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The Continuing Saga of the Marine Polyether Biotoxins

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Lead-in

Brevetoxin B emerged from the sea and into the laboratories of Nakanishi and Clardy who, in 1981, reported its magnificent and unprecedented structure. With its ladder-like fused polyether molecular architecture, potent toxicity, and fascinating voltage-sensitive sodium channel-based mechanism of action, it immediately captured the imagination of chemists around the world. Their synthetic escapades resulted in numerous new synthetic methods and strategies for the construction of cyclic ethers, and culminated in several impressive total syntheses of this imposing molecule and some of its equally challenging siblings that followed. Indeed, many more brevetoxin-type marine polyethers have been reported since 1981 with maitotoxin being not only the most complex and most toxic of the class, but also the largest non-polymeric natural product known to date. In this article, we begin with a brief history of these biotoxins and the phenomena that led to their isolation and highlight their biological properties and mechanism of action. We then review the chemical synthesis endeavors so far published in this long running saga, placing particular emphasis on the new synthetic methods and technologies discovered, developed and applied to their total syntheses over the last few decades. Finally, we conclude with a discussion of the, as yet unfinished, story of maitotoxin, and project into the future of this fascinating area of research.

Keywords

biotoxins; maitotoxin; natural product; polyether; synthesis

1. Introduction

Marine organisms have proven to be rich reservoirs of natural products notable for both their enchanting molecular architectures and potent toxicities. These compounds, representative samplings of which are shown in Figure 1 – Figure 3, have been implicated as causative agents in many seafood-related poisonings, including tetrodotoxin poisoning [tetrodotoxin, (1, Figure 1)], diarrhetic shellfish poisoning [DSP: okadaic acid (2, Figure 1)], azaspiracid poisoning [AZP: azaspiracid-1 (3, Figure 1)], amnesic shellfish poisoning [ASP: domoic acid (4, Figure 1)], paralytic shellfish poisoning [PSP: saxitoxin (5, Figure 1)], neurotoxic shellfish poisoning [NSP: brevetoxins A and B (7 and 6, Figure 2)], and ciguatera fish poisoning [CFP: ciguatoxin 3C (9, Figure 2), gambierol (10, Figure 2) and maitotoxin (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

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

biologists towards the isolation, characterization, biological evaluation and chemical synthesis of these legendary molecules.

A particularly diverse and celebrated set of these marine biotoxins are the ladder-like polycyclic ethers, displayed in Figure 2 and Figure 3. Since the disclosure of the first member of this family, brevetoxin B (6) in 1981,[2] scientists have discovered numerous, more or less complex, 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 maitotoxin (13, Figure 3), the largest non-biopolymer substance known to date. These polyether biotoxins 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 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 sources can lead to additional congeners of the natural products.[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 that greatly facilitated their investigations.[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. Their presence along this food chain provided the persistent interest to isolate and characterize them in order to lay the foundation to combat their production and poisonous effects. The brevetoxin-producing dinoflagellate *Karenia brevis* (formerly known as *Gymnodynium breve*) residing within the oceans is responsible for the toxicity of “red tide” algal blooms which frequently occur around the world causing massive fish kills and horrific marine mammal deaths.[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 consuming the seafood. Most notably, the cause of the ominous ciguatera fish poisoning (CFP) has been attributed to the ciguatoxins (e.g. **9**), gambierol (**10**), and maitotoxin (**13**), all produced by dinoflagellates. CFP is characterized by temperature sensitivity, diarrhea, vomiting, muscle pain and itching, symptoms that, in extreme cases, can persist for years.[6] The majority of the polyether marine natural products are neurotoxins, exerting 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 their biological 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 be carried short and long distances by virtue of their own ability to swim, by other marine organisms and ocean currents, or by shipping practices and hurricanes. When the concentration of *Karenia brevis* in the water (normally about 1000 cells per liter of water) reaches 5000 or more, the alarming signs of 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, ranging from 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 *Karenia brevis* growth, to nutrient pollution from farms, factories and cities connected to the ocean through canals and rivers. Be that as it may, 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 contributing to advances ranging from chemical synthesis, to chemical biology and from neurobiology to drug discovery.[11]

The repetitive structural motifs contained within the stunning structures of the polyether marine natural products do little to mask the awesome complexity embedded within their molecular architectures. Indeed, and as such, these molecules presented daunting synthetic problems and unprecedented challenges for synthetic organic chemists. Despite this fact, a number of research groups have taken on the challenge, completing total syntheses of several of these molecules (for their structures, see Figure 2). Due to the unprecedented structures of these targets, these synthetic endeavors necessitated and led to the discovery and invention of new synthetic technologies. Many of these novel bond-forming reactions have found extensive applications in the construction of the ladder-like polyether marine natural products and beyond. In this review, and following a brief discussion of the biological properties of these ladder-like polyether marine natural products, we will summarize these synthetic technologies and highlight their applications to the total synthesis of these biotoxins. We will conclude with recent advances and ongoing research directed toward higher efficiency synthetic technologies and more complex structures within this growing and fascinating class of natural products.

2. Biological Properties and Mechanism of Action

Although most of the ladder-like marine biotoxins exhibit similar activities and mechanisms of action, some of them show distinct 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] Today, the biological activities and precise mode of action of maitotoxin is an active field of investigation despite the fact that its biological target within the cell membrane remains elusive. Maitotoxin was shown to cause calcium ion influx into a variety of cells,[13] including synaptosomes[14] and erythrocyte ghosts[15] (empty vesicles made up by cell membranes), but not artificial phospholipid vesicles,[16] suggesting 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] 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 molecule's lipophilic domain (rings R through F′, C_{82}–C_{142}, note that only 3 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 through Q, C_1–C_{81}, note that this domain includes 24 OH groups and 2 sulfate groups) remains outside the cell membrane as shown in 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 both inhibit maitotoxin-induced calcium ion influx into rat glioma C6 cells,[15] suggesting that maitotoxin may exhibit recognition of its receptor through binding at multiple sites through its different domains.[24]

The understanding of the precise interaction of the ladder-like polyether natural products with cell membranes has been recognized in general as being both important and challenging. 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) in that respect. They differ from them, however, in that while the polyethers bind to and open membrane protein ion channels, the polyenepolyols exert their activity through binding to membrane lipids.

Despite the ever-increasing number of the ladder-like polyethers (more than 50 have been discovered so far), studies on their mode of action are lagging behind due to their scarcity and the complexity of their biological interactions. Their activities range broadly from ichthyotoxicity [e.g. brevetoxins A (**7**) and B (**6**, Figure 2), ciguatoxin 3C (**9**, Figure 2) and the glycoside containing prymnesin-1 (**16**) and prymnesin-2 (**17**, Figure 6)],[26] to cytotoxicity (e.g. gymnocin A (**12**, Figure 2)][9] and antifungal activity [e.g. gambieric acid A (**18**, Figure 6)],[8] whose potency as an antifungal agent exceeds, impressively, that of amphotericin B by a factor of two thousand.

The biological target of brevetoxins B (**6**) and A (**7**) and of ciguatoxins 1B and 3C (**9**) has been identified and, interestingly, is common to all of them.[27] These molecules bind with high affinities to the same binding site of a voltage-sensitive sodium channel protein. It is generally thought that the ladder-like polyethers bind to their receptors through weak interactions involving primarily hydrogen bonding [N–H---O and C_α–H---O bonds][28] as shown by the hypothetical model depicted in Figure 7 for brevetoxin B (**6**). Thus, when the polyether 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 as shown, leading to manifestation of the molecule's biological action. Interestingly, the 5.40 Å pitch of the α-helix matches quite well with the average distance ($d_{O–O}$) of 5.15 Å (X-ray data)[29] between the same-side neighboring ether oxygen atoms of the brevetoxin B ladder.

Yessotoxin (**15**, Figure 5) a ladder-like polyether biotoxin isolated from dinoflagellate *Protoceratium reticulatum*[30] was found to induce apoptosis through a mitochondrial signal transduction pathway.[31] Their studies are exemplary in that they provide insights into the mode of action of this class of biomolecules. Thus, it was determined that 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, which was also exerted by brevetoxin B, is thought to be elicited by these molecules through specific binding to a lipophilic α-helix of the protein as demonstrated in Figure 7 for brevetoxin B. Significantly, polyethylene glycol did not induce dissociation of oligomeric aggregates of glycophorin A, underscoring the importance of the rigid ladder-like 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 7-, 8- or 9-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 H-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 due to their opposite pyran orientations which results in minimizing their net polarity. Hence their low water solubility as opposed to those of the more water soluble naturally occurring biotoxins in which this regularity-based cancellation of ring dipole moments is disturbed by the 7-, 8- or 9-membered rings present within their structures. This recognition may be useful in designing artificial ladder-like polyethers as models of the natural biotoxins and as biological tools to be used in chemical biology studies within this fascinating, and yet infant, area of research.

3. Synthetic Technologies

The discovery and disclosure of the structure of brevetoxin B (**6**, Scheme 1) served as the impetus for the search of new synthetic technologies for the construction of its unique structural motifs.[32] Thus, 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* as shown in Scheme 1. In fact, in a grant application to NIH in 1982 (GM31398-01, received February 24, 1982)[35] we had proposed such a cascade (**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 were running against the face of the Baldwin rules of ring closure,[36] and 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 ladder-like structures of brevetoxin B (**6**) and other molecules like it. Later on, cascade reactions to construct more than one ring were sought and successfully developed. These synthetic technologies will be briefly reviewed below in approximately the order in which they were reported.

In 1985, the Nicolaou group reported the first regio- and stereoselective cyclization for the synthesis of cyclic ethers involving hydroxy epoxide openings and 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 as shown in Scheme 2. Thus, under acidic conditions, hydroxy epoxide **21** underwent exclusive 6-*endo* ring closure to afford bis-pyran 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 arising from *endo* attack (transition state **22**, Scheme 2), an effect not present during the hypothetical *exo* attack (transition state **24**, Scheme 2). This stereoselective method for cyclic ether formation has the additional advantages of easy access to enantiomerically enriched substrates[38] and the synthetically fertile nature of the products. As a consequence, this synthetic technology found extensive use in the total synthesis of several of the polyether marine natural products as will become evident from the following section.

A method particularly suitable for cyclic polyether construction that proceeds through the intermediacy of cyclic mixed *O,S*-acetals was developed by the Nicolaou group in the 1980's.[39] The initially reported method in 1986[39a] involved reaction of a hydroxy dithioketal (e.g. **26**, Scheme 3) with NCS in the presence of $AgNO_3$, SiO_2, 3 Å MS and 2,6-lutidine to afford, in excellent yield, the mixed *O,S*-acetal (e.g. **28**), presumably through thionium species **27**. The same mixed cyclic acetal could, in principle, be generated directly from the hydroxy ketone (e.g. **29**) by treatment with EtSH in the presence of $Zn(OTf)_2$ as demonstrated with other examples.[40] Processing of product **28** with a reducing agent (e.g. Ph_3SnH) under radical conditions (e.g. AIBN cat.) led stereoselectively and in high yield, to oxocene **30**. On the other hand, *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 carrying H or Me substitutents adjacent to the oxygen atom as demonstrated in Scheme 3.

The Nicolaou group then turned their attention to the idea of employing lactones to form cyclic ethers, a concept of considerable merit given the abundance of such structural motifs both in nature and the laboratory. This reasoning led to a series of discoveries and practical methods ranging from the aesthetically pleasing bridging of macrocycles to bicycles to the practical vinyl phosphate or triflate/stannane Stille or *B*-alkyl Suzuki couplings as we shall discuss below.

The Nicolaou group recognized early in the 1980's the potential of medium-sized ring lactones as precursors to the same-sized ring ethers, a desirable circumstance due to the ease of formation of the former through the many efficient lactonization protocols available at the time.[41] As direct addition/alkylation of lactones would almost invariably result in ring rupture, the Nicolaou team turned to thionolactones as suitable precursurs due to 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, dithionolactone **32**, readily available from the corresponding dilactone 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-mixed *O,S*-acetal **34**. Reductive radical-based removal of the two methylthio groups then led to tetracyclic polyether **35** in high yield. Alternatively, photo-irradiation of dithionolactone **32** furnished the stable 1,2-dithiatane 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**) obtained through the sodium naphthalenide route discussed above.

In a modification of their photo-induced bicyclic ether formation from macrocyclic dithionolactones, the Nicolaou group exploited the use of open chain dithionolactones (obtained from the corresponding diesters by treatment with Lawesson's reagent) to form oxepane rings through photolytic irradiation as shown in Scheme 5 (**37** → **38** → **39** → **40**).[44]

In yet another twist of the use of thionolactones to form cyclic ethers, the Nicolaou group employed a nucleophilic addition/reduction sequence as demonstrated in Scheme 6 for an oxocane. Thus, thionolactone **41** (obtained from its lactone counterpart by treatment with Lawesson's reagent) was, sequentially and in one pot, reacted with MeLi and MeI to afford methylthio ether **43** through tetrahedral intermediate **42**. Subsequent reduction of **43** with Ph_3SnH under radical conditions (AIBN cat.) furnished bicycle **44** as a single isomer as shown in 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 championed and developed early on by the Nicolaou group.[46] As seen in Scheme 7, exposure of hydroxy α,β-unsaturated ester **45** to sodium hydride results in the stereoselective formation of bicycle **47** representing the J/K ring system of brevetoxin B. The stereoselectivity of this reaction as ensured by the chair-like transition state **46** made this hydroxy Michael addition method a favorite choice in total synthesis as will be demonstrated in the next section.

In 1989, the Nicolaou group reported a direct method for the formation of cyclic ethers from hydroxy ketones.[44] As demonstrated in Scheme 8, this method relied on a reductive cyclization of hydroxy ketones with Et_3SiH in the presence of a Lewis acid (e.g. TMSOTf), a combination of reagents that was inspired by the pioneering work of Olah.[47] While the stereoselectivity observed with oxepane systems is not perfect (e.g. **48** → **49**, Scheme 8a, ca. 4:1 ratio of diastereomers), the construction of pyran systems usually proceeds with complete stereocontrol as demonstrated later on by Sasaki et al. with the conversion of hydroxy ketone **52** to cyclic ether **53** (Scheme 8c).[48] The P. A. Evans group extended the method by employing silyl derivatives of hydroxy ketones (e.g. **50**) to prepare tetrahydropyrans (e.g. **51**) through the action of Et_3SiH in the presence of $BiBr_3$ catalyst (Scheme 8b).[49]

Two similar methods for the formation of polyether rings involving allyl tin cyclizations of aldehydes and acetals were reported by Y. Yamamoto and co-workers, in 1991[50] and 2001,[51] respectively. These methods are based on intramolecular diastereoselective allylations of allyl stannane aldehydes through Lewis acid activation as shown in Scheme 9. Thus, treatment

of aldehyde **54** with BF_3•Et_2O (Scheme 9a) led to intramolecular allylation through the presumed mechanism depicted by representation **55**, furnishing, stereoselectively, 6,7-bicycle **56** in near quantitative yield, while at the same time setting two new and contiguous stereogenic centers. This exquisite diastereoselectivity was attributed to the postulated transition state **55**, in which undesired diaxial interactions are minimized. The selectivity is unique to the formation of 7-membered rings as formation of 6-membered rings was demonstrated to suffer from diminished stereoselectivity due to competing chelation effects. Similarly, exposure of acetal **57** to $MgBr_2$•Et_2O presumably led to the formation of oxonium species **58**, which underwent intramolecular allylation to afford tricycle **59** obtained as a single stereoisomer (Scheme 9b).

While 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, for their stereochemical outcomes are often unpredictable.[52] Furthermore, such processes are also plagued with difficulties associated with intrinsic geometrical constraints within such systems. The venerable ring-closing metathesis[53] is one of the few methods that overcomes such difficulties and, is, therefore one of the most commonly employed reactions in forming medium ring compounds today.

Inspired by the pioneering work of Grubbs[54,55] [Scheme 10 (**60** → **62**; **63** → **64**) and Scheme 11 (**66** → **67** → **68**)] and recognizing the potential of the ring closing metathesis reaction in the polyether field, the Nicolaou group developed, and reported in 1996,[56] a new method for forging cyclic ethers that involves convergent coupling of growing fragments through esterification followed by ester methylenation and ring closing metathesis. Illustrated in Scheme 12 (**69** → **70** → **71** → **72** → **73** → **74**) in its general form, this method employed the Tebbe reagent[57] 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 such as those shown in Scheme 13.[56] Thus, tricyclic polyether **77** was synthesized from bicyclic acetate **75** through Tebbe methylenation/metathesis via presumed intermediate **76** (Scheme 13a) while its oxepane homologue **80** was constructed from bicyclic system **78** through the intermediacy of **79** by the same method (Scheme 13b). In an expedient and impressive way, this highly convergent method delivered the linear ladder-like polypyran system **84** (Scheme 13c). Thus, 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 of the latter led to ketone **83**, whose desilylation and ring closure through the hydroxy ketone cyclization method furnished hexacyclic polyether **84** (Scheme 13c).

Of particular interest were the stereoselective syntheses of the tricyclic systems **88** and **92** representing the JKL and VUW ring domains of maitotoxin (Scheme 14).[58] Thus, upon treatment with Tebbe reagent, bicyclic JK ester **85** led, through bis-olefin **86**, to tricyclic system **87**, which was then stereoselectively functionalized by hydroboration/oxidation to the targeted JKL maitotoxin fragment **88** (Scheme 14a). A similar sequence involving one-pot methylenation/metathesis converted VW ester **89** to tricyclic enol ether **91** via intermediate **90**, and thence to the VUW 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] Thus, and as shown in Scheme 15a, ester **93** was first converted to enol ether **94** and the latter was treated with Schrock's metathesis initiator **61** [61] to accomplish the metathesis step, furnishing bicyclic enol ether **95**. The same initiator

was also used to cyclize bis-olefinic substrate **96** (Scheme 15b) to obtain bicyclic ether **97**, whose double bond could be moved into conjugation with the oxocene oxygen by exposure to Wilkinson's catalyst,[62] leading to bicyclic enol ether **98** (Scheme 15b).

A method somewhat related to the ester methylenation/metathesis approach to cyclic ethers discussed above was developed by Takeda et al.[63] As shown in Scheme 16, these investigators found that 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 would, later on, apply this method in their total synthesis of ciguatoxin 3C (see next section).

A novel ring expansion of a tetrahydropyran system to an oxepane system was demonstrated en route to hemibrevetoxin by Nakata et al. in 1996 as shown in Scheme 17.[64] Thus, treatment of mesylate **103** with $Zn(OAc)_2$ in aqueous acetic acid induced stereoselective ring expansion, yielding oxepane derivative **105** as a single stereoisomer, presumably through 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 previously underutilized sulfonyl-stabilized oxiranyl anions which can readily be prepared from the corresponding epoxysulfones and *t*BuLi.[65] Thus, alkylation of triflate **106** with the sulfonyl-stabilized oxiranyl anion **107** yielded epoxide **108**. Treatment of epoxide **108** with *p*TsOH resulted in 6-*endo* cyclization with concomitant expulsion of the sulfonic acid residue, yielding 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 polypyran synthesis, 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 $BF_3{\bullet}Et_2O$,[66] yielding oxepanes such as **110** shown in Scheme 18.

A particularly useful method for the conversion of the more readily available medium-sized lactones to the corresponding cyclic ethers is the vinyl phosphate/cross-coupling method that proceeds through the corresponding vinyl phosphates (ketene acetal phosphates) was reported by the Nicolaou group in 1997.[67] As shown in Scheme 19, the team demonstrated their palladium catalysis-based method by using the Stille cross-coupling reaction to form functionalized medium-sized cyclic ethers. Thus, generation of the vinyl phosphate **112** from the corresponding lactone (**111**) followed by palladium-catalyzed $[Pd(PPh_3)_4]$ Stille coupling with tri-*n*-butyl vinyl stannane furnished 7-membered ring cyclic ether **113** which could be elaborated further to a variety of cyclic ethers. These vinyl phosphates complement the reactivity of vinyl triflates which perform well in pyran systems but are less stable in medium-sized rings in contrast to the phosphates which are easily manipulated in such circumstances. As such, this method could be extended to all ring sizes from 6- to 9-membered and beyond, and found several applications in total synthesis of marine polyethers. Vinyl triflates had previously been introduced as intermediates to construct simple cyclic ethers by Murai et al. [68] and were employed and championed by the Nicolaou group in their total synthesis of brevetoxin B (**6**, see next section).

A number of variations of the vinyl phosphate/cross-coupling method have also been developed, the most prominent one being the vinyl phosphate/*B*-alkyl Suzuki coupling method for cyclic ether formation. Thus, the Sasaki group extended the Nicolaou vinyl phosphate technology for cyclic ether formation by adopting the boron-alkyl Suzuki cross-coupling reaction as a means to grow the molecule as shown in Scheme 19.[69] Thus, exocyclic enol ether **114** was first stereoselectively hydroborated with 9-BBN, and the resulting alkyl borane

(**115**) was directly coupled with cyclic vinyl phosphate **116** through the action of catalytic amounts of $Pd(PPh_3)_4$ and $NaHCO_3$, affording bicyclic enol ether **117**.

In 1999, Sasaki and Tachibana et al. disclosed a method for the construction of cyclic polyethers from mixed phenylthio acetals.[70] Thus, as shown in Scheme 20, reaction of bicyclic *O,S*-acetal **118** with $n Bu_3SnH$ 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 diaxial interactions. This method allows an additional ring to be subsequently forged through olefin metathesis from a bis-olefin **121**, obtained in a few steps from the initial product, as outlined in Scheme 20. The ability to construct two adjacent ether rings between two coupled fragments endows this strategy with additional advantages by virtue of its high level of convergency.

Building on the idea of intramolecular 1,4-additions, Nakata et al. introduced, in 1999, a SmI_2-induced reductive cyclization to form 6- and 7-membered cyclic ethers as shown in 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 and transient intermediate radicals **125** and **126**, respectively.[72] Coordination between the samarium-complexed ketyl radical oxygen 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, forming 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, allowing its application to the construction of polyethers from relatively simple substrates.

In 2000, the Fujiwara/Murai[73] and Nakata[74] groups reported independently, and almost simultaneously, a bis-cyclic ether formation method from acetylenic substrates. As shown in Scheme 22, these researchers reacted the same acetylene (**131**) with $NaIO_4$ in the presence of RuO_2 (cat.) and obtained 1,2-diketone **132**, an intermediate they used as a substrate for their tetracycle formation (**132** → **133**) induced by acid catalysis in methanol. The resulting bis-methoxy bis-acetal was then reductively converted to tetracyclic polyether **134** by the action of Et_3SiH and TMSOTf. A few months later, the Mori group 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 Nakata et al. in 2002.[76] As shown in Scheme 23, these investigators converted ynone **135** to methoxy enone **136** in two steps, and then to cyclic enone **138** through an acid-catalyzed reaction that presumably involved transient intermediate **137**.

Inspired by Nakanishi's polyepoxide biosynthetic proposal for brevetoxin B and related polyether marine natural products,[33] a number of investigators attempted to design partial cascades in order to construct polycyclic ethers, and possibly gain insights into nature's postulated pathway. Thus, besides Nicolaou's original method for controlling the 6-*exo* cyclization over the kinetically favored 5-*endo* 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 et al. accomplished, albeit in low yield (9 %) and as shown in Scheme 24, the conversion of hydroxy triepoxide **139** to 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 as shown (Scheme 24).

Also in 2000, McDonald et al. demonstrated an oligoepoxide opening cascade with a substrate possessing a *tert*-butyl carbonate as an initiator group and a Lewis acid as a catalyst.[78] Shown in Scheme 25, this study involved Shi epoxidation[79] of tetraolefin **143** to afford tetraepoxide **144** (80% yield), which was exposed to BF_3•Et_2O to furnish, upon aqueous work-up, the trioxepane system **146**, through the presumed intermediacy of species **145**, in 20 % yield.

The next example of a directed polyepoxide opening cascade came in 2003 from the Jamison group.[80] As shown in Scheme 26, these researchers used triene **147** equipped with the three strategically placed TMS groups in the hope that they would direct the desired 6-*endo* cyclizations to produce the fused tetrapyran system (**149**). Thus, Shi epoxidation of **147** furnished triepoxide **148** in 45 % yield. Treatment of **148** with Cs_2CO_3 and CsF, followed by acetylation (Ac_2O, py.), led to tetrapyran system **149** in 20 % overall yield.

The Jamison group also reported the next advance in the field, a rather spectacular hydroxy 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 as shown in Scheme 27.[81] Vilotijevic and Jamison speculated that such non-enzymatic zip-type reactions may be nature's way to the ladder-like polyether natural products. The required hydroxy triepoxide **152** was prepared from the triacetylene **150** by Li/liq. NH_3 reduction to afford triene **151** followed by Shi epoxidation and desilylation (35% overall yield, ca. 3:1 dr of innermost epoxide). The remarkably ring-selective polycyclization to **153** was carried out simply by heating tri-epoxide **152** in water at 70 °C and proceeded in 53 % yield. Interestingly, these researchers 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 ladder-like polyether marine natural product in the early 1980's, 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 occurred because of the lack of methods suitable for their construction. As the repertoire of synthetic technologies, however, became more enriched with powerful methods such as the ones discussed above, and due to 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 recorded to date 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 formidable structures of brevetoxin B (**6**) in 1981,[2] and of brevetoxin A (**7**) in 1985,[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 its higher order siblings. Besides, hemibrevetoxin (**8**) was an ideal platform to test the applicability and scope of the synthetic technologies so far developed by virtue of its relative simplicity, yet highly relevant structure. With no less than nine total and formal syntheses of this molecule so far reported, the topic provides an instructive survey of the applications of the developed methods for cyclic ether formation in total synthesis.

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 group.[84] As seen in Scheme 28, the

team's strategy was based on their thionolactone functionalization technology (twice, to form both oxepane rings) and their selective 6-*endo* hydroxy epoxide opening reaction. 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 to come in the polyether total synthesis field. Following elaboration to the appropriate epoxide (**155**), the action of catalytic amounts of CSA regioselectively forged the B ring, generating bicyclic polyether **156**. After subsequent formation of thionolactone **157**, an improved version of the thionolactone nucleophilic functionalization method was applied to cast the oxepane tricyclic system **158**, whose conversion to the final target molecule required a short sequence that involved reiteration of the thionolactone nucleophilic functionalization (**159**) process as outlined in Scheme 28.

It would not be until 1995 that the second total synthesis of hemibrevetoxin (**8**) would appear in the literature. In this synthesis (Scheme 29),[85] the Y. Yamamoto group employed similar tactics to those used by the Nicolaou team to start (D-mannose, **154**) and propagate (6-*endo* epoxide opening, **160** → **161**) their total synthesis. The Y. Yamamoto allyl tin method was utilized to construct both oxepane rings in high yield as shown (**162** → **163**; **164** → **165**). Side chain elaboration along the lines of the Nicolaou strategy completed the total synthesis of hemibrevetoxin (**8**). It is interesting to note that, while the side chains and rings of the target molecule were constructed in the same order in the first two total syntheses of hemibrevetoxin (**8**) discussed above, 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 group (Scheme 30).[64,86] Their strategy involved Sharpless asymmetric epoxidation to introduce chirality in their prochiral starting material (geraniol: **166** → **167**), and two 6-*exo* epoxide openings (**167** → **168**; **169** → **170**) to forge the bicyclic sulfonate precursor **171** to their key double ring expansion that produced the bis-oxepane ring system **172** (DC ring system). From there on they utilized the directed 6-*endo* epoxide opening to forge ring B (**173** → **174**), and an allylation reaction on the cyclic methyl acetal to cast ring A (**175** + **176** → **177**). The synthesis was completed by simple functional group manipulations and oxidation state adjustment to install the terminal aldehyde functionality.

In 1997, the Mori group completed a formal total synthesis of hemibrevetoxin (**8**) that was based on their oxiranyl anion chemistry (Scheme 31).[87] They employed the chiral pool-derived tri-*O*-acetyl-D-glucal starting material (**178**) which was conveniently converted to ring A intermediate **179**, from which their first oxiranyl anion (**180**) addition/cyclization proceeded smoothly to form ring B (**181**). The second oxiranyl anion (**107**) addition/cyclization event required an aldehyde electrophile (**182**), and was accompanied by ring expansion to generate ring C (**183**). The third and final oxiranyl anion (**185**) addition/cyclization process also required ring expansion in order to reach its goal, tetracyclic intermediate (**186**), which had previously been converted to hemibrevetoxin (**8**) by the Y. Yamamoto group.[85]

Another formal total synthesis of hemibrevetoxin (**8**) was published by Rainier et al. in 2001 (Scheme 32).[88] This synthesis employed the Clark version of the methylenation/metathesis approach to cyclic ethers originally introduced by the Nicolaou group, and delivered 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. Employing 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] these investigators arrived at bicyclic system **191**, which was elaborated to advanced intermediate **193** through **192**, ready for another ring closing

metathesis. Following that event, isomerization of the olefinic bond led to enol ether **194** which was elaborated into Mori's intermediate **186** (Scheme 31), thus completing their formal total synthesis of hemibrevetoxin (**8**).

In 2001, Nelson et al. reported an elegant, bi-directional approach to T. Nakata's bicyclic intermediate **199** as outlined in Scheme 33.[90] Thus, metathesis/dimerization of **195**, followed by epoxidation of the resulting *E*-olefin led to racemic epoxide **196**, which was cyclized with concomitant equilibration to bicyclic compound **197**. After elaboration of this mixed bis-acetal, a Jacobsen enantioselective epoxide hydrolysis[91] of the resulting centrosymmetric intermediate (**198**), led to enantiopure product **194**. Since this intermediate had previously been converted to hemibrevetoxin (**8**) by Nakata et al.,[86] its construction constituted a formal asymmetric total synthesis of hemibrevetoxin (**8**).

The total synthesis of hemibrevetoxin (**8**) reported by Holton et al. in 2003 had, in addition to a number of other elegant elements, the distinction of being the first to employ a convergent strategy (Scheme 34).[92] Thus, dipping into the chiral pool, the team selected tri-*O*-acetyl-D-glucal (**178**) and benzyl-β-D-arabinopyranoside (**200**) as their starting materials which they converted through a series of reactions to 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 hydroxy olefinic epoxide **204**. In the presence of *N*-(phenylseleno)phthalimide[94] and in the apparently crucial solvent HFIP, the latter compound entered into an impressive cascade that forged both rings B and C, affording phenylseleno intermediate **205**. This intermediate was then converted to bis-olefin **206**, which underwent smooth ring closing metathesis under the influence of Grubbs II catalyst to form tetracycle **207**, which was converted to hemibrevetoxin (**8**) by standard elaboration.

Fujiwara et al. reported, in 2004,[95] a convergent formal total synthesis (the eighth) of hemibrevetoxin (**8**) that reached Y. Yamamoto's advanced intermediate **215**[85] in enantiomerically pure form (Scheme 35). Starting from γ-butyrolactone (**208**) and tri-*O*-acetyl-D-glucal (**178**), these investigators constructed building blocks **209** (through a sequence featuring ring closing metathesis) and **210** (through standard chemistry) and coupled them through alkylation technology to afford bicyclic product **211**. The remaining two rings were forged using Nicolaou's synthetic technologies for forming cyclic ethers, namely, hydroxy ketone reductive cyclization (**212** → **213**) and mixed *O*,*S*-acetal formation/methylation (**214** → **215**) as outlined in Scheme 35.

In 2007, Y. Yamamoto reported a second generation synthesis (the ninth) of his hemibrevetoxin precursor **221**, thus accomplishing a now formal total synthesis of this molecule (Scheme 36).[96] This route began with bicyclic intermediate **217**, which was used in the team's first synthesis of hemibrevetoxin (**8**), and linear precursor (**216**), available from γ-butyrolactone (**208**). Coupling of these two building blocks afforded ester (**218**), which, upon further elaboration, led to enol stannane precursor **219**. The latter compound underwent smooth allyl tin cyclization according to the authors' previous protocol to furnish tricyclic system **220**. A ring closing metathesis facilitated by Grubbs II catalyst then completed the required tetracycle **221**, whose conversion to hemibrevetoxin (**8**) had previously been accomplished.[85]

While the summarized 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

Being the first member of the class of the ladder-like marine neurotoxins to be isolated and structurally elucidated, brevetoxin B (**6**) holds a special place in the annals of natural products in general, and of this class in particular. Appearing in the literature in 1981, brevetoxin B was isolated from the dinoflagellate *Karenia brevis* (then *Gymnodinium breve*) and structurally elucidated by Nakanishi and Clardy.[2] Its stunning molecular architecture inspired awe in the minds of synthetic organic chemists and spurred the discovery and development of the synthetic methods discussed in the preceeding sections of this article. In 1995, and after a twelve-year synthetic odyssey, the Nicolaou team reported the first total synthesis of this molecule.[35,97]

The Nicolaou et al. total synthesis of brevetoxin B (**6**) is summarized in Scheme 37 – Scheme 39 with only the main events highlighted. 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 7-ring row 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** to phosphonium salt **245**, Wittig coupling with the IJK fragment (**244**), a hydroxy dithioketal cyclization/reduction to form the H ring (**246** → **247**), and a few final touches as outlined in Scheme 39.[97]

The second total synthesis of brevetoxin B (**6**) reported by Nakata et al. is summarized in Scheme 40 and Scheme 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 starting material used in the Nicolaou synthesis [2-deoxy-D-ribose (**222**)], their route (Scheme 40) to the IJK ring system (**244**) 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 utilized 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**). Both the coupling of the two large fragments and the final stages of the synthesis mirrored the sequence developed earlier by the Nicolaou team and afforded brevetoxin B (**6**) as already highlighted above in Scheme 39.[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 that brevetoxin B (**6**) (10 vs. 11), but a higher degree of ring diversity.[82,99] Indeed, in its imposing structure brevetoxin A included all ring sizes from 5- to 9-membered and, therefore, constituted the ultimate challenge at the time for cyclic ether construction, 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 group undertook its total synthesis, and in 1998, reported the accomplishment of this demanding task.[101]

The Nicolaou et al. total synthesis of brevetoxin A (**7**) is summarized in Scheme 42 – Scheme 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 afford, upon further bis-functionalization, bis-vinyl phosphate **265**, which was converted to bis-vinyl stannane **266** through Stille coupling. The latter intermediate underwent double cuprate addition and, after further elaboration, the product was converted to 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**.

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/methylation to cast ring G (**278** → **279**), and final elaboration.

A Horner–Wittig type coupling between **271** and **280** (Scheme 44) followed by another hydroxy dithioketal cyclization/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. And while the ciguatoxins target the same voltage-sensitive sodium channels as the brevetoxins, they do so with 25- to 400-fold stronger binding affinities, and hence their higher toxicities. In 2001, the Hirama group published the first and only total synthesis of a ciguatoxin, that of CTX3C (**9**, Scheme 47).[102]

Hirama's convergent synthesis of ciguatoxin 3C (**9**) proceeded through advanced intermediates **291** (ABCDE fragment, Scheme 45) and **303** (HIJKLM fragment, 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 (rings A and E), and then converging back to a single track (**287** + **288** → **289** →

290 → **291**) that also employed a ring closing metathesis (ring D). The final ring in this segment was formed through a hydroxy ketone reductive cyclization (ring C).

The synthesis of the HIJKLM fragment (Scheme 46) involved construction of building blocks **296** (HI fragment) and **300** (LM fragment) and their coupling and elaboration through a sequence that featured an esterification and intramolecular carbene-ester addition to forge ring J, and a reductive etherification to form 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 an oxiranyl anion addition/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, proceeded through intermediates **298** and **299**, and involved a saponification/lactonization process and a spiroketalization as shown in Scheme 46.

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 olefin metathesis precursor **305**. Finally, ring closing metathesis and deprotection led to the target molecule, ciguatoxin 3C (**9**).

8. Gambierol

In 1993, a new polyether was isolated from *Gambierdiscus toxicus*, gambierol (**10**).[103] The new natural product exhibited similar toxic properties as the ciguatoxins, 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 this article in the context of a total synthesis.

The first total synthesis of gambierol (**10**) was reported by Sasaki and co-workers in 2002.[105] Demonstrating the power of the vinyl phosphate/*B*-alkyl Suzuki coupling, this convergent synthesis required building blocks **312** (ABC fragment, Scheme 48) and **320** (EFGH fragment, Scheme 49). The ABC fragment **312** was constructed from 2-deoxy-D-ribose (**222**)[101d] through intermediates **306–311** as summarized in Scheme 48. The route featured an intramolecular hydroxy Michael reaction to form ring A (**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** as outlined in 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/vinyl phosphate formation [to form ring E (**319** → **320**)].

The two fragments (**312** and **320**) were joined through a Suzuki-type coupling to generate ABDEFGH ring system **321**, which was elaborated to gambierol (**10**) through intermediates **322–323** as shown in Scheme 50. The final ring closure to forge ring D relied on a mixed *O,S*-acetal formation/reduction protocol that was based on Nicolaou's dithioketal cyclization/reduction method for cyclic ether formation.

The second total synthesis of gambierol (**10**) was reported from the Y. Yamamoto laboratories.[106] Its convergency relied on the construction of the ABC and FGH fragments **326** (Scheme 51) and **333** (Scheme 52), which were coupled through esterification (Scheme 53). Just like

Sasaki's route to gambierol (**10**), 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 (as opposed to a 6-*endo* epoxide opening) was employed to forge ring C (**324** → **325**) as shown in 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**), a 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**, Scheme 53) through esterification and further elaboration, an allyl tin-based cyclization ensured the installation of ring D producing a bis-olefin (**334** → **335**), which underwent smooth ring closing metathesis (**335** → **10**) to complete the required row of cyclic ethers that eventually led to synthetic gambierol (**10**) as outlined in Scheme 53.

