Natural Products

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The Continuing Saga of the Marine Polyether Biotoxins

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Dedicated to Professor E. J. Corey on the occasion of his 80th birthday

The unprecedented structure of the marine natural product brevetoxin B was elucidated by the research group of Nakanishi and Clardy in 1981. The ladderlike molecular architecture of this fused polyether molecule, its potent toxicity, and fascinating voltage-sensitive sodium channel based mechanism of action immediately captured the imagination of synthetic chemists. Synthetic endeavors resulted in numerous new methods and strategies for the construction of cyclic ethers, and culminated in several impressive total syntheses of this molecule and some of its equally challenging siblings. Of the marine polyethers, maitotoxin is not only the most complex and most toxic of the class, but is also the largest nonpolymeric natural product known to date. This Review begins with a brief history of the isolation of these biotoxins and highlights their biological properties and mechanism of action. Chemical syntheses are then described, with particular emphasis on new methods developed and applied to the total syntheses. The Review ends with a discussion of the, as yet unfinished, story of maitotoxin, and projects into the future of this area of research.

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1. Introduction

Marine organisms have proven to be rich reservoirs of natural products with enchanting molecular architectures and potent toxicities. Some of these compounds have been implicated as causative agents in many seafood-related poisonings, including tetrodotoxin poisoning (by **1**, Figure 1), diarrhetic shellfish poisoning (DSP, by **2**), azaspiracid poisoning (AZP, by **3**), amnesic shellfish poisoning (ASP, by **4**), paralytic shellfish poisoning (PSP, by **5**), neurotoxic shellfish poisoning (NSP, by **6** and **7**; Figure 2), and ciguatera fish poisoning (CFP, by **9** and **10**, Figure 2 and **13**, Figure 3).[1] These agents are also responsible for many of the massive fish kills which have been observed throughout history and around the world. As such, enormous efforts have been expended by chemists and biologists towards the isolation, characterization, biological evaluation, and chemical synthesis of these molecules.

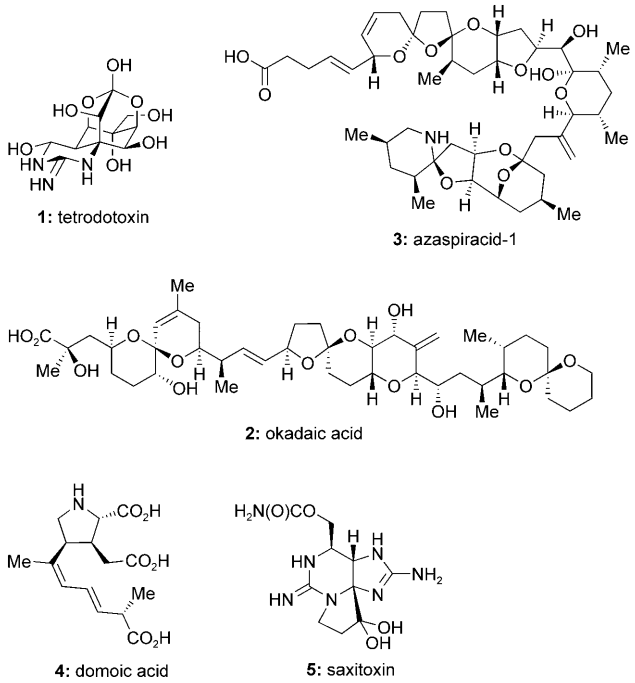

Figure 1. Molecular structures of selected marine biotoxins.

A particularly diverse and celebrated set of these marine biotoxins are the ladderlike polycyclic ethers (Figures 2 and 3). Since the disclosure of the first member of this family, brevetoxin B (**6**) in 1981,[2] scientists have discovered numerous members of this ever increasing class of naturally occurring substances, ranging from the relatively small hemibrevetoxin (**8**, Figure 2) and brevenal (**11**, Figure 2) to the more complex maitotoxin (**13**, Figure 3), the largest nonbiopolymer substance known to date. These polyethers are produced by dinoflagellates, and have been isolated from cultures of these unicellular algae, filtrates of the microorganisms on which the dinoflagellates typically reside, and

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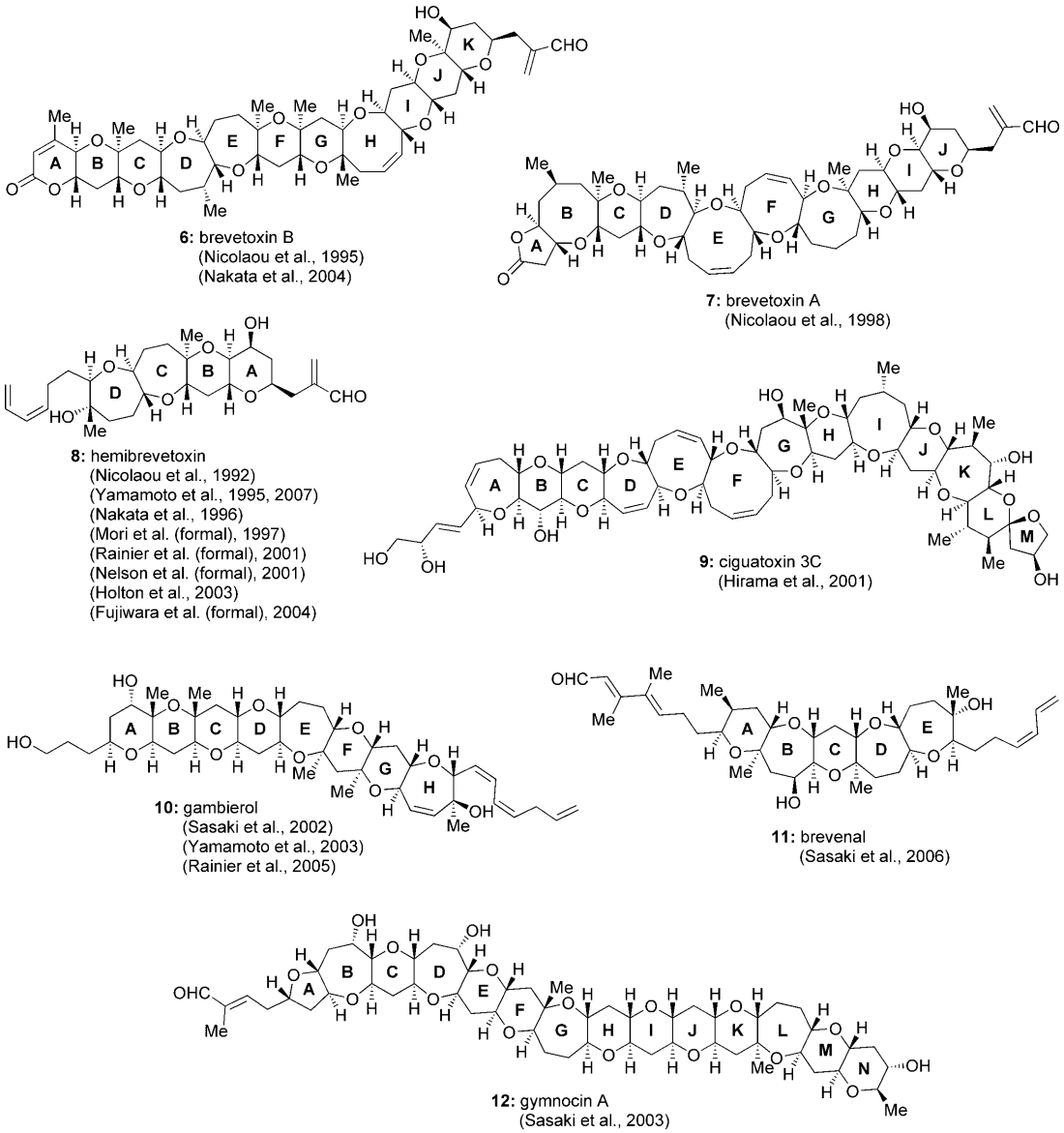

Figure 2. Molecular structures of ladderlike polyether marine biotoxins (**6**–**12**) constructed by total synthesis.

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Michael O. Frederick was born in White Bear Lake, Minnesota in 1981. He received his BS in chemistry from the University of Minnesota while working with Professor Richard Hsung on the chemistry of ynamides. He is currently pursuing PhD research at The Scripps Research Institute under the guidance of Professor K. C. Nicolaou where he has worked on the total syntheses of azaspiracids-1, -2, and -3, and is currently pursuing the total synthesis of other marine biotoxins. He has been the recipient of an NSF predoctoral fellowship.

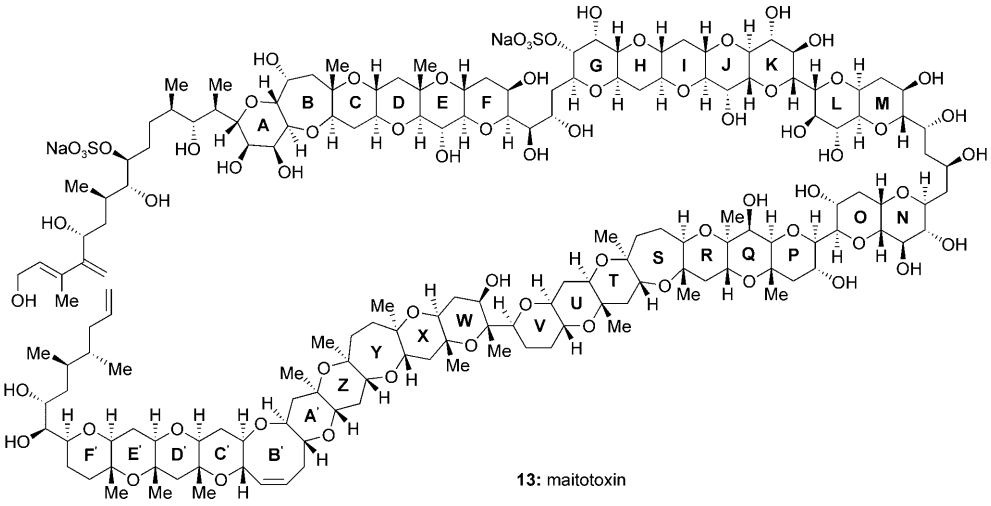

Figure 3. Molecular structure of maitotoxin (**13**), the largest of the polyether marine biotoxins and of any nonpolymeric natural product isolated to date.

fish that ingest the algae. In certain cases, such as with ciguatoxin 3C (**9**), enzymatic modification of the polyether backbone by the fish consuming the algal dinoflagellates can lead to further derivatives.[3] The scarcity of these substances and the difficulties in isolating them demanded Herculean efforts for their structural elucidation. Admirably, chemists have been able to isolate and characterize these daunting structures with the aid of powerful technological advances in chromatography, NMR spectroscopy, and mass spectrometry.[4]

The potent biotoxicity of the polyether marine toxins can be traced through every step of the food chain—from their unicellular producers to humans. The isolation and characterization of these toxins would lay the foundation to combat their production and poisonous effects. The brevetoxin-producing dinoflagellate *Karenia brevis* (formerly known as *Gymnodynium breve*) is responsible for the toxicity of "red tide" algal blooms which frequently occur around the world and cause massive fish kills and death of marine mammals.[5] Many species of fish ingest other marine organisms, including the toxin-producing dinoflagellates, without experiencing toxicity themselves, but, in turn, pass the toxins onto humans who consume the seafood. Most notably, the cause of ciguatera fish poisoning (CFP) has been attributed to the ciguatoxins such as **9**, gambierol (**10**), and maitotoxin (**13**), all of which are produced by dinoflagellates. CFP is characterized by temperature sensitivity, diarrhea, vomiting, muscle pain, and itching; these symptoms can, in extreme cases, persist for years.[6] The majority of the polyether marine natural products are neurotoxins, which exert their biological activities through activation of voltage-sensitive ion channels.[7] Interestingly, a number of these polyethers also display potent antifungal[8] and antitumor[9] activities. However, the evaluation of these natural products with regards to their biological properties and targets remains incomplete, as will be further discussed in the following section.

The "red tide" algal blooms are becoming a menace to many coastal areas around the world, with Florida experiencing almost annual catastrophic outbreaks.[10] Dinoflagellates can move short distances by virtue of their own ability to swim, and can be carried long distances by other marine organisms, ocean currents, ships, and hurricanes. When the concentration of *Karenia brevis* per liter of water (normally about 1000 cells) reaches 5000 or more, the blooms become evident. The initiating event for such blooms and the source of the nutrients to sustain them as well as the terminating causes are still debated. A number of hypotheses have been proposed, including African winds carrying iron dust that contributes to the growth of the bacterium *Trichodesmium*, which, in turn, manufactures bioavailable forms of nitrogen from atmospheric nitrogen and thus fuels the growth of *Karenia brevis*. Another postulated source is nutrient pollution from farms, factories, and cities connected to the ocean through canals and rivers. However, much research is needed before these phenomena can be understood and controlled. In the meantime, the emergence of these unique molecules is stimulating much science, thus contributing to advances ranging from chemical synthesis to chemical biology and from neurobiology to drug discovery.[11]

Repetitive structural motifs are contained within the stunning structures of the polyether marine natural products, whose synthesis represented an unprecedented challenge. Despite this fact, a number of research groups have taken on the challenge, completing the total syntheses of several of these molecules shown in Figure 2. These synthetic endeavors necessitated and led to the discovery and invention of bond-forming reactions, which have found extensive applications in the construction of the ladderlike polyether marine natural products. After a brief discussion of the biological properties

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of these marine natural products, we will summarize these synthetic methods and highlight their applications in the total syntheses. We will conclude with recent advances and ongoing research directed toward more-efficient synthetic methods of the more complex structures within this growing and fascinating class of natural products.

2. Biological Properties and Mechanism of Action

Although most of the ladderlike marine biotoxins exhibit similar activities and mechanisms of action, some of them show unique properties. In this section we will discuss some of their similarities and differences, beginning with the largest member of the group, maitotoxin. Maitotoxin is especially toxic to mammals, exerting its biological activity through binding to a membrane protein and thus inducing calcium ion influx into cells.[12] The biological activity and precise mode of action of maitotoxin is currently an active field of investigation, despite the fact that its biological target within the cell membrane remains elusive. Maitotoxin has been shown to cause calcium ion influx into a variety of cells[13]—including synaptosomes[14] and erythrocyte ghosts (empty vesicles made up by cell membranes)[15]—but not artificial phospholipid vesicles,[16] which suggests the existence of a non-phospholipid target for this molecule within the membrane of the cell. The calcium influx induced by maitotoxin leads to secondary effects such as muscle contraction,[17] secretion of norepinephrin,[18] dopamine,[19] and insulin[20] as well as phosphoinositide breakdown,[21] arachidonic acid release,[22] and acrosome reaction in sperm.[23]

Based on NMR spectroscopic analysis, a model for maitotoxin anchoring into the cell membrane has been proposed by Murata and co-workers.[11,24] They proposed an interaction of maitotoxin with cell membranes similar to that of glycolipids with the lipophilic domain of the molecule (rings R to F′, C82–C142; note that only three OH groups are present in this domain, two of which are at the tail end) anchoring it into the membrane, while its hydrophilic domain (rings A to Q, C1–C81; note that this domain includes 24 OH groups and 2 sulfate groups) remains outside the cell membrane (Figure 4). It was suggested that four or more maitotoxin molecules form a channel-like assembly across the membrane that—unlike amphotericin B—involves participation of a receptor other than lipids or steroids. Interestingly, brevetoxin B (**6**), which mimics the lipophilic domain of maitotoxin, and certain small molecules that mimic the hydrophobic part of the molecule inhibit maitotoxin-induced calcium ion influx into rat glioma C6 cells,[15] thus suggesting that maitotoxin may recognize its receptor through binding at multiple sites through its different domains.[24]

The understanding of the precise interaction of the ladderlike polyether natural products with cell membranes is an important and a challenging task. Increasing ion influx into cells, as they do, these dinoflagellate-derived secondary metabolites resemble the antifungal polyenepolyol type natural products, such as amphidinol 3 (AM3, **14**; Figure 5),[25] which is also a dinoflagellate metabolite. They differ from them, however, in that while the polyethers bind

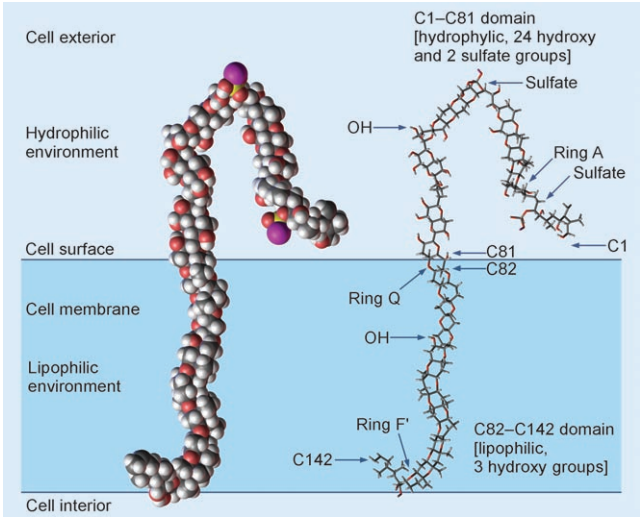


Figure 4. Model of the anchoring of maitotoxin into the cell membrane (according to Murata and co-workers).[11,24]

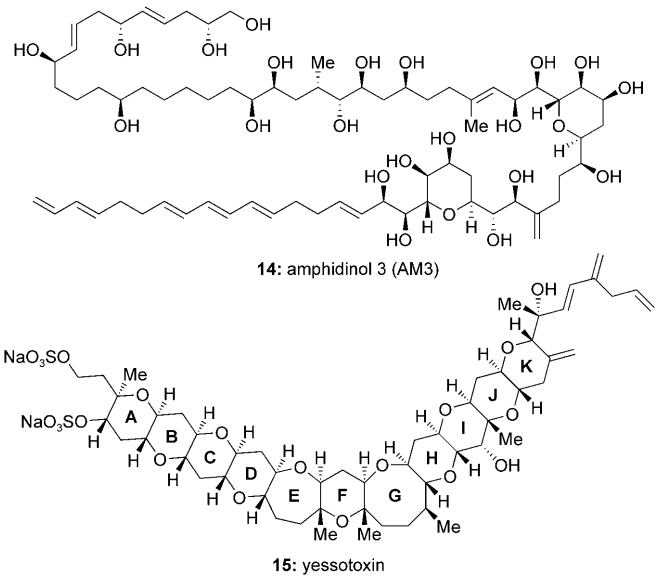


Figure 5. Structures of amphidinol 3 (AM3, **14**) and yessotoxin (**15**).

to and open membrane protein ion channels, the polyenepolyols exert their activity through binding to membrane lipids.

Despite the ever-increasing number of ladderlike polyethers (more than 50 have been discovered so far), studies on their mode of action are lagging behind because of their scarcity and the complexity of their biological interactions. Their activities range broadly from ichthyotoxicity (for example, **6**, **7**, and **9** Figure 2; as well as glycoside-containing **16** and **17**, Figure 6)[26] to cytotoxicity (for example, **12**; Figure 2)[9] and antifungal activity (for example, **18**; Figure 6),[8] whose potency exceeds that of amphotericin B by a factor of two thousand.

Brevetoxins B (**6**) and A (**7**) as well as ciguatoxins 1B and 3C (**9**) exhibit high affinities to the same binding site of a voltage-sensitive sodium channel protein.[27] It is generally thought that the ladderlike polyethers bind to their receptors

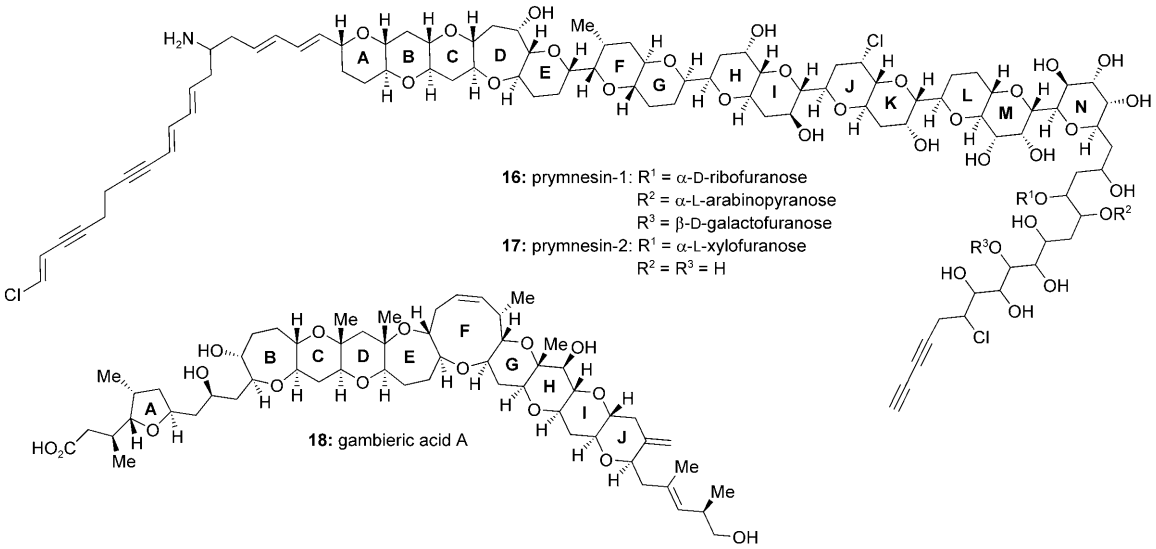


Figure 6. Structures of prymnesin-1 (**16**) and prymnesin-2 (**17**) and gambieric acid A (**18**).

through weak interactions involving primarily N–H···O and C_α–H···O hydrogen bonds;[28] Figure 7 shows the hypothetical model for brevetoxin B (**6**). Thus, when the polyether

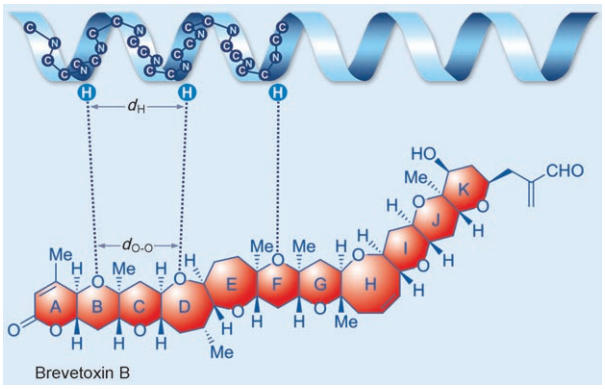


Figure 7. Hypothetical model for the binding of ladderlike polyethers to their receptor α-helix motifs of membrane protein ion channels as exemplified by brevetoxin B (according to Murata et al.).[11]

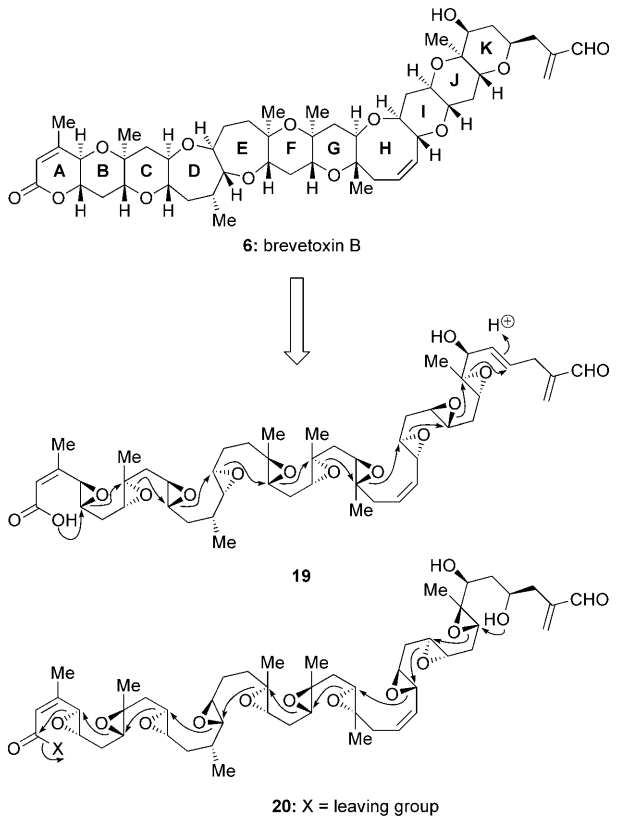
arrangement of the biotoxin complements the protein structural motif of the target protein, usually an α helix, the match results in binding through a network of hydrogen bonds, which leads to the biological action of the toxin. Interestingly, the pitch of the α helix (5.40 Å) matches quite well with the average distance ($d_{O\text{-}O}$) between the same-side neighboring ether oxygen atoms of the brevetoxin B ladder structure (5.15 Å), as determined by X-ray analysis.[29]

Yessotoxin (**15**, Figure 5), a ladderlike polyether biotoxin isolated from dinoflagellate *Protoceratium reticulatum*,[30] was found to induce apoptosis through a mitochondrial signal transduction pathway.[31] Both yessotoxin and its desulfated counterpart bind to the transmembrane domain of glycophorin A and cause the dissociation of clusters of the protein.[31] This dissociating activity is thought to be elicited by these molecules through specific binding to a lipophilic α helix of the protein (see Figure 7). Significantly, polyethylene glycol did not induce dissociation of oligomeric aggregates of glycophorin A, thus underscoring the importance of the rigid ladderlike structures of the polyether marine natural products for binding and, hence, for their biological activity.

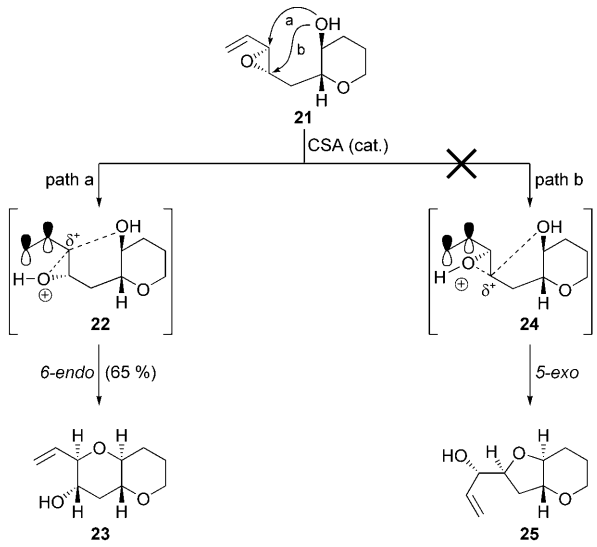
The unique structures of the polyether marine natural products endow them with special physical and chemical properties which may be important for their biological action. Interrupted by the usually more flexible seven-, eight-, or nine-membered rings, which act like hinges, these predominantly polypyran, and therefore rigid, structures uniformly exhibit affinity to membrane-bound α helices of ion channel proteins, primarily through hydrogen bonding and/or electrostatic forces.[11] It is notable that, while tetrahydropyran itself has a large dipole moment, linearly fused, exclusively polypyran structures such as those domains found in the polyether marine natural products have little, if any, dipole moment because of the alternating orientations of the pyran rings. Hence, they have lower water solubility than naturally occurring biotoxins in which this regularity-based cancellation of ring dipole moments is disturbed by the seven-, eight-, or nine-membered rings present within their structures. This recognition may be useful in designing artificial ladderlike polyethers as models of the natural biotoxins and as tools in biological studies.

3. Synthetic Methods

The discovery and disclosure of the structure of brevetoxin B (**6**, Scheme 1) served as the impetus for the search of new synthetic methods for the construction of its unique structural motifs.[32] Soon after the initial report on the structure of brevetoxin B in 1981,[2] a particularly elegant hypothesis for its biogenetic origin was put forth by Nakanishi et al.[33,34] Specifically, it was proposed that a zip-type cascade reaction involving polyepoxide precursor **19** or **20** may be responsible for its enzymatic formation in *Karenia brevis*



Scheme 1. Nakanishi's proposed biosynthetic hypothesis for brevetoxin B (**6**).[33]



Scheme 2. The 6-*endo* hydroxy epoxide opening method for cyclic ether formation (Nicolaou et al., 1985).[37]

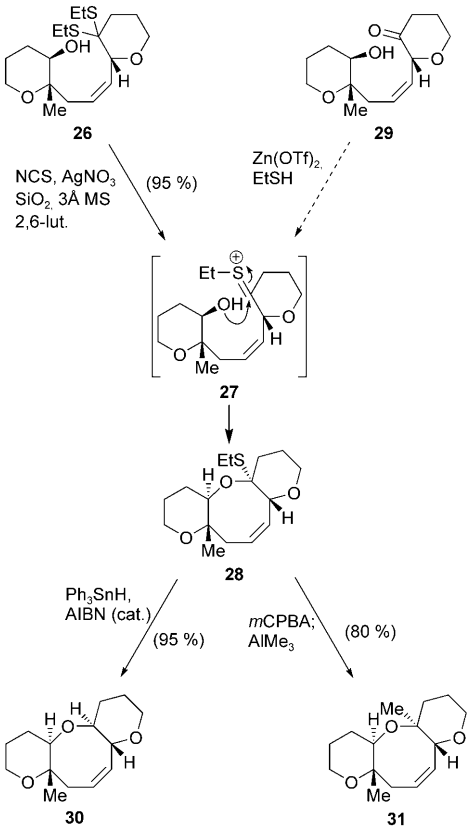
(Scheme 1). In fact, The Nicolaou research group had proposed such a cascade in an NIH grant application in 1982[35] (**20**→**6**, Scheme 1) as a hypothetical strategy for the total synthesis of brevetoxin B. In the absence of enzymes, however, this strategy was not considered feasible in the laboratory, since some of the S_N2-type reactions required for its implementation contravened the Baldwin rules of ring closure,[36] and because of the lack of suitable methods to construct the precursor polyepoxide.

