turn formed in 91% and 68% yields and with a high degree of α/β selectivity at C1 (**10b** = 80 : 1 and **10d** = 7 : 1). This large difference in selectivity is explained by the planar nature of the oxocarbenium ion intermediate formed from glucals, which can be accessed from both faces by approaching nucleophiles during anomeric bond formation, whereas in galactals the β-face is hindered by the tethered silanediyl resulting in preferential approach of the nucleophile from the α-face.[9,11]

The utility of this ring-expansion protocol toward polyoxygenated oxepanes was demonstrated by subjecting cyclopropanated galactal **9** to treatment with TMSOTf in presence of silylketene acetal **11** to afford oxepine **12** in 77% yield and 80 : 1 dr (Scheme 3). The olefin moiety in **12** underwent dihydroxylation from the α-face (>100 : 1 selectivity) under Upjohn conditions to provide **13** in a 59% yield. Other strategies have also been utilized for olefin functionalization such as epoxidation, halogenation and hydroboration–oxidation to obtain the respective oxepane systems with yields ranging from 40–90%.[10]

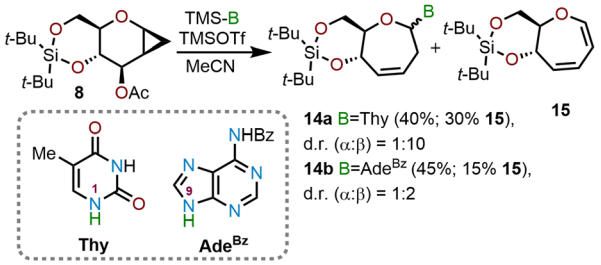
Sabatino and coworkers used a similar cyclopropanation/ring-expansion protocol for the synthesis of oxepane nucleic acids (ONAs) (Scheme 4).[12] ONAs are sugar phosphate oligomers in which the pentafuranose ring of DNA and RNA is replaced with a seven-membered oxepane ring. These unnatural analogs have been probed in biological studies which have provided new insights into the structure and function of natural and unnatural genetic systems. The same glycal donor



Scheme 2 Hoberg and coworkers' ring expansion to access oxepanes using silylated *C*-nucleophiles.[7–11]



Scheme 3 Advancement of cyclopropanated sugar **9** toward polyoxygenated oxepanes through Hoberg's ring-expansion protocol and dihydroxylation.[10]

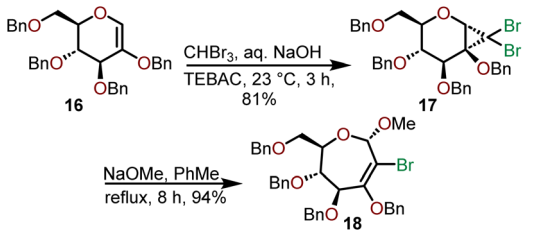


Scheme 4 Synthesis of oxepane nucleic acids (ONAs) *via* cyclopropanation strategy.[12]

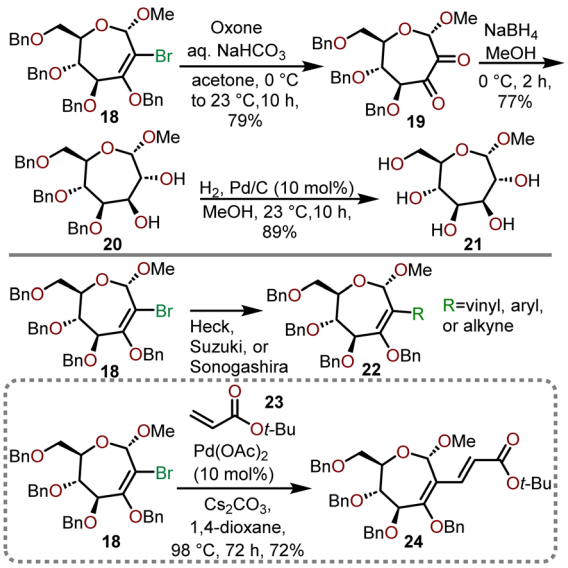
8 used by Hoberg and coworkers was treated with TMSOTf in acetonitrile solvent in presence of a persilylated thymine (Thy) or persilylated N^6-benzoyladenine (Ade^{Bz}) nucleophile. The reaction affords oxepine nucleosides **14a** or **14b** in 40% and 45% yield respectively alongside 15–30% of diene **15**. The product distribution of the ring opening reaction was found to be dependent on the potency of the nucleophile and in the case of persilylated thymine the reaction proceeded at a slower rate with an observed α : β selectivity of 1 : 10, whereas for persilylated N^6-benzoyladenine the α : β selectivity was only 1 : 2.[12] The oxepine products **14a** (N1) and **14b** (N9) were then desilylated using tetrabutylammonium fluoride (TBAF) and the olefinic moiety at C3–C4 (oxepine numbering) was reduced using standard catalytic hydrogenation conditions (Pd/C, 1 atm H_2, MeOH) to obtain the saturated ONAs in 60–63% yield over these two-steps.

A ring-expansion strategy to access oxepanes has also been used by Dey and coworkers who investigated the expansion of dihalocyclopropane oxyglycals (Scheme 5).[13,14] Their efforts began with a methylene insertion into the globally Bn-protected oxyglycal **16** using dibromocarbene generated *via* a haloform reaction under phase-transfer conditions using benzyltriethylammonium chloride (TEBAC).

The dihalocyclopropyl unit is then opened using sodium methoxide in refluxing toluene to afford 2-bromooxepine **18**, which can serve as a versatile intermediate that can be subjected to further oxidation or used in organometallic transformations as shown in Scheme 6.[13,14]



Scheme 5 Synthesis of dibromocyclopropane oxyglycal *via* ring-expansion.[13,14]

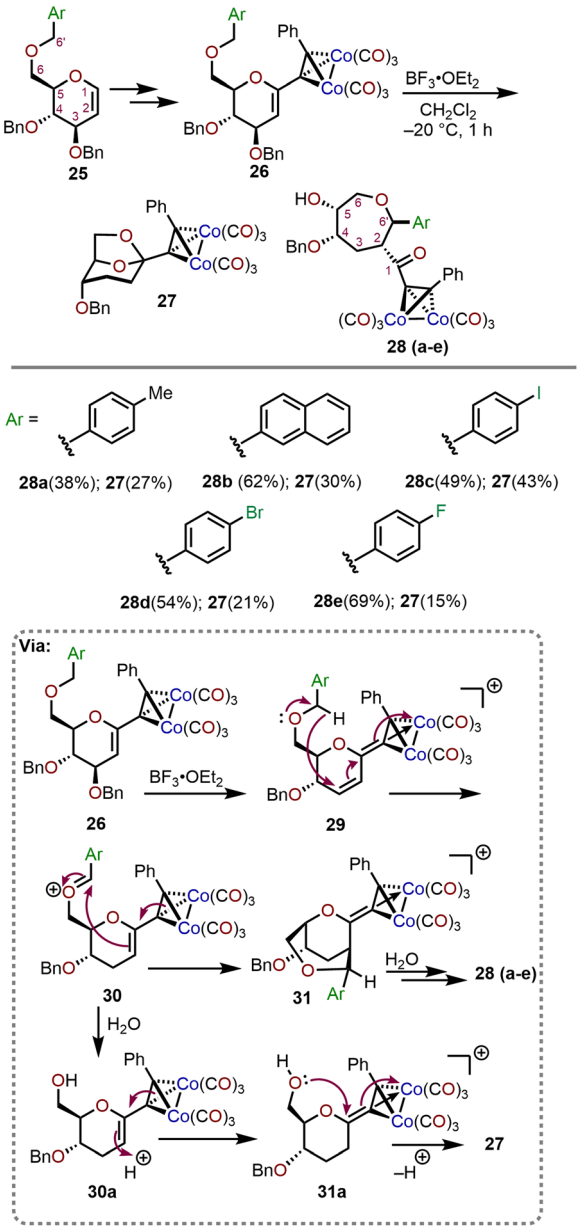


Scheme 6 Examples of further functionalization and advancement of key intermediate **18** toward polyoxygenated oxepanes.[13,14]

Epoxidation of key intermediate **18** with *in situ* generated dimethyldioxirane (DMDO) under aqueous alkaline conditions provides dione **19**, which can be subsequently reduced with sodium borohydride ($NaBH_4$) to afford the diol **20**. Catalytic hydrogenolysis with palladium on carbon was sufficient to globally deprotect the remaining benzyl ethers to yield polyhydroxylated oxepane **21** in good yield. The ability of **18** to engage in C–C bond-forming reactions mediated by transition metals further highlights its versatility as a key intermediate towards polyoxygenated oxepanes (**18** → **22**). Dey and coworkers demonstrate that the vinyl bromide functional handle in **18** can undergo a Heck coupling with *tert*-butyl acrylate (**23**) in the presence of $Pd(OAc)_2$ catalyst to provide desired oxepane **24** in 72% yield (Scheme 6).[13,14]

2.2 Nicholas–Ferrier rearrangement of pyranosidic cations

The Ferrier rearrangement and Nicholas reaction are widely explored synthetic transformations which involve the formation of cationic intermediates.[15,16] Gómez and coworkers have studied the behavior of Nicholas pyranosidic cations leading towards the formation of polyhydroxylated oxepanes from C6 *O*-arylated derivatives of D-glucal sugars (Scheme 7).[17]



Scheme 7 Formation of oxepanes *via* Nicholas–Ferrier rearrangement.[17]

The precursors to the pyranosidic cations (**26**) were prepared in four steps from D-glucals (**25**). Beginning with treatment of the Nicholas products **26** with boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) in methylene chloride solvent, the transformation takes place through a three-step reaction sequence (Scheme 7; bottom). The process involves: (i) a 1,6-hydride transfer onto the cyclic double bond of the C3 debenzylated intermediate **29** to generate the more reactive oxocarbenium species **30**, (ii) a two-step electrophilic addition (Ad_E) by the olefin moiety in **30** to form bicyclic system **31**, and (iii) pyranosidic ring opening by way of an intermediate hemiacetal to obtain the desired oxepane system **28**. The reaction can be conducted with a variety of aryl substituents on C6–OH (pyranose numbering) and through removal of adventitious water with 4 Å molecular sieves, the corresponding oxepanes were formed in moderate to high yields. The oxepane product **28** is formed preferentially over the 1,6-anhydro product **27** when molecular sieves are utilized to prevent the hydrolysis of oxocarbenium ion intermediate **30**, which leads to **27** by way of **30a** and **31a** (Scheme 7).

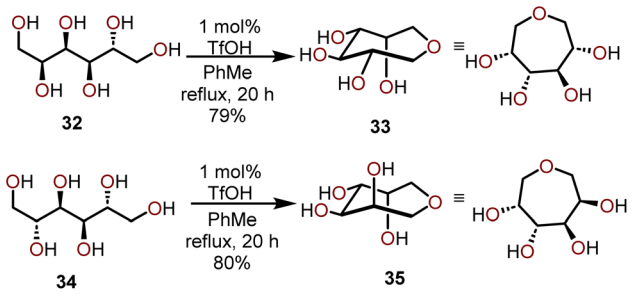
Further studies were conducted with electronically differentiated aryl substituted glycals allowing for synthesis of the respective oxepanes (**28a–e**) with yields ranging from 38–69%. As observed in Scheme 7, the substrates with electron-withdrawing groups favor the formation of the oxepane system, whereas electron-rich aryl systems result in a less electrophilic oxocarbenium **30** and are prone to hydrolysis by adventitious water affording greater amounts of **27**. Furthermore, two stereogenic centers are formed during the process and the stereochemical outcome at C2 (carbohydrate numbering) is governed by the geometric restrictions imposed on the approach of the of C6 substituent (carbohydrate numbering). The stereogenic center at C6′ (carbohydrate numbering) is dictated by the preferred rotamer of oxocarbenium **30** rotating the aryl group away from the bulky dicobalt hexacarbonyl moiety. The presence of a benzyl-type substituent at C6 (pyranose numbering) triggers the formation of substituted oxepanes and can be eliminated by use of a different substituent (*e.g.*, TBS) at the same position.

2.3 Cyclization of sugar-based polyhydric alcohols

Another approach that harnesses the innate stereochemistry of sugar-based starting materials to access polyoxygenated oxepanes is the use of polyhydric alcohols. Pavlik and coworkers have demonstrated that the formation of larger cyclic ethers can be accomplished by utilizing carbohydrate-based starting materials such as mannitol or sorbitol.[18] This approach is useful to generate five, seven, and eight-membered cyclic ethers without the need for protection of pendant hydroxyl units, and furthermore, the ring closure proceeds with retention of stereochemistry. The authors first observed this reactivity when D-sorbitol (**32**) was treated with 1 mol% of triflic acid (TfOH) in refluxing toluene, which upon careful NMR analysis was found to have afforded 1,6-anhydrosorbitol (**33**) as a single product, which was isolated in a 79% yield (Scheme 8).

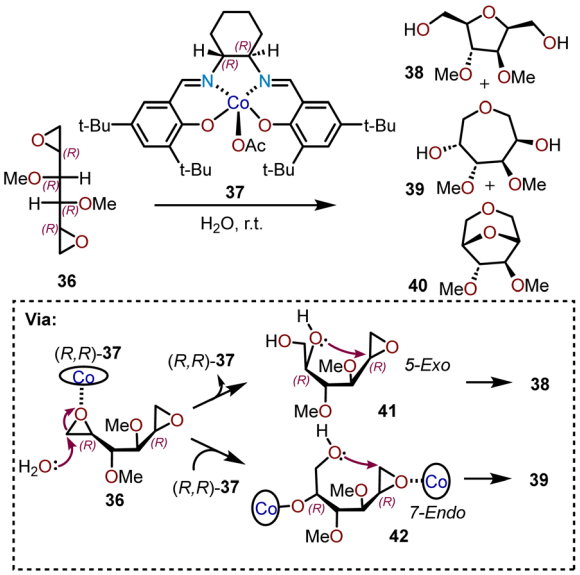
Similarly, when D-mannitol (**34**) was treated with 1 mol% TfOH under the same conditions, they observed the formation of a single tetrahydroxy oxepane product **35**, which was isolated in an 80% yield. The stereochemistry of the hydroxyl units in the starting materials was retained in both reactions, and the formed products were found to be stable under acidic conditions. The structure of the product obtained from the reaction of D-mannitol (**34**) was unambiguously determined to be 1,6-anhydromannitol (**35**) by spectroscopic comparison to a synthetic standard of **35** prepared in a six-step sequence from a 2,3-*O*-isopropylidene-D-erythronolactone commercial starting material.

An alternative strategy for utilizing chiral dianhydrosugars for regio- and stereoselective cyclizations has been demon-



Scheme 8 Synthesis of oxepanes *via* cyclization of polyhydric alcohols.[18]

strated by Satoh and coworkers.[19] The *C*2-symmetric dianhydrosugar **36** with a (2*R*,5*R*)-configuration contains two epoxy groups with similar reactivity. As depicted in Scheme 9, a (*R*,*R*)-(salen)-Co(III)Ac catalyst **37** is able to promote the cyclization of **36** at room temperature with a substrate : catalyst ratio of 200 : 1, producing *ca.* 28% of 1,6-anhydro-3,4-di-*O*-methyl-D-mannitol (**39**) along with *ca.* 57% of 2,5-anhydro-3,5-di-*O*-methyl-D-glucitol (**38**) and *ca.* 6% of a bicyclic dianhydro product 1,6:2,5-dianhydro-3,4-di-*O*-methyl-D-glucitol (**40**). The oxepane product **39** arises from the enantioselective hydrolysis of one of the epoxides by (*R*,*R*)-**37**, followed by cyclization of resulting diol into the other epoxide (*e.g.*, **42**; Scheme 9). First, the starting material **36** is coordinated with catalyst (*R*,*R*)-**37** to allow the *endo* cleavage of one of the epoxide groups in presence of water. During the process, the hydroxyl group remains coordinated to the catalyst and upon coordination of the other epoxy group with another molecule of (*R*,*R*)-**37** catalyst, an intramolecular 7-*endo*-cyclization affords oxepane **39**.[19–21] By-product **38** results from 5-*exo*-cyclization of the secondary hydroxyl (*e.g.*, **41**; Scheme 9). It is important to note that

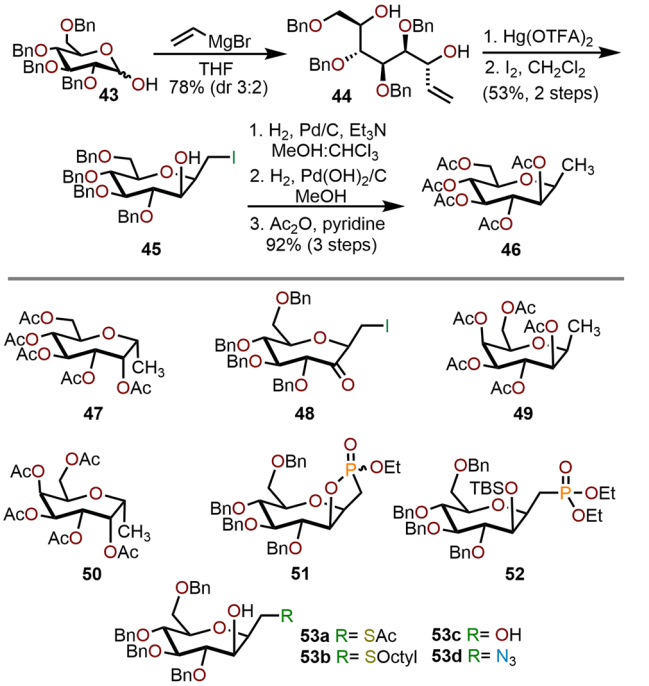


Scheme 9 Cyclization of dianhydrosugar alcohols.[19]

oxepane **39** is formed by a 7-*endo* cyclization of the initially formed epoxy alcohol, meaning that its formation is not affected by inherent stereoelectronic preference for the intramolecular *exo*-attack for cyclization as predicted by Baldwin's rules.[21] The mechanism of formation of seven-membered ring by *endo* attack was confirmed by the increase in the molar fraction of the (*R*,*R*)-**37** catalyst in the reaction system led to increasing yields of oxepane **39**.

2.4 Stepwise homologation of pyranoses and furanoses

Homologation of commercially available pyranose derivatives provides another useful strategy towards the synthesis of polyoxygenated oxepanes.[22] Vannam and Peczuh have demonstrated a concise synthesis of oxepanes *via* electrophilic C–O cyclization of allylic alcohols prepared from pyranose lactols as illustrated in the Scheme 10.[23] Their synthesis began with addition of vinylmagnesium bromide to tetra-*O*-benzyl-D-glucose **43** to give a 3 : 2 mixture of diastereomeric allylic alcohols. Treatment of the major isomer, **44**, with $Hg(OTFA)_2$ in THF initiated a diastereoselective electrophilic cyclization to an organomercuric species that was subsequently iodinated in methylene chloride to obtain compound **45** in a 53% yield. To facilitate the characterization, a three-step sequence of dehalogenation, hydrogenolysis, and acetate protection was performed to give **46** with a 92% yield. The minor isomer, epimeric at the allylic alcohol, produced **47** as a major product. When tetra-*O*-benzyl-D-galactose is used as the starting pyranose, the transformation yielded **49** and **50** in 84% and 92% yields, respectively.

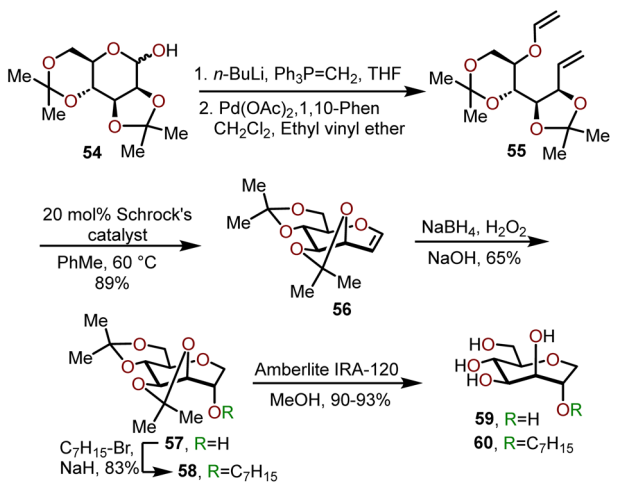


Scheme 10 Stepwise homologation of pyranoses to synthesize polyoxygenated oxepanes.[23]

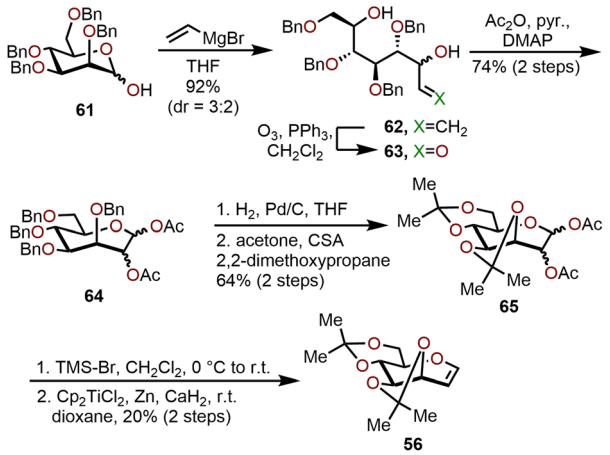
Compound **45** can be further derivatized using a variety of nucleophiles under known conditions to obtain fully functionalized oxepanes (**53a–d**) with yields ranging from 62–95%. Protection of the C2 hydroxyl group as the TBS ether followed by phosphonate formation gave **52** with a 65% yield over two steps. Alternatively, if the C2 hydroxyl group was left unprotected, attack by triethyl phosphite gave cyclic phosphonate **51** in 80% yield as a mixture of diastereomers. Finally, oxidation of the C2 hydroxyl group using pyridinium chlorochromate (PCC) provided ketone **48** in 92% yield.

A stepwise homologation approach has also been employed for the synthesis of biologically active, C1 unsubstituted oxepanes (*e.g.*, **59** and **60**) by Peczuh, Ernst, and coworkers.[24] Oxepane **60** was found to serve as an excellent mannopyranoside mimic adopting the same hydrogen bond network as parent antagonists for the mannose-specific lectin FimH receptor on bacterial pili of uropathogenic *E. coli*; which mediates attachment of the pathogen to urothelial cells thereby playing an essential role in the first step of urinary tract infections. The synthetic route to access **59** and **60** involved the preparation of oxepine **56** from 2,3,4,5-diisopropylidene-D-mannose **54**, which allowed for further functionalization of the olefin (Scheme 11).[24,25] The sequence begins with subjecting **54** to a Wittig olefination followed by vinyl ether formation using a catalytic amount $Pd(OAc)_2$ to afford diene **55**. Cyclization of **55** was achieved *via* a ring closing metathesis (RCM) mediated by 20 mol% of Schrock's catalyst to afford acetonide protected oxepine **56** in a 89% overall yield.[25,26] Next, a regio- and diastereoselective hydroboration-oxidation of **56** afforded access to oxepane **57** in 65% yield. Alternatively, *O*-alkylation of **57** with heptyl bromide afforded oxepane **58** in 83% yield.[24] Lastly, the acetonide groups were deprotected using Amberlite IRA-120 resin to obtain polyhydroxylated oxepane **59** in a 90% yield and *O*-alkylated oxepane **60** in a 93% yield.

An alternative, scalable route to acetonide-protected oxepine **56** utilizes a vinylation–cyclic hemiacetal formation strategy as illustrated in Scheme 12.[27] The synthesis starts with



Scheme 11 Synthesis of C2 substituted oxepanes *via* a RCM strategy.[24]

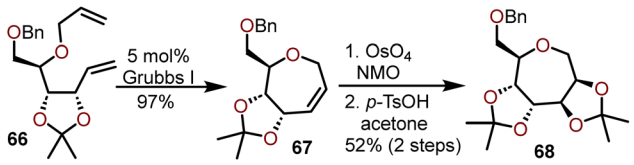


Scheme 12 Alternative strategy for synthesis of oxepine **56** required to access polyoxygenated oxepanes **59** and **60**.[27]

2,3,4,6-tetra-*O*-benzyl-D-mannose (**61**), which was treated with vinylmagnesium bromide to obtain allylic alcohol **62** in 92% yield and a 3 : 2 diastereomeric mixture. The diastereomeric mixture of allylic alcohol **62** was directly subjected to ozonolysis conditions and trapped as the seven-membered oxacycle *via* acetate protection to obtain a 1,2-di-*O*-acetyl-3,4,5,7-tetra-*O*-benzyl mannoseptanoside **64** with 74% yield over the two steps. Global benzyl deprotection of **64** was achieved by hydrogenolysis, then an acid-catalyzed acetonide protection using 2,2-dimethoxypropane afforded 1,2-di-*O*-acetyl-3,4,5,7-diisopropylidene mannoseptanoside **65** in a 64% yield over two steps. Bromination of septanose **65** followed by a Schwartz reductive elimination with titanocene dichloride yields acetonide protected oxepine **56** in a 20% yield over the two steps.[27] The above strategy was demonstrated to be a scalable synthesis for several polyoxygenated oxepanes with inexpensive starting materials and reagents, thereby it is complementary to RCM methods requiring Mo- or Ru-based catalysts.

Wong and coworkers have reported the synthesis of polyoxygenated oxepanes using a RCM strategy enabled by Grubb's 1st generation catalyst; the method is compatible with substrates accessible from pentose sugars.[28] An illustrative example of the protocol with diene **66**, available from D-ribose is shown in the Scheme 13.[28]

The intramolecular olefin metathesis of **66** at a concentration of 0.02 M afforded oxepine **67** in 97% yield. Advancement of **67** to afford polyoxygenated oxepane **68** in 52% yield was accomplished in a two-step process by Upjohn dihydroxylation of the olefin and acetonide protection of the resulting diol. Highly oxygenated substrates such as **66** worked well under these conditions to afford better overall yields of oxepine product in comparison to non-oxygenated substrates. While it may seem trivial, the use of a pentose *versus* a hexose sugar as a starting material not only alters the final position of the olefin in the generated oxepine, but it dictates which metal catalyst should be used for a successful RCM reaction. Wong and coworkers as well as Van Boom and coworkers successfully



Scheme 13 Polyoxygenated oxepanes by RCM strategy from furanoses.[28]

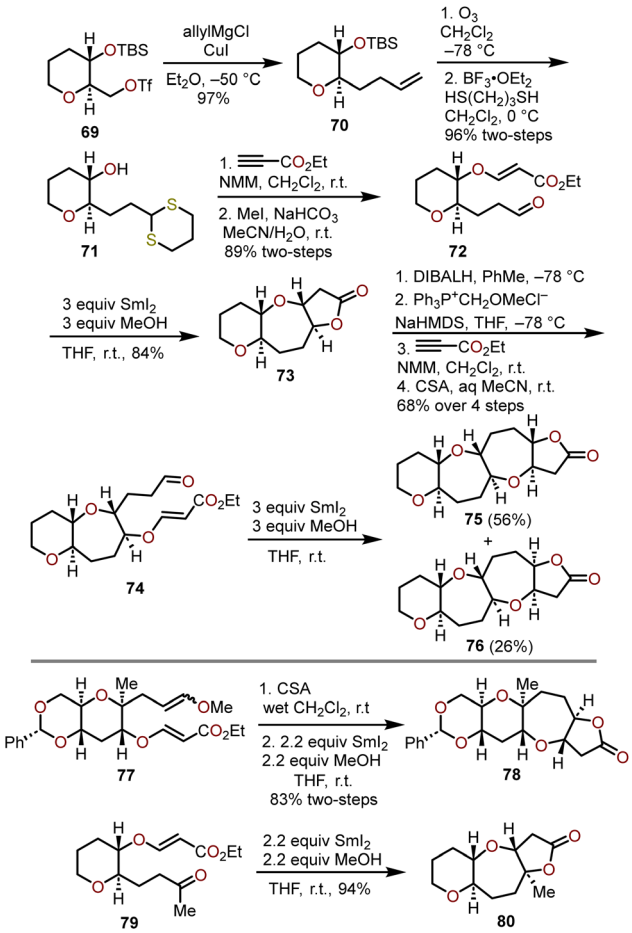
used the Grubb's 1st generation catalyst to perform a RCM with pentose-derived dienes, but when hexose-derived dienes were used by Peczuh and Snyder in a related oxepine synthesis strategy, the Grubb's 1st generation catalyst was found to be much less effective and the more reactive Schrock catalyst was required to afford the desired oxepines.[25,28,29] Both RCM strategies are very efficient and provide access to C1–C2 or C2–C3 oxepine targets with high selectivity allowing advancement to a variety of polyoxygenated oxepanes.