A third total synthesis of gambierol (**10**), this time from the Rainier group, 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 re-iterative methylenation/metathesis sequences to cast rings B (**338** → **339**) and C (**340** → **341**), generating the required ABC fragment (**342**) of the molecule as shown in Scheme 54.

The team's synthesis of the other required advanced building block (**346**, FGH fragment) began with tri-*O*-acetyl-D-glucal (**178**) and employed another methylenation/metathesis protocol [to form ring F (**343** → **344**)] and an acid-induced cyclization/functionalization to forge the oxepane ring (ring H, **345** → **346**) as summarized in Scheme 55.

As shown in Scheme 56, the final stages of the Rainier et al. synthesis of gambierol involved esterification coupling of fragments **342** and **346**, followed by another methylenation/metathesis sequence that formed ring E (**346** → **347**). Subsequent elaboration to hydroxy ketone **348**, followed by an *O*,*S*-acetal formation/reduction process ensured the closing of the last required ring and paved the way to the final functional group manipulations that furnished gambierol (**10**).

9. Gymnocin A

Gymnocin A (**12**), the second largest fully characterized polyether marine natural product known to date, was reported by the Satake group in 2001.[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, preventing it from reaching the fish's gills.

In 2003, the Sasaki group reported a highly convergent total synthesis of gymnocin A (**12**) that made extensive use of the vinyl phosphate/*B*-alkyl Suzuki 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 vinyl phosphate/*B*-alkyl Suzuki coupling to furnish ABD enol ether **351** (Scheme 57).[106c] The latter intermediate was elaborated to ABD ketone **352**, whose conversion to the required ABCD fragment **353** involved an *O*,*S*-acetal formation/reduction as the ring-casting operation.

The synthesis of the larger, FGHIJKLMN fragment (**363**, 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 to vinyl phosphate **354**, and 2-deoxy-D-ribose (**222**) was functionalized to exocyclic olefin **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/reduction process then furnished, after simple functional group adjustments, the target tricyclic compound **358**.

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

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

10. Brevenal

In 2004, yet another marine polyether was isolated from *Karenia brevis*.[111] One of the simplest members of the class, brevenal (**11**, Scheme 63) possesses intriguing biological properties. Thus, it was claimed not only to displace brevetoxins A (**7**) and B (**6**) from their binding site on the voltage-sensitive sodium channels, but also to antagonize their neurotoxicity.[112]

In 2006, the Sasaki group accomplished a total synthesis of the reported structure of brevenal (C_{18}-epimer of **11**, Scheme 63) only to prove that it was erroneous.[113] Employing their developed synthetic technology, however, they soon constructed the correct structure of brevenal, which turned out to be the one depicted by **11** in Scheme 63.[114] The convergent synthesis of brevenal (**11**) required the AB ring vinyl phosphate **370** and the DE ring enol ether **375**, whose constructions are summarized in Scheme 61 and Scheme 62, respectively. Thus, after convergent union and subsequent elaboration of starting materials **366** and **367** (Scheme 61), hydroxy epoxide **368** was synthesized and subjected to a 6-*endo* epoxide opening to form the first ring of the molecule (ring A, compound **369**), which was then elaborated to the AB fragment **370** through the usual lactonization/vinyl phosphate formation method.

The 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 the vinyl phosphate/*B*-alkyl Suzuki-based merger of the AB (**370**) and DE (**375**) fragments to afford the ABDE domain (**376**), and an *O,S*-acetal formation/methylation sequence that installed both the missing ring (ring C) and the required methyl group on that ring according to Nicolaou's protocol. Further elaboration, including extension of the side chains, led to brevenal (**11**) (and its C_{18}-epimer, the originally proposed structure).

The above syntheses provide a clear picture of the evolution of the strategies towards complex, ladder-like polyether structures such as those found in nature. They are also indicative of the applicability and scope of certain methods for cyclic ether formation. Among them, the 6-*endo* epoxide opening (Nicolaou), cyclic *O*,*S*-acetal formation/reduction or methylation (Nicolaou), dithionolactone bridging (Nicolaou), thionolactone nucleophilic addition (Nicolaou), intramolecular hydroxy Michael addition (Nicolaou), hydroxy ketone reductive cyclization (Nicolaou), allyl tin radical cyclization (Y. Yamamoto), methylenation/metathesis (Grubbs/Nicolaou/Clark/Takeda), ring expansion (Nakata), oxiranyl anion addition/cyclization (Mori), vinyl 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 polyepoxide opening 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 incidentally 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 gut of the surgeon fish *Ctenochaetus striatus*[115] and later in the dinoflaggelate *Gambierdiscus toxicus*[116] in the late 1970's. 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, $2^{99}=6.3\times 100,000,000,000,000,000,000,000,000,000$ possible stereoisomers), maitotoxin stands as the largest and most toxic, non-polymeric natural product isolated and characterized to date. Due to the size of the molecule and its low natural abundance, its structure could not be derived directly from NMR spectroscopic analysis alone, so the investigators had to resort to a combination of degradative and synthetic studies in order to finally be able to propose, in phases, its molecular architecture.

First, the Yasumoto group subjected maitotoxin (**13**, Scheme 64) to sodium periodate oxidative degradation that cleaved the molecule at every 1,2-diol site, producing, after $NaBH_4$ reduction, three compounds, the C_1–C_{36} fragment **378**, C_{37}–C_{135} fragment **380**, and C_{136}–C_{142} fragment **382** (Scheme 64).[118] Exhaustive acetylation of fragments **378** and **380** furnished peracetates **379** and **381**, respectively (Scheme 64). With these compounds in hand, and through extensive NMR spectroscopic analysis, these investigators were able to propose, in 1993, the gross structure of maitotoxin with relative stereochemistry for all its cyclic domains.[119] They were unable, however, to determine the relative stereochemistry of the acyclic regions of the molecule (C_1–C_{15}, C_{35}–C_{39}, C_{63}–C_{68} and C_{134}–C_{142}). These assignments had to wait several more years while the Kishi and Tachibana 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** in Scheme 64. These studies are summarized below.

The determination of the relative stereochemistry of the acyclic regions of maitotoxin and the absolute stereochemistry 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 groups responded successfully to this challenging task.

Scheme 65 summarizes the efforts that led to the determination of the relative stereochemistry of the C_1–C_{15} 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. The Kishi team, instead of synthesizing all 128 possible diasteomers of the C_1–C_{15} domain, divided this region in two and synthesized, instead, the eight possible stereoisomers of the C_1–C_{11} structure **383** and the eight possible stereoisomers of the C_{11}–C_{15} 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 those of the other isomers. In order to assign the relative stereochemistry 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 C_1–C_{15} domain of maitotoxin, thus allowing them to make their final stereochemical assignments to this region of the molecule. The Tachibana team, on the other hand, synthesized the C_5–C_{15} 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, allowing them to make the same stereochemical assignment to this domain of maitotoxin.[121] With two independent studies reaching the same conclusion, it seemed secured that the C_1–C_{35} relative stereochemistry of maitotoxin was as depicted in structure **13** (Scheme 64).

Aiming to assign the relative stereochemistry of the C_{35}–C_{39} region of the maitotoxin molecule, the Kishi team 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** as outlined in Scheme 66.[120] The ^{13}C NMR spectroscopic data for the shown diastereomer (**393**, Scheme 66) exhibited the closest match to those of the same region of maitotoxin, pointing to this particular stereochemical arrangement for the C_{35}–C_{39} domain of the natural product. Similar synthetic studies by the Tachibana 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, leading, through spectroscopic analysis, to the same conclusion.[122]

Moving on to the C_{63}–C_{68} segment of the molecule, and as shown in Scheme 67, the Kishi [120] and Tachibana[123] groups synthesized the four diastereomers of each of the LMNO fragments **401** and **405**. Starting with the enantiopure LM and NO fragments (**399**, **398**, and **403**, **402**), they employed chemistry that allowed them to synthesize all four C_{64}/C_{65} diastereomers of **401** and **405** through intermediates **400** and **404**, respectively. Of the four diastereomers each group synthesized, they found that the ones depicted in Scheme 67 (i.e. **401** and **405**) exhibited the closest ^{13}C NMR spectroscopic data to the corresponding values reported for maitotoxin, providing the foundation for the stereochemical assignments of that region of the molecule.

Although the VW (C_{99}–C_{100}) junction of maitotoxin was assigned by the Yasumoto group in their original reports,[118,119] there remained a small cloud of uncertainty with regards to the relative stereochemistry between the UV and WX domains of the molecule owing to the presence of the methyl group on the W ring that prevented unambiguous assignment of stereochemistry at that site through 2-D NMR spectroscopy. To confirm Yasumoto's assignment, Kishi et al. synthesized the two possible C_{99}–C_{100} diastereomers as shown in Scheme 68.[124] Thus, starting with enantiopure WX fragment **406** and racemic U fragment **407**, they constructed two diasteromers of **408**, and then forged ring V through a reductive hydroxy ketone cyclization to afford their two targeted diastereomers of **409**. Upon separation of the two, 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 et al.[119] around the VW rings was most likely correct.

The relative stereochemistry of the C_{134}–C_{142} domain of maitotoxin was the last to be determined. The Kishi group 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 group was able to solve, and report in 1996, the puzzle of the complete relative stereochemistry of maitotoxin.[120] It would be left up to the Tachibana group, however, to cast the final nail on the coffin of the maitotoxin structure by determining its absolute stereochemistry. Thus, about the same time as Kishi's disclosure of the relative stereochemistry of maitotoxin, the Tachibana group reported, also in 1996, the synthesis of the four enantiomers of the C_{136}–C_{142} fragment of maitotoxin (Scheme 69) and, through chiral GC comparison with the same maitotoxin-derived fragment (Scheme 64), their assignment of the absolute stereochemistry of this domain of the molecule (as that depicted to **382**, Scheme 69), and, hence, of maitotoxin itself (as that depicted by **13**, Scheme 64).[125]

Recently, the stereochemistry of maitotoxin came under scrutiny, with Gallimore and Spencer questioning the JK ring junction (C_{51} and C_{52}).[34] These investigators based their insightful and seemingly logical objection on Nakanishi's proposal[33] for the biosynthesis of the ladder-like polyether marine natural products, shown in Scheme 70 for the case of maitotoxin (**13**). 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 (C_{51}–C_{52}) would have to be derived from an epoxide unit with the opposite stereochemistry to all the other epoxides of the polyepoxide precursor (**411**). This anomaly led to one of two conclusions: either there were errors in the structural assignment of maitotoxin, a possibility because of the difficulties encountered in assigning all the signals within this region of the molecule due to considerable overlaps in its NMR spectra, [118,119] or the proposed biosynthesis needed to be revised, at least for that region of the maitotoxin molecule.

Because of this serious stereochemical issue of maitotoxin, the Nicolaou group set out to determine whether revisions needed to be made. They first turned to computational chemistry that allowed them to calculate the ^{13}C NMR chemical shifts for three GHIJKLM ring domains. [126] Figure 8 shows the three structures subjected to these calculations. Structure **412** possessing the originally proposed stereochemistry at the JK ring junction (C_{51}–C_{52}), structure **413** where the JK ring junction (C_{51}–C_{52}) was inverted to agree with the Nakanishi/Gallimore–Spencer biosynthetic hypothesis, and structure **414** where the C_{50}–C_{55} stereocenters were inverted to agree with both the biosynthetic hypothesis and the reported nOe's of that region of maitotoxin (**13**). As Figure 8 shows, the structure with the originally proposed stereochemistry (**412**) had the strongest agreement with the reported spectra for maitotoxin, with a maximum difference ($\Delta\delta$) of 2.1 ppm, and an average difference ($\Delta\delta$) of 0.78 ppm for the C_{48}–C_{55} region. Structures **413** and **414** differed more from maitotoxin, with maximum differences ($\Delta\delta$) of 7.5 and 5.0, and average differences ($\Delta\delta$) of 3.03 and 2.98 ppm, respectively. This data lends support for the originally proposed structure of maitotoxin (**13**); but the skeptical mind would not rest with that evidence alone, and, therefore, further experimental evidence was deemed necessary.

In search of such evidence, the Nicolaou group set out to synthesize the GHIJK (**444**, Scheme 76) and GHIJKLMNO domains (**459**, Scheme 78) of maitotoxin in order 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 technologies for the construction of cyclic ethers. Towards this end, the group developed two new general methods for the construction of substituted pyrans of the type found in the maitotoxin structure. The first one was specifically developed to take advantage of the easily accessible acyl furans (e.g. **417**) from substituted furans (**415**) through metalation/acylation (**416**, Scheme 71), and in order to exploit recent advances in asymmetric catalysis (i.e. Noyori reduction, **417** → **419**, Scheme 71)[128] and to apply the Achmatowicz rearrangement[129] to access the highly desirable substituted pyrans (**419** → **420** → **421** → **422**) through elaboration of the obtained lactol enones (**421**) as indicated in Scheme 71.

The second method for the construction of substituted pyrans developed by the Nicolaou group 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**) as shown in Scheme 72. The resulting cyclic enones (**425**) can then be manipulated to an array of products such as **426** as indicated in Scheme 72.

Application of these two technologies 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 Scheme 73–Scheme 76.[127a] Thus, metallation 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, in 89 % yield and ≥95 % ee, alcohol **429** (Scheme 73). Achmatowicz rearrangement of the latter induced by NBS, followed by pivaloate formation, led to enone **430**, which was elaborated stereoselectively to the required maitotoxin J fragment (**431**) through reduction of the carbonyl moiety, dihydroxylation of the double bond, and further elaboration.

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/Achmatowicz rearrangement method (**434** → **435** → **436**) through a sequence that involved reduction of the carbonyl group, epoxidation of the enone, epoxide opening, and elimination to furnish the exocyclic olefin shown (**437**).

Scheme 75 highlights the construction of the maitotoxin IJK vinyl triflate fragment **441** by a sequence that involves initial acetylide (**438**) addition 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, enone **440**, whose functionalization to the final IJK ring domain **441** proceeded both efficiently and stereoselectively.

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

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 the C_{42}–C_{53}) as shown in Figure 9. The rather large differences for the two sets of ^{13}C chemical shifts corresponding to the two edges of the molecule are obviously due to the drastically different functional groups present at these ends, and which become apparent by glancing at the G and L rings of maitotoxin shown in 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 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 metallation led to acyl furan **446**, whose Noyori asymmetric reduction furnished hydroxy furan **447** in 98% yield and ≥95% ee. Achmatowicz rearrangement (NBS, H_2O) of the latter, followed by pivaloation of the resulting lactol, led to enone **448**, which was efficiently and stereoselectively converted to bicycle **449**. From **449**, the route diverged, delivering, after a few steps, the requisite LM acetylenic fragment **450** and the ketophosphonate fragment **451**.

Scheme 78 summarizes the assembly of intermediates **431** (Scheme 73), **437** (Scheme 74), **450** (Scheme 77) and **451** (Scheme 77), 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, hydroxy ynone cyclization to afford the JKLM enone **453**. Elaboration of this tetracyclic intermediate to the pentacyclic IJKLM vinyl triflate **454** through lactonization/triflate formation, followed by vinyl triflate/*B*-alkyl Suzuki coupling with the borane derived from G ring **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/mixed acetal formation which was accompanied by unmasking of all the hydroxyl groups, except those protected as benzyl ethers, to afford mixed acetal **456**. The superfluous methoxy group was removed from the latter compound through a 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 coupling led to enone **458**, whose stereoselective elaboration through its epoxide led to the targeted GHIJKLMNO domain **459**.

Figure 10 graphically depicts the observed ^{13}C chemical shift differences between the respective carbon atoms of the synthetic GHIJKLMNO fragment **459** and of natural maitotoxin as reported by Yasumoto et al.[118,119] Indeed, the matching of the two sets of δ values for the C_{42}–C_{73} 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 due to the different functional groups associated with them, see rings G and 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 cloud 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 with regards 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 magic of nature's 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 in order to address the synthetic challenges posed by them. Such was the case with the marine polyether class of biotoxins, inaugurated in 1981 by its flagship member, 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 ladder-like polyether marine natural products. To be sure, however, it was the daunting nature of brevetoxin's molecular architecture and the initial hopelessness of synthetic chemists to answer the gauntlet thrown by 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. And while a number of these unique and magnificent structures have been conquered by total synthesis (i.e. 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 technologies, more structures will yield to the power of the art of 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 their siblings who are destined to be discovered in the future. The history of the field as chronologically laid out in this article speaks volumes of its accomplishments 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, developments that should also spark further investigations into their fascinating world of chemical biology.

Abbreviations

Ac, acetyl
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
cat., catalytic
CFP, ciguatera fish poisoning
Cp, cyclopentadienyl
*m*CPBA, *meta*-chlorperbenzoic acid
CSA, camphor sulfonic acid
CTX3C, ciguatoxin 3C
DABCO, 1,4-diazabicyclo[2.2.2]octane
DMP, Dess–Martin periodinane
DSP, diarrhetic shellfish poisoning
ee, enantiomeric excess

GC, gas chromatography
HFIP, hexafluorisopropanol
HWE, Horner–Wadsworth–Emmons
KHMDS, potassium hexamethyldisilazide
LDA, lithium diisopropylamide
Liq., Liquid
MOM, methoxymethyl
Ms, methanesulfonyl
MS, molecular sieves
NAP, naphthyl
NBS, *N*-bromosuccinimide
NCS, *N*-chlorosuccinimide
NMR, nuclear magnetic resonance
nOe, nuclear Overhauser effect
NSP, neurotoxic shellfish poisoning
Piv, trimethylacetyl
PMB, *para*-methoxybenzyl
PMP, *para*-methoxyphenyl
PSP, paralytic shellfish poisoning
Py., Pyridine
Red-Al, sodium bis(2-methoxyethoxy)aluminumhydride
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
THF, tetrahydrofuran
TIPS, triisopropylsilyl
TMEDA, tetramethylethylenediamine
TMS, trimethylsilyl
TMSE, 2-(trimethylsilyl)-ethyl
Tol, *para*-tolyl
Tr, trityl
Ts, *para*-toluenesulfonyl

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Biographies

Professor K.C. Nicolaou, born in Cyprus and educated in England and the United States, is currently Chairman of the Department of Chemistry at The Scripps Research Institute where he holds the Darlene Shiley Chair in Chemistry and the Aline W. and L. S. Skaggs Professorship in Chemical Biology as well as Professor of Chemistry at the University of California, San Diego. The impact of his career on chemistry, biology and medicine flows from his contributions to chemical synthesis, which have been described in numerous publications and patents. His dedication to chemical education is reflected in his training of hundreds of graduate students and postdoctoral fellows. His books *Classics in Total Synthesis I* and *II*, and his book *Molecules That Changed the World*, which he has co-authored with his students Erik J.

Sorensen, Scott A. Snyder, and Tamsyn Montganon, respectively, are used around the world as a teaching tool and source of inspiration for students and practitioners of the art of chemical synthesis.

Michael O. Frederick was born in White Bear Lake, Minnesota in 1981. He received his B.S. in chemistry from the University of Minnesota while working with Professor Richard Hsung on the chemistry of ynamides. He is currently pursuing his Ph.D. 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 maitotoxin. He has been the recipient of a NSF predoctoral fellowship.

Robert J. Aversa was born in Philadelphia, Pennsylvania in 1984. He received his B.A. in chemistry and biochemistry from Cornell University in 2006, performing research under the tutelage of Professor Tadhg Begley. He joined the lab of Professor K.C. Nicolaou at the Scripps Research Institute later the same year as a graduate student, where he has been working towards the total synthesis of maitotoxin.

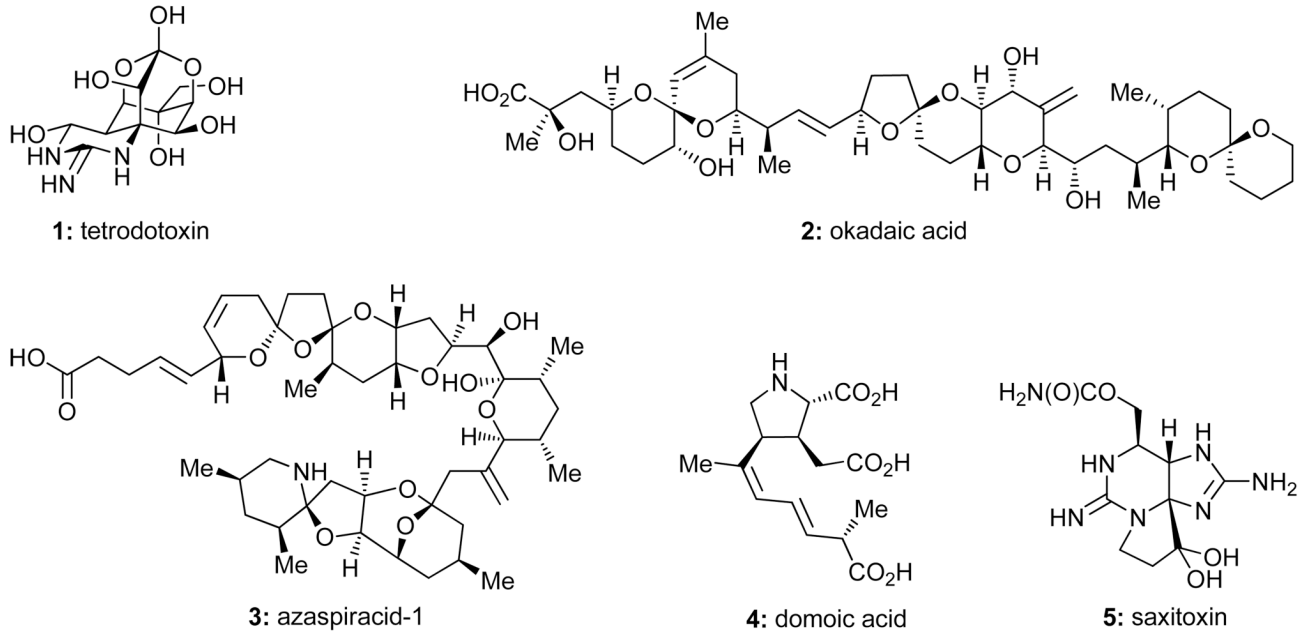


Figure 1.
Molecular structures of selected marine biotoxins.

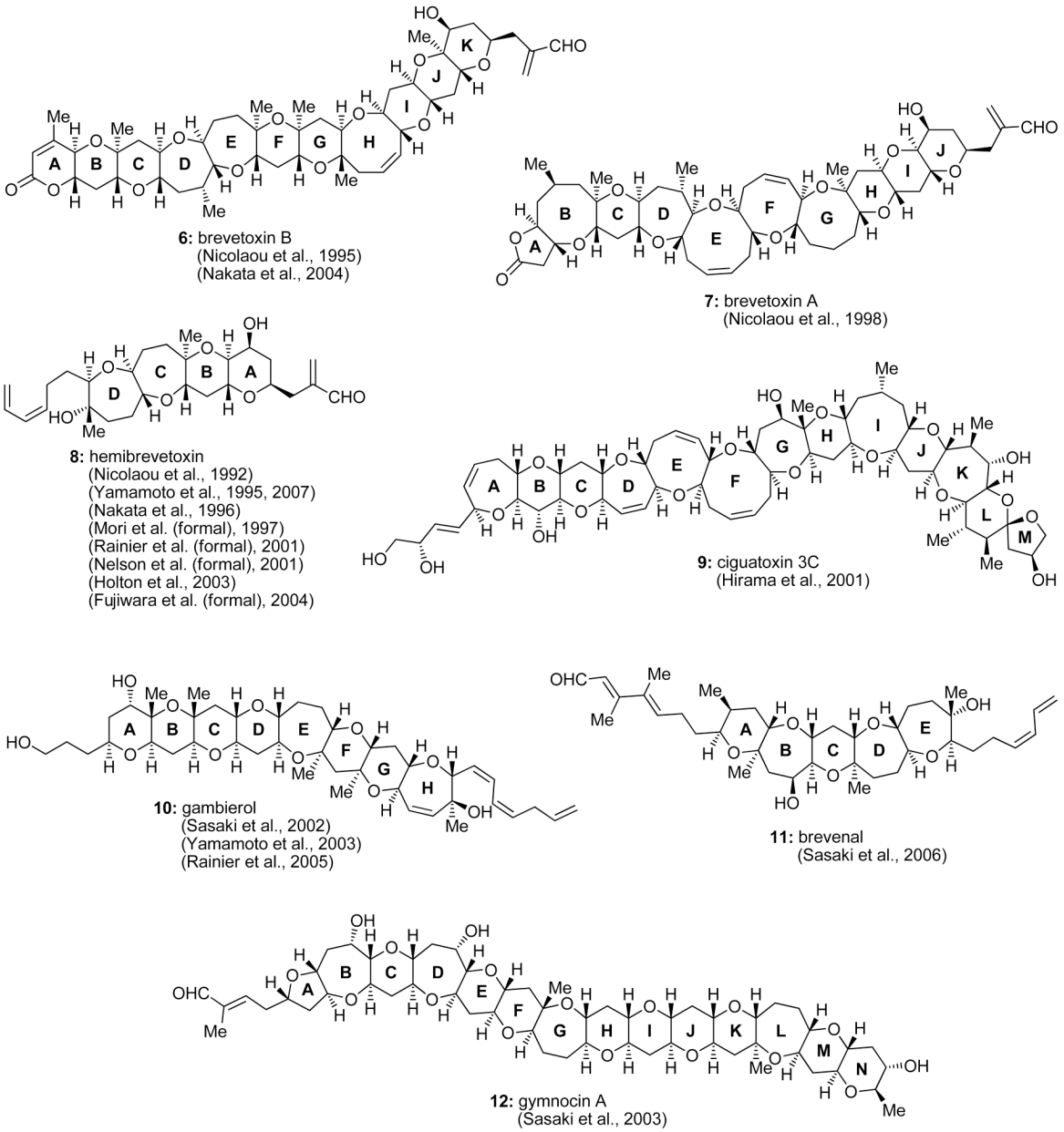


Figure 2.

Molecular structures of ladder-like polyether marine biotoxins (**6–12**) constructed in the laboratory by total synthesis.

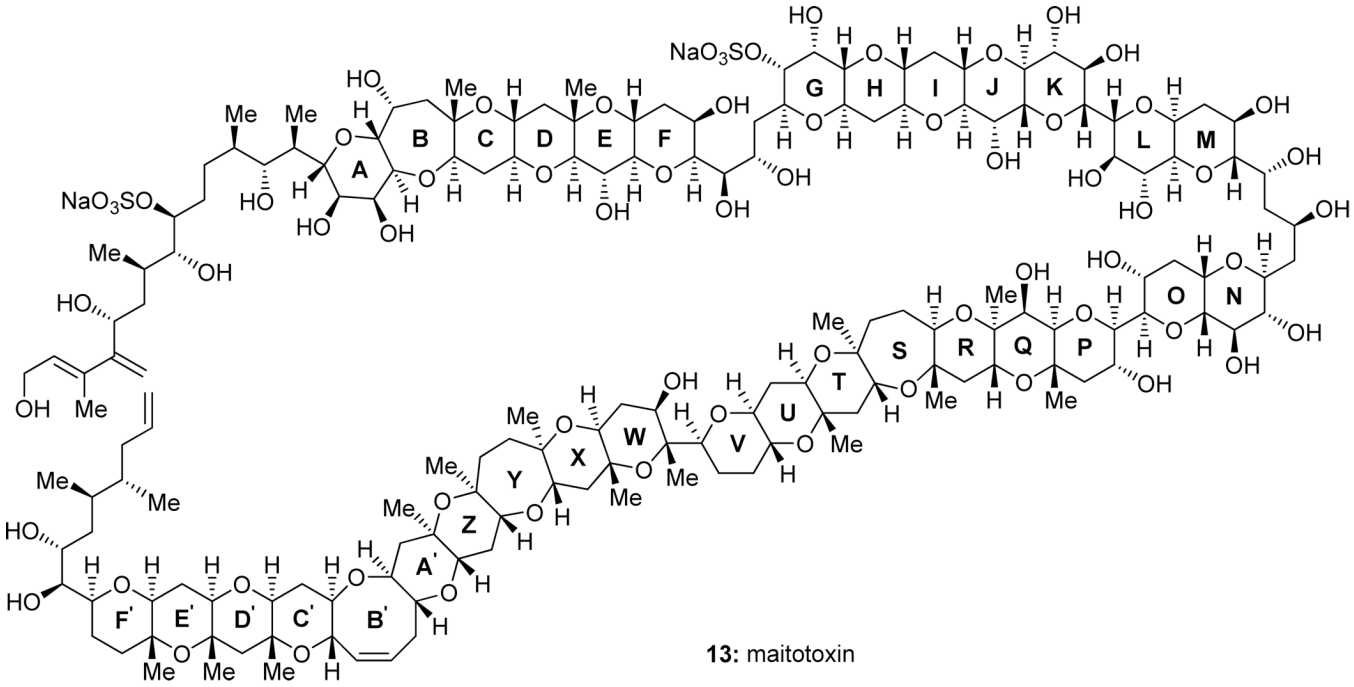


Figure 3.
Molecular structure of maitotoxin (**13**), the largest of the polyether marine biotoxins and of any non-polymeric natural product isolated to date.

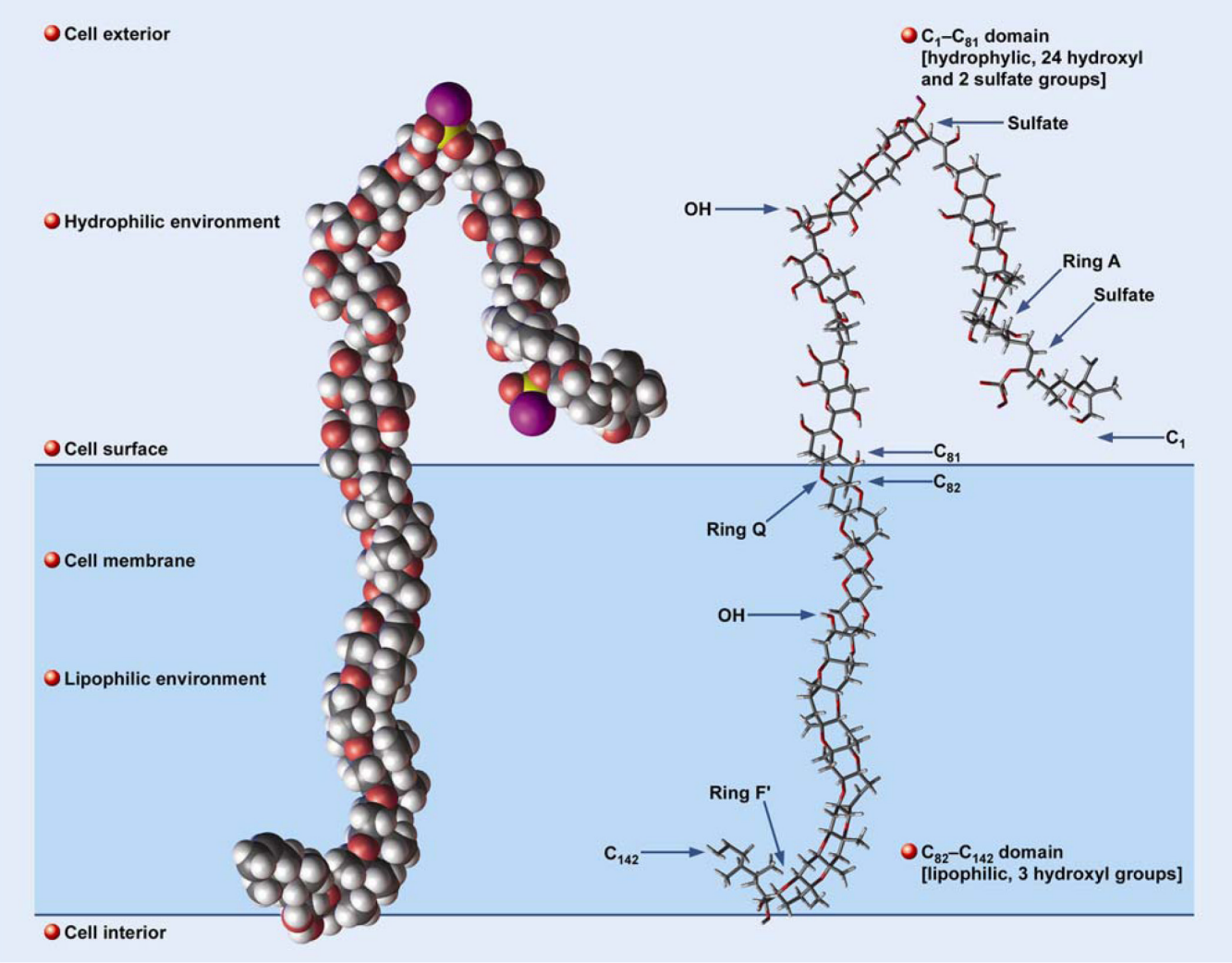


Figure 4.
Model of the anchoring of maitotoxin into the cell membrane (see Murata et al.).[11,24]

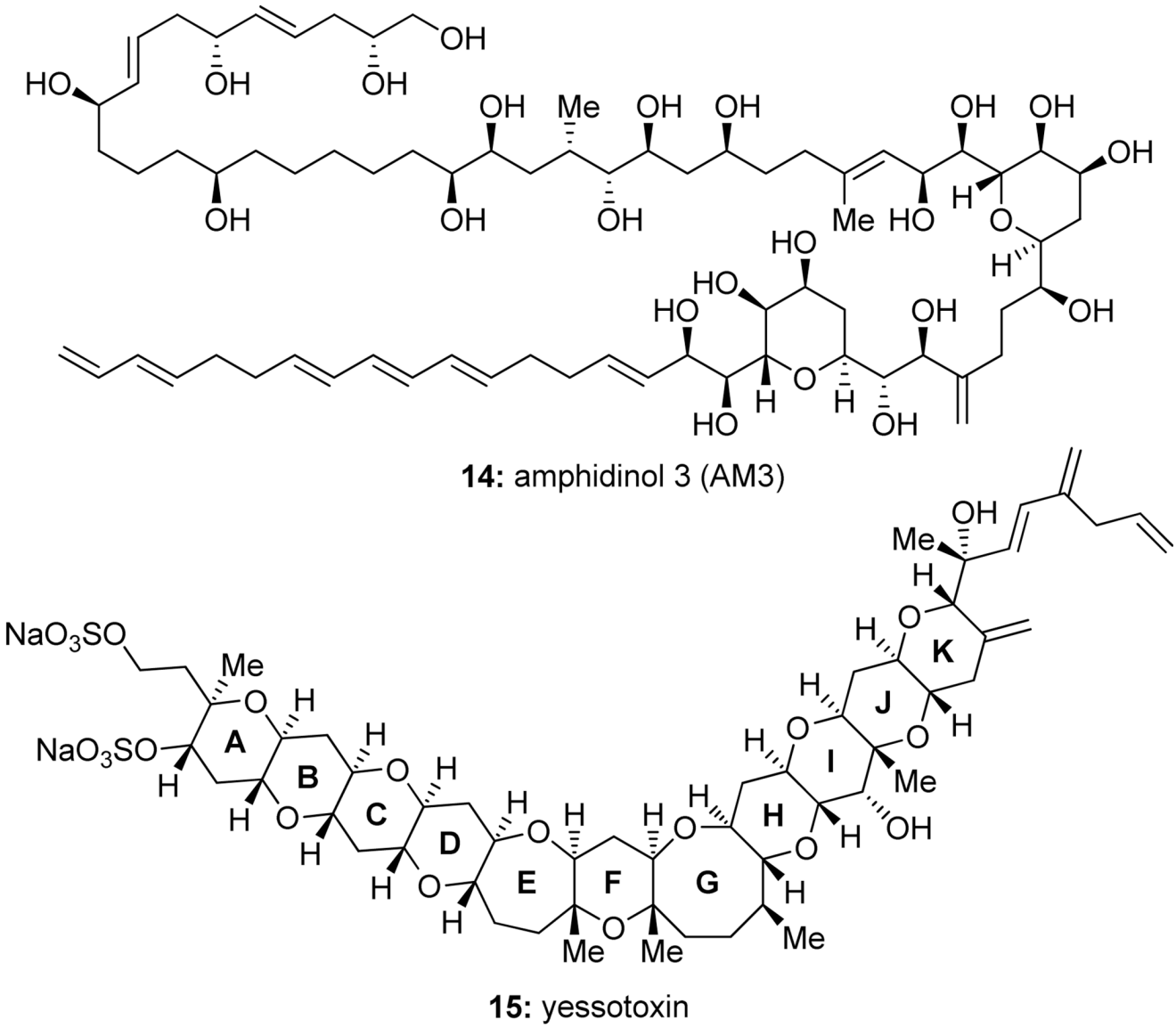


Figure 5.
Structures of amphidinol 3 (AM3, **14**) and yessotoxin (**15**).