A number of stepwise approaches to single ether rings were, therefore, sought in the beginning, with the hope that such methods could be combined to construct the ladderlike structures of brevetoxin B (**6**) and related molecules. Cascade reactions to construct more than one ring were later sought and successfully developed. These synthetic methods will be briefly reviewed below in approximately the order in which they were reported.

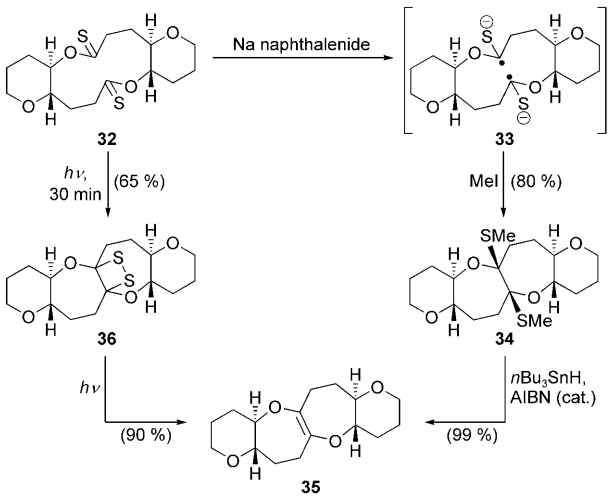
In 1985, the Nicolaou research group reported the first regio- and stereoselective synthesis of pyrans involving the opening of epoxides with a hydroxy group, specifically directed toward the eventual total synthesis of brevetoxin B (**6**).[37] They were able to override the natural preference for the undesired 5-*exo* cyclization by placing a carbon–carbon double bond adjacent to the epoxide moiety (Scheme 2). Thus, under acidic conditions, hydroxy epoxide **21** underwent exclusive 6-*endo* ring closure to afford bispyran system **23**, rather than the alternate 5-*exo* product **25** (Scheme 2). This reversal of ring selectivity is attributed to the stabilization by the proximal π orbital of the developing electron-deficient carbon atom in transition state **22** arising from *endo* attack (Scheme 2), an effect not present during the hypothetical *exo* attack proceeding through transition state **24** (Scheme 2). This stereoselective method for the formation of a cyclic ether has the additional advantages of easy access to enantiomerically enriched substrates[38] and the synthetic versatility of the products. As a consequence, this synthetic method found extensive use in the total synthesis of several of the polyether marine natural products, as will become evident from the following sections.

A method particularly suitable for the construction of cyclic polyethers that proceeds through the intermediacy of cyclic O,S acetals was developed by the Nicolaou research group in the 1980s.[39] The initially reported method in 1986[39a] involved reaction of a hydroxy dithioketal such as **26** (Scheme 3) with NCS in the presence of $AgNO_3$, SiO_2, 3 Å molecular sieves, and 2,6-lutidine to afford, in excellent yield, the O,S-acetal **28**, presumably through thionium species **27**. The same mixed cyclic acetal could, in principle, be generated directly from the hydroxy ketone **29** by treatment with EtSH in the presence of $Zn(OTf)_2$, as demonstrated with other examples.[40] The radical reaction of **28** with Ph_3SnH (in the presence of AIBN) led stereoselectively, and in high yield, to oxocene **30**. Alternatively, *m*CPBA oxidation to the corresponding sulfoxide or sulfone, followed by in situ addition of $AlMe_3$ furnished the methylated oxocene **31** in excellent yield. Thus, the foundation was set for constructing the relatively abundant cyclic ether structural motifs with H or Me substitutents adjacent to the oxygen atom (Scheme 3).

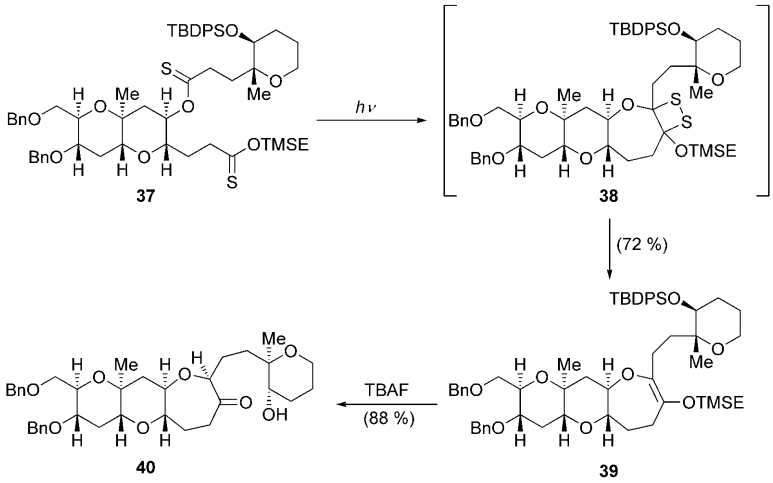
The Nicolaou research group then turned their attention to the formation of cyclic ethers from lactones, since such structural motifs are present in numerous natural and synthetic compounds. This reasoning led to a series of discoveries and practical methods ranging from the bridging of macrocycles to the Stille coupling (of stannanes) or Suzuki



Scheme 3. The hydroxy dithioketal cyclization method involving O,S-acetals for cyclic ether formation (Nicolaou et al., 1986).[39]



Scheme 4. The bis(thionolactone) bridging method for cyclic ether formation (Nicolaou et al., 1986).[42]



Scheme 5. The bis(thionoester) photolytic cyclization method for cyclic ether formation (Nicolaou et al., 1989).[44]

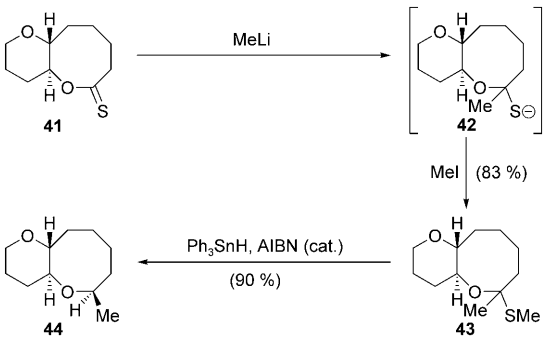
coupling reactions (of alkyl boron compounds) with vinyl phosphates or triflates.

The Nicolaou research group recognized early in the 1980s the potential of medium-sized ring lactones as precursors to the same-sized ring ethers, a desirable circumstance because of the ease of formation of the former through the many efficient lactonization protocols available.[41] As direct addition/alkylation of lactones would almost invariably result in ring rupture, Nicolaou et al. turned to thionolactones as suitable precursors because of the expected higher stability of the initially formed tetrahedral intermediates upon nucleophilic attack. The bridging of dithionolactones to bicyclic ethers as demonstrated in Scheme 4 is a stellar example of this concept.[42] Thus, bis(thionolactone) **32**, readily available from the corresponding bislactone through reaction with Lawesson's reagent,[43] reacted with sodium naphthalenide (an electron source) to afford dianion diradical **33**, which was quenched with MeI to give the bis(O,S-acetal) **34**. A radical reduction removed the two methylthio groups and led to tetracyclic polyether **35** in high yield. Alternatively, photoirradiation of bis(thionolactone) **32** furnished the stable 1,2-dithietane system **36** (dithiatopazine), the first of its kind as a stable crystalline compound.[42b,c,e] Further photolysis of **36** led to the same tetracycle **35**.

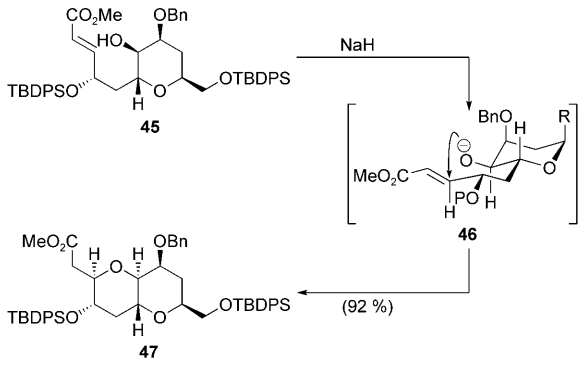
In a modification of their photoinduced method, the same research group exploited the use of open-chain bis(thionolactones) (obtained from the corresponding diesters by treatment with Lawesson's reagent) to form oxepane rings through photolytic irradiation (**37**→**38**→**39**→**40**; Scheme 5).[44]

A nucleophilic addition and reduction sequence (Scheme 6) of thionolactone **41** (obtained from its lactone counterpart by treatment with Lawesson's reagent) led to oxocane **44**. Thus, **41** was treated sequentially in one pot with methyllithium to give tetrahedral intermediate **42** and then with methyl iodide to afford methylthio-substituted ether **43**. Radical reduction of **43** with Ph_3SnH in the presence of AIBN furnished **44** as a single isomer (Scheme 6).[45]

Another useful method for the construction of pyran ring systems which relies on an intramolecular attack of a hydroxy group on a Michael acceptor was developed by the Nicolaou research group.[46] Deprotonation of the hydroxy group in α,β-unsaturated ester **45** with sodium hydride resulted in the stereoselective formation of bicycle **47**, which represents the J/K ring system of brevetoxin B (Scheme 7). The stereoselectivity of this reaction, as ensured by the chairlike transition



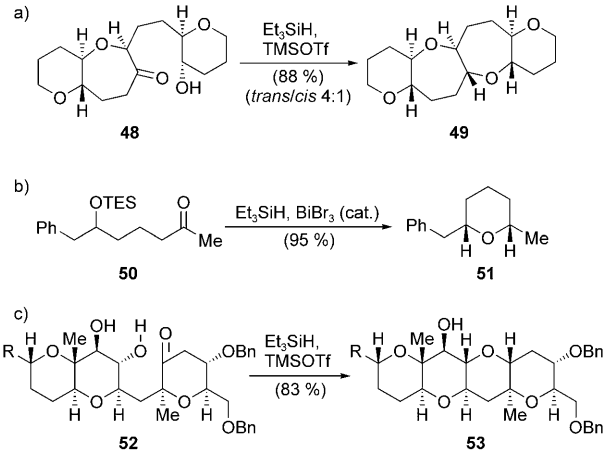
Scheme 6. The thionolactone nucleophilic addition/reduction method for cyclic ether formation (Nicolaou et al., 1987).[45]



Scheme 7. The intramolecular hydroxy Michael addition reaction for cyclic ether formation (Nicolaou et al., 1989).[46] P = TBDPS, R = $CH_2OTBDPS$.

state **46**, made this hydroxy Michael addition method a favorite choice in total synthesis (see the following sections).

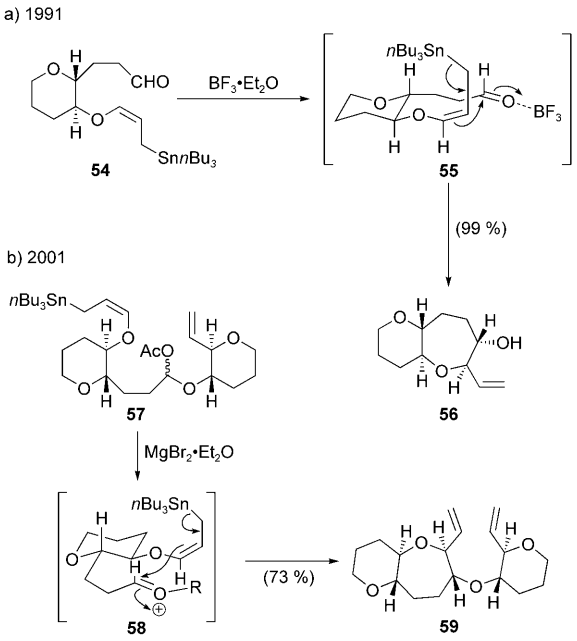
In 1989, Nicolaou et al. reported a direct method for the formation of cyclic ethers from hydroxy ketones (Scheme 8).[44] This method relied on a reductive cyclization of hydroxy ketones with Et_3SiH in the presence of a Lewis



Scheme 8. The hydroxy ketone reductive cyclization method for cyclic ether formation (a: Nicolaou et al., 1989,[44] b: Evans et al., 2003;[49] c: Sato and Sasaki, 2007).[48]

acid (for example, TMSOTf), a combination of reagents that was inspired by the pioneering work of Olah and co-workers.[47] While the stereoselectivity observed with oxepane systems is not perfect (for example, **48**→**49** in Scheme 8a: *trans*/*cis* ca. 4:1), the construction of pyran systems usually proceeds with complete stereoselectivity, as demonstrated later on by Sato and Sasaki with the conversion of hydroxy ketone **52** into cyclic ether **53** (Scheme 8c).[48] The Evans research group extended the method by employing silyl derivatives of hydroxy ketones such as **50** to prepare tetrahydropyrans (for example, **51**) through the action of Et_3SiH in the presence of a $BiBr_3$ catalyst (Scheme 8b).[49]

Two similar methods for the formation of polyether rings involving allyl tin cyclizations of aldehydes and acetals were reported by Yamamoto and co-workers in 1991[50] and 2001,[51] respectively. These methods are based on intramolecular diastereoselective allylations effected by Lewis acid activation. Thus, activation of aldehyde **54** with $BF_3{\cdot}Et_2O$ (Scheme 9a) led to intramolecular allylation and the stereo-



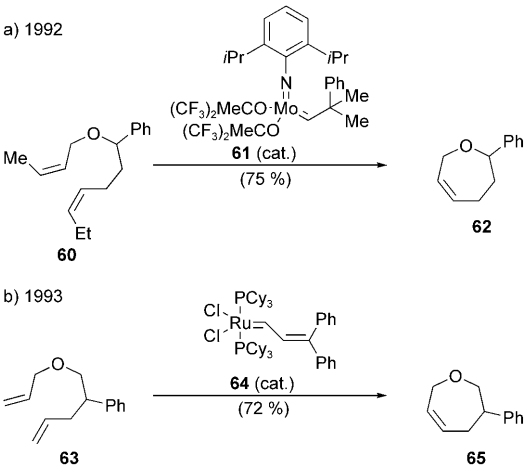
Scheme 9. The allyl tin cyclization method for cyclic ether formation (Yamamoto et al., 1991,[50] 2001).[51]

selective formation of 6,7-bicycle **56** in near quantitative yield. The diastereoselectivity was attributed to the postulated transition state **55**, in which undesired interactions between two axial groups are minimized. The selectivity is limited to the formation of seven-membered rings; six-membered rings suffer from diminished stereoselectivity because of competing chelation effects. Similarly, exposure of acetal **57** to $MgBr_2{\cdot}Et_2O$ presumably led to the formation of oxonium species **58**, which underwent intramolecular allylation to afford tricycle **59** as a single stereoisomer (Scheme 9b).

Although the usually well-defined conformations of the transition states involved in pyran-forming reactions allowed their stereochemical outcomes to be easily discerned in

advance, reactions leading to medium-sized rings present unique challenges, as their stereochemical outcomes are often unpredictable.[52] Furthermore, such processes are also plagued with difficulties associated with intrinsic geometrical constraints within such systems. Ring-closing metathesis[53] is one of the few methods that overcomes such difficulties and, thus, commonly employed to form medium-sized ring compounds.

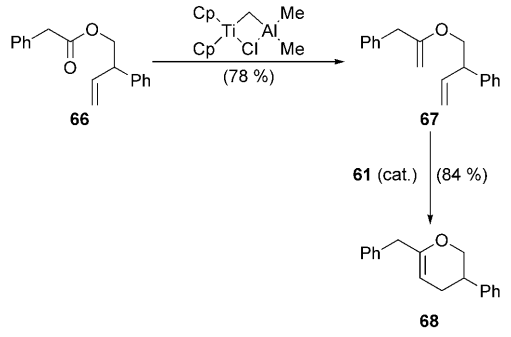
Inspired by the pioneering work of Grubbs and co-workers[54,55] (**60**→**62** and **63**→**65** in Scheme 10 as well as **66**→**67**→**68** in Scheme 11) and recognizing the potential of the



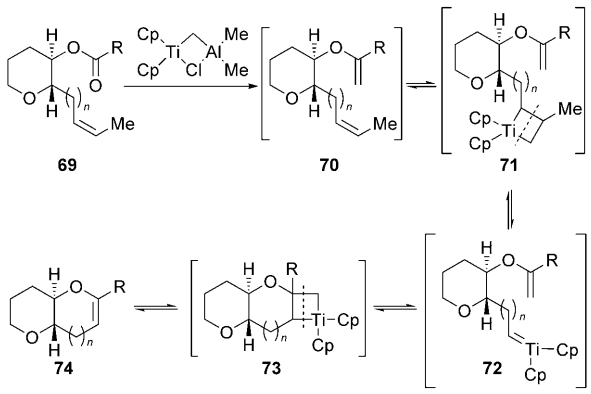
Scheme 10. First examples of the formation of cyclic ethers by ring-closing metathesis (Grubbs and co-workers, a: 1992; b: 1993).[55a,b]

ring closing metathesis reaction for the synthesis of polyethers, the Nicolaou research group developed a new method for forging cyclic ethers. This method involves convergent coupling of growing fragments through esterification followed by ester methylenation and ring-closing metathesis.[56] Scheme 12 shows the sequence from **69** to **74** (proceeding through intermediates **70**–**73**) in its general form, with the Tebbe reagent[57] used as both the methylenating agent and the metathesis initiator.

The power of this highly convergent method was demonstrated in the construction of numerous polycyclic ethers.[56] Thus, tricyclic polyether **77** was synthesized from bicyclic



Scheme 11. Early example of the formation of a cyclic enol ether by ring-closing metathesis (Grubbs and co-workers, 1994).[55c]



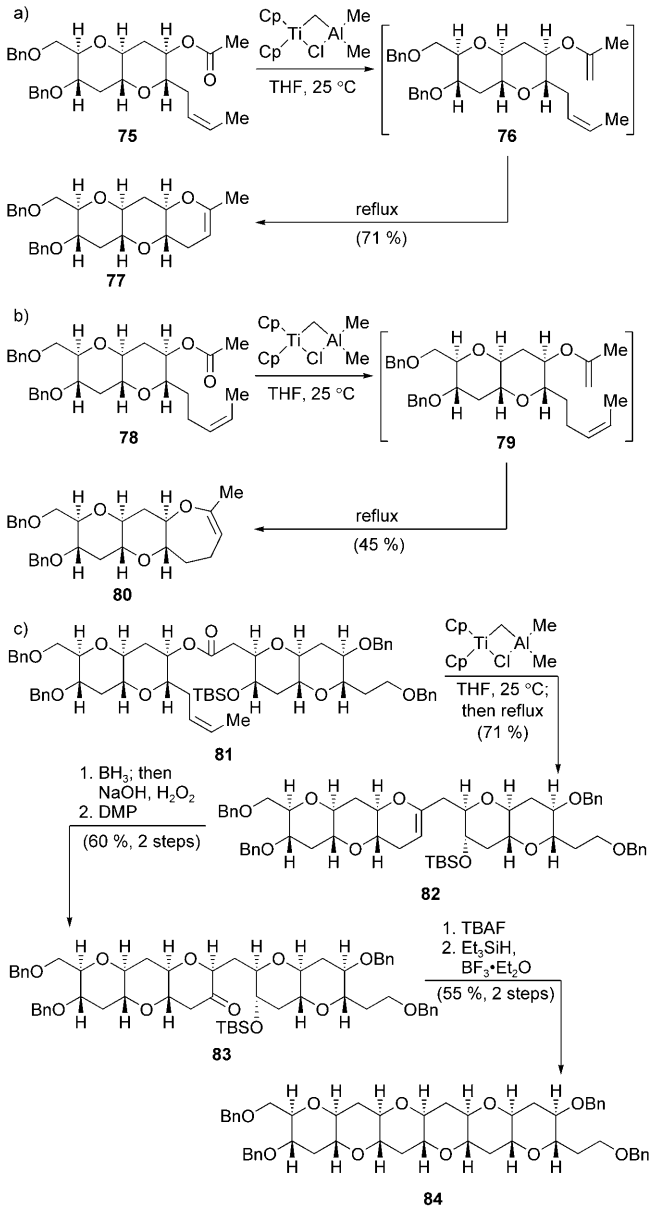
Scheme 12. General, one-pot ester methylenation/metathesis method for the formation of cyclic polyethers (Nicolaou et al., 1996).[56]

acetate **75** through Tebbe methylenation, via the presumed intermediate **76**, followed by metathesis (Scheme 13a). The corresponding oxepane **80** was constructed from bicyclic system **78** through the intermediacy of **79** by the same method (Scheme 13b). This highly convergent method also delivered the linear ladderlike polypyran system **84** in an expedient and impressive way (Scheme 13c): two bicyclic systems were combined through esterification to afford tetracyclic ester **81**, which was subjected to the methylenation/metathesis method to generate pentacyclic enol ether **82**. Stereo- and regioselective hydroboration and oxidation of the latter led to ketone **83**, whose desilylation to the hydroxy ketone and ring closure furnished hexacyclic polyether **84** (Scheme 13c).

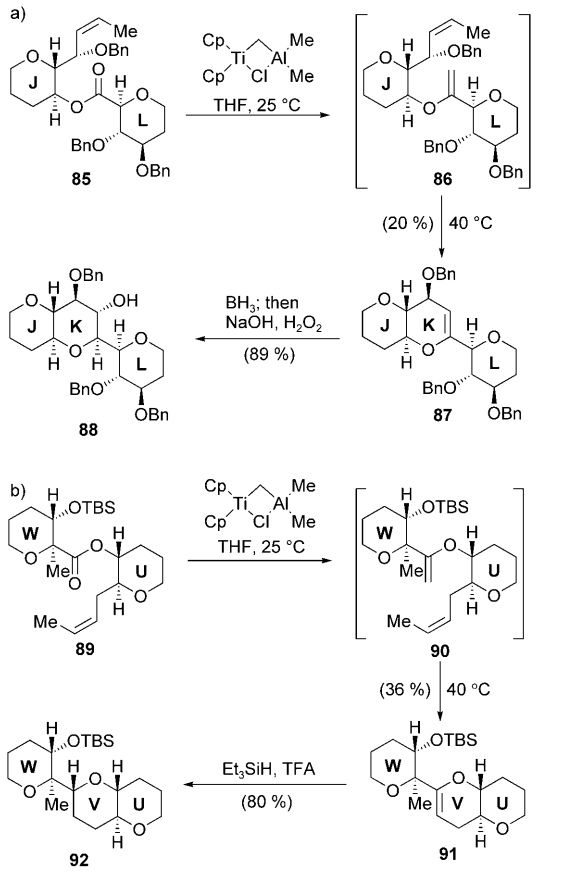
Of particular interest were the stereoselective syntheses of the tricyclic systems **88** and **92**, which represent the JKL and UVW ring domains of maitotoxin (Scheme 14).[58] Thus, treatment of bicyclic JL ester **85** with Tebbe reagent led, via bisolefin **86**, to tricyclic system **87**, which was then stereoselectively functionalized by hydroboration and oxidation to the targeted JKL maitotoxin fragment **88** (Scheme 14a). A similar sequence involving one-pot methylenation and metathesis converted ester **89** into tricyclic enol ether **91** via intermediate **90**, and thence to the UVW maitotoxin fragment **92** through a stereoselective TFA/Et_3SiH-induced reduction of the enol ether moiety (Scheme 14b).

Following the initial report of the ester methylenation/metathesis approach to polyethers,[56] Clark et al. extended the method by employing the high-yielding Takai protocol[59] to prepare the required enol ether substrates.[60] Ester **93** was first converted into enol ether **94** and the latter was treated with Schrock's catalyst **61**[61] to accomplish the metathesis step, thereby furnishing bicyclic enol ether **95** (Scheme 15a). Complex **61** was also used to cyclize diolefinic substrate **96** (Scheme 15b) to give oxocene **97**, which in the presence of the Wilkinson catalyst underwent a double-bond shift to give bicyclic enol ether **98**.[62]

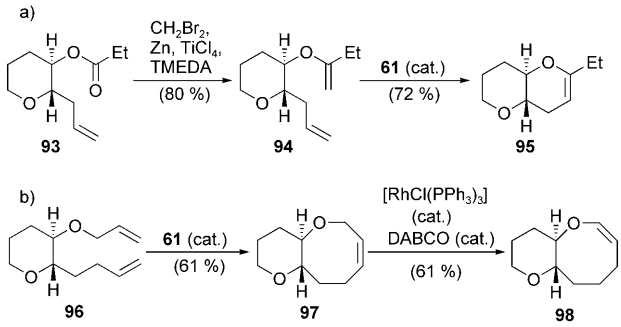
A method somewhat related to the ester methylenation/metathesis approach to cyclic ethers discussed above was developed by Takeda and co-workers (Scheme 16).[63] Treatment of the ester dithioketal **99** with $[Cp_2Ti\{P(OEt)_3\}_2]$ furnished bicyclic ether **102**, presumably through transient intermediates **100** and **101**. Hirama and co-workers later



Scheme 13. The ester methylenation/metathesis method in the construction of complex polycyclic ethers (Nicolaou et al., 1996).[56]



Scheme 14. The ester methylenation/metathesis method in the synthesis of the JKL (**88**, a) and UVW (**92**, b) model systems of maitotoxin (Nicolaou et al., 1996).[58]

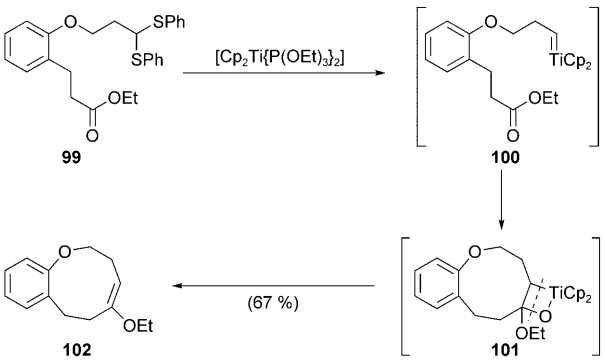


Scheme 15. The two-step version of the methylenation/metathesis method for the formation of cyclic ethers (Clark et al., 1997).[60]

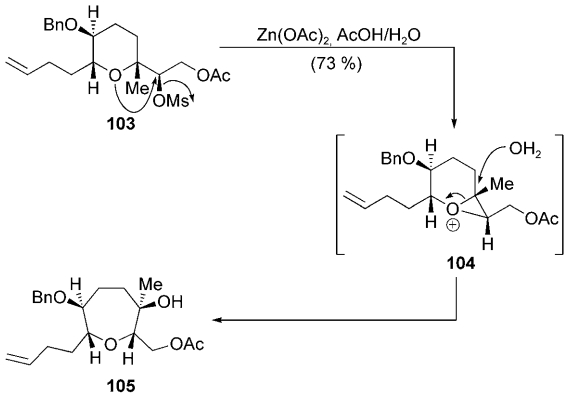
applied this method in their total synthesis of ciguatoxin 3C (see Section 7).

A novel ring expansion of a tetrahydropyran system to an oxepane system was demonstrated en route to hemibrevetoxin by Nakata et al. in 1996 (Scheme 17).[64] Treatment of mesylate **103** with $Zn(OAc)_2$ in aqueous acetic acid induced a stereoselective ring expansion to yield oxepane derivative **105** as a single stereoisomer, presumably via oxonium species **104**.

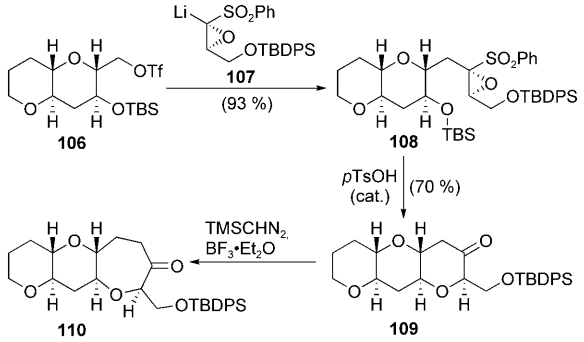
A novel approach to the iterative construction of pyran rings that could also be used to form oxepanes through ring expansion was introduced by Mori et al. in 1996 (Scheme 18). This method involves the sulfonyl-stabilized oxiranyl anions, which can readily be prepared from the corresponding epoxysulfones and *t*BuLi.[65] Alkylation of triflate **106** with the sulfonyl-stabilized oxiranyl anion **107** yielded epoxide **108**. Treatment of **108** with *p*TsOH resulted in 6-*endo* cyclization with concomitant expulsion of the sulfonic acid residue to yield keto-pyran **109**. The observed regioselectivity of this epoxide opening was attributed to the electron-withdrawing properties of the sulfonyl group, as it destabilizes the cationic charge resulting from the 5-*exo* attack. In the synthesis of a polypyran, ketone **109** would normally be stereoselectively reduced and elaborated to the next alkylation substrate for reiteration of the process. However, a ring expansion can also be carried out through the sequential use of $TMSCHN_2$ and $BF_3{\cdot}Et_2O$[66] to afford oxepanes such as **110** (Scheme 18).