2.5 Radical cyclizations

Radical cyclizations of advanced glucal-derived intermediates offer another avenue to quickly access complex polyoxygenated oxepane targets. Reductive couplings promoted by samarium diiodide have been widely used in natural product synthesis and have been harnessed to construct polycyclic ethers with embedded oxepanes.[30,31] Nakata and coworkers were the first to explore the application of SmI_2-induced reductive couplings toward the synthesis of oxepanes (Scheme 14), which was expanded upon from their method to construct polycyclic tetrahydrofurans.[32,33]

Beginning with optically active triflate **69**, available from tri-*O*-acetyl-D-glucal in three steps,[35,36] allylation with allylmagnesium chloride and copper(I) iodide afforded olefin **70** in high yield. Ozonolysis and dithiane protection of the resulting aldehyde proceeded efficiently with concomitant desilylation to afford alcohol **71** in a 96% yield over the two steps. Treatment of **71** with ethyl propiolate in the presence of *N*-methylmorpholine (NMM) base resulted in a hetero-Michael addition between the secondary alcohol and ethyl propiolate, which was followed by dethioacetalization with methyl iodide in aqueous MeCN solvent to afford aldehyde **72**. Upon exposure of aldehyde **72** to three equivalents of SmI_2, reductive cyclization of the *in situ* generated ketyl radical with the tethered α,β-unsaturated ester afforded the lactone-containing 2,7-*syn*-2,3-*trans*-oxepane **73** as the sole product in 84% yield. Further advancement of **73** was accomplished through a DIBAL-H reduction of the lactone, Wittig reaction to install the methyl enol ether, a hetero-Michael addition of the free alcohol with ethyl propiolate, and treatment with camphor sulfonic acid to afford to aldehyde **74**, which allowed for the demonstration of the iterative power of the SmI_2 reductive cyclization to construct fused polyoxygenated oxepanes **75** and **76** in 56% and 26% yields respectively (Scheme 14).

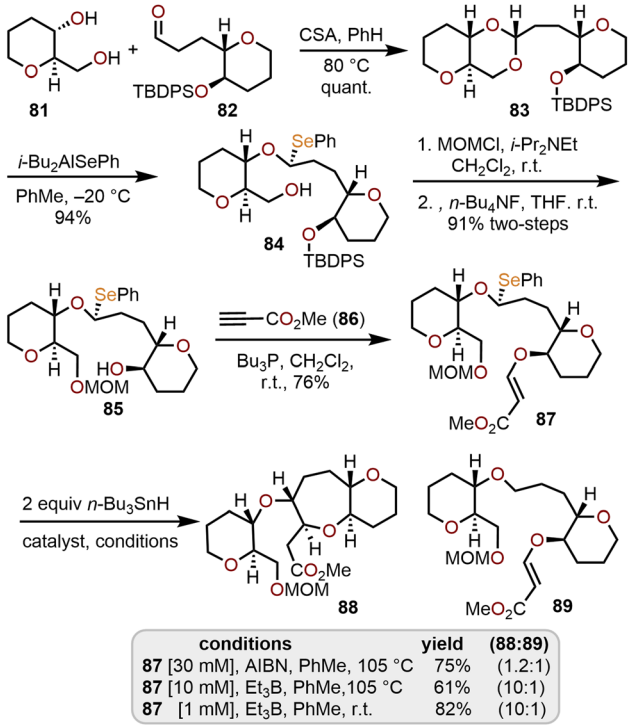
Nakata and coworkers followed up on their investigations and found that the reductive cyclization protocol can be conducted with 2.2 molar equivalents of SmI_2 (*e.g.*, **77** → **78**) and the aldehyde can be replaced with a methyl ketone to afford fused oxepanes containing an angular methyl group (*e.g.*, **79** → **80**) in excellent overall yield.[34]



Scheme 14 SmI_2 mediated radical cyclization strategy toward fused polyoxygenated oxepanes.[32,34]

Sasaki and coworkers investigated the use of monoselenoacetals (*e.g.*, **87** in Scheme 15) as precursors to α-alkoxyalkyl radicals and demonstrated that an efficient radical cyclization with a tethered β-alkoxyacrylate provides access to *O*-linked oxepane ring systems such as **88** in good yield.[37] To access the requisite monoselenoacetal **87**, diol **81** and aldehyde **82**, both available from tri-*O*-acetyl-D-glucal,[35,36] were treated with camphorsulfonic acid (CSA) to afford acetal **83**. Regioselective cleavage of the acetal was accomplished with diisobutylaluminum phenylselenide at low temperature to afford a single diastereomer of monoselenoacetal **84**.

This selectivity is presumed to arise from a tight-ion paired S_N1-type mechanism involving regioselective coordination of the bulky *i*-$Bu_2AlSePh$ reagent with the less sterically hindered oxygen of the acetal followed by intramolecular attack of the phenylselenide anion *syn* to the cleaved C–O bond.[37] Further advancement to **87** required manipulation of the hydroxyl protecting groups to give alcohol **85** followed by hetero-Michael addition to methyl propiolate.

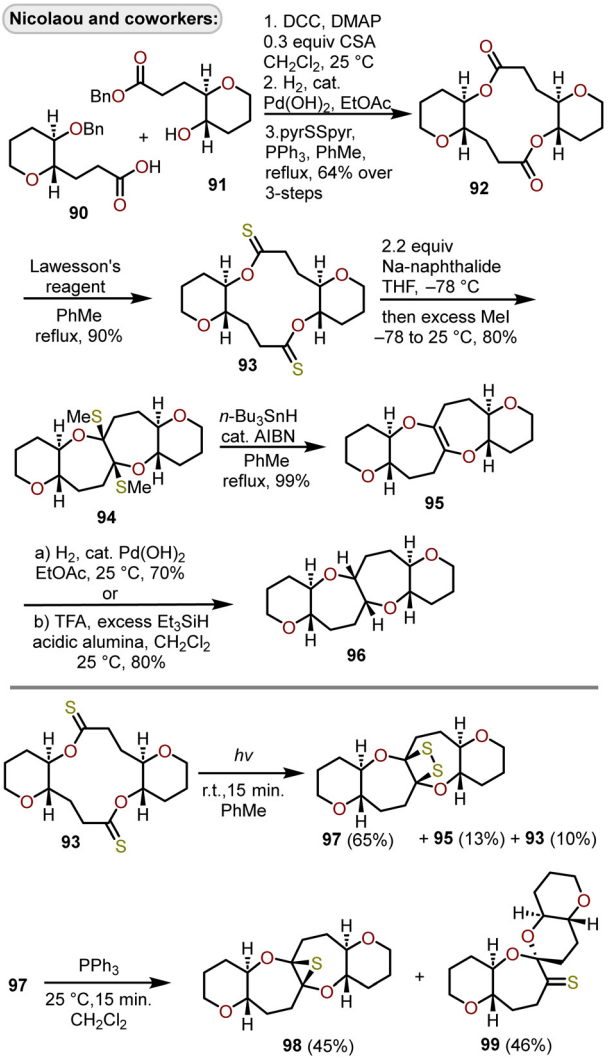


conditions	yield	(88:89)
87 [30 mM], AIBN, PhMe, 105 °C	75%	(1.2:1)
87 [10 mM], Et_3B, PhMe,105 °C	61%	(10:1)
87 [1 mM], Et_3B, PhMe, r.t.	82%	(10:1)

Scheme 15 Radical cyclization strategy using monoselenoacetals to access *O*-linked oxepanes.[37]

A handful of conditions were screened to achieve the key intramolecular radical cyclization and it was found that both 2,2′-azobisisobutyronitrile (AIBN) and triethylborane (Et_3B) in the presence of tributyltin hydride (*n*-Bu_3SnH) were effective radical initiators. To prevent formation of the reduction product **89** room temperature and high dilution conditions (1 mM) with Et_3B as the initiator were necessary to provide good yields of **88** (Scheme 15). This protocol has been demonstrated and adapted for the construction of key fragments of ciguatoxin, a complex polyether natural product *vide infra*.[38,39]

A radical cyclization of bridged dithionolides was developed by Nicolaou and coworkers to provide entry into tetracyclic ring systems containing polyoxygenated oxepanes (Scheme 16).[36,40] Beginning with benzylated hydroxy acid derivatives **90** and **91** that are derived from tri-*O*-acetyl-D-glucal,[36,40–42] sequential esterification through DCC coupling of the two fragments, debenzylation, and Corey–Nicolaou macrolactonization afforded diolide **92** in 64% yield over the three steps. Lawesson's reagent was used to access bridged dithionolide **93**, which upon exposure to sodium naphthalide in THF solvent at −78 °C then quenching with methyl iodide afforded the *cis*-bridged tetracycle **94** in 80% yield. Removal of the methylsulfides was accomplished using *n*-Bu_3SnH with azobisisobutyronitrile (AIBN) as an initiator afforded olefin **95** in excellent yield. Catalytic hydrogenation of **95** with Pearlman's catalyst or treatment with triethylsilane (Et_3SiH) under protic conditions afforded the 6/7/7/6-tetracycle **96**, which possessed the *cis*-fused oxepane rings. Attempts were



Scheme 16 Access to 6/7/7/6-tetracyclic ring systems *via* radical cyclization of bridged dithionolides.[36,40,45]

made to reduce **94** to the *trans*-fused oxepane ring system using Et_3SiH in the presence of silver tetrafluoroborate and were initially reported as successful,[40] however subsequent studies revealed these conditions resulted in rearrangement to a 6/6–6/6-system.[43,44] When dithionolide **93** was exposed to UV light for a short period of time, in contrast to treatment with sodium naphthalide, it was converted to dithiatopazine **97** in a 65% yield, alongside small amounts of recovered starting material **93** and olefin **95** (Scheme 16).[45] Treatment of **97** with triphenylphosphine at 25 °C resulted in extrusion of one of the sulfur atoms resulting in episulfide-containing oxepane **98** and spiro ketal-thioketone **99** in near equal quantities.

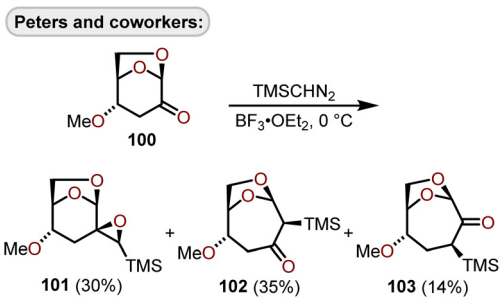
2.6 Lewis acid-catalyzed methods

Lewis acid-catalyzed ring expansions as well as cyclizations have been developed to construct polyoxygenated oxepanes from advanced intermediates which arise from glucals or erythrose sugars and have been used to construct oxepanes

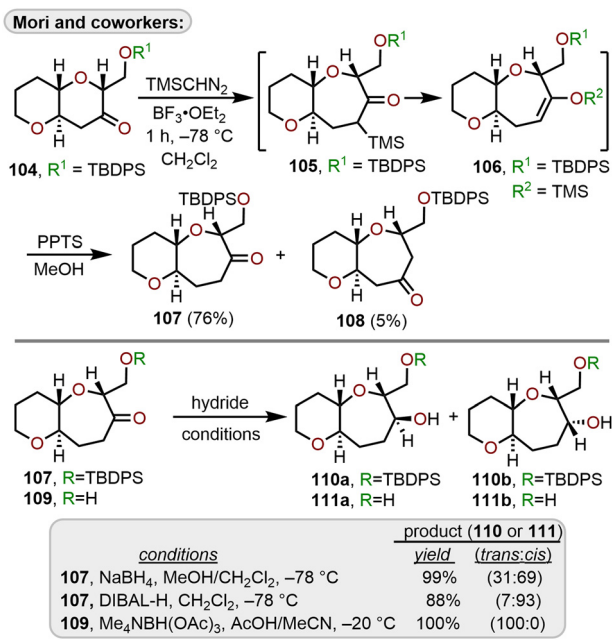
within fused polycyclic ether scaffolds. Peters and coworkers in their efforts towards polycyclic ether containing natural products advanced a $BF_3{\cdot}OEt_2$-mediated ring expansion to homologate 4-methoxylevoglucosenone derivative (**100**) with (trimethylsilyl)diazomethane ($TMSCHN_2$)[46] to afford a mixture of structural isomers **101**, **102**, and **103** (Scheme 17).[47]

The ring expansion to oxepanes **102** and **103** proceeds diastereoselectively affording products with the trimethylsilyl group on the β-face. The 4-methoxy substituent was found to be important to achieve high diastereofacial selectivity, and furthermore, unfunctionalized levoglucosenone resulted in competing 1,2- and 1,4-addition of $TMSCHN_2$ without ring expansion to the oxepane.[47]

Mori and coworkers have developed conditions using $TMSCHN_2$ to minimize the production of multiple homologation products arising from Lewis acid-catalyzed ring expansions of cyclic ketones using diazomethane (Scheme 18).[35,48,49]



Scheme 17 Lewis acid-catalyzed ring expansion of 1,6-anhydrohexos-2-uloses with (trimethylsilyl)diazomethane.[47]



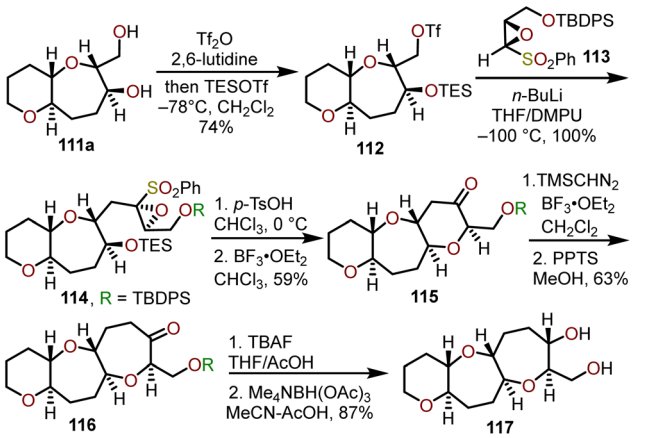
conditions	product (110 or 111) yield	(trans:cis)
107, $NaBH_4$, $MeOH/CH_2Cl_2$, –78 °C	99%	(31:69)
107, DIBAL-H, CH_2Cl_2, –78 °C	88%	(7:93)
109, $Me_4NBH(OAc)_3$, AcOH/MeCN, –20 °C	100%	(100:0)

Scheme 18 Access to 6/7-bicyclic ring systems *via* Lewis acid-catalyzed ring expansion of bicyclic ketones with (trimethylsilyl) diazomethane.[51]

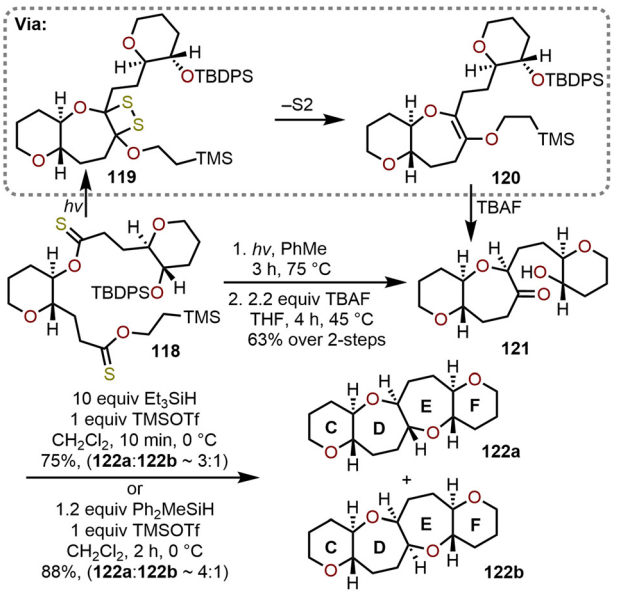
Starting with the *trans*-fused 6,6-bicyclic ketone **104**, which was constructed using an oxiranyl anion alkylation/6-*endo* cyclization strategy from **81**,[35,50] it was found that cryogenic temperatures using $BF_3{\cdot}OEt_2$ as the Lewis acid engendered formation of **105**, which after acid hydrolysis afforded **107** in 76% isolated yield over regioisomeric ketone **108**. The trimethylsilyl group directs the initial formation of the less sterically hindered α-trimethylsilyl ketone **105**, which quickly rearranges to silyl enol ether **106** thereby preventing the production of multiple homologation products. The selective reduction of ketone **107** with sodium borohydride ($NaBH_4$) or diisobutylaluminum hydride (DIBAL-H) afforded *cis* alcohol **110b** over *trans* alcohol **110a**, with DIBAL-H providing greater selectivity over $NaBH_4$ (Scheme 18).

By removal of the silyl protecting group on **107** to afford hydroxy ketone **109**, a selective, hydroxyl-directed reduction using tetramethylammonium triacetoxyborohydride provided *trans* alcohol **111a** quantitatively. Mori and coworkers advanced diol **111a** to ketone **116** and demonstrated the utility of this ring expansion protocol in an iterative approach to construct *trans*-fused 6/7/7-tricyclic ketone **116** which could be reduced to *trans*-fused 6/7/7-tricyclic diol **117** that is primed for further iterations of this sequence to construct larger polycyclic ether systems within natural products (Scheme 19).[51]

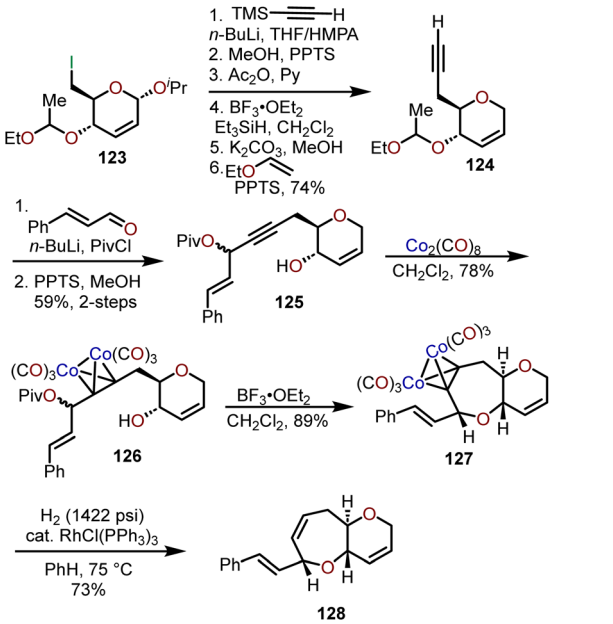
Complementary to the radical-based cyclizations of bridged dithionolides detailed in section 2.5 above,[36,52] Nicolaou and coworkers showed that tethered dithionoesters such as **118** could be cyclized into hydroxy ketone-containing oxepanes (*e.g.*, **121**, Scheme 20).[44,52] The process is proposed to proceed through a 1,2-dithietane intermediate (*e.g.*, **119**), which through expulsion of disulfur under the reaction conditions produce didehydrooxepanes (*e.g.*, **120**). Fluoride-mediated desilylation of **120** afforded hydroxy ketone-containing oxepane **121**, which enabled access to *trans*-fused 6/7/7/6-tetracyclic ring systems, such as the CDEF-ring skeleton of brevetoxin B (**122a**), through a TMSOTf-catalyzed reductive cyclization in the presence of trialkylsilanes (Scheme 20).[44,53,54] Of



Scheme 19 Access to *trans*-fused 6/7/7-tricyclic ring systems *via* Lewis acid-catalyzed ring expansion of bicyclic ketones with (trimethylsilyl) diazomethane.[51]



Scheme 20 Access to *trans*-fused 6/7/7/6-tetracyclic ring systems *via* Lewis acid-catalyzed reductive cyclization of hydroxy ketones with TMSOTf and trialkylsilanes.[44,52]

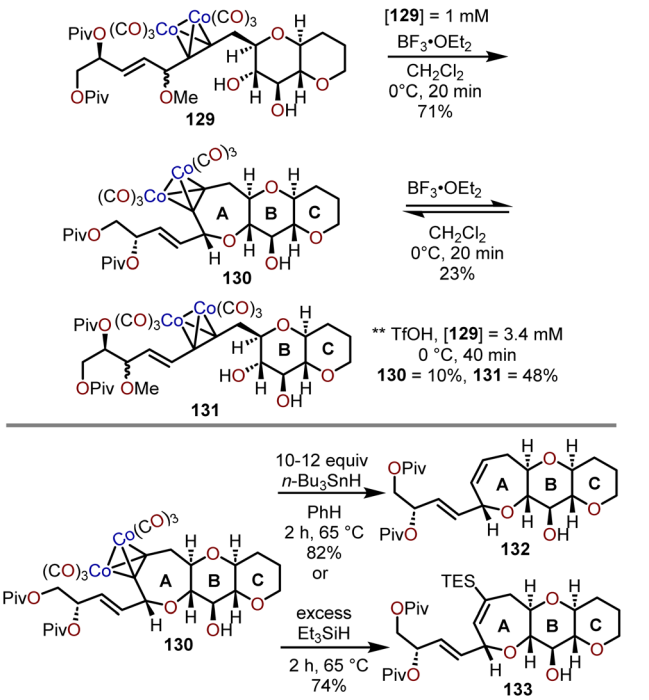


Scheme 21 Access to *syn–trans* fused 6/7-bicyclic ethers through Lewis acid-catalyzed generation of propargyl cations from dicobalt intermediates.[57]

the trialkylsilanes evaluated, Et_3SiH was found to be an effective reductant, but methyldiphenylsilane (Ph_2MeSiH) resulted in better overall yield and selectivity (*ca.* 4 : 1) for the desired *trans*-fused 6,7,7,6-tetracyclic ring system **122a** over **122b** (Scheme 20). Reductive cyclizations of hydroxy ketones are often used to construct oxepanes within the cores of complex natural products *vide infra*.[55,56]

Isobe and coworkers have leveraged the ability of dicobalt intermediates (*e.g.*, **126**) to participate in the Nicholas reaction in the presence of a Lewis or Brønsted acid to afford a stable propargylic cation and have shown that intramolecular trapping by a tethered alcohol can afford *syn–trans* fused 6/7-bicyclic ethers (*e.g.*, **128**; Scheme 21).[57] The exemplified sequence in Scheme 21 was refined from their earlier work on Brønsted acid-catalyzed cyclizations[58–60] and begins with iodide **123** prepared from glucal triacetate, which allows for conversion to acetylene **124**.[61,62] Addition of the lithium acetylide of **124** to cinnamaldehyde and trapping of the resulting alkoxide with pivaloyl chloride afforded the propargylic pivalate **125**. Acetylene dicobalt hexacarbonyl complex **126** was generated in good yield upon exposure of **125** to dicobalt octacarbonyl and when treated with $BF_3{\cdot}OEt_2$ underwent cyclization to the oxepane affording *syn–trans* fused 6/7-bicyclic ether **127** in 89% yield. Wilkinson's catalyst was used under high pressure hydrogenation conditions to remove the cobalt complex to afford **128**.

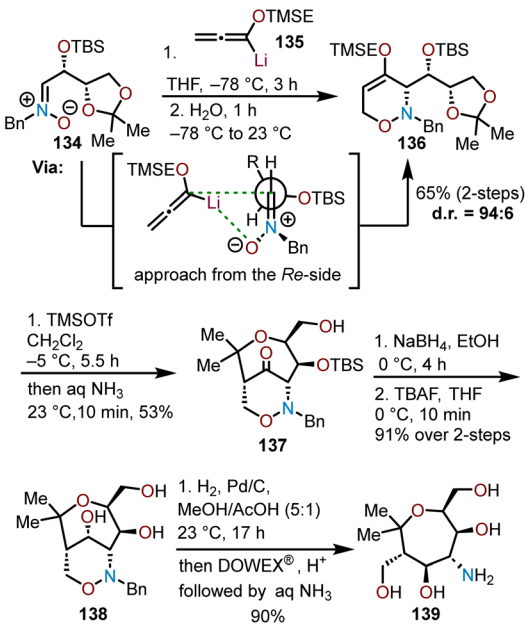
When the method was applied to systems (*e.g.*, **129**), which lacked additional stabilization through conjugation with an aryl system as in **126**, adjustments in temperature, concentration and time were needed to decrease the formation of the more stable open chain isomer **131** and shift the equilibrium towards formation of polycyclic ether **130**; which contains the ABC ring skeleton of ciguatoxin (Scheme 22).[57,62] Of note, the use of TfOH resulted in primarily open chain isomer **131** and only a 10% yield of **130**. Given the utility of **130** as a skeletal fragment of ciguatoxin, Isobe and coworkers developed



Scheme 22 Access to *syn–trans,trans*-fused 7/6/6-tricyclic ethers systems *via* Lewis acid-catalyzed cyclization of dicobalt hexacarbonyl acetylenes and reductive methods for decomplexation.[57,63]

alternative methods for decomplexation of dicobalt hexacarbonyl acetylenes that were more mild than previously employed with high pressure hydrogenation conditions (Scheme 22).[63] The use of an excess of *n*-Bu_3SnH as a reductant and heating to 65 °C affords the resultant oxepine (*e.g.*, **132**) with the cobalt complex functioning as the radical initiator for decomplexation. Alternatively, the use of Et_3SiH enabled a hydrosilative decomplexation to afford vinylsilane-containing oxepines with high regio- and stereoselectivities resulting in the silyl group oriented away from the more sterically encumbered substituent (*e.g.*, **133**). Variations of this approach have been advanced using dicobalt hexacarbonyl acetylenes to construct polyoxygenated oxepanes through the recyclization of sugar acetylenes,[64,65] the opening of dihydropyrans and recyclization,[60] and in the synthesis of the natural product ciguatoxin 1B.[61,62,66,67]

Bouché and coworkers used enantiopure nitrones (*e.g.*, **134**) that are readily prepared from erythrose sugars to access chiral 1,2-oxazines through a [3 + 3]-cyclization with lithiated TMSE-allene (**135**) and advanced the resulting 1,2-oxazines to poly(hydroxy)aminooxepanes through a Lewis acid-mediated rearrangement and reduction sequence (Scheme 23).[68] The key 1,2-oxazine intermediate **136** was formed with excellent diastereoselectivity (dr = 96 : 4) from the addition of **135** to enantiopure nitrone **134**. The high degree of diastereoselectivity observed for this transformation is attributable to *Re*-side attack of the nitrone by the lithiated TMSE-allene and is rationalized by a Felkin–Ahn model with coordination of the lithium cation to the nitrone oxygen further assisting to enhance selectivity.[68] Addition of TMSOTf to 1,2-oxazine **136** consequently forms ketone **137** in moderate yield *via* a Lewis acid-mediated rearrangement that proceeds through an intramolecular aldol reaction of an enol ether with an activated acetal in a Prins-type cyclization. Subsequent reduction of ketone **137** with sodium borohydride ($NaBH_4$) and desilylation with TBAF afforded triol **138**. Subsequent cleavage of the benzyl group in **138** under hydrogenolysis conditions followed by filtration through an acidic DOWEX® resin, and elution with aqueous ammonia afforded poly(hydroxy)aminooxepane **139** in a 90% yield. The route offers a modular approach to highly oxygenated aminooxepanes allowing for additional azide, alkynyl, and aryl-containing derivatives to be prepared.[68]



Scheme 23 Diastereoselective Lewis-acid rearrangement to afford enantiopure poly(hydroxy)aminooxepanes.[68]

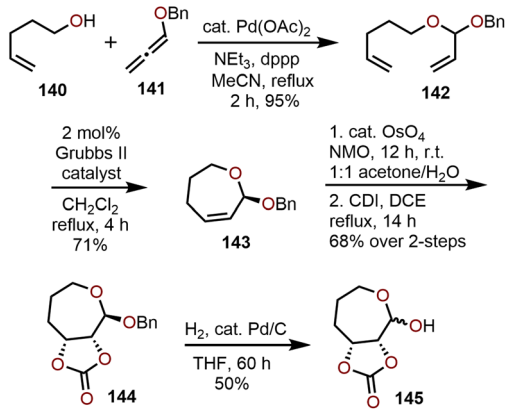
3. Synthesis of oxepanes from non-sugar-based starting materials

The inherent oxygenation and ability to relay stereochemical information provided by sugar-based starting materials has substantial advantages in the synthesis of polyoxygenated oxepanes. In the same vein, the use of non-sugar-based feedstocks can offer modularity and orthogonal avenues for diversification of the oxepane scaffold leading to polyoxygenated oxepanes that are not easily accessed from sugar-based feedstocks. The approaches used in *de novo* syntheses of oxepanes are often built upon strategies developed for sugar-based approaches and include cyclization by RCM, Lewis acid-mediated cyclizations, and ring-expansions through skeletal rearrangements.

3.1 Ring closing metathesis approaches

Access to polyoxygenated oxepanes through oxidation of seven-membered oxepines, which are easily accessible from RCM methods using functionalized dienes as starting materials prepared *via* olefination and *O*-allylation. The position of the olefin within the oxepine product can be easily varied by choice of starting materials.