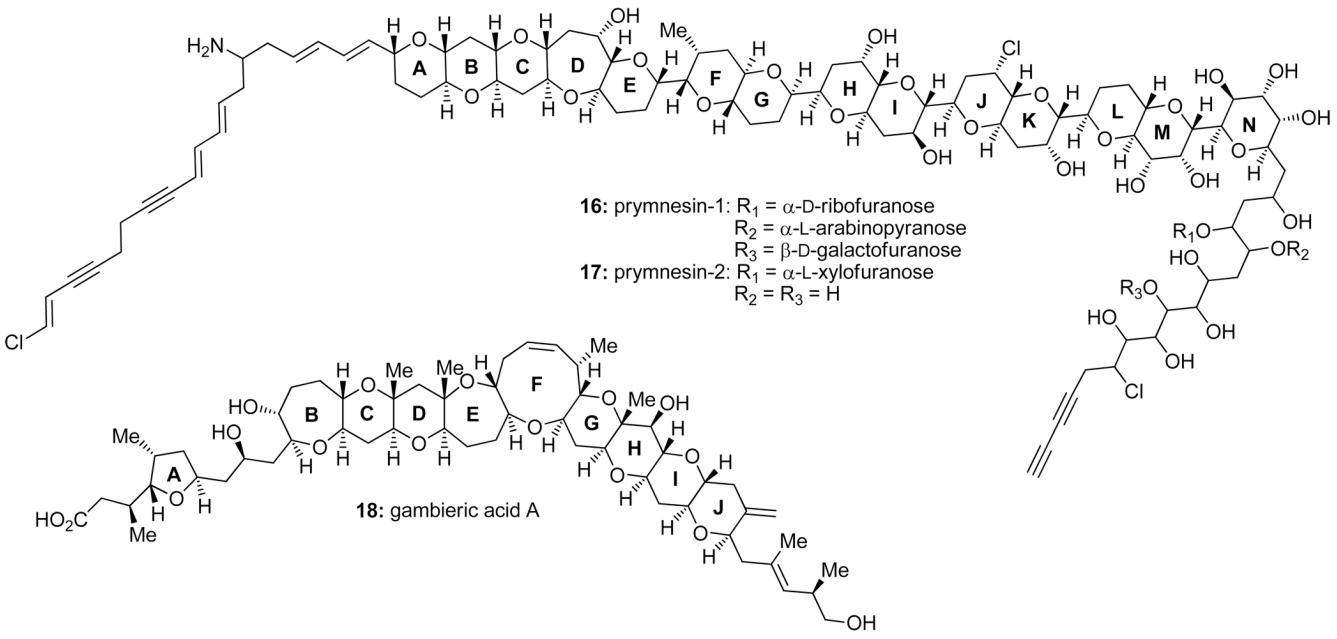


Figure 6.
Structures of prymnesin-1 (**16**) and prymnesin-2 (**17**) and gambieric acid A (**18**).

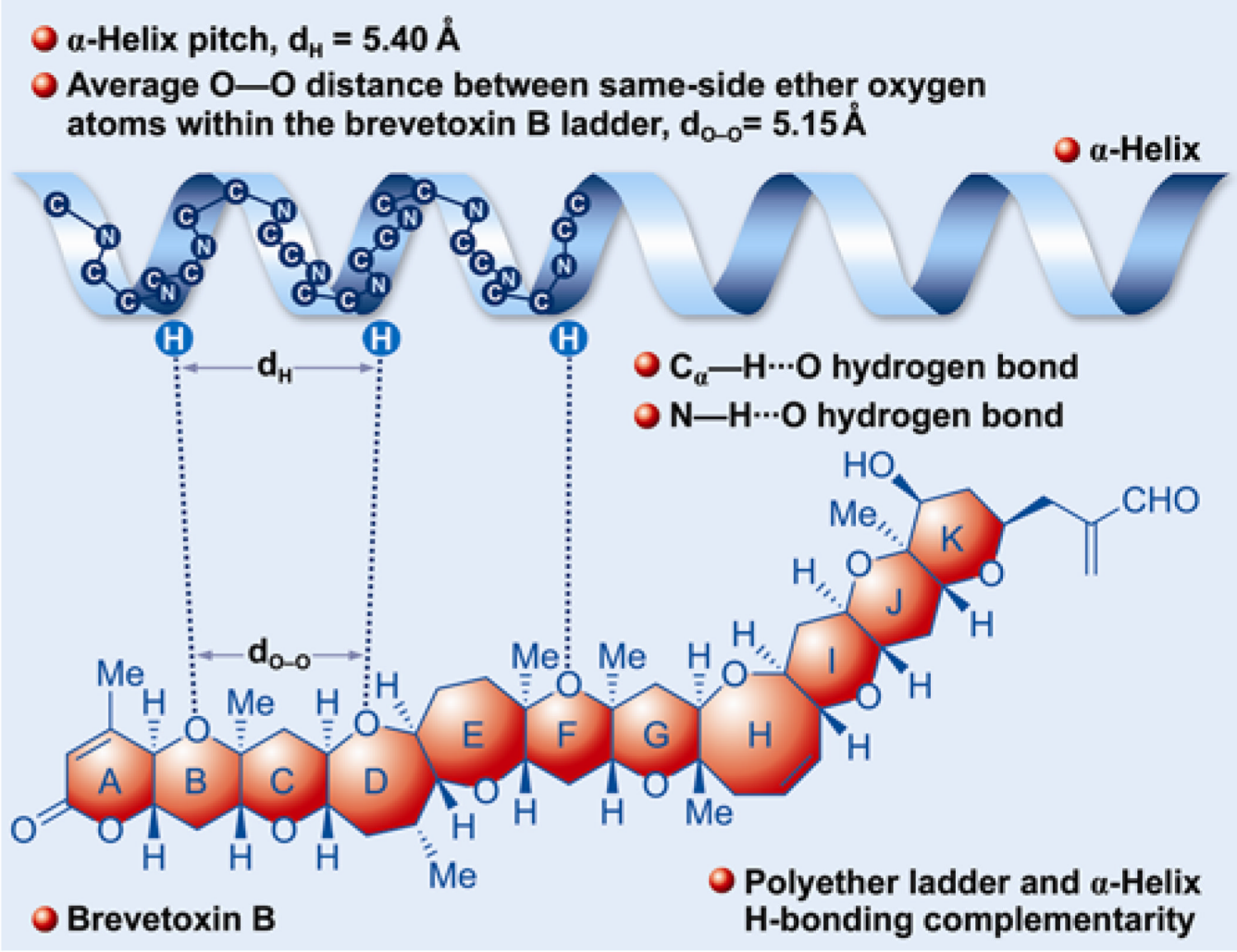


Figure 7.
Hypothetical model for the binding of ladder-like polyethers to their receptor a-helix motifs of membrane protein ion channels as exemplified by brevetoxin B (precise oxygens involved in the binding not defined (see Murata et al.).[11]

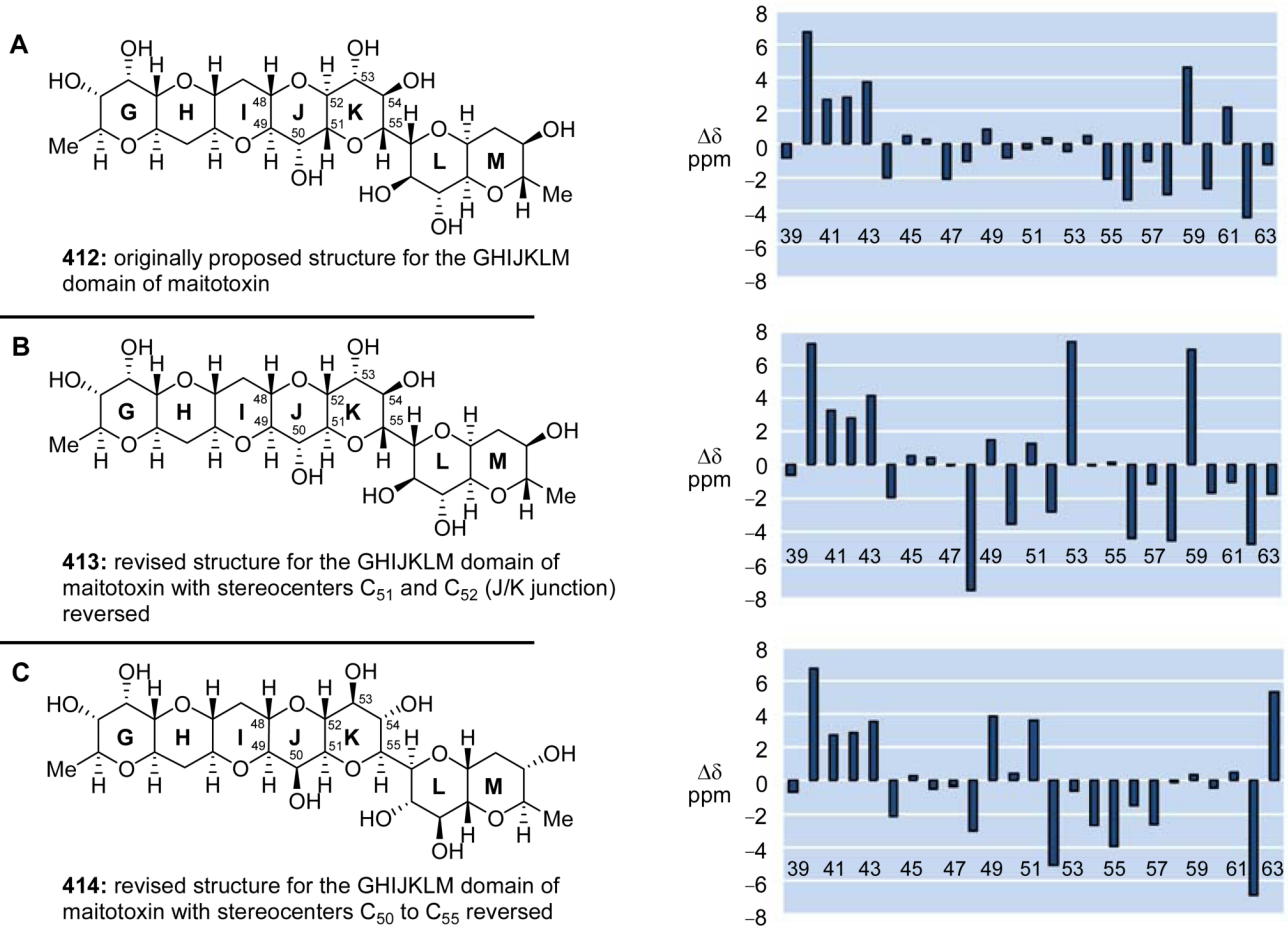


Figure 8.

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

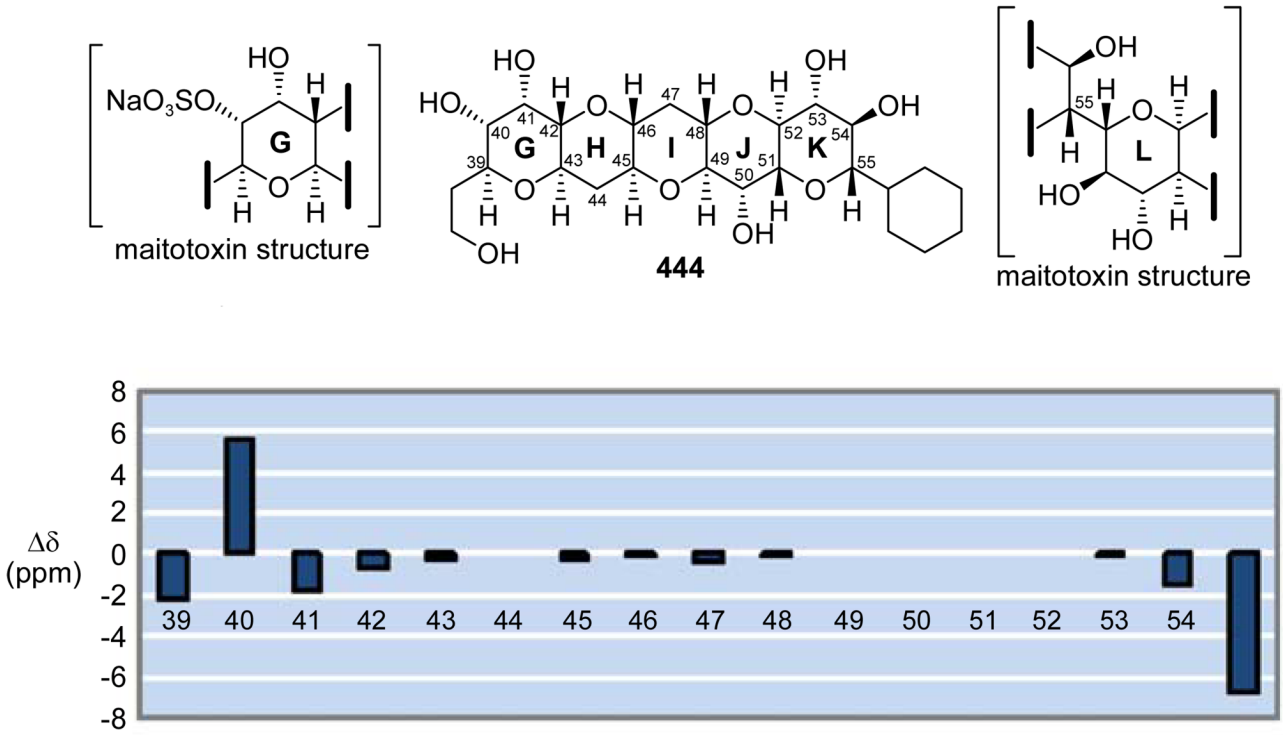


Figure 9.
Comparison of the ^{13}C chemical shifts of the GHIJK domain **444** with those reported for the same domain of maitotoxin (Nicolaou et al., 2007).[127a]

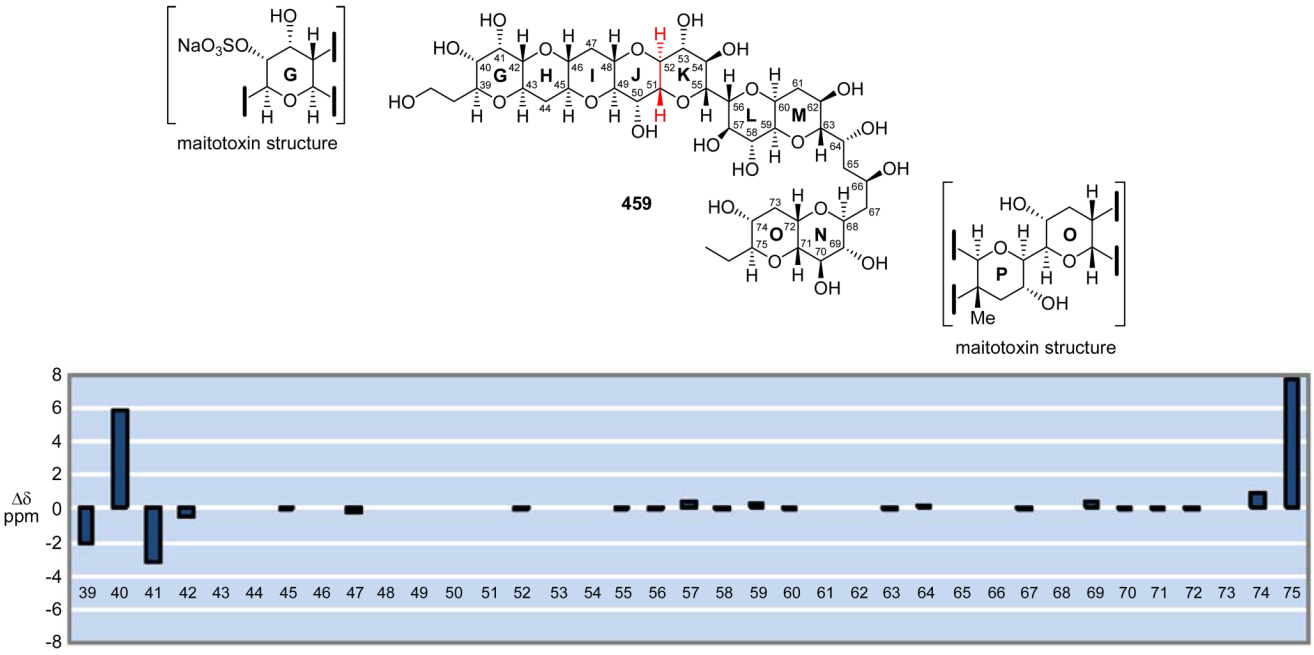
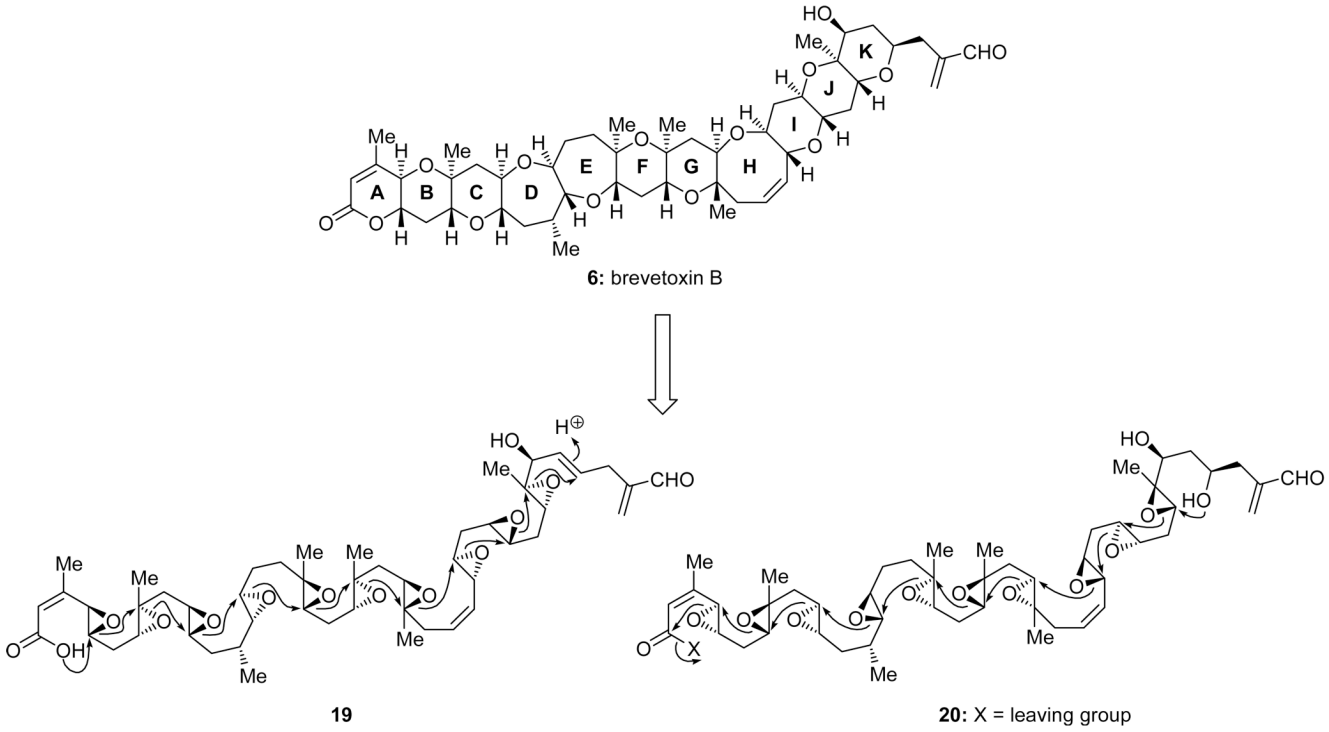
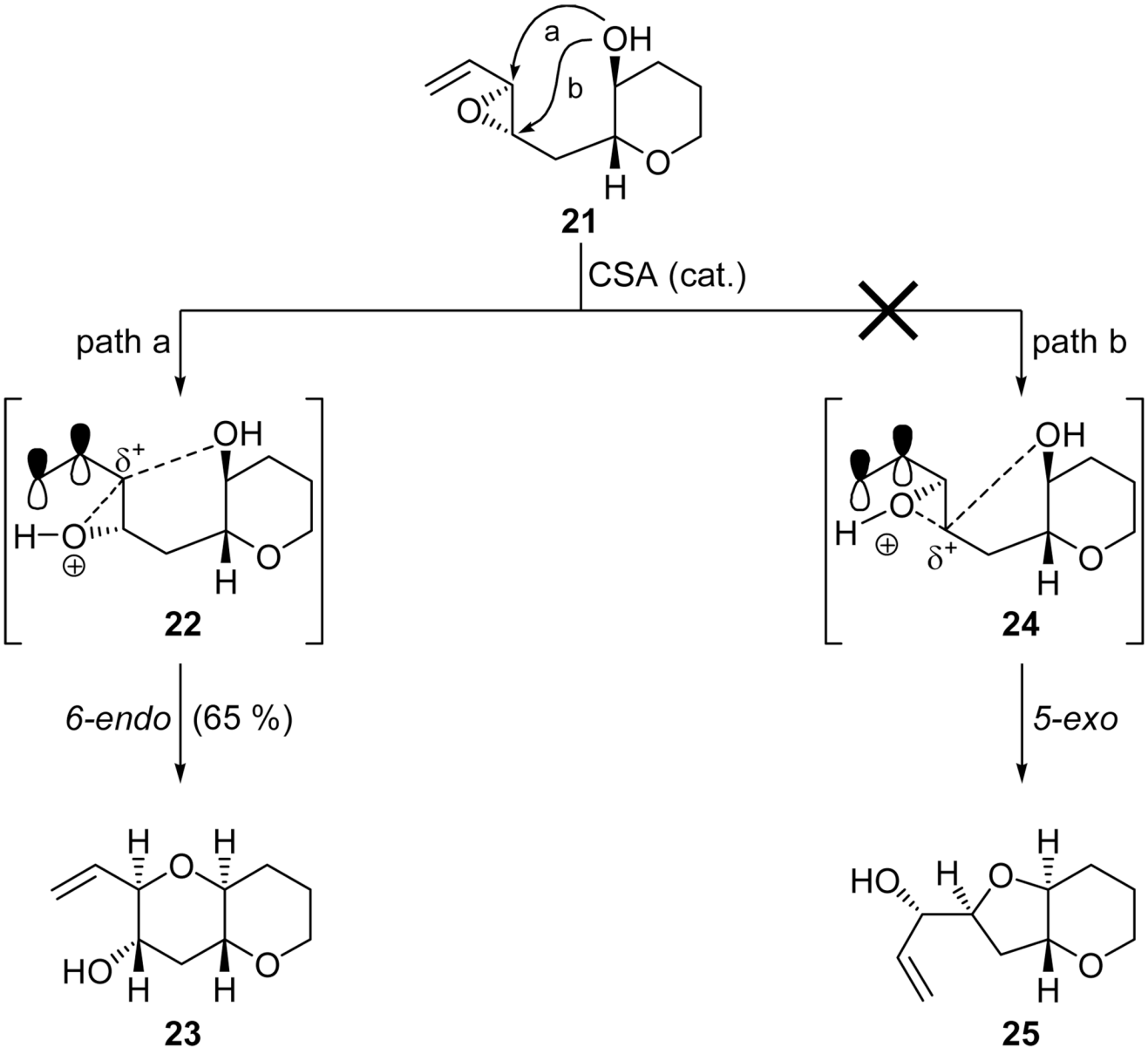


Figure 10.

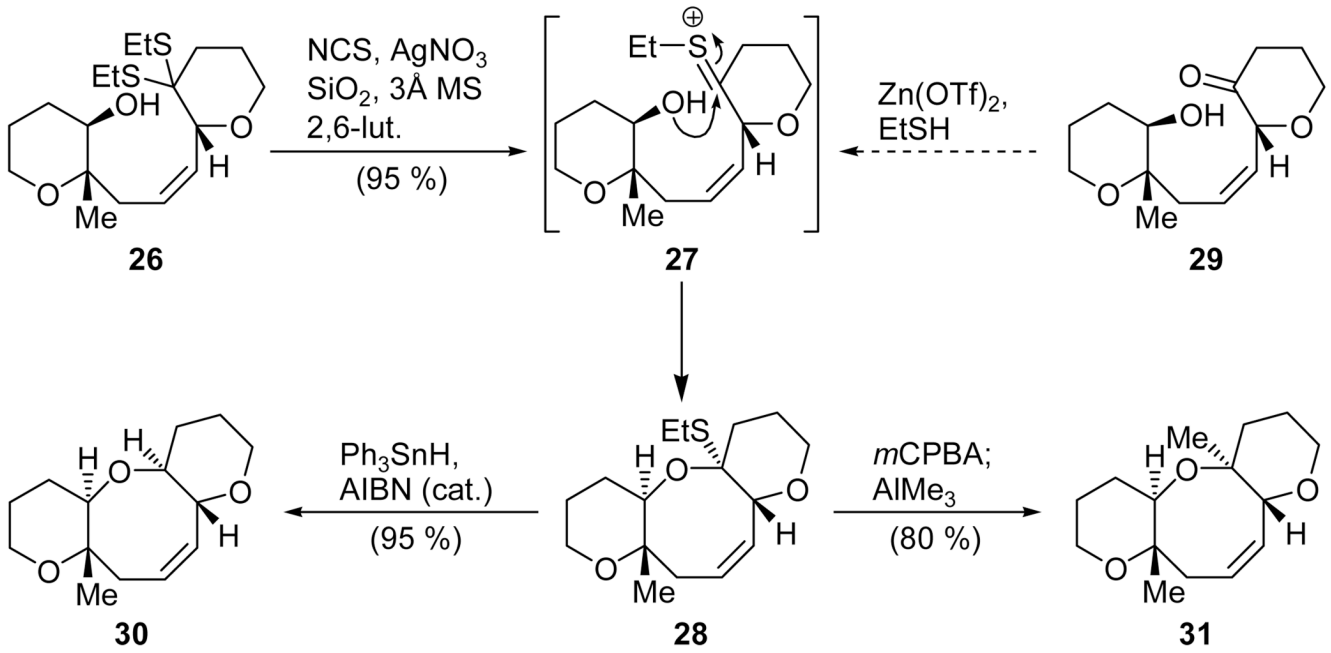
Comparison of the ^{13}C chemical shifts of the maitotoxin GHIJKLMNO domain (**459**) with those reported for the same domain of maitotoxin (Nicolaou et al., 2007).[127b]



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

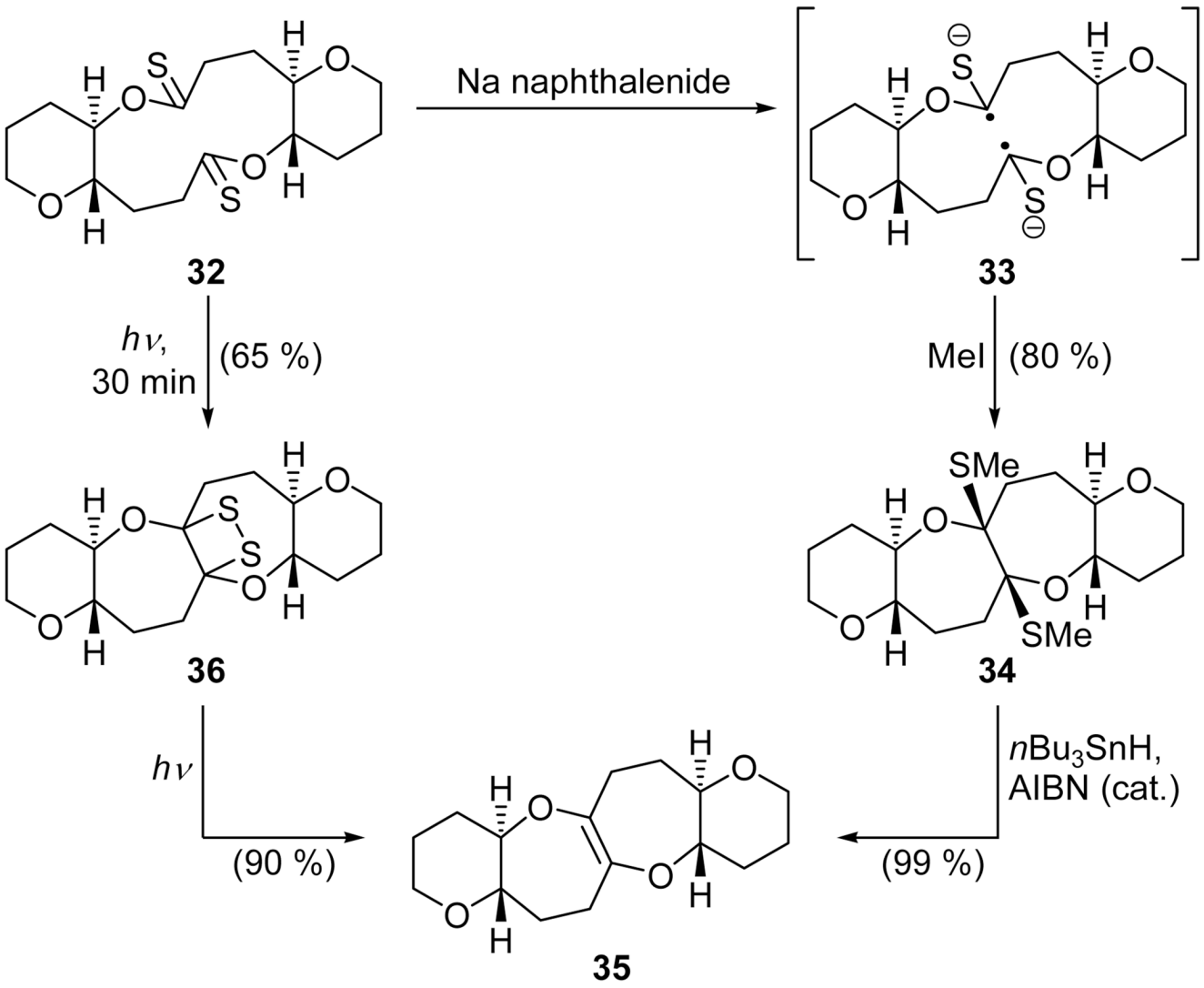


Scheme 2.
The 6-*endo* hydroxy epoxide opening method for cyclic ether formation (Nicolaou et al., 1985). [37]

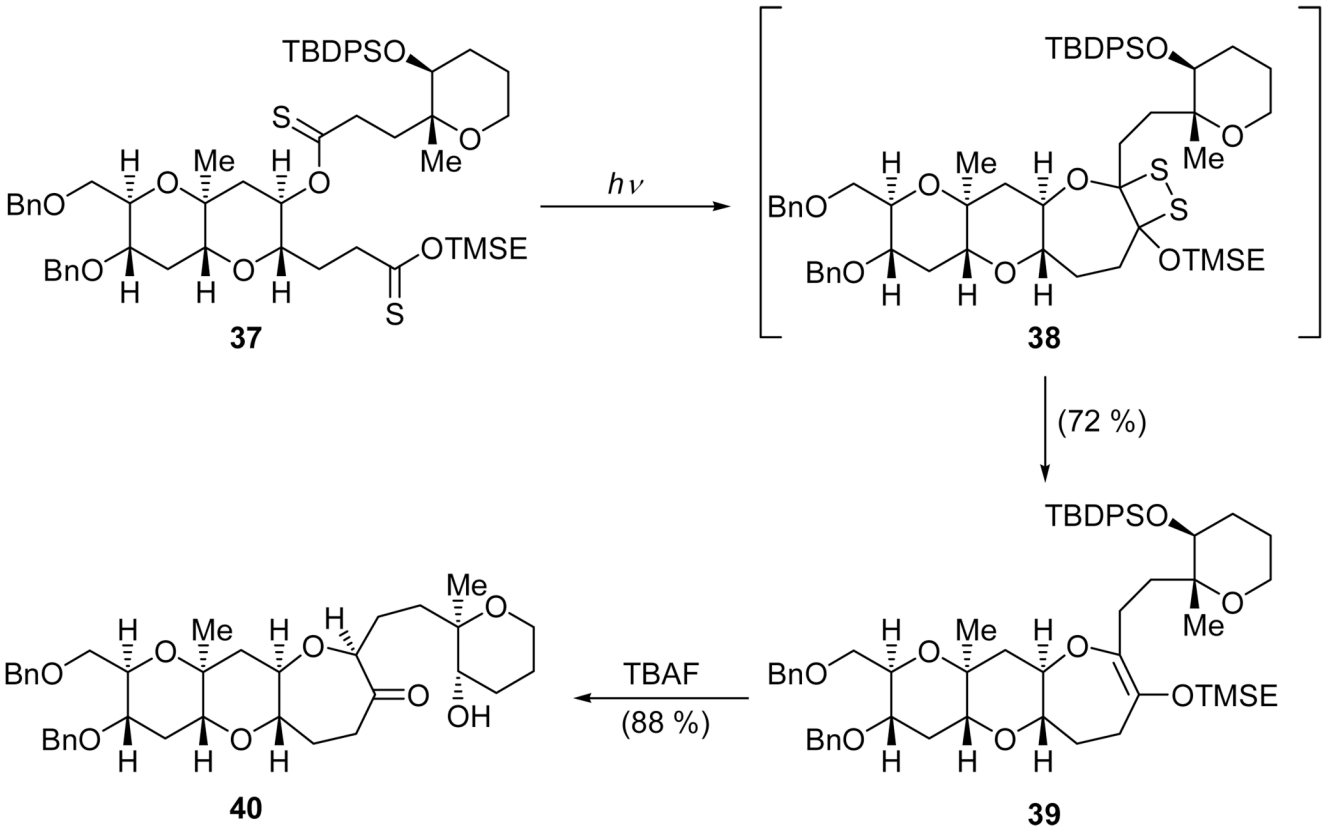


Scheme 3.