Scheme 16. Intramolecular carbene-ester addition method for cyclic ether formation (Takeda and co-workers, 1997).[63]

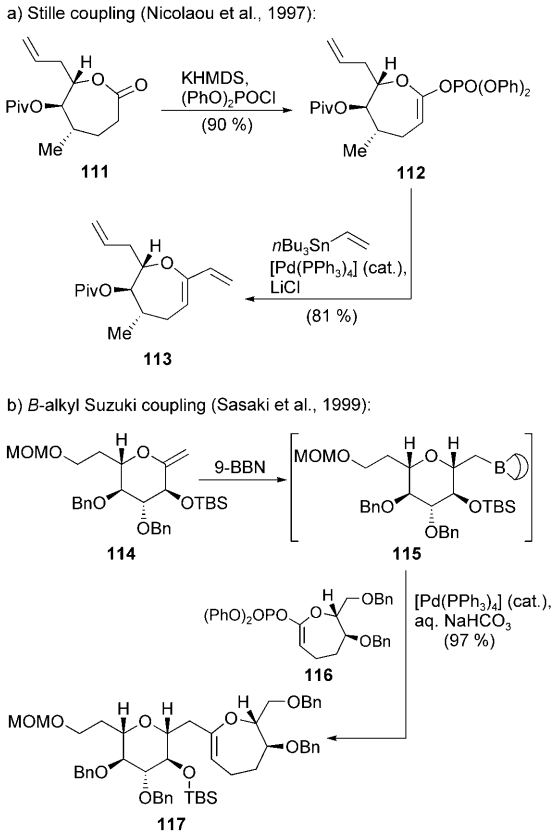


Scheme 17. A ring-expansion-based method for oxepane formation (Nakata et al., 1996).[64]



Scheme 18. The oxiranyl anion addition/cyclization method for cyclic ether formation (Mori et al., 1996).[65]

A particularly useful method reported by the Nicolaou research group in 1997 for the conversion of the more readily available medium-sized lactones into the corresponding cyclic ethers is the palladium-catalyzed Stille cross-coupling reaction with vinyl phosphates (ketene acetal phosphates; Scheme 19).[67] The vinyl phosphate **112** generated from lactone **111** was coupled with tri-*n*-butylvinylstannane in the presence of $[Pd(PPh_3)_4]$ to furnish the seven-membered ring cyclic ether **113**, which could be elaborated further into a variety of cyclic ethers. Vinyl phosphates complement the reactivity of vinyl triflates, which perform well in pyran systems but give poorer results in the synthesis of medium-sized rings. As such, this method could be extended to the

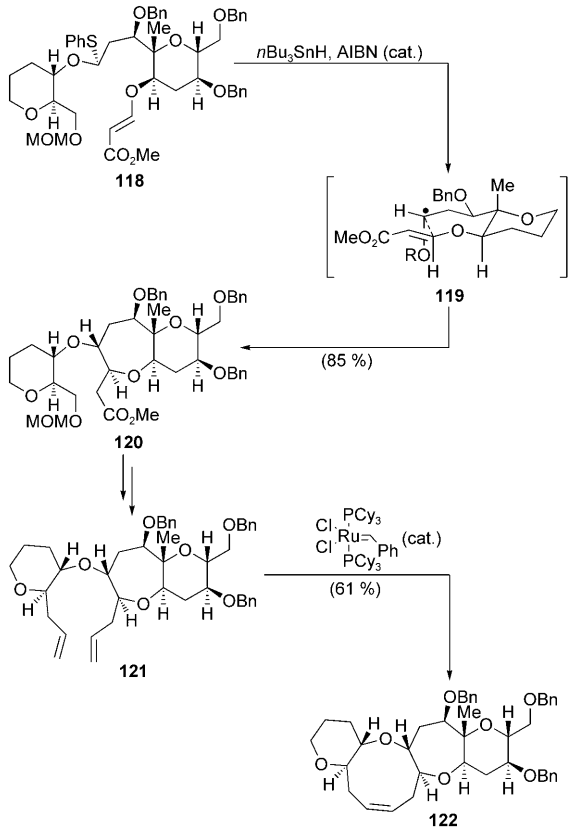


Scheme 19. The vinyl phosphate/cross-coupling method for the formation of cyclic ethers (a: Nicolaou et al., 1997;[67] b: Sasaki et al., 1999).[69]

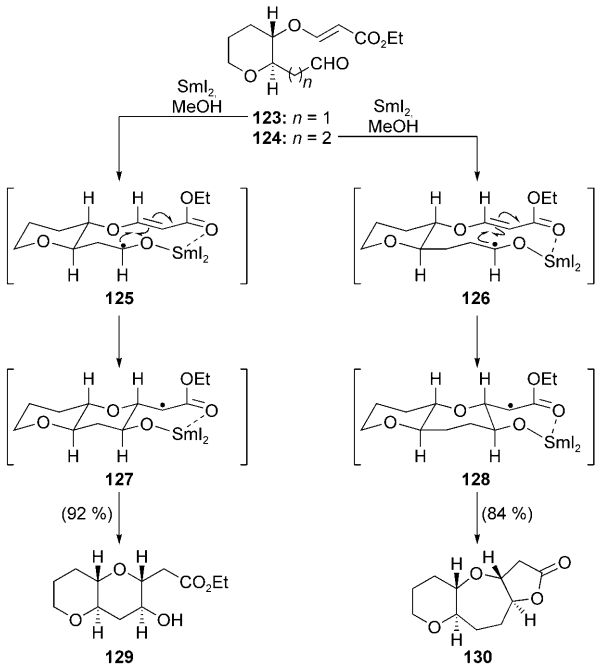
synthesis of six- to nine-membered rings, and has found several applications in the total synthesis of marine polyethers. Vinyl triflates had previously been introduced by Murai and co-workers to construct simple cyclic ethers.[68] The Nicolaou research group later used this approach in their total synthesis of brevetoxins B and A (**6** and **7**, see Sections 5 and 6).

A number of variations of the vinyl phosphate/cross-coupling method have also been developed for the formation of cyclic ethers, the most prominent one being the vinyl phosphate/*B*-alkyl Suzuki coupling method developed by the Sasaki research group as a means to extend the molecule backbone (Scheme 19b).[69] Thus, exocyclic enol ether **114** was first stereoselectively hydroborated with 9-BBN, and the resulting alkyl boron species **115** was directly coupled with cyclic vinyl phosphate **116** in the presence of $[Pd(PPh_3)_4]$ and $NaHCO_3$ to afford bicyclic enol ether **117**.

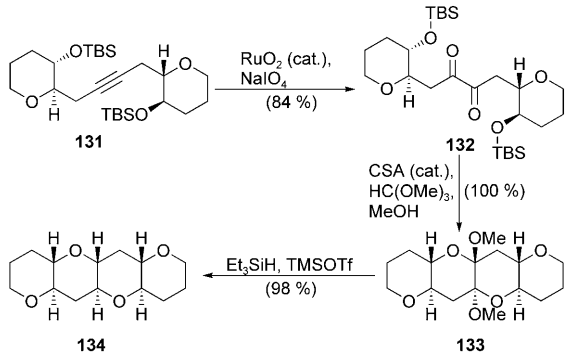
In 1999, Sasaki et al. disclosed a method for the construction of cyclic polyethers from mixed phenylthio acetals (Scheme 20).[70] Reaction of bicyclic O,S-acetal **118** with nBu$_3$SnH in the presence of AIBN proceeded, presumably through radical species **119**, to afford tricyclic polyether **120** stereoselectively and in 85% yield. The observed stereoselectivity was attributed to the preferred transition state **119**, which minimizes unfavorable interactions between two axial substituents. This method allows an additional ring to be subsequently forged (**122**) in a few steps through olefin



Scheme 20. The mixed O,S-acetal radical cyclization/ring-closing metathesis sequence for the formation of cyclic ethers (Sasaki et al., 1999).[70]



Scheme 21. The SmI_2-induced reductive cyclization method for the formation of cyclic ethers (Nakata and co-workers, 1999).[71]



Scheme 22. Alkyne functionalization/cyclization methods (Fujiwara/Murai et al.,[73] Nakata and co-workers,[74] and Mori et al., 2000).[75]

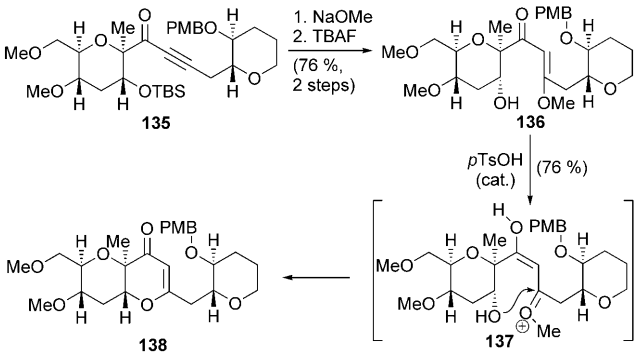
metathesis from a diolefin **121** (Scheme 20). The ability to construct two adjacent ether rings between two coupled fragments is another advantage of this highly convergent strategy.

An intramolecular 1,4-addition also played a role in the SmI_2-induced reductive cyclization introduced in the same year by Nakata and co-workers for the generation of six- and seven-membered cyclic ethers (Scheme 21).[71] Thus, treatment of enol ether substrates **123** ($n=1$) and **124** ($n=2$) with SmI_2 in methanol promoted, first, single-electron reduction of the aldehyde moiety to form the presumed radicals **125** and **126**, respectively.[72] Coordination between the samarium-complexed ketyl radical oxygen atom and the carbonyl group of the proximal Michael acceptor was invoked to explain the stereoselective intramolecular 1,4-addition of the radical species to the α,β-unsaturated carbonyl moiety to form intermediate radicals **127** and **128**, which proceeded to form bicycle **129** and tricycle **130**, respectively. Interestingly, in the case of **124** ($n=2$) a third ring is formed, leading to tricycle **130**. This SmI_2-induced reductive cyclization method generates two contiguous stereocenters, thus allowing its application to the construction of polyethers from relatively simple substrates.

In 2000, the research groups of Fujiwara and Murai[73] as well as Nakata[74] reported independently, and almost simultaneously, a method for the formation of two cyclic ethers from acetylenic substrates (Scheme 22). In both cases the same acetylene **131** was treated with $NaIO_4$ in the presence of RuO_2 (cat.) to obtain 1,2-diketone **132**. After acid catalysis in methanol to give the tetracycle (**132**→**133**), the resulting bis(methoxy acetal) was then reductively converted into tetracyclic polyether **134** by the action of Et_3SiH and TMSOTf. A few months later, Mori et al. reported a similar method for the construction of polypyrans.[75]

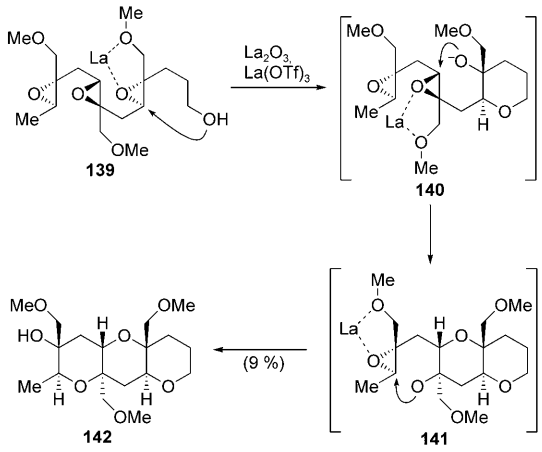
A second method based on acetylenic substrates for the formation of cyclic enol ethers was reported by Suzuki and Nakata in 2002 (Scheme 23).[76] The ynone **135** was converted into methoxy enone **136** in two steps, and then to cyclic enone **138** through an acid-catalyzed reaction that presumably involved intermediate **137**.

Inspired by Nakanishi's proposal that the biosynthesis of brevetoxin B and related polyether marine natural products occurred via polyepoxides,[33] a number of research groups attempted to design partial cascades to construct polycyclic ethers, and possibly gain insights into the postulated pathway in nature. Thus, besides Nicolaou's original method for



Scheme 23. Hydroxy methoxyenone cyclization in the formation of cyclic ethers (Suzuki and Nakata, 2002).[76]

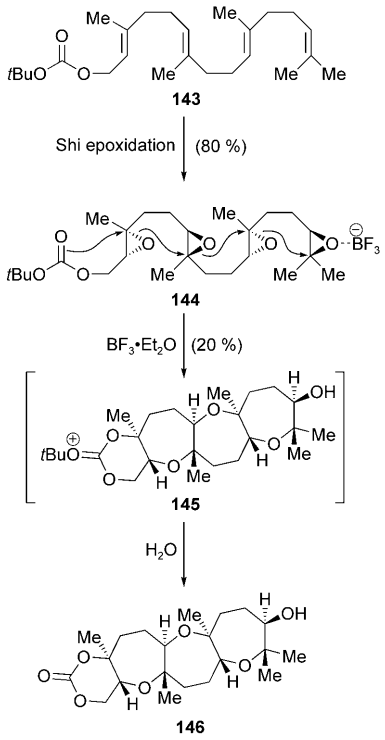
controlling the 6-*endo* cyclization over the kinetically favored 5-*exo* cyclization through the installment of an olefinic bond, a number of other methods aiming to achieve the same goal, and to form polycyclic ethers, have since been reported. In 2000, Murai and co-workers accomplished, albeit in low yield (9%), the conversion of hydroxy triepoxide **139** into tricycle **142** by exposure to La_2O_3 and $La(OTf)_3$.[77] The cascade sequence involved in this synthesis was presumed to proceed through transition states **140** and **141**, in which the strategically placed methoxy groups play a directing role (Scheme 24).



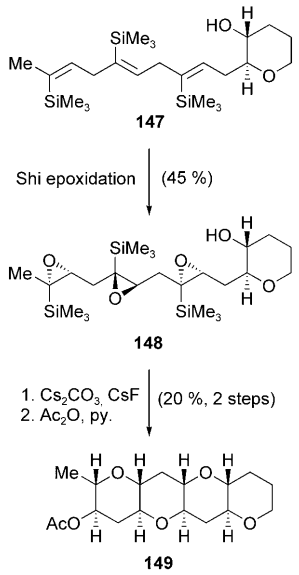
Scheme 24. Methoxymethyl-directed cascade opening of epoxide rings to give fused pyran systems (Murai and co-workers, 1999).[77]

In the same year, McDonald et al. reported a Lewis acid catalyzed oligoepoxide opening cascade starting with a substrate possessing a *tert*-butyl carbonate group (Scheme 25).[78] A Shi epoxidation[79] of tetraolefin **143** afforded tetraepoxide **144** (80% yield), which cyclized, presumably via the intermediate **145**, upon exposure to $BF_3{\cdot}Et_2O$. After aqueous work-up, the trioxepane system **146** was obtained in 20% yield.

The next example of a directed polyepoxide opening cascade came in 2003 from the Jamison research group.[80] They used triene **147** equipped with the three strategically placed TMS groups (Scheme 26) in the hope of directing the desired 6-*endo* cyclizations to produce the fused tetrapyran system **149**. Thus, Shi epoxidation of **147** furnished triepoxide



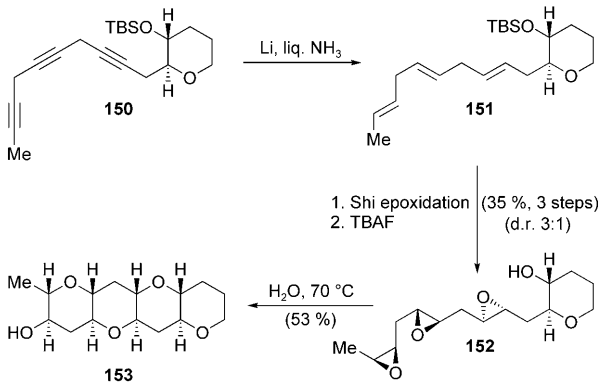
Scheme 25. Lewis acid promoted epoxide-opening cascade to give fused polyoxepane systems (McDonald et al., 2000).[78]



Scheme 26. TMS-directed epoxide-opening cascade to form fused polypyran systems (Jamison and co-workers, 2003).[80]

148 in 45% yield. Treatment of **148** with Cs_2CO_3 and CsF followed by acetylation led to tetrapyran system **149** in 20% overall yield.

The Jamison research group also reported the next advance in the field, a rather spectacular polyepoxide-opening cascade in water that proceeded, without the aid of directing groups or additives, through 6-*endo* ring closures to furnish a fused polypyran system (Scheme 27).[81] Vilotijevic



Scheme 27. Thermally induced epoxide-opening cascade in water (Vilotijevic and Jamison, 2007).[81]

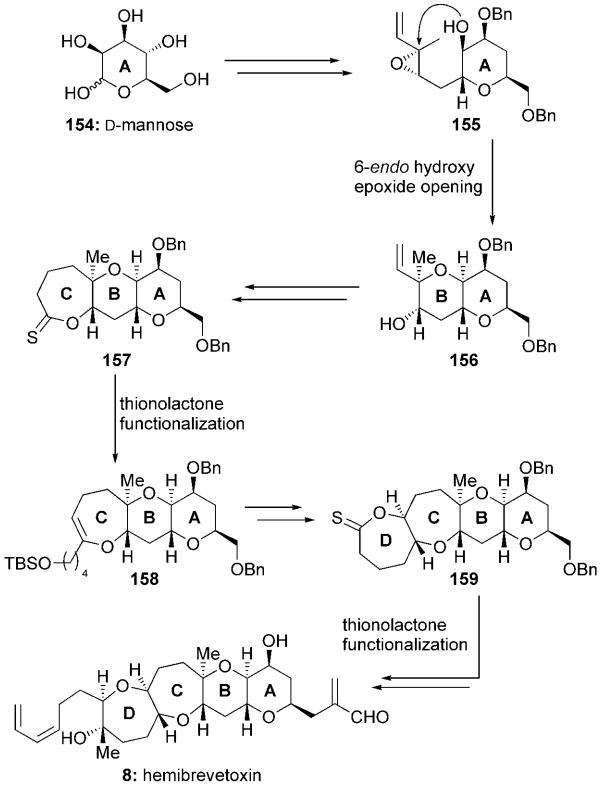
and Jamison speculated that such non-enzymatic zip-type reactions may be nature's way of making the ladderlike polyether natural products. The required hydroxy triepoxide **152** was prepared from the triacetylene **150** by reduction with lithium in liquid ammonia to afford triene **151**, followed by Shi epoxidation and desilylation (35% overall yield, d.r. ≈ 3:1 of innermost epoxide). The remarkably ring-selective polycyclization to give **153** was carried out simply by heating triepoxide **152** in water at 70°C, and proceeded in 53% yield. Interestingly, it was found that a preformed tetrahydropyran ring was necessary, as in **152**, for the success of this cascade reaction. These results provide support for the notion that, indeed, such reactions are possible without enzymatic assistance, and promise intriguing applications in future synthetic endeavors.

4. Hemibrevetoxin

Despite the disclosure of the first ladderlike polyether marine natural product in the early 1980s, it would not be until 1992 that the first such compound was synthesized in the laboratory. This lapse of time was due not only to the structural complexity of these molecules, but also because of the lack of methods suitable for their construction. As the repertoire of synthetic methods increased (such as those described in Section 3), together with the persistent efforts of the participating research groups, these molecules began to yield, one after another, to total synthesis. The total syntheses of members of the polyether marine natural products will be reviewed below in the order they appeared in the literature. Emphasis will be placed on the innovative methods used to construct the various ether rings.

Following the disclosures of the structures of brevetoxin B (**6**) in 1981,[2] and of brevetoxin A (**7**) in 1986,[82] the structure of a less daunting molecule, that of hemibrevetoxin (**8**), was reported in 1989.[83] This tetracyclic molecule was isolated from the same dinoflagellate *Karenia brevis* (then known as *Gymnodinium breve*) as the two brevetoxins mentioned above, but was approximately half their size. As such, it provided an enticing target to the synthetic chemists that were struggling with the synthesis of the brevetoxins. Besides, the relative simplicity, yet highly relevant structure, of hemibrevetoxin (**8**) made it an ideal platform to test the applicability and scope of the synthetic methods so far developed. With no less than nine total and formal syntheses of this molecule so far reported, it provides an instructive survey of the applications of the developed methods for the formation of cyclic ethers.

The first total synthesis of hemibrevetoxin (**8**), which is also the first of any member of the polyether class, was reported in 1992 by the Nicolaou research group (Scheme 28).[84] Their strategy was based on the functional-



Scheme 28. The first total synthesis of hemibrevetoxin (**8**; Nicolaou et al., 1992).[84]

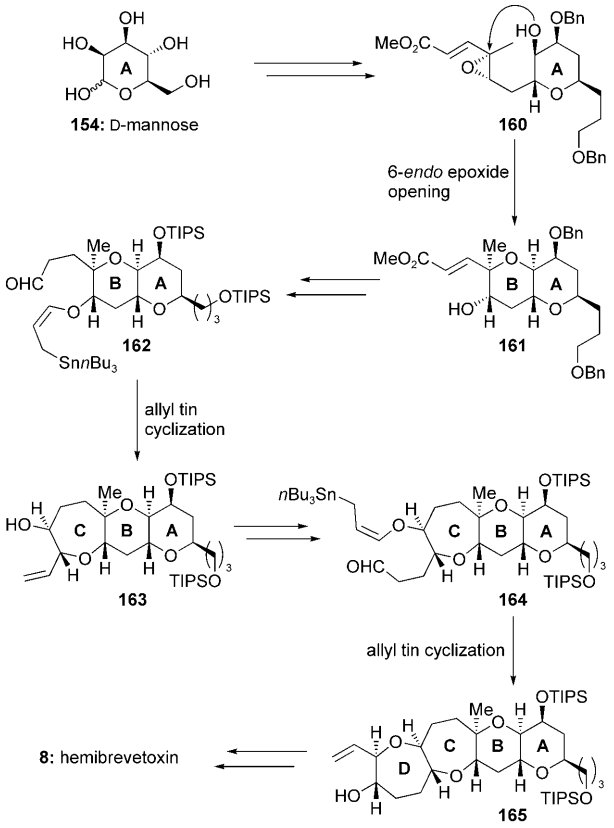
ization of a thionolactone (twice, to form both oxepane rings) and their selective 6-*endo* epoxide opening reaction (opening of an epoxide by a hydroxy group and a selective 6-*endo* ring closure). The enantioselectivity of the synthesis was ensured by the use of D-mannose (**154**) as the starting material, in line with the then-popular chiral pool tradition, a theme that was to persist for some time in the field of polyether total synthesis. Following elaboration to epoxide **155**, the action of catalytic amounts of CSA regioselectively forged the B ring, thereby generating bicyclic polyether **156**. After subsequent formation of thionolactone **157**, an improved version of the thionolactone nucleophilic functionalization method led to the oxepane tricyclic system **158**, whose conversion into the final target molecule **8** required a short sequence involving another thionolactone **159** (Scheme 28).

It was not until 1995 that the second total synthesis of hemibrevetoxin (**8**) appeared in the literature. In this syn-

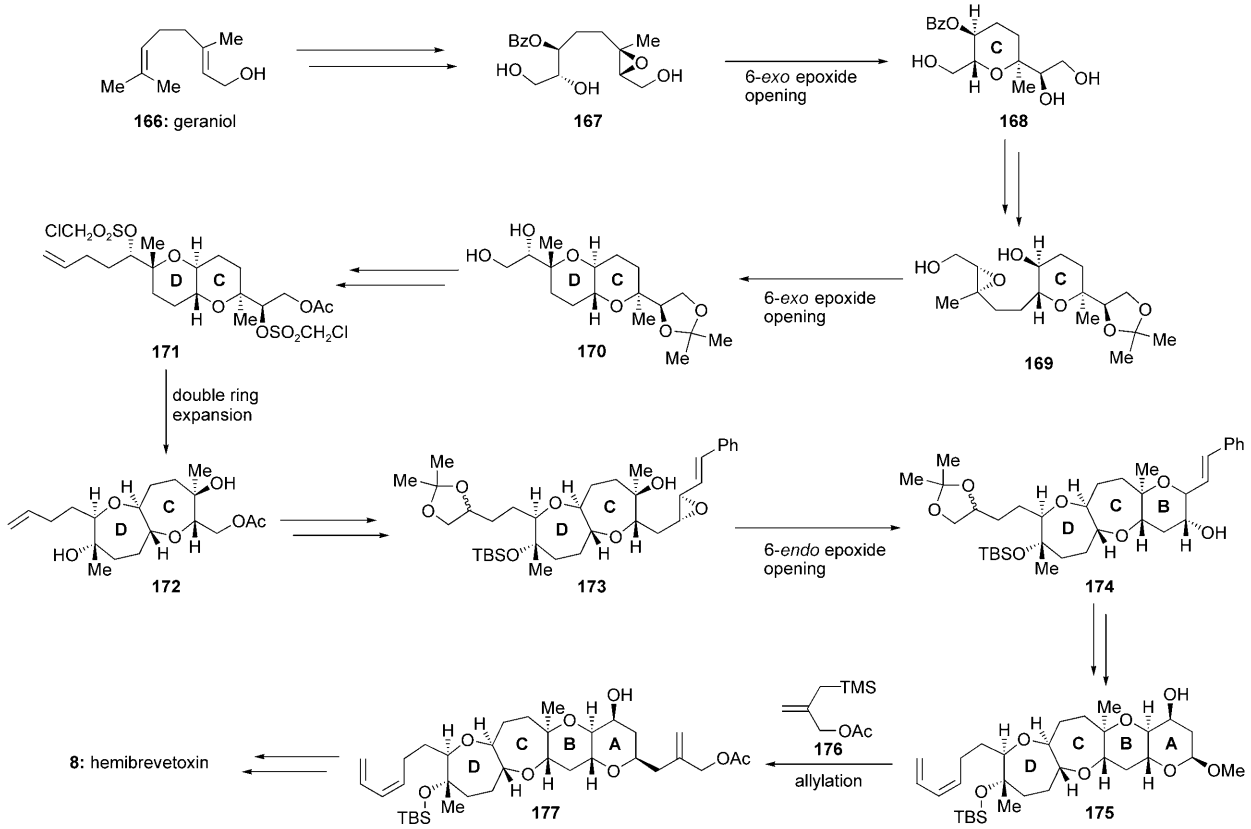
thesis (Scheme 29),[85] the Yamamoto research group employed similar tactics to those used by Nicolaou et al. to start (D-mannose, **154**) and propagate (6-*endo* epoxide opening, **160**→**161**) their total synthesis, but they used an allyl tin method to construct both oxepane rings in high yield (**162**→**163** and **164**→**165**). Side-chain elaboration similar to that used in the Nicolaou strategy completed the total synthesis of hemibrevetoxin (**8**). It is interesting to note that, although the side chains and rings of the target molecule were constructed in the same order in these two total syntheses, one can already begin to notice the diversity of methods that began to emerge as means to forge the challenging cyclic ether rings of these natural products.

The third total synthesis of hemibrevetoxin (**8**) was reported in 1996 by the Nakata research group (Scheme 30).[64,86] Their strategy involved Sharpless asymmetric epoxidation to introduce chirality into their prochiral starting material geraniol (**166**→**167**), and two 6-*exo* epoxide openings (**167**→**168** and **169**→**170**) to forge the bicyclic sulfonate **171** as the substrate for the key double ring expansion that produced the bisoxepane **172** (CD ring system). From there on they utilized the directed 6-*endo* epoxide opening to forge ring B (**173**→**174**), and after formation of ring A the methyl acetal was allylated (**175**+**176**→**177**). The synthesis was completed by simple installation of the terminal aldehyde functionality.