An example of an RCM strategy utilizing readily available, non-sugar based starting materials by Yu, Blagg and coworkers is shown in Scheme 24.[69] Through vinylation of 4-pentene-1-ol



Scheme 24 Synthesis of oxepanes *via* RCM using Grubbs II catalyst by Yu, Blagg, and coworkers.[69]

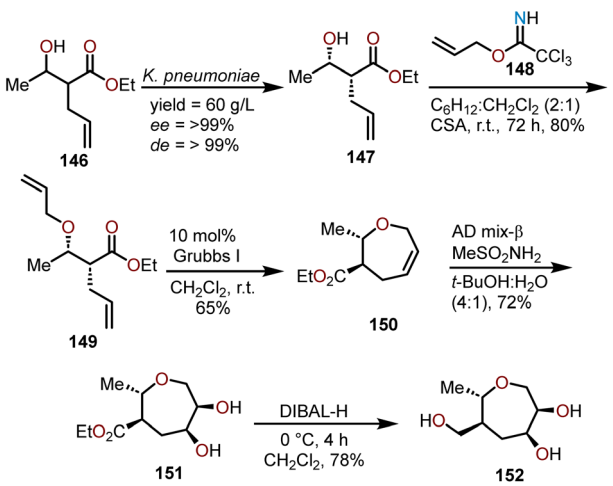
(**140**) with benzyloxy allene **141** in presence of $Pd(OAc)_2$ as a catalyst, RCM precursor **142** was accessed in 95% yield.[29] RCM using 2 mol% Grubbs II catalyst provides oxepine **143** in 71% yield and advancement through Upjohn oxidation to the *cis*-diol and trapping with 1,1-carbonyl diimidazole (CDI) affords the carbonate-containing oxepane **144** in 68% yield over two steps. Unfortunately, removal of the benzyl protecting group results in **145** being isolated as a 3 : 2 mixture of anomers (Scheme 24). This strategy has also been used by others to prepare small libraries of oxepanes by changing the substitution pattern on the diene and allene.[29,70]

Using a RCM strategy, Das and coworkers have been able to develop a synthesis of enantiopure oxepanes as carbohydrate mimics (Scheme 25).[71] Beginning with achiral β-hydroxyester **146**, a biocatalytic reduction with a ketoreductase from *Klebsiella pneumoniae* allows for a dynamic kinetic reductive resolution to afford essentially enantiopure **147**. The alcohol in **147** is protected as its *O*-allyl ether using allyl trichloroimidate **148** to obtain **149** in 80% yield, which was followed by an RCM reaction using 10 mol% of the Grubbs first-generation catalyst to produce an oxepine **150** in a 65% yield. Sharpless asymmetric dihydroxylation of the olefin affords bis-hydroxyoxepane **151** in a 72% yield, which was then treated with DIBAL-H to reduce the ester group to the primary alcohol affording polyhydroxylated oxepane **152** in a 78% yield. A unique feature of this synthetic strategy is, by utilizing biocatalytically derived β-hydroxy esters, synthesis of enantiopure polyhydroxylated oxepanes is possible with a good overall yield.

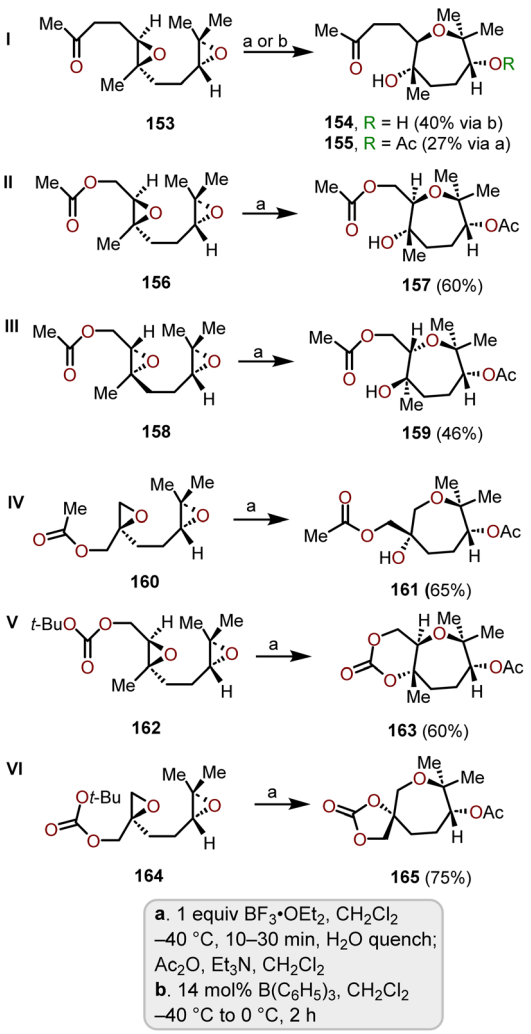
3.2 Lewis acid-mediated cyclizations of bis-epoxides

The synthesis of various polycyclic ethers through tandem oxacyclizations have been reported. Naturally, *exo*-oxacyclizations predominant over *endo*-oxacyclizations, which have been used to form polycyclic ethers. McDonald and coworkers expanded on this concept for the synthesis of polyhydroxylated oxepanes *via* a Lewis acid-mediated tandem *endo*-selective oxacyclization of 1,5-diepoxides.[72]

The starting materials for the cyclization reactions were prepared from commercially available geranyl acetone and it was derivatized *via* enantioselective Shi epoxidation conditions to obtain the 1,5-diketone system. After screening several Lewis acid-mediated cyclizations, $BF_3{\cdot}OEt_2$ in DCM at −40 °C was identified as the best condition for the majority of the substrates evaluated.[72,73] The 1,5-diepoxyketone **153** was able to be cyclized using $B(C_6H_5)_3$ in DCM solvent, which provided a 40% yield of **154**, whereas using the general conditions using $BF_3{\cdot}OEt_2$ work-up with acetic anhydride was required to isolate corresponding acetate **155** (Scheme 26, I).[73] With diepoxide acetate esters **156** and **158**, the yields were improved (60% and 46%) using the original conditions (*i.e.*, $BF_3{\cdot}OEt_2$ in DCM at −40 °C). McDonald and coworkers further demonstrated the stereospecificity of the oxacyclization from diastereomeric epoxide diacetate **158** (Scheme 26, III), which produced **159** with a slightly lower yield (46%).



Scheme 25 Synthesis of oxepanes using Grubbs I catalyst by Das and coworkers.[71]



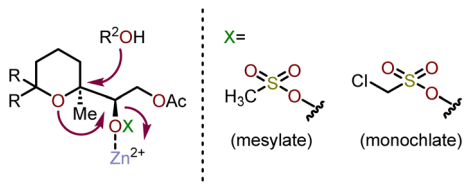
Scheme 26 Lewis acid-mediated cyclization of 1,5-diepoxides to synthesize oxepanes.[72,73]

Diepoxide acetate **160** bearing a different substitution pattern underwent cyclization to obtain **161** with a slightly better 65% yield (Scheme 26, IV). Altering the terminal functional group from acetate to *tert*-butyl carbonate provided fused- and spiro-bicyclic carbonate oxepane systems **163** and **165** with higher yields (60% and 75%) than the acetate bearing starting material (Scheme 26, V and VI). The mechanism of these bis-epoxide oxacyclizations involve Lewis acid activation of the terminal epoxide followed by an intramolecular nucleophilic addition from the internal epoxide oxygen to obtain a bicyclic intermediate. This intermediate is then attacked by a carbonyl group on the side chain to form the seven-membered oxacycles. Nucleophilic attack of the internal epoxide oxygen is primarily *endo* in the highlighted examples, which is governed by the carbonyl group of the side chain. Using the above strategy affords oxepanes and bis-oxepanes with high selectivity *via* tandem *endo*-selective and *trans*-stereoselective cyclization processes, which makes this transformation a powerful tool for synthetic chemists. Furthermore, this approach is viable from an abundant variety of commercially available starting materials.

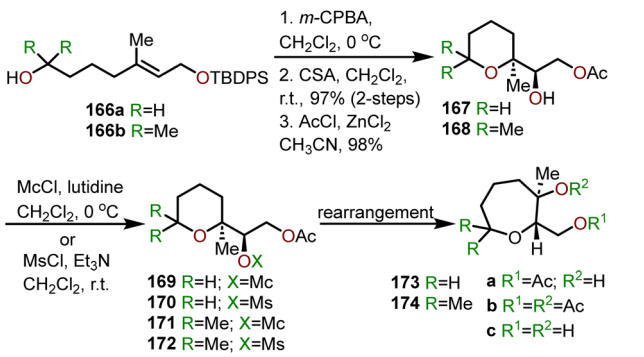
3.3 Ring expansion *via* skeletal rearrangements

One of the less intuitive techniques to synthesize polyhydroxylated oxepanes is *via* skeletal rearrangement of functionalized tetrahydropyrans. Such strategies are very useful for the synthesis of natural products containing polycyclic ethers like brevetoxin B or isolaurepinnacin.[74,75] In addition to these natural product syntheses, such strategies can also be utilized for the elaboration of functionalized oxepanes. Hori and coworkers have demonstrated that a $Zn(OAc)_2$ mediated rearrangement-ring expansion strategy of functionalized tetrahydropyrans to obtain oxepane **173** and **174**. Six membered cyclic ethers **167** and **168** were prepared from geraniol derivatives **166a** and **166b** *via* a three-step procedure involving epoxidation, *exo*-cyclization then silyl deprotection and subsequent acetate protection with AcCl-$ZnCl_2$ (Scheme 27). Intermediates (**167** and **168**) were further reacted with monochlate chloride (McCl) or methanesulfonyl chloride (MsCl) to obtain the desired precursor for the rearrangement (*e.g.*, **169–172**).[76] Treatment of **169** with $Zn(OAc)_2$ under reflux in AcOH : H_2O solvent for 30 min produced 2,3-*trans* oxepane **173a** and **173c** with 89% combined yield. Maintaining the same reaction for a longer period of time (3.5 h) at 80 °C produced a mixture of products **173a** (68%) and **173b** (19%). When the same transformation was carried out without the presence of Zn $(OAc)_2$, oxepanes **173a** and **173c** were produced in a 72% combined yield. The corresponding mesylate **170** produced **173a** and **173b** in 53% and 42% yield, respectively, when refluxed in AcOH : H_2O solvent in presence of $Zn(OAc)_2$.

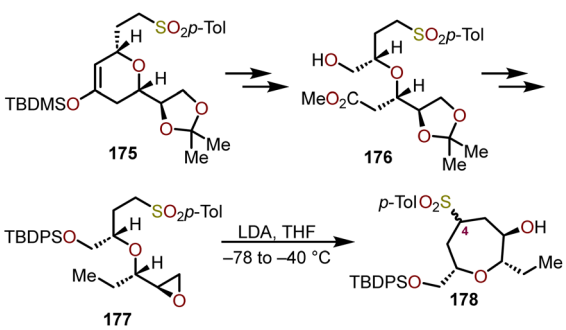
The rearrangement of monochlate **171** produced oxepane **174a** exclusively in a 92% yield when refluxed for 24 h in AcOH : H_2O in the presence of $Zn(OAc)_2$, whereas **174c** is exclusively produced when refluxed in a dioxane : H_2O mixture for 4 days. Using $Sc(OTf)_3$ under dioxane : H_2O reflux conditions, monochlate **171** produced an 82% combined yield of **174a** and **174c** after 6 h. Mesylate **172**, when refluxed with $Zn(OAc)_2$ in AcOH : H_2O produced **174a** with 90% overall yield in 2 h. The above stereoselective rearrangement is proposed to occur *via* a concerted mechanism to afford a single diastereomer as shown in Scheme 28. It was concluded that the ring expansion proceeds for monochlates under milder conditions, which were more effective than the corresponding mesylates.[75,76] The rearrangement reactions using monochlate with $Zn(OAc)_2$ in AcOH : H_2O have been successfully applied to the synthesis of hemibrevetoxin B by Morimoto and coworkers.[77] Mujica and coworkers have demonstrated a similar strategy for the synthesis of enantiopure oxepanes (Scheme 29).[78] Using (*R*)-glyceraldehyde acetonide as a chiral pool starting material, cyclic ether **175**, can be accessed *via* a Diels–Alder reaction with the requisite diene. This cycloadduct was then transformed into a linear ether *via* a three-step reaction sequence. The cyclic ether **175** was elaborated *via* ozonolysis followed by $NaBH_4$ reduction of the resulting aldehyde and methylation of the acid using



Scheme 28 Concerted mechanism for synthesis of oxepanes *via* skeletal rearrangement.[76]



Scheme 27 Oxepanes *via* skeletal rearrangement of functionalized tetrahydropyrans.[75,76]

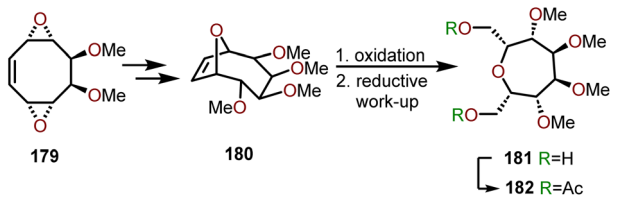


Scheme 29 Synthesis of enantiopure oxepanes *via* epoxide ring opening.[78]

diazomethane to afford **176**. Silyl protection of **176** with *tert*-butyldiphenylsilyl chloride (TBDPSCl), followed by reduction of the methyl ester and deoxygenation of the resulting primary alcohol was accomplished *via* tosylation and treatment with $LiAlH_4$. Acetonide deprotection and a final epoxide formation afforded enantiopure oxepane precursor **177**.[78] When **177** was treated with four equivalents of LDA in THF at −65 °C, the oxepane **178** was obtained as a 1 : 1 mixture of epimers at C4 (oxepane numbering) with 96% yield. Despite the mixture of epimers, the sulfone of **178** can be interconverted into a prochiral ketone after silyl protection of the free hydroxyl, treatment with LDA, then subsequent oxidation with MoOPh.[78] A key benefit of such transformation allows the established stereocenters to dictate nucleophilic additions into the oxepane C4.

In the above methodology, it is important to note that formation of the carbanion and attack on the electrophilic epoxide are two major transformations which give rise to oxepane system. Although both *endo* and *exo* attack of the nucleophile on the epoxide can occur, the formation of products from *exo* attack were not observed. This article has demonstrated a strategy for making functionalized oxepanes with a high degree of stereocontrol which can be useful for the synthesis of a variety oxepane-containing natural products.

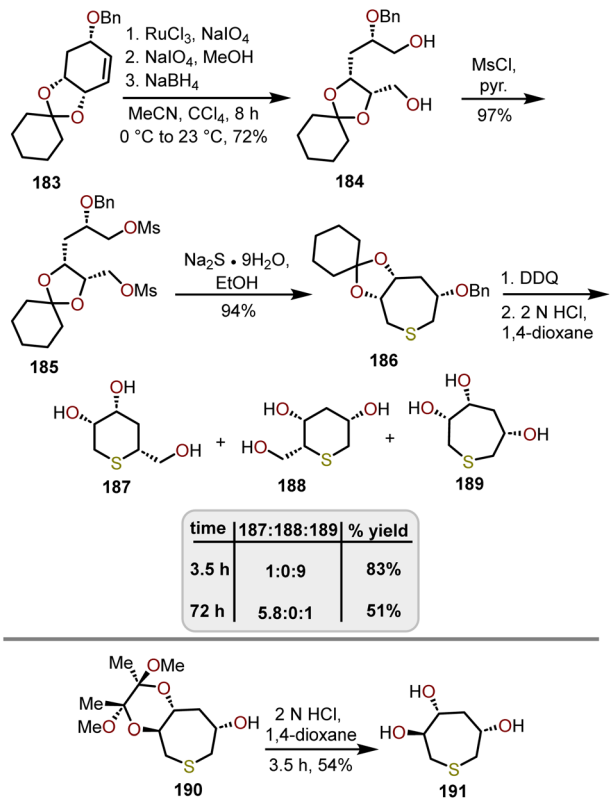
Armbruster and coworkers have demonstrated a strategy to synthesize *meso* persubstituted oxepanes using cyclooctatetraene *via* a modified skeletal rearrangement and ring contraction.[79] Synthesis of polyhydroxylated oxepane **181** or **182** started *via* cyclooctene **179** which containing two adjacent dimethyl ethers within a bis-epoxide system (Scheme 30). Intermediate **179** is obtained from a cyclooctatetraene, which was treated with trifluoroperacetic acid to yield a bis-1,5-epoxide system followed by a selective dihydroxylation using OsO_4/NMO.[80,81] For installation of *O*-functionality *via* allylic substitution in the above diepoxide system, a monofunctional nucleophile such as water was selected. The nucleophilic attack of water and ensuing epoxide-opening sequence affords bicycle **180**, thus providing the starting material to access fully functionalized oxepanes. Subjection of **180** to ozonolysis conditions followed by a reductive work-up afforded **181** with the stereochemistry shown in Scheme 30. Acetylation allowed isolation of polyoxygenated oxepane **182** with isolated yields in the range of 50–60%. Above is an excellent strategy to form polyhydroxylated oxepanes with a high degree of stereocontrol, with no observed epimerization in the intermediate steps. Modifying the nucleophile from water to primary amines allows access to *N*-substituted azepanes *via* a similar reaction sequence.[79]



Scheme 30 Synthesis of oxepanes *via* functionalized cyclooctatetraene.[79–81]

4. Synthesis of polyhydroxylated thiepanes

Unnatural sugar analogs such as thiepanes have been synthesized in similar fashion to their carbohydrate counterparts. Shih and coworkers developed a procedure to readily prepare 3,4,6-trihydroxythiepanes from D-(−)-quinic acid (Scheme 31).[82] After sequential dihydroxylation and oxidative cleavage of **183** with $RuCl_3$ and $NaIO_4$, and reduction with $NaBH_4$ gave diol **184** in an 72% yield. After mesylation of **184** to afford bis-mesylate **185**, incorporation of the sulfur with $Na_2S{\cdot}9H_2O$ provides thiepane **186** in a 94% yield. Deprotection of the benzyl group was carried out with DDQ, followed by acetal deprotection with 2 N HCl for 3.5 h to afford the desired 3,4,6-trihydroxythiepane **189** in an 83% yield. Longer reaction times led to the formation of the ring-contracted thiopyranyl isomers **187** and **188**. Specifically, with the reaction stirring for 3 days, the relative ratio of **187** to **188** to **189** was reported as 5.8 : 0 : 1. Alternatively, Shih and coworkers investigated the use of acetal protected thiepane **190**, which upon treatment with 2 N HCl for 3.5 h, exclusively provided polyhydroxylated thiepane **191** in a 54% yield. Decomposition of thiepane **191** was observed with longer reaction times affording thiopyrans. Nonetheless, literature is scarce in the development of synthetic methods that afford polyhydroxylated thiepanes and should be considered as an area of research in the future.



Scheme 31 Synthetic route to thiepane *via* a ring-expansion strategy.[82]

5. Applications to natural product total synthesis

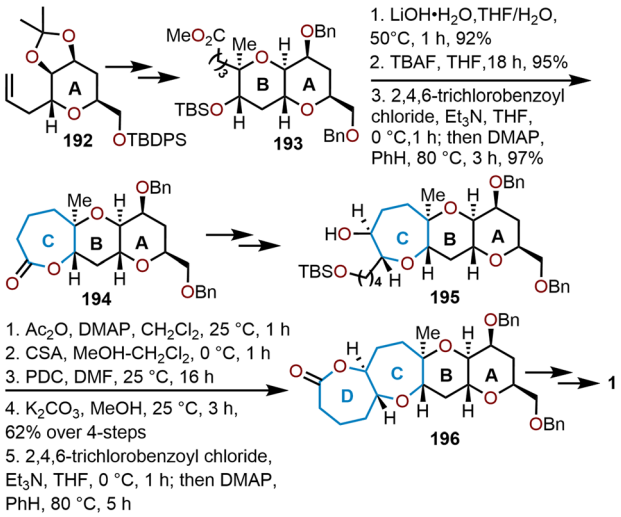
A key application of the highlighted synthetic methods for accessing polyoxygenated oxepanes is found in target-oriented synthesis. These seven-membered oxacycles are found within a variety of advanced scaffolds in natural products, whose assembly is a challenging task to synthetic chemists. In addition to the inherent structural complexity of oxepane-containing target molecules, some express notable bioactivities which makes them relevant for pharmaceuticals. Consequently, the discovery of these natural products has served as motivation for the development of novel synthetic methodologies to form oxepanes in various complex systems, which showcases the robustness of these transformations. This section will focus on the key synthetic efforts utilized to access natural products that possess polyoxygenated oxepane motifs.

5.1. Total synthesis of hemibrevetoxin B

A large family of natural products bearing the oxepane moiety are the brevetoxins. These highly bioactive compounds possess a ladder of polycyclic ethers and have been noted for their potent neurotoxicity. Amongst these biologically relevant molecules are the hemibrevetoxins, which are speculated to be biosynthetic metabolites to the brevetoxins. In 1989, Prasad and Shimizu elucidated the structure of hemibrevetoxin B, a *trans*-fused tetracyclic scaffold with two tetrahydropyrans adjacent to two oxepanes.[83] Hemibrevetoxin B contains ten stereogenic centers embedded within the 6/6/7/7-polycyclic array. Moreover, hemibrevetoxin B (**1**) was shown to exhibit cytotoxicity towards mouse neuroblastoma cells with an IC_{50} = 5 μM.[83] As a result of its bioactivity and its structural complexity, hemibrevetoxin B became a target molecule which was initially targeted and synthesized by the groups of Nicolaou, Yamamoto, Nakata, and Mori.[50,77,84,85]

The first total synthesis of hemibrevetoxin B was accomplished in 1992 by Nicolaou and coworkers whom used a linear, sugar-based approach starting from pyranose **192**, which is derived from readily available D-mannose (Scheme 32).[84] This allowed for the sequential construction of the 6/6 ring system after several transformations to afford key intermediate **193** and setting the stage for oxepane formation.

Sequential saponification, desilylation, then Yamaguchi lactonization gives the seven-membered lactone **194** from **193** in an 85% yield over the three-step sequence (Scheme 32). Elaboration of the tricyclic intermediate led Nicolaou and coworkers to the TBS-ether **195**. The free hydroxyl of **195** was capped with acetic anhydride and the TBS silyl-ether was cleaved with camphorsulfonic acid (CSA), whereupon oxidation of resulting primary alcohol with pyridinium dichromate (PDC) affords a carboxylic acid. Lastly, potassium carbonate was used to cleave the acetate protecting group and set the stage for the macrolactonization under Yamaguchi's standard protocol to give dioxepane **196**. The synthesis of hemibrevetoxin B (**1**) was completed in twenty additional steps from **196**. The work from Nicolaou's group demonstrates that dioxepane systems can be



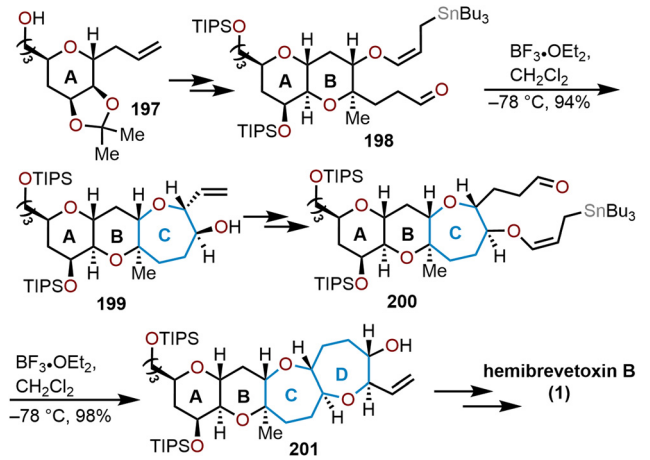
Scheme 32 Nicolaou and coworkers' strategy to access hemibrevetoxin B.[84]

successfully installed through Yamaguchi macrolactonizations, allowing for an iterative elaboration of the polycyclic system.

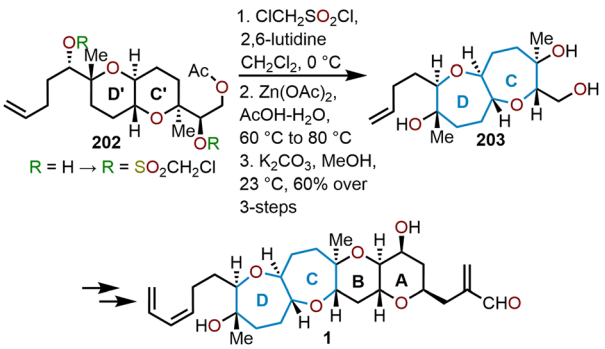
Another linear, sugar-based approach for the total synthesis of hemibrevetoxin B was accomplished by Yamamoto and coworkers in 1995.[85] Their route for the 6/6 ring system was closely inspired by Nicolaou's group, but the construction of the 7/7 rings were executed in a different manner. From D-mannose, known pyranose **197** was derived, whereupon several transformations provided key intermediate **198**. Aldehyde **198** underwent a stereoselective Lewis acid-mediated intramolecular condensation with the tethered allylstannane to rapidly access oxepane **199** in a 94% yield (Scheme 33).[85] The second oxepane ring **201** was also constructed *via* an intramolecular Lewis-acid mediated cyclization of **200**, which was elaborated over 14 additional steps to eventually afford hemibrevetoxin B. Kadota and Yamamoto reported an improved and stereocontrolled route to **1** in 1998 that constructed the A and B ring oxepanes in a similar manner.[86]

In their total synthesis of hemibrevetoxin B reported in 1996, Nakata and coworkers relied on a double ring expansion of the pyranyl moieties to construct the bis-oxepane (Scheme 34).[77] The bicyclic ether **202** was treated with chloromethanesulfonyl chloride in the presence of 2,6-lutidine to give a bis-chloromethanesulfonate that was then treated with zinc(II) acetate in acetic acid to perform the double rearrangement-ring expansion, thus yielding bicyclic septanoside **203** as shown in Scheme 34.[77] A unique feature of this transformation was the retention of stereochemistry, which results from the proposed concerted mechanism shown in Scheme 28.

Mori and coworkers demonstrate the high utility of oxiranyl anions in their 1997 formal synthesis of hemibrevetoxin B (Scheme 35).[50] Their innovative approach offers a stereocontrolled synthesis of **1** by leveraging their developed protocols with sulfonyl-stabilized oxiranyl anions (Scheme 19). For example, readily prepared epoxysulfone **205** is deprotonated with *n*-butyllithium at cold temperatures to form the oxiranyl



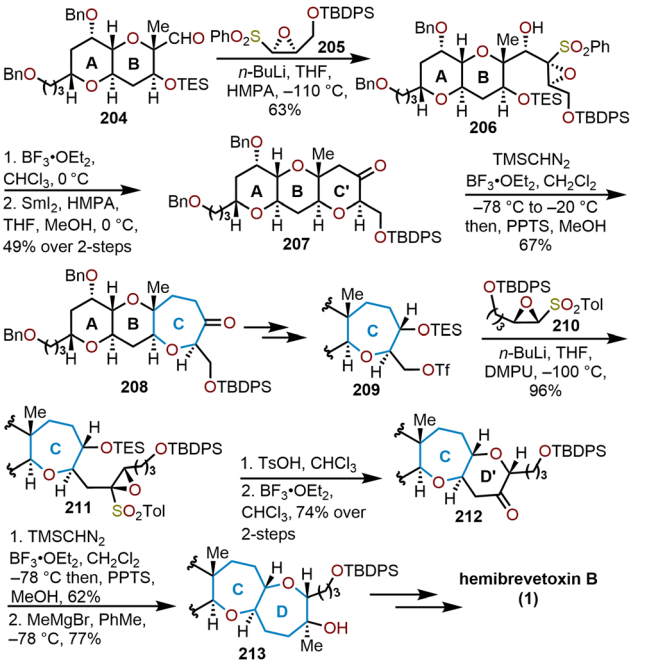
Scheme 33 Yamamoto and coworkers' strategy to access hemibrevetoxin B.[85,86]



Scheme 34 Nakata and coworkers' strategy to access hemibrevetoxin B.[77]

anion, which reacts with aldehyde **204** in a stereoselective fashion (3 : 1 mixture) to afford the desired alcohol **206** in 63% yield. Lewis acid-mediated cyclization with boron trifluoride etherate ($BF_3{\cdot}OEt_2$) led to the formation of a tricyclic hydroxy ketone, whereupon addition of SmI_2 removes the hydroxyl group to produce ketone **207**.

Oxepane formation was then achieved through a homologation event with $TMSCHN_2$ in the presence of $BF_3{\cdot}OEt_2$ (see Scheme 18 above) to give the 6/6/7-tricyclic ketone **208** in 67% yield. After several transformations Mori and coworkers performed this sequence again with triflate **209**. Coupling of the triflate and the epoxy sulfone **210** proceeded smoothly to afford the tethered tricycle **211** in great yield. Treatment of **211** with *p*-TsOH and $BF_3{\cdot}OEt_2$ formed the tetracyclic ketone **212** in 74% over two steps. Subsequent homologation of **212** with $TMSCHN_2$ gave the 6/6/7/7-tetracyclic system, which upon treatment with methylmagnesium bromide afforded alcohol **213**. After the complete formation of the tetracyclic scaffold, protecting group manipulation allowed access to a common intermediate employed by Yamamoto and coworkers[85] enabling a formal synthesis of hemibrevetoxin B in nine steps from **213**. The strategy used by Mori and coworkers displays the unique approach



Scheme 35 Mori and coworkers' strategy to access hemibrevetoxin B.[50]

to form six-membered ethers *via* addition of oxiranyl anions to electrophiles, followed by a Lewis acid-mediated cyclization. This synthetic strategy was nicely used to prepare for the homologation to arrive at the seven-membered rings.