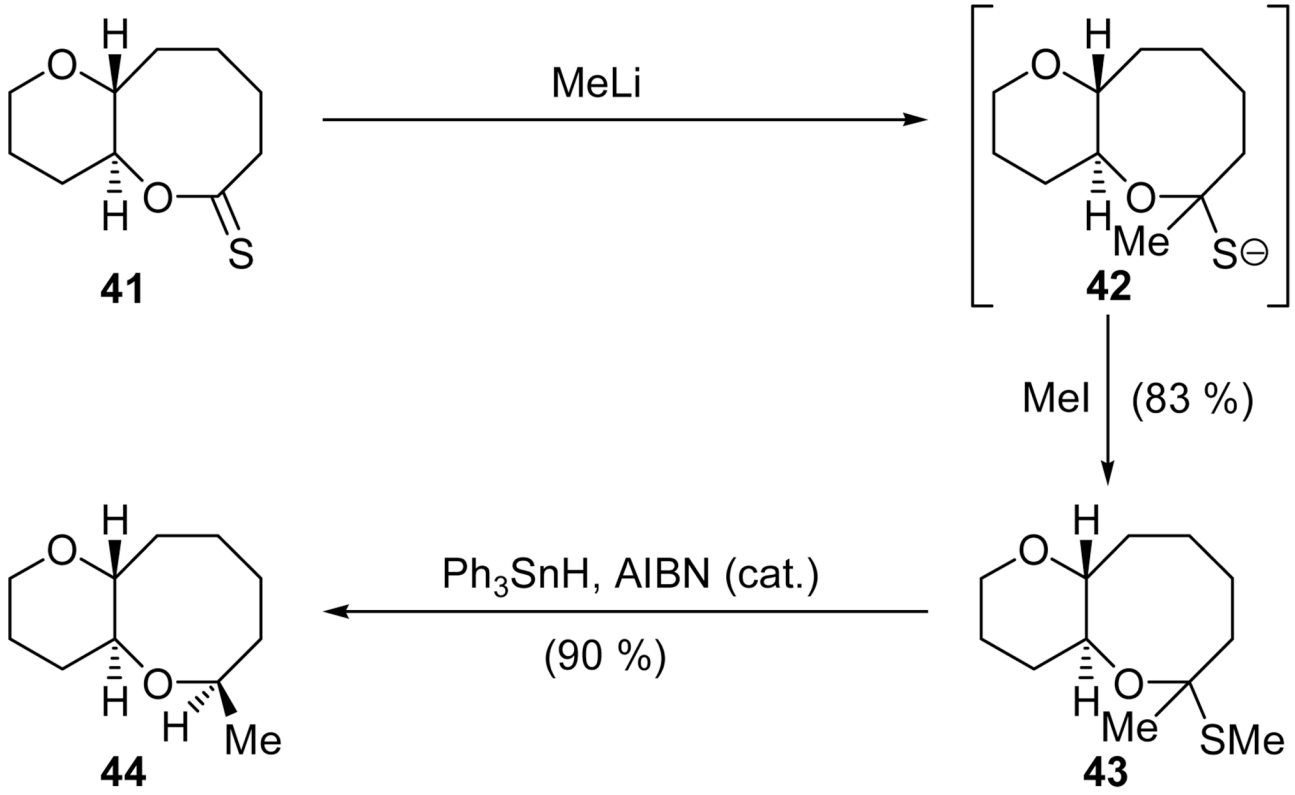
The hydroxy dithioketal cyclization method involving mixed *O*,S-acetals for cyclic ether formation (Nicolaou et al., 1986).[39]



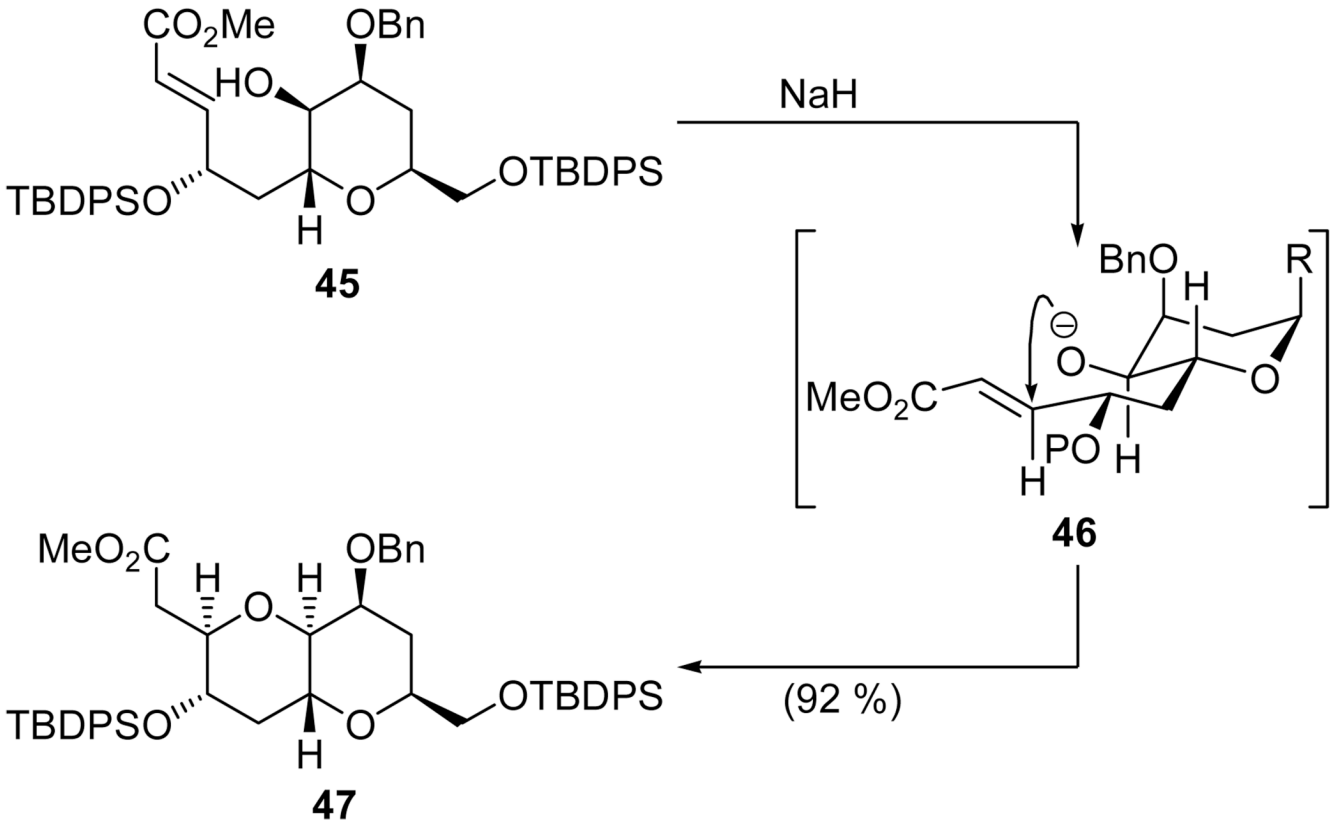
Scheme 4.
The dithionolactone bridging method for cyclic ether formation (Nicolaou et al., 1986).[42]



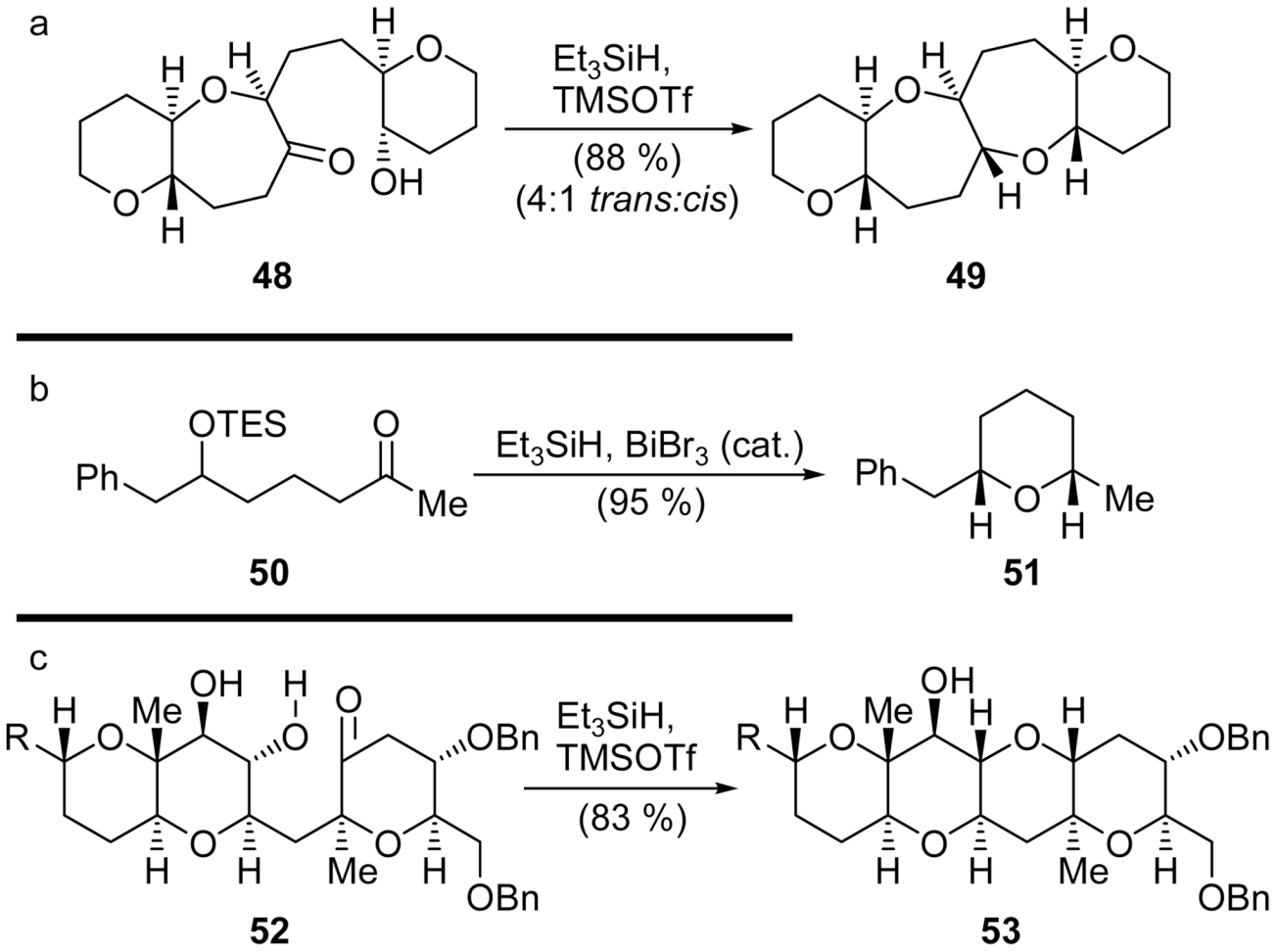
Scheme 5.
The dithionoester photolytic cyclization method for cyclic ether formation (Nicolaou et al., 1989).[44]



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

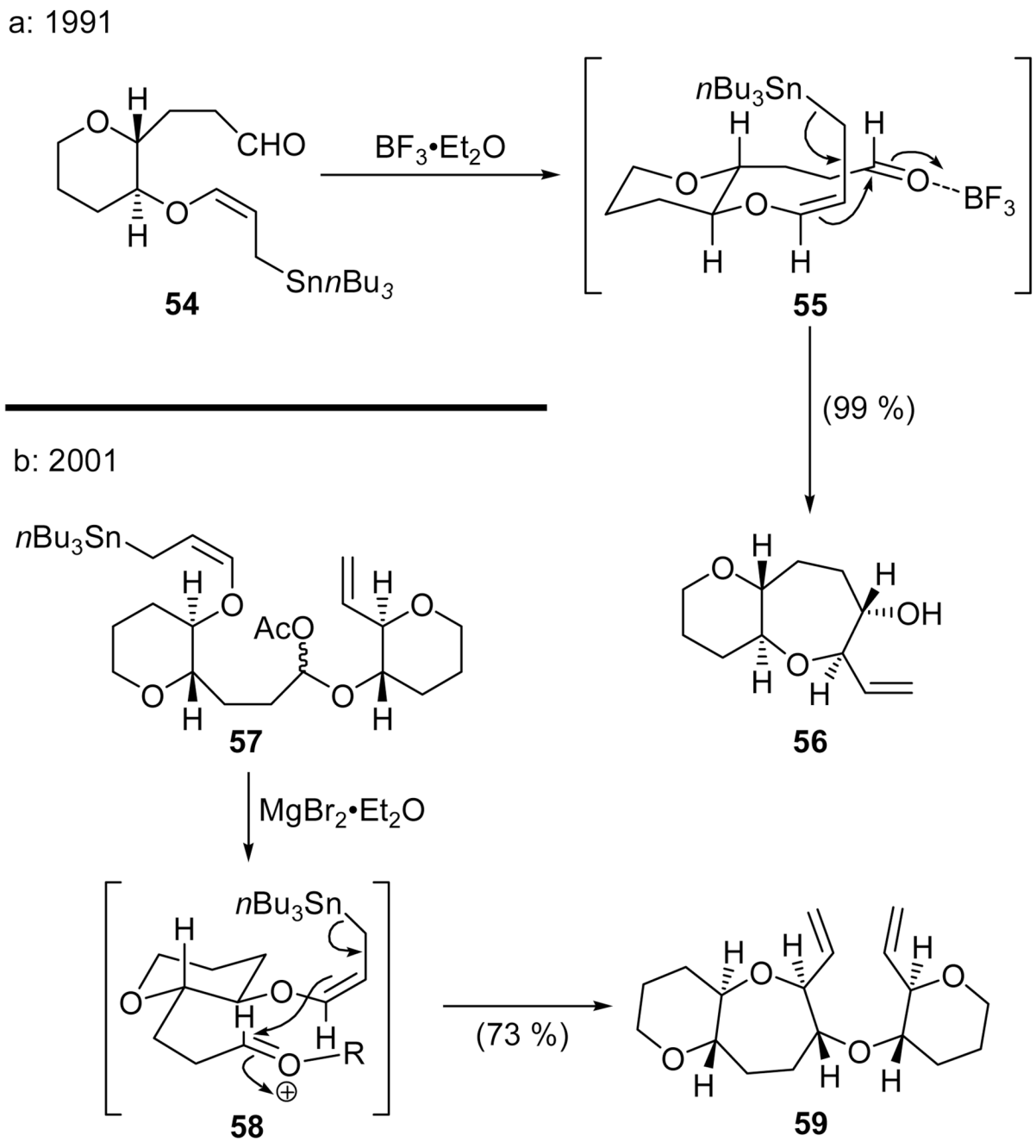


Scheme 7.
The intramolecular hydroxy Michael addition reaction for cyclic ether formation (Nicolaou et al., 1989).[46]

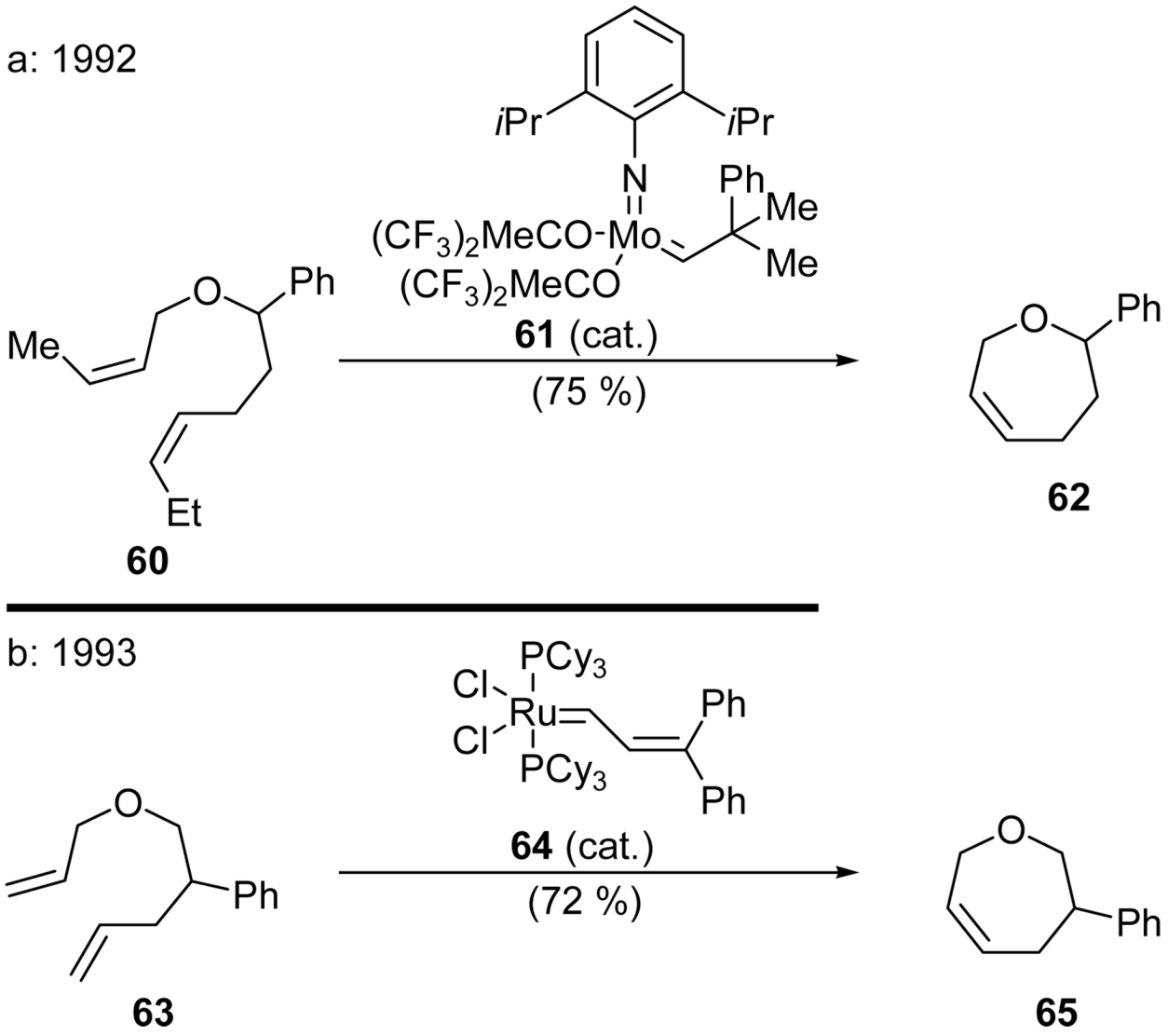


Scheme 8.

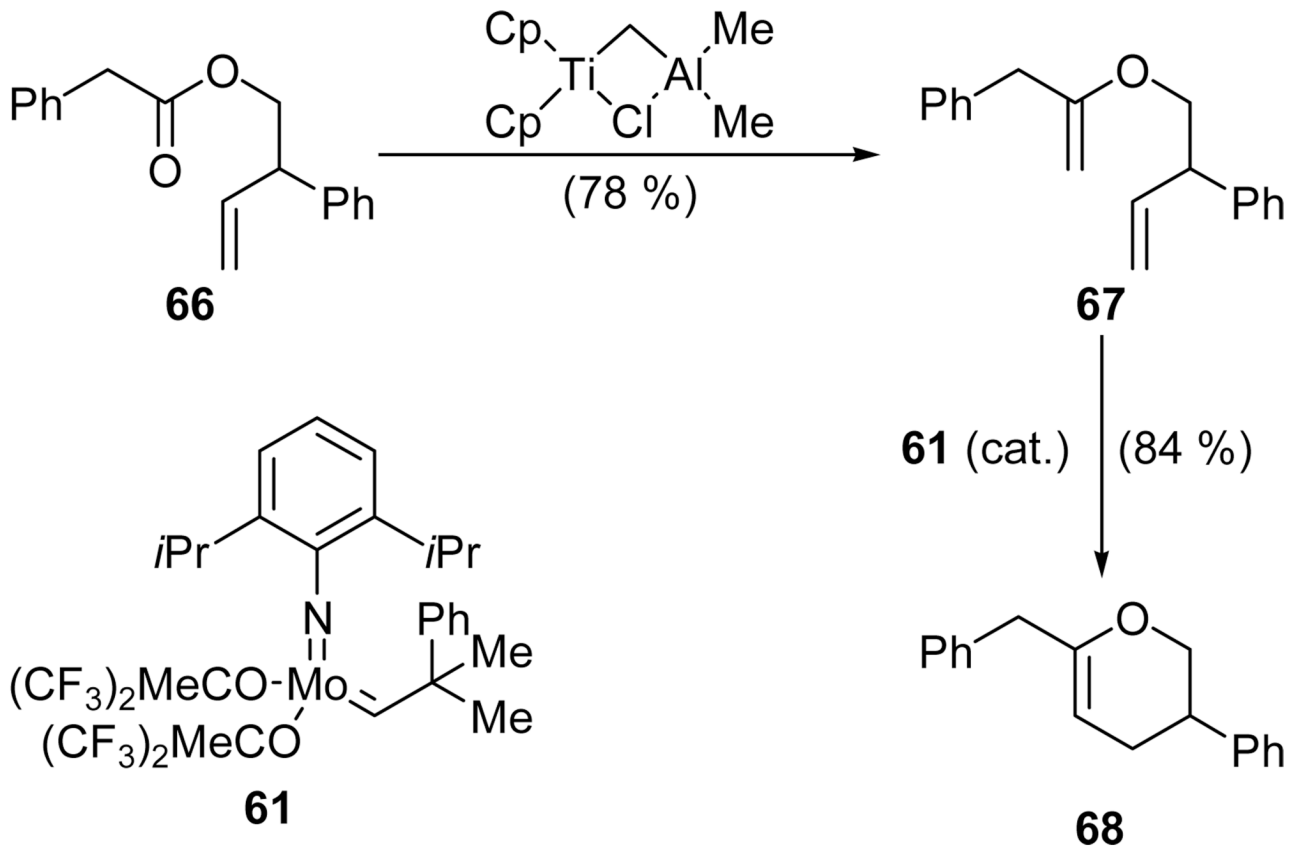
The hydroxy ketone reductive cyclization method for cyclic ether formation (a: Nicolaou et al., 1989,[44] b: Evans et al., 2003;[49] c: Sasaki et al., 2007).[48]



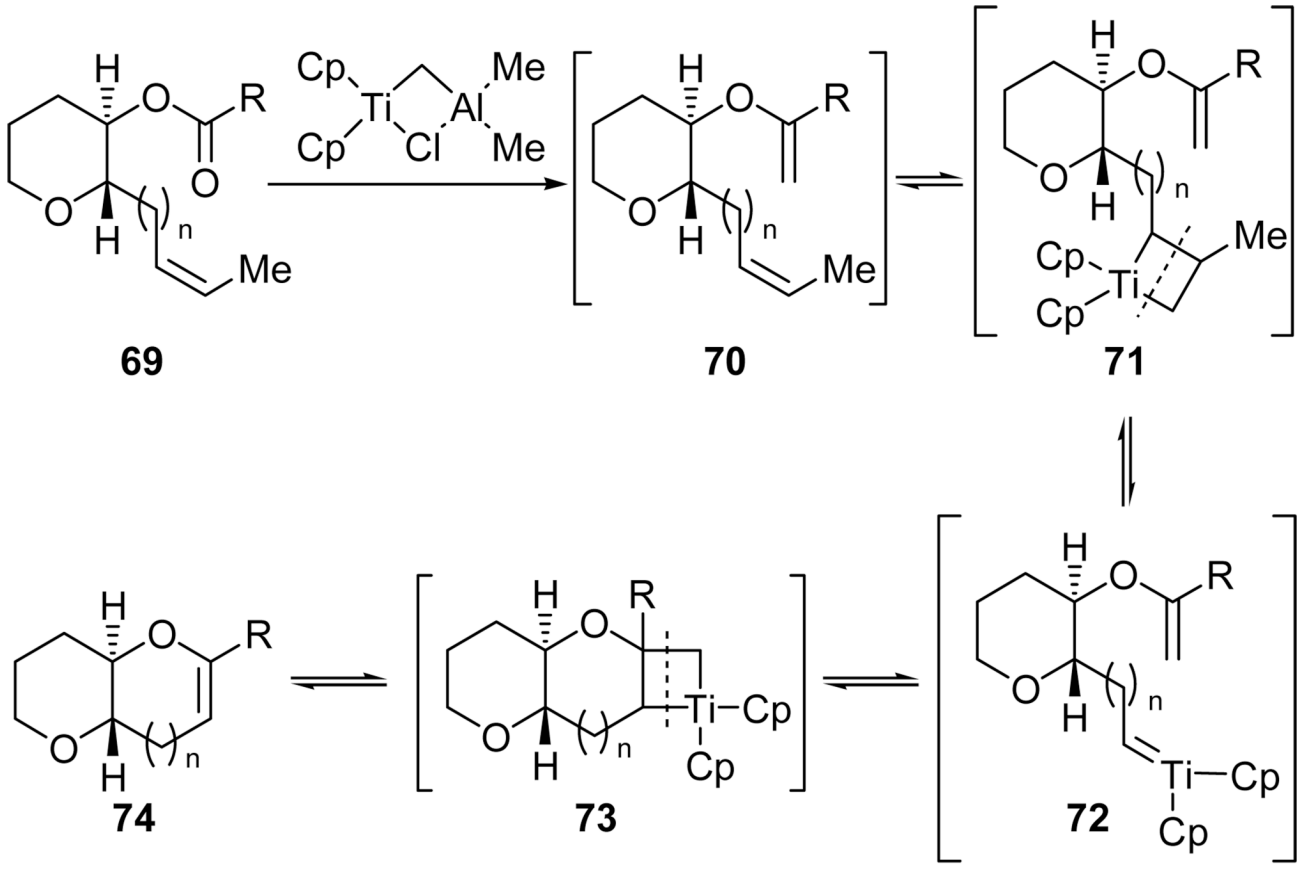
Scheme 9.
The allyl tin cyclization method for the formation of cyclic ethers (Yamamoto et al., 1991, [50] 2001).[51]



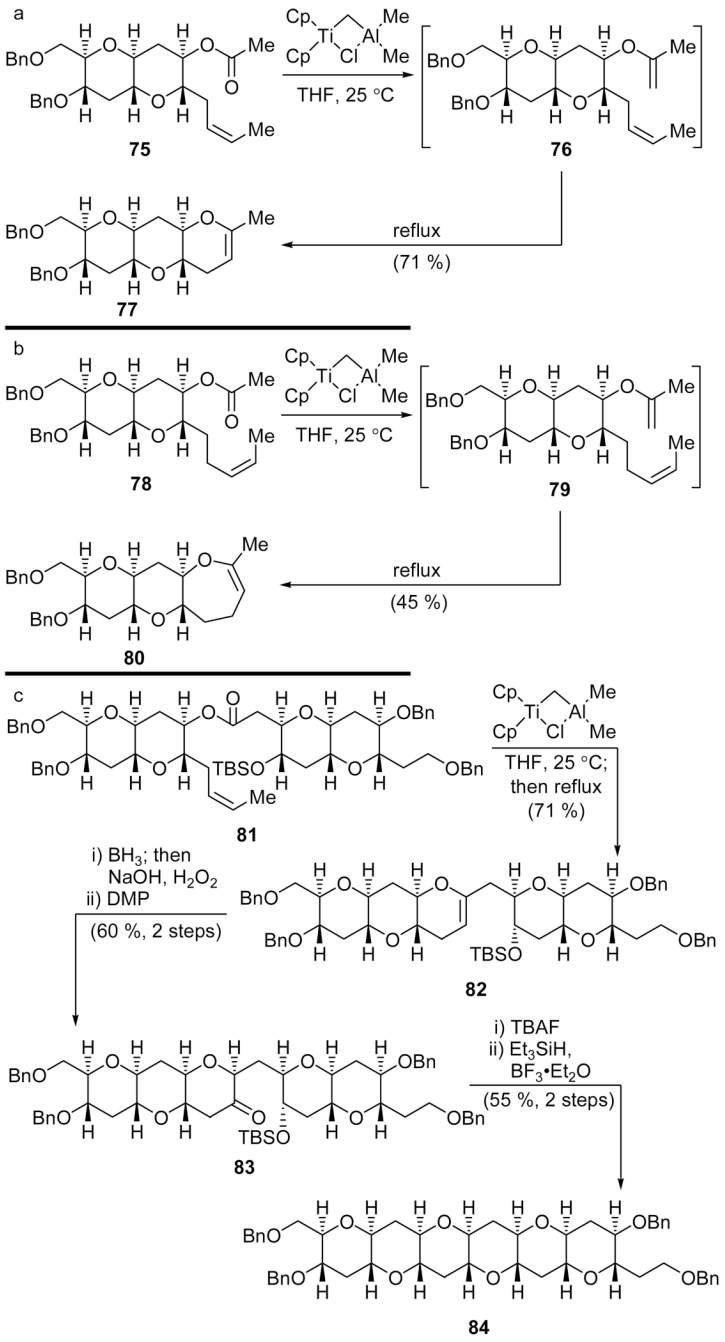
Scheme 10.
First examples of cyclic ether formation by ring closing metathesis (Grubbs et al., a: 1992; b: 1993).[55a,b]



Scheme 11.
Early example of cyclic enol ether formation by ring closing metathesis (Grubbs et al., 1994). [55c]

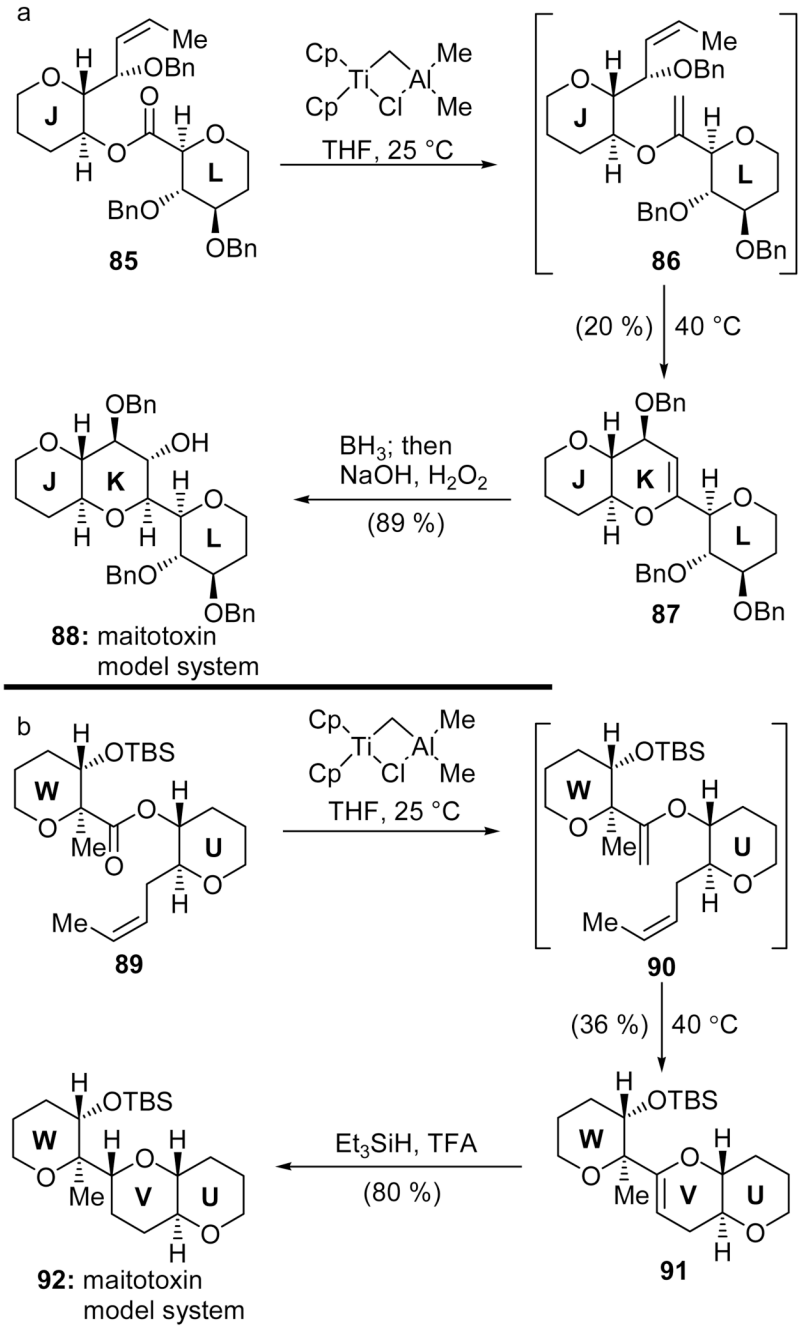


Scheme 12.
General, one-pot, ester methylenation/metathesis method for the formation of cyclic polyethers (Nicolaou et al., 1996).[56]



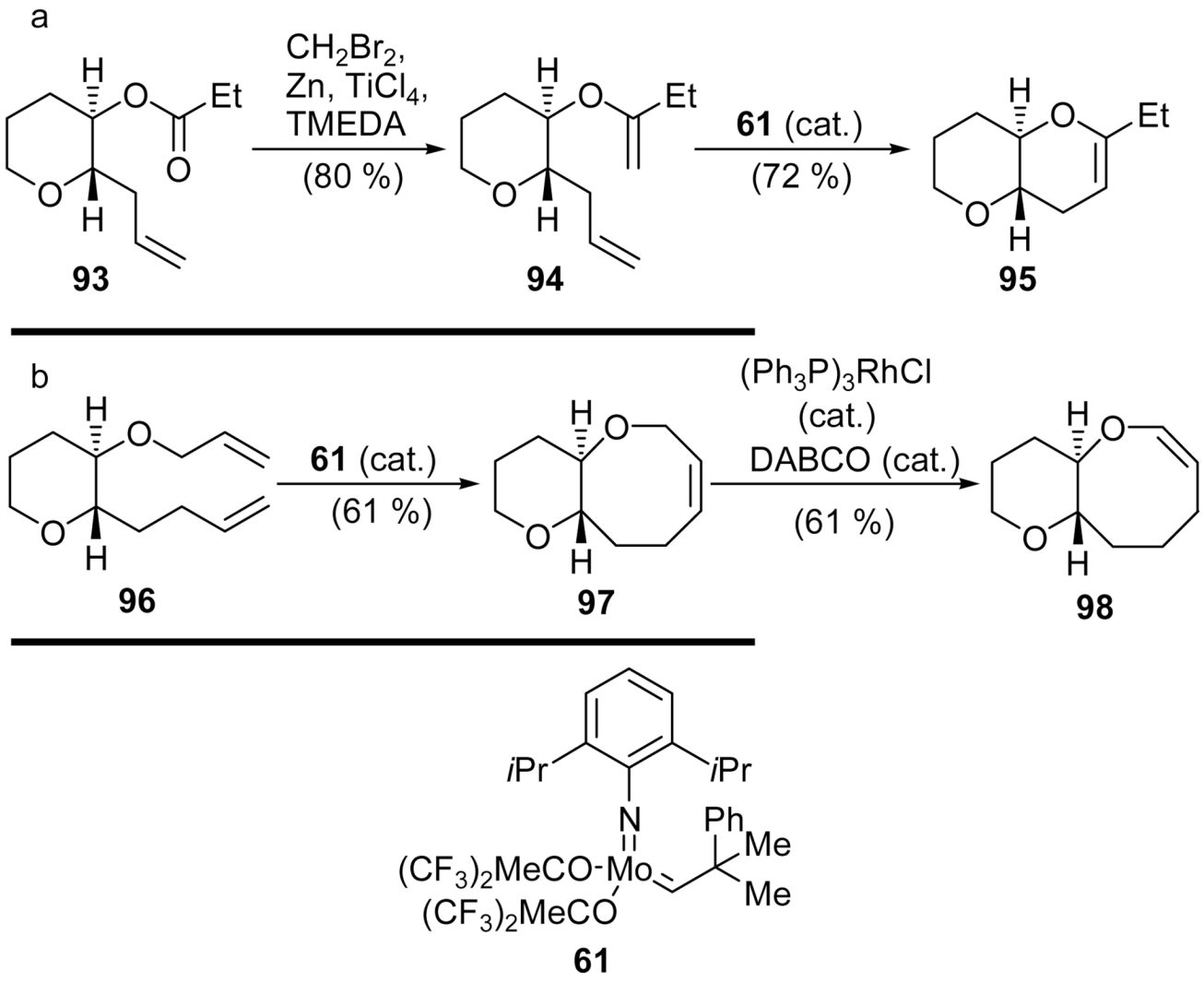
Scheme 13.

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



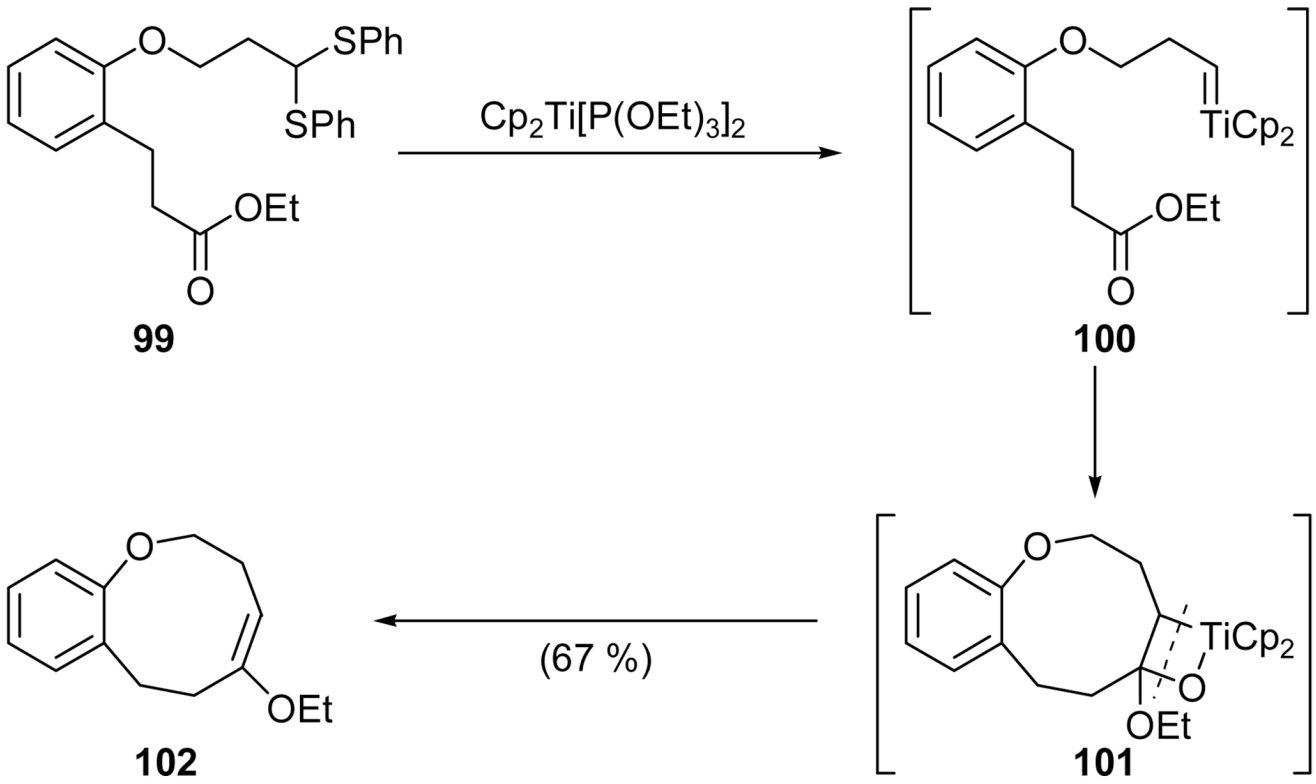
Scheme 14.

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

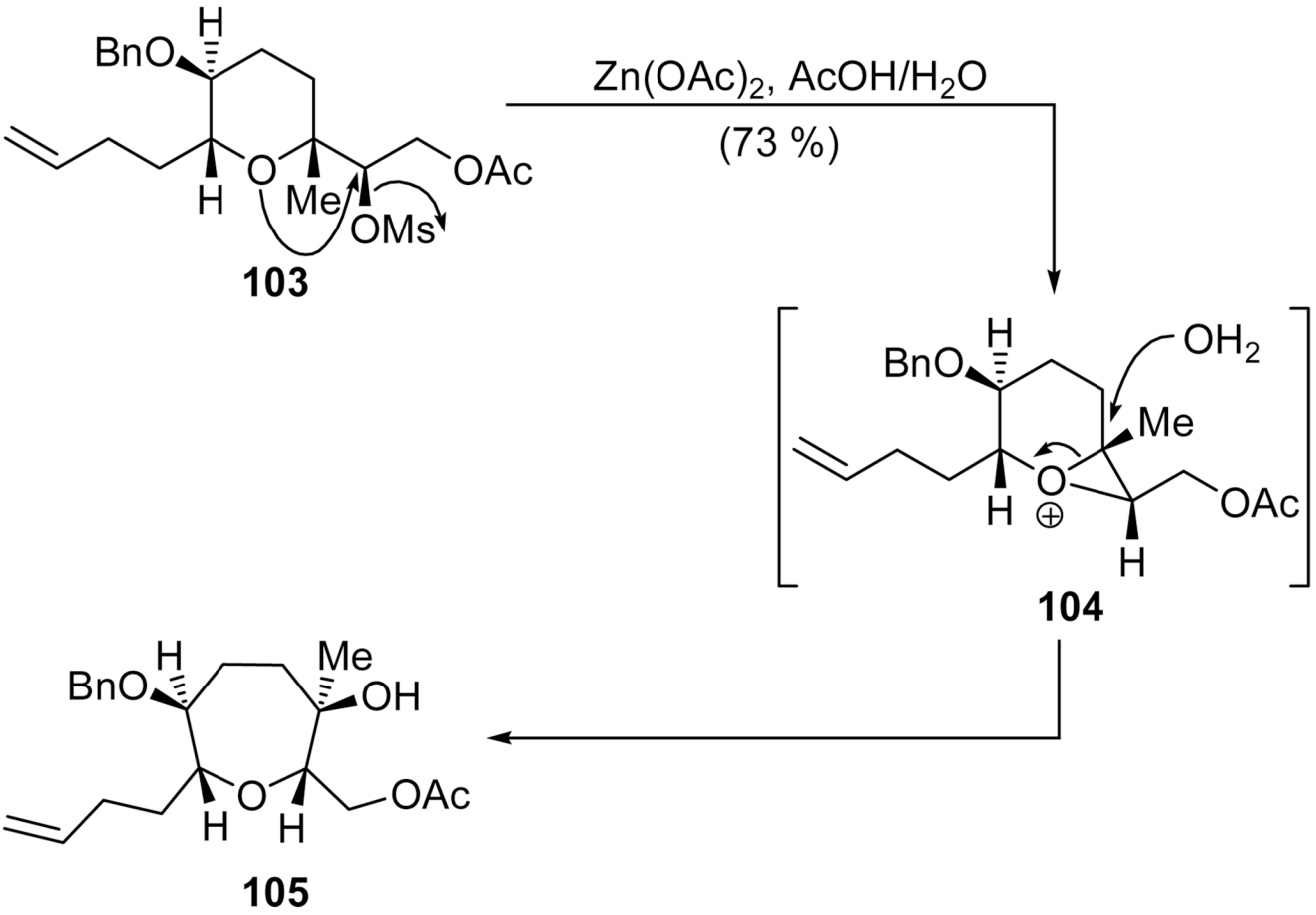


Scheme 15.