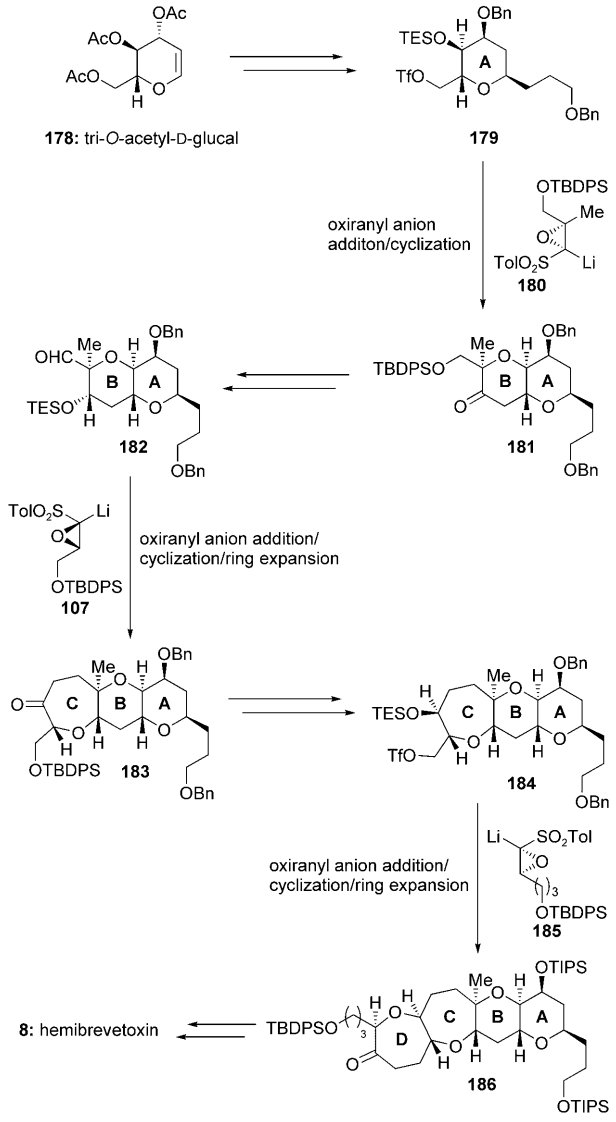
In 1997, the Mori research group completed a formal total synthesis of hemibrevetoxin (**8**, Scheme 31).[87] They employed tri-*O*-acetyl-D-glucal (**178**) from the chiral pool as



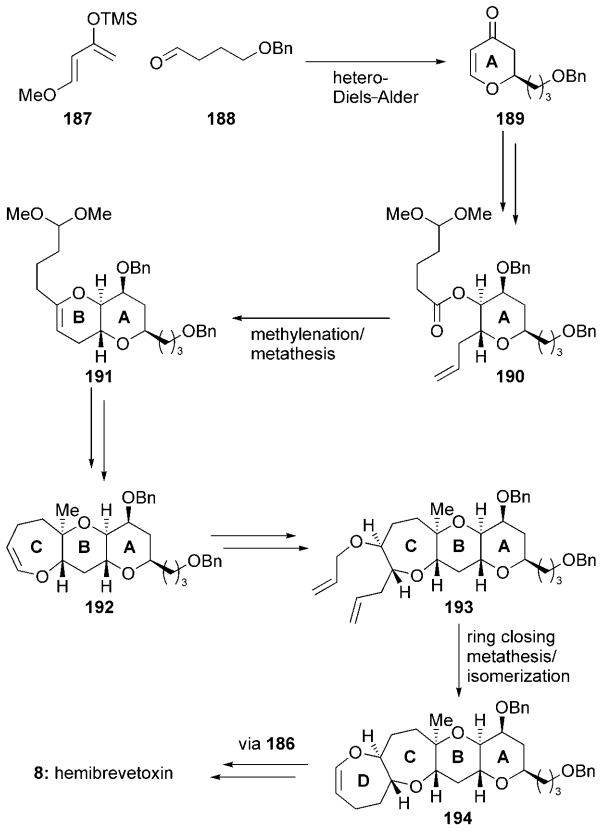
Scheme 29. Second total synthesis of hemibrevetoxin (**8**; Yamamoto and co-workers, 1995).[85]



Scheme 30. Third total synthesis of hemibrevetoxin (**8**; Nakata and co-workers, 1996).[86]



Scheme 31. Fourth total synthesis of hemibrevetoxin (**8**; Mori et al., 1997).[87]



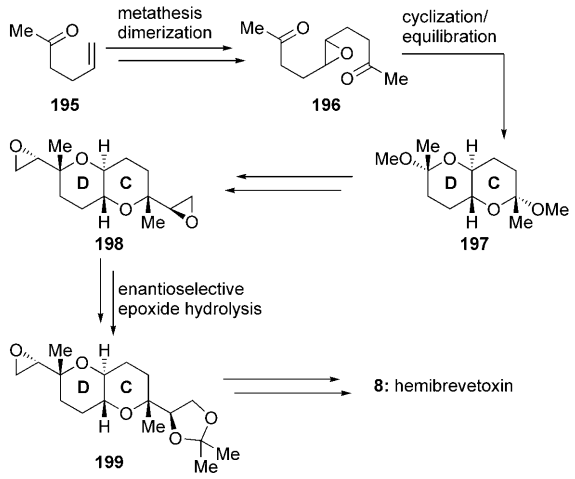
Scheme 32. Fifth total synthesis of hemibrevetoxin (**8**; Rainier et al., 2001).[88]

the starting material. This was conveniently converted into ring A intermediate **179**, from which the addition of the first oxiranyl anion **180** followed by cyclization proceeded smoothly to form ring B (**181**). The second sequence with oxiranyl anion **107** required an aldehyde electrophile **182**, and was accompanied by ring expansion to generate ring C (**183**). The third and final addition of an oxiranyl anion **185** followed by cyclization also required ring expansion to reach its goal, tetracyclic intermediate **186**, which had previously been converted into hemibrevetoxin (**8**) by the Yamamoto research group.[85]

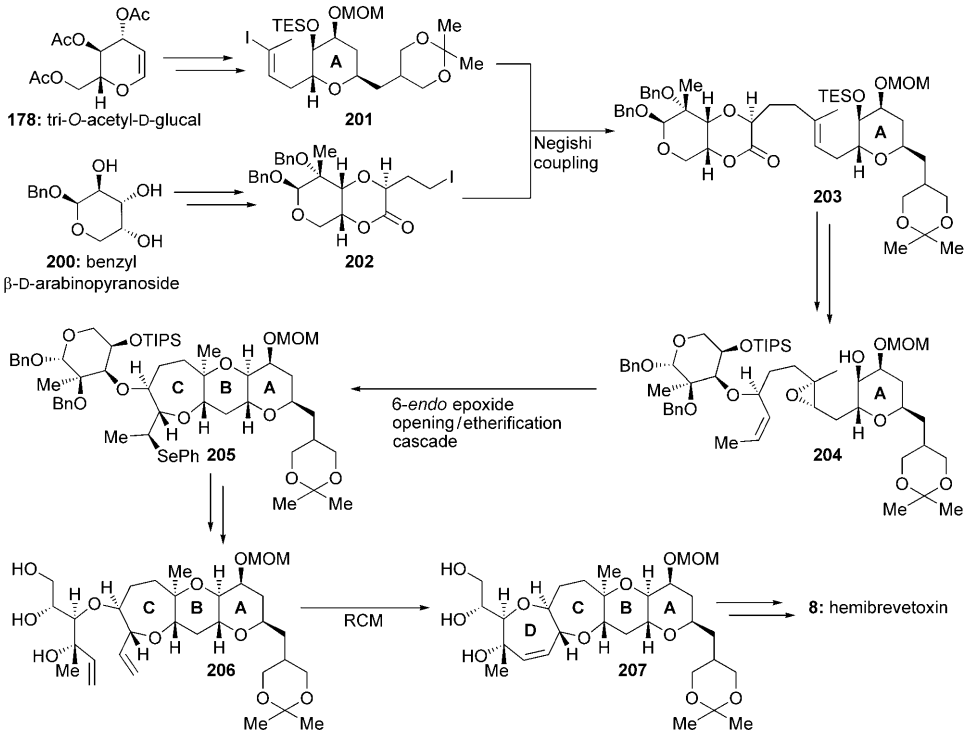
Another formal total synthesis of hemibrevetoxin (**8**) was published by Rainier et al. in 2001 (Scheme 32).[88] They employed Clark's variation of the methylenation/metathesis approach to cyclic ethers to deliver Mori's intermediate **186** (Scheme 31) in racemic form.[87] Their strategy began with a Diels–Alder reaction between diene **187**[89] and aldehyde **188** to form pyran system **189**, which was elaborated to ring A intermediate **190** containing the requisite olefinic ester structural motif for the intended methylenation/metathesis sequence. By using the improved protocol reported by Clark, in which a Takai olefination[59] is initially employed, followed by exposure of the resulting enol ether to Grubbs II catalyst,[53] the intermediate **190** was converted into bicyclic system **191**, which was elaborated to advanced intermediate **193** via **192**. After another ring-closing metathesis, isomerization of the olefinic bond led to enol ether **194**, which was elaborated into intermediate **186** from Mori's synthesis (Scheme 31), thus completing their formal total synthesis of hemibrevetoxin (**8**).

In 2001, Nelson and co-workers reported an elegant approach to Nakata's bicyclic intermediate **199** (Scheme 33).[90] Thus, **195** was dimerized to the *E*-configured olefin by metathesis and then epoxidized to racemic epoxide **196**, which was cyclized with concomitant equilibration to bicyclic compound **197**. After elaboration of this mixed bisacetal, a Jacobsen enantioselective epoxide hydrolysis[91] of the resulting centrosymmetric intermediate **198** led to enantiopure product **199**. Since this intermediate had previously been converted into hemibrevetoxin (**8**) by Nakata and co-workers,[86] its construction constituted a formal asymmetric total synthesis of hemibrevetoxin (**8**).

The total synthesis of hemibrevetoxin (**8**) reported by Holton and co-workers in 2003 had, in addition to a number of other elegant elements, the distinction of being the first convergent strategy (Scheme 34).[92] They used tri-*O*-acetyl-D-



Scheme 33. Sixth total synthesis of hemibrevetoxin (**8**; Nelson and co-workers, 2001).[90]



Scheme 34. Seventh total synthesis of hemibrevetoxin (**8**; Holton and co-workers, 2003).[92]

glucal (**178**) and benzyl-β-D-arabinopyranoside (**200**) from the chiral pool as their starting materials, which they converted through a series of reactions into vinyl iodide **201** (ring A fragment) and primary iodide **202**, respectively. These two fragments were united through a Negishi coupling[93] to afford product **203**, which was elaborated to **204**. In the presence of *N*-(phenylseleno)phthalimide[94] and in the apparently crucial solvent HFIP, **204** entered into an impressive 6-*endo* epoxide opening/etherification cascade that forged both rings B and C. This sequence afforded phenylseleno intermediate **205**, which was then converted into diolefin **206**. Ring-closing metathesis under the influence of the Grubbs II catalyst led to tetracycle **207**, which was converted into hemibrevetoxin (**8**) by standard elaboration.

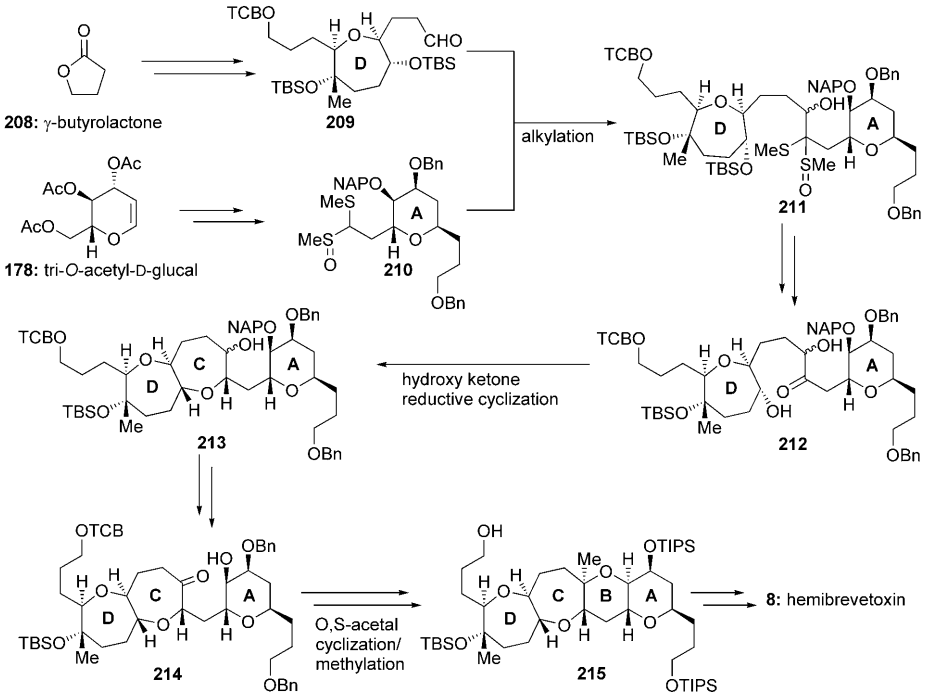
Fujiwara et al. reported in 2004[95] a convergent formal total synthesis of hemibrevetoxin (**8**) that reached the advanced intermediate **215**[85] from Yamamoto's synthesis in enantiomerically pure form (Scheme 35). Starting from γ-butyrolactone (**208**) and tri-*O*-acetyl-D-glucal (**178**), the building blocks **209** (through a sequence featuring ring-closing metathesis) and **210** (through standard chemistry) were constructed and coupled through alkylation to afford bicyclic product **211**. The remaining two rings were forged using a reductive cyclization of a hydroxy ketone (**212**→**213**) and a formation of an O,S-acetal followed by methylation (**214**→**215**; see Scheme 35).

In 2007, Yamamoto and co-workers reported a second generation synthesis of their hemibrevetoxin precursor **221** (Scheme 36).[96] This formal synthesis began with bicyclic intermediate **217**, which was used in their first synthesis of hemibrevetoxin (**8**), and linear precursor **216**, available from γ-butyrolactone (**208**). Coupling these two building blocks afforded ester **218**, which was transformed into **219**. The latter compound underwent smooth cyclization involving the allyl tin group to furnish tricyclic system **220**. A ring-closing metathesis facilitated by the Grubbs II catalyst then afforded the required tetracycle **221**, whose conversion into hemibrevetoxin (**8**) had previously been accomplished.[85]

While the syntheses of hemibrevetoxin discussed above display the impressive variety and applicability of some of the developed technologies for the construction of cyclic polyethers, the power of these methods in chemical synthesis will become even more evident in the following sections that deal with the construction of the more complex members of this class of natural products.

5. Brevetoxin B

Brevetoxin B (**6**) was the first member of the class of ladderlike marine neurotoxins to be isolated and structurally elucidated. Brevetoxin B was isolated from the dinoflagellate *Karenia brevis* (then *Gymnodinium breve*) and structurally elucidated by Nakanishi and Clardy in 1981.[2] Its stunning molecular architecture spurred the discovery and develop-



Scheme 35. Eighth total synthesis of hemibrevetoxin (**8**; Fujiwara et al., 2004).[95]

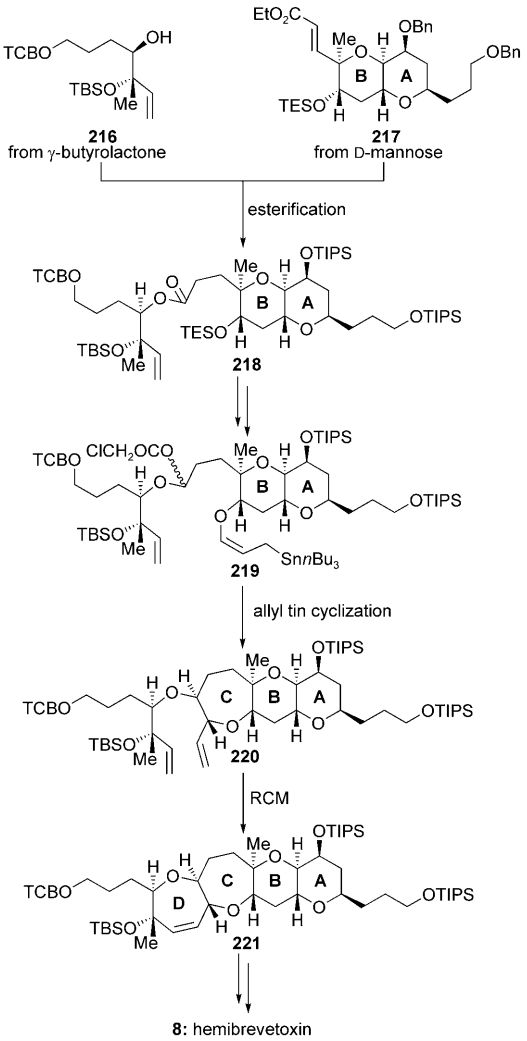
ment of the synthetic methods discussed in the preceeding sections. In 1995, and after a 12-year synthetic odyssey, the Nicolaou research group reported the first total synthesis of this molecule (Schemes 37–39).[35b,97]

Scheme 37 shows the construction of the ABCDEFG fragment **238** starting with 2-deoxy-D-ribose (**222**).[97] The synthesis proceeded through intermediates **223**–**237** and featured three 6-*endo* epoxide openings (**223**→**224**, **225**→**226**, and **235**→**236**), two lactonization/vinyl triflate formation/cross-coupling sequences to cast the two oxepane rings (**226**→**227**→**229** with cuprate **228**; and **229**→**230**→**232** with aldehyde **231**), a hydroxy Michael cyclization (**233**→**234**), and an intramolecular HWE reaction (**237**→**238**) to complete the row of seven rings of the targeted polyether ladder.

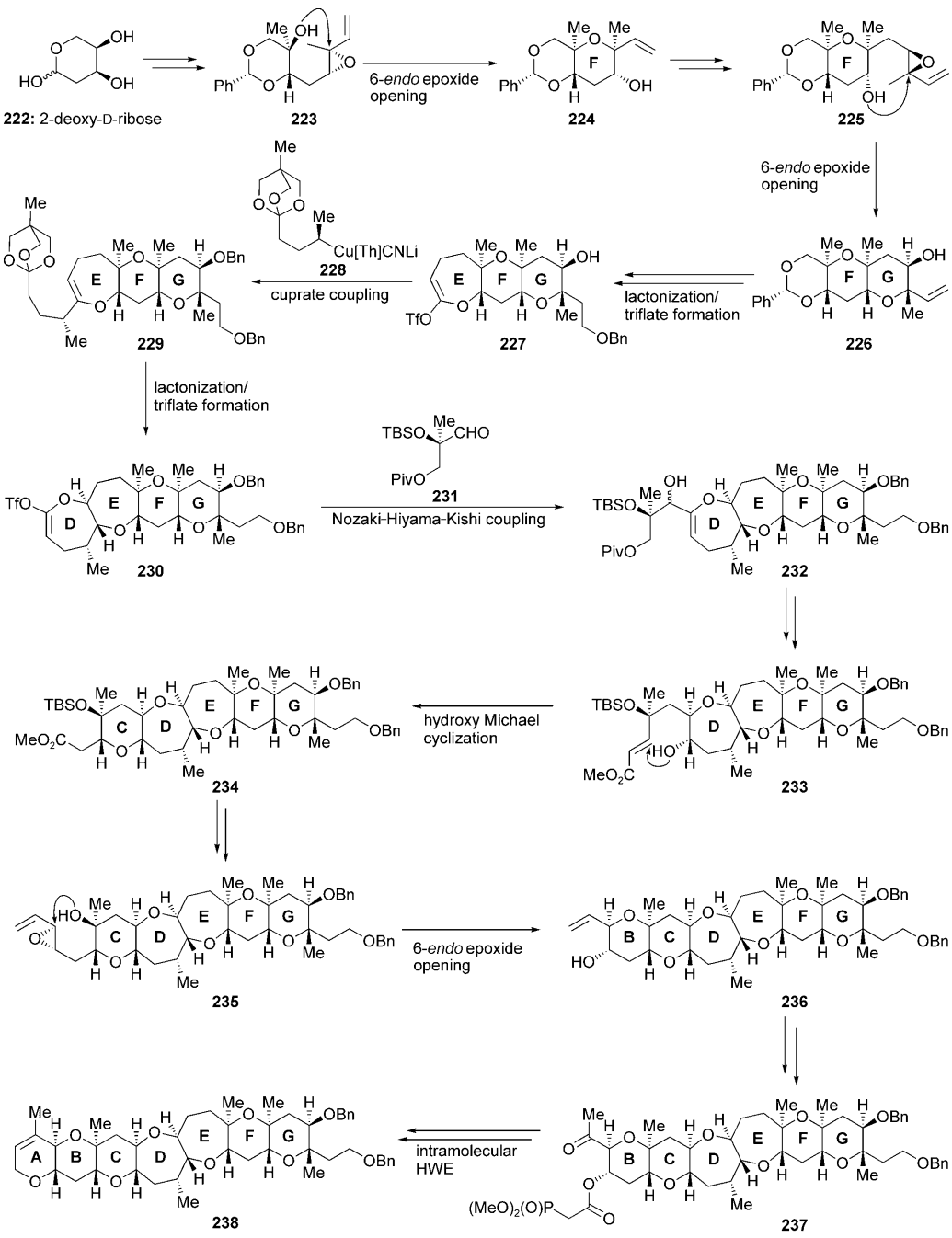
The construction of the IJK fragment **244** was accomplished starting with D-mannose pentaacetate (**239**) as outlined in Scheme 38.[97] Proceeding through intermediates **240**–**243**, this sequence featured a hydroxy Michael cyclization (**240**→**241**) and a 6-*endo* epoxide opening (**242**→**243**). The completion of the synthesis of brevetoxin B (**6**, Scheme 39) involved conversion of the ABCDEFG fragment **238** into phosphonium salt **245**, Wittig coupling with the IJK fragment (**244**), and a hydroxy dithioketal cyclization with subsequent reduction to form the H ring (**246**→**247**) and a few final touches.[97]

The second total synthesis of brevetoxin B (**6**) reported by Nakata and co-workers is summarized in Schemes 40 and 41.[98] Their synthesis relied on SmI_2 chemistry and 6-*endo* epoxide openings to form the majority of the rings. Thus, beginning with the same 2-deoxy-D-ribose (**222**) starting material used in the Nicolaou synthesis, their route (Scheme 40) to the IJK ring system **254** proceeded through intermediates **248**–**253** and featured two SmI_2-induced reductive cyclizations (**248**→**249** and **252**→**253**) and a 6-*endo* epoxide opening (**250**→**251**).

Their construction of the ABCDEFG ring system **262** (Scheme 41) started with tri-*O*-acetyl-D-glucal (**178**) and proceeded through intermediates **255**–**261**.[98] In this sequence, the researchers used three SmI_2-induced reductive cyclizations (**255**→**256** and **257**→**258**),[71] three 6-*endo* epoxide openings (**259**→**260** and **261**→**262**), and a ring-closing metathesis (**260**→**261**) were used. Both the coupling of the two large fragments and the final stages of the synthesis mirrored the sequence developed earlier by Nicolaou et al. (see Scheme 39).[97]



Scheme 36. Ninth total synthesis of hemibrevetoxin (**8**; Yamamoto and co-workers, 2007).[96]

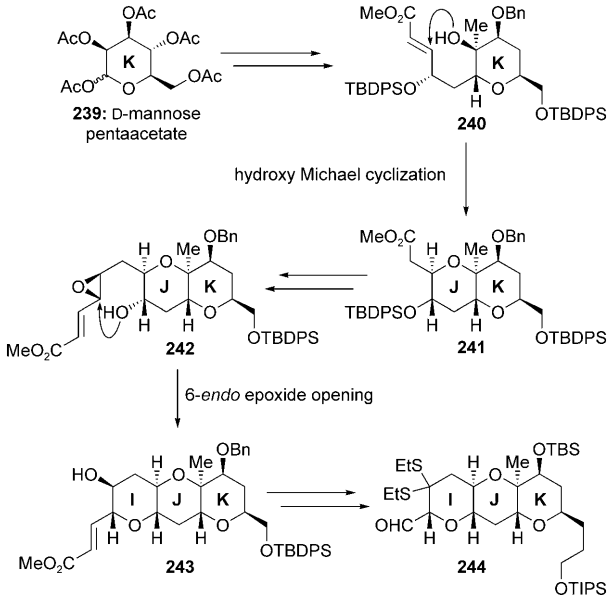


Scheme 37. The first total synthesis of brevetoxin B (**6**). Construction of the ABCDEFG domain **238** (Nicolaou et al., 1995).[97]

6. Brevetoxin A

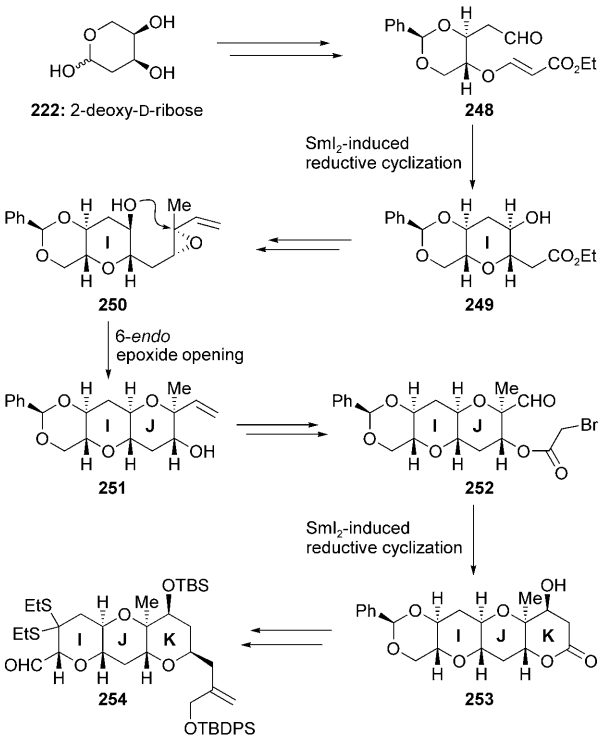
While the campaign for brevetoxin B was raging, another brevetoxin was isolated from *Gymnodinium breve* (later renamed *Karenia brevis*). Characterized and reported by Shimizu et al., the new substance named brevetoxin A (**7**, Figure 2) exhibits one less ring than brevetoxin B (**6**), but a higher degree of ring diversity.[82,99] Indeed, in its imposing structure, brevetoxin A included all the ring sizes from five- to nine-membered and, therefore, constituted the ultimate challenge at the time for the construction of cyclic ethers, especially in light of the well recognized difficulties in forging medium-sized rings. Furthermore, brevetoxin A (**7**) was reported to possess higher potency in activating voltage-sensitive sodium channels.[100] Intrigued by the architecture and biological activity of the molecule, the Nicolaou research group undertook its total synthesis, and in 1998, reported the accomplishment of this demanding task.[101]

The total synthesis of brevetoxin A (**7**) by Nicolaou et al. is summarized in Schemes 42–44.[101] This highly convergent synthesis required construction of advanced intermediates **271** (Scheme 42) and **280** (Scheme 43). Starting with D-glucose (**263**), dihydroxy dicarboxylic acid **264** (Scheme 42) was synthesized and subjected to a double lactonization to

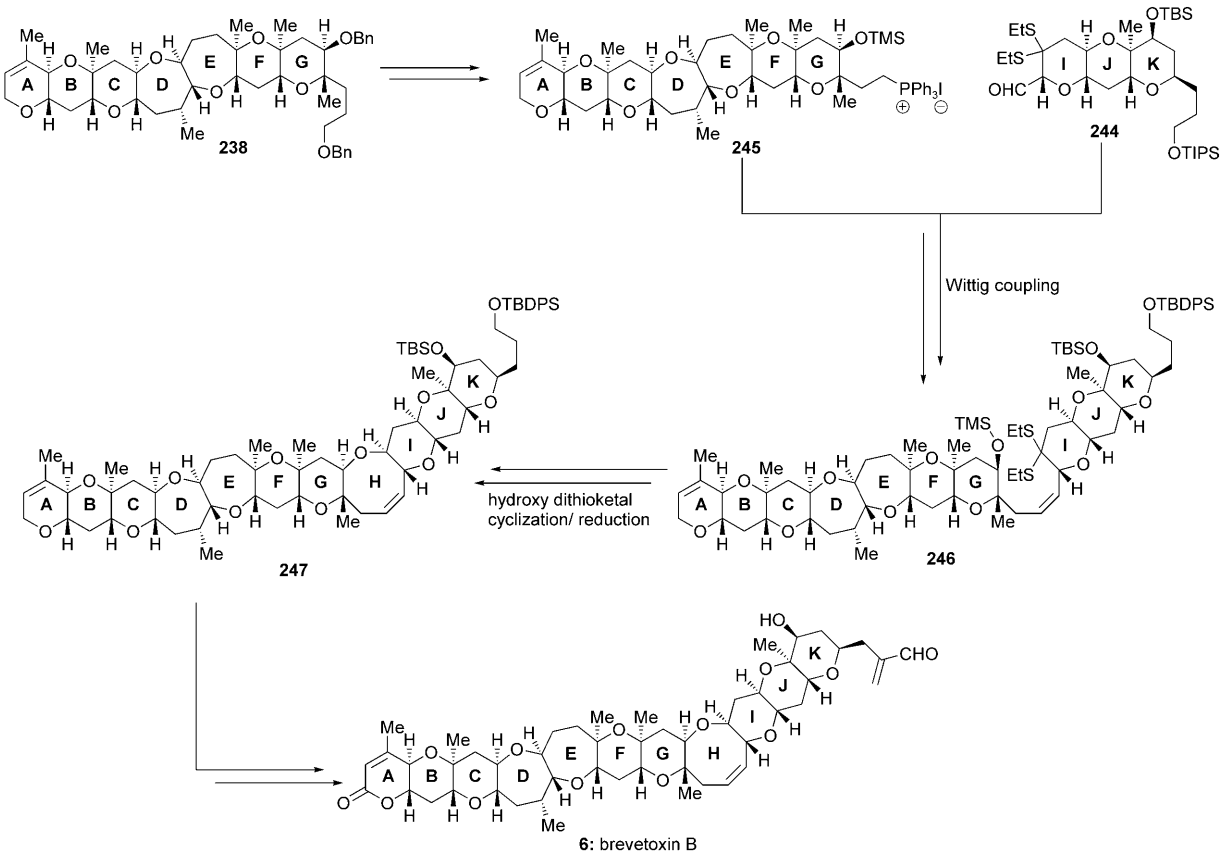


Scheme 38. The first total synthesis of brevetoxin B (**6**). Construction of the IJK domain **244** (Nicolaou et al., 1995).[97]