Two additional formal syntheses of hemibrevetoxin B were completed by the Rainier[87] and Nelson[88] groups in 2001, and in 2003 the Holton[89] group completed a shorter, convergent total synthesis of **1** in 39 steps with a 4% overall yield. Rainier and coworkers' formal synthesis[87] used an annulation reaction that proceeded through a mixed acetal to construct the C ring oxepane and a RCM reaction using Grubbs I catalyst to construct the D ring oxepane, which allowed advancement to a common intermediate employed by Mori and coworkers.[50] Nelson and coworkers' formal synthesis did not tackle the construction of oxepanes, but used a desymmetrization of a centrosymmetric diepoxide through an enantioselective epoxide hydrolysis to access an epoxy acetal that contained both A and B ring tetrahydropyrans and was used by Nakata and coworkers.[77] In Holton and coworkers' convergent synthesis of **1**[89] the C ring oxepane was formed through a biomimetic epoxy alcohol cyclization[72,73] (see Scheme 26 above) using *N*-(phenylseleno)phthalimide as the electrophile in HFIP solvent, and the D ring oxepane was constructed through a RCM reaction using Grubbs II catalyst.

5.2 Total synthesis of brevetoxin B

The brevetoxins are a widely known family of polycyclic ethers that are potent neurotoxins found in the marine organism *Gymnodinium breve* Davis.[90] Brevetoxin B (Fig. 2, **214**) contains 11 *trans*-fused oxacycles with 6,7, and 8-membered rings with 23 stereocenters, thereby presents a challenging target for total synthesis and attracted the interest of several synthetic groups.

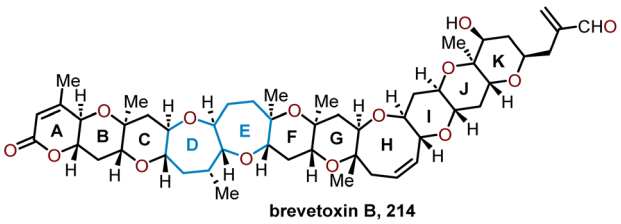
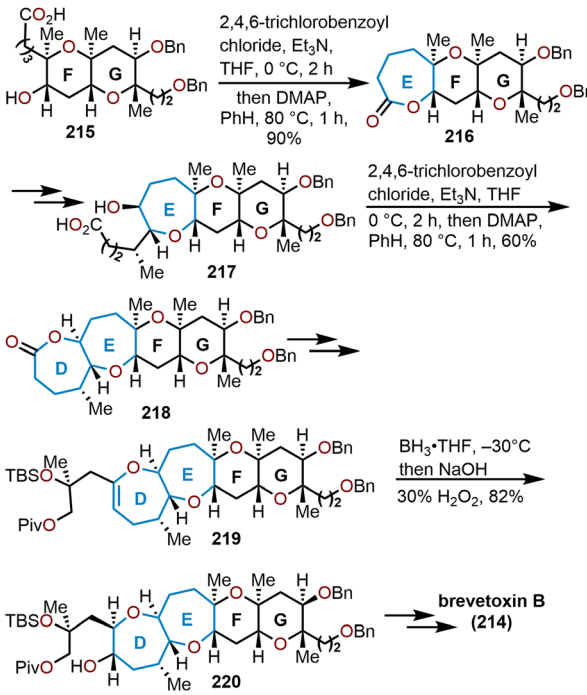


Fig. 2 Structure of brevetoxin B.

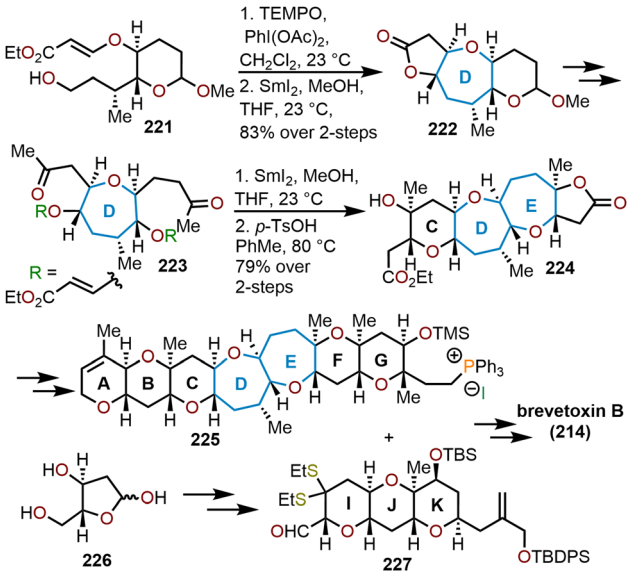


Scheme 36 Nicolaou and coworkers' route to brevetoxin B.[91–93]

Nicolaou and coworkers were the first to access **214** in 1995 from a sugar-based convergent synthetic route (Scheme 36).[91–93]

Their approach involved the assembly of the ABCDEFG and IJK ring systems, whereupon after convergence, the H ring would be stitched together *via* a hydroxydithioketal cyclization. The route towards **214** began with 2-deoxy-D-ribose as the starting material to construct the FG ring system in hydroxy acid **215** enabling macrolactonization under Yamaguchi conditions to give the seven-membered lactone **216** in 90% yield and stitch on the E ring (Scheme 36).[91] This intermediate was advanced to form a second hydroxy acid **217** to perform another Yamaguchi macrolactonization to furnish bis-oxepane **218** in 60% yield, now containing the D ring. Elaboration of **218** to oxepine **219** and hydroboration-oxidation to hydroxy oxepane **220**, which contains an alkyl tether with the requisite atoms for C-ring construction to further advance the left flank and eventually arrive at brevetoxin B.

The total synthesis of brevetoxin B was also accomplished by Nakata and coworkers in 2004.[94] A bidirectional strategy consisting of a double radical-induced reductive cyclization method was successfully employed to construct the CDE ring



Scheme 37 Nakata and coworkers' route to brevetoxin B.[94]

system as depicted in Scheme 37. Starting with commercially available tri-*O*-acetyl-D-glucal, the α,β-unsaturated ester **221** was produced after several steps. Oxidation of the alcohol with TEMPO and PIDA forms the aldehyde whereupon treatment with SmI_2 in methanol promotes their developed radical cyclization (Scheme 14) to furnish the 5/7/6 tricyclic lactone **222** with an 83% over the two steps.

Cleavage of the lactone and acetal led Nakata and coworkers to eventually arrive at the bis(methyl ketone) **223** on both flanks of the D ring. The bidirectional radical cyclization was able to furnish the CDE ring system **224** in a stereoselective fashion after treatment with *p*-TsOH. From the CDE lactone, the outer rings were constructed to afford the ABCDEFG ring system in **225**, which was coupled to the IJK ring system **227** available from 2-deoxy-D-ribose (**226**), eventually arriving at brevetoxin B.

5.3 Total synthesis of brevetoxin A

The most potent sodium channel activator of the brevetoxins is brevetoxin A, whose scaffold is composed of polycyclic ether ladder with one 5-membered lactone, four pyranyl units, one oxepane, three 8-membered oxacycles, and one 9-membered oxacycle (Fig. 3). The structural complexity of brevetoxin A is

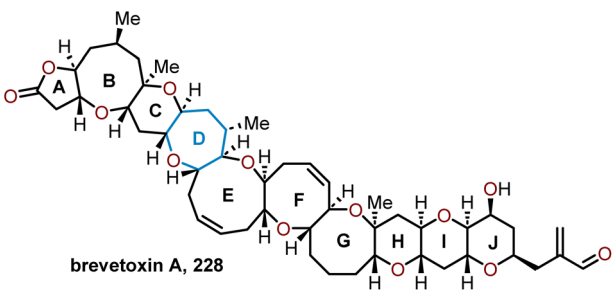
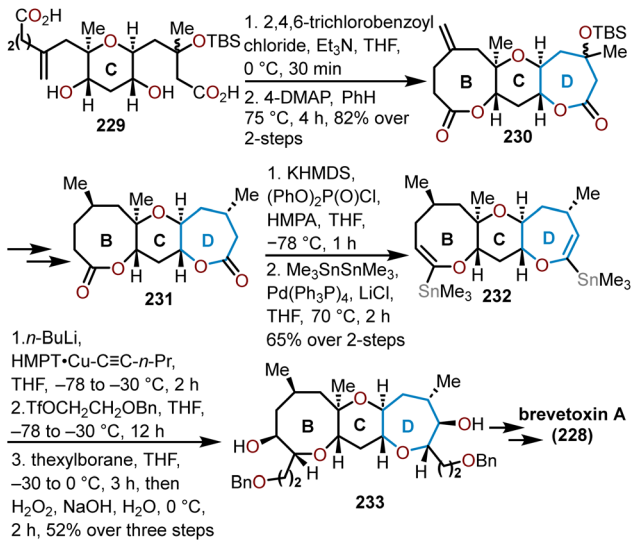


Fig. 3 Structure of brevetoxin A.

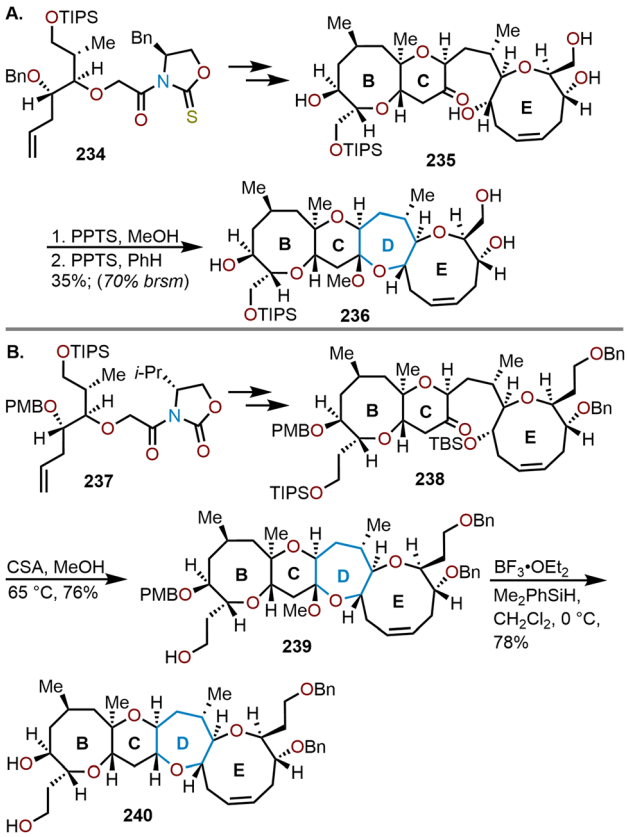
further compounded from the slow conformational changes within its skeletal to cause a 90° twist at one of the rings.[95]

The first total synthesis of brevetoxin A (**228**) was accomplished by Nicolaou and coworkers in 1998.[95] A sugar-based, convergent synthetic route was employed to stitch together the BCDE and the GHIJ ring systems. In the construction of the BCDE ring system, D-glucose was appointed as the starting material to obtain diacid **229** over 18 steps (Scheme 38). The B and D rings were formed in a single step *via* a double Yamaguchi macrolactonization to give bis-lactone **230** in 82% yield. Desilylation, followed by hydrogenation of the *exo*-methylene in **230** afforded the key intermediate **231**. A bidirectional approach was taken by Nicolaou and coworkers to afford bis(vinylstannane) **232** from **231** in 65% yield in a one-pot sequence. Tin-lithium exchange of the bis(vinylstannane) **232** with *n*-butyllithium followed by transmetallation with the copper acetylide of 1-pentyne provided a mixed cuprate, which was treated with benzyloxyethyl triflate to afford an intermediate bis(vinylether) that was subjected to hydroboration with t-hexylborane and basic hydrogen peroxide work-up to give diol **233** in 52% yield over three sequential steps. From the 8/6/7 tricycle, Nicolaou and coworkers were able to utilize the functionality on both flanks to complete the total synthesis of brevetoxin A.

The second group to accomplish the total synthesis of brevetoxin A was Crimmins and coworkers in 2009 (Scheme 39).[96] From their efforts, a stereoselective synthesis of the BCDE fragment was realized *via* a glycolyl thioimide auxiliary **234** (Scheme 39A).[97] After several synthetic transformations the BCE ring system was afforded and set the stage for an intramolecular cyclization event of the keto alcohol **235** using pyridinium *p*-toluenesulfonate (PPTS) to construct the D-ring. The cyclization event resulted in a 35% yield of oxepane **236** or 70% based on recovered starting material (brsm). Given bottlenecks in this original route, Crimmins



Scheme 38 Nicolaou and coworkers' route to brevetoxin A.[95]



Scheme 39 Crimmins and coworkers' synthesis of brevetoxin A.[97,98]

and coworkers developed a second-generation route to access brevetoxin A from glycocyl imide **237** (Scheme 39B).[98] The formation of the oxepane in ring D was improved upon by employing camphorsulfonic acid (CSA), which greatly increased the overall efficiency by cleaving the TBS-silyl ether in **238** to promote direct cyclization and afford **239** in 76% yield. Reduction of the mixed methyl ketals was carried out with $BF_3{\cdot}Et_2O$ and dimethylphenylsilane (see Scheme 20 above) to complete the construction of the BCDE fragment **240** in a 78% yield.

5.4 Total synthesis of brevenal

Brevenal (Fig. 4, **241**) was also isolated from the same species of dinoflagellate as the brevetoxins thus shares the same structural and stereochemical complexity inherent to this class of molecules. This pentacyclic polyether consists of two pyranyl units and three oxepane units with 13 stereogenic centers. An important feature of this natural product was observed from

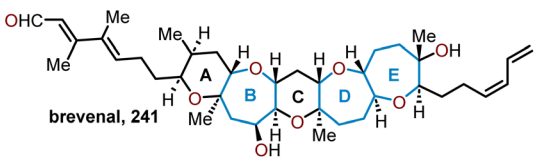


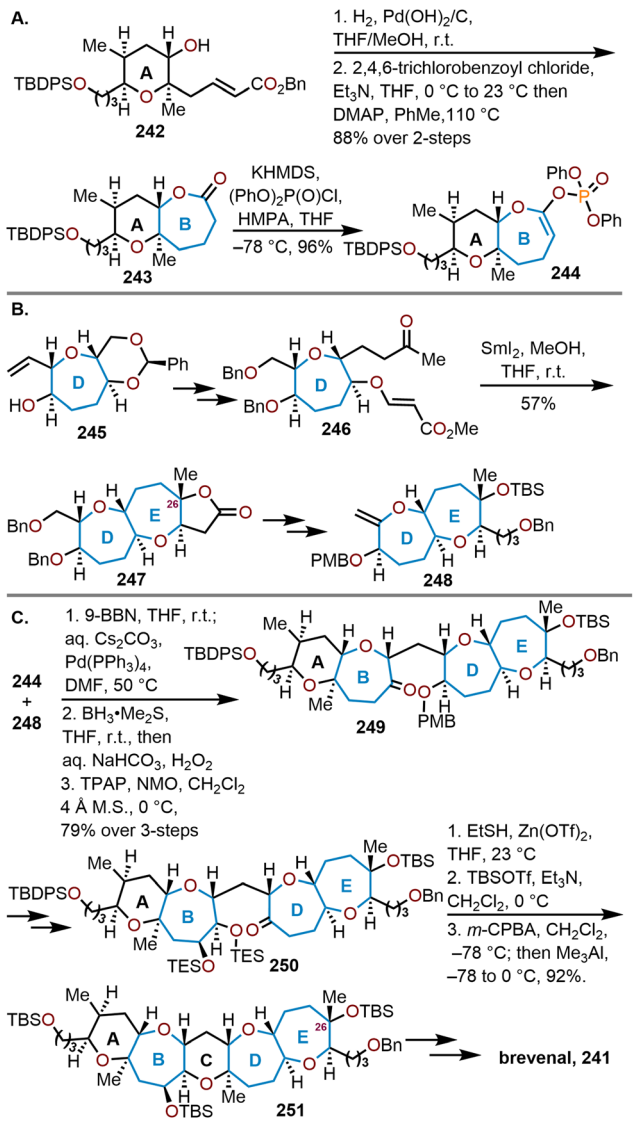
Fig. 4 Structure of brevenal.

its ability to improve tracheal mucus velocity in picomolar concentrations, which could be harnessed as a therapeutic for treating a variety of lung diseases.[99] The potential of medicinal applications made brevenal a target molecule for several groups.

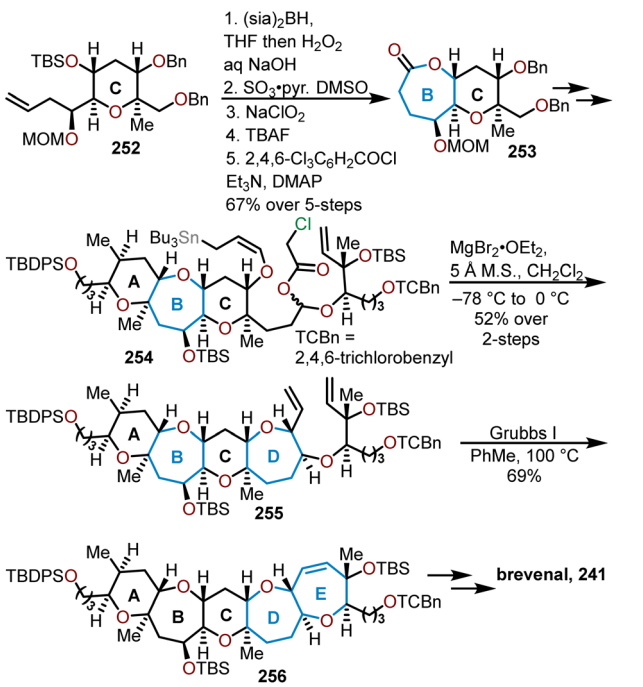
Sasaki and coworkers were the first group to complete the total synthesis of brevenal in 2006 (Scheme 40).[100] A convergent synthesis strategy was employed to couple the AB and DE fragments (**244** and **248**) through a Suzuki cross-coupling to afford **249** (Scheme 40C). The AB fragment was derived from a non-sugar starting material, which was eventually converted to α,β-unsaturated pyranyl ester **242** (Scheme 40A). Deprotection of the benzyl ester *via* hydrogenolysis followed by Yamaguchi macrolactonization afforded the AB ring system **243** in an 88% yield over the two steps. The lactone was then converted to enol phosphate **244** in preparation for the Suzuki cross-coupling. The DE ring system was derived starting from Nicolaou and coworkers known oxepane **245**.

After several transformations, α,β-unsaturated ester **246** was prepared (Scheme 40B). The E ring was formed *via* a reductive cyclization of **246** with SmI_2 (see Scheme 14 above) to afford dioxepane lactone **247** in 57% yield. Advancement to dioxepane **248** was accomplished over 12 steps, which enabled the hydroboration of the exocyclic enol ether in **248** with 9-BBN to provide a suitable coupling partner for Suzuki coupling with enol phosphate **244**, which was accomplished in the presence of $Pd(PPh_3)_4$ and Cs_2CO_3 to give a single stereoisomer (Scheme 31C). A hydroboration–oxidation of the resulting endocyclic enol ether furnishes an alcohol, which is afterwards oxidized to form the ABDE ring system **249** in an 79% yield over the three steps. Six additional steps from **249** were required to arrive at the bis-triethylsilyl ether **250** to carry out the final cyclization of ring C. The cyclization event proceeded with zinc triflate [$Zn(OTf)_2$] and ethanethiol to form a trapped thioketal. With the thioketal, a one-pot oxidation–methylation reaction with *m*-CPBA and trimethylaluminum ($AlMe_3$) was sequentially carried out to produce the completed pentacyclic scaffold **251**. Brevenal would be afforded in 18 additional synthetic steps after several more peripheral transformations of the sidechains and included the structural reassignment of the C26 stereocenter.

Another total synthesis of brevenal was completed in 2009 by Kadota and coworkers as shown in Scheme 41.[101] A linear route to brevenal was envisioned from the central C ring. Tetrahydropyran **252** was readily prepared from known procedures and advanced to a hydroxy acid *via* a hydroboration–oxidation, stepwise oxidation, and silyl deprotection in prepa-



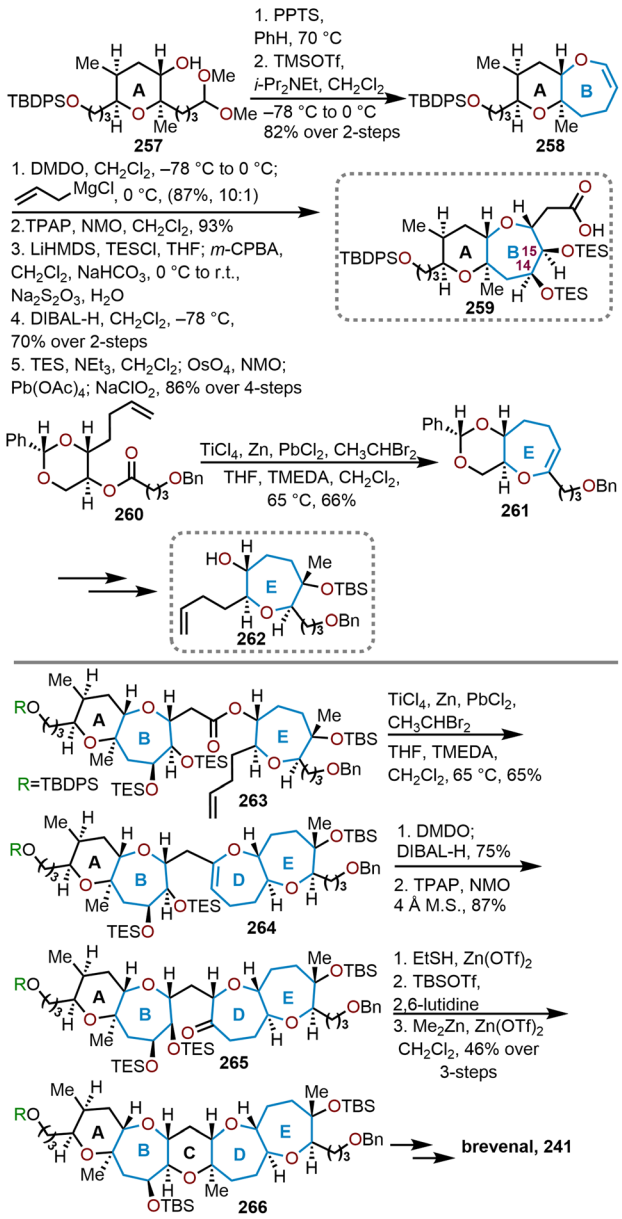
Scheme 40 Sasaki and coworkers' convergent strategy to access brevenal.[100]



Scheme 41 Kadota and coworkers' linear approach to brevenal.[101]

ration for a Yamaguchi macrolactonization to afford the seven-membered lactone **253**. After 21 additional synthetic transformations, Kadota and coworkers arrived at allylstannane **254**. In the presence of magnesium bromide, an intramolecular allylation closes the D ring to give the 6/7/6/7-tetracyclic diene **255** in a stereoselective manner. Furthermore, this prepares for the formation of the E ring *via* a Grubbs cross-metathesis to form oxepine **256**. From intermediate **256**, brevenal was afforded in 12 additional steps.

The Rainier group was also completed the total synthesis of brevenal (**241**) in 2011.[102] A convergent route was taken to couple the AB and E ring systems, where they would fuse the central C and D rings to complete the pentacyclic scaffold as shown in Scheme 42. A unique, unprecedented cyclization strategy using olefinic-esters served as inspiration to construct brevenal.[103] Starting with simple building blocks, acetal **257** was derived in seven linear steps utilizing previous chemistry developed in their efforts towards hemibrevetoxin B.[104] A two-step acid-mediated cyclization to a mixed acetal, followed by elimination of methanol afforded oxepine **258** in an 82% yield over the two steps. This two-step approach was more effective than a previously investigated one-step approach using PPTS and pyridine due to the sensitivity of **257** to PPTS at 130 °C.[105,106] Epoxidation of the olefin with DMDO, and subsequent allylation with allyl Grignard furnished allyl oxepane **259** in an 87% yield and 10 : 1 mixture of diastereomers. This intermediate was further advanced through a Ley oxidation of the C15 hydroxyl group, Rubottom oxidation to install the C14 hydroxyl group as a 6 : 1 mixture of the desired stereoisomer, a stereoselective DIBAL-H reduction to reinstate the C15 hydroxyl group, silyl protection of the diol with TESCl, dihydroxylation of the olefin, lead tetraacetate diol cleavage and oxidation afforded key acid **259** in 56% yield over the sequence. After constructing the AB core, Rainier and coworkers began to forge the DE ring system. The olefinic-ester **260** is available from L-glyceraldehyde acetonide in four linear steps and served as the starting point for the E ring. Rainier and coworkers optimized the olefinic-ester cyclization to form oxepine **261** in 66% yield, using an *in situ*-generated reduced titanium ethylidene reagent from titanium tetrachloride, zinc, lead(II) chloride, and 1,1-dibromoethane. After eight synthetic transformations, hydroxyl-containing oxepane **262** was afforded to be coupled to the AB ring system in **259** *via* a Shiina esterification. After successful coupling, ketone **263** was subjected to the same olefinic-ester cyclization conditions for preparing oxepine **261** to give ABDE ring system **264** in 65% yield. Epoxidation, *in situ* reductive opening with DIBAL-H, and Ley oxidation gives ketone **265** in 65% yield over the two steps. The central C ring was fused together *via* a Lewis acid-mediated cyclization with concomitant cleavage of the triethylsilyl (TES) ethers in **265**. Addition of ethanethiol forms a trapped thioketal allowing methylation to be accomplished from the procedure developed by Kadota and coworkers.[85] After completion of the pentacyclic system, 10 additional synthetic steps were required for side chain incorporation, which allowed Rainier and coworkers to complete the shortest synthesis of brevenal to-date in 38 linear steps and 0.99% overall yield.