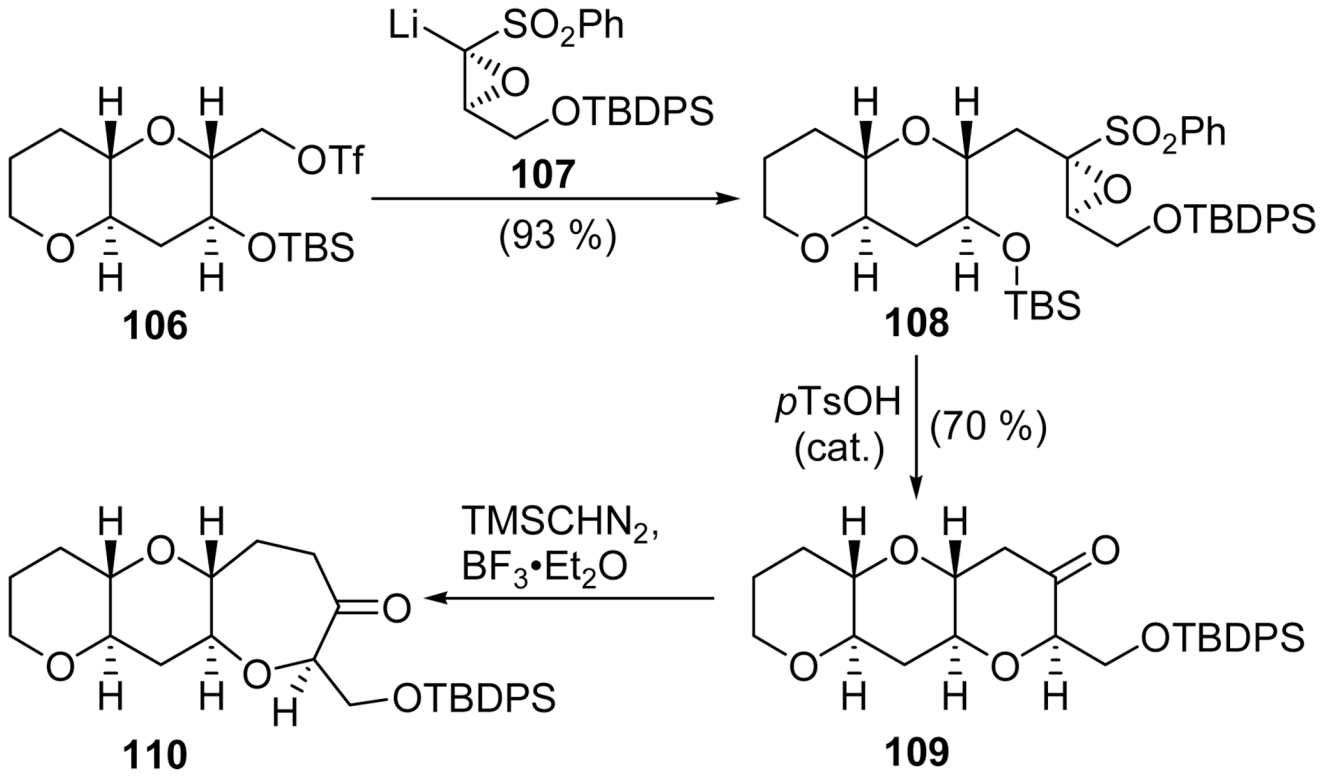
The two-step version of the methylenation/metathesis method for cyclic ether formation (Clark et al., 1997).[60]



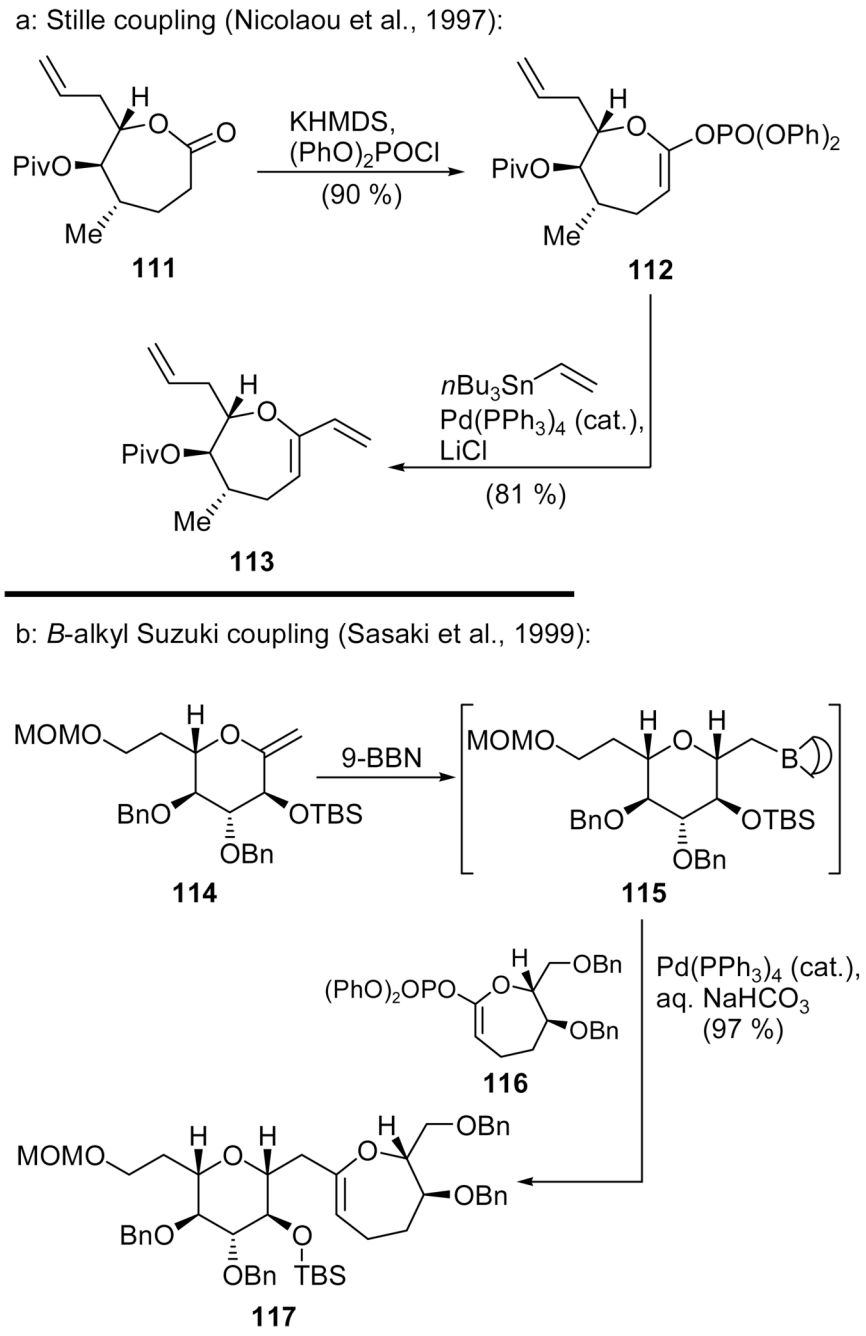
Scheme 16.
Intramolecular, carbene-ester addition method for the formation of cyclic ethers (Takeda et al., 1997).[63]



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

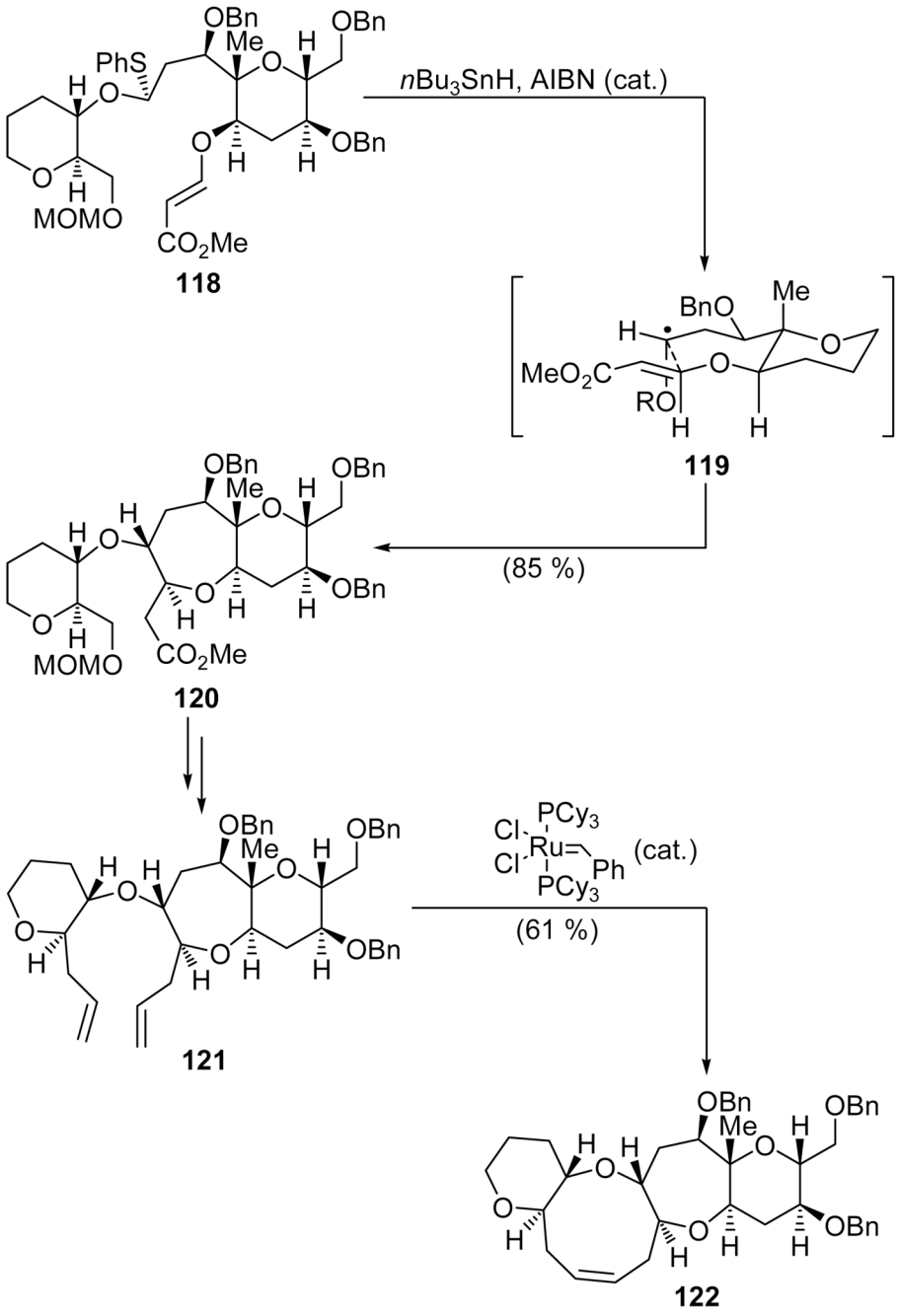


Scheme 18.
The oxiranyl anion addition/cyclization method for the formation of cyclic ethers (Mori et al., 1996).[65]



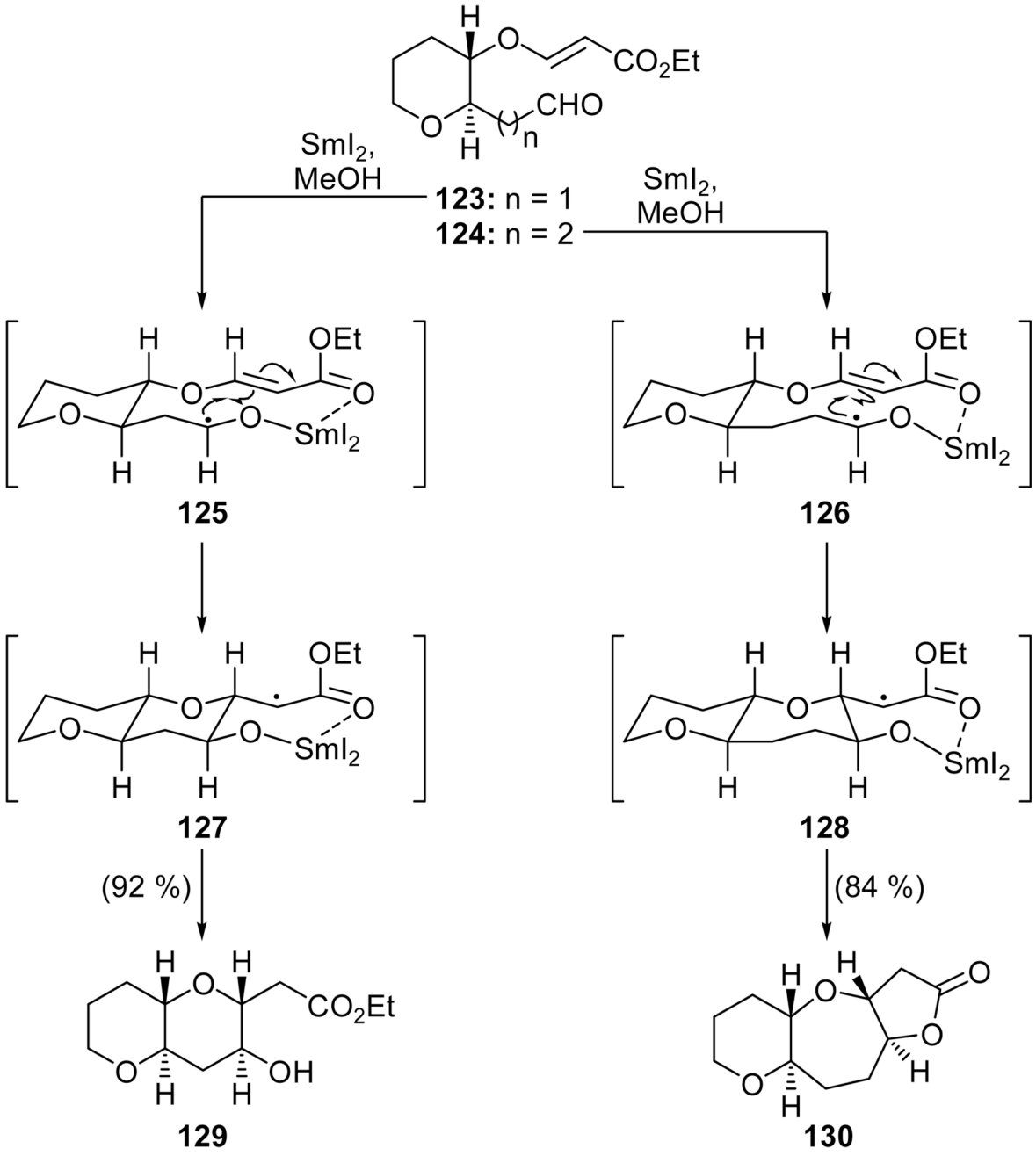
Scheme 19.

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

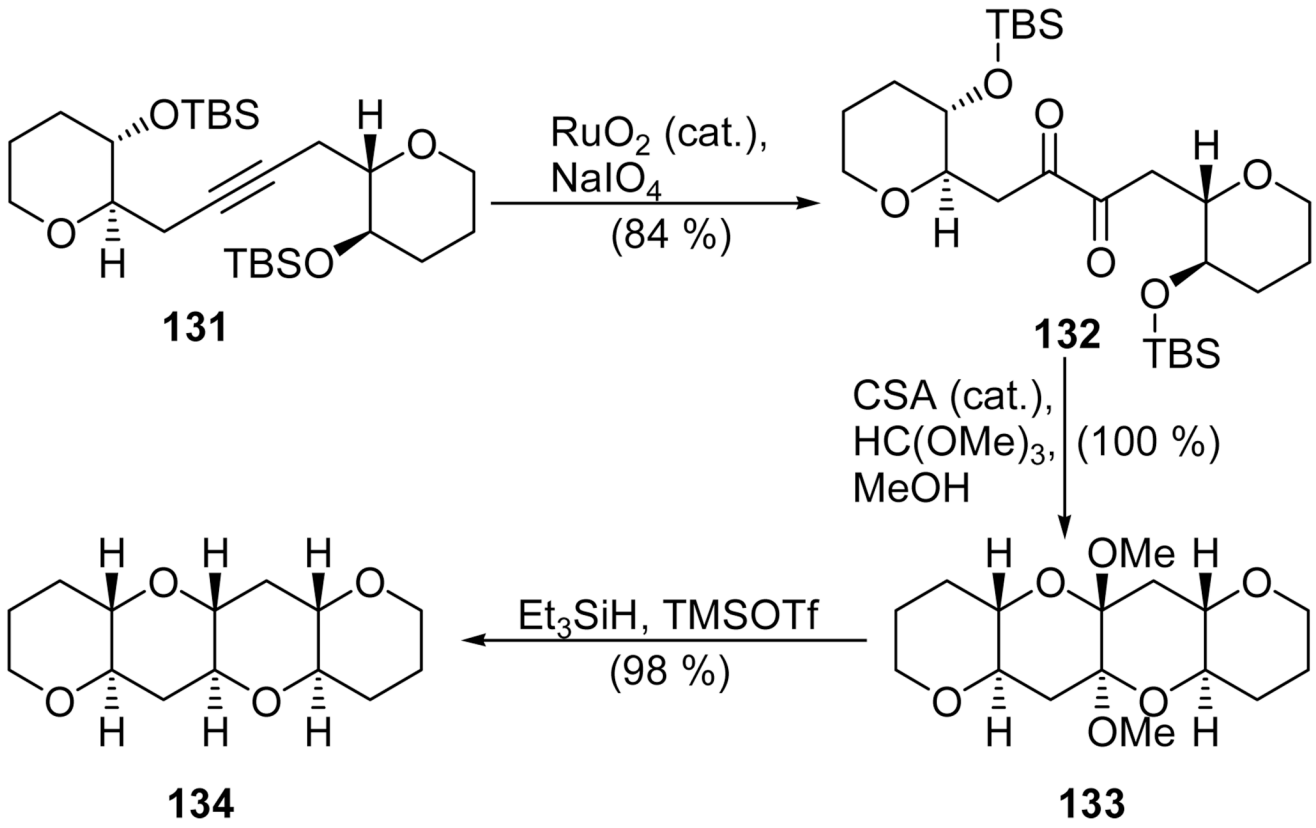


Scheme 20.

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

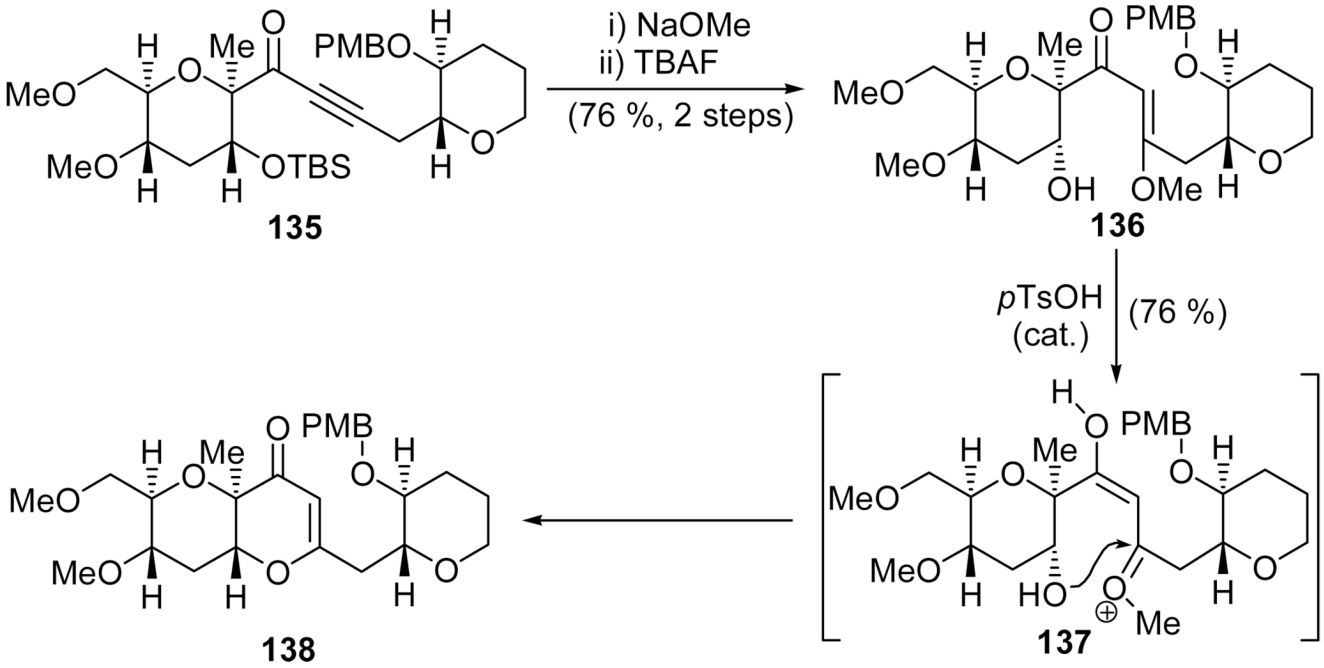


Scheme 21.
The SmI_2-induced reductive cyclization method for the formation of cyclic ethers (Nakata et al., 1999).[71]

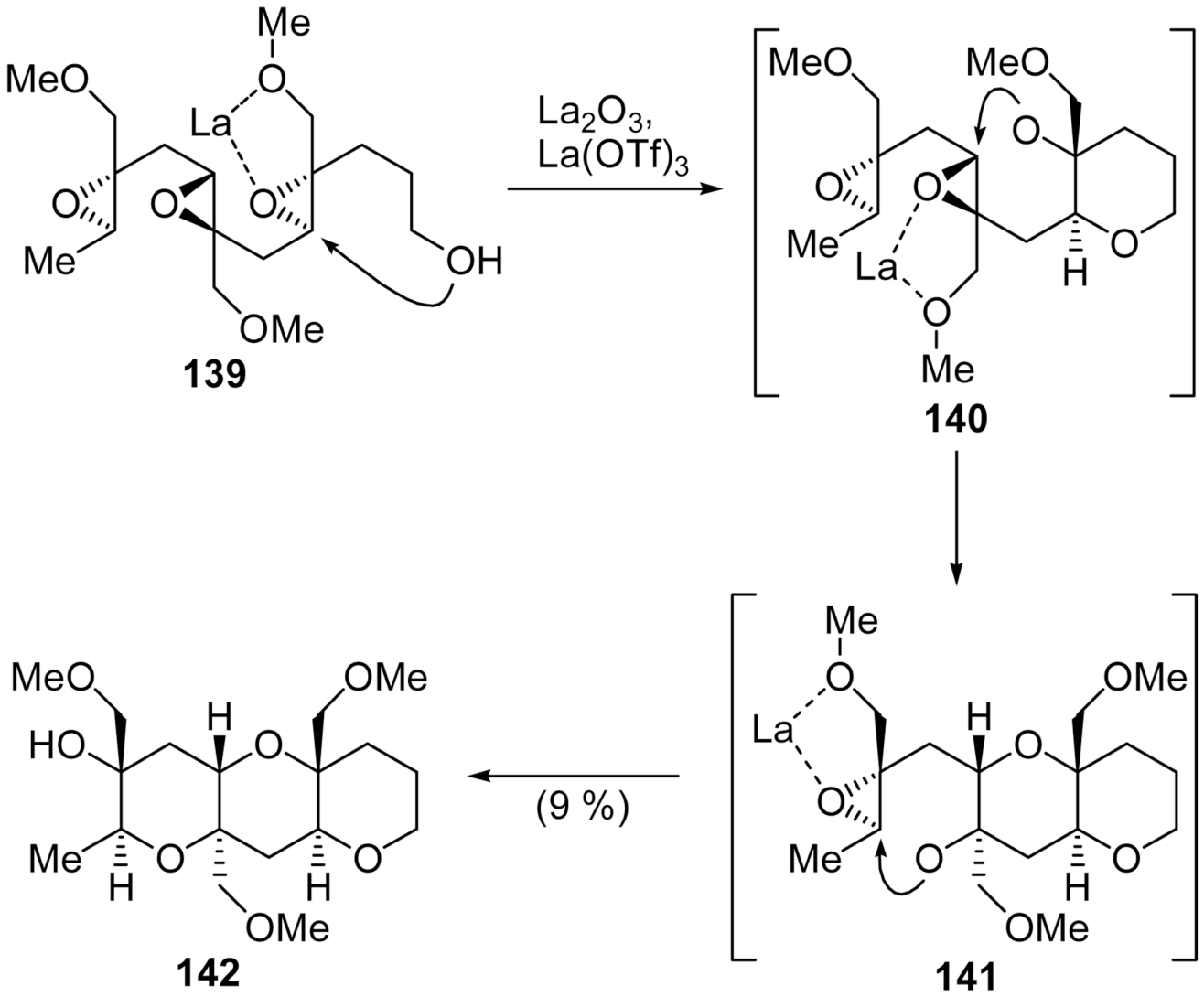


Scheme 22.

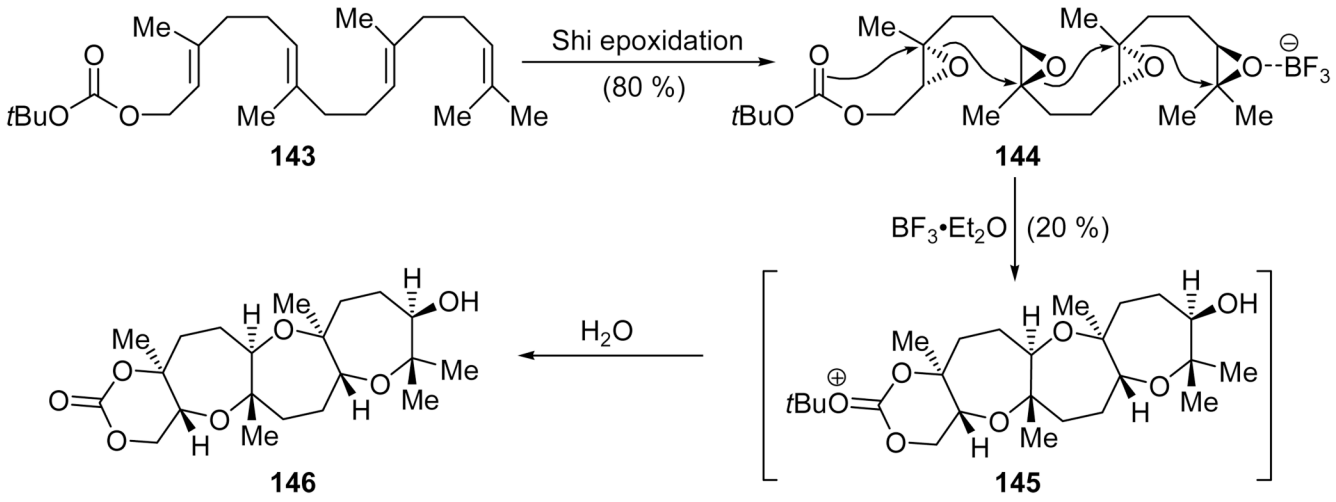
Alkyne functionalization/cyclization methods (Fujiwara/Murai et al.,[73] Nakata et al.,[74] and Mori et al., 2000).[75]



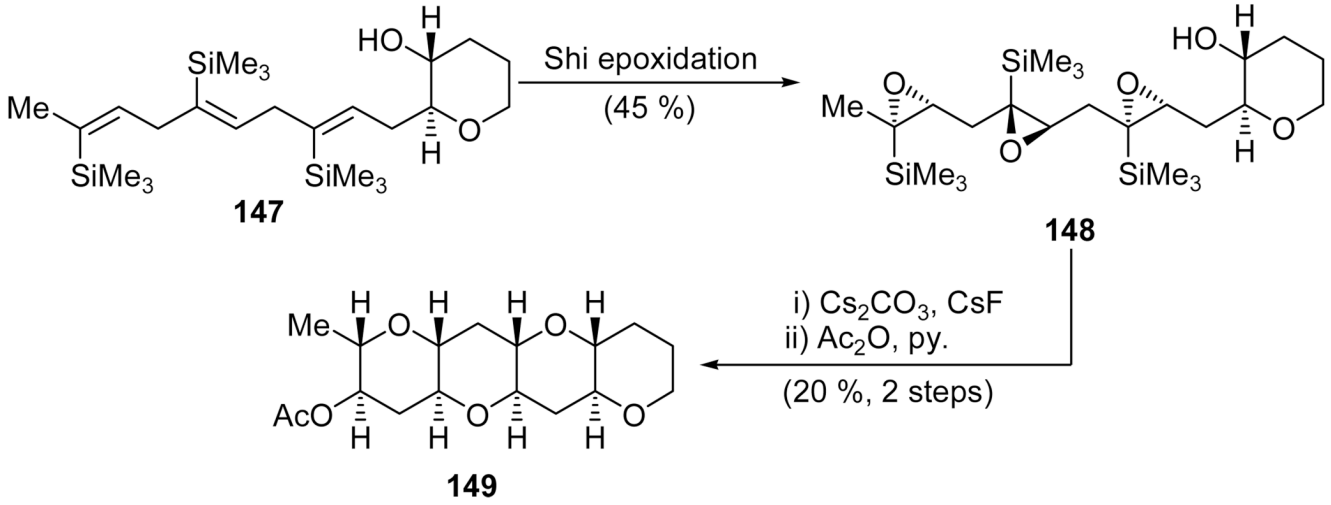
Scheme 23.
Hydroxy methoxyenone cyclization in the formation of cyclic ethers (Nakata et al., 2002). [76]



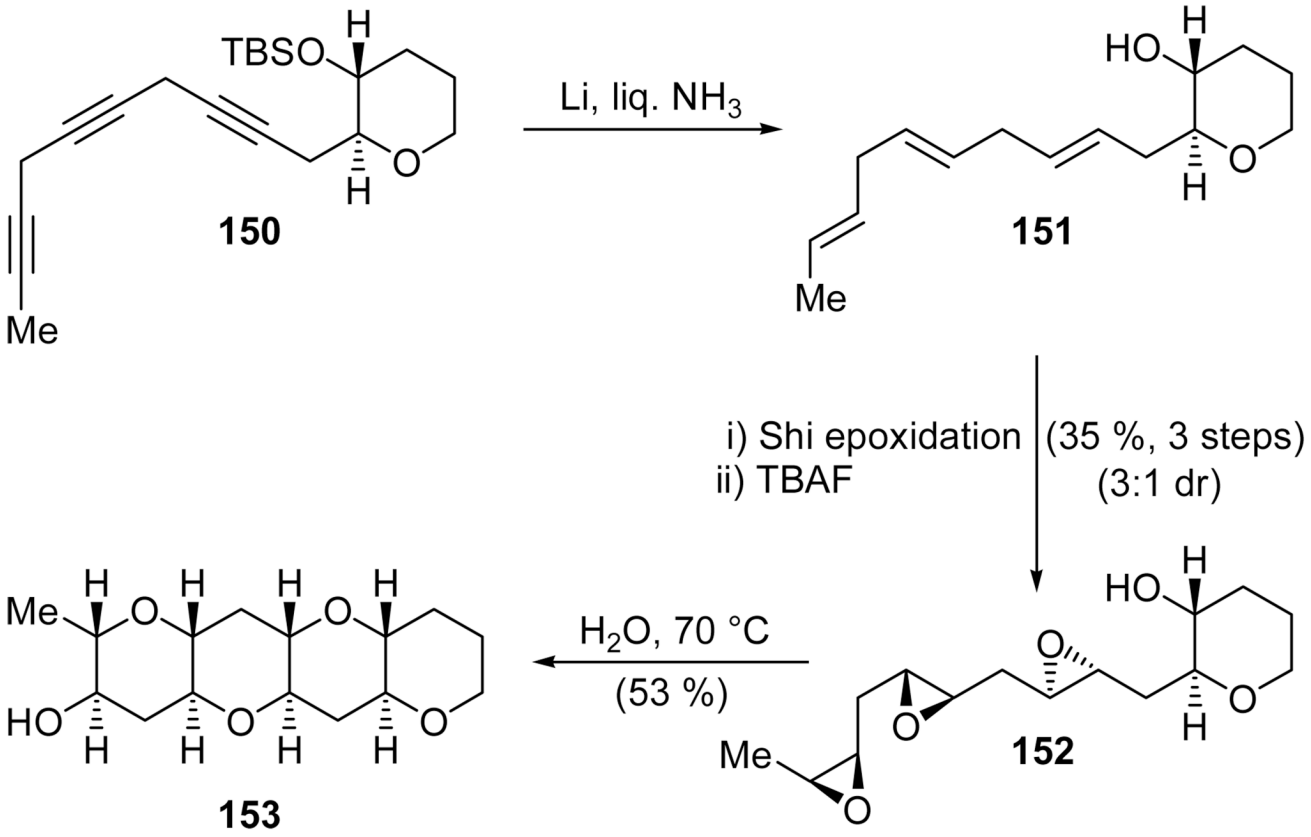
Scheme 24.
Methoxymethyl-directed cascade hydroxy epoxide opening to fused pyran systems (Murai et al., 1999).[77]



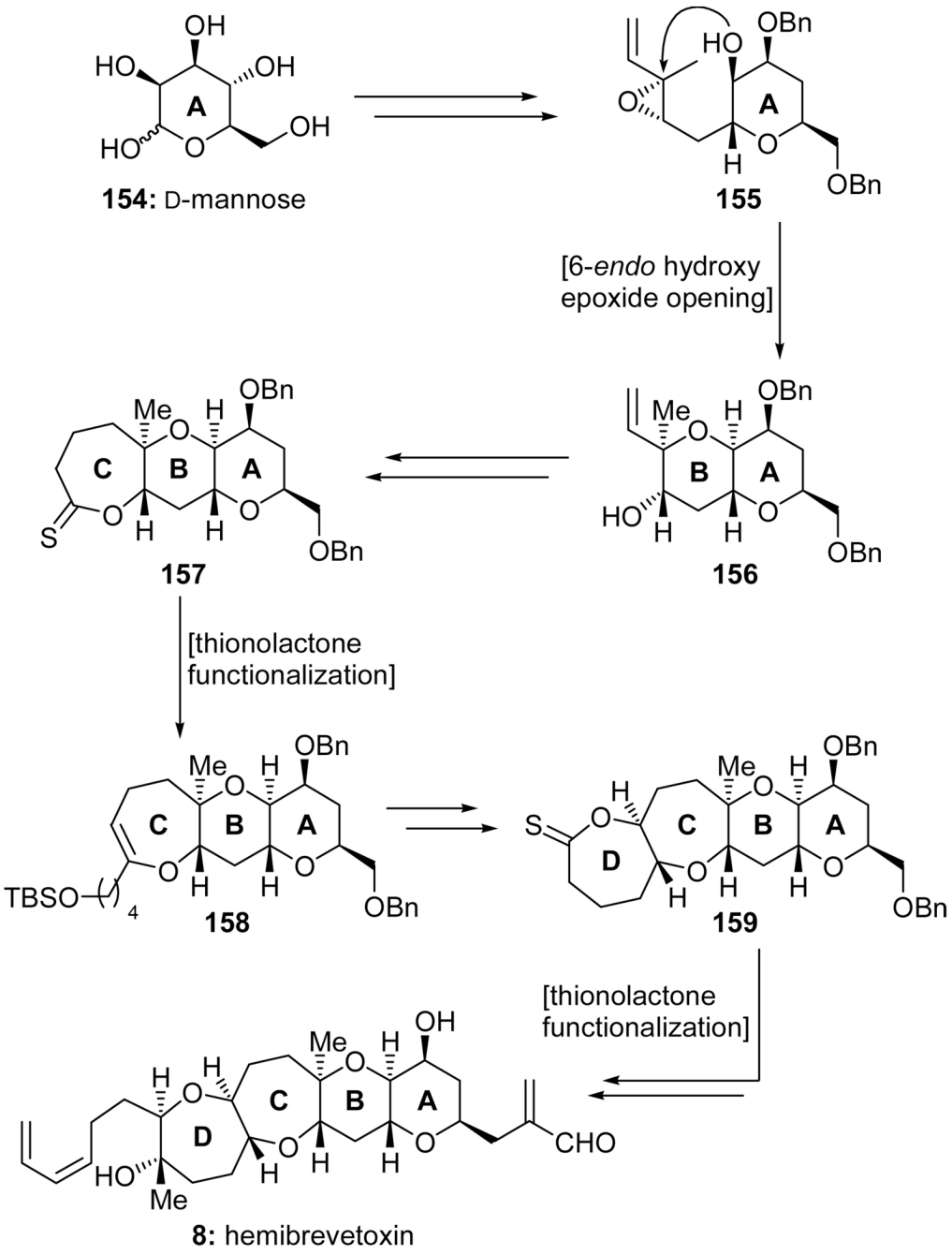
Scheme 25.
Lewis acid-promoted, carbonate polyepoxide opening cascade to fused polyoxepane systems (McDonald et al., 2000).[78]