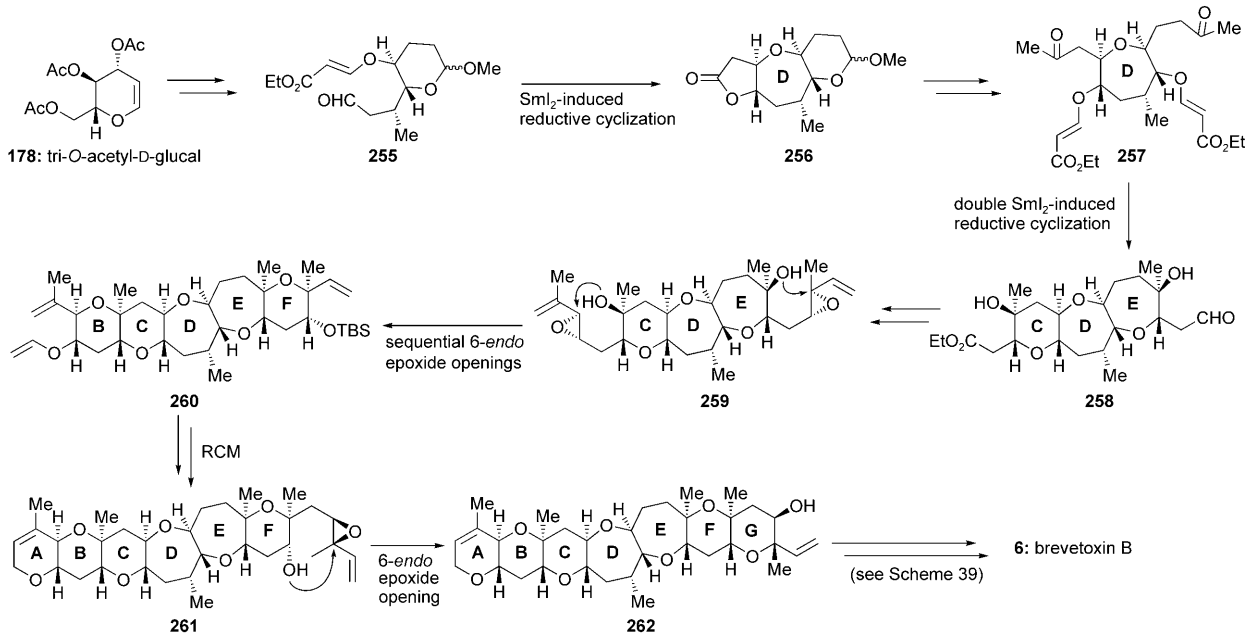
afford, upon further bis-functionalization, bis(vinyl phosphate) **265**, which was converted into bis(vinyl stannane) **266**. The latter intermediate underwent double cuprate addition and, after further elaboration, the product was converted into



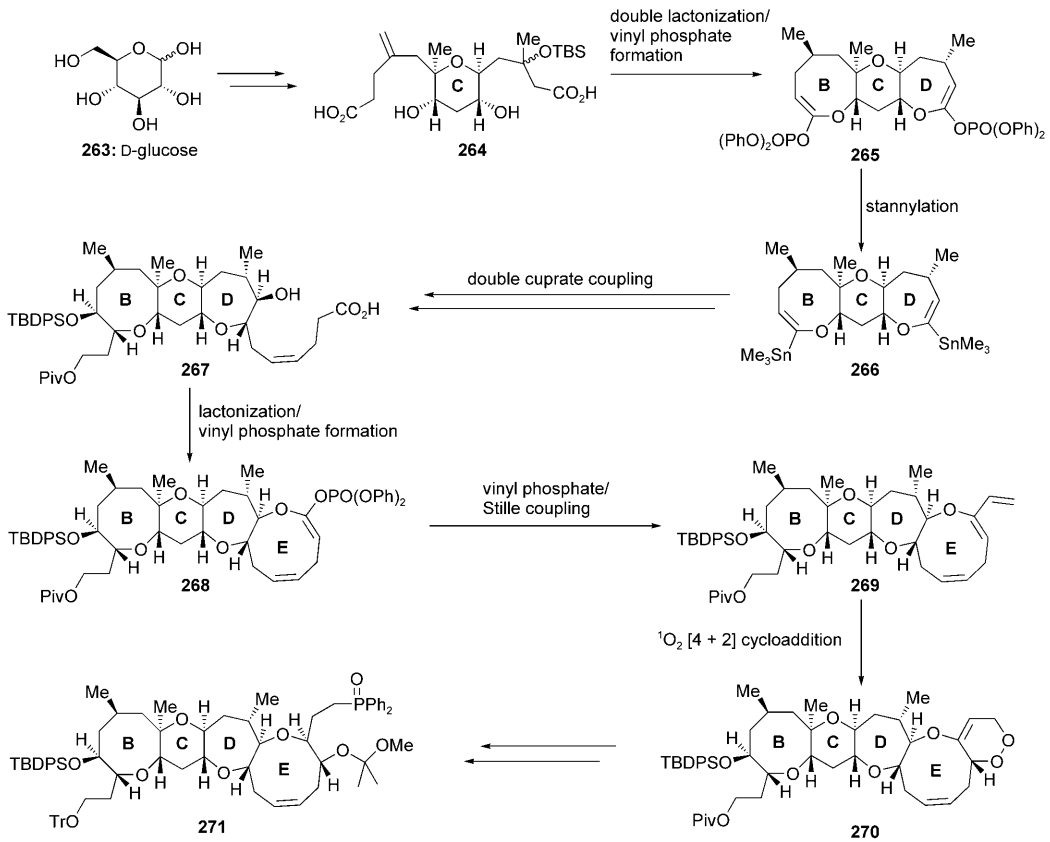
Scheme 40. Second total synthesis of brevetoxin B (**6**). Construction of the IJK fragment **254** (Nakata and co-workers, 2004).[98]



Scheme 39. Completion of the total synthesis of brevetoxin B (**6**; Nicolaou et al., 1995).[97]

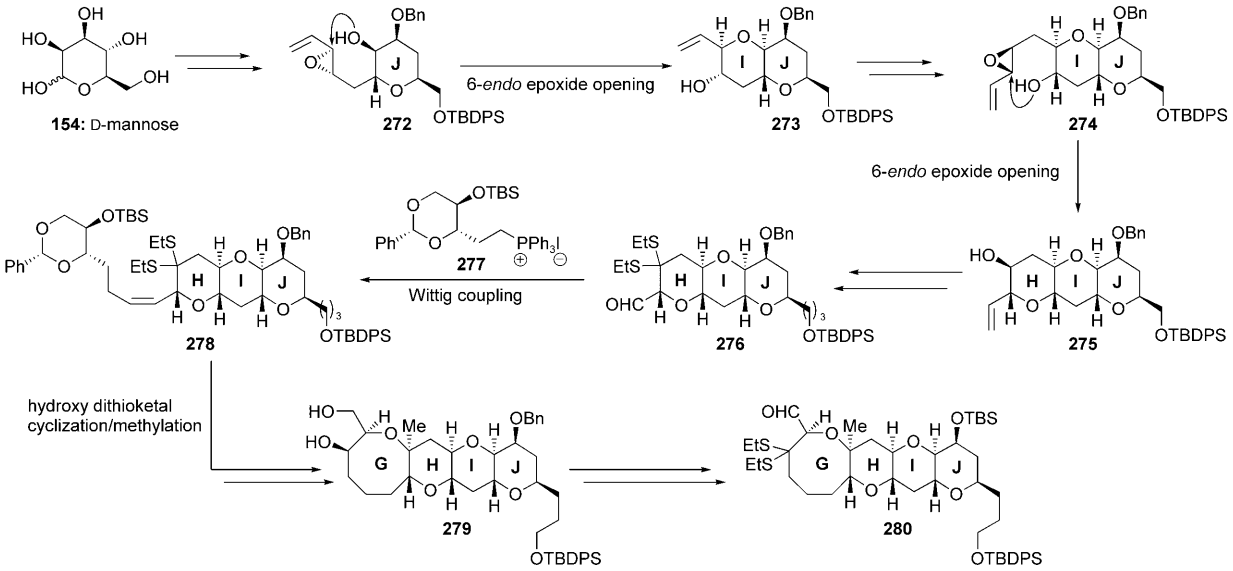


Scheme 41. Second total synthesis of brevetoxin B (**6**). Construction of the ABCDEFG fragment **262** and completion of the synthesis (Nakata and co-workers, 2004).[98]



Scheme 42. The total synthesis of brevetoxin A (**7**). Construction of the BCDE fragment **271** (Nicolaou et al., 1998).[101]

carboxylic acid **267**. Lactonization of the latter, followed by further elaboration led to vinyl phosphate **268**, whose Stille coupling with vinyl stannane gave the BCDE ring fragment **269**. A singlet oxygen [4+2] cycloaddition reaction involving the conjugated diene unit of fragment **269** then led to the endoperoxide **270**, whose rupture and further elaboration furnished the targeted BCDE phosphine oxide fragment **271**.



Scheme 43. The total synthesis of brevetoxin A (**6**). Construction of the GHIJ fragment **280** (Nicolaou et al., 1998).[101]

The construction of the required dithioketal aldehyde **280** (GHIJ fragment) began with D-mannose (**154**) and proceeded through intermediates **272**–**279** as shown in Scheme 43. The successful sequence featured two 6-*endo* epoxide openings (**272**→**273** and **274**→**275**), a Wittig coupling (**276** + **277**→**278**), a hydroxy dithioketal cyclization to cast ring G followed by methylation (**278**→**279**), and final elaboration.

A Horner–Wittig coupling between **271** and **280** (Scheme 44) followed by another hydroxy dithioketal cyclization and reduction then furnished the nonacyclic intermediate **281**, onto which the final ring was forged through lactonization (**282**). The remaining side-chain functionalities were then installed to provide brevetoxin A (**6**).

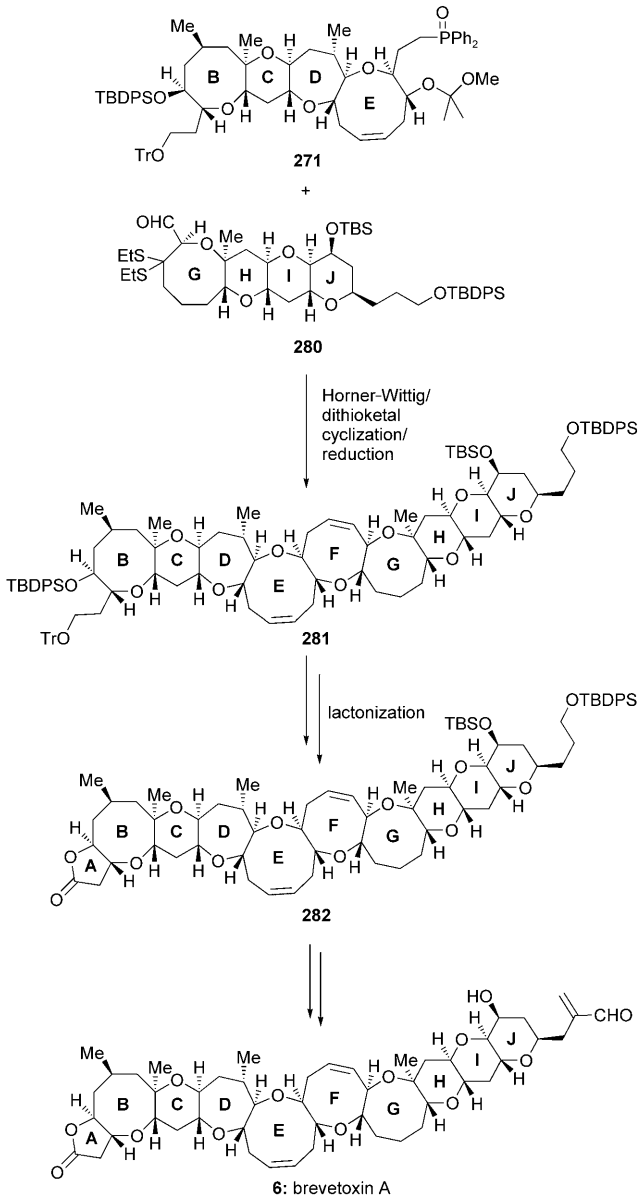
7. Ciguatoxin 3C

While the polyether biotoxins associated with the red tides can be devastating to fish and other marine creatures, their toxic effects on humans are mild compared to the polyether marine toxins produced by the dinoflagellate *Gambierdiscus toxicus*. These polyether biotoxins are the causative agents of the so-called ciguatera fish poisoning, the most widespread and fearful form of seafood poisoning with debilitating and, sometimes, lethal effects on humans. The first members of this class of compounds were reported in 1989.[3,26] Termed ciguatoxins, these marine polyethers were isolated both from the producing dinoflagellate and the ingestive fish that carry them. Interestingly, while the less oxygenated members of the ciguatoxin family are thought to be directly produced by the dinoflagellate species, the more oxygenated congeners are believed to arise by enzymatic modification within the carrier fish. Although the ciguatoxins target the same voltage-sensitive sodium channels as the brevetoxins, they do so with 25- to 400-fold stronger binding affinities, hence their higher toxicities. In 2001, the Hirama research group published the first and only total synthesis of a ciguatoxin, that of CTX3C (**9**, Scheme 47).[102]

Their convergent synthesis of ciguatoxin 3C (**9**) proceeded through advanced intermediates **291** (see Scheme 45) and **303** (see Scheme 46) which were coupled and elaborated to the target molecule (**9**, Scheme 47). The construction of the ABCDE fragment **291** commenced with D-glucose (**263**) and proceeded through a route that diverged into two paths (**283**→**285**→**287** and **284**→**286**→**288**), each employing a ring-closing metathesis (to form rings A and E, respectively), before **287** and **288** were coupled to give **289**. A ring-closing metathesis was used to form ring D (**290**) before the final ring (ring C) in this segment was formed through a reductive cyclization of a hydroxy ketone (**291**).

The synthesis of the HIJKLM fragment (Scheme 46) involved esterification of building blocks **296** (HI fragment) with **300** (LM fragment). An intramolecular addition of a carbene to the ester group forged ring J, and a reductive etherification formed ring K. The preparation of the HI fragment started with 2-deoxy-D-ribose (**222**) and proceeded through a sequence involving intermediates **292**–**295** that featured a ring-closing metathesis (**292**→**293**) and addition of an oxiranyl anion followed by cyclization (**294** + *ent*-**180**→**295**) as the means to cast the two rings. The preparation of the LM fragment **300** required benzyl-(*S*)-glycidol (**297**) as a starting material; saponification and lactonization of intermediate **298** gave **299**, which underwent spiroketalization to give **300**.

Scheme 47 highlights the final stages of the total synthesis of ciguatoxin 3C (**9**). Thus, coupling of the ABCDE and HIJKLM fragments **291** and **303** proceeded through formation of an O,S-acetal to afford, after suitable elaboration, substrate **304**, which was subjected to a radical-based cyclization and further manipulation to furnish **305**. Finally, ring-closing metathesis and deprotection led to the target molecule, ciguatoxin 3C (**9**).

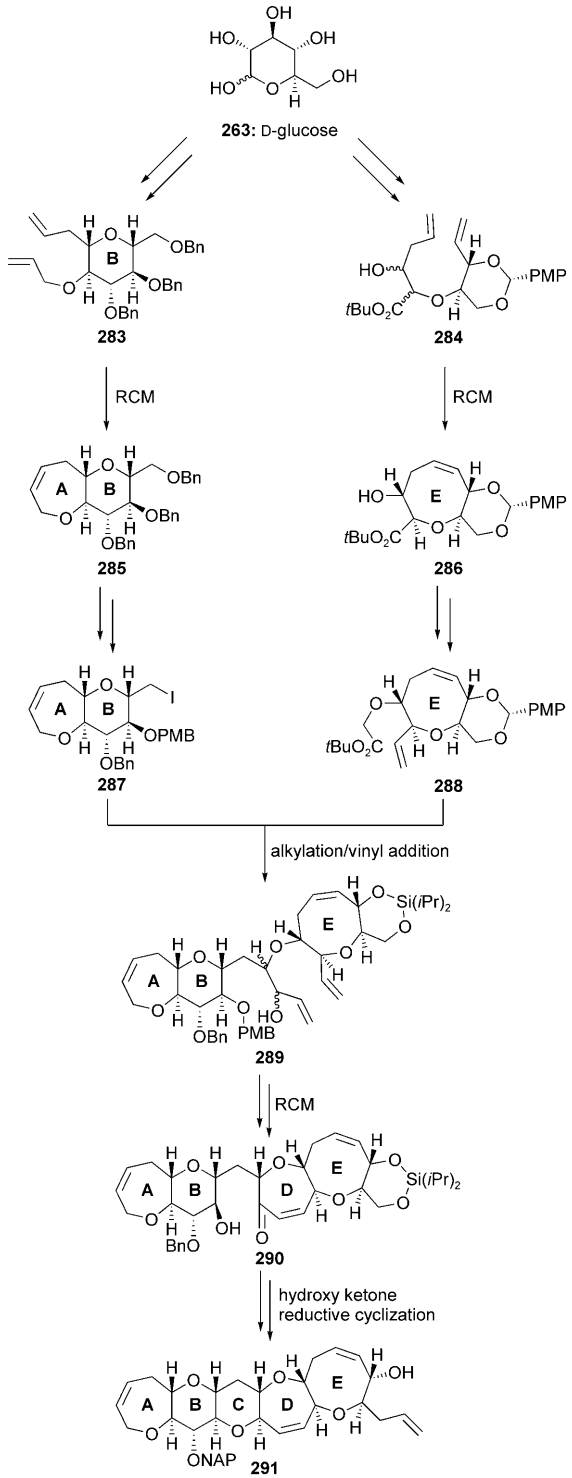


Scheme 44. Completion of the total synthesis of brevetoxin A (**6**; Nicolaou et al., 1998).[101]

8. Gambierol

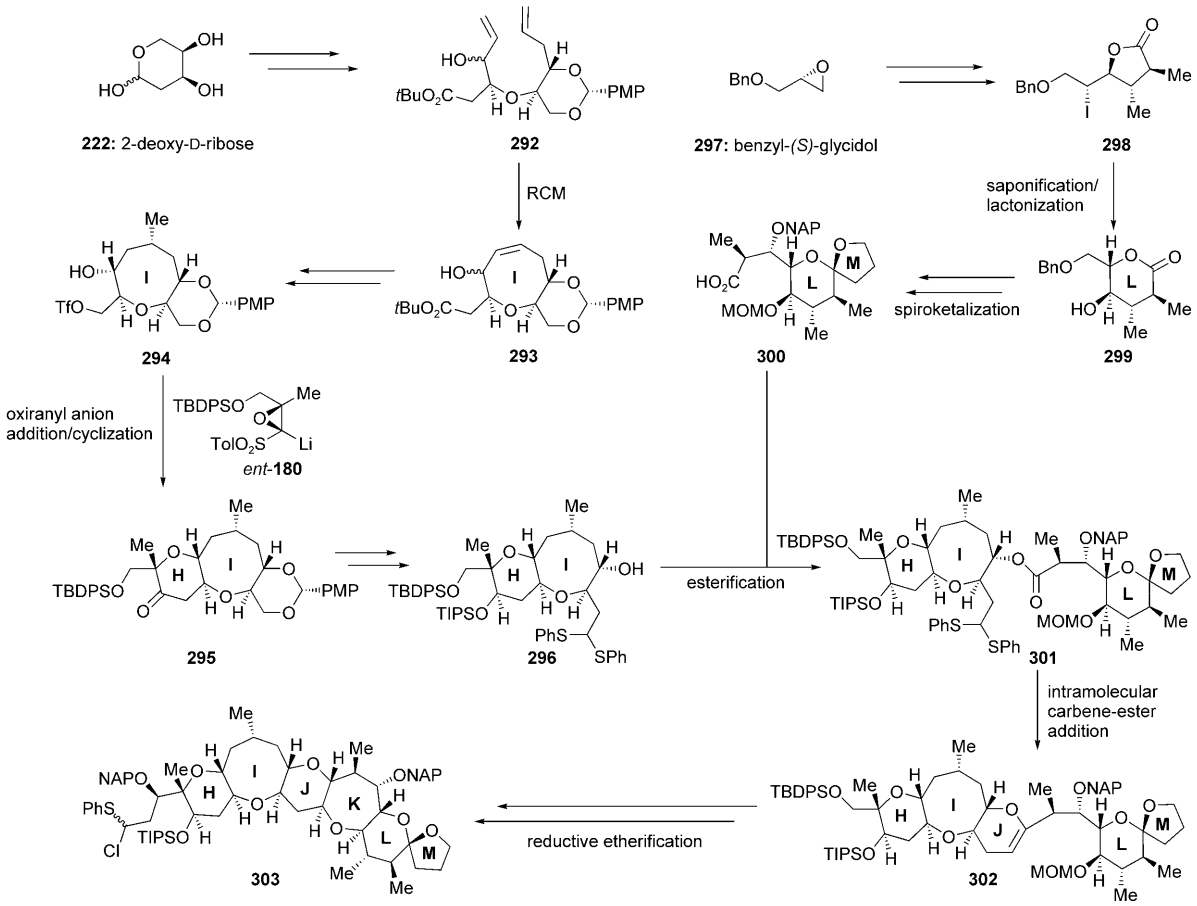
Gambierol (**10**) was isolated from *Gambierdiscus toxicus* in 1993.[103] The polyether exhibited similar toxic properties as the ciguatoxins, thus leading to speculation that these substances share biological targets.[104] However, the lack of sufficient amounts of gambierol (**10**) from natural sources precluded a complete evaluation of its biological properties, thus making a chemical synthesis increasingly valuable. Three total syntheses of gambierol have been reported to date; each one provides an illustration of some method of cyclic ether formation that has not yet been discussed in the context of a total synthesis.

The first total synthesis of gambierol (**10**) was reported by Sasaki and co-workers in 2002.[105] This convergent synthesis



Scheme 45. Total synthesis of ciguatoxin 3C (**9**). Construction of the ABCDE fragment **291** (Hirama and co-workers, 2001).[102]

required building blocks **312** (ABC fragment, Scheme 48) and **320** (EFGH fragment, Scheme 49), and demonstrated the power of the vinyl phosphate/*B*-alkyl Suzuki coupling. The ABC fragment **312** was constructed from 2-deoxy-D-ribose (**222**)[101d] through intermediates **306–311**. The route featured an intramolecular hydroxy Michael reaction to form ring A



Scheme 46. Total synthesis of ciguatoxin 3C (**9**). Construction of the HIJKLM fragment **303** (Hirama and co-workers, 2001).[102]

(**308**→**309**) and two 6-*endo* epoxide openings to cast rings B (**306**→**307**) and C (**310**→**311**).

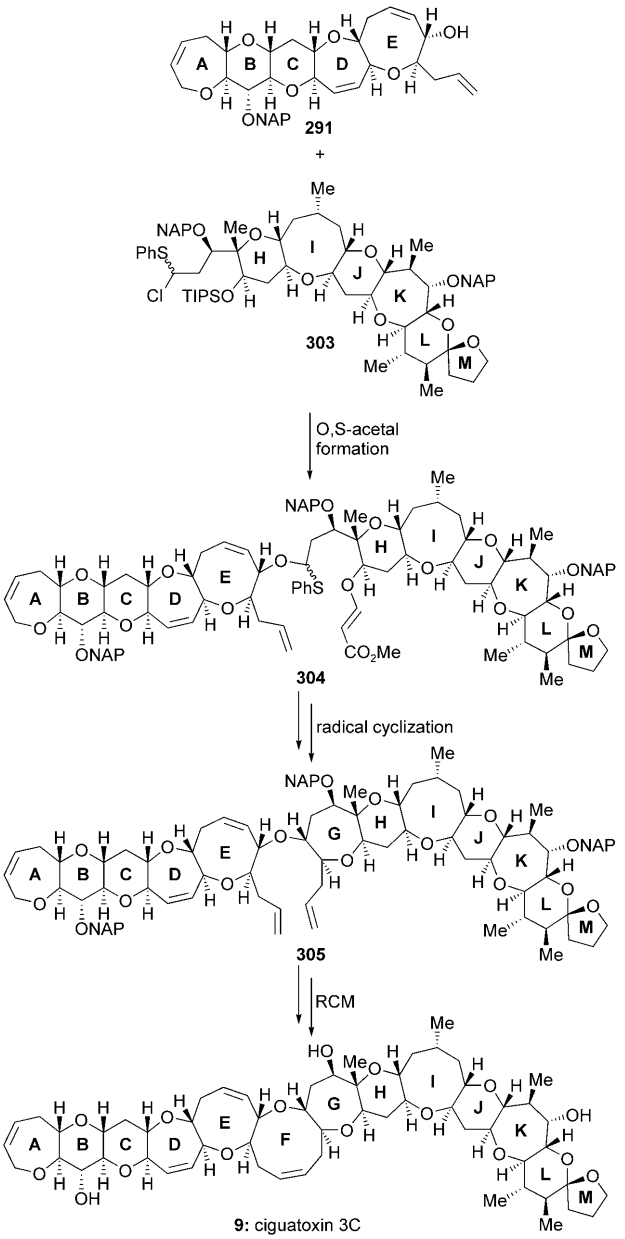
2-Deoxy-D-ribose (**222**) was also the starting material for the EFGH fragment **320**,[105] whose construction proceeded through intermediates **313**–**319** (Scheme 49). This synthesis efficiently exploited two Nakata SmI_2-induced cyclizations to form rings H (**313**→**314**) and F (**317**→**318**), a Nicolaou 6-*endo* epoxide opening to form ring G (**315**→**316**), and a Nicolaou lactonization with subsequent vinyl phosphate formation to form ring E (**319**→**320**).

The two fragments **312** and **320** were joined through a Suzuki coupling to generate ABCEFGH ring system **321**, which was elaborated to gambierol (**10**) through intermediates **322** and **323** (Scheme 50). The final ring closure to forge ring D relied on the formation of an O,S-acetal followed by reduction, a protocol based on Nicolaou's dithioketal cyclization and reduction method.

The second total synthesis of gambierol (**10**) was reported by Yamamoto and co-workers.[106] Its convergency relied on the construction of the ABC fragment **326** (Scheme 51) and the FGH fragment **333** (Scheme 52), which were coupled through esterification (Scheme 53). Similar to the route used by Sasaki and co-workers, the sequence to construct the ABC fragment **326** started from 2-deoxy-D-ribose (**222**) and exploited a 6-*endo* epoxide opening to form ring B (**306**→**307**), and a hydroxy Michael addition to form ring A (**308**→**309**), but this time a SmI_2-induced reductive cyclization was employed to forge ring C (**324**→**325**; Scheme 51).[105c]

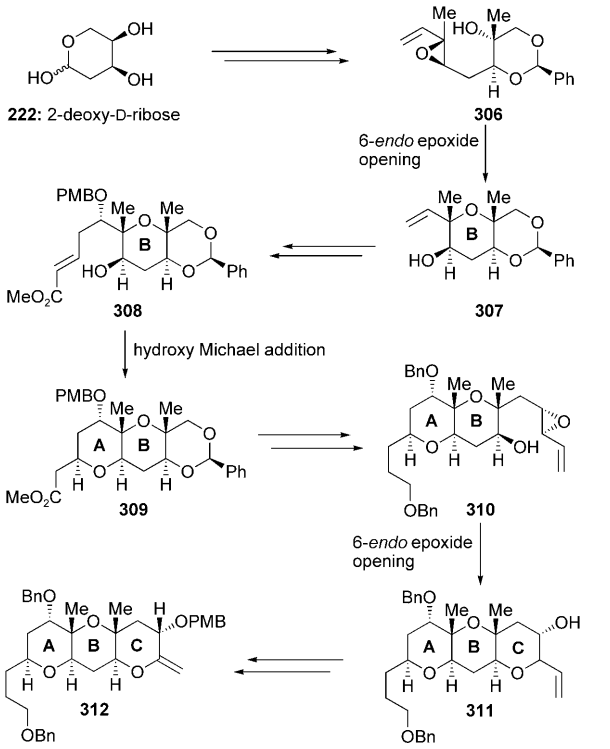
The construction of the FGH fragment **333** began with 2-deoxy-L-ribose (*ent*-**222**).[106] As summarized in Scheme 52, this synthesis proceeded through intermediates **327**–**332** and involved a 6-*endo* epoxide opening to cast ring G (**327**→**328**), an SmI_2-induced reductive cyclization to form ring F (**329**→**330**), and an allyl tin cyclization to generate ring H (**331**→**332**).[107] After union of the two fragments **326** and **333** through esterification and further elaboration, cyclization of the allyl tin species **334** ensured the installation of ring D. This diolefin **335** underwent smooth ring-closing metathesis to complete the required row of cyclic ethers that eventually led to synthetic gambierol (**10**, Scheme 53).