Scheme 42 Rainier and coworkers' strategy to access brevenal.[102]

5.5 Total synthesis of ciguatoxin 1B (CTX1B)

Ciguatoxins are a family of polycyclic ethers, which have been known to be highly potent neurotoxins found in marine dinoflagellate *Gambierdiscus toxicus*. The prominent ciguatoxin is ciguatoxin 1B (CTX1B, **267a**, Fig. 5) and its structure was elucidated in 1989 by Yasumoto and coworkers.[107] CTX1B was found to possess a *trans*-fused polycyclic ring system consisting of 13 oxacycles of various ring sizes (five to nine) and 33 stereogenic centers. Due to its unprecedented ladder-like ring system and its scarcity in nature, CTX1B became a target molecule for many groups. The first group to complete a total syn-

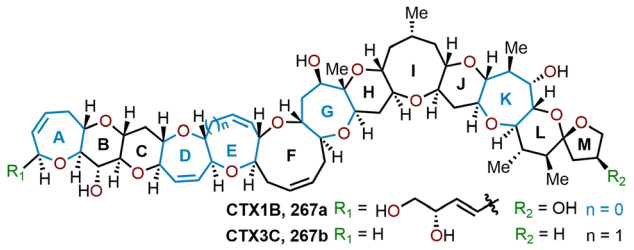
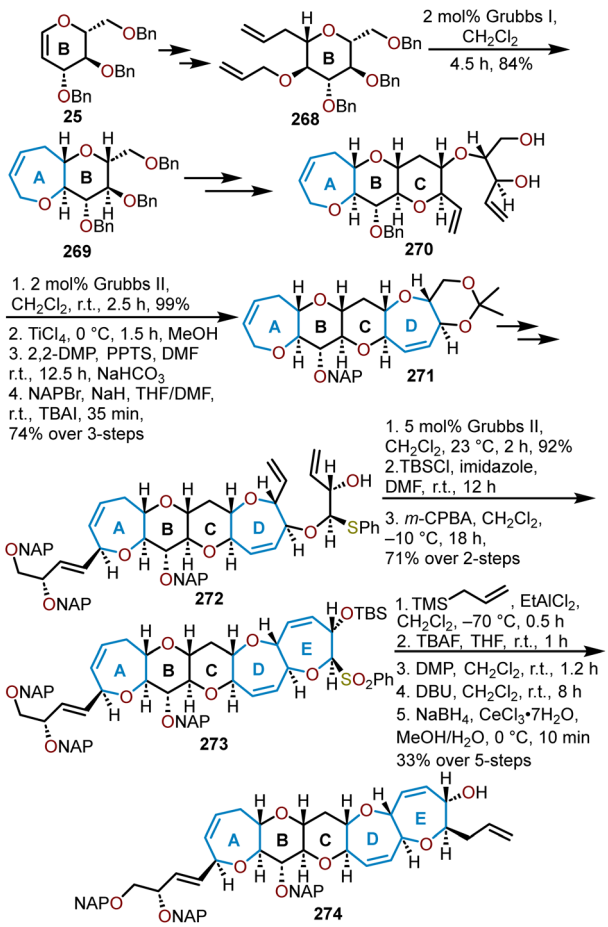


Fig. 5 Relevant ciguatoxin target molecules.

thesis of CTX1B (**267a**) was that of Inoue, Hirama and coworkers in 2006.[108]

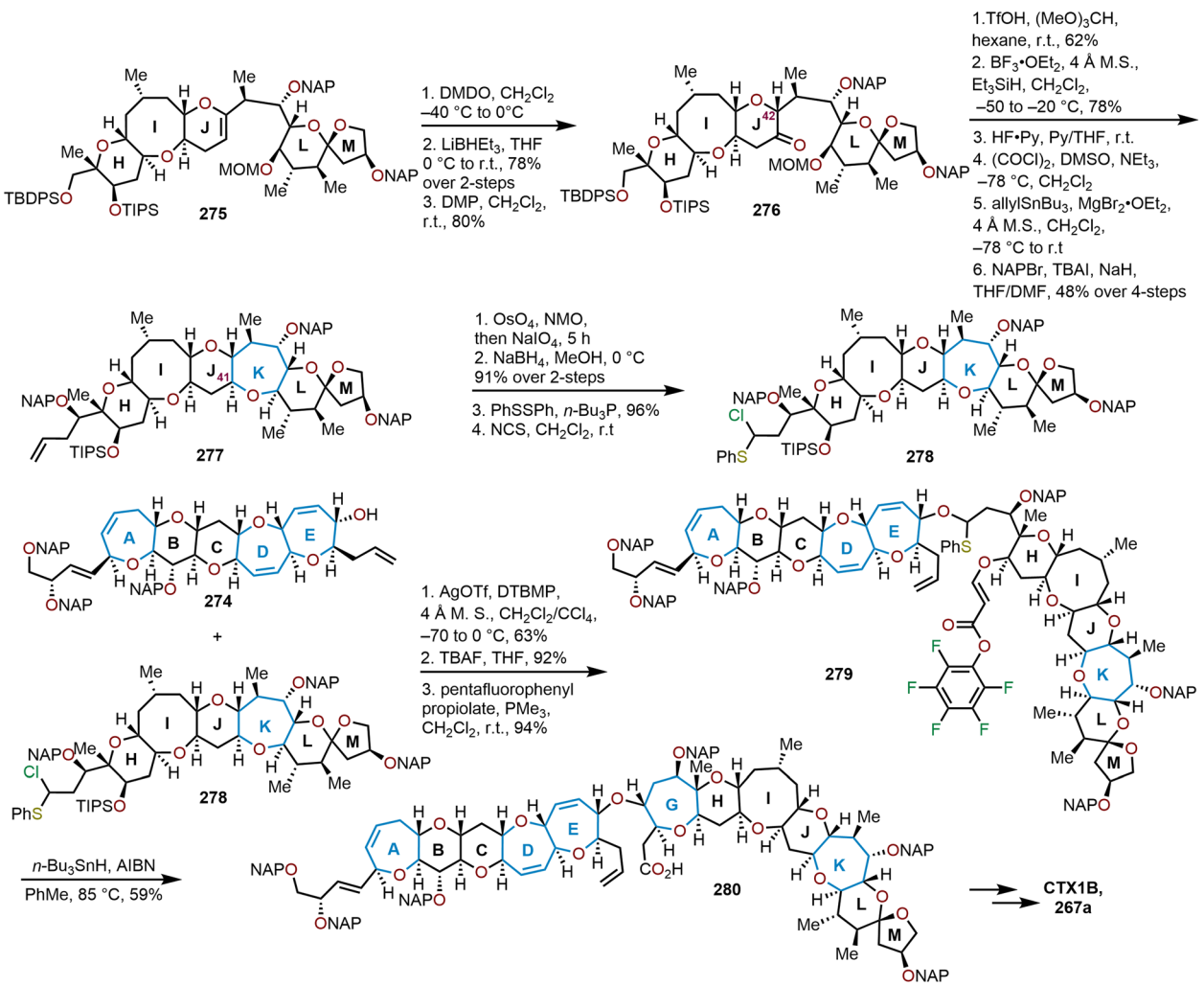
Inoue, Hirama and coworkers were able to synthesize CTX1B *via* a convergent synthesis using sugar-based starting materials. Their efforts are highlighted throughout several publications that entail the routes taken to synthesize each fragment.[108–118] The seven-membered oxacycles (rings A, D, E, G, and K) were afforded by various chemical routes as shown in Schemes 43 and 44. For example, in the construction of the AB fragment, Hirama and coworkers started from the sugar-derived tri-*O*-benzyl-D-glucal **25** and in three steps *via* bromination with NBS, basic epoxide formation and opening with allylmagnesium bromide, and *O*-allylation with allyl bromide provided a reliable route to diene **268** (Scheme 43). This sequence set the stage for RCM with Grubbs' first-generation catalyst to form the A ring **269** in 84% yield.[110,114] Oxepine **269** is then advanced in 13 synthetic steps to diene **270** containing the ABC ring system, which was then poised for a second RCM for D-ring formation. Of note, to afford a high yield of RCM product, the free hydroxy groups and Grubbs' second-generation catalyst were required.



Scheme 43 Inoue, Hirama, and coworkers' synthesis of the A, D, and E oxepanes in CTX1B.[110,114,115]

Subsequent debenzylation, acetal protection with 2,2-dimethoxypropane (2,2-DMP), and reprotection of the secondary alcohol a 2-napthylmethyl group (NAP) afforded acetal **271** in 74% yield.[110] Acetal **271** served as the starting point for side-chain elaboration and E ring construction. Side chain installation was accomplished *via* olefin migration within the A ring with Wilkinson's catalyst and DBU, enol ether oxidation with lead tetraacetate, and a stereoselective nickel-catalyzed coupling of the resulting allyl acetate with an alkenylborate variant of the TBS-protected sidechain. An additional 10 synthetic steps were required to access diene **272**, which was able to undergo RCM with Grubbs' second-generation catalyst to construct the E-ring of CTX1B in 92% yield. Protection of the secondary alcohol with TBSCl and *m*-CPBA oxidation of the sulfide afforded sulfone **273**. Allylation of sulfone **273** allyltrimethylsilane and $EtAlCl_2$, TBS removal, Dess–Martin periodinane oxidation, epimerization with DBU, and stereoselective reduction under Luche conditions afforded key ABCDE coupling fragment **274** in 33% yield over the five steps.[110] After construction of the left wing of CTX1B, Inoue, Hirama, and coworkers turned their attention towards the right wing fragment (rings HIJKLM) as shown in Scheme 44.

The strategy used to make the right wing fragment of **267a** was to couple the HI and LM ring systems *via* a Yamaguchi protocol followed by J ring construction with a low-valent titanium reagent to afford **275**, and finally fusion of the seven-membered K ring allowed completion of the ring-wing.[116,117] Fusion of the K ring was initiated by DMDO oxidation of the enol ether in **275** followed by a stereoselective, reductive-opening of the epoxide with $LiBHEt_3$ to afford the desired C42 stereochemistry, which subsequent oxidation of the hydroxyl group with Dess–Martin periodinane afforded ketone **276**. In the presence of triflic acid (TfOH) and trimethyl orthoformate, the K ring was formed *via* acetalization to a seven-membered methoxy acetal, which was followed by a reductive etherification to set the C41 stereocenter. Sidechain elaboration was then initiated with deprotection of the primary alcohol, followed by Swern oxidation, allylation with allyltributylstannane, and protection of the resulting secondary alcohol with a 2-napthylmethyl group to afford **277**. Further elaboration of **277** to requisite α-chlorosulfide **278** was accomplished *via* dihydroxylation, $NaIO_4$ cleavage to an aldehyde, reduction with $NaBH_4$, thioether formation, and chlorination with *N*-chlorosuccinimide (NCS). The pinnacle of the first total synthesis of CTX1B **267a** was observed in the coupling of the ABCDE **274** (from Scheme 43) and HIJKLM **278** fragments.[108]

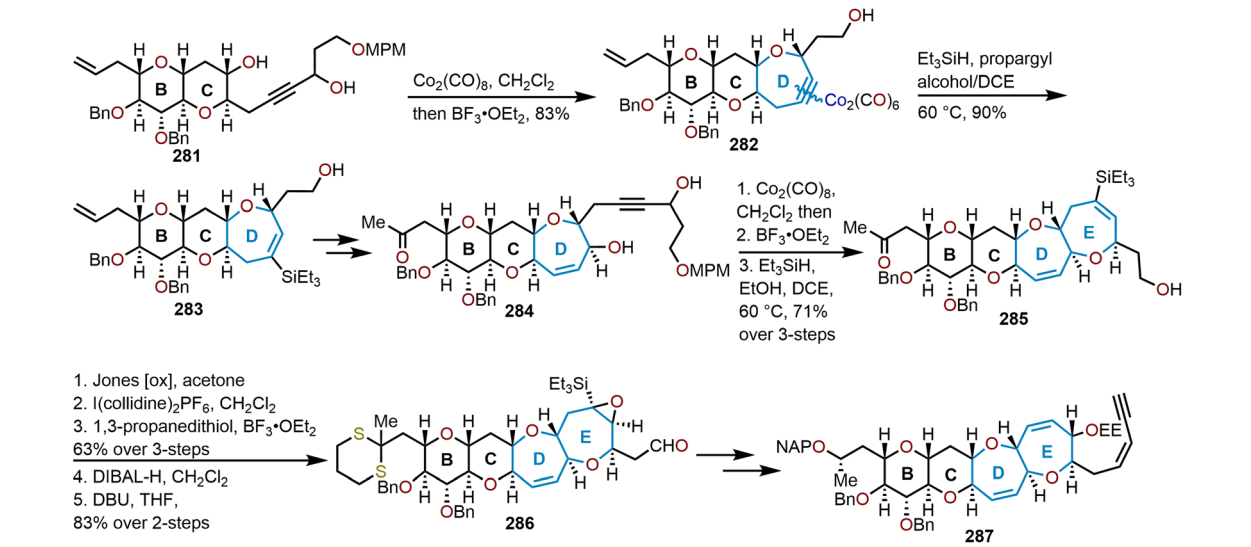


Scheme 44 Inoue, Hirama, and coworkers' synthesis of the K and G oxepanes of CTX1B (**267a**).[108,116–118]

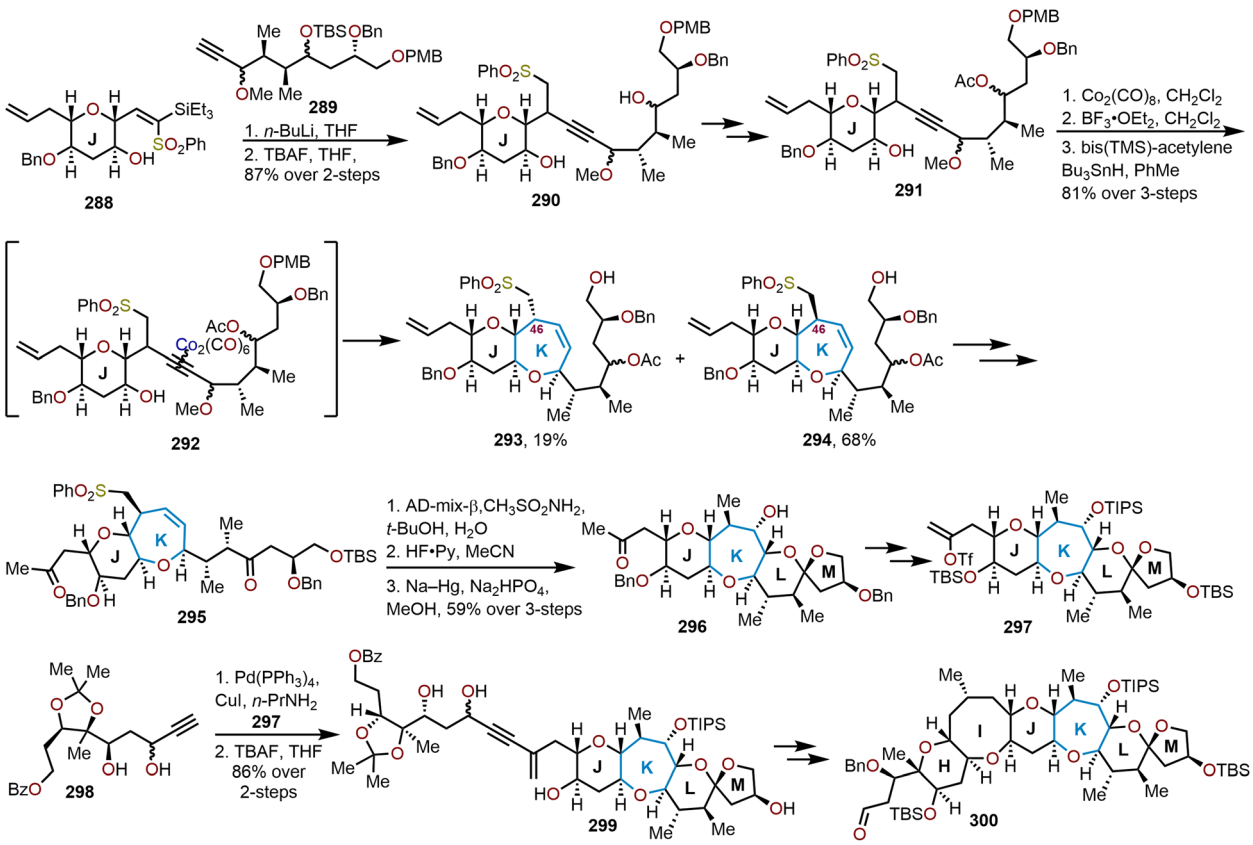
The coupling was accomplished in a 63% yield in the presence of an excess of silver(I) triflate and di-*tert*-butylmethylpyridine (DTBMP). Removal of the TIPS ether with TBAF and treatment with pentafluorophenyl propiolate and trimethylphosphine provided pentafluorophenyl acrylate **279** for G ring construction *via* a stereoselective, 7-*exo* radical cyclization that proceeded in 59% yield to give **280**.

Ciguatoxin 1B was afforded after subsequent elaboration of the carboxylic acid to a terminal olefin to allow for a Grubbs cross-metathesis to form the final F ring and removal of the NAP protecting groups provided **267a** in six additional steps from **280**. The highlights of the oxepane construction within Inoue, Hirama, and coworkers' ciguatoxin 1B synthesis were A, D, and E ring construction *via* RCM, K ring creation *via* methyl acetal formation and reductive etherification, and G ring construction *via* a 7-*exo* radical cyclization mediated by tributyltin hydride and AIBN.

A few years later in 2009, Isobe and coworkers became the second group to accomplish the total synthesis of CTX1B (**267a**).[67] The Isobe group sought to employ their recently developed methods for preparing cyclic ethers *via* acetylene-dicobalt hexacarbonyl complexes, which has shown to give *syn*, *trans* polycyclic systems in a stereoselective manner (see Schemes 21 and 22 above).[47,55–64,66,119,120] Their unique cyclization strategy was used to construct the BCDE[66,121] and HIJKLM[120] fragments, and to forge the central F and G rings (Schemes 45–47). The construction of the BCDE ring system (Scheme 45) began with the addition of dicobalt octacarbonyl and boron trifluoride etherate known propargylic alcohol **281**, which was available in 31 synthetic steps from methyl-α-D-glucoside.[66,121] Cyclization of **281** to form the D ring resulted in Nicholas adduct **282**, which underwent hydrosilylation with triethylsilane in propargyl alcohol/dichloroethane (DCE) solvent to afford vinylsilane **283** in 75% yield over two steps. Sidechain elaboration and oxidation of the oxepine over 14 additional synthetic steps led to propargylic alcohol **284**, wherein the iterative cyclization–hydrosilylation sequence *via* the dicobalt hexacarbonyl adduct forms the E ring in **285** in 71% yield over three steps. Jones oxidation of the primary alcohol, iodolactonization, protection of the methyl ketone to

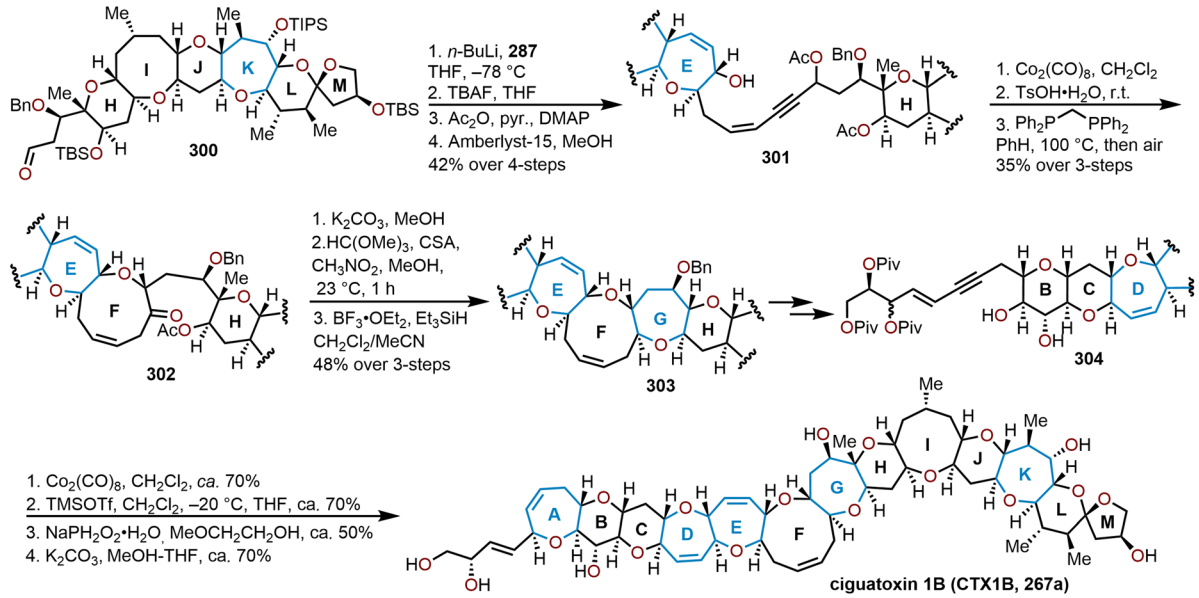


Scheme 45 Isobe and coworkers' route to access the BCDE fragment.[66]



Scheme 46 Isobe and coworkers' route to access the HIJKLM fragment.[67,120,122]

afford the dithioketal, DIBAL-H reduction of the lactone, and subsequent treatment with DBU led to the formation of epoxysilane **286** in 52% over five steps. The requisite BCDE coupling fragment **287** was completed from an additional nine synthetic steps from **286** and was used for the coupling to the HIJKLM fragment. Previously Isobe and coworkers optimized routes to access vinyl sulfone **288** in 22 steps from methyl-α-D-glucoside and acetylene **289** in 20 steps from tri-*O*-acetyl-D-glucal which served as starting points for HIJKLM ring construction as illustrated in Scheme 46.[120,122] A heteroconjugate addition[123] of



Scheme 47 Isobe and coworkers' convergent route to complete CTX1B.[67]

the lithium acetylide of **289** to vinylsulfone **288** and TBS deprotection provided alkyne **290**.

After further protecting group manipulation to afford acetate **291** and using their iterative cyclization–hydrosilylation sequence *via* the dicobalt hexacarbonyl adduct **292** the K ring was installed. Epimerization during the process at C46 led to the formation of diastereomers, **293** and **294** in 19% and 68% yields, respectively. Fortunately, the major product **294** was needed to move forward in the sequence. Following protecting group manipulations, IBX oxidation of the secondary alcohol, and Wacker oxidation afforded dione **295**. Dihydroxylation of the oxepine under Sharpless conditions followed by removal of the TBS ether promoted spiroketalization to furnish the L and M rings and subsequent desulfurization provided **296** in 59% over the three steps.

Lastly, silyl ether protection of the free hydroxyl with TIPSCl, debenzylation/reprotection with TBSCl, and vinyl triflate formation provided **297**, which was poised for a Sonogashira coupling with known alkyne **298** available from tri-*O*-acetyl-D-glucal.[120,124] From the coupled alkyne **299**, the dicobalt hexacarbonyl mediated cyclization–hydrosilylation strategy fused together the I ring, enabled H ring construction, and allowed further advancement to aldehyde **300** in 15 steps from **299** in order to set up the coupling with the BCDE ring system **287**.

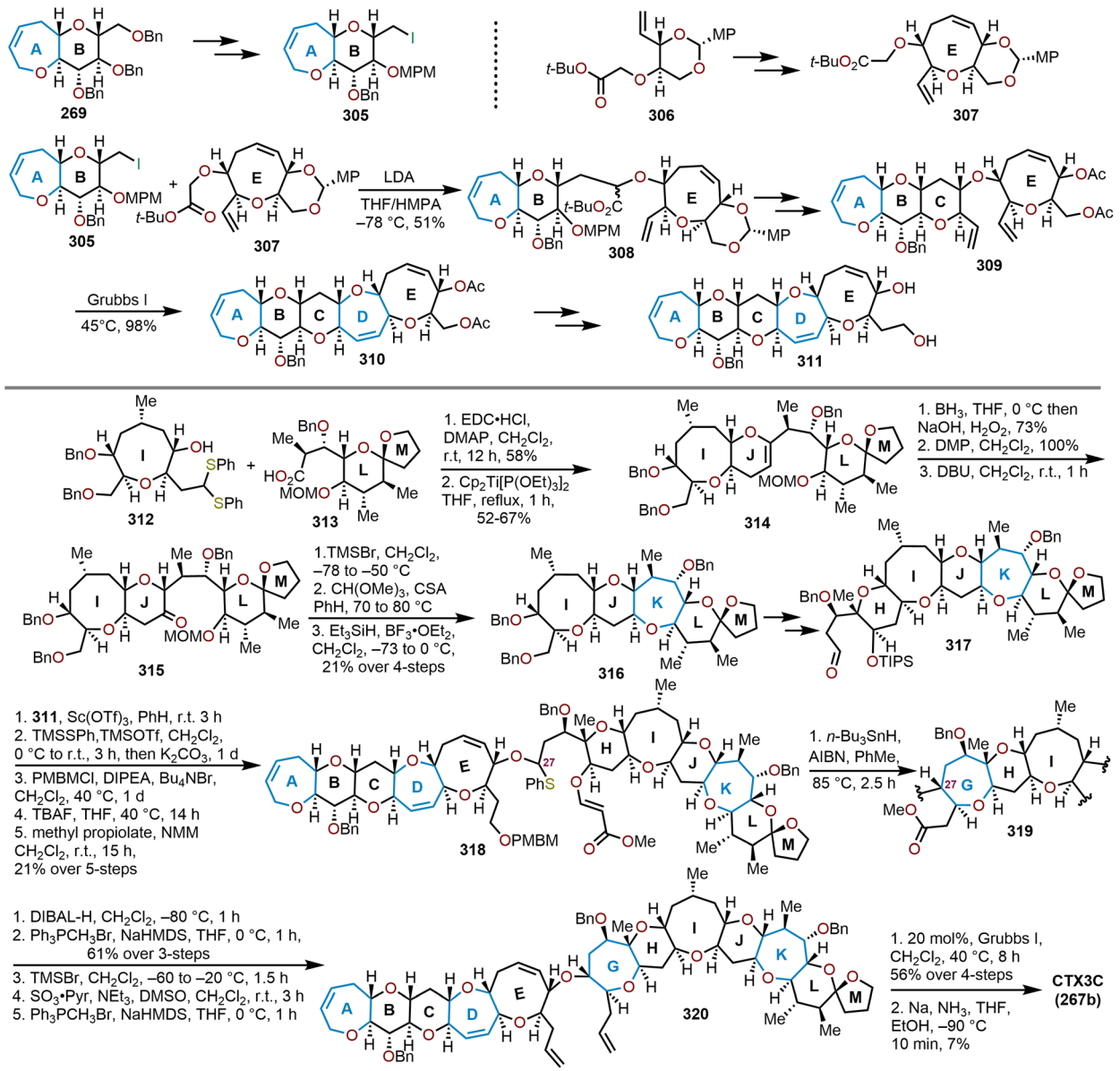
The coupling of BCDE and HIJKLM fragments was achieved *via* 1,2-addition of the lithium acetylide of **287** to aldehyde **300**, which was followed by global deprotection of the TBS ethers, global acetate installation, and removal of the ethoxyethyl acetal (EE) to afford enyne **301** (Scheme 47).[67] Treatment of **301** with dicobalt octacarbonyl, *p*-TsOH, and oxidative decomplexation using bis(diphenylphosphino)methane (dppm) with exposure of air produced ketone **302** now containing the F ring. After acetate deprotection of **302**, acetalization using trimethyl orthoformate and camphorsulfonic acid (CSA) followed by a reductive etherification resulted in construction of the G-ring oxepane to afford **303**. Functionalization of the left flank on the B ring in 7 synthetic steps provides enyne **304** in prelude to the final cyclization event using dicobalt octacarbonyl. Formation of the propargyl cation required TMSOTf, but THF was also needed to scavenge excess Lewis acid in order to promote the cyclization to form the A ring oxepine. Lastly, reductive decomplexation of the cobalt complex and global acetate deprotection affords ciguatoxin 1B (CTX1B; **267a**).

The highlights of the oxepane construction within Isobe and coworkers' ciguatoxin 1B synthesis were the use of an iterative set of cyclizations of acetylene-dicobalt hexacarbonyl complexes followed by a hydrosilylation or decomplexation to form and elaborate the A, D, E, and K rings as well as an acetalization and reductive etherification sequence to form the G ring oxepane.

5.6 Total synthesis of ciguatoxin 3C (CTX3C)

The structure of ciguatoxin 3C (CTX3C; **267b**), a simplified congener of CTX1B, was elucidated in 1975 by Yasumoto and coworkers.[125] The scaffold of **267b** consists of 13 embedded oxacycles of 5, 6, 7, 8, and 9-membered rings that are *trans*-fused, and contains 31 stereocenters (Fig. 5). Inoue, Hirama and coworkers were able to synthesize CTX3C (**267b**) in 2001 through a convergent route (Scheme 48).[113,115,118,126,127]

The left wing fragment consisting of the ABCDE ring system[126,128] **311** and the right wing fragment consisting of the HIJKLM ring system[126,129,130] **317** were individually prepared, then coupled together. The remaining F and G were fused lastly to complete the scaffold. The left wing fragment was con-



Scheme 48 Hirama and coworkers' efforts to synthesize CTX3C.[113,115,118,126,127]

structed by implementing an RCM strategy using a Grubbs catalyst. The A ring in **269** was constructed using the RCM strategy described in Scheme 43 above from CTX1B, and then advanced to iodide **305**.[115] Methoxybenzylidene (MP) acetal **306** was advanced to construct the E ring and afford **307**, which upon treatment of LDA generated the lithium enolate that was coupled to iodide **305** to eventually arrive at **308**. Following C ring construction and advancement over 6 synthetic steps to diene **309**, cyclization of the D ring was possible *via* another intramolecular Grubbs cross-metathesis to furnish the ABDE ring system **310**.[128] Five additional synthetic steps were required to afford diol **311**. To construct the right wing portion of CTX3C, dithioacetal **312** containing the I ring and carboxylic acid **313** containing the L and M rings were condensed to allow for J ring construction using the Takeda low-valent titanium reagent to afford **314**.[131] Oxidation of the J ring enol ether and epimerization afforded ketone **315**. Acetalization and reductive etherification allowed construction of the K ring oxepane to afford IJKLM fragment **316**, which after 16 synthetic steps was advanced to aldehyde **317**.[126,130] The key coupling of **311** and **317** was accomplished *via* Sc(OTf)$_3$-catalyzed *O*,*O*-acetalization and conversion to a *O*,*S*-acetal using phenylthiotrimethylsilane and TMSOTf. Protection of the primary hydroxyl as a *p*-methoxybenzyloxymethyl (PMBM) ether, deprotection of the TIPS group, and installation of the methyl acrylate afforded **318** in 21% over the five-step sequence. Formation of the G ring oxepane was accomplished by treatment with tributyltin hydride and AIBN to promote a stereo- and chemo-selective radical cyclization of the C27 radical with the α,β-unsaturated ester to afford **319**.