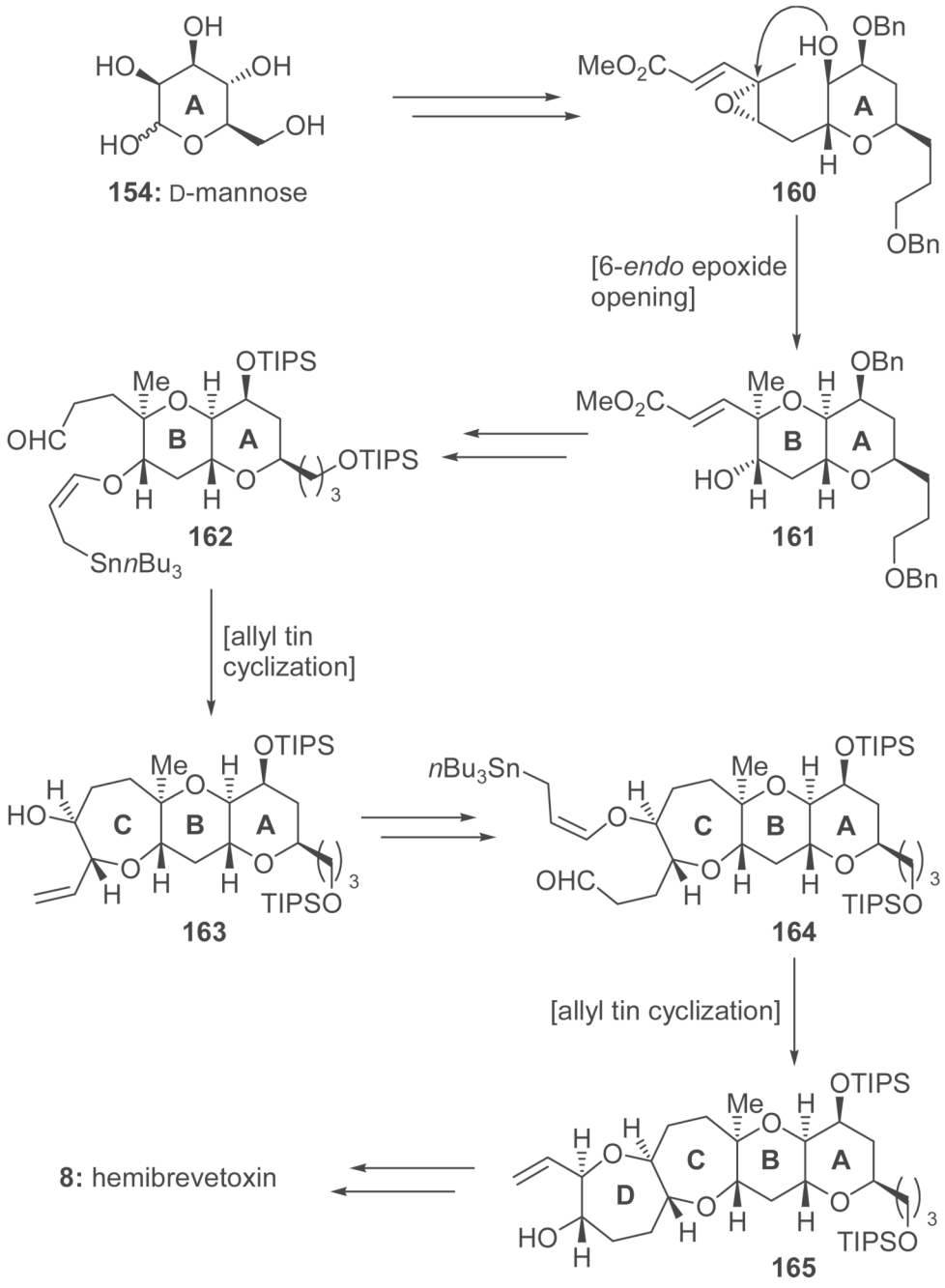
Scheme 26.
TMS-directed hydroxy polyepoxide opening cascade to form fused polypyran systems (Jamison et al., 2003).[80]



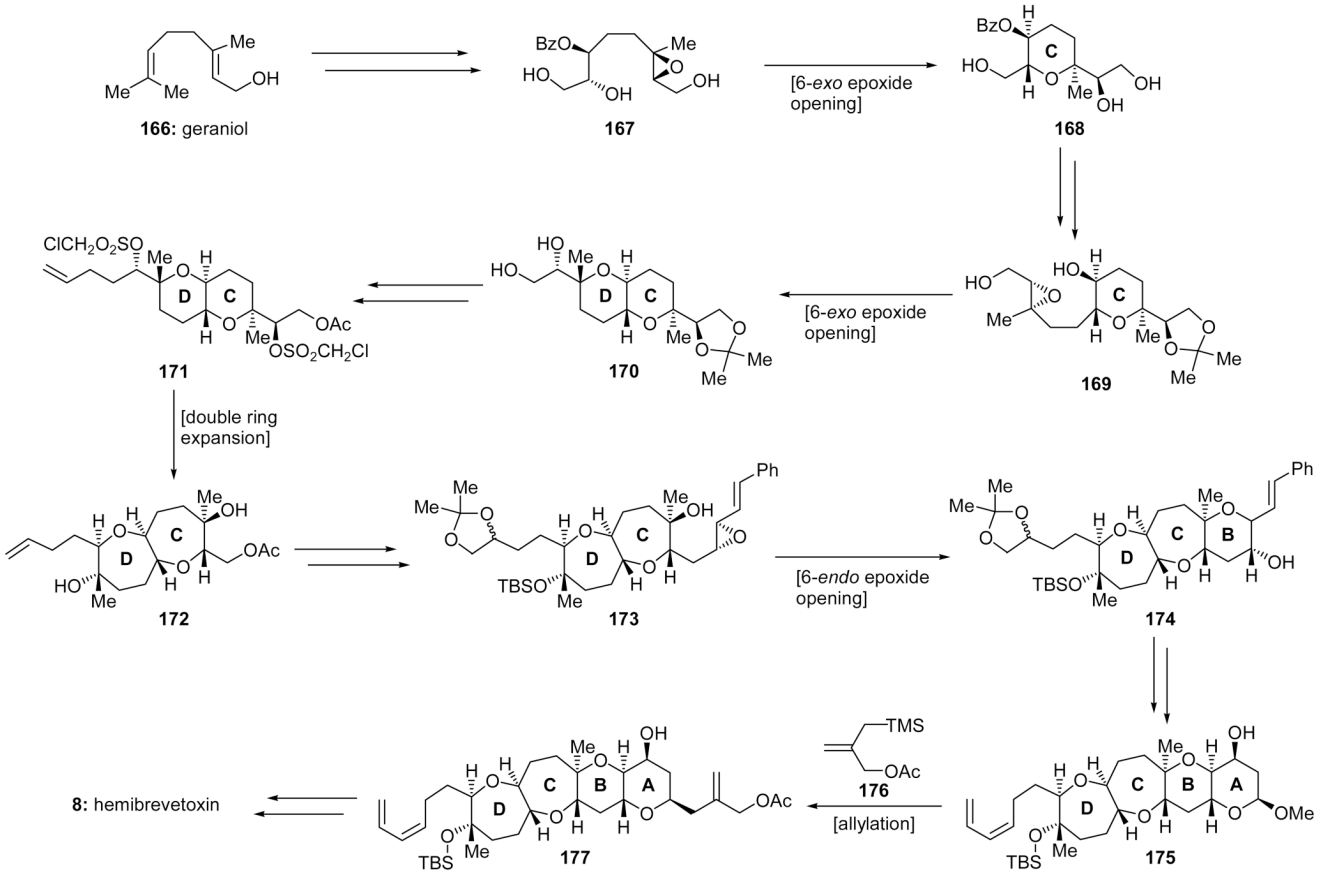
Scheme 27.
Thermally-induced hydroxy polyepoxide opening cascade in water (Vilotijevic and Jamison, 2007).[81]



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

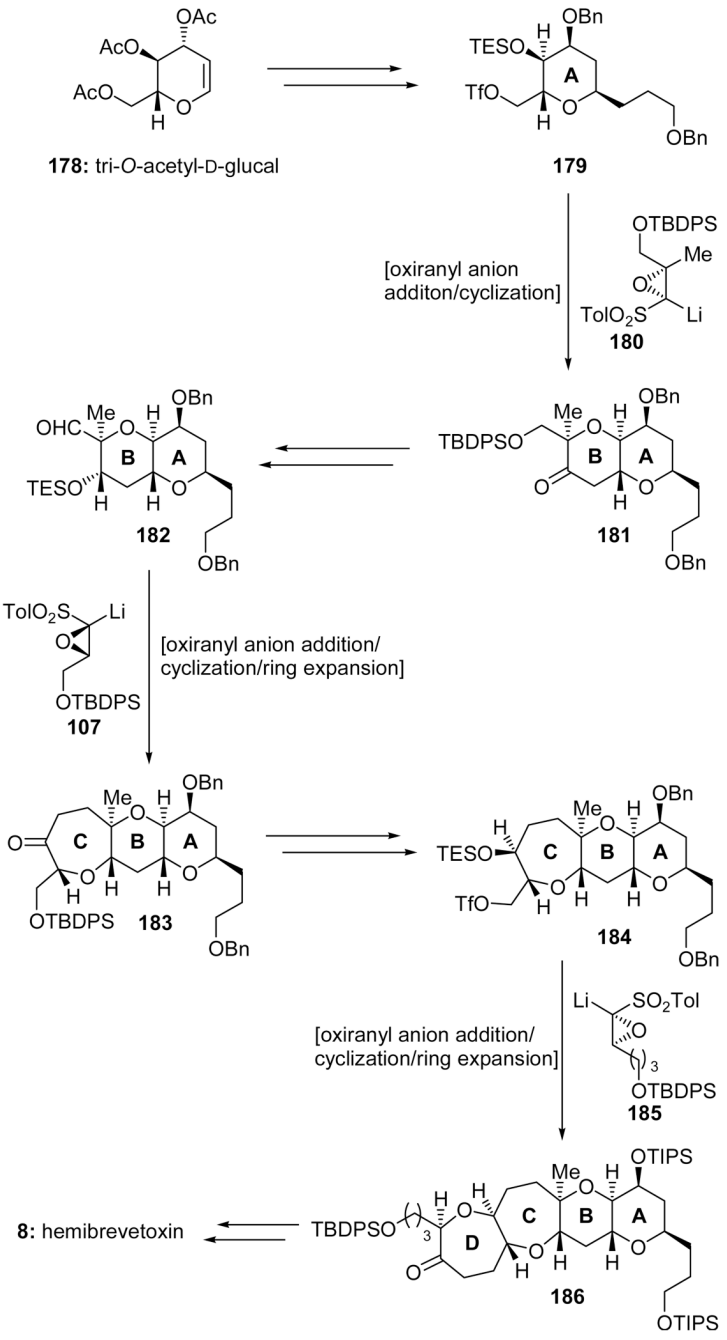


Scheme 29.
Second total synthesis of hemibrevetoxin (**8**) (Y. Yamamoto et al., 1995).[85]



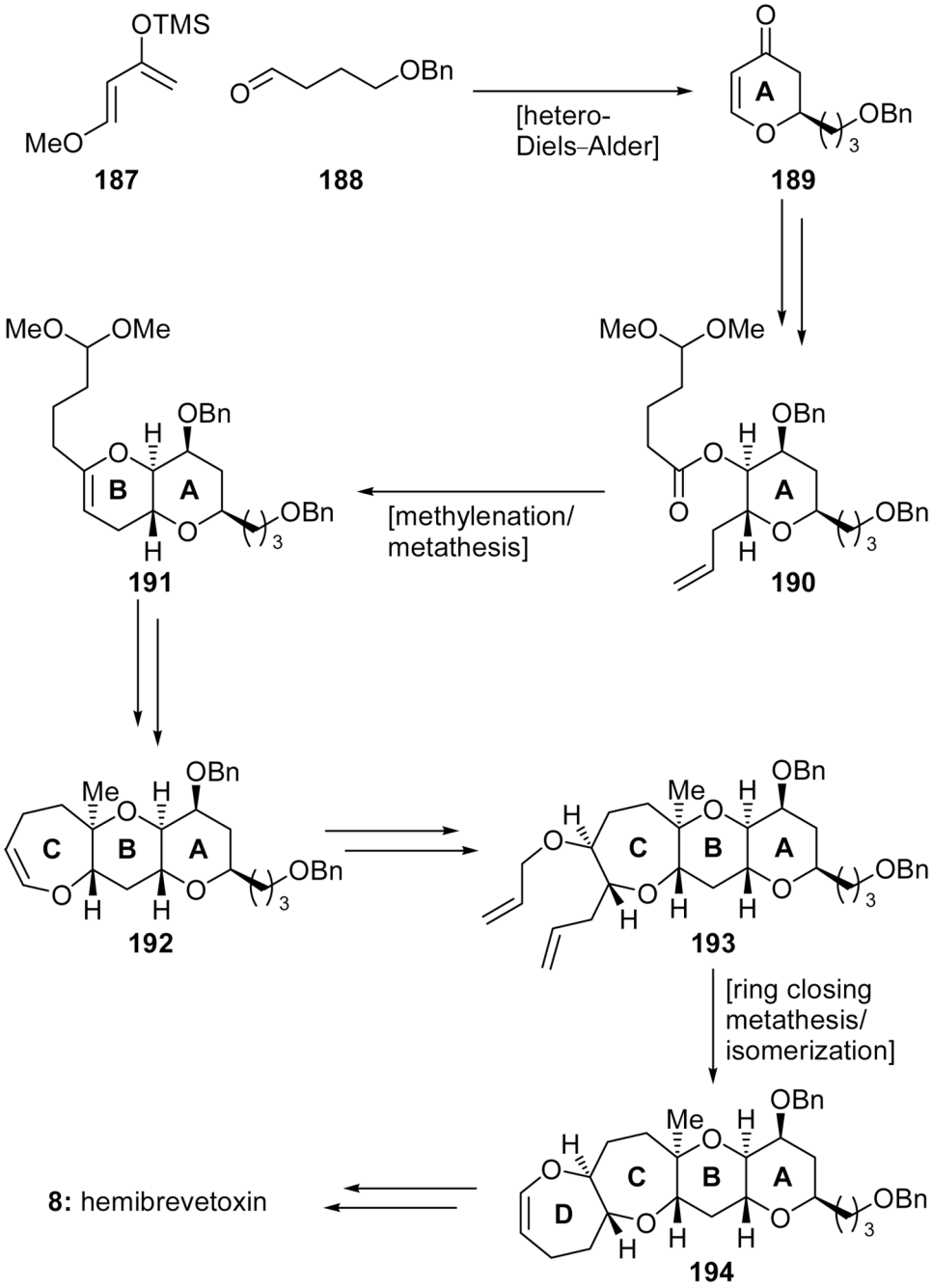
Scheme 30.

Third total synthesis of hemibrevetoxin (**8**) (Nakata et al., 1996).[86]

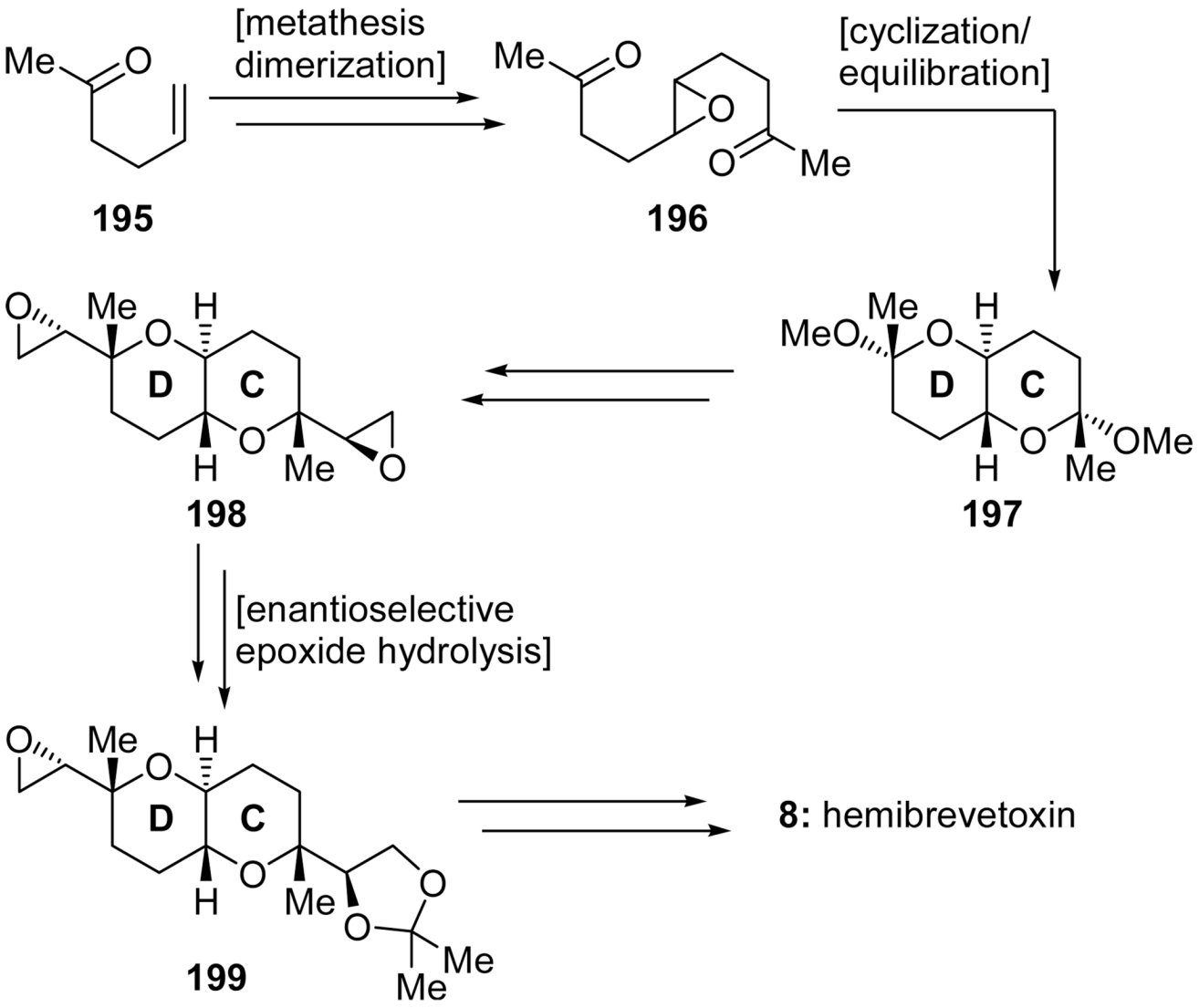


Scheme 31.

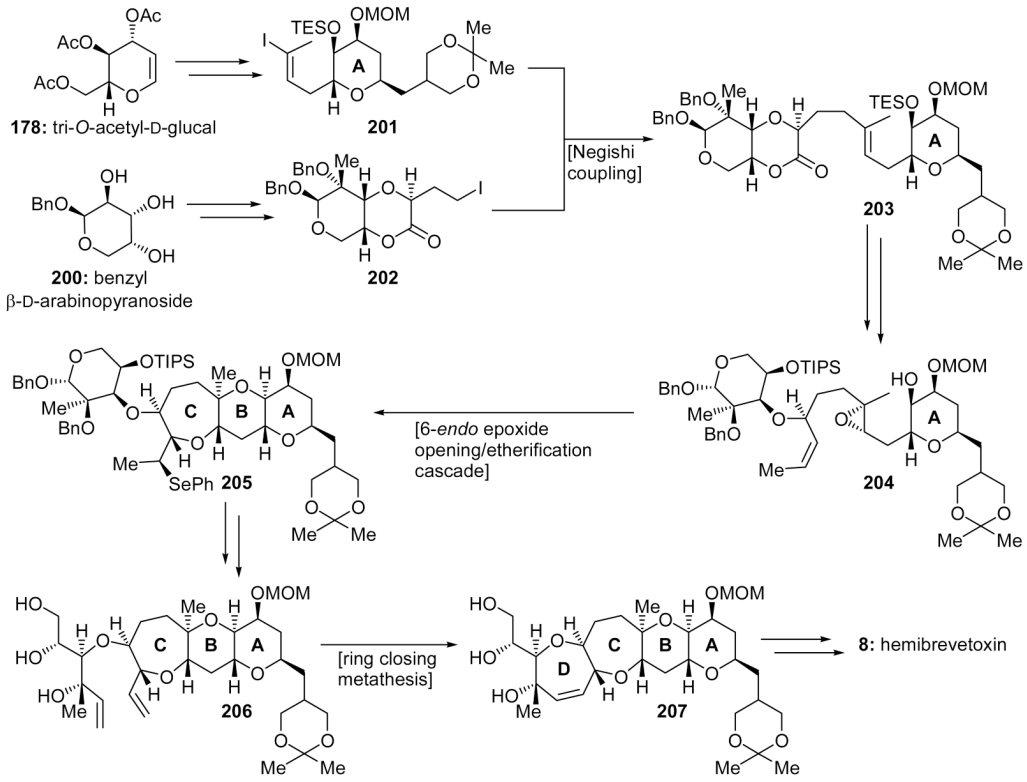
Fourth (formal) total synthesis of hemibrevetoxin (**8**) (Mori et al., 1997).[87]



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

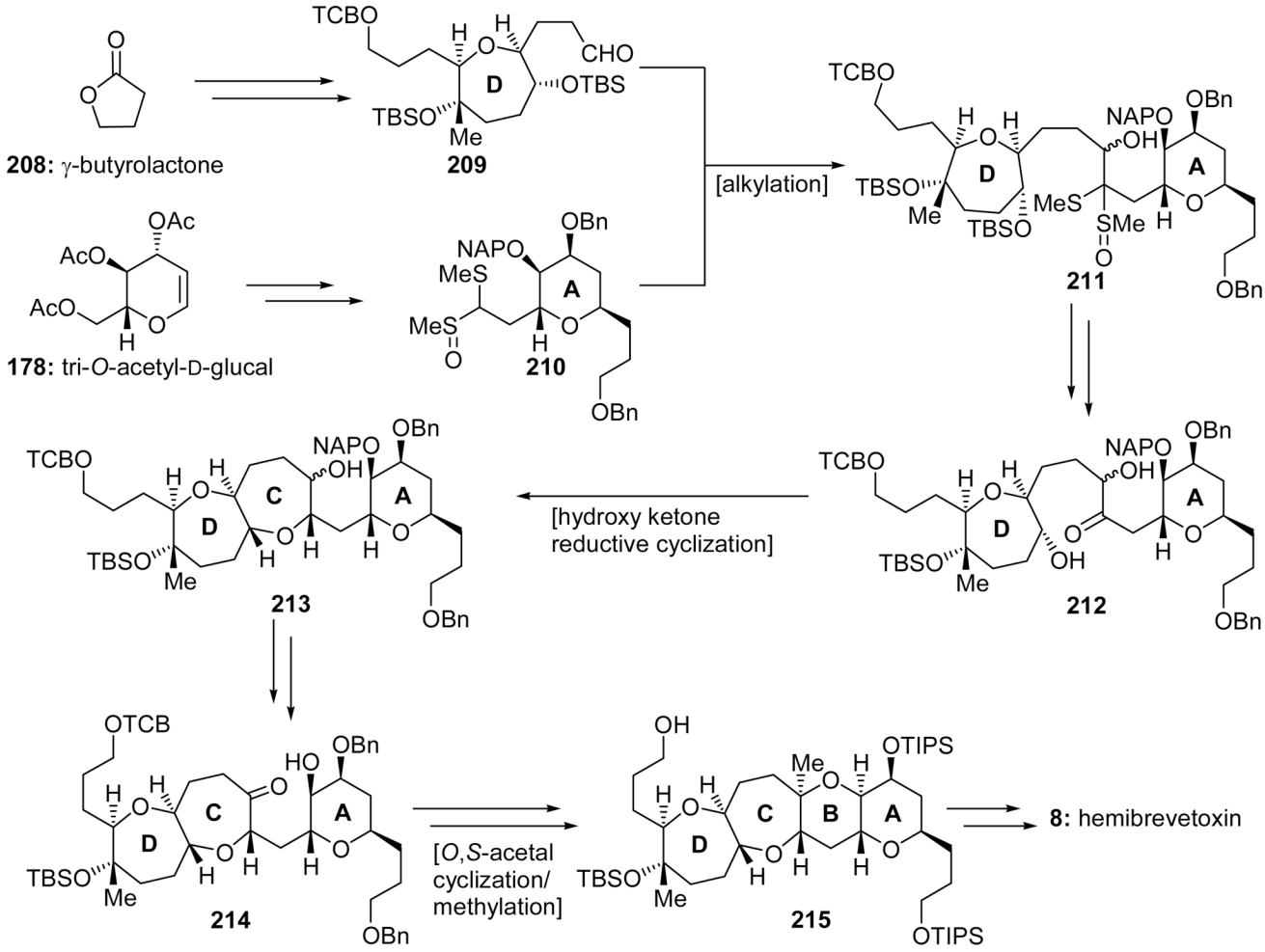


Scheme 33.
Sixth (formal) total synthesis of hemibrevetoxin (**8**) (Nelson et al., 2001).[90]

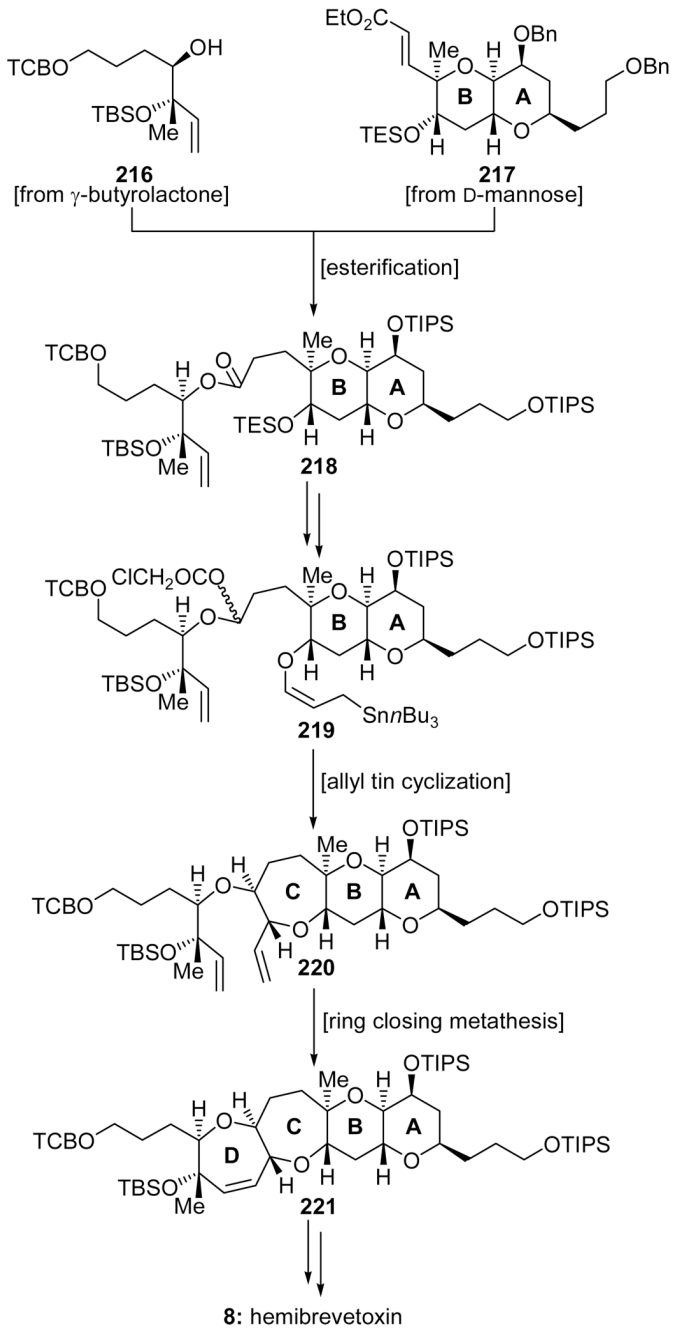


Scheme 34.

Seventh total synthesis of hemibrevetoxin (**8**) (Holton et al., 2003).[92]

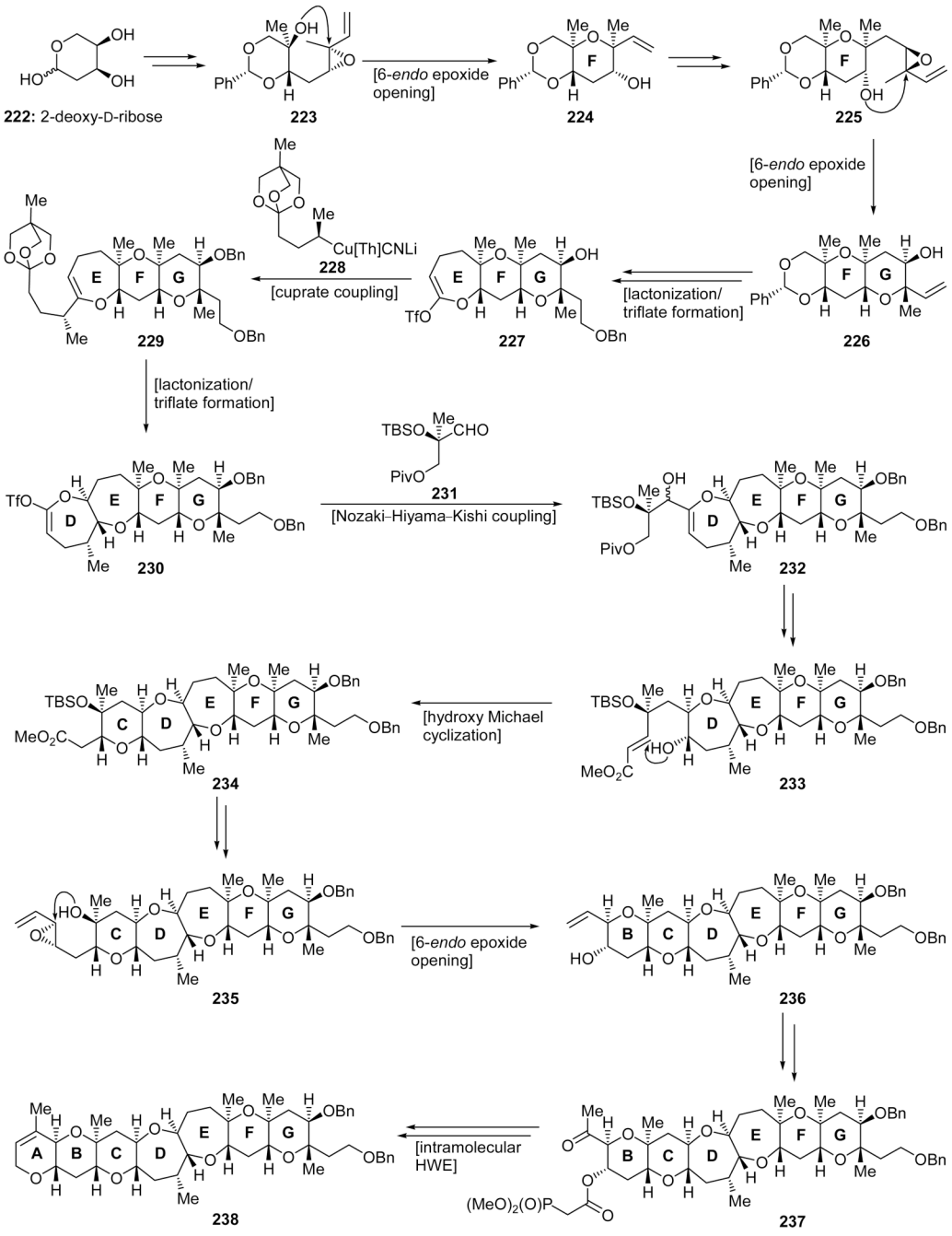


Scheme 35.
Eighth (formal) total synthesis of hemibrevetoxin (**8**) (Fujiwara et al., 2004).[95]



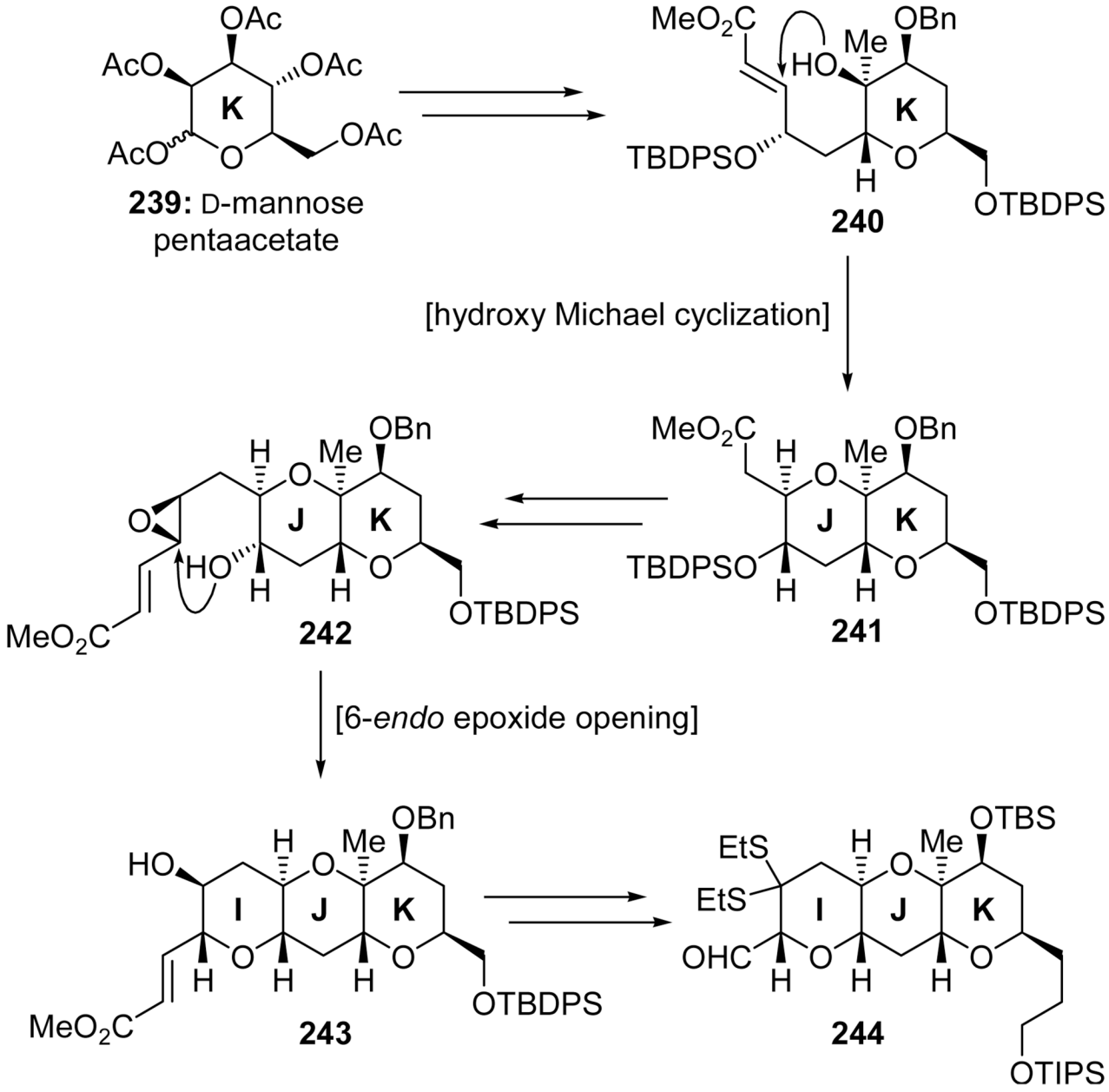
Scheme 36.