A third total synthesis of gambierol (**10**), this time from Rainier and co-workers, was reported in 2005.[108] Based on a convergent strategy, this synthesis relied on an asymmetric Diels–Alder reaction[109] to construct ring A (**188** + **336**→**337**), and two reiterative methylenation/metathesis sequences to cast rings B (**338**→**339**) and C (**340**→**341**), thereby generating the required ABC fragment **342** (Scheme 54). The other required advanced building block **346** (FGH fragment) began with tri-*O*-acetyl-D-glucal (**178**) and employed another methylenation/metathesis protocol (to



Scheme 47. Total synthesis of ciguatoxin 3C (**9**). Final stages of the synthesis (Hirama and co-workers, 2001).[102]

form ring F; **343**→**344**) and an acid-induced cyclization and subsequent functionalization of **345** to forge the oxepane ring (ring H, →**346**; Scheme 55). The final stages of this synthesis of gambierol involved coupling fragments **342** and **346** through esterification (Scheme 56), followed by another methylenation/metathesis sequence that formed ring E (**347**). Subsequent elaboration to hydroxy ketone **348**, followed by the formation of an O,S-acetal and reduction, ensured the closing of the last required ring and paved the way to the final functional group manipulations that furnished gambierol (**10**).



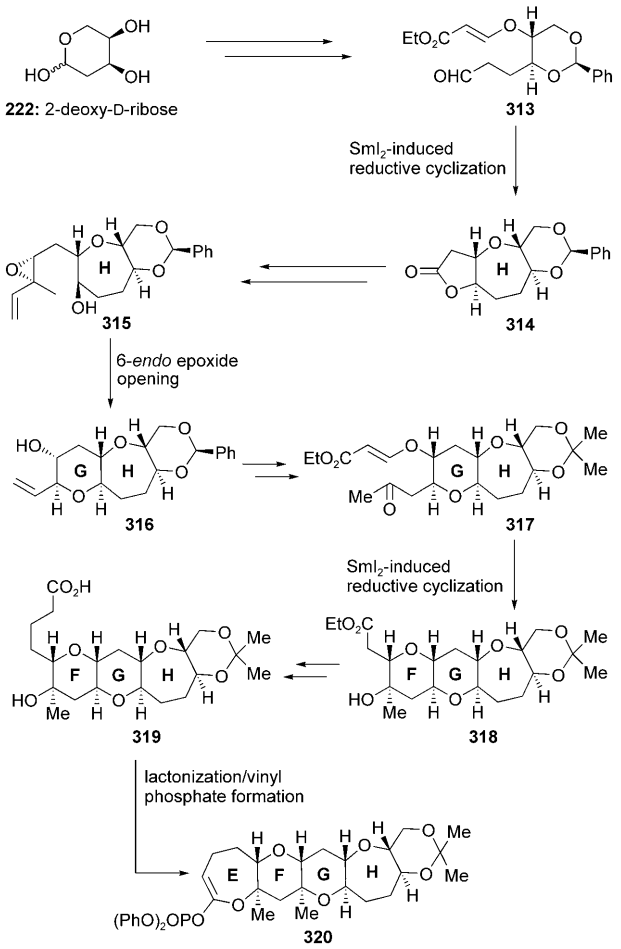
Scheme 48. The first total synthesis of gambierol (**10**). Synthesis of the ABC domain **312** (Sasaki and co-workers, 2002).[105]

9. Gymnocin A

The synthesis of gymnocin A (**12**), the second largest fully characterized polyether marine natural product known to date, was reported by the Satake research group in 2003.[9] Isolated from the red tide dinoflaggelate *Karenia mikimotoi*, this biotoxin, although cytotoxic, is only weakly toxic to fish, presumably because of its low solubility in water, which prevents it from reaching the fish's gills.

In 2003, Sasaki et al. reported a highly convergent total synthesis of gymnocin A (**12**) that made extensive use of the vinyl phosphate/*B*-alkyl Suzuki coupling method to couple smaller fragments into larger ones, and, at the same time, allowed the casting of several of the cyclic ether moieties of the molecule.[110] Thus, the ABCD fragment **353** (Scheme 57) of gymnocin A was constructed from 2-deoxy-D-ribose (**222**) by a route that first diverged to deliver vinyl phosphate **349** and enol ether **350**, and then converged through a Suzuki coupling to furnish ABD enol ether **351** (Scheme 57).[106c] The latter intermediate was elaborated to ABD ketone **352**, whose conversion into the required ABCD fragment **353** involved formation of an O,S-acetal followed by reduction.

The synthesis of the larger FGHIJKLMN fragment **363** (see Scheme 59) required the construction of the tricyclic compound **358**, which was employed as a common intermediate in the temporarily divergent strategy deployed in the final stages of the synthesis of the FGHIJKLMN fragment. The construction of **358** is summarized in Scheme 58. Thus, geraniol (**166**) was converted into vinyl phosphate **354**, and 2-deoxy-D-ribose (**222**) was functionalized to exocyclic olefin

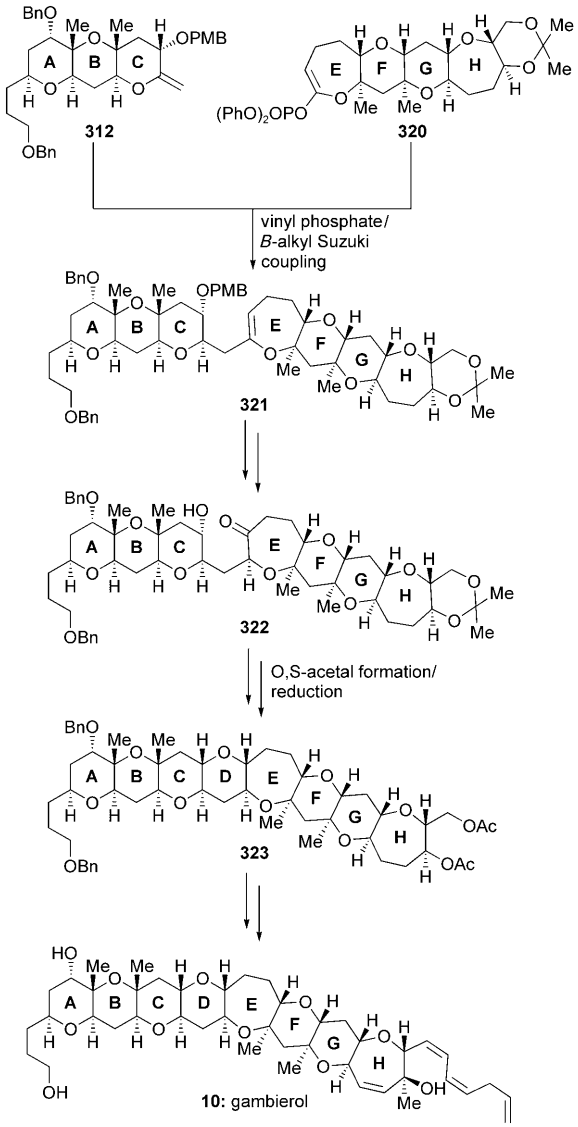


Scheme 49. The first total synthesis of gambierol (**10**). Synthesis of the EFGH domain **320** (Sasaki and co-workers, 2002).[105]

355. The two fragments were then subjected to a vinyl phosphate/*B*-alkyl Suzuki coupling to afford tricyclic system **356**, whose further manipulation led to hydroxy ketone **357**. An O,S-acetal cyclization followed by reduction then furnished, after simple functional group adjustments, the target tricyclic compound **358**.

This intermediate was utilized by Sasaki et al. as a common precursor to both the GHI enol ether fragment **359** and the KLMN vinyl phosphate **360** needed for their next Suzuki coupling to afford the heptacyclic intermediate **361** (GHIKLMN fragment; Scheme 59). This intermediate was then elaborated to the next desired vinyl phosphate **363** through a process that utilized the formation of yet another O,S-acetal and reduction (**362**→**363**) to cast the final ring of the targeted structure.

In the final stages of the synthesis (Scheme 60), a vinyl phosphate/*B*-alkyl Suzuki coupling was employed to join the two large fragments **353** and **363** to afford tridecacyclic enol ether **364**, which was swiftly converted into its ketone counterpart **365** in preparation for the next reaction that forged the last ring. The formation of an O,S-acetal and reduction was called upon once again to complete the task, and gymnocin A (**12**) emerged after minor functional group adjustments.

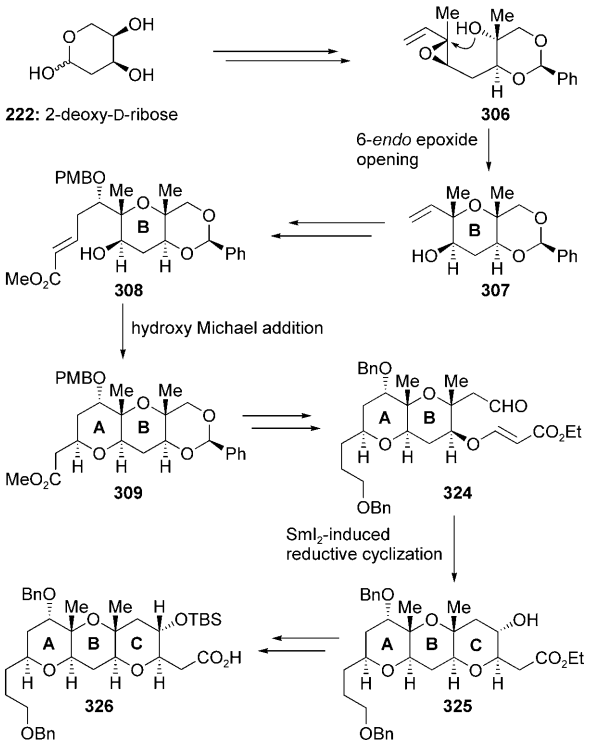


Scheme 50. Completion of the first total synthesis of gambierol (**10**; Sasaki and co-workers, 2002).[105]

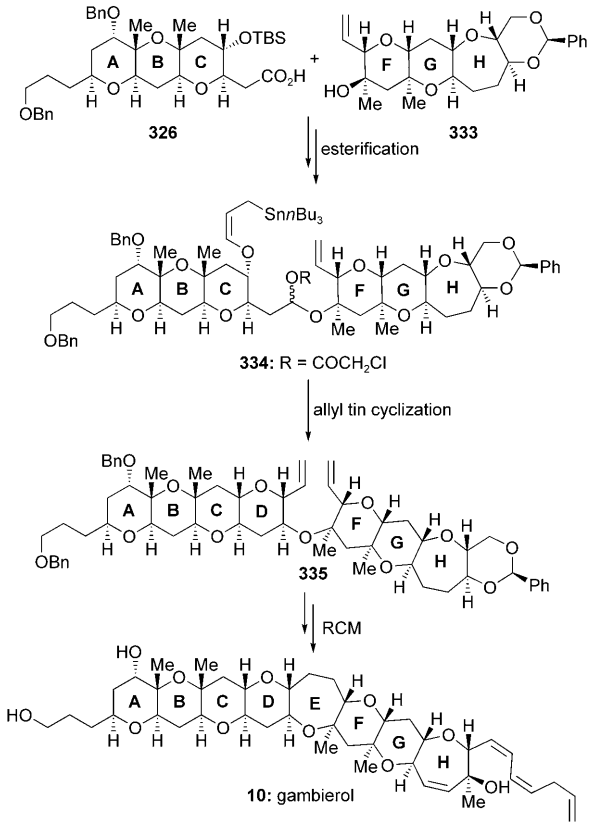
10. Brevenal

In 2004, yet another marine polyether was isolated from *Karenia brevis*.[111] One of the simplest members of the class, brevenal (**11**, Figure 2) possesses intriguing biological properties. Thus, it was claimed not only to displace brevetoxins A (**7**) and B (**6**) from their binding sites on the voltage-sensitive sodium channels, but also to antagonize their neurotoxicity.[112]

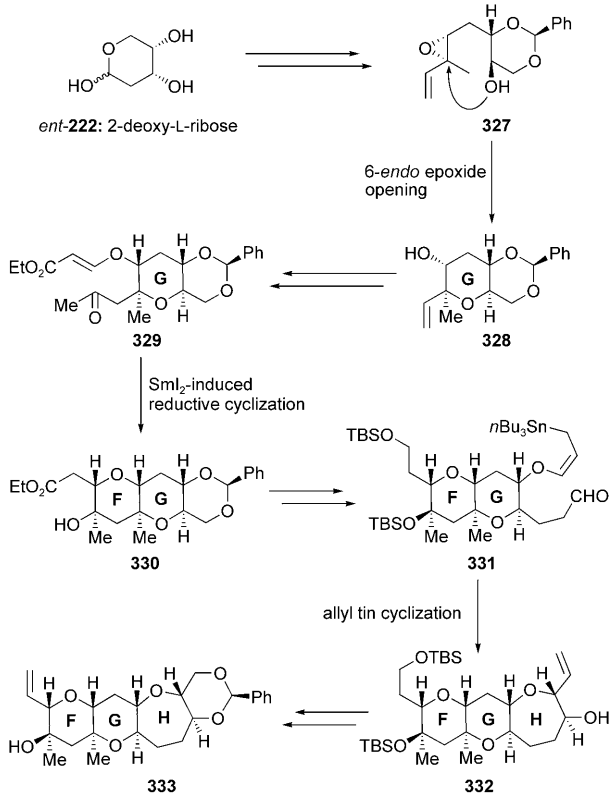
In 2006, the Sasaki research group accomplished a total synthesis of the reported structure of brevenal (C18 epimer of **11**, see Scheme 63), only to prove that it was erroneous.[113] By employing their developed synthetic methods, however, they soon constructed the correct structure of brevenal (**11**, see Scheme 63).[114] The convergent synthesis of brevenal (**11**) required the AB ring vinyl phosphate **370** (Scheme 61) and the DE ring enol ether **375** (Scheme 62).



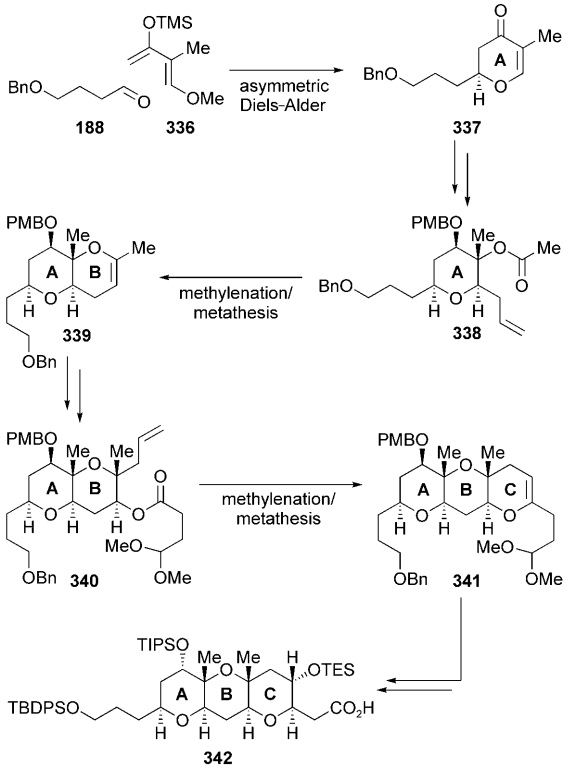
Scheme 51. Second total synthesis of gambierol (**10**). Construction of the ABC domain **326** (Yamamoto and co-workers, 2003).[106]



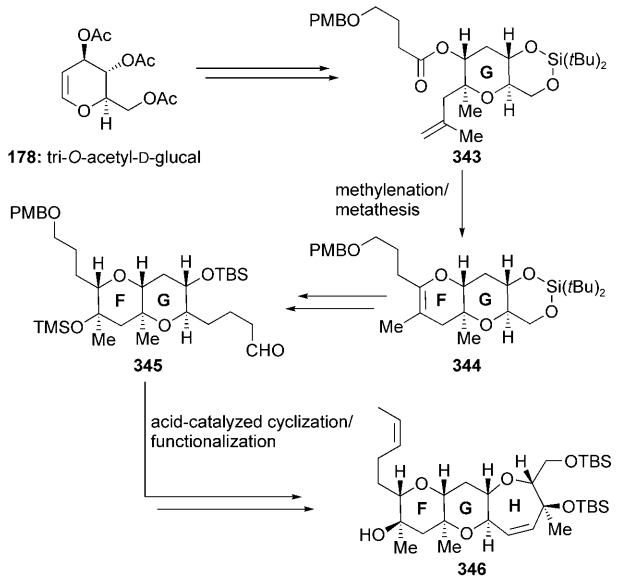
Scheme 53. Completion of the second total synthesis of gambierol (**10**; Yamamoto and co-workers, 2003).[106]



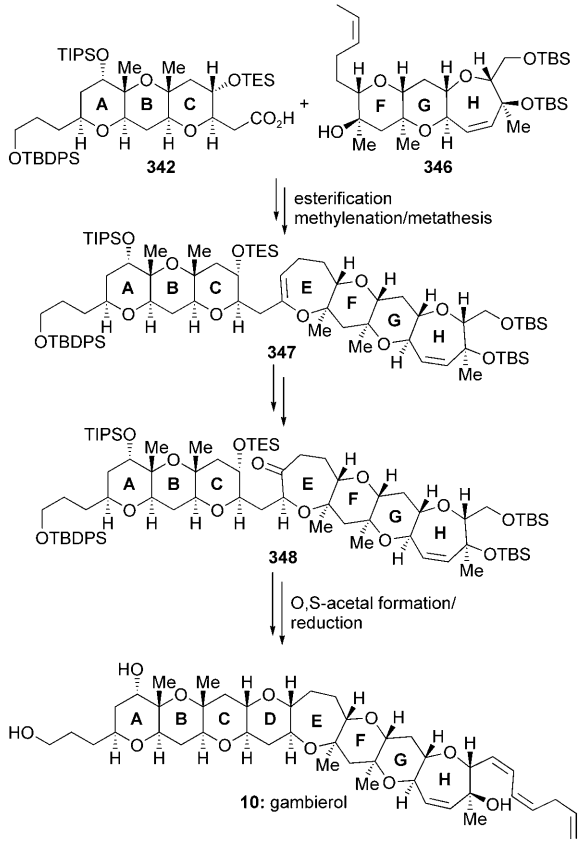
Scheme 52. Second total synthesis of gambierol (**10**). Construction of the FGH domain **333** (Yamamoto and co-workers, 2003).[106]



Scheme 54. Third total synthesis of gambierol (**10**). Construction of the ABC fragment **342** (Rainier and co-workers, 2005).[108]

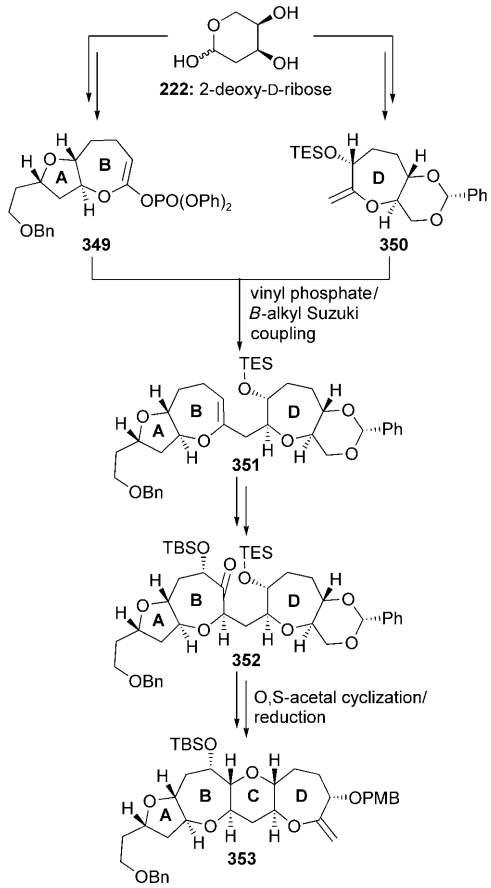


Scheme 55. Third total synthesis of gambierol (**10**). Construction of the FGH domain **346** (Rainier and co-workers, 2005).[108]



Scheme 56. Completion of the third total synthesis of gambierol (**10**; Rainier et al., 2005).[108]

Thus, after convergent union of starting materials **366** and **367** (Scheme 61), hydroxy epoxide **368** was synthesized and subjected to a 6-*endo* epoxide opening to form ring A (→ **369**), which was then elaborated to the AB fragment **370** through lactonization and formation of a vinyl phosphate. The

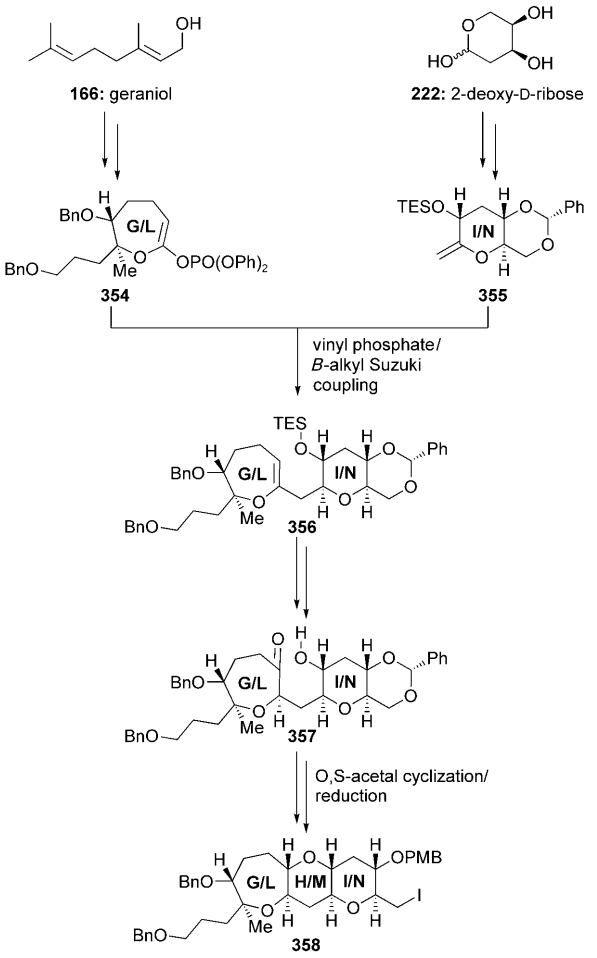


Scheme 57. Total synthesis of gymnocin A (**12**). Construction of the ABCD domain **353** (Sasaki et al., 2003).[110]

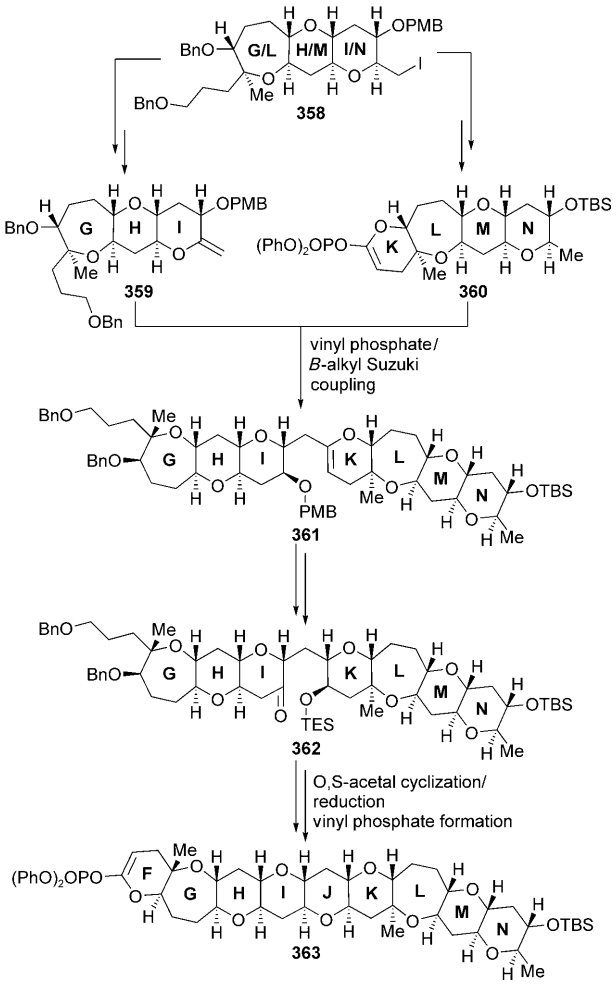
other required fragment, cyclic enol ether **375** (DE fragment), was prepared from 2-deoxy-D-ribose (**222**) through a sequence (Scheme 62) that relied on two SmI_2-induced reductive cyclizations to construct the two rings D (**371**→**372**) and E (**373**→**374**) and further elaboration (**374**→**375**).

The final stages of the synthesis of brevenal (**11**, Scheme 63) involved a vinyl phosphate/B-alkyl Suzuki coupling of the AB (**370**) and DE (**375**) fragments to afford the ABDE domain **376**, and the formation of an O,S-acetal followed by methylation that installed both ring C and the required methyl group according to Nicolaou's protocol. Further elaboration, including extension of the side chains, led to brevenal (**11**; and its C18 epimer).

The above syntheses provide a clear picture of the evolution of the strategies towards complex, ladderlike polyether structures such as those found in nature. They are also indicative of the applicability and scope of certain methods for the formation of cyclic ethers. Among them, the 6-*endo* epoxide opening (Nicolaou), cyclic O,S-acetal formation/reduction or methylation (Nicolaou), bis(thionolactone) bridging (Nicolaou), thionolactone nucleophilic addition (Nicolaou), intramolecular hydroxy Michael addition (Nicolaou), hydroxy ketone reductive cyclization (Nicolaou), allyl tin radical cyclization (Yamamoto), methylenation/metathesis (Grubbs/Nicolaou/Clark/Takeda), ring expansion (Nakata), oxiranyl anion addition/cyclization (Mori), vinyl



Scheme 58. Total synthesis of gymnocin A (**12**). Synthesis of the common precursor **358** (Sasaki et al., 2003).[110]



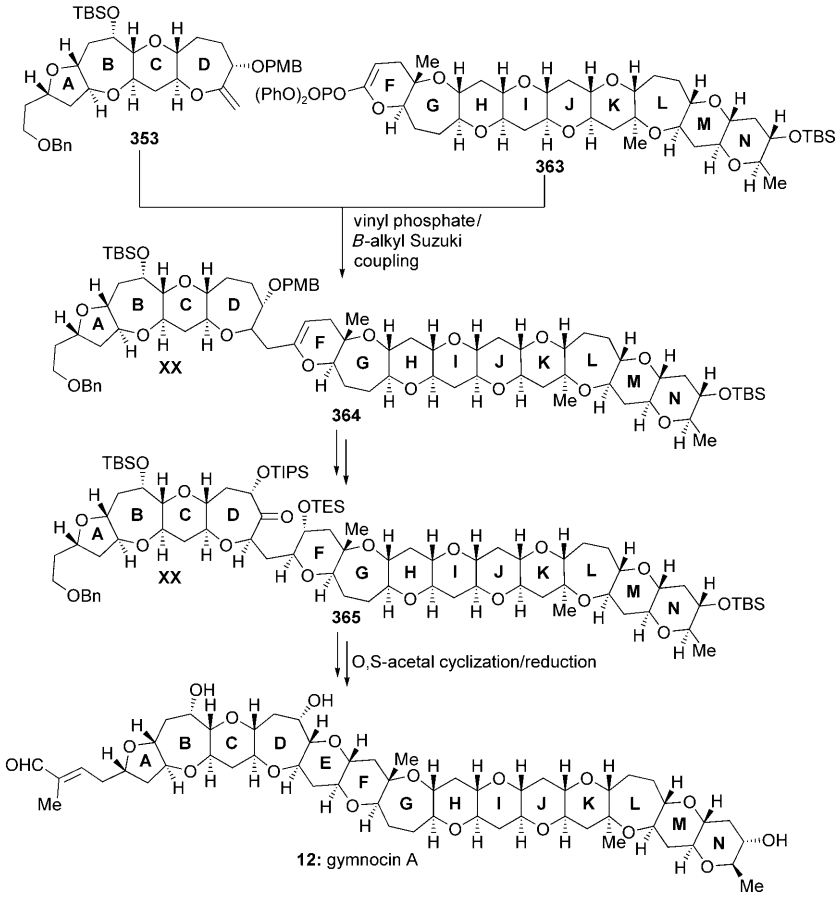
Scheme 59. Total synthesis of gymnocin A (**12**). Construction of the FGHIJKLMN domain **363** (Sasaki et al., 2003).[110]

phosphate/Stille or *B*-alkyl Suzuki coupling (Nicolaou/Sasaki), O,S-acetal radical cyclization (Tachibana), SmI_2-induced reductive cyclization (Nakata), alkyne oxidation/cyclization (Fujiwara and Murai/Nakata/Mori), hydroxy methoxy enone cyclization (Nakata), and hydroxy polyepoxides cyclization cascades (Murai/McDonald/Jamison) have been, so far, the most commonly used in natural product synthesis. In surveying these syntheses, it also became clear that, thus far, carbohydrates were the preferred starting materials, with 2-deoxy-D-ribose (**222**)—which was the starting point for the first total synthesis of brevetoxin B—as perhaps the most favorite choice.