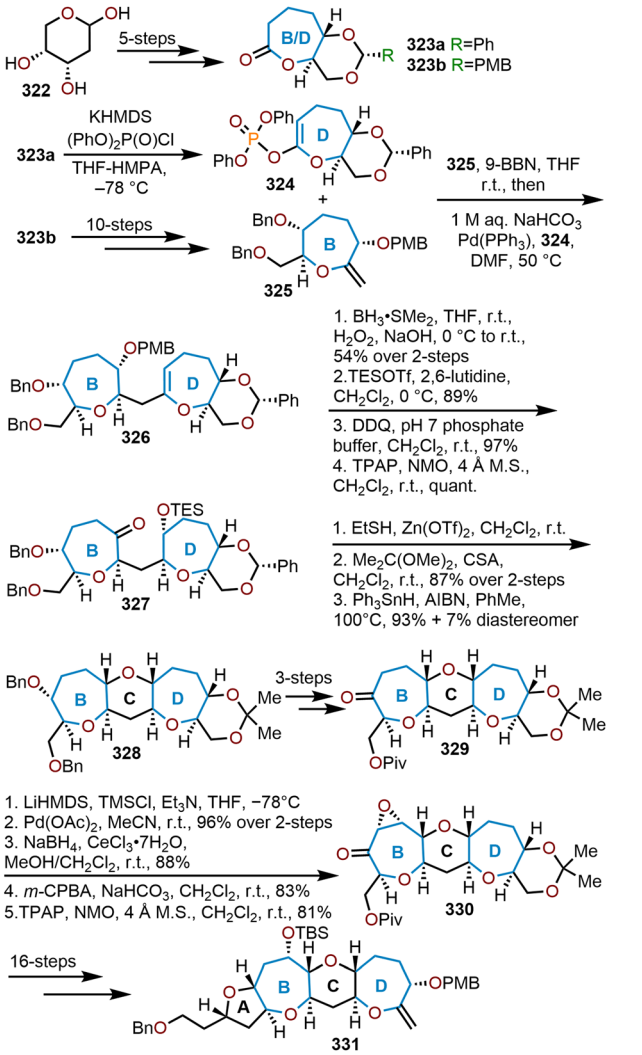
Further advancement to diene **320** enabled the formation of the final F ring oxepine through a RCM with Grubbs' first-generation catalyst, and global debenzylation using Birch reduction conditions provided the first total synthesis of CTX3C (**267b**). Inoue, Hirama, and coworkers later reported an improved protecting-group strategy to enable a shorter total synthesis of CTX3C.[115–118,127]

The highlights of the oxepane construction within Inoue, Hirama, and coworkers' ciguatoxin 3C syntheses were the use of a RCM strategy to prepare the A and D rings, an acetalization/reductive etherification to construct the K ring, and a stereo- and chemoselective radical cyclization to construct the G ring.

5.7 Total synthesis of gymnocin A

The isolation of gymnocin A from the dinoflagellate *Karenia mikimotoi*, was reported in 2002 by Satake and coworkers.[132] The architecture of gymnocin A contains a ladder of 14 contiguous cyclic ethers embedded with 31 stereogenic centers (Fig. 6, **321**). While gymnocin A is a potent toxin found in the red tide algae, the natural product exhibits an EC_{50} value of 1.26 μM against P388 leukemia cells.[133] As a result of its structural complexity and its inherent bioactivities, gymnocin A became a target molecule for many groups. The first total synthesis of gymnocin A was completed in 2003 by Sasaki and coworkers.[133] A convergent route was taken to stitch together ABCD (Scheme 49),[134] and the GHI and KLMN fragments (Scheme 50)[135] *via* a Suzuki cross-coupling (Scheme 51).[133]

Initial efforts were carried out to construct the ABCD fragment (Scheme 49).[134] Their route began with 2-deoxy-D-ribose (**322**) which was elaborated to **323a** or **323b** over five steps, with ring closure accomplished *via* a Yamaguchi lactonization. From **323a**, access to vinyl phosphonate ester **324** in one step and from **323b** access to oxepane **325** in 10 synthetic steps was possible. Hydroboration of the olefin in **325** and subsequent Suzuki coupling with vinyl phosphonate ester **324** joined the two B and D oxepane rings to allow for D ring oxygenation and oxidation of the B ring to afford **327** in preparation for C ring construction; which was accomplished *via* a thioketalization followed by desulfurization to afford **328**. Advancement of **328** to ketone **329** allowed for oxygenation of the B ring oxepane *via* a Saegusa–Ito oxidation to an enone, followed by a Luche reduction. Epoxidation of the corresponding allylic alcohol with *m*-CPBA and Ley oxidation provided epoxy ketone **330**, which upon further advancement in 16-synthetic steps provided the ABCD ring system and key olefin **331** for coupling to



Scheme 49 Sasaki and coworkers' synthesis of the ABCD fragment for gymnocin A.[133,134]

the GHIJKLMN fragment. Concurrent to their efforts to the ABCD ring system, Sasaki and coworkers constructed the GHI and KLMN fragments (Scheme 50), which were advanced to the GHIJKLMN fragment (Scheme 51).[135]

Oxepane formation was achieved by Yamaguchi lactonization of hydroxy acid **333** to seven-membered lactone **334** in 62% yield, which was used to provide the G and L oxepane rings in Gymnocin A. Phosphonation of lactone **334** gave vinyl phosphonate **335**, which set the stage for an *in situ* Suzuki

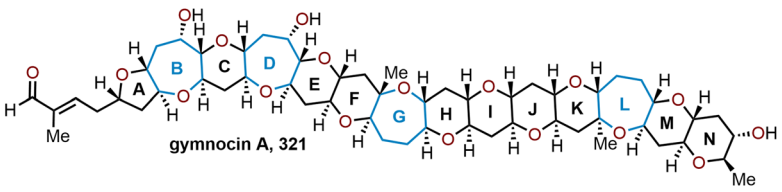
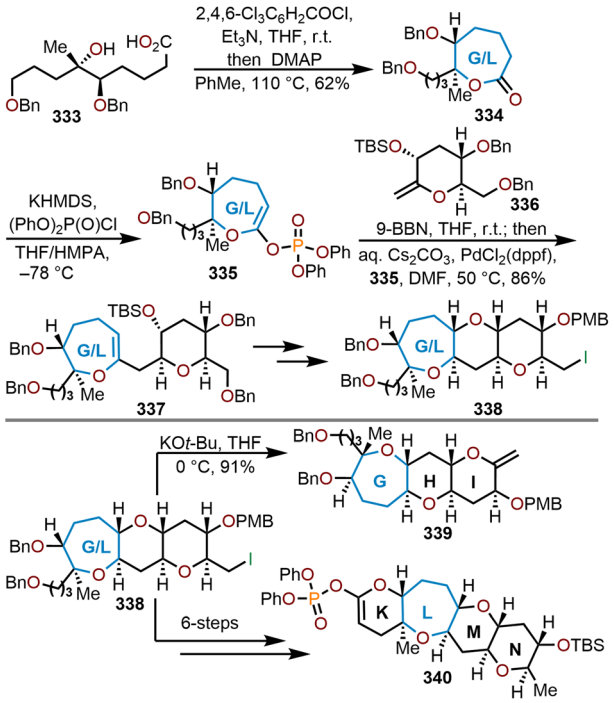


Fig. 6 Structure of gymnocin A.



Scheme 50 Sasaki and coworkers' synthesis of the GHI and KLMN fragments for gymnocin A.[135]

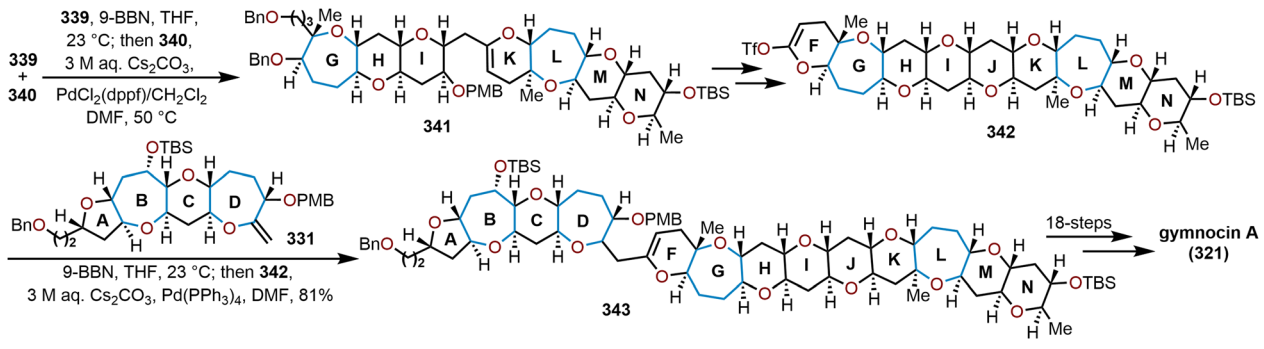
cross-coupling with olefin **336** to afford **337** in 86% yield. After 9 or 11 (recycling an undesired diastereomer) synthetic steps from **337**, iodide **338** was obtained, which served as a versatile intermediate. Given the pseudo-symmetry of the GHI and KLMN fragments, Sasaki and coworkers elaborated **338** to form the GHI fragment (**339**) by elimination of the iodide and the KLMN fragment (**340**) after 6 synthetic steps as illustrated in Scheme 50. They used their optimized *in situ* Suzuki cross-coupling method to stitch the GHI (**339**) and KLMN (**340**) fragments together to arrive at polycycle **341** (Scheme 51). The F and J rings were subsequently installed over 9 synthetic steps to give vinyl triflate **342**. The corresponding vinyl phosphonate failed to couple to the ABCD fragment (**331**), thus **342** was used to accomplish the Suzuki coupling with **331** to afford the desired product **343** in 81% yield. From **343**, the E ring installation, protecting group manipulation as well as installation of the aldehyde sidechain required 18 additional synthetic steps to achieve the first total synthesis of gymnocin A.

Oxepane construction and elaboration in Sasaki and coworkers' gymnocin A synthesis was facilitated by construction of seven-membered lactones (*e.g.*, **323a**, **323b**, and **334**) *via* a Yamaguchi lactonization of hydroxy ketones. The lactone was then able to be elaborated to a vinyl triflate, vinyl phosphonate, or exocyclic olefin to enable construction of the polycyclic ether core through a key *B*-alkyl Suzuki–Miyaura coupling strategy. Lactones **323a** and **323b** were diverged to provide both the B and D oxepane rings, and due to the pseudo symmetry of the GHI and KLMN fragments, lactone **334** was able to provide the G and L oxepane rings. Further oxygenation of the intermediate oxepines was accomplished using hydroboration conditions and thioketalization followed by desulfurization fused the oxepanes to the C, H and M tetrahydropyran rings. Sasaki and coworkers further detailed this developed chemistry in a full account published in 2005.[136]

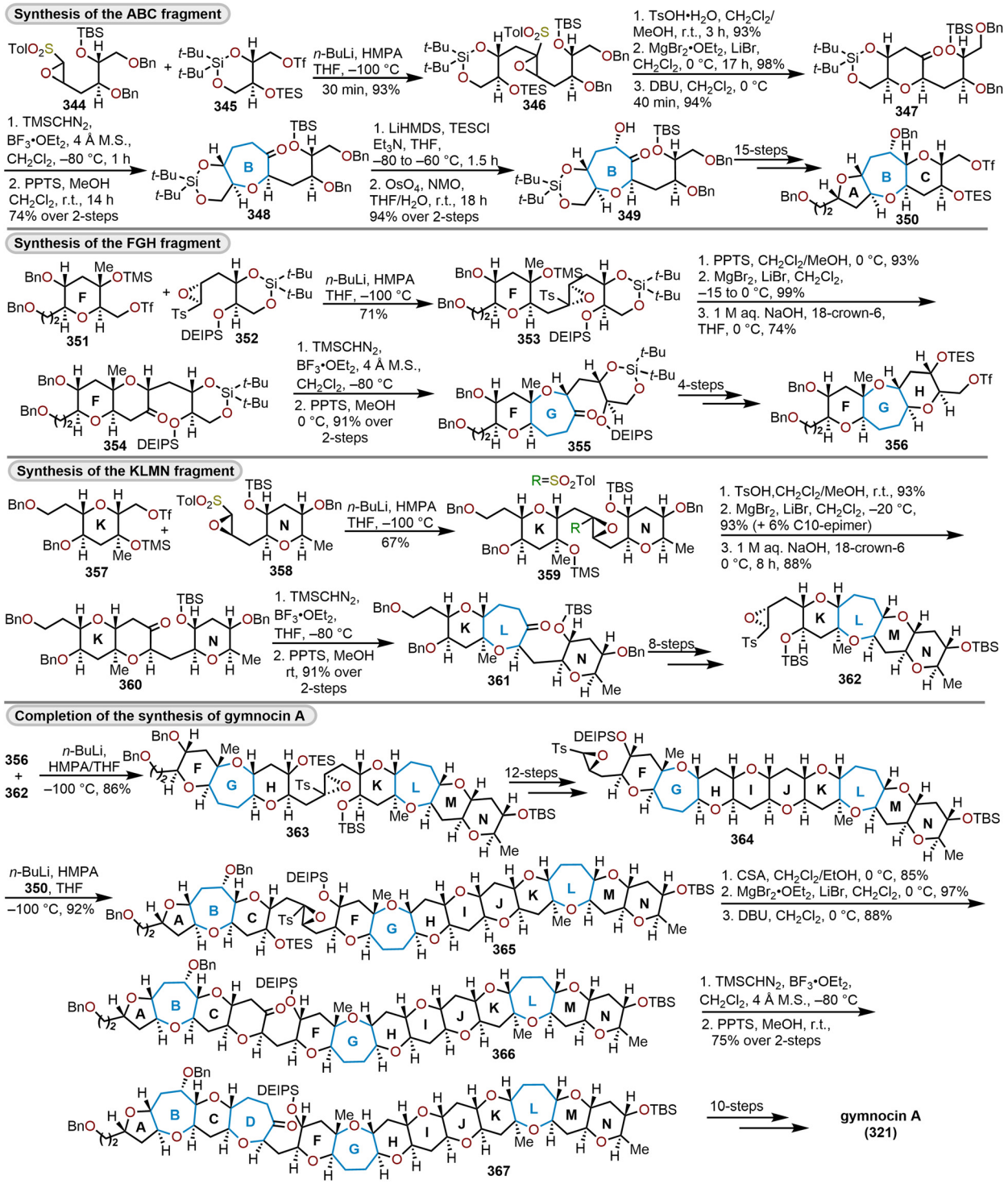
Mori and coworkers were also able to complete the total synthesis of gymnocin A in 2015 (Scheme 52),[137] by implementing their developed oxiranyl anion approach to polycyclic ethers (see Schemes 18 and 19).

Beginning with epoxy sulfone **344** available in 6 synthetic steps from 2-deoxy-D-ribose, the oxiranyl anion was generated using *n*-butyllithium with HMPA as an additive in THF solvent, then added to cyclic triflate **345** to form epoxide **346**. The use of the cyclic-protected triflate **345** was important since the acyclic benzyl-protected triflate was unstable. Removal of the triethylsilyl protecting group, treatment with magnesium bromide diethyl etherate furnished an intermediate α-bromoketone, that upon treatment with DBU provided cyclic ketone **347**. Then using their developed methodology for Lewis acid-catalyzed ring expansions of cyclic ketones using $TMSCHN_2$ (Schemes 18 and 19),[35,48,49,51] **347** was homologated to afford oxepane **348** containing the B ring.

Oxygenation of **348** was accomplished through silyl enol ether formation and dihydroxylation under Upjohn conditions to afford hydroxylated oxepane **349** as single diastereomer. Further advancement of **349** to key ABC coupling fragment **350** was accomplished after 15 additional synthetic steps.[138] The



Scheme 51 Sasaki and coworkers' union of all fragments to complete the total synthesis of gymnocin A.[135]



Scheme 52 Mori and coworkers' total synthesis of gymnocin A.[137–139]

FGH ring fragment **356** was constructed in a similar manner from triflate **351** and epoxy sulfone **352**, which required a diethylisopropylsilyl (DEIPS) for selective deprotection of the trimethylsilyl group in the subsequent step.[137] The utility of the oxiranyl anion strategy also enabled the construction of the KLMN fragment **362** from triflate **357** and epoxy sulfone **358**.[139] Mori and coworkers' Lewis acid-catalyzed ring expansions of cyclic ketones using $TMSCHN_2$ also enabled the construction of the G and L oxepanes embedded within these fragments. Further demonstrating the iterative nature of this strategy, the FGH **356** and KLMN **362** fragments were joined using the oxiranyl anion chemistry to provide **363** that was advanced

in 12 synthetic steps to epoxy sulfone **364** containing the FGHIJKLMN rings to be joined to the ABC ring fragment **350** using the same chemistry, which provided epoxide **365**. Silyl deprotection of **365**, α-bromoketone formation, and treatment with DBU gave ketone **366** which was ring expanded using $TMSCHN_2$ to afford **367** containing the D ring oxepane. An additional 10 synthetic steps were required from **367** for E ring formation, protecting group manipulations, and side chain installation to access gymnocin A (**321**).[137]

5.8 Total synthesis of gymnocin B

The second largest polycyclic ether of marine origin was isolated by Yasumoto and coworkers in 2005 from the cells of dinoflagellate *Karenia mikimotoi* and was found to exhibit cytotoxicity against mouse lymphoide P388 cells at 1.7μg mL^{-1}.[140] Gymnocin B (**368**) contains a ladder-like scaffold consisting of 15 oxacycles, 5 of which are oxepanes, along with 33 stereogenic centers (Fig. 7). The first total synthesis of gymnocin B was accomplished by Sittihan and Jamison in 2019, who utilized a biomimetic two-phase synthetic approach.[141] A unique biosynthesis of these marine ladder polyethers was proposed by Nakanishi in 1985, which involved an epoxide-opening cascade.[142] This plausible biosynthesis inspired Sittihan and Jamison to develop bromonium-mediated, Lewis acid-catalyzed, water promoted,[143] and base-mediated epoxide-opening cascades to construct 10 out of 15 oxacycles in gymnocin B.[141]

Four different strategies were used to construct the B, G, H, J, and O ring oxepanes in gymnocin B (Scheme 53). The first oxepane targeted in their synthetic efforts was the B ring oxepane, which was prepared through a bromonium-initiated 7-*endo*-5-*exo* epoxide cascade from hydroxy epoxide **369**, available in 16 linear synthetic steps from 2-deoxy-D-ribose (Scheme 53).[141] Using *N*-bromosuccinimide as the initiator in hexafluoroisopropanol, the AB rings were forged with complete regio- and diastereoselectivity to give the 5/7/6/6 tetracyclic ABCD system **370** in 68% yield. Advancement of **370** in 7 additional synthetic steps provided **371** in 24-steps from 2-deoxy-D-ribose.

In another sequence the GH dioxepane system was forged *via* an epoxide-opening cascade of triepoxide **372**, which was available from geraniol in 8 linear synthetic steps. A Lewis-acid mediated cyclization using boron trifluoride etherate assembled the GH dioxepane system and TBSCl was then added to protect the free hydroxyl to give **373** in 24% over two steps. Advancement of **373** to enol triflate **374** required for attachment of the FGH ring system to the ABCD ring system required 8 synthetic steps.

Assembly of the O ring oxepane was achieved *via* a Yamaguchi lactonization of hydroxy acid **375**,[144] available from 2-deoxy-D-ribose in 5 synthetic steps,[145] which was followed by vinyl phosphonate formation to provide known oxepine **376**.[146] Adopting the *B*-alkyl Suzuki–Miyaura coupling strategy advanced by Sasaki and coworkers for their gymnocin A synthesis, Sittihan and Jamison were able to couple **376** to olefin **377** to adjoin the KLM and O ring fragments to provide polycycle **378**.

Advancement of **378** to alcohol **379** to allow for construction of the J ring oxepane required 10 additional synthetic steps. A regioselective hydroboration/oxidation of the olefin in **379** was employed followed by an oxidative lactonization with the nitroxyl oxidant TEMPO to afford the corresponding lactone in 89% yield over the two steps, which was then converted to vinyl phosphonate **380** in 99% yield.

Olefin **371** containing the ABCD ring fragment and enol triflate **374** containing the FGH ring fragment were also united by a *B*-alkyl Suzuki–Miyaura coupling to afford **381** that was further advanced in 7 synthetic steps to olefin **382**. Vinyl phosphonate **380** with the JKLMNO ring system was then joined to olefin **382** possessing the ABCDEFGH ring system in yet another a *B*-alkyl Suzuki–Miyaura coupling to afford polycycle **383** containing all five oxepane rings. The construction of the I ring, protecting group manipulations, and sidechain installation required 12 additional synthetic steps to complete the first total synthesis of gymnocin B in 45-steps from the longest linear sequence (LLS).

Highlights of the oxepane construction in Sittihan and Jamison's gymnocin B synthesis included B ring formation through an NBS-mediated epoxide cyclization cascade, a Lewis acid-mediated epoxide cyclization cascade to afford the GH dioxepane ring system, a Yamaguchi lactonization to prepare the O ring oxepane, and a TEMPO-mediated oxidative lactonization provided access to the J ring oxepane.

5.9 Total synthesis of gambierol

Gambierol (Fig. 8, **3**) is another potent toxin responsible for ciguatera poisoning. This *trans*-fused octacyclic ether was isolated in 1993 by Yasumoto and coworkers, whose characterization determined the presence of two seven-membered oxacycles, 18 stereogenic centers, and a triene sidechain containing a (*Z*,*Z*)-diene.[147,148]

The first total synthesis of **3** was completed by Sasaki and coworkers in 2002.[149] A convergent route was taken to couple the ABC and DEFGH fragments *via* a *B*-alkyl Suzuki–Miyaura

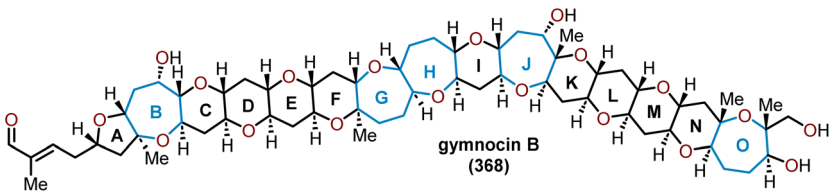
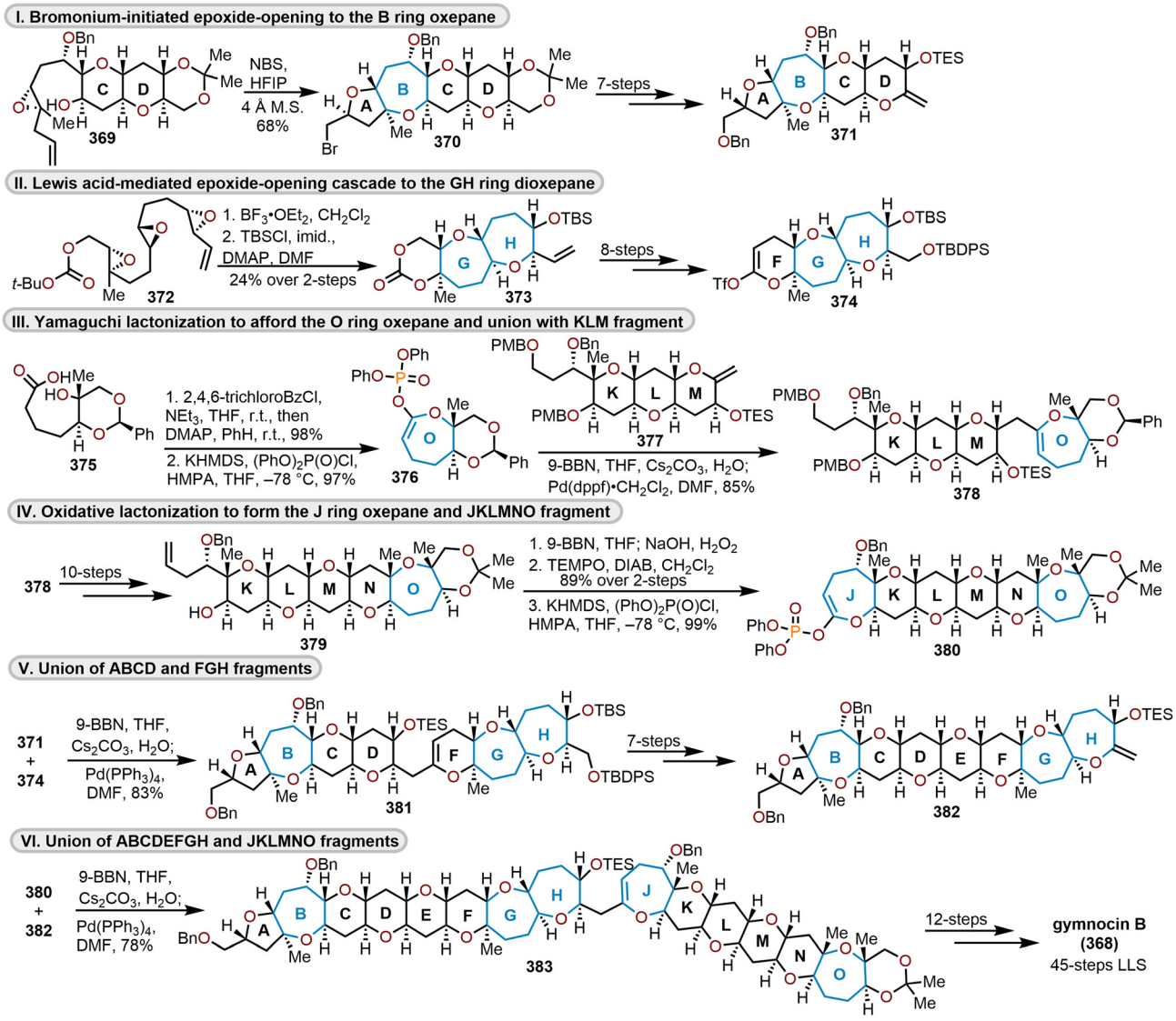


Fig. 7 Structure of gymnocin B.



Scheme 53 Jamison and coworkers' various strategies to access oxepane motifs in gymnocin B.[141]

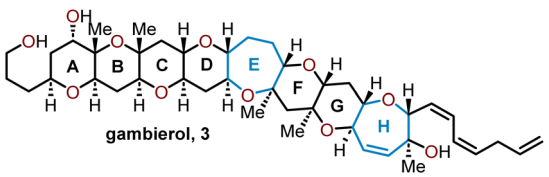
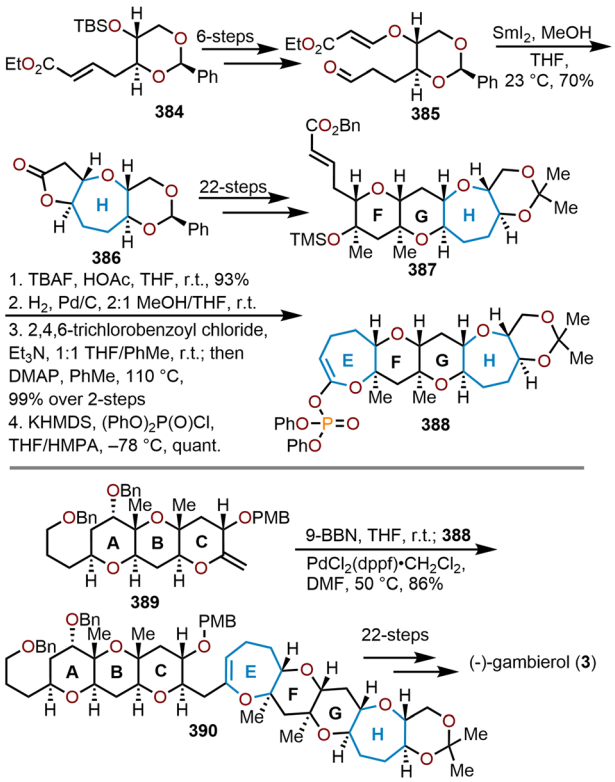


Fig. 8 Structure of gambierol.

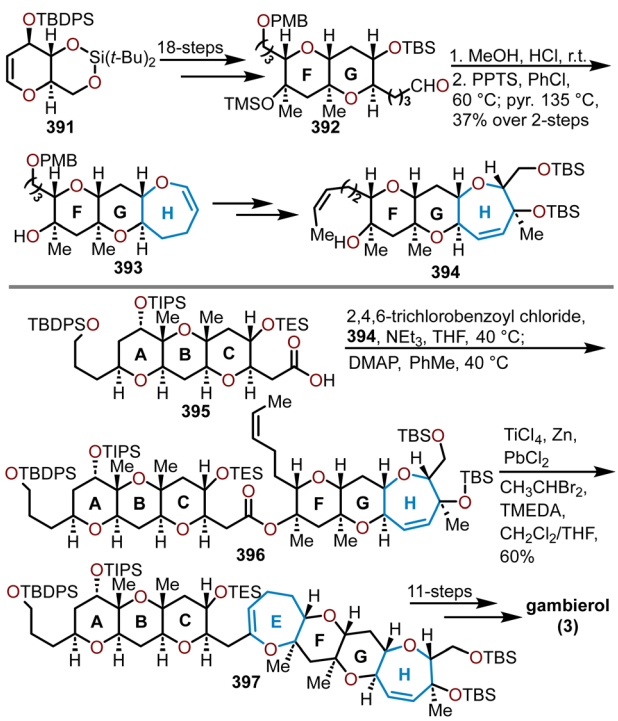
cross-coupling strategy (Scheme 54). Two strategies were used to construct the oxepine (ring H) and oxepane (ring E), a SmI_2-mediated reductive cyclization (see Scheme 14)[32,34] and a Yamaguchi lactonization, respectively. Sasaki and coworkers began constructing the DEFGH fragment with known ester[150] **384**.[149] After 6 synthetic transformations, aldehyde **385** was afforded, which allowed for a SmI_2 reductive cyclization to give lactone **386**, containing the H ring oxepane, in 70% yield (Scheme 54).[149] Lactone **386** was advanced to **387** now containing the FGH ring system, which is poised for E ring formation. Respective deprotection of the trimethylsilyl (TMS) ether and benzyl ester reveals a hydroxy acid, which underwent a Yamaguchi lactonization. The corresponding lactone was converted to ketene acetal phosphate **388** in 92% yield over the four steps in preparation for the coupling of the ABC (**389**) and EFGH (**388**) fragments *via* a *B*-alkyl Suzuki–Miyaura cross-coupling to afford polycycle **390**. Following the coupling, Sasaki and coworkers successfully stitched the D ring *via* Lewis acid-mediated cyclization, installed the triene sidechain, and completed protecting group manipulations in 22 additional synthetic steps to complete the first total synthesis of gambierol (**3**).[149]

A few years later in 2005, Rainier and coworkers published the second total synthesis of gambierol (**3**).[151] An iterative C-glycoside/enol ether-olefin ring closing metathesis strategy



Scheme 54 Sasaki and coworkers' strategy to access gambierol.[149]

was employed to construct the subunits of gambierol and to stitch together the octacyclic core (Scheme 55). Aldehyde **392**, prepared in 18-steps from D-glucal derivative **391**,[152] was subjected to HCl in MeOH to afford both cyclic and acyclic acetals, which upon treatment with pyridinium *p*-toluenesulfonate, pyridine and heat[105] resulted in the formation of oxepine **393** in 37% yield over the two steps.