Ninth (formal) total synthesis of hemibrevetoxin (**8**) (Y. Yamamoto et al., 2007).[96]

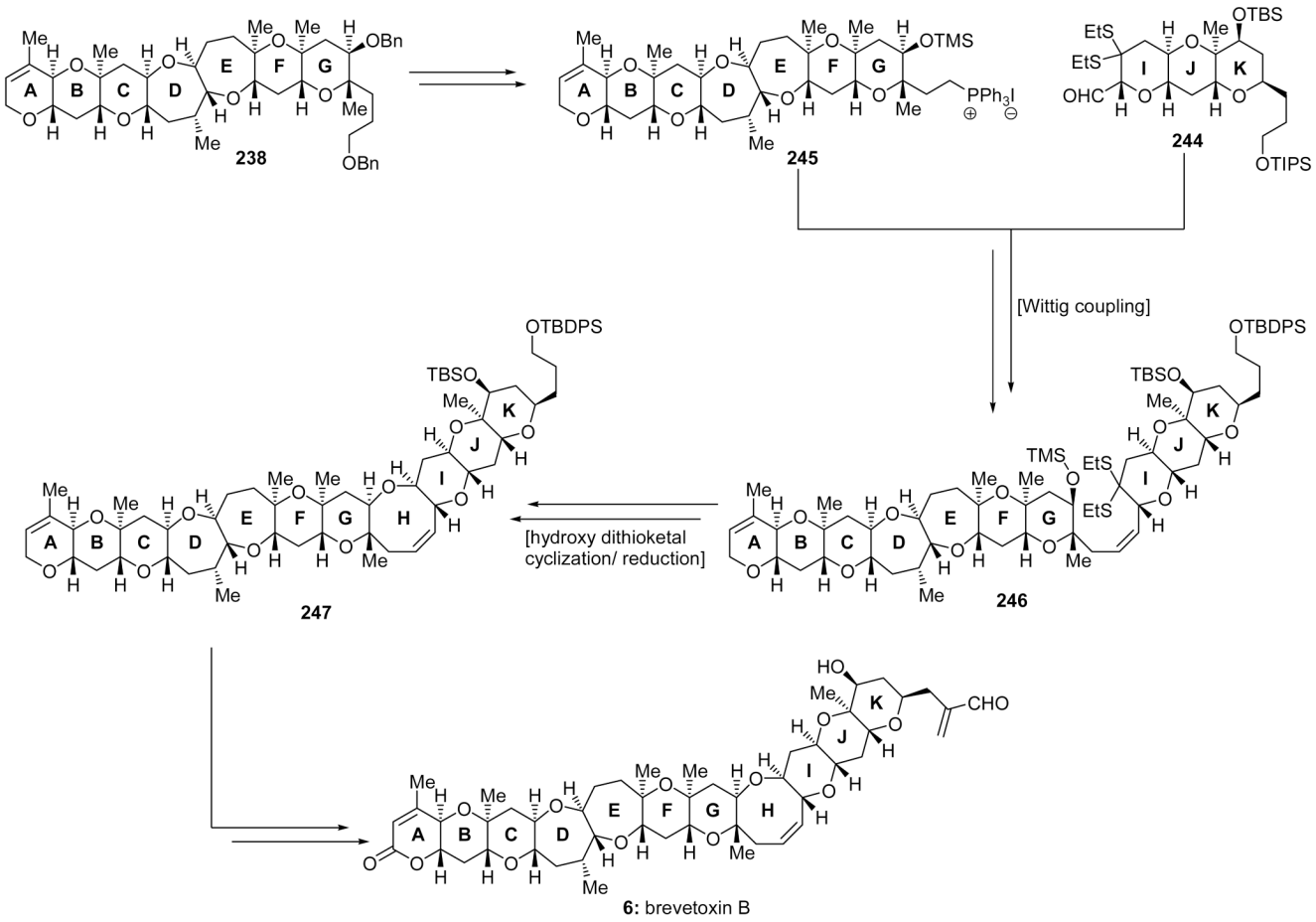


Scheme 37.

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

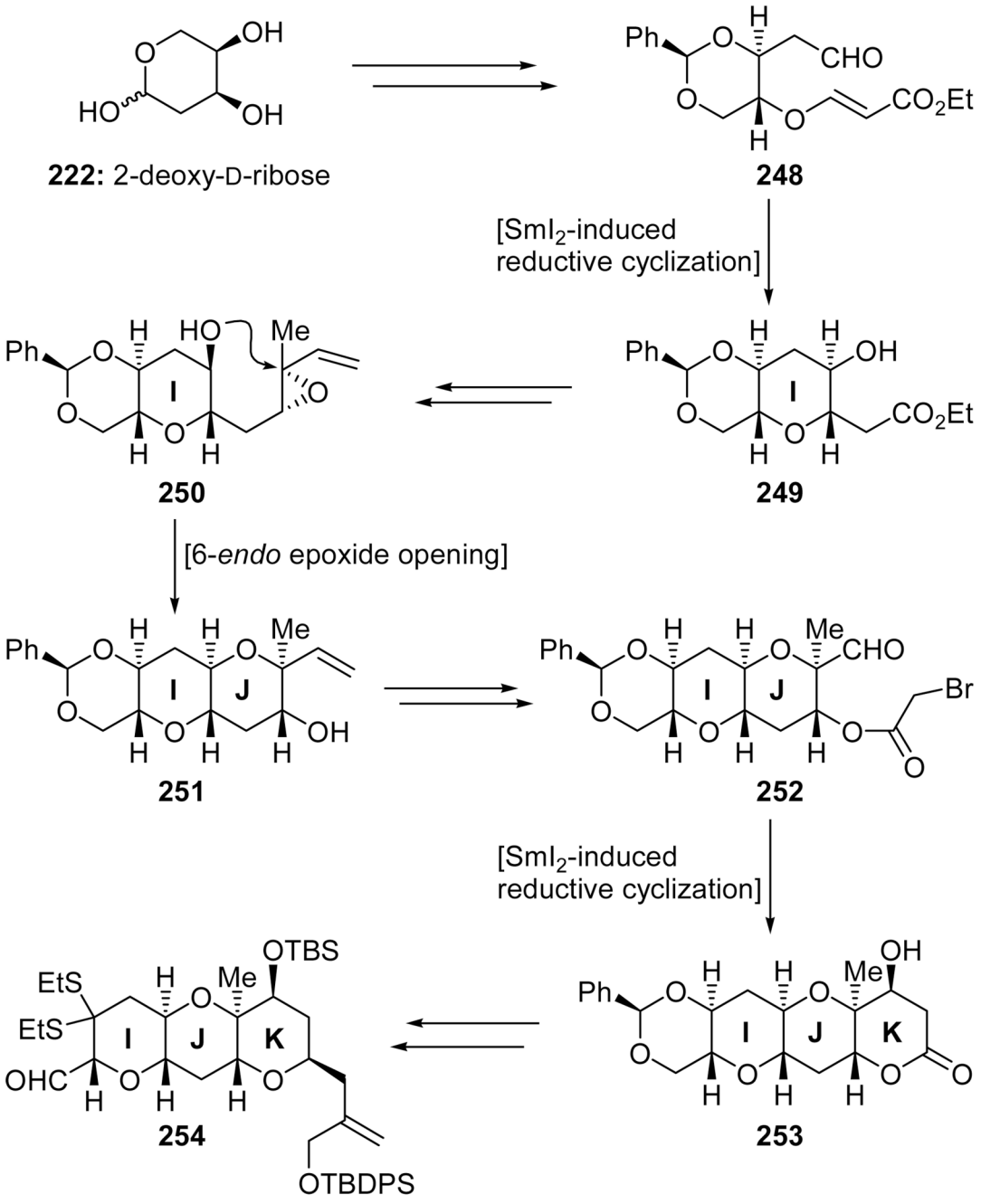


Scheme 38.
The first total synthesis of brevetoxin B (**6**). Construction of the IJK domain (**244**) (Nicolaou et al., 1995).[97]



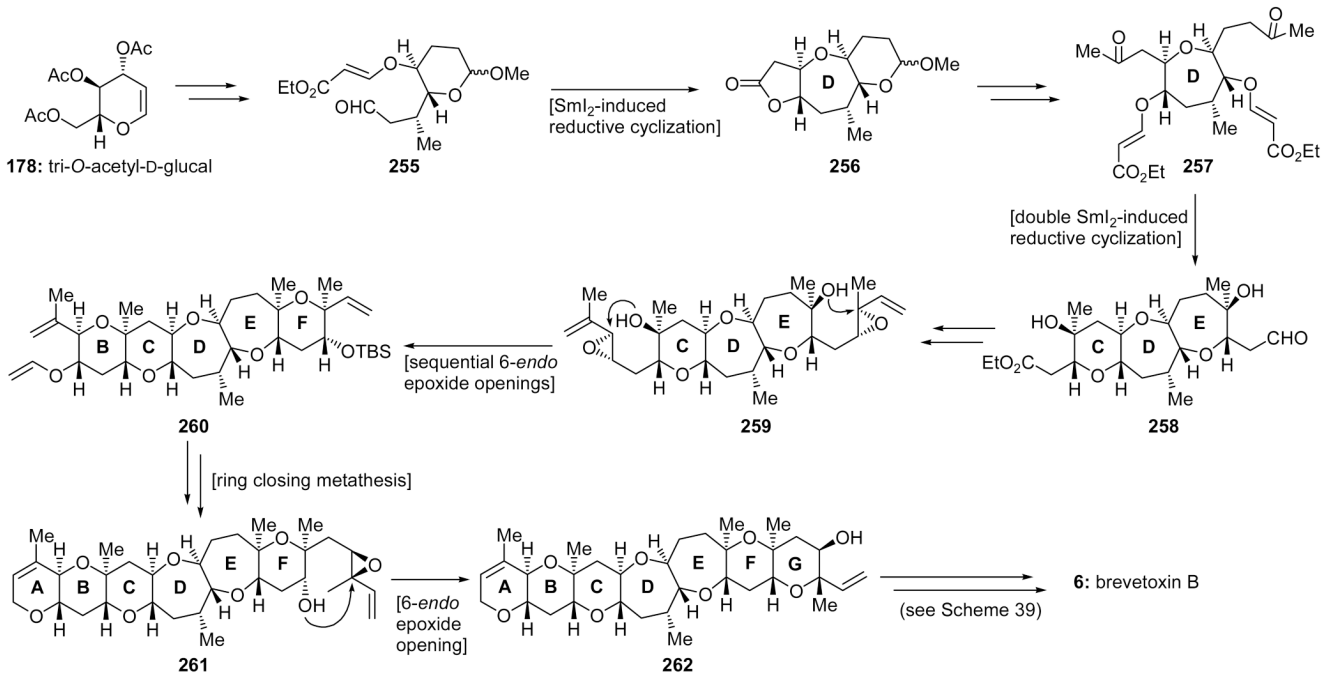
Scheme 39.

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



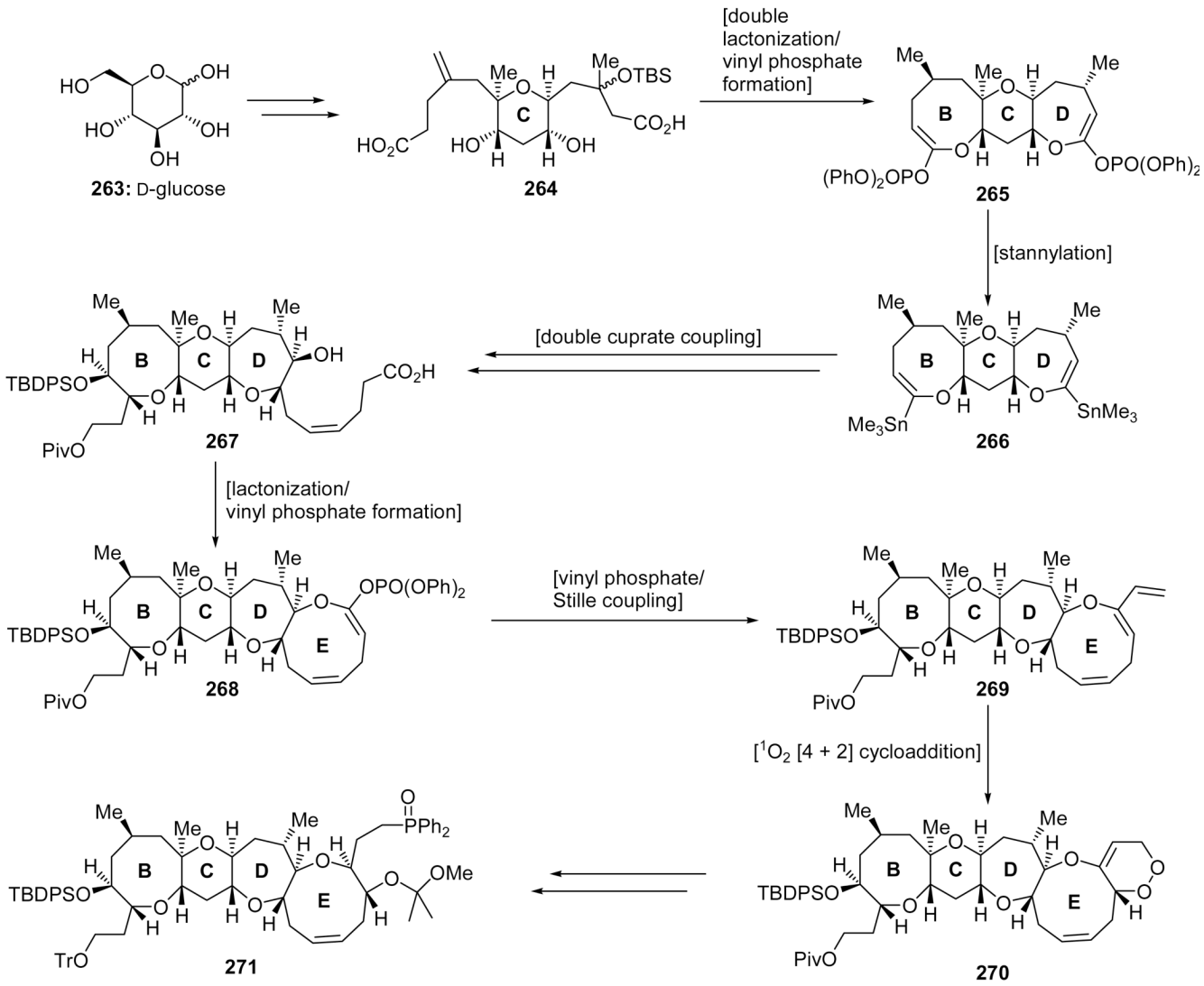
Scheme 40.

Second total synthesis of brevetoxin B (**6**). Construction of the IJK fragment (**244**) (Nakata et al., 2004).[98]



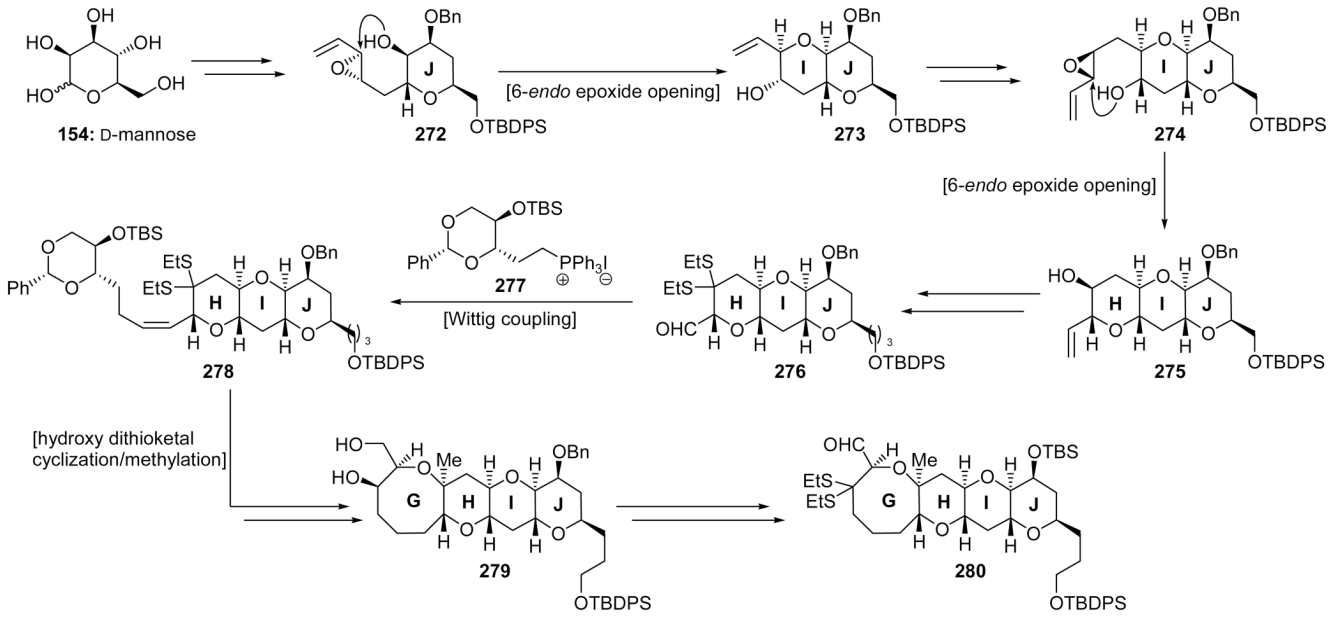
Scheme 41.

Second total synthesis of brevetoxin B (**6**). Construction of the ABCDEFG fragment (**2627**) and completion of the synthesis (Nakata et al., 2004).[98]



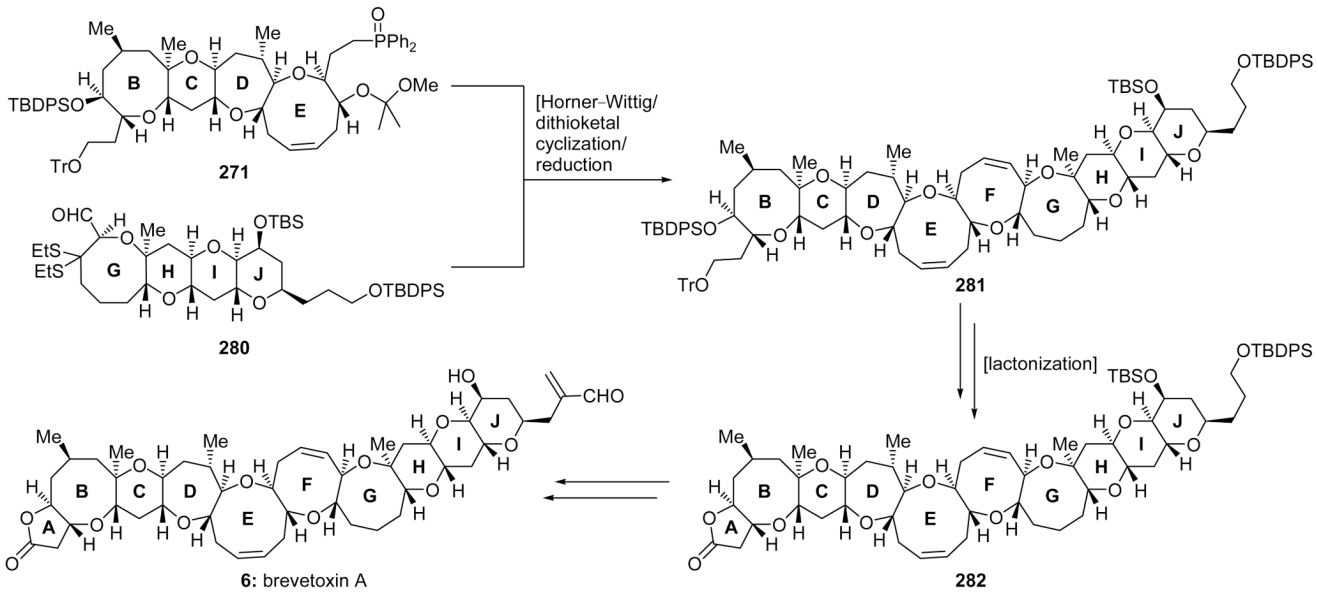
Scheme 42.

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



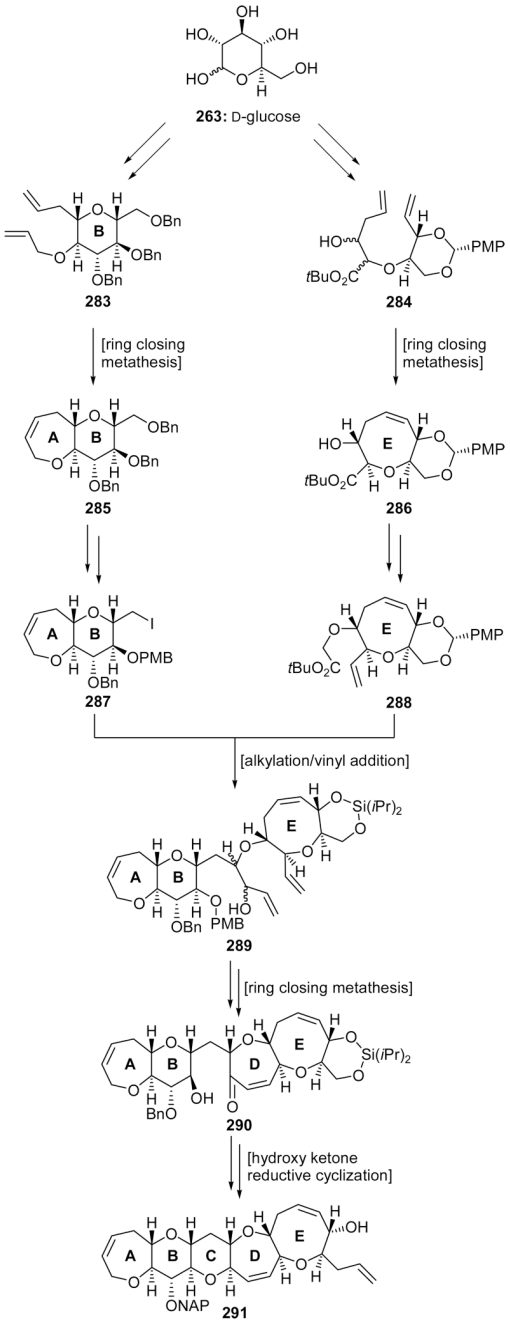
Scheme 43.

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



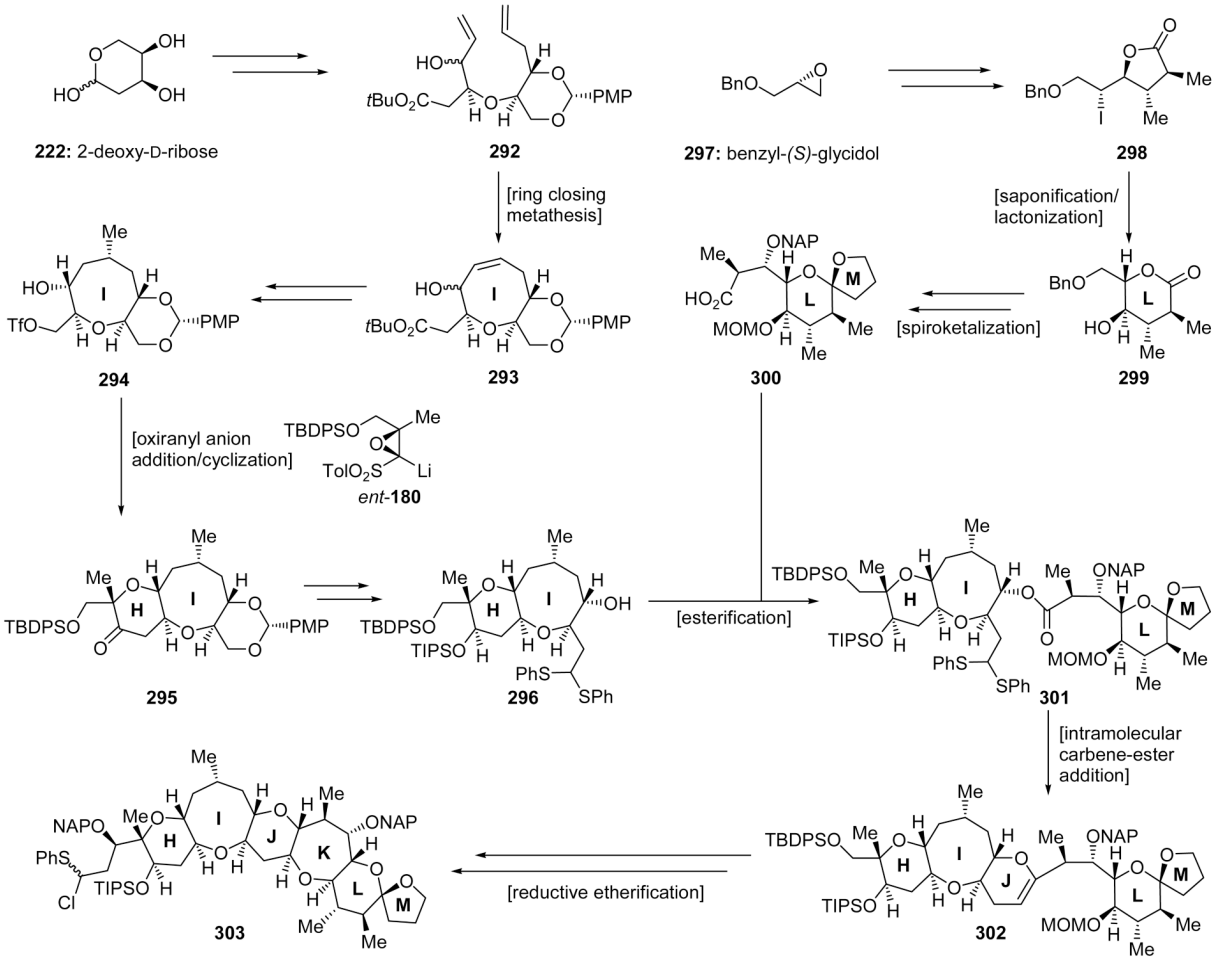
Scheme 44.

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



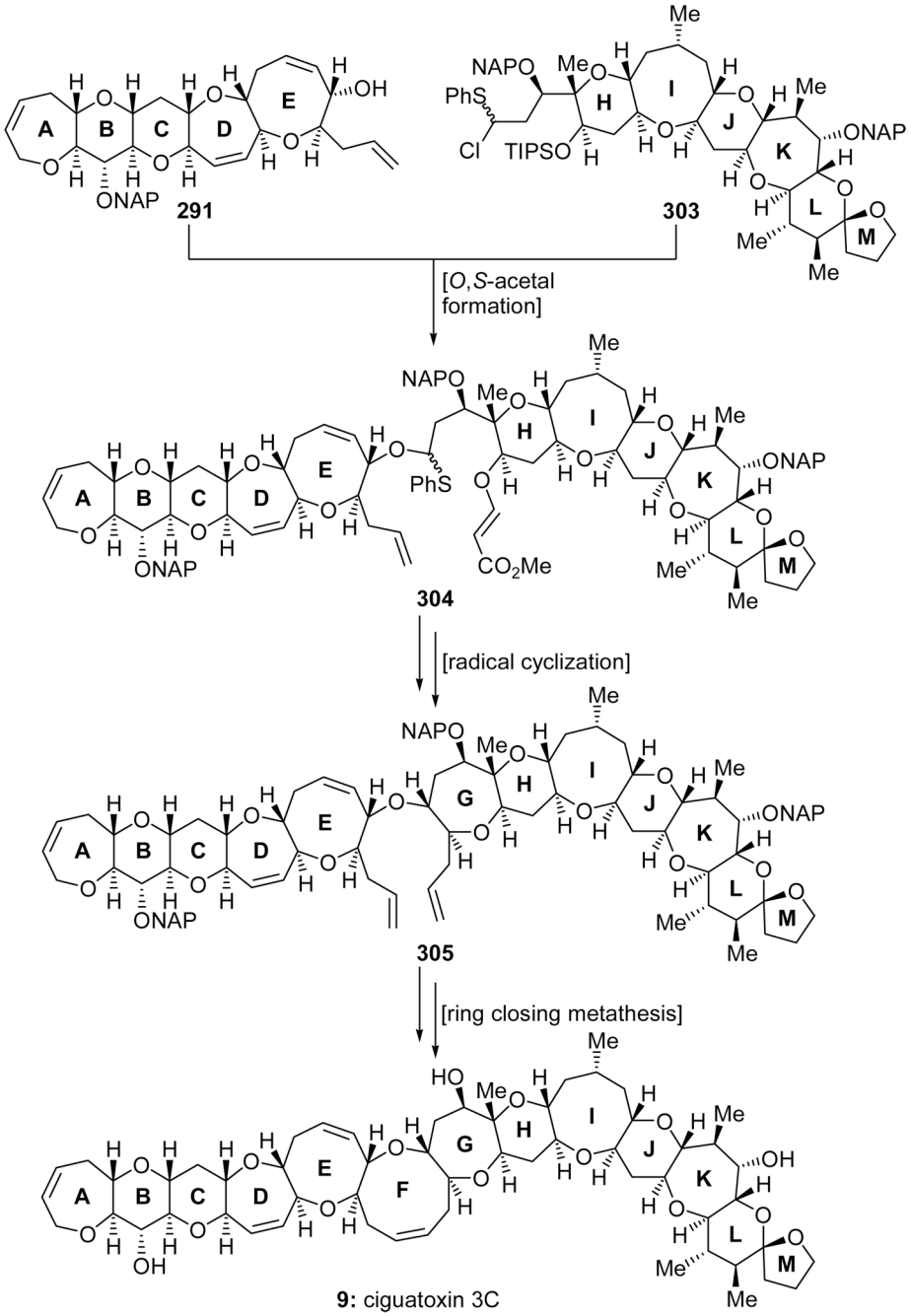
Scheme 45.

Total synthesis of ciguatoxin 3C (**9**). Construction of the ABCDE fragment (**291**) (Hirama et al., 2001).[102]



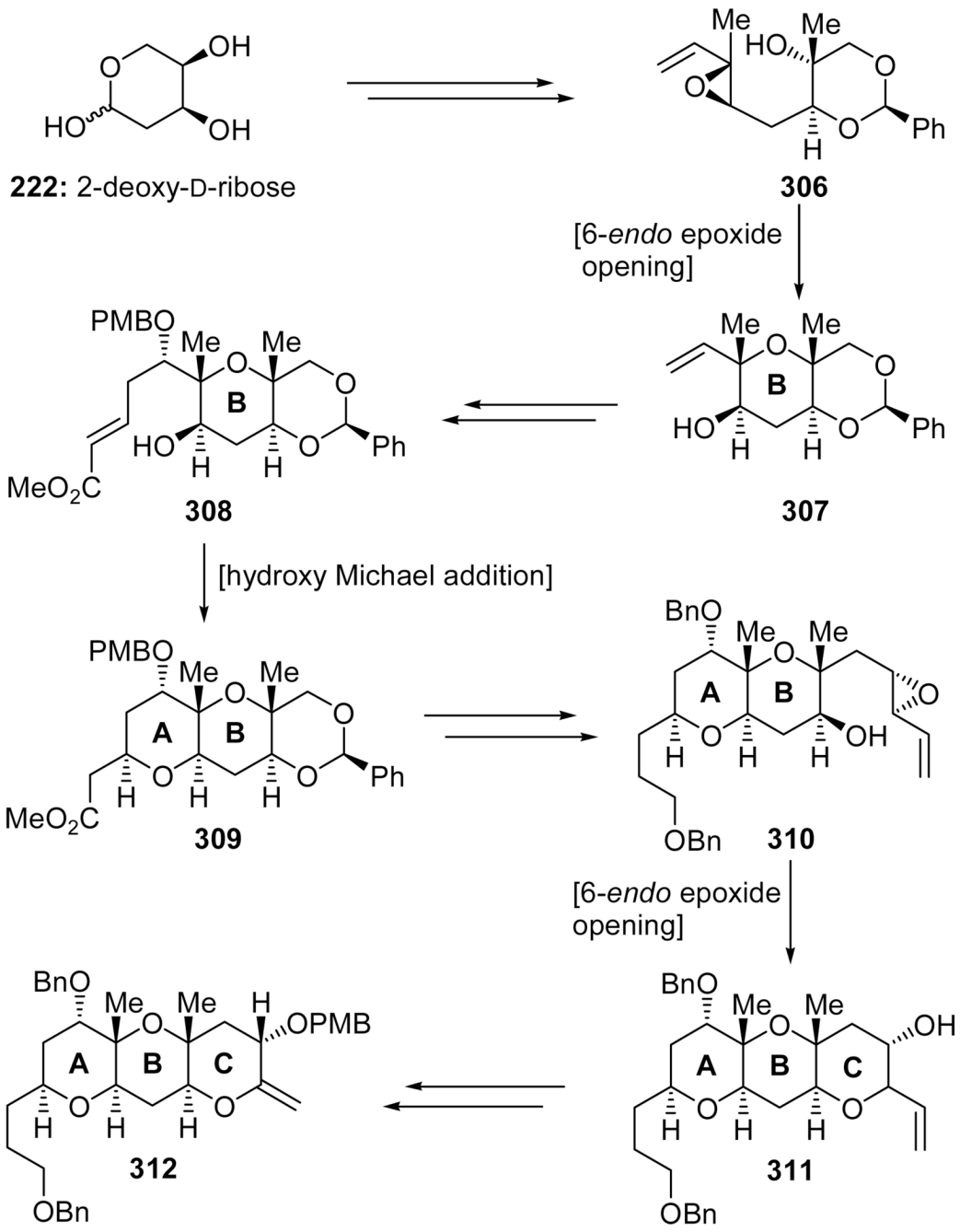
Scheme 46.

Total synthesis of ciguatoxin 3C (**9**). Construction of the HIJKLM fragment (**303**) (Hirama et al., 2001).[102]



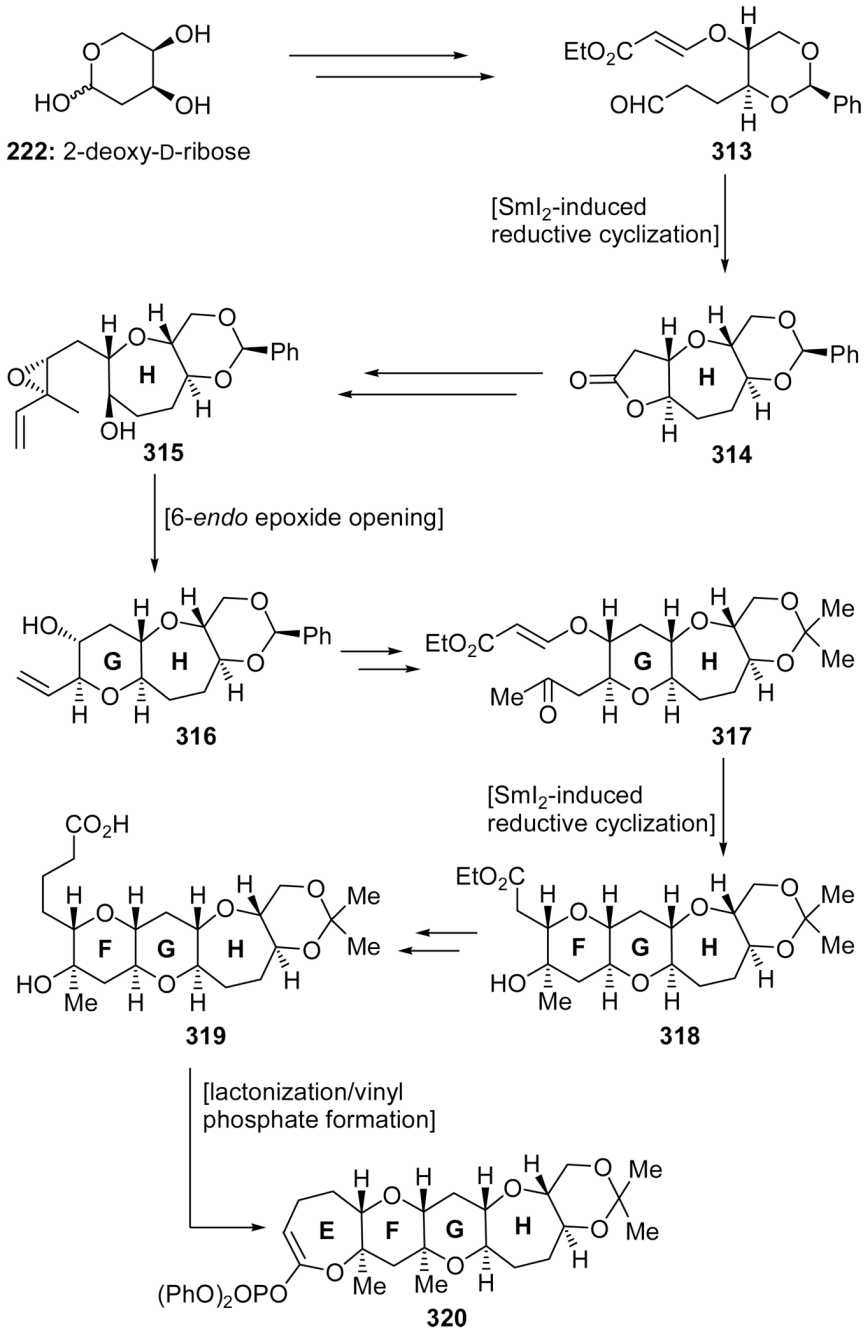
Scheme 47.

Total synthesis of ciguatoxin 3C (**9**). Final stages of the synthesis (Hirama et al., 2001).[102]



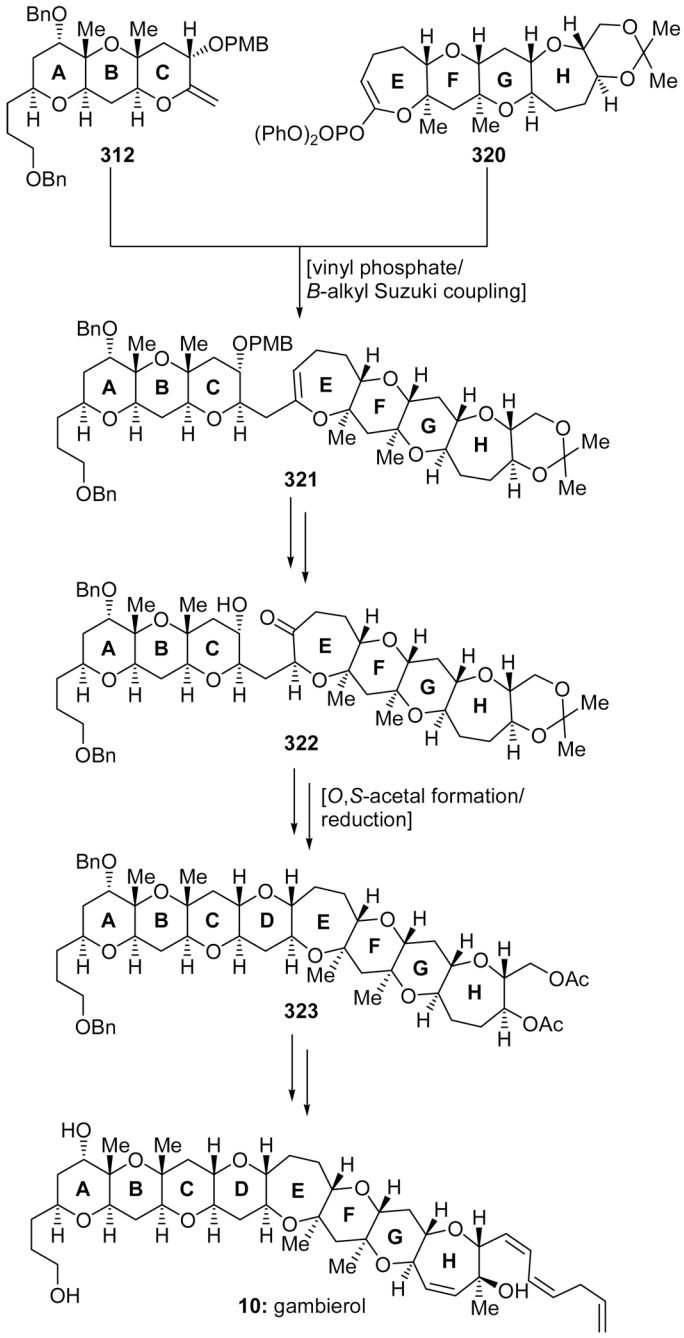
Scheme 48.