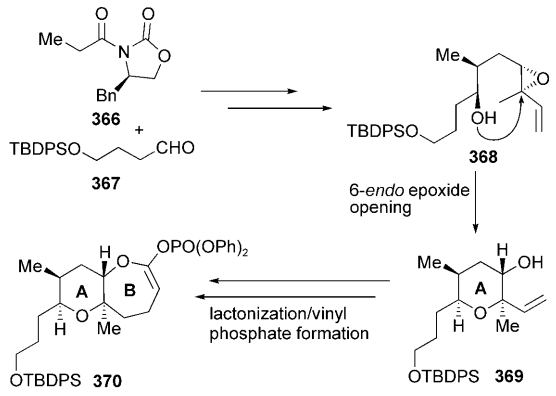
11. Maitotoxin

Maitotoxin was first detected in the late 1970s in the gut of the surgeon fish *Ctenochaetus striatus*[115] and later in the dinoflaggelate *Gambierdiscus toxicus*.[116] However, it would not be until 1988 that Yasumoto and co-workers would isolate the molecule from a broth of the dinoflaggelate.[117] With a molecular weight of 3422 Daltons ($C_{164}H_{256}O_{68}S_2Na_2$), 32 rings, and 99 elements of stereochemistry—98 stereogenic centers and 1 trisubstituted double bond—there are $2^{99} = 6.3 \times 100\,000\,000\,000\,000\,000\,000\,000\,000\,000$ possible stereoisomers, and maitotoxin stands as the largest and most toxic, non-polymeric natural product isolated and characterized to date. The size of the molecule and its low natural abundance meant that its structure could not be derived directly from NMR spectroscopic analysis alone, so a combination of degradative and synthetic studies were needed.

First, Yasumoto and co-workers subjected maitotoxin (**13**, Scheme 64) to oxidative degradation with sodium periodate to cleave the molecule at every 1,2-diol site. After reduction with $NaBH_4$, three compounds were obtained: C1–C36 fragment **378**, C37–C135 fragment **380**, and C136–C142 fragment **382** (Scheme 64).[118] Exhaustive acetylation of fragments **378** and **380** furnished peracetates **379** and **381**, respectively (Scheme 64), which were analyzed by NMR spectroscopy. In 1993, the gross structure of maitotoxin with the relative configuration for all its cyclic domains was proposed.[119] Yasumoto and co-workers were unable, however, to determine the relative stereochemistry of the acyclic regions of the molecule (C1–C15, C35–C39, C63–C68, and C134–C142). These assignments had to wait several more



Scheme 60. Final stages in the total synthesis of gymnocin A (**12**). (Sasaki et al., 2003).[110]

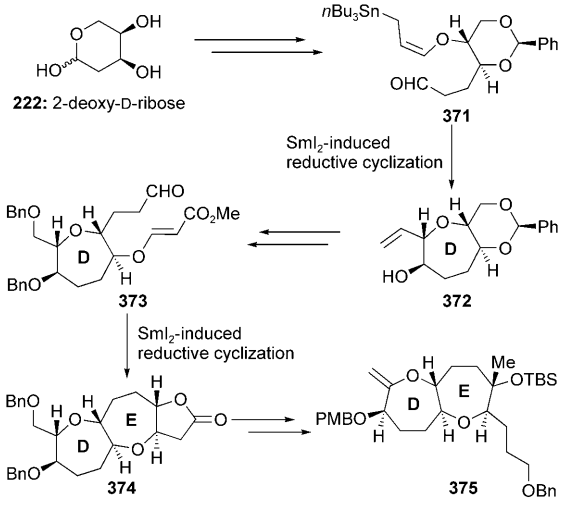


Scheme 61. Total synthesis of brevenal (**11**). Construction of the AB ring system **370** (Sasaki and co-workers, 2006).[114]

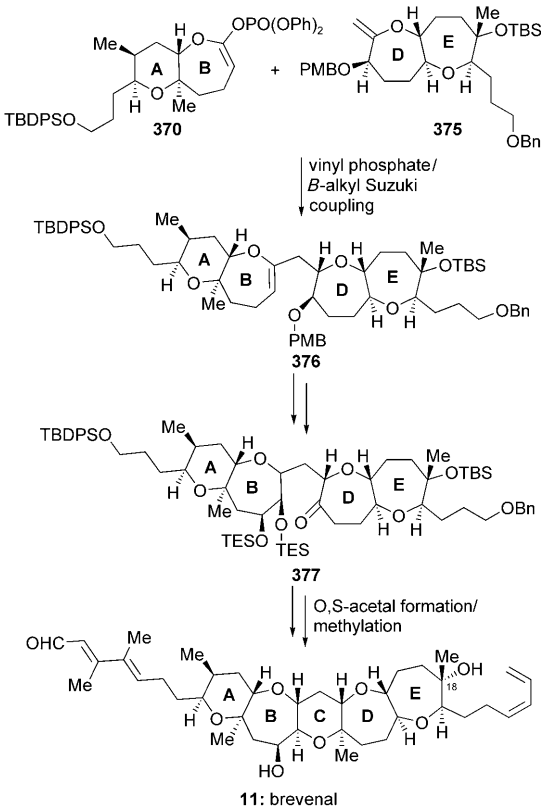
years while the Kishi and Tachibana research groups independently synthesized a number of fragments corresponding to certain domains of maitotoxin before the complete structure of the molecule was finally proposed with confidence as that depicted by **13** (Scheme 64).

The determination of the relative configuration of the acyclic regions of maitotoxin and the absolute configuration of its entire structure required, in addition to sophisticated spectroscopic techniques,[11] chemical synthesis, and structural analysis of a number of synthetic fragments, and comparisons of their physical properties to those of the corresponding regions of the natural product. With their elegant studies, the Kishi and Tachibana research groups responded successfully to this challenging task.

Scheme 65 summarizes the efforts that led to the determination of the relative stereochemistry of the C1–C15 domain of maitotoxin, which mainly relied on ^{13}C spectroscopic data comparisons of various synthetic diastereomers of certain fragments corresponding to those of the same region of the molecule. Kishi and co-workers, instead of synthesizing all 128 possible diastereomers of the C1–C15 domain, divided this region in two and synthesized, instead, the eight possible stereoisomers of the C1–C11 structure **383** and the eight possible stereoisomers of the C11–C15 structure **384** (Scheme 65).[120] They found the ^{13}C NMR spectroscopic data of isomers **383** and **384** to match more closely those of the corresponding domains of maitotoxin than did those of the other isomers. To assign the relative configuration between the two fragments **383** and **384**, they prepared the two diastereomers of **388** (Scheme 65) by coupling the enatiomerically pure diastereomer **385** with the two enantiomers of **386** and elaborating the two products **387** to the two diastereomers of **388**. They found that the ^{13}C NMR spectroscopic data of diastereomer **388** shown in Scheme 65 matched very closely those of the C1–C15 domain of maitotoxin, thus allowing them to make their final stereochemical assignments to this region of the molecule. Tachibana and co-workers, on the other hand, synthesized the C5–C15 fragment **389** (suspected to be the correct one) and found its ^{13}C NMR spectroscopic data to match closely those of the same region of maitotoxin, thus allowing them to make the same stereochemical assignment to this domain of maitotoxin.[121]



Scheme 62. Total synthesis of brevenal (**11**). Construction of the DE ring system **375** (Sasaki and co-workers, 2006).[114]



Scheme 63. Completion of the total synthesis of brevenal (**11**; Sasaki and co-workers, 2006).[114]

With two independent studies reaching the same conclusion, it seemed secured that the relative configuration of the C1–C35 domain of maitotoxin was as depicted in **13** (Scheme 64).

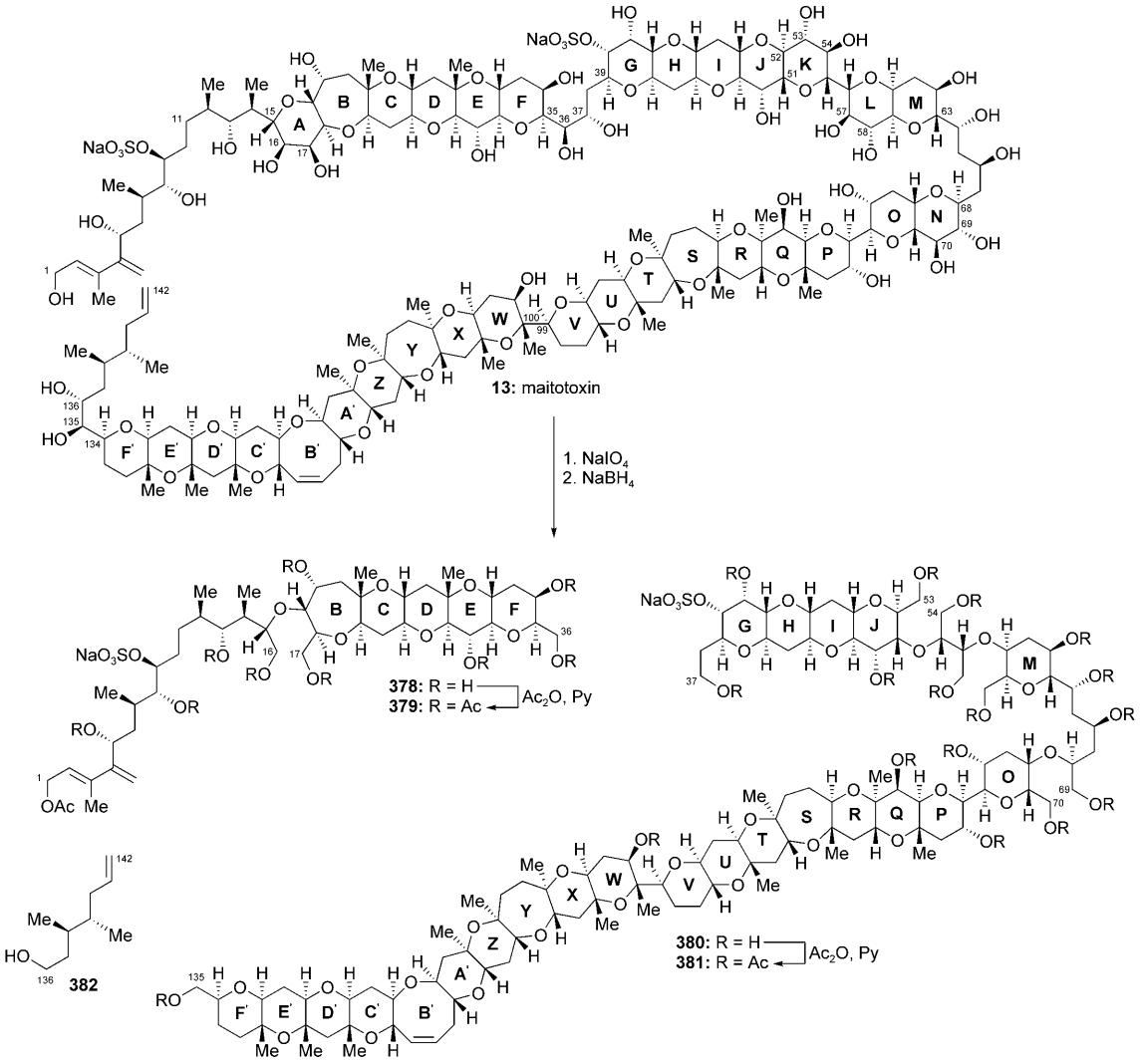
For the assignment of the relative configuration of the C35–C39 region of the maitotoxin molecule, Kishi and co-workers synthesized the eight possible diastereomers of the EFGH fragment **393** starting from enantiopure GH fragment **390**, and the two enantiomers of the EF fragment **391** through the two acetylenic diastereomers of EFGH fragment **392**.[120] The ^{13}C NMR spectroscopic data for the diastereomer **393** shown in Scheme 66 exhibited the closest match to those of the same region of maitotoxin, thus pointing to this particular stereochemical arrangement for the C35–C39 domain of the natural product. Similar synthetic studies by the Tachibana research group starting with EF and GH fragments **394** and **395** furnished, through intermediate **396**, diastereomer **397** (which was suspected to be the right one) as summarized in Scheme 66. Spectroscopic analysis of this diastereomer led to the same conclusion as that reached by Kishi and co-workers.[122]

Moving on to the C63–C68 segment of the molecule, the research groups of Kishi[120] and Tachibana[123] synthesized the four diastereomers of each of the LMNO fragments **401** and **405**, respectively. Starting with the enantiopure LM and NO fragments (**399**, **398**, and **403**, **402**, respectively), they used a route that allowed them to synthesize all four C64/C66 diastereomers of **401** and **405** through intermediates **400** and **404**, respectively. Of the four diastereomers that each group synthesized, they found that **401** and **405** depicted in Scheme 67 exhibited the closest ^{13}C NMR spectroscopic data to those reported for the corresponding region of maitotoxin, thus providing the foundation for the stereochemical assignments of that region of the molecule.

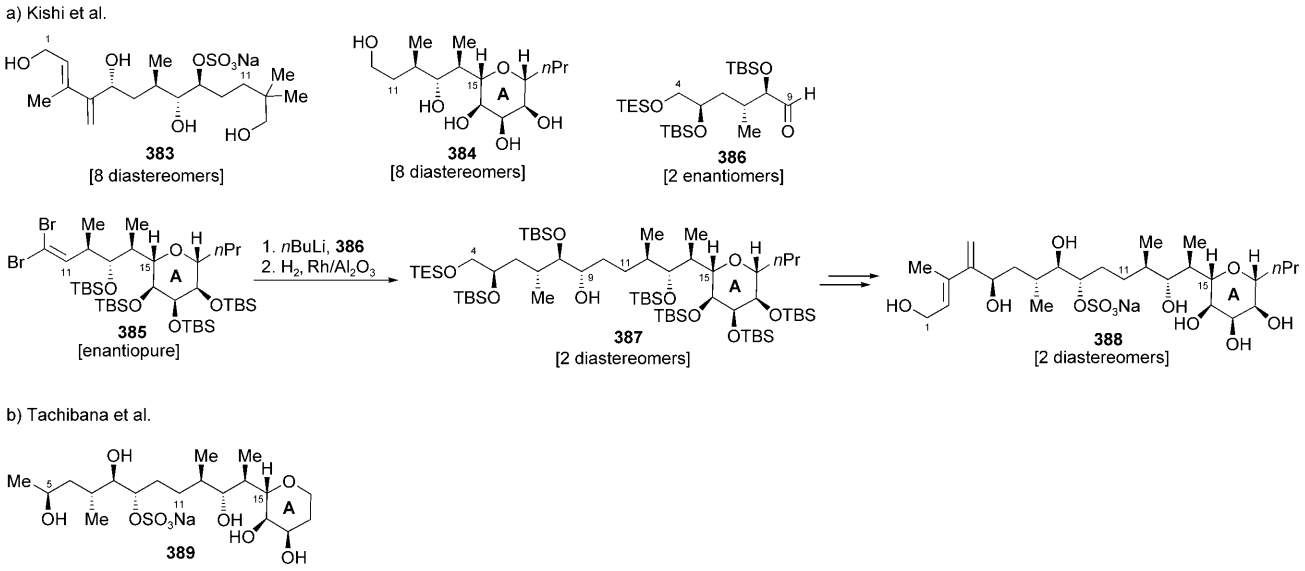
Although the configuration of the VW (C99 and C100) junction of maitotoxin was assigned by the Yasumoto research group in their original reports,[118,119] there remained a small cloud of uncertainty with regards to the relative configuration between the UV and WX domains of the molecule because of the presence of the methyl group on the W ring that prevented unambiguous assignment on the basis of 2D NMR spectroscopy. To confirm Yasumoto's assignment, Kishi and co-workers synthesized the two possible C99–C100 diastereomers (Scheme 68).[124] Thus, starting with enantiopure WX fragment **406** and racemic U fragment **407**, they constructed two diastereomers of **408**, and then forged ring V through a reductive cyclization of a hydroxy ketone to afford their two targeted diastereomers of **409**. Upon separation of the two diastereomers, and comparison of their ^{13}C chemical shifts with those of the corresponding domain of maitotoxin, they concluded that, indeed, the originally assigned stereochemistry by Yasumoto and co-workers[119] around the VW rings was most likely correct.

The relative configuration of the C134–C142 domain of maitotoxin was the last to be determined. Kishi and co-workers found, through chemical synthesis of the 16 possible diastereomers of the corresponding maitotoxin fragment **410** (Scheme 69) and NMR spectroscopic analysis, that the ^{13}C NMR spectral data of diastereomer **410** of the F′E′ fragment exhibited the closest agreement with those reported for the corresponding region of the natural product. It was with this final piece of information that the Kishi research group was able to solve in 1996 the puzzle of the complete relative configuration of maitotoxin.[120] It would be left up to Tachibana and co-workers, however, to determine the absolute configuration of maitotoxin. Thus, about the same time as Kishi's disclosure of the relative configuration of maitotoxin, the Tachibana research group reported the synthesis of the four enantiomers of the C136–C142 fragment of maitotoxin. Comparison of the fragments by gas chromatography on a chiral stationary phase with the same maitotoxin-derived fragment (Scheme 64) led to their assignment of the absolute configuration of this domain of the molecule as **382** (Scheme 69), and, hence, of maitotoxin itself (**13**, Scheme 64).[125]

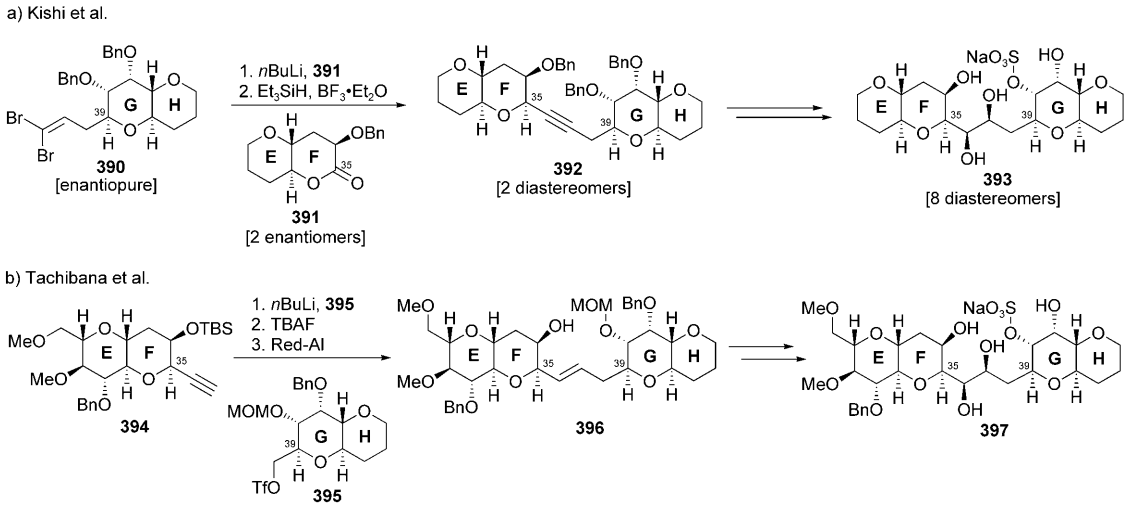
Recently, the configuration of maitotoxin came under scrutiny, when Gallimore and Spencer questioned the JK ring junction (C51 and C52).[34] Their insightful and seemingly logical objection was based on Nakanishi's proposal[33] for the biosynthesis of the ladderlike polyether marine natural products. Thus, and according to Nakanishi,[33] and later Gallimore and Spencer,[34] the regularity of maitotoxin (**13**) could be explained by it being derived from a polyepoxide intermediate (**411**, Scheme 70). The problem with maitotoxin, however, in the eyes of Gallimore and Spencer is that the JK ring junction (C51–C52) would have to be derived from an epoxide unit with the opposite configuration to all the other epoxides of the polyepoxide precursor **411**. This anomaly led to one of two conclusions: either there were errors in the



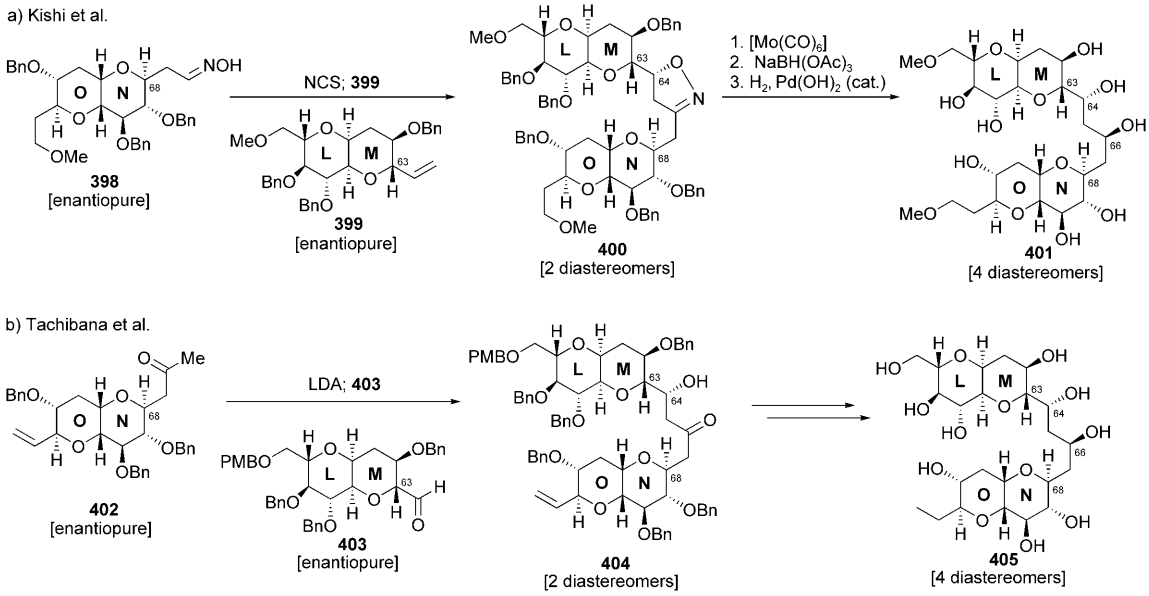
Scheme 64. Degradation of maitotoxin (**13**) (Yasumoto and co-workers, 1992).[118]



Scheme 65. Determination of the relative configuration of the C1–C15 domain of maitotoxin (a: Kishi and co-workers, 1996;[120] b: Tachibana and co-workers, 1996[121]).



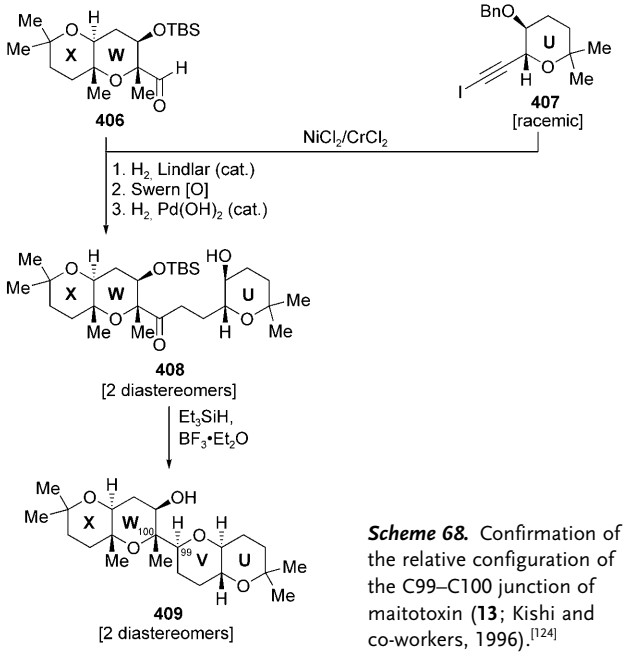
Scheme 66. Determination of the relative configuration of the C35–C39 domain of maitotoxin (**13**; a: Kishi and co-workers, 1996;[120] b: Tachibana and co-workers, 1995[122]).



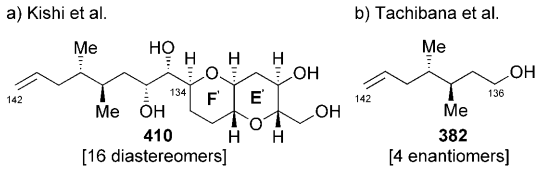
Scheme 67. Determination of the relative configuration of the C63–C68 domain of maitotoxin (**13**; a: Kishi and co-workers, 1996;[120] b: Tachibana and co-workers, 1995[123]).

structural assignment of maitotoxin, a possibility because of the difficulties encountered in assigning all the signals within this region of the molecule as a result of considerable overlap of signals in its NMR spectra,[118,119] or the proposed biosynthesis needed to be revised, at least for that region of the maitotoxin molecule.

This situation prompted the Nicolaou research group to determine whether revisions needed to be made to the structure of maitotoxin. They first turned to computational chemistry that allowed them to calculate the ^{13}C NMR chemical shifts for three GHIJKLM ring domains (Figure 8):[126] Structure **412**, which possesses the originally proposed configuration at the JK ring junction (C51–C52), structure **413**, where the configuration at C51–C52 was inverted to agree with the Nakanishi as well as Gallimore and Spencer biosynthetic hypothesis, and structure **414** where the C50–C55 stereocenters were inverted to agree with both the biosynthetic hypothesis and the reported NOE interactions of that region of maitotoxin (**13**). The structure **412** with the originally proposed stereochemistry had the strongest agreement with the reported spectra for maitotoxin, with a maximum and an average difference ($\Delta\delta$) of 2.1 and 0.78 ppm, respectively, for the C48–C55 region. Structures **413** and **414** differed more from maitotoxin, with maximum differences ($\Delta\delta$) of 7.5 and 5.0 ppm, and average differences ($\Delta\delta$) of 3.03 and 2.98 ppm, respectively. Although this data lends support for the originally proposed structure of maitotoxin (**13**), further experimental evidence was deemed necessary.

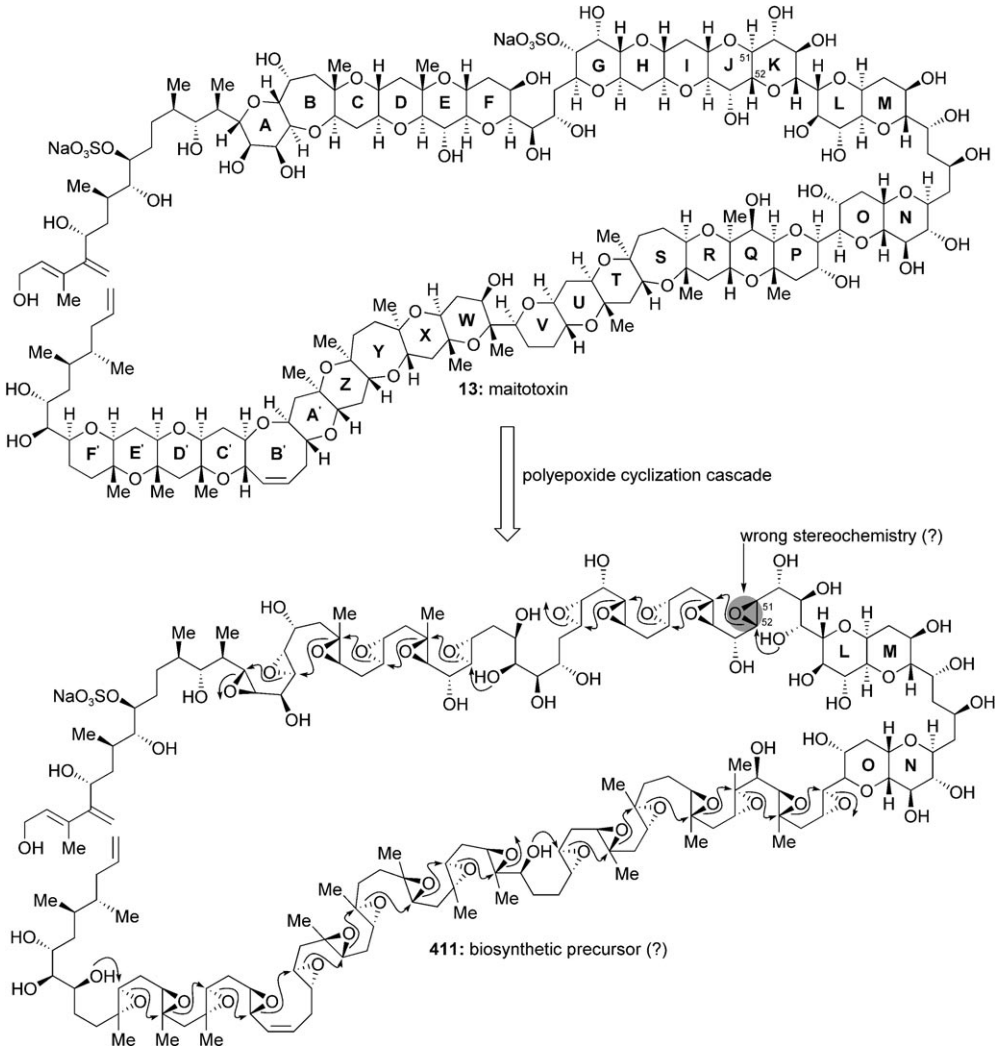


Scheme 68. Confirmation of the relative configuration of the C99–C100 junction of maitotoxin (**13**; Kishi and co-workers, 1996).[124]



Scheme 69. Determination of the relative configuration of the C134–C142 domain (a: Kishi and co-workers, 1996)[120] and of the absolute configuration of maitotoxin (**13**; b: Tachibana and co-workers, 1996).[125]

In search of such evidence, the Nicolaou research group set out to synthesize the GHIJK domain **444** (Scheme 76) and GHIJKLMNO domain **459** (Scheme 78) of maitotoxin to compare their ^{13}C NMR spectral data with those of the corresponding region of maitotoxin.[127] They also considered this challenge to be yet another opportunity to develop new synthetic methods for the construction of cyclic ethers. Towards this end, two new general methods were developed for the construction of substituted pyrans of the type found in



Scheme 70. The postulated hypothesis from Nakanishi as well as Gallimore and Spencer for the biosynthesis of maitotoxin (**13**) that brings into question the JK ring junction (C51 and C52).