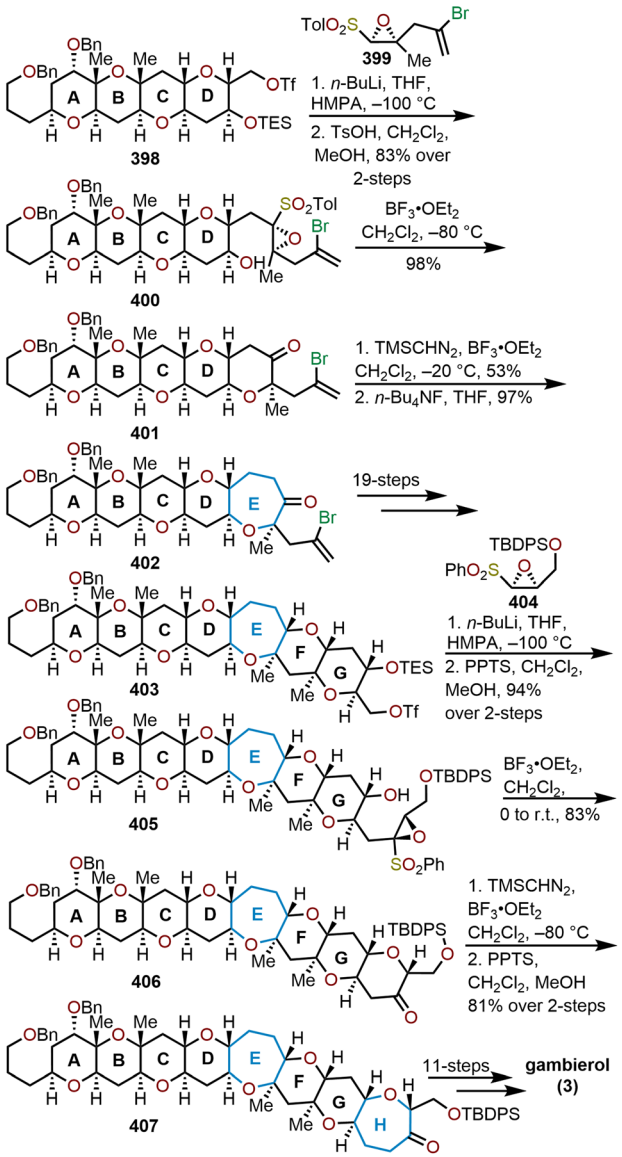
Scheme 55 Rainier and coworkers' strategy to access gambierol.[151]

After swapping protecting groups and oxidizing the ring H oxepine, Rainier and coworkers accessed tricycle **394**. Yamaguchi coupling of the free hydroxyl group in **394** to the acid-containing ABC fragment **395**[153] afforded the necessary precursor **396** to attempt their enol ether-olefin ring-closing metathesis strategy to construct the E ring oxepane. Initially, the Takai–Utimoto titanium methylidene protocol[154] proved to be insufficient for the cyclization of the E ring, as a key finding was that olefin degradation was prevailing over the cyclization. Rainier and coworkers overcame this obstacle by substituting the traditional 1,1-dibromomethane with 1,1-dibromoethane to generate the titanium alkylidene, which was able to afford the desired oxepine **397** in 60% yield from ester **396**. The total synthesis of gambierol was completed in 11 additional steps from **397** following a reductive cyclization to forge the D ring, addition of the triene sidechain, and protecting group manipulations. The Rainier and coworkers' synthesis of gambierol was completed in 44-steps (LLS) from D-glucal and in 1.2% yield.

Mori and coworkers also accomplished the total synthesis of gambierol (**3**) in 2009 as shown in Scheme 56.[155] Similar to their strategy in the total synthesis of hemibrevetoxin B (Scheme 35), the strategy relied on the use of oxiranyl anions to carry out sulfonyl-assisted 6-*endo* cyclizations followed by a Lewis acid-promoted homologation with $TMSCHN_2$ to afford the oxepanes. The addition of the oxiranyl anion of **399** to triflate **398**, containing the ABCD ring system,[156] yielded epoxy sulfone **400**. The 6-*endo* cyclization was promoted by addition of $BF_3{\cdot}OEt_2$ to give the pyranyl ring in **401**, whereupon addition of $TMSCHN_2$ in the presence of $BF_3{\cdot}OEt_2$ furnished the E ring oxepane to yield **402**. Installation of the F and G rings and advancement to triflate **403** required 19 synthetic steps from **402** and was set-up to use their oxiranyl addition/cyclization/expansion strategy. Addition of the anion of epoxy sulfone **404** to **403** afforded hydroxy epoxide **405**, whereupon treatment with $BF_3{\cdot}OEt_2$ furnished ketone **406**. Again, a homologation with $TMSCHN_2$ in the presence of $BF_3{\cdot}OEt_2$ was used to access the H ring oxepane to afford **407** in 81% yield over two steps. From there, Mori and coworkers were able to complete the total synthesis of gambierol (**3**) in 11 additional steps following the addition of the triene sidechain and protecting group manipulations.

5.10 Total synthesis of gambieric acid A

In 1992, Nagai, Yasumoto and coworkers isolated a toxin from the dinoflagellate *Gambierdiscus toxicus*, whose structure consists of ten cyclic ethers of varying sizes (five, six, seven, and nine-membered) with 27 stereogenic centers (Fig. 9).[157] Interestingly, (+)-gambieric acid A (**408a**) displays highly potent antifungal activities, thus making the gambieric acids sought after target molecules. Access to the A–E subunit of the gambieric acids was reported by Roberts and Rainier in 2007[158]



Scheme 56 Mori and coworkers' strategy to access gambierol.[155]

and more recently access to the A–D subunit was described in 2015 by Clark and coworkers,[159] but thus far, a single total synthesis of gambieric acid A was reported by Fuwa, Sasaki and coworkers in 2012. Furthermore, during studies of model subunit systems Fuwa, Sasaki, and coworkers reassigned the absolute stereochemistry of the polycyclic ether region in 2008,[160,161] which helped facilitate their efforts to complete **408a**.

Their route began with known alcohol **409**, which was advanced to diol **410** in three steps (Scheme 57).[162] An oxoammonium salt-mediated oxidative lactonization procedure was carried out using TEMPO and PIDA to form the seven-membered lactone **411** in 86% yield. A vinyl phosphonate was prepared from the lactone to carry out a palladium-catalyzed methoxycarbonylation to afford the α,β-unsaturated ester **412**. Reduction of the ester with DIBAL-H revealed a primary alcohol which was capped with a TBS protecting group, then hydroboration of the oxepine olefin with thexylborane and hydrogen peroxide afforded the desired alcohol **413** in a 57% yield. After several transformations, Fuwa, Sasaki, and coworkers were able to prepare olefin **414**, which contained the B ring oxepane and A ring sidechain. A *B*-alkyl Suzuki–Miyaura coupling with **415**, followed by a RCM using the Grubb's 2nd generation catalyst yielded **416** with the tethered the D ring that was advanced in 17 synthetic steps to the ABCD ring fragment **417**.

Using their previously prepared GHIJ ring fragment,[163,164] they were able to access polycycle **418**. A three-step sequence of TBS deprotection, an oxoammonium salt-mediated oxidative lactonization with TEMPO and PIDA, and vinyl phosphonate formation provided oxepine **419** containing the F′ ring. Then another *B*-alkyl Suzuki–Miyaura coupling of **419** with **417** afforded **420** in 95% yield. The F′ ring oxepine was then subjected to a hydroboration–oxidation, oxidation of the resulting alcohol with the Dess Martin periodinane, and epimerization of the C25 center with DBU to arrive at the seven-membered ketone **421**. Silyl enol ether formation, α-hydroxylation of the ketone, and $Pb(OAc)_4$-mediated oxidative cleavage of the α-hydroxy ketone severed the F′ seven-membered ring. The intermediate aldehyde was then methylenated to produce **422** in a 55% yield over the 4-steps. Deprotection of D ring TMS-

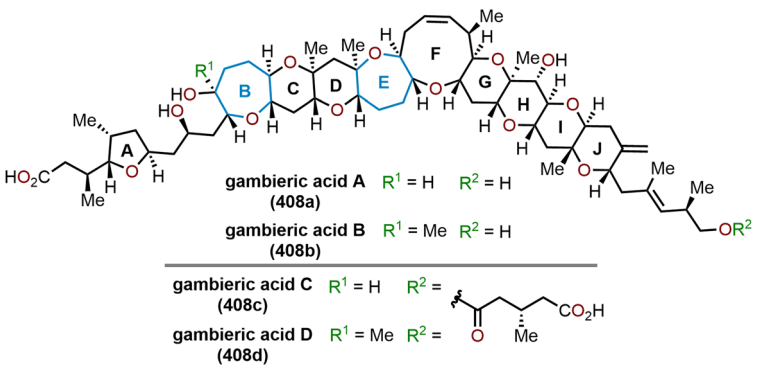
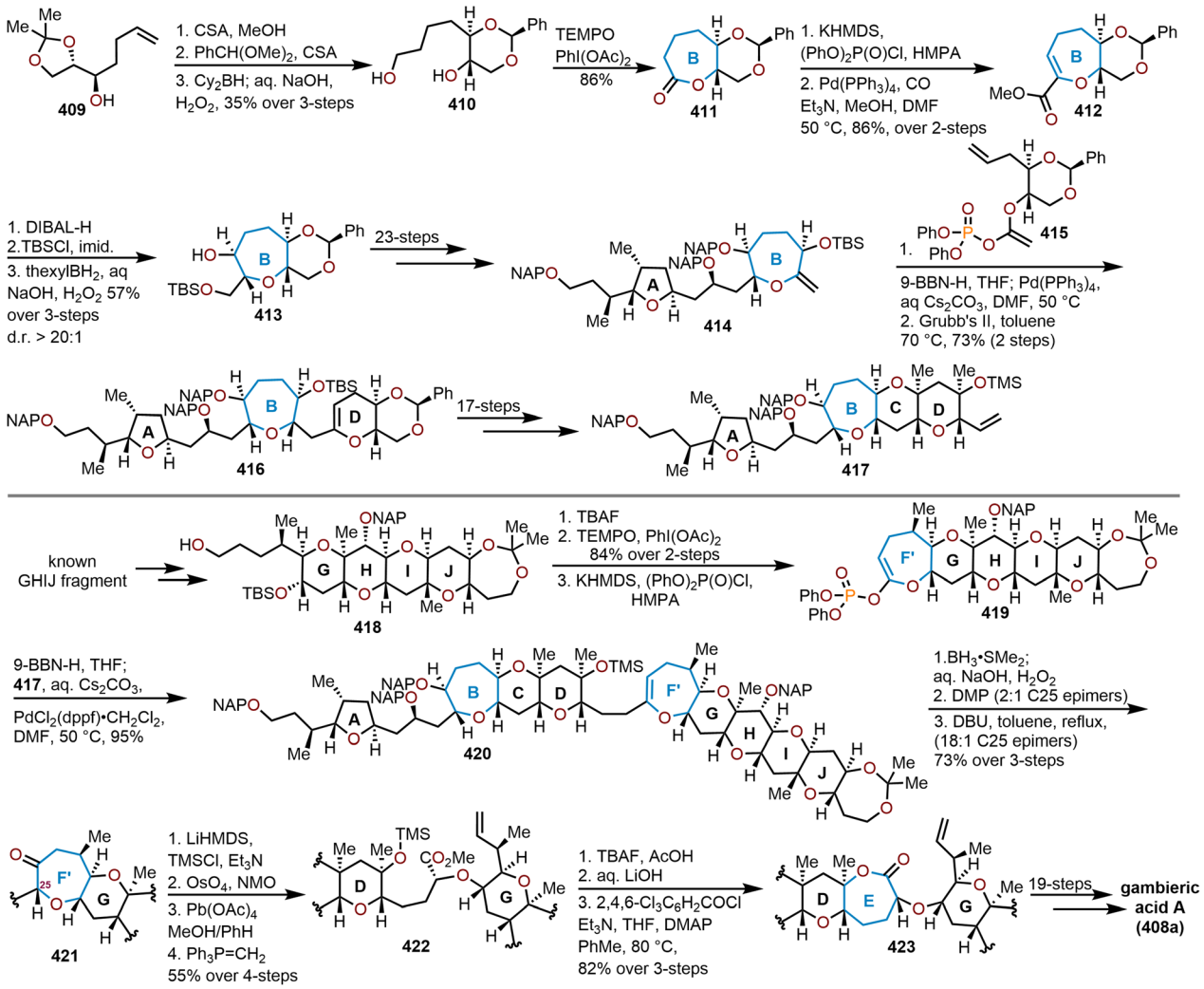


Fig. 9 Structure of gambieric acids A–D.

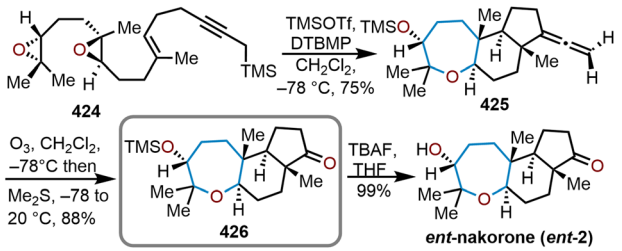


Scheme 57 Fuwa, Sasaki, and coworkers' route to gambieric acid A.[162]

protected alcohol was carried out with TBAF, saponification of the methyl ester, and subsequent lactonization of the intermediate hydroxy acid under Yamaguchi conditions to yield lactone **423**, containing the E ring oxepane, in 82% yield over the 3-steps. Following F-ring construction, the sidechain installation on the J ring, oxidation of the A ring sidechain, and protecting group manipulations, the first total synthesis and structural confirmation of gambieric acid A (**408a**) was completed by Fuwa, Sasaki, and coworkers.[162] The oxepane rings within **408a** were constructed by two methods. The first exploited an *in situ* generated oxoammonium salt prepared by using TEMPO and PIDA to mediate an oxidative lactonization providing versatile seven-membered lactones, which allowed the construction and elaboration of the B ring oxepane as well as set-up a key oxidative cleavage of an F′ oxepane to allow for E ring construction and a RCM strategy to construct the 9-membered F ring. The commonly employed Yamaguchi lactonization, as seen in other syntheses above, was the second method used for E ring oxepane construction.

5.11 Total synthesis of *ent*-nakorone

In the late 1990s, a family of highly condensed oxepane-cycloalkane terpenoids were isolated from Red Sea sponges and were shown to exhibit cytotoxic bioactivities. McDonald and coworkers successfully synthesized the tricyclic septanoside natural product, *ent*-nakorone (*ent*-**2**) inspired by a biomimetic approach through tandem oxa- and carbacyclizations (Scheme 58).[165] The biomimetic synthesis began with farnesol to arrive at diepoxide **424** in 4-steps through lithiation of 1-farensyl *p*-tolyl sulfone and alkylation with 1-bromo-4-trimethylsilyl-2-butyne, a regio- and diastereoselective epoxidation using the Shi catalyst, and reductive desulfonylation. The oxepane ring was constructed from the enyne diepoxide **424** using TMSOTf in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) to promote cyclization with the propargylsilane nucleophile to yield tricyclic allene **425**. The allene was cleaved *via* ozonolysis to give tricyclic ketone **426**, a versatile intermediate that was used by McDonald and coworkers to



Scheme 58 McDonald and coworkers' strategy toward *ent*-nakorone.[165]

form *ent*-abudinol B an additional septanose natural product (see Scheme 59). The total synthesis of **2** was completed after removal of the trimethylsilyl ether in **426** by addition of TBAF.

5.12 Total synthesis of *ent*-abudinol B

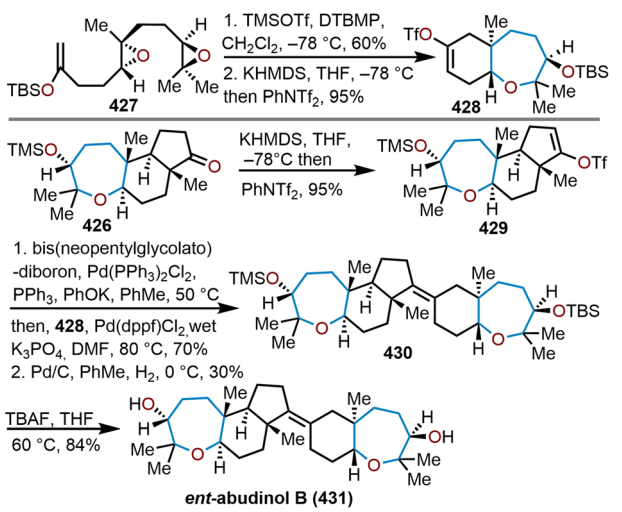
In addition to the total synthesis of *ent*-nakorone (*ent*-**2**), McDonald and coworkers were able to use **426** to afford *ent*-abudinol B (**431**) *via* a palladium-catalyzed cross-coupling (Scheme 59).[165] Enolsilane diepoxide **427**, accessible in four steps from geranylacetone, was subjected to a TMSOTf-mediated cyclization and triflation to afford oxepane-containing vinyl triflate **428**. Tricyclic ketone **426** was also advanced to vinyl triflate **429** in a 95% yield. Miyaura borylation of vinyl triflate **429** was employed to enable a Suzuki coupling with **428**, and a subsequent hydrogenation was successfully employed to derive the tetrasubstituted olefin **430**. The synthesis of **431** was completed following desilylation of the TMS and TBS ethers of **430** with excess TBAF at reflux.

5.13 Total synthesis of heliannuol C

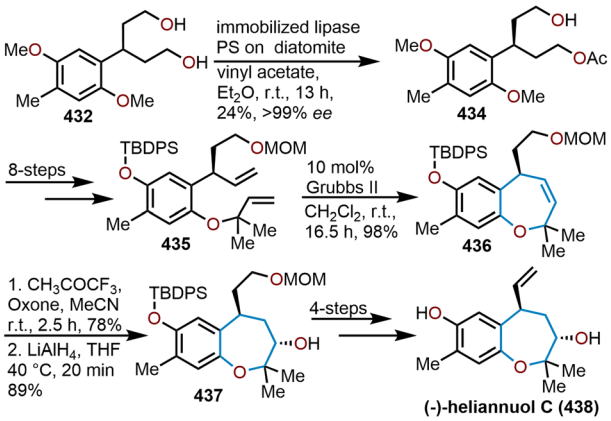
Heliannuol C is a sesquiterpenoid isolated from the cultivar sunflower *Helianthus annus* that contains a hydroxylated oxepane core structure.[166] Shishido and coworkers were the first to accomplish a total synthesis of (−)-heliannuol C (**438**) in 2003, in 16 linear steps from diol **432** (Scheme 60).[167] Their synthesis relied on an enzymatic desymmetrization of **432** to afford hydroxy acetate **434**. From there, 8 steps were required to access diene **435** that was used to construct oxepine **436** *via* a RCM using Grubbs' second generation catalyst. Dioxirane-mediated epoxidation of the olefin and reductive opening with $LiAlH_4$ afforded hydroxylated oxepane **437** and four additional steps afforded (−)-heliannuol C (**438**).

Vyvyan and coworkers were also successful in completing a 6-step total synthesis of (±)-heliannuol C in 2005, which relied on a regioselective aromatic Clasien rearrangement and a biomimetic 7-*endo* phenol epoxide cyclization (Scheme 61).[168]

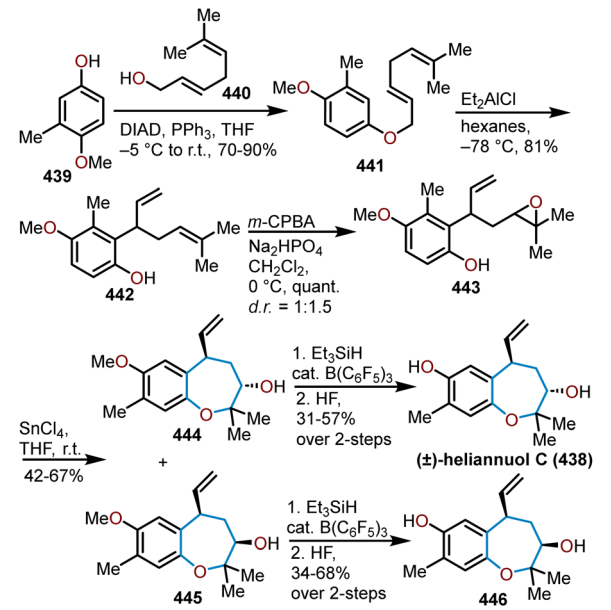
Mitsunobu etherification of phenol **439** with **440** provided diene **441** that when treated with Et_2AlCl at low temperatures underwent a facile Claisen rearrangement to afford **442**.



Scheme 59 McDonald and coworkers' strategy toward *ent*-Abudinol B.[165]



Scheme 60 Shishido and coworkers' synthetic strategy to (−)-heliannuol C.[167]

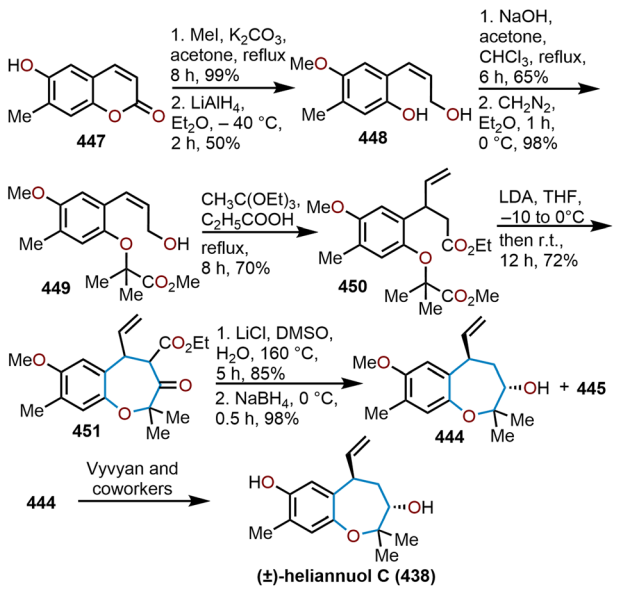


Scheme 61 Vyvyan and coworkers' total synthesis of (±)-heliannuol C.[168]

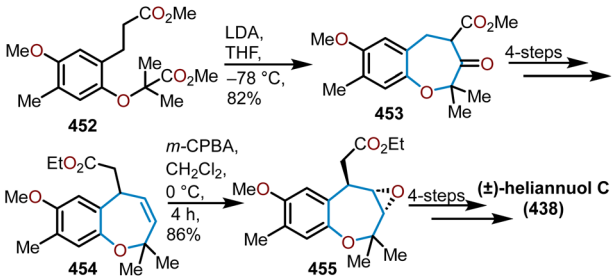
Epoxidation of the more substituted olefin with *m*-CPBA afforded an inseparable 1 : 1.5 diasteromeric mixture of epoxides **443**. Treatment with $SnCl_4$ mediated a regioselective 7-*endo*-cyclization to afford a separable mixture of benzoxepanes (**444** and **445**). Demethylation of **444** afforded (±)-heliannuol C (**438**) and epimer **445** afforded *epi*-heliannuol C (**446**).

Venkateswaran and coworkers developed a formal synthesis of (±)-heliannuol C (**438**) in 2006 that used a Bargellini condensation, a Claisen rearrangement, and a Dieckmann cyclization of a diester to construct the benzoxepane in **438** (Scheme 62).[169] Starting with 6-hydroxycoumarin **447**, methylation and reduction afforded diol **448** that then underwent a selective Bargellini condensation with chloroform and acetone, and the resulting acid was then converted to methyl ester **449** using diazomethane. The allylic alcohol in **449** was then subjected to a Claisen orthoester rearrangement to afford diester **450**. Treatment of the diester with LDA promoted a Dieckmann cyclization to afford β-ketoester **451**. A Krapcho decarboxylation and sodium borohydride reduction of the ketone provided the same separable mixture of benzoxepanes (**444** and **445**) that Vyvyan and coworkers obtained (Scheme 61), thus formally provided access to **438**. They also reported a slightly modified formal route to (±)-heliannuol C (**438**) in 2007, which also relied on a Dieckmann cyclization of **450** to afford **451** and the benzoxepane core of (**438**).[170]

Roy and coworkers also completed a formal synthesis of (±)-heliannuol C **438** in 2017 that similarly constructed the benzoxepane *via* a Dieckmann cyclization of the diester **452** to give **453** (Scheme 63).[171] After 4 additional synthetic steps, benzoxepane **454**, was afforded. Epoxidation using *m*-CPBA afforded a (70 : 30) diastereomeric mixture of epoxide **455**. After concomitant reduction of the ethyl ester and epoxide



Scheme 62 Venkateswaran and coworkers' formal synthesis of (±)-heliannuol C.[169]



Scheme 63 Roy and coworkers' synthetic strategy to access (±)-heliannuol C.[171]

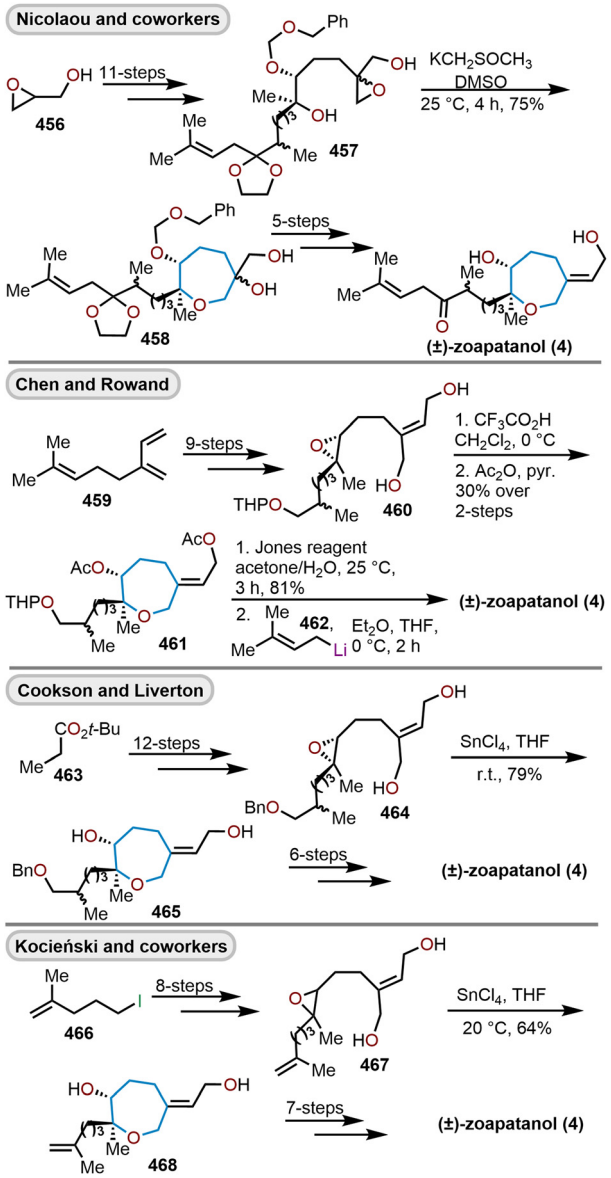
opening with $LiAlH_4$, the dehydration of the primary alcohol *via* elimination of a *p*-nitrophenyl selenate provided **444** the same benzoxepane that Vyvyan and coworkers obtained (Scheme 61), thus formally provided access to (±)-heliannuol C (**438**).

5.14 Total synthesis of zoapatanol

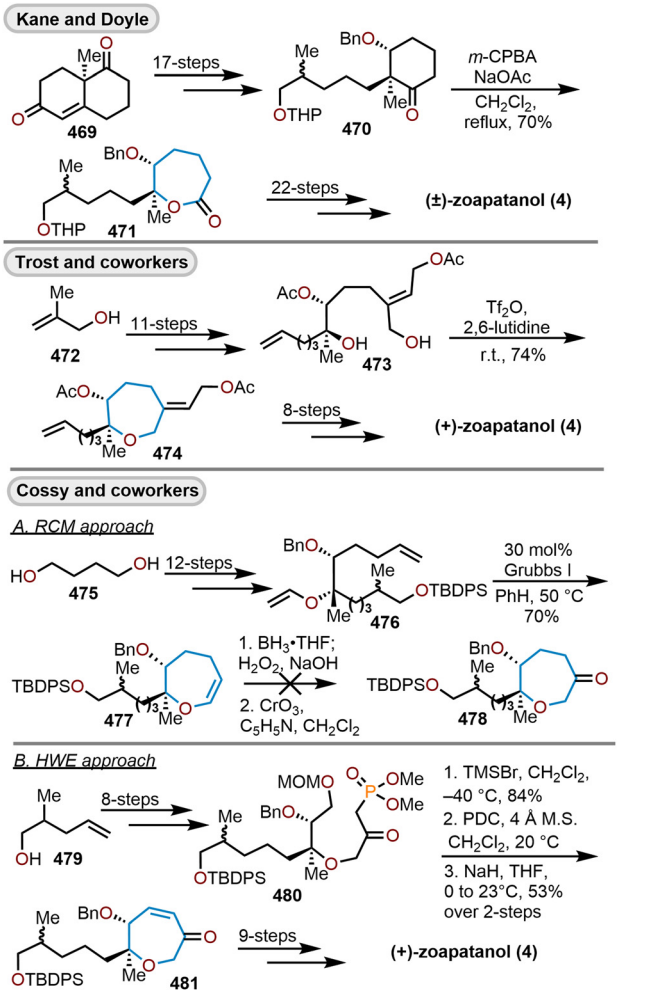
A family of diterpenoid oxepane natural products were isolated in 1979 from the Mexican-native plant *Montanoa tomentosa*, as this plant has been historically used in folk medicine as a form of contraceptive.[172] Amongst these natural products zoapatanol **3** received the most attention owing to its potential as an antifertility agent, with several syntheses having been completed since its isolation.[173] The different aspects of the oxepane construction and oxygenation will be highlighted here. In 1980, Chen and Rowand as well as Nicolaou and coworkers were the first two groups to complete the total synthesis of (±)-zoapatanol (**4**).[174,175]

The approach taken by Nicolaou and coworkers revolved around a key epoxide-ring opening to construct the oxepane moiety (Scheme 64).[174] This key cyclization was carried out with the dihydroxy epoxide **457** which was derived from commercially available epoxide **456**. Exposure of **457** to dimsyl potassium in DMSO promoted a regioselective, intramolecular epoxide-opening to afford the desired oxepane **458** in 75% yield. The total synthesis of zoapatanol was completed in five additional steps following oxidative cleavage of the diol, a Horner–Wadsworth Emmons olefination, ester reduction, and protecting group removal. In contrast to Nicolaou and coworkers' approach which used basic conditions to form the oxepane ring, Chen and Rowand used an acid-catalyzed cyclization of dihydroxy epoxide **460**, available in 9 synthetic steps from myrcene (**459**), to afford diacetate **461**. Deprotection of the THP alcohol and oxidation with Jones reagent afforded the acid that was treated with an excess of organolithium **462** to install the side chain and afford (±)-zoapatanol (**4**).[175]

Cookson and Liverton also accessed **4** using a $SnCl_4$ acid-catalyzed cyclization of dihydroxy epoxide **464**, available in 12 synthetic steps from *tert*-butyl ester **463**, to afford oxepane **465** in 79% yield, which required 6 additional steps to access (±)-zoapatanol (**4**).[176] Beginning with iodide **466** Kocieński and



Scheme 64 Routes to (±)-zoapatanol using epoxide openings to construct the oxepane ring.[174–178]



Scheme 65 Various synthetic strategies investigated to access (+)-zoapatanol.[179–183]

coworkers accessed dihydroxy epoxide **467** in 8 synthetic steps, which also underwent a $SnCl_4$ acid-catalyzed cyclization to afford **468** in 64% yield, which allowed them to prepare (±)-zoapatanol (**4**) after 7 additional synthetic steps.[177,178] All four of these routes to **4** relied on an epoxide opening to construct the central oxepane ring.

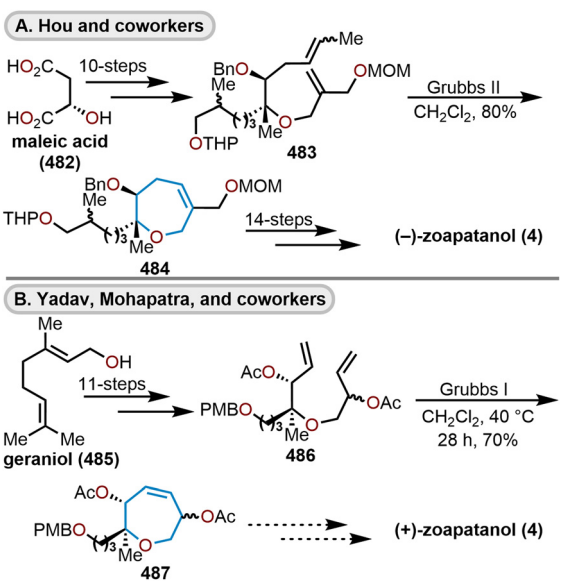
Other approaches to the oxepane of **4** include a Baeyer–Villiger expansion of cyclohexanones, cyclization of alkyl triflates, RCM of dienes, and a Horner–Wadsworth–Emmons olefination (Scheme 65).[179–183] Kane and Doyle employed the Wieland–Miescher ketone **469** to access substituted cyclohexanone **470** in 17 synthetic steps, which was then subjected to Baeyer–Villiger ring expansion conditions to access seven-membered lactone **471** in 70% yield (Scheme 65).[179,180] From lactone **471**, another 22-synthetic steps were required to access (±)-zoapatanol (**4**). In 1994, Trost and coworkers reported the first asymmetric synthesis of (+)-zoapatanol (**4**) from methallyl alcohol **472** (Scheme 65).[181] A Sharpless epoxidation was used to introduce chirality along the way and provided access to diol **473**, which upon conversion to the triflate cyclized to afford oxepane **474** with the correct absolute and relative stereochemistry. Eight additional steps were required to access (+)-zoapatanol (**4**).

Cossy and coworkers also completed an enantioselective total synthesis of **4** (Scheme 65).[182,183] Starting with readily available 1,4-butanediol (**475**), Cossy and coworkers were able to afford diene **476** after an enantioselective Sharpless dihydroxylation was employed to set the desired stereocenters. A RCM was successful using the Grubbs first-generation catalyst to produce the oxepine **477** from **476** in 70% yield. Unfortunately, this initial route ended up being unsuccessful as oxepine **477** was unreactive under hydroboration and oxidation conditions, thus preventing access to ketone **478** that was needed to advance to **4**. As a result, an enantioselective Sharpless dihydroxylation route was combined with a Horner–Wadsworth–Emmons (HWE) olefination strategy to circumvent

these difficulties. Starting with 2-methylpent-4-en-1-ol (**479**), alkyl phosphonate **480** could be accessed in 8 synthetic steps. The pre-installation of the ketone in **480** avoided the difficulties with oxidation in the previous approach, while setting up the HWE olefination. Deprotection of the methoxymethyl (MOM) ether with TMSBr revealed the primary alcohol in 84%. Subsequent oxidation with pyridinium chromate (PDC) afforded the aldehyde, whereupon exposure to base allowed for an intramolecular HWE olefination producing oxepinone **481** in 53% yield over the two steps. Nine additional synthetic steps were required to access (±)-zoapatanol (**4**).

In 2012, Hou and coworkers were able to employ an RCM strategy to access the oxepane core and complete a formal asymmetric synthesis of (−)-zoapatanol (**4**) (Scheme 66A).[184] Beginning with L-maleic acid (**482**) Hou and coworkers were able to access diene **483** in 10 steps to allow for an RCM to construct the oxepane ring **484** using the Grubbs second-generation catalyst. Hou and coworkers' formal access to (−)-zoapatanol (**4**)[184] requires 14 synthetic steps from **484** with 6 additional steps to intercept a common intermediate used in Cossy and coworkers' synthesis.[182] Likewise, Yadav and coworkers (Scheme 66B) were able to access **486** from geraniol (**485**) in 11 steps to construct the central oxepane using a Grubbs first-generation catalyst to access diacetate **487** in 70%, further advancement of **487** towards (+)-zoapatanol (**4**) was described, but efforts to install the sidechain have not yet been reported.[185]

In summary, methods for construction of the central oxepane in **4** include: acid and base-catalyzed cyclizations of dihydroxy epoxides (Scheme 64), Baeyer–Villiger ring expansions of cyclohexanones (Scheme 65), cyclization by displacement of alkyl triflates (Scheme 65), an intramolecular HWE-olefination (Scheme 65), and RCM methods (Schemes 65 and 66).



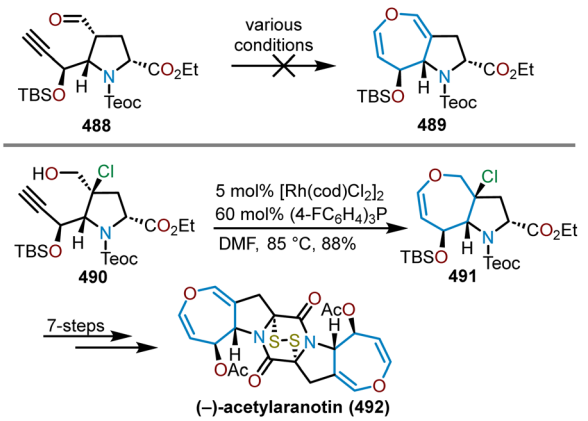
Scheme 66 RCM strategies to access zoapatanol.[184,185]

5.15 Total synthesis of (−)-acetylaranotin

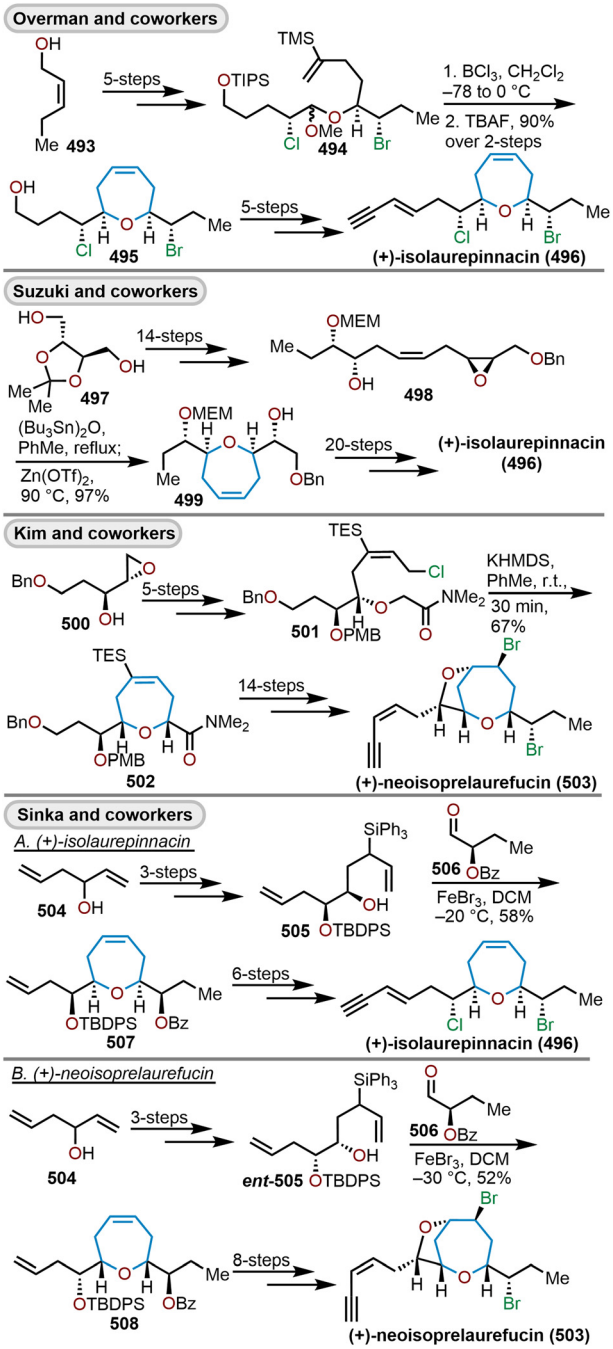
Epidithiodiketopiperazines (ETPs) are a unique family of fungal metabolite natural products that exhibit various bioactivities and those containing a dihydrooxepine motif have posed a challenge for synthetic chemists. Over 40 years after its isolation, Reisman and coworkers accomplished the first enantioselective total synthesis of the dihydrooxepine ETP, (−)-acetylaranotin (**492**) in 2011.[186] To construct the peripheral dihydrooxepine, Reisman and coworkers envisioned a transition metal-catalyzed heterocycloisomerization (Scheme 67). Initial studies were taken with aldehyde **488** available from ethyl glycinate in 9 steps; however, the dihydrooxepine **489** was never obtained with only recovery of epimerized starting material or complete decomposition being observed. As an alternative, chlorohydrin **490** was evaluated. The metal vinylidene-mediated 7-*endo* cycloisomerization was achieved with catalytic [Rh(cod)-Cl]$_2$ and tris(4-fluorophenyl)phosphine in *N*,*N*-dimethylformamide (DMF) solvent at 85 °C to give the chlorotetrahydrooxepine **491** in 88% yield. Elimination of the chloride to give the dihydrooxepine core was achieved in the presence of lithium chloride and lithium carbonate at 100 °C in DMF solvent as part of seven additional synthetic steps needed to access **492** from **491**.

5.16 Enantioselective total syntheses of (+)-isolaurepinnacin and (+)-neoisoprelaurefucin

(+)-Isolaurepinnacin (**496**) and (+)-neoisoprelaurefucin (**503**) are two halogenated marine natural products isolated from red seaweeds of the genus *Laurencia* that contain central seven-membered cyclic ethers. The first total synthesis of a member of this family of natural products was completed in 1993 by Overman and coworkers who enantioselectively prepared (+)-isolaurepinnacin (**496**) in 12 synthetic from *cis*-2-penten-1-ol (**493**) (Scheme 68).[187,188] The key oxepane forming step in the synthesis was accomplished *via* a Prins-type cyclization of a β-haloacetal which was generated *in situ* from **494** by treatment with BCl_3 at low temperature. Subsequent desilylation



Scheme 67 Reisman and coworkers' heterocycloisomerization strategy to synthesize tetrahydrooxepine **491** enroute to (−)-acetylaranotin (**492**).[186]



Scheme 68 Synthetic routes to the oxepane cores in the syntheses of (+)-isolaurepinnacin and (+)-neoisoprelaurefucin.[187–189,192,193]

with TBAF afforded alcohol **495** that was advanced to the target molecule in 5 additional steps. In 2001, Suzuki and coworkers reported a formal synthesis of (+)-isolaurepinnacin (**496**) by intercepting one of Overman and coworkers' late-stage intermediates (Scheme 68).[189] While Suzuki and coworkers formal synthesis was much longer, their oxepane ring construction was accomplished by cyclization of hydroxy epoxide **498**, available in 14 steps from chiral diol **497**. Using their developed $(Bu_3Sn)_2O/Zn(OTf)_2$ system,[190,191] they were able to promote the cyclization of **498** to oxepane **499**. From **499** another 20 steps were required to formally access (+)-isolaurepinnacin (**496**) including the steps of Overman's route.

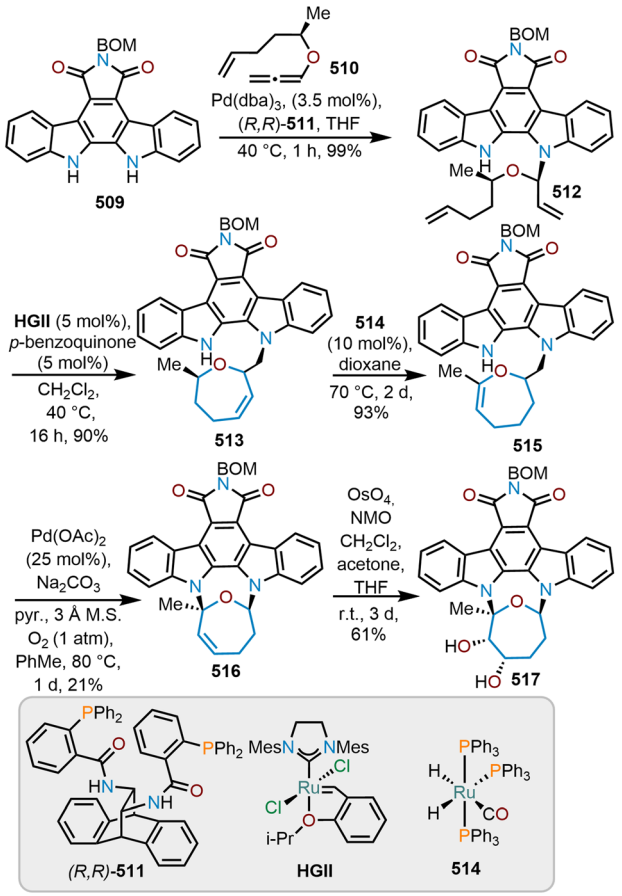
In 2003, Kim and coworkers reported the first total synthesis as well as confirmed the absolute configuration of (+)-neoisoprelaurefucin (**503**).[192] Beginning with chiral epoxide **500**, they were able to access amide **501**, which upon treatment with KHMDS resulted in an intramolecular alkylation by displacement of the allylic chloride to afford the triethylsilyloxepine **502**, which was advanced to (+)-neoisoprelaurefucin (**503**) in 14 steps. In 2022, Sinka and coworkers developed the shortest known enantioselective total syntheses of (+)-isolaurepinnacin (**496**) and (+)-neoisoprelaurefucin (**503**) to date.[193] The *cis*-oxepane ring was constructed using a Prins–Peterson cyclization of chiral silyl alcohol **505** with chiral aldehyde **506** promoted by iron(III) bromide to afford **507** in a 58% yield, which was advanced to **496** in only 6 additional steps (Scheme 68). Beginning with the opposite enantiomer of silyl alcohol **505** the same Prins–Peterson cyclization with aldehyde **506** affords **508** that can be advanced to **503** in 8 additional steps (Scheme 68).

5.17 Synthesis of unnatural septanose analog of 7-oxostaurosporine

From a medicinal chemistry perspective, septanosides can be formed as unnatural analogs to biologically relevant natural products. In 2022, Rhee and coworkers showcased the successful synthesis of an unnatural septanoside analog of 7-oxostaurosporine (**517**) *via* sequential metal catalysis (Scheme 69).[194] A palladium-catalyzed coupling of indolocarbazole **509** and alkoxyallene **510** was able to afford an acyclic allylic acetal **512** in near quantitative yield and in a 9 : 1 dr when ligand (*R*,*R*)-**511** was used. Ring-closing metathesis (RCM) with the second-generation Hoveyda–Grubbs catalyst (HGII) was employed to form the seven-membered oxacycle, **513** which set the stage for a successful olefin migration facilitated by ruthenium hydride catalyst **514**. Using palladium acetate ($Pd(OAc)_2$) under an oxygen atmosphere allowed for an oxidative cyclization to install the second *N*-glycosidic bond to give compound **516**. Lastly, osmium tetraoxide (OsO_4) mediated *syn*-hydroxylation affords the desired unnatural septanose analog of 7-oxostaurosporine **517**.

5.18 Synthesis of artemisinin and its derivatives

Malaria remains as a prominent disease in many underdeveloped countries. Many therapeutics have been developed to combat malaria, but adverse side-effects have remained a pressing issue. As an alternative, artemisinin combination treatments (ACTs) have recently been the recommended therapeutic to combat malaria, and have been showcased in the World Health Organization's (WHO) list of "essential medicines".[195] Surprisingly, the antimalarial activity of artemisinin (Fig. 1, **5**) is not stereospecific, thus making this natural product and its derivatives highly sought after potential therapeutic agents.[196] These sesquiterpene endoperoxides possess an unprecedented scaffold and have been infamously challen-

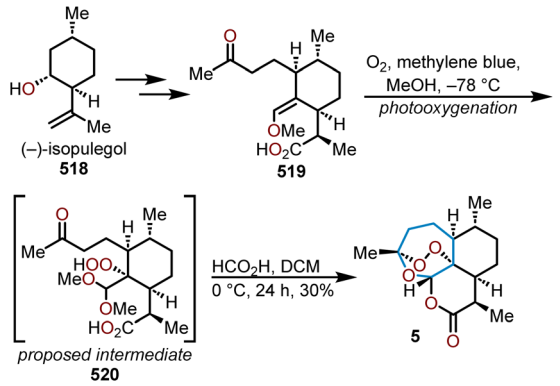


Scheme 69 Oxidative cyclization strategy to access unnatural analog to 7-oxostaurosporine.[194]

ging target molecules, as one must take necessary precautions when constructing the peroxide on a large scale. Since its isolation in 1979, artemisinin (**5**) and its derivatives became target molecules for many groups.

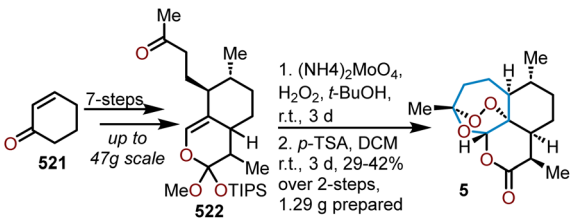
From the 1980s through early 2000s many groups accomplished total syntheses of artemisinin.[197–207] The first group to synthesize artemisinin was Schmid and Hofheinz at Hoffman-LaRoche in 1983 (Scheme 70).[197] Starting with the commercially available terpene, (−)-isopulegol (**518**), Schmid and coworkers were able to arrive at the enol ether **519**. From there, a key photooxygenation step of **519** through an ene reaction with singlet oxygen in the presence of methylene blue at cold temperatures afforded the proposed peroxide acetal intermediate **520**, which upon acid hydrolysis forms the lactone, endoperoxide and oxepane in a single step to arrive at (+)-artemisinin (**5**) in a 30% yield. This installation of the *endo* peroxide coinciding with oxepane formation using singlet oxygen is common throughout the early synthetic routes to **5**.[204]

A notable concise and enantioselective total synthesis of (+)-artemisinin (**5**) from inexpensive starting materials was achieved by Cook and coworkers in 2012 (Scheme 71).[208] Their efforts began with commercially available cyclohexenone (**521**), which was elaborated *via* a key [4 + 2] annulation to the orthoester-containing methyl ketone **522** in 7 steps with reactions run on as high as 47 g scale. A unique aspect of the Cook synthesis is that by using ammonium molybdate a controlled decomposition of hydrogen peroxide into singlet oxygen allowed for the oxidation of the enol olefin in **522**, which upon treatment with acid completed the final oxidative rearrangement to afford (+)-artemisinin **5** on gram scale.

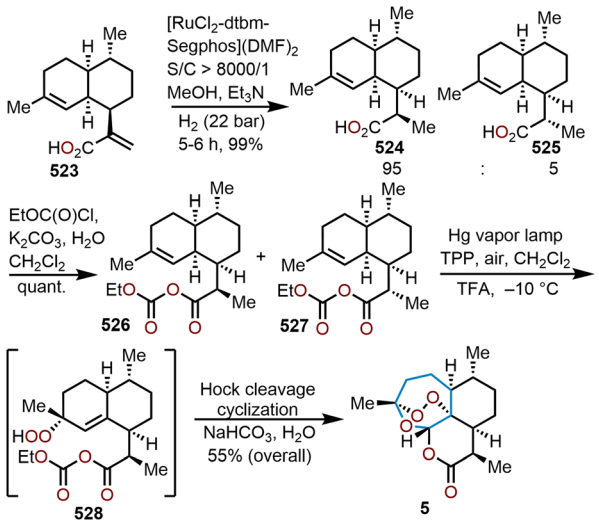


Scheme 70 First reported total synthesis of (+)-artemisinin from (−)-isopulegol by Schmid and Hofheinz in 1983.[197]

While the direct total syntheses of **5** are notable feats and have advanced new chemical methods, current routes are not scalable enough (*e.g.*, high costs of terpene-based starting materials, elaborate synthetic routes, low-yielding reactions, and safety) to be able to meet the high demand of artemisinin which is currently accessed through plant-based extractions. To provide an alternative pathway to **5**, Sanofi and others have pursued the development of alternative semi-syntheses from artemisinic acid (**523**); the proposed biosynthetic precursor to artemisinin (**5**). Biosynthetic access to artemisinic acid is available from the fermentation of sugar using genetically engineered yeast, which has been exploited to prepare over 60 metric tons of **5** in 2014 through a three-step semi-synthetic route developed by Sanofi that involves diastereoselective hydrogenation, acyl substitution, and photooxygenation (Scheme 72).[209] Starting with artemisinic acid **523**, the diastereoselective reduction was carried out with an optimized catalyst/ligand set $\{RuCl_2[(R)\text{-DTBM-Segphos}](DMF)_n\}$ to obtain **524** and **525** with a respective dr of 95 : 5. Addition of ethyl chloroformate to the diastereomeric mixture gives the mixed anhydrides **526** and **527** in a quantitative yield. Next, a mercury vapor lamp is used to initiate a regioselective Schenck



Scheme 71 Cook and coworkers' route to (+)-artemisinin.[208]



Scheme 72 Optimized semi-synthesis of artemisinin from artemisinic acid.[209]

ene reaction, whereupon subsequent Hock cleavage and concomitant oxidative cyclization of proposed intermediate **528** afforded (+)-artemisinin (**5**) isolated in 55% yield over the three-steps (average batch isolation of 370 kg).

6. Summary and outlook

Recent advancements toward the preparation of oxepanes have been extensively covered. The synthetic strategies to access this moiety can arise from cyclic or acyclic start materials. Commonly, feedstock pyranoses are used in *de novo* syntheses to prepare oxepanes from cyclic precursors. Benefits to using sugar-based reagents is that they are often an affordable source of cyclic reagents with nearly all stereocenters established, which can be quickly elaborated. However, there are demerits for employing carbohydrate starting materials: often solubility and selectivity issues arise, which requires the extensive use of protecting groups to alleviate these difficulties. Alternatively, oxepanes have also been successfully prepared from acyclic, yet readily available starting materials.

The use of acyclic, non-sugar-based starting materials have been strategically used in literature to circumvent the problems established during sugar-based syntheses. Typically, solubility and selectivity issues can be avoided by starting with carefully chosen reagents; however, this comes at the expense of having to set the desired stereocenters. Nonetheless, literature has shown over the years how both methods can be viable to carry out a total synthesis of biologically relevant natural products.

The formation of cyclopropanated glycals from the readily available sugar-based starting materials, allows rapid access to oxepanes. Furnishing the pyranose with a ketone opens the opportunity to carry out a homologation, thus affording the seven-membered oxacycles. This tactic was commonly employed by Mori and coworkers for their endeavors in natural product total synthesis of hemibrevetoxin B[50] and gambierol.[155] A unique approach is also offered from functionalization of glucals, whereupon a Nicholas–Ferrier rearrangement can execute the ring expansion of the pyranyl system. Isobe and coworkers showcased the utility of this transformation from their efforts in the total synthesis of the ciguatoxins.[67]

Various cyclization strategies have been developed to afford the seven-membered oxacycle. Amongst the plethora of tactics, Lewis acid-mediated cyclizations are the most widely applicable method. Epoxide-opening cascades provide an excellent example of this transformation, which has been notably used by Jamison and coworkers for their construction of gymnocin B.[141] Radical cyclization strategies have also been advanced to afford oxepanes from the assistance of samarium iodide. This reductive radical cyclization was used extensively by Fuwa, Sasaki and coworkers as advertised from their works in the total synthesis of brevenal[100] and gambierol.[149] Ring closing metathesis is another common cyclization strategy for the construction of oxepanes from tethered dienes. Employing the RCM with Grubbs I or Grubbs II has been heavily pioneered in total synthesis, which was the prevailing method to preparing the seven-membered oxacycles by Inoue, Hirama and coworkers in efforts to the ciguatoxins.[108]

The current progression of advancements in the synthesis of oxepanes reveals that new methodologies and opportunities will continue to arise from endeavors in the total synthesis of biologically relevant natural products. While there have been extensive breakthroughs in oxepane synthesis as highlighted in this review, photocatalytic,[210] biocatalytic, and biomimetic strategies[211] that use cascade reactions and incorporate aspects of green chemistry are primed areas for advancement over the next decade to expedite access to complex oxepane natural products.

Author contributions

All authors conceptualized, discussed the concept of this article, and contributed to the scientific writing of the original manuscript. All authors have read and approved the final manuscript.

Conflicts of interest

There are no conflicts to declare.

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