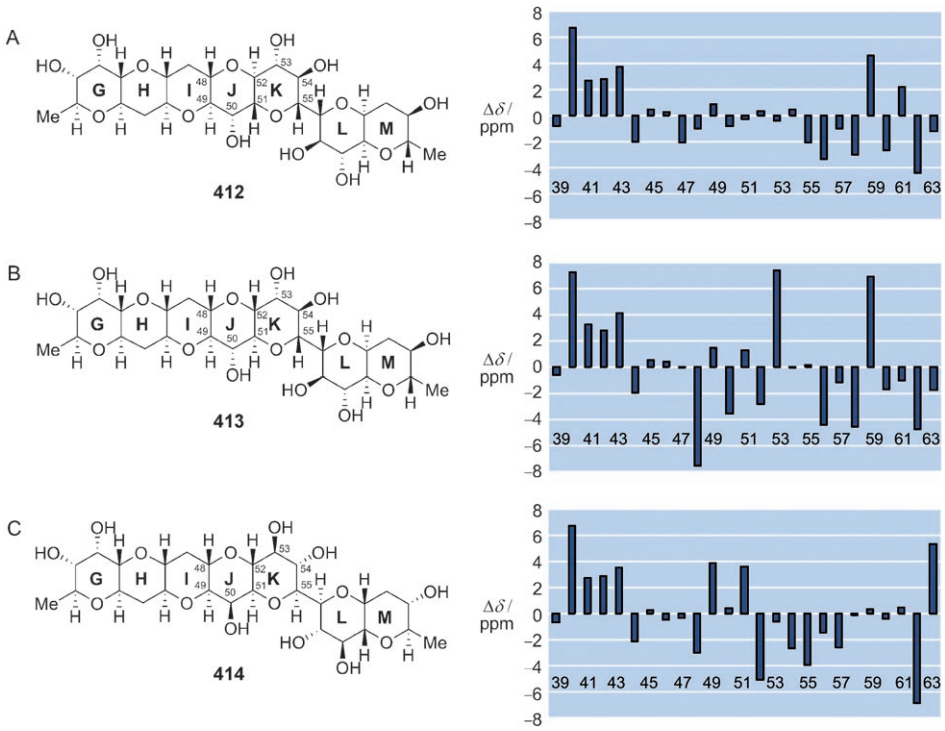
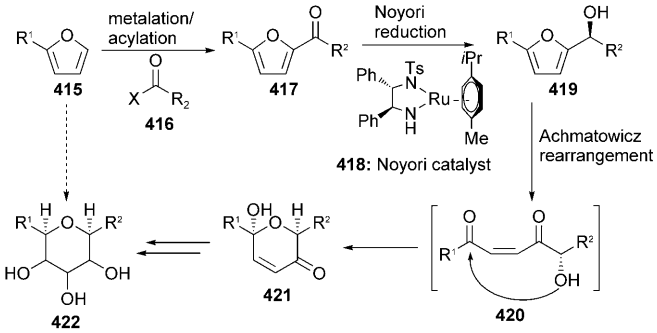


Figure 8. Differences in calculated and experimental ^{13}C chemical shifts ($\Delta\delta$, in ppm) for compounds **412**, **413**, and **414** (Nicolaou et al., 2007).[126]

the maitotoxin structure. The first one was specifically developed to take advantage of the acyl furans **417** readily accessible from substituted furans (**415**) through metalation followed by acylation with **416** (Scheme 71). A Noyori

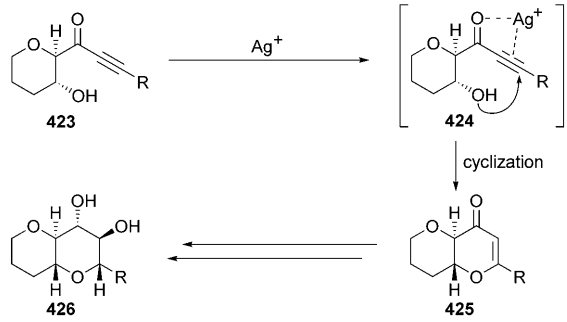


Scheme 71. Asymmetric synthesis of substituted pyrans from furans through a Noyori reduction and Achmatowicz rearrangement (Nicolaou et al., 2007).[127] X = leaving group.

reduction led to the enantioselective intermediate **419**,[128] which then underwent an Achmatowicz rearrangement[129] to give **421** (via **420**). Elaboration of the obtained lactol enones **421** afforded the highly desirable substituted pyrans **422** (Scheme 71).

The second method for the construction of substituted pyrans developed by the Nicolaou[127] and Forsyth research groups[130] involved direct cyclization of hydroxy ynones **423** facilitated by AgOTf,[130] a reagent thought to activate the ynone functionality through binding simultaneously to its acetylenic and carbonyl moieties (**424**, Scheme 72). The resulting cyclic enones **425** can then be manipulated to an array of products (such as **426**).

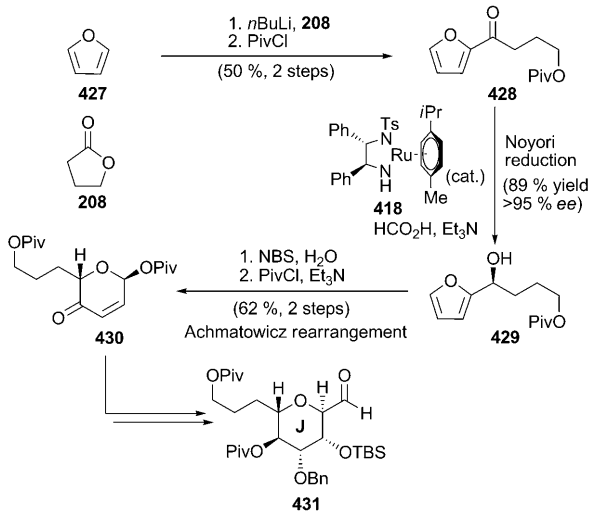
Application of these two methods to the synthesis of the desired GHIJK ring system **444** of maitotoxin resulted in a convergent and highly efficient route to this molecule as summarized in Schemes 73–76.[127a] Thus, metalation of furan (**427**), followed by acylation with γ-butyrolactone (**208**) and pivaloate formation furnished furanyl ketone **428**, which was asymmetrically reduced with Noyori catalyst (**418**) to afford alcohol **429** in 89% yield and in greater than 95% *ee* (Scheme 73). An Achmatowicz rearrangement of the latter induced by NBS, followed by pivaloate formation, led to enone **430**, which was elabo-



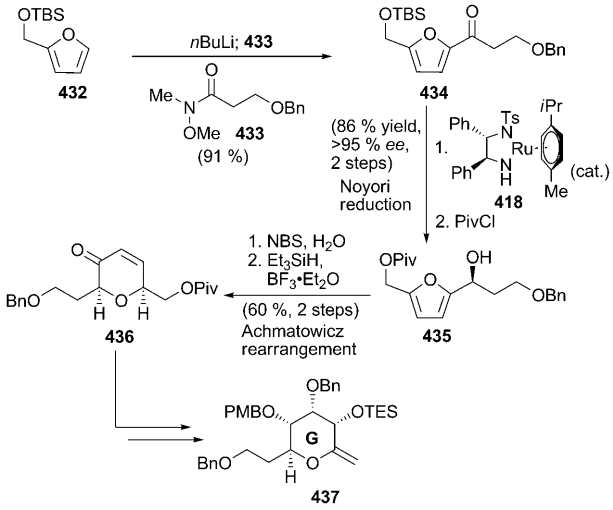
Scheme 72. Silver-promoted cyclization of hydroxy ynones for the formation of fused cyclic ethers (Nicolaou et al., 2007).[127]

rated stereoselectively to the required maitotoxin J fragment **431** through reduction of the carbonyl moiety and dihydroxylation of the double bond.

Scheme 74 summarizes the construction of the maitotoxin G fragment **437** starting with furan derivative **432** and Weinreb amide **433**, and featuring the Noyori reduction and Achmatowicz rearrangement method (**434**→**435**→**436**). Reduction of the carbonyl group, epoxidation of the enone, epoxide opening, and elimination furnish the exocyclic olefin **437**. Scheme 75 highlights the construction of the maitotoxin IJK vinyl triflate fragment **441** by a sequence that involves initial addition of acetylide **438** to the J ring aldehyde **431**, followed by elaboration to hydroxy enone **439**. The latter underwent a smooth AgOTf-induced cyclization to the JK ring fragment. Functionalization of enone **440** to the final IJK ring domain **441** proceeded both efficiently and stereoselectively.

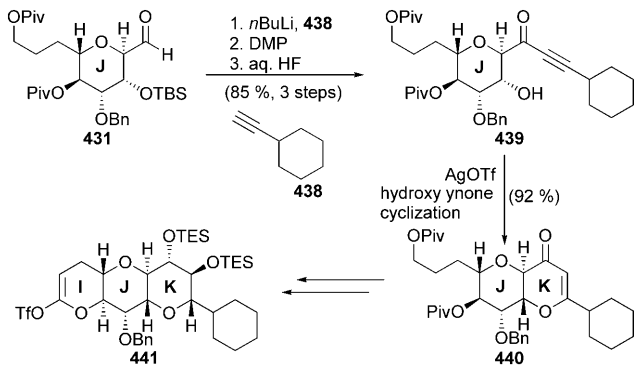


Scheme 73. Construction of the J-ring fragment **431** of maitotoxin through a Noyori reduction and Achmatowicz rearrangement (Nicolaou et al., 2007).[127a]



Scheme 74. Construction of the G-ring fragment **437** of maitotoxin through a Noyori reduction and Achmatowicz rearrangement (Nicolaou et al., 2007).[127a]

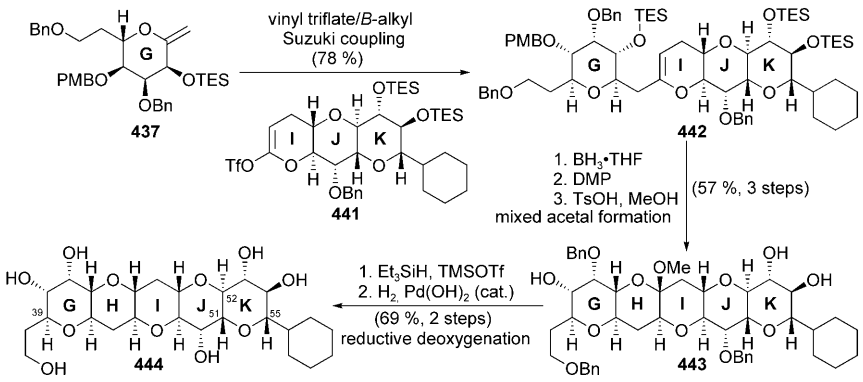
The final stages of the synthesis of the maitotoxin GHIJK ring system are summarized in Scheme 76. Thus, a Suzuki coupling between IJK vinyl triflate **441** and the alkyl boron compound derived from G-ring fragment **437** and 9-BBN yielded GIJK fragment **442**, whose further elaboration featured hydroboration, oxidation, and ring closure through formation of a mixed acetal to cast the entire row of rings in **443**. Removal of the methoxy group through reductive deoxygenation and global deprotection afforded the desired compound **444** (Scheme 76).



Scheme 75. Construction of the IJK fragment **441** of maitotoxin through a silver-promoted cyclization of hydroxy ynones (Nicolaou et al., 2007).[127a]

Comparison of the ^{13}C chemical shifts exhibited by the synthetic fragment **444** to those reported for the same domain of maitotoxin revealed striking agreement (maximum difference $(\Delta\delta) = 0.6$ ppm, average difference $(\Delta\delta) = 0.1$ ppm for C42–C53; Figure 9). The rather large differences for the two sets of ^{13}C chemical shifts corresponding to the two edges of the molecule are clearly due to the drastically different functional groups present at these ends (see rings G and L of maitotoxin; Figure 9). Nevertheless, while these experimental data provide support for the originally proposed structure of maitotoxin, comparison involving a larger synthetic fragment corresponding to a larger domain of the natural product would have provided an even more convincing case for its structural assignment. To this end, the Nicolaou research group targeted a fragment corresponding to the GHIJKLMNO domain of maitotoxin (**459**, Scheme 78).

Scheme 77 summarizes the furan-based strategy to the bicyclic system **449**, which served as a common intermediate to construct the additional fragments required for the synthesis of the targeted GHIJKLMNO domain of maitotoxin. Thus, coupling of furan (**427**) with amide **445** through metalation led to acyl furan **446**, whose Noyori asymmetric reduction furnished hydroxy furan **447** (98% yield and over 95% *ee*). An Achmatowicz rearrangement, followed by pivaloation of the resulting lactol, led to enone **448**, which was efficiently and stereoselectively converted into bicycle **449**. From **449**, the route diverged, delivering, after a few



Scheme 76. Synthesis of the GHIJK fragment **444** of maitotoxin (Nicolaou et al., 2007).[127a]

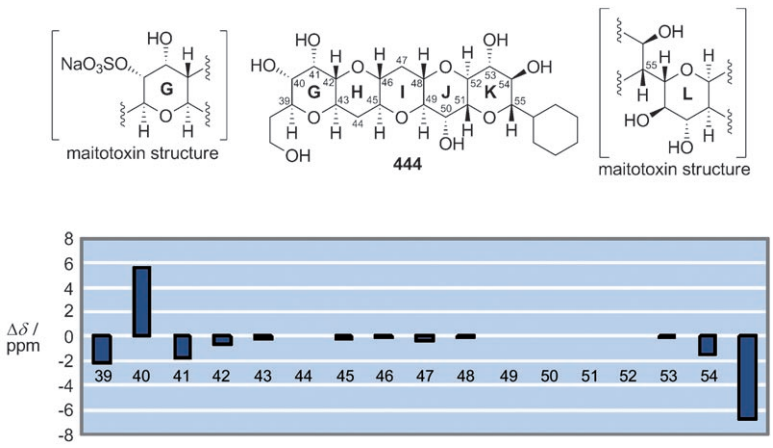
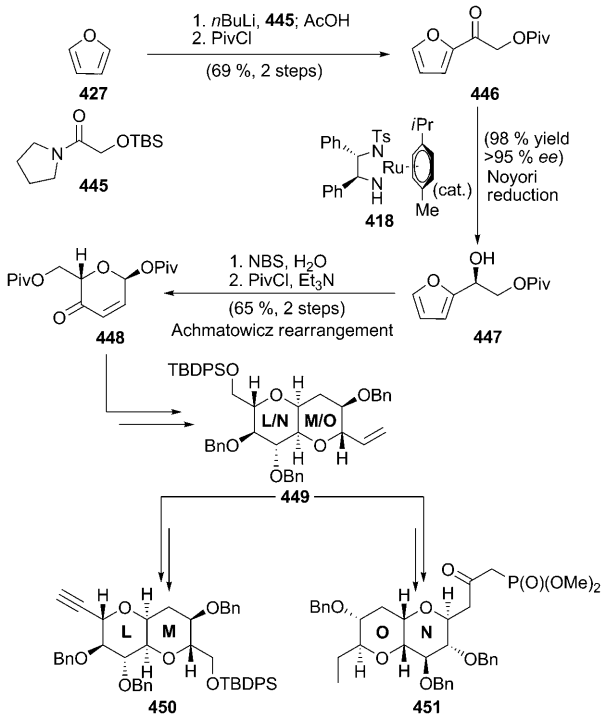


Figure 9. Comparison of the ^{13}C chemical shifts of the GHIJK domain **444** with those reported for the same domain of maitotoxin (Nicolaou et al., 2007).[127a]



Scheme 77. Synthesis of the LM and NO fragments **450** and **451** of maitotoxin through a Noyori reduction and Achmatowicz rearrangement (Nicolaou et al., 2007).[127b]

steps, the requisite LM acetylenic fragment **450** and the NO ketophosphonate fragment **451**.

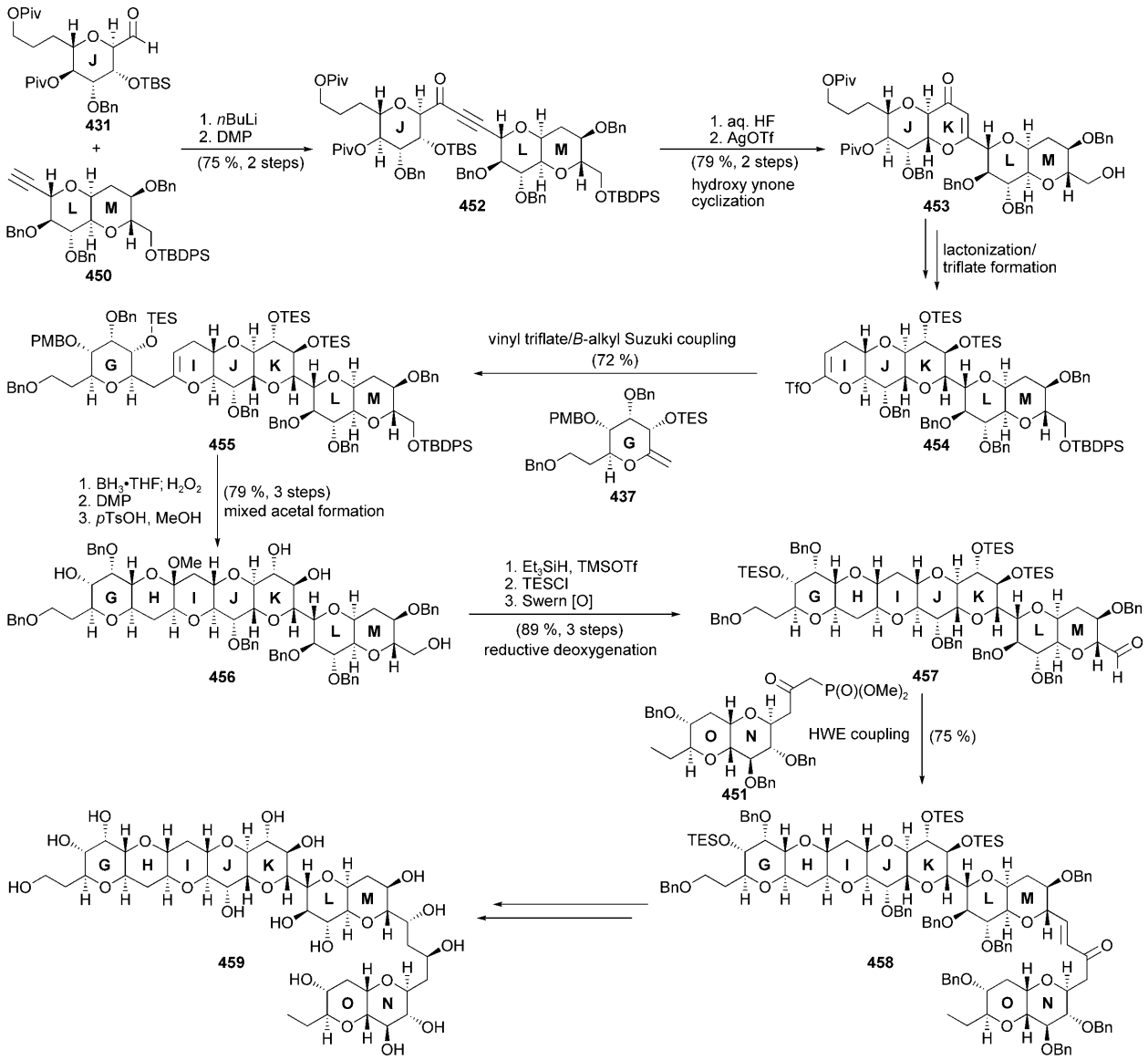
Scheme 78 summarizes the assembly of intermediates **431**, **437**, **450**, and **451**, and the final stages of the synthesis of the maitotoxin GHIJKLMNO fragment **459**.[127b] Thus, coupling of J-ring aldehyde **431** with the acetylide anion derived from LM intermediate **450** furnished, after oxidation, ynone **452**. Desilylation of **452** led to the corresponding hydroxy ynone, which underwent the expected, silver-promoted cyclization to afford the JKLM enone **453**. Elaboration of this tetracyclic intermediate to the pentacyclic IJKLM vinyl triflate **454** through lactonization and triflate formation, followed by Suzuki coupling with the alkyl boron species derived from the G-ring fragment **437** and 9-BBN, furnished the GIJKLM hexacyclic enol ether **455**, from which only ring H was missing before the entire ladder of the desired fragment was complete. This final ring was forged through a sequence involving hydroboration/oxidation and acid-induced cyclization with formation of a mixed acetal which was accompanied by unmasking of all the hydroxy groups, except those protected as benzyl ethers, to afford mixed acetal **456**. The superfluous methoxy group was removed from the mixed acetal through an Et_3SiH-induced reductive deoxygenation, the resulting tetraol was persilylated with TESCl, and the product was subjected to Swern oxidation to furnish aldehyde **457**. Coupling of this aldehyde with ketophosphonate **451** through a Horner–Wadsworth–Emmons reaction led to enone **458**, whose stereoselective elaboration through epoxidation of the double bond and further elaboration led to the targeted GHIJKLMNO domain **459**.

Figure 10 shows a comparison between the differences in the observed ^{13}C chemical shifts between the respective carbon atoms of the synthetic GHIJKLMNO fragment **459** and of natural maitotoxin as reported by Yasumoto and coworkers.[118,119] Indeed, the matching of the two sets of δ values for the C42–C73 domain of the two molecules (maximum difference $\Delta\delta = 0.4$ ppm; average difference $\Delta\delta =$ 0.09 ppm) is remarkable (and closer than with the GHIJK fragment, see above), and provides a compelling case for the correctness of the originally assigned structure of maitotoxin (again the ends of the two molecules exhibit, as expected, relatively large differences in the ^{13}C chemical shift values because of the different functional groups associated with them; see ring G and the OP regions, Figure 10). To be sure, and despite these striking results, a scintilla of doubt regarding the absolute structure of maitotoxin may still remain in the minds of some. This residual doubt may be cleared only through X-ray crystallography or chemical synthesis.

With the originally proposed GHIJKLMNO domain of maitotoxin (**13**) most likely correct, there is still the problem with the proposed biosynthetic hypothesis in regard to the JK ring junction, especially if one considers the consistency observed with all the other fused polyether natural products known to date. Although a possible explanation of this seemingly anomalous occurrence may lie in the prefabrication of ring K prior to the polyepoxide cascade invoked by the biosynthetic hypothesis, a full demystification of this puzzle may require further insights into the natural biosynthetic pathway and/or further chemical synthesis efforts.

12. Summary and Outlook

The isolation and structural elucidation of new classes of natural products often provide stimulus for synthetic organic chemists to discover and invent new methods to address the synthetic challenges posed by them. Such was the case with



Scheme 78. Synthesis of the GHIJKLMNO domain **459** of maitotoxin (Nicolaou et al., 2007).[127b]

the discovery of the first marine polyether brevetoxin B. The unprecedented molecular architecture of this molecule, coupled with its powerful and catastrophic toxicity, and fascinating voltage-sensitive ion-channel mechanism of action, has seeded the widespread and still growing interest in the ladderlike polyether marine natural products. To be sure, however, it was the daunting nature of brevetoxin's molecular architecture and the initial inability of synthetic chemists to respond to the challenge of this molecule that served as the continuous impetus for the intense, and still ongoing, research in this area of chemical synthesis. The harvest is already rich in terms of discoveries and inventions in chemistry, ranging from novel methods to forge cyclic ethers and convergent strategies to construct complex molecules, to admirable accomplishments in total synthesis. Included among the new synthetic methods are ionic-type reactions, radical processes, palladium-catalyzed cross-coupling reactions, metathesis reactions, asymmetric processes, and biomimetic-type cascades. Although a number of these unique and magnificent structures have been conquered by total synthesis (hemibrevetoxin, brevetoxin B, brevetoxin A, ciguatoxin 3C, gambierol, gymnocin A, and brevenal), others remain defiant. No doubt, however, and with the pace of developments in new synthetic methods, more structures will yield to total synthesis and the will of its practitioners. Most importantly, the future is bound to bring higher efficiencies and shorter routes to these valuable synthetic targets, and related compounds who are destined to be discovered in the future. The history of the field as chronologically laid out in this Review speaks volumes of the accomplishments achieved and bodes well for its future successes. We dare predict that the saga of the marine polyether biotoxins will continue for some time to come, both in terms of their discovery from nature and their chemical synthesis in the laboratory, devel-

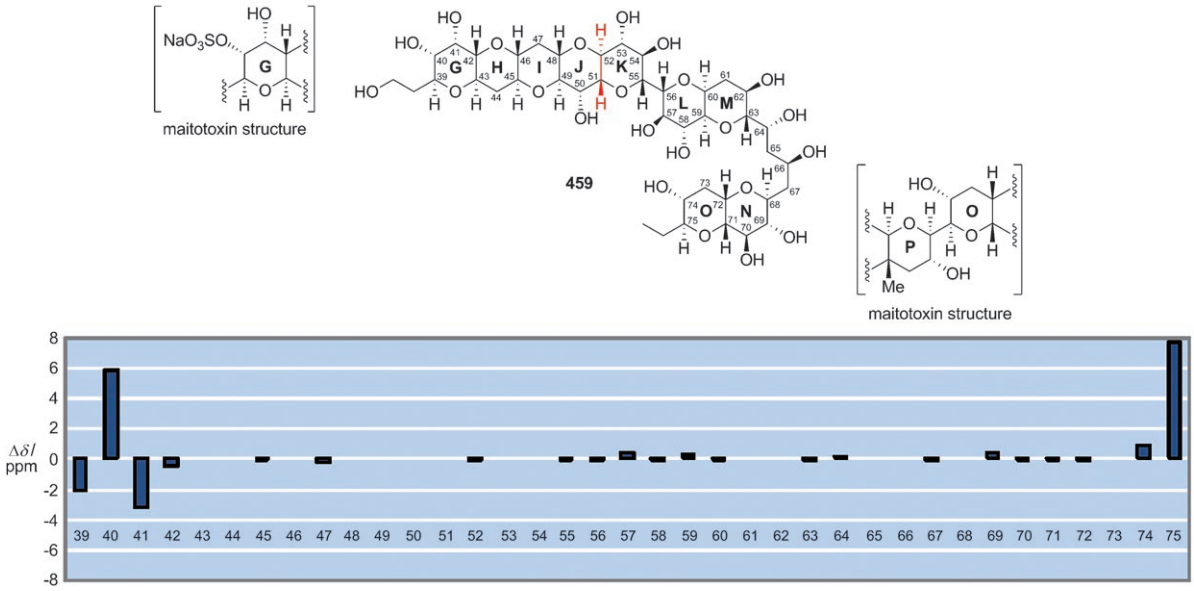


Figure 10. Comparison of the ^{13}C chemical shifts of the maitotoxin GHIJKLMNO domain **459** with those reported for the same domain of maitotoxin (Nicolaou et al., 2007).[127b]; red: questioned JK ring junction.

opments that should also spark further investigations into their fascinating world of chemical biology.

Abbreviations

AIBN	2,2′-azobis(2-methylpropionitrile)
AM3	amphidinol 3
ASP	amnesic shellfish poisoning
AZP	azaspiracid poisoning
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Bz	benzoyl
CFP	ciguatera fish poisoning
Cp	cyclopentadienyl
*m*CPBA	*meta*-chloroperbenzoic acid
CSA	camphor sulfonic acid
CTX3C	ciguatoxin 3C
DABCO	1,4-diazabicyclo[2.2.2]octane
DMP	Dess–Martin periodinane
DSP	diarrhetic shellfish poisoning
HFIP	hexafluoroisopropanol
HWE	Horner–Wadsworth–Emmons
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
MOM	methoxymethyl
Ms	methanesulfonyl
M.S.	molecular sieves
NAP	naphthyl
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NOE	nuclear Overhauser effect
NSP	neurotoxic shellfish poisoning
Piv	trimethylacetyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
PSP	paralytic shellfish poisoning
Py	Pyridine
RCM	ring-closing metathesis
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TCB	2,4,6-trichlorobenzyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
Th	2-thienyl
TIPS	triisopropylsilyl
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TMSE	2-(trimethylsilyl)ethyl
Tol	*para*-tolyl
Tr	trityl
Ts	*para*-toluenesulfonyl

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