The first total synthesis of gambierol. Synthesis of the ABC domain (**312**) (Sasaki et al., 2002). [105]



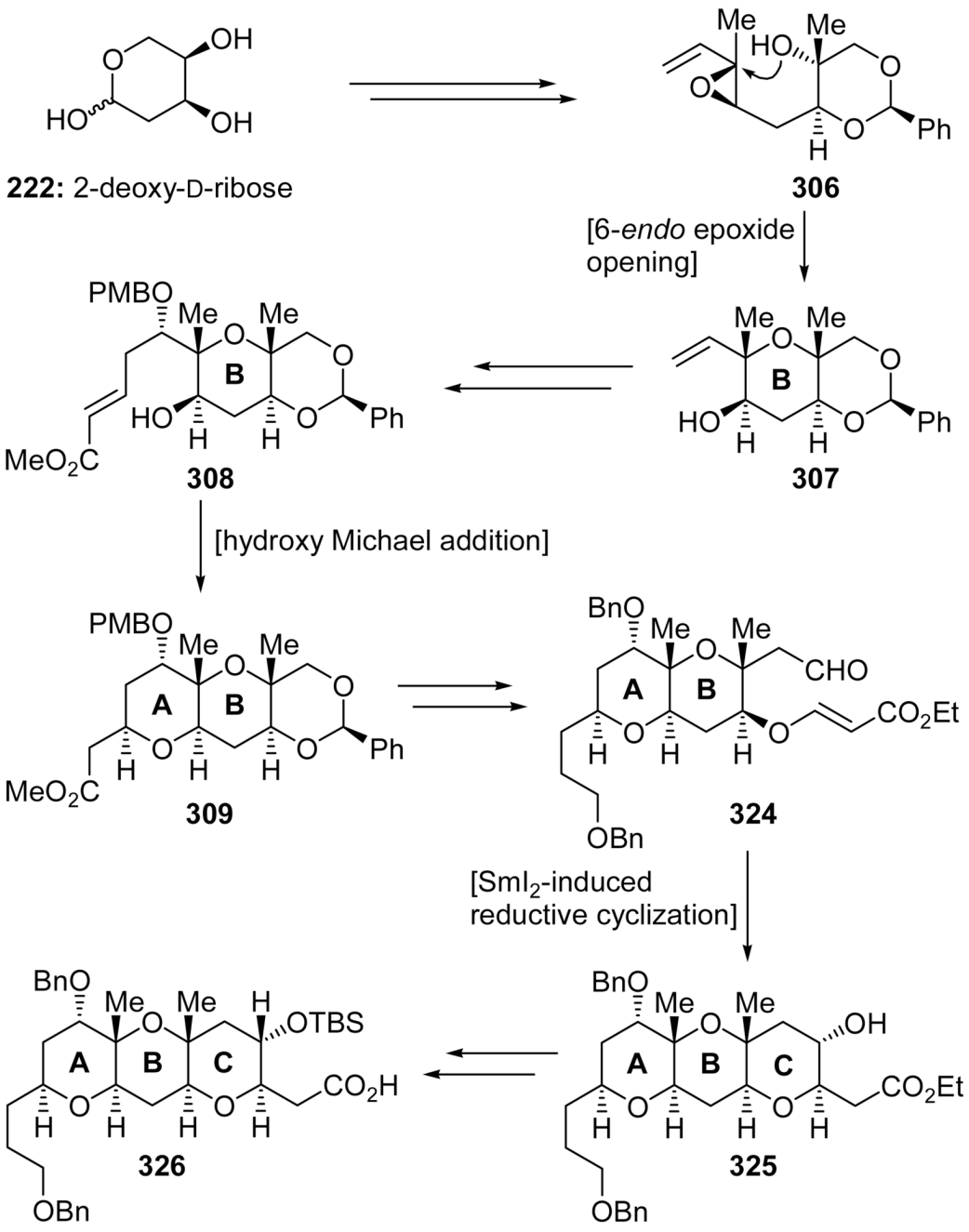
Scheme 49.

The first total synthesis of gambierol (**10**). Synthesis of the EFGH domain (**320**) (Sasaki et al., 2002).[105]

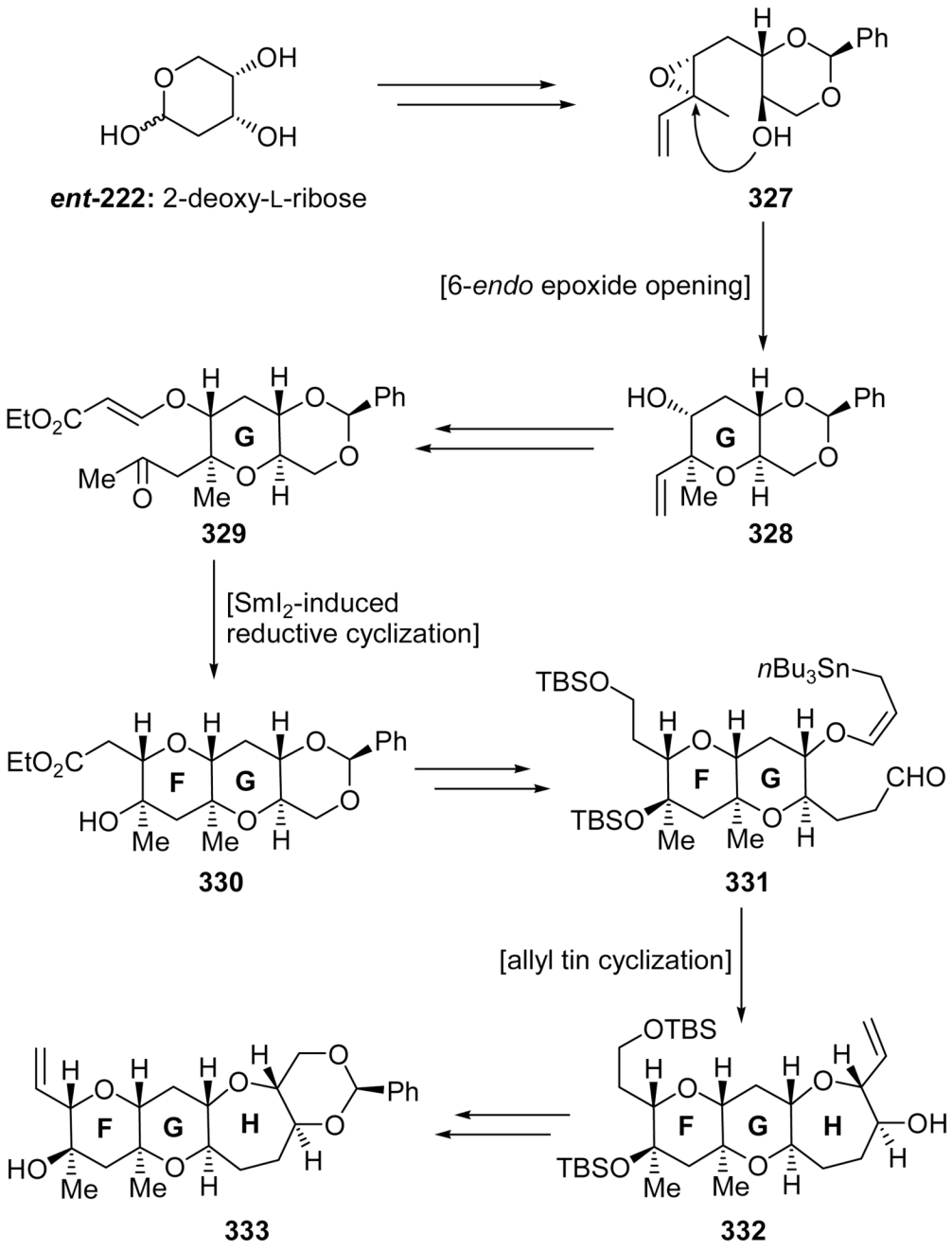


Scheme 50.

The first total synthesis of gambierol (**10**). Final stages of the synthesis (Sasaki et al., 2002). [105]

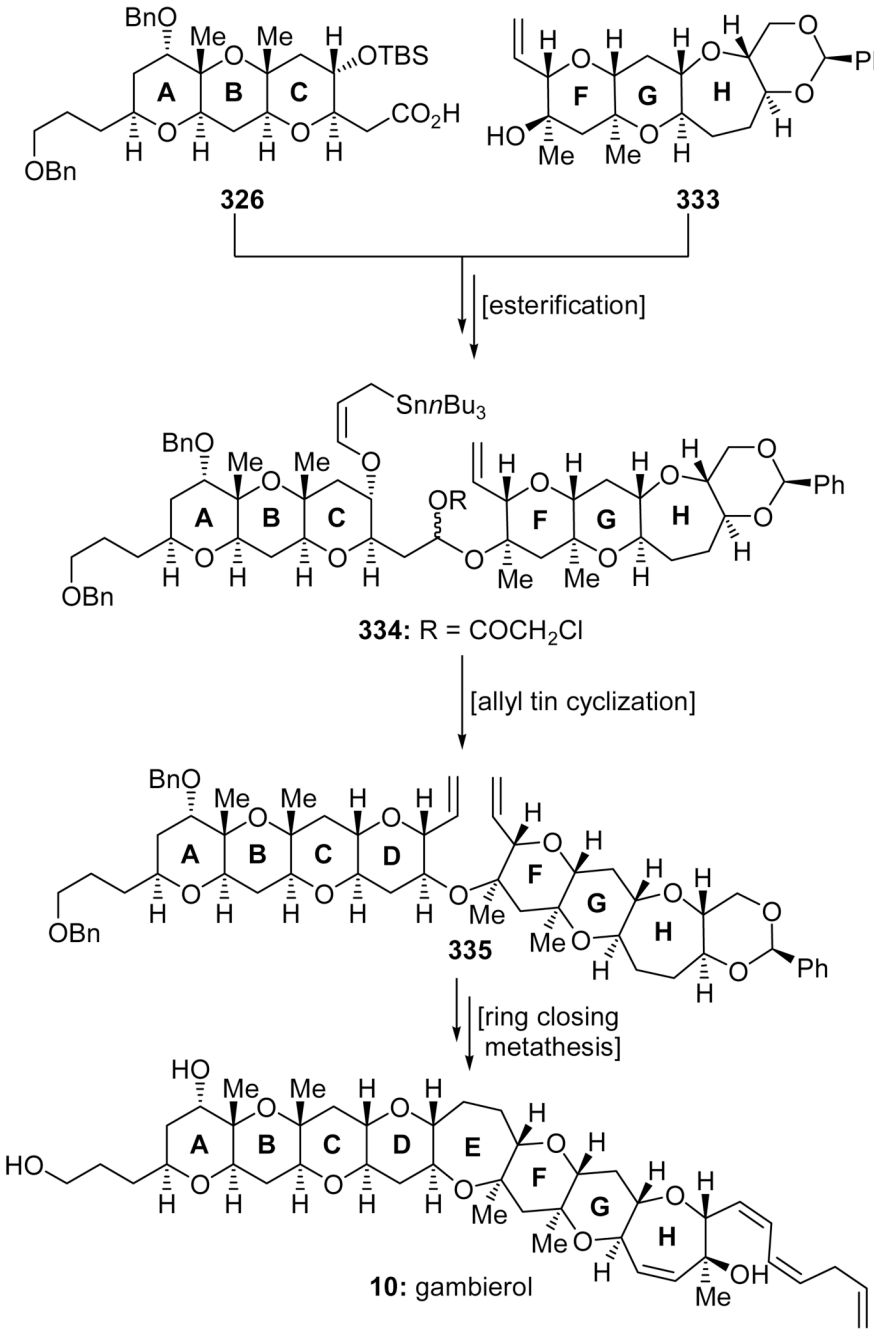


Scheme 51.
Second total synthesis of gambierol (**10**). Construction of ABC domain (**326**) (Y. Yamamoto et al., 2003).[106]



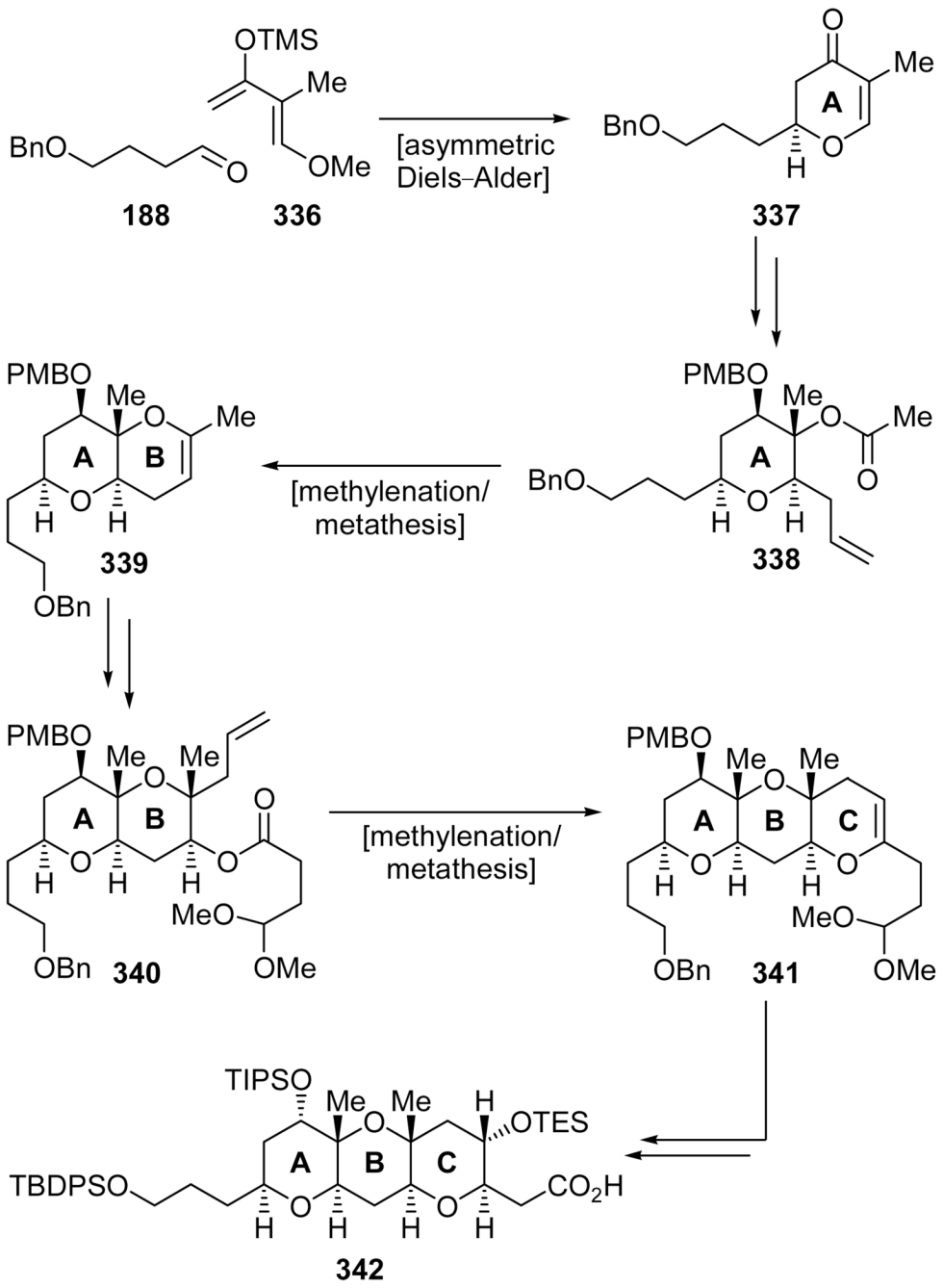
Scheme 52.

Second total synthesis of gambierol (**10**). Construction of FGH domain (**333**) (Y. Yamamoto et al., 2003).[106]



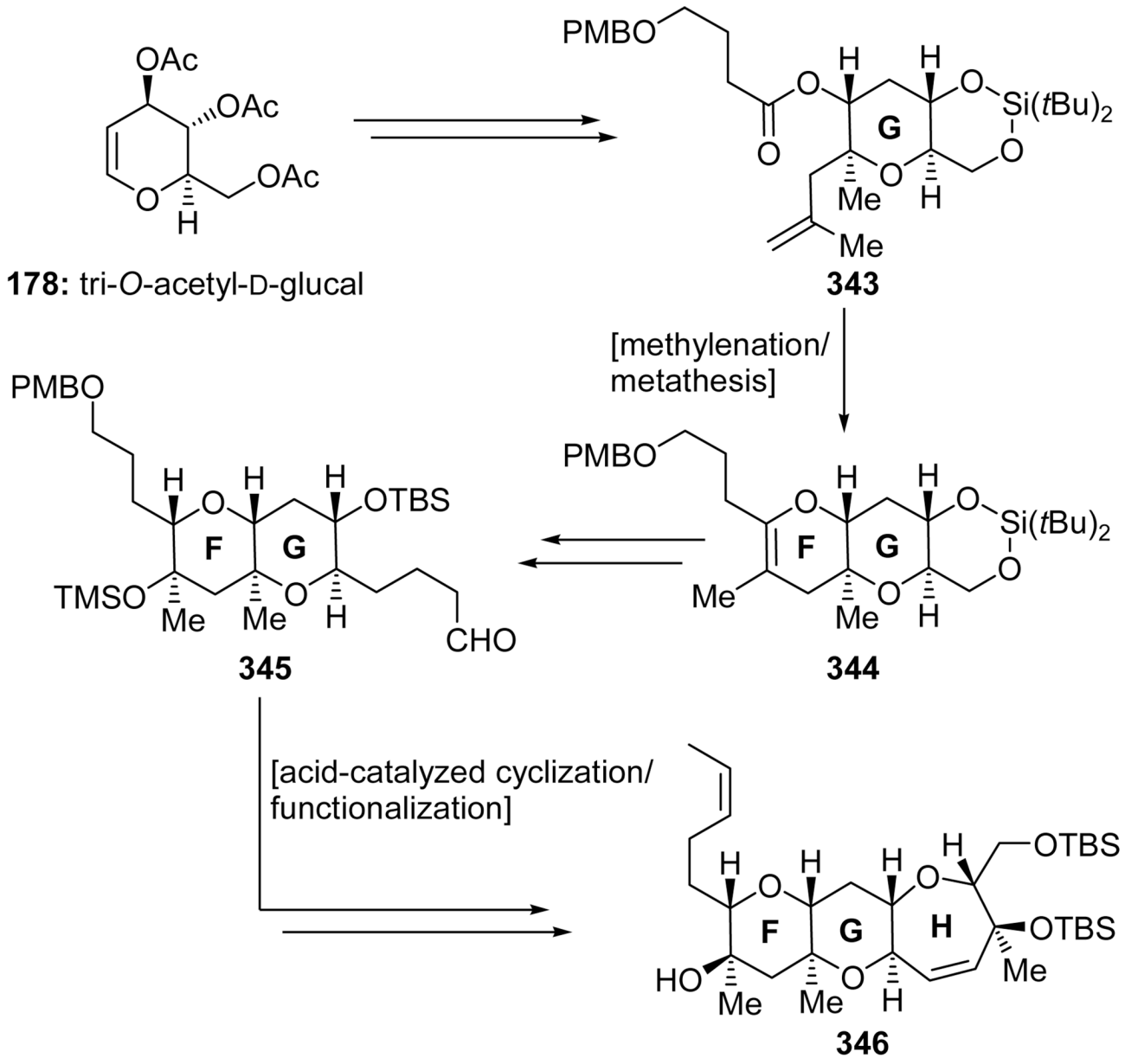
Scheme 53.

Second total synthesis of gambierol (**10**). Completion of the synthesis (Y. Yamamoto et al., 2003).[106]

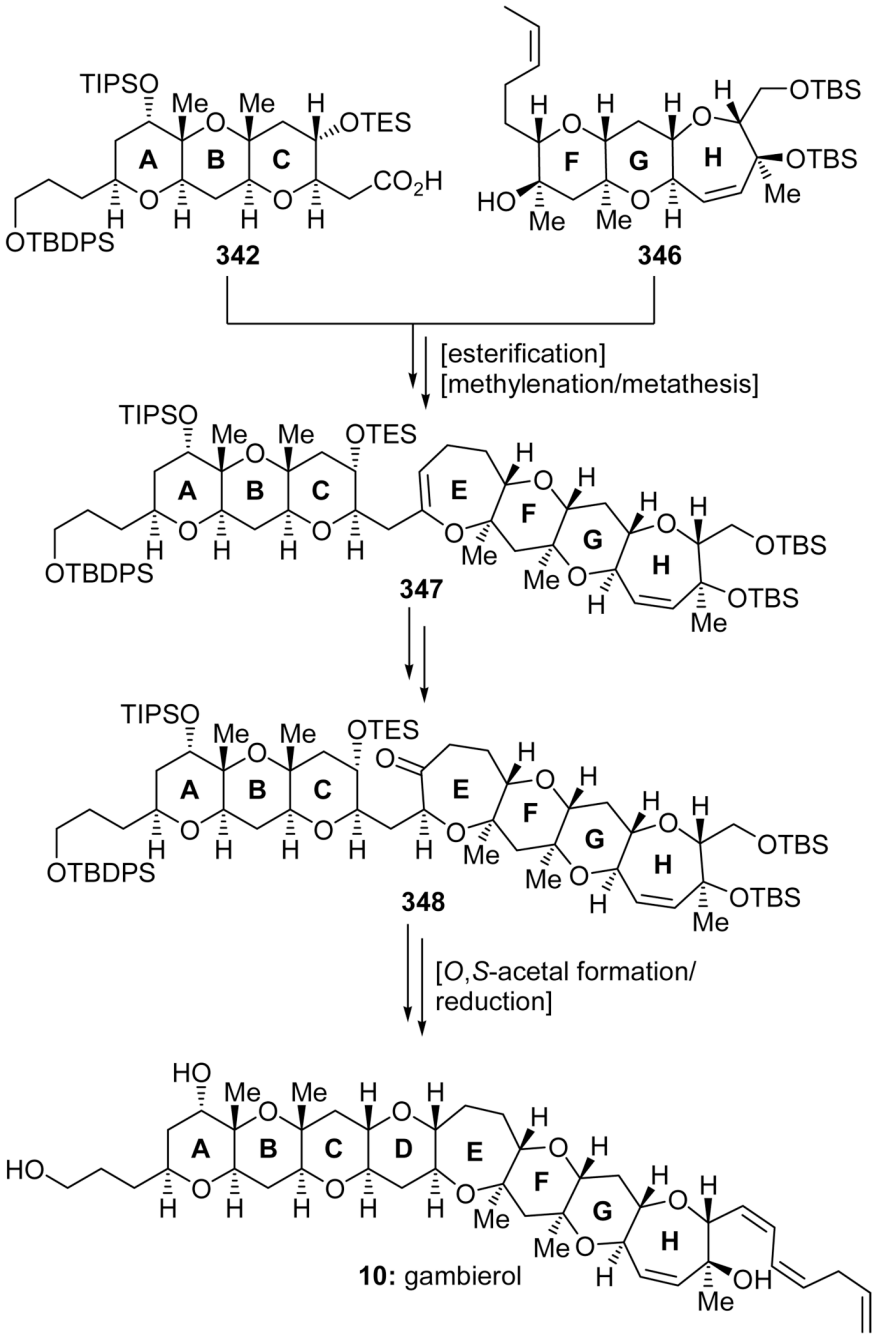


Scheme 54.

Third total synthesis of gambierol (**10**). Construction of the ABC fragment (**342**) (Rainier et al., 2005).[108]

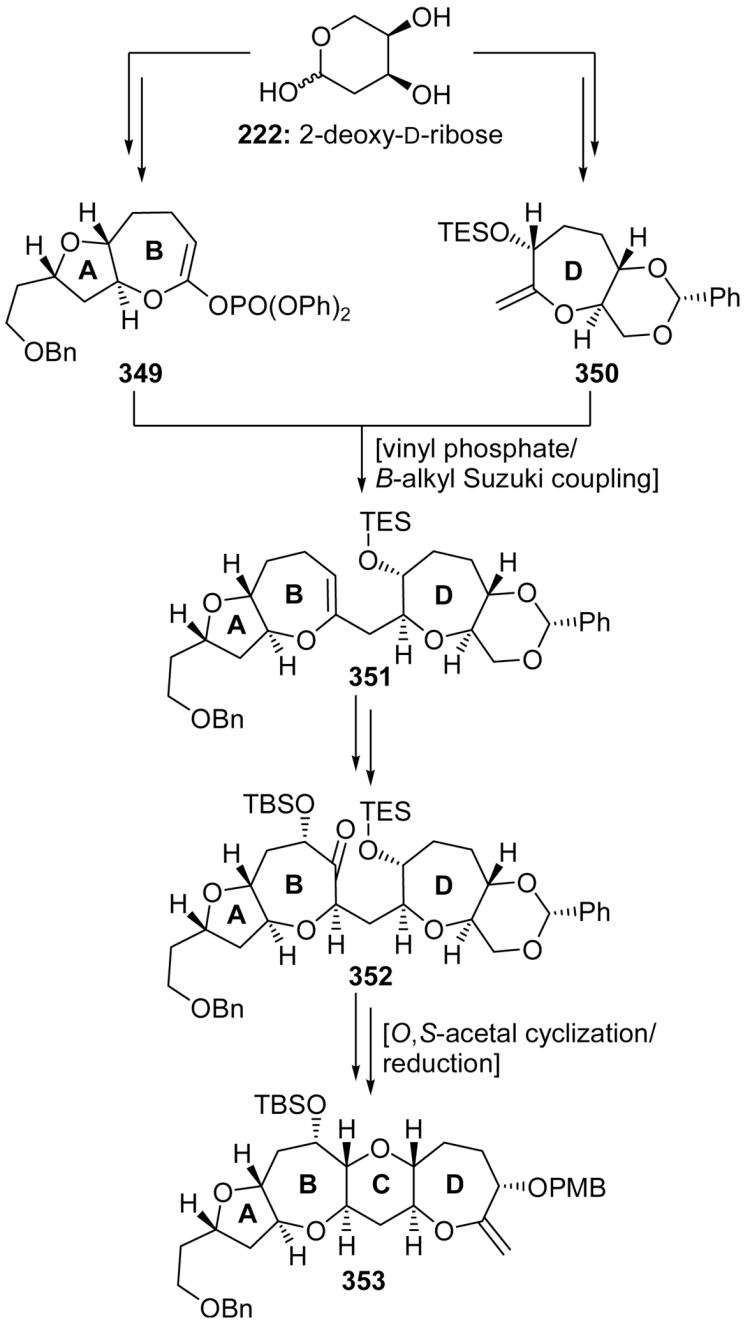


Scheme 55.
Third total synthesis of gambierol (**10**). Construction of the FGH domain (**346**) (Rainier et al., 2005).[108]

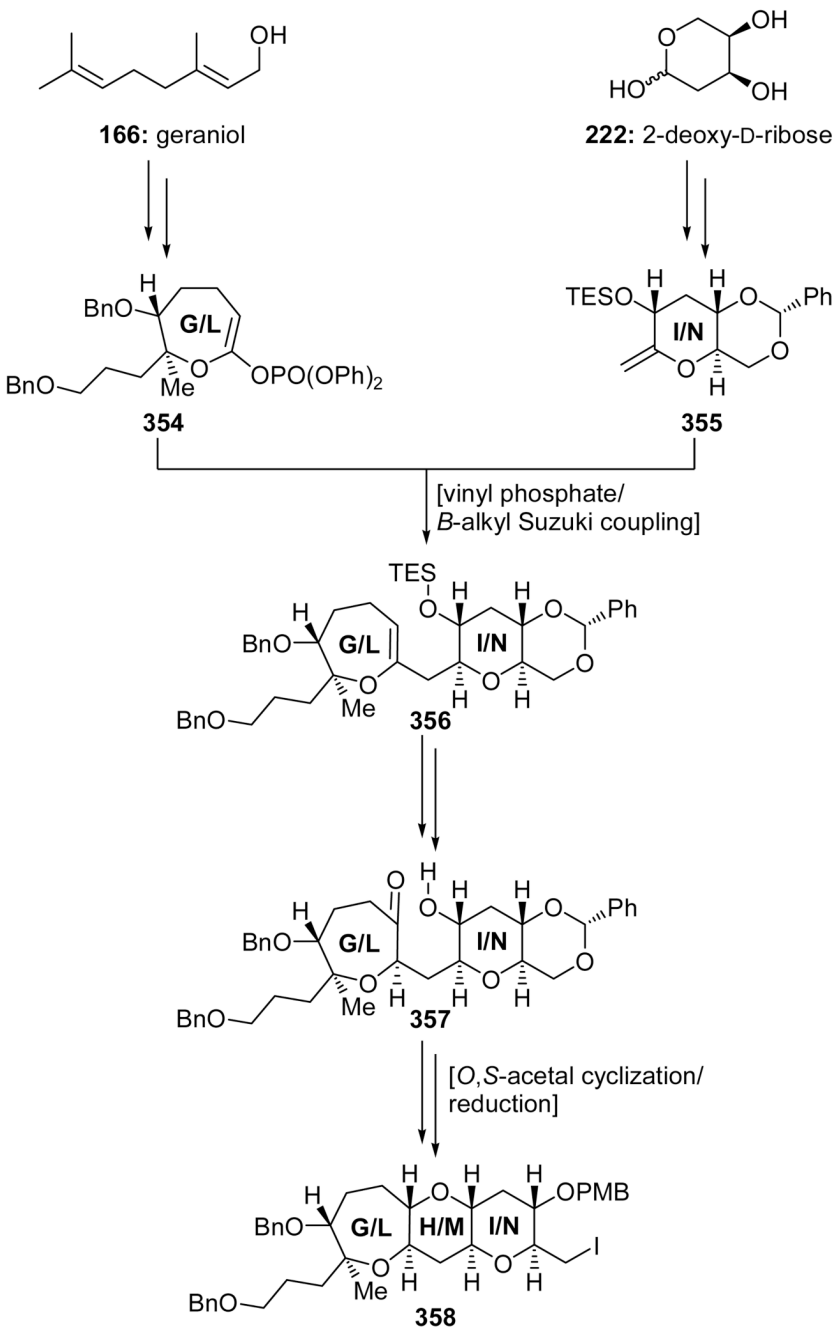


Scheme 56.

Third total synthesis of gambierol (**10**). Completion of the synthesis (Rainier et al., 2005). [108]

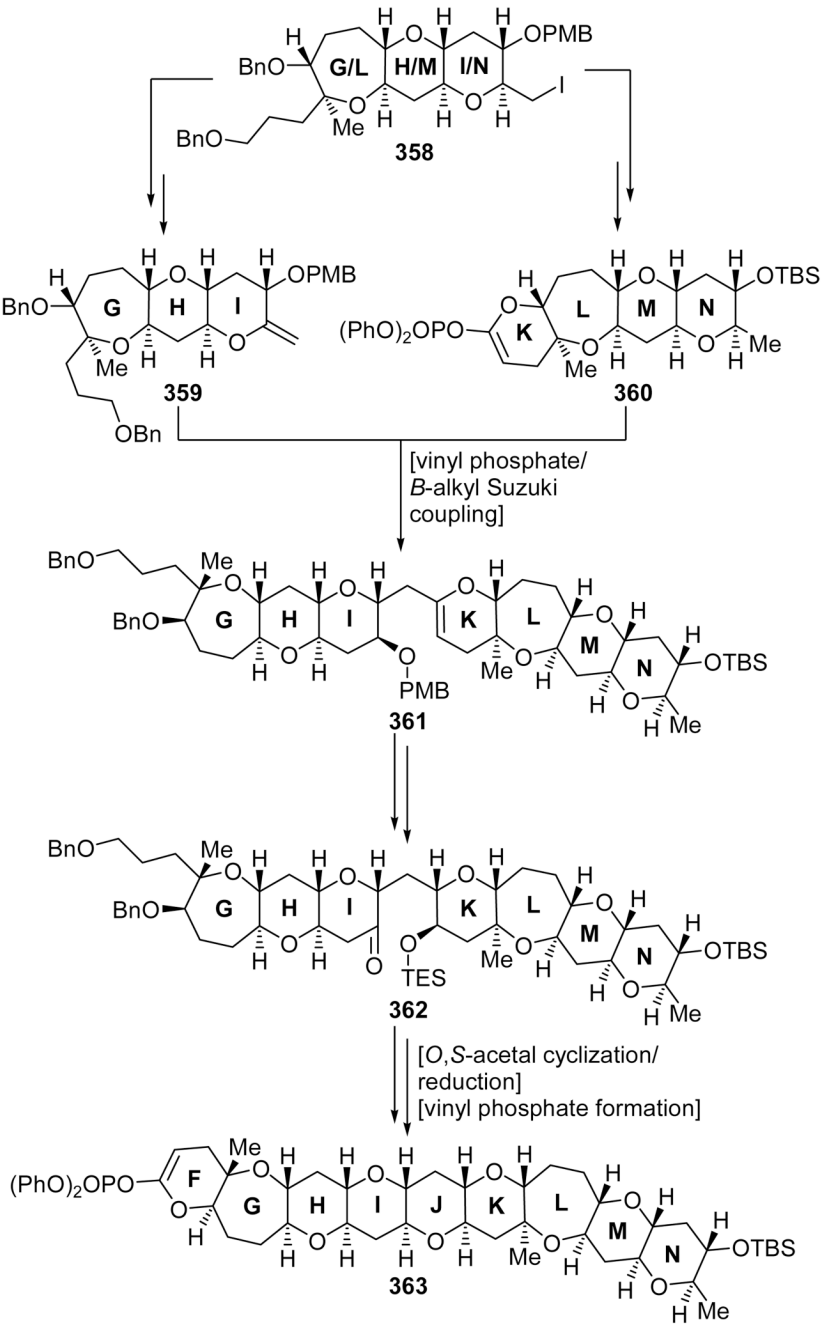


Scheme 57.
Total synthesis of gymnocin A (**12**). Construction of ABCD domain (**363**) (Sasaki et al., 2003). [110]



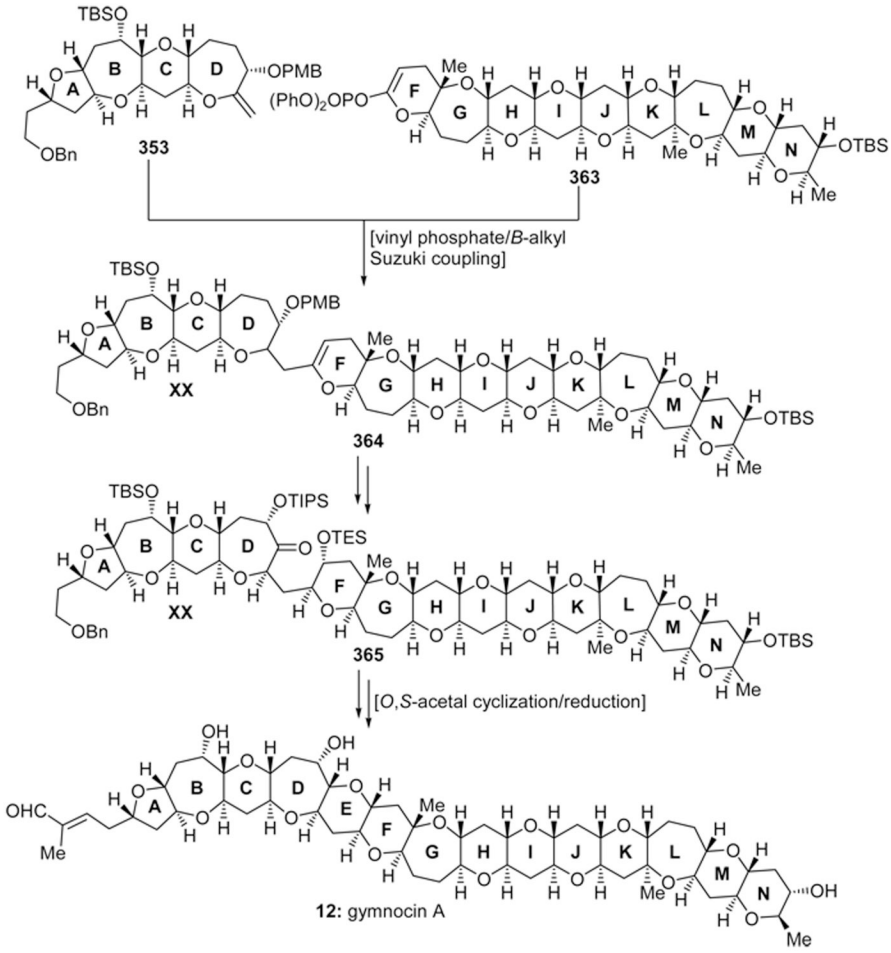
Scheme 58.

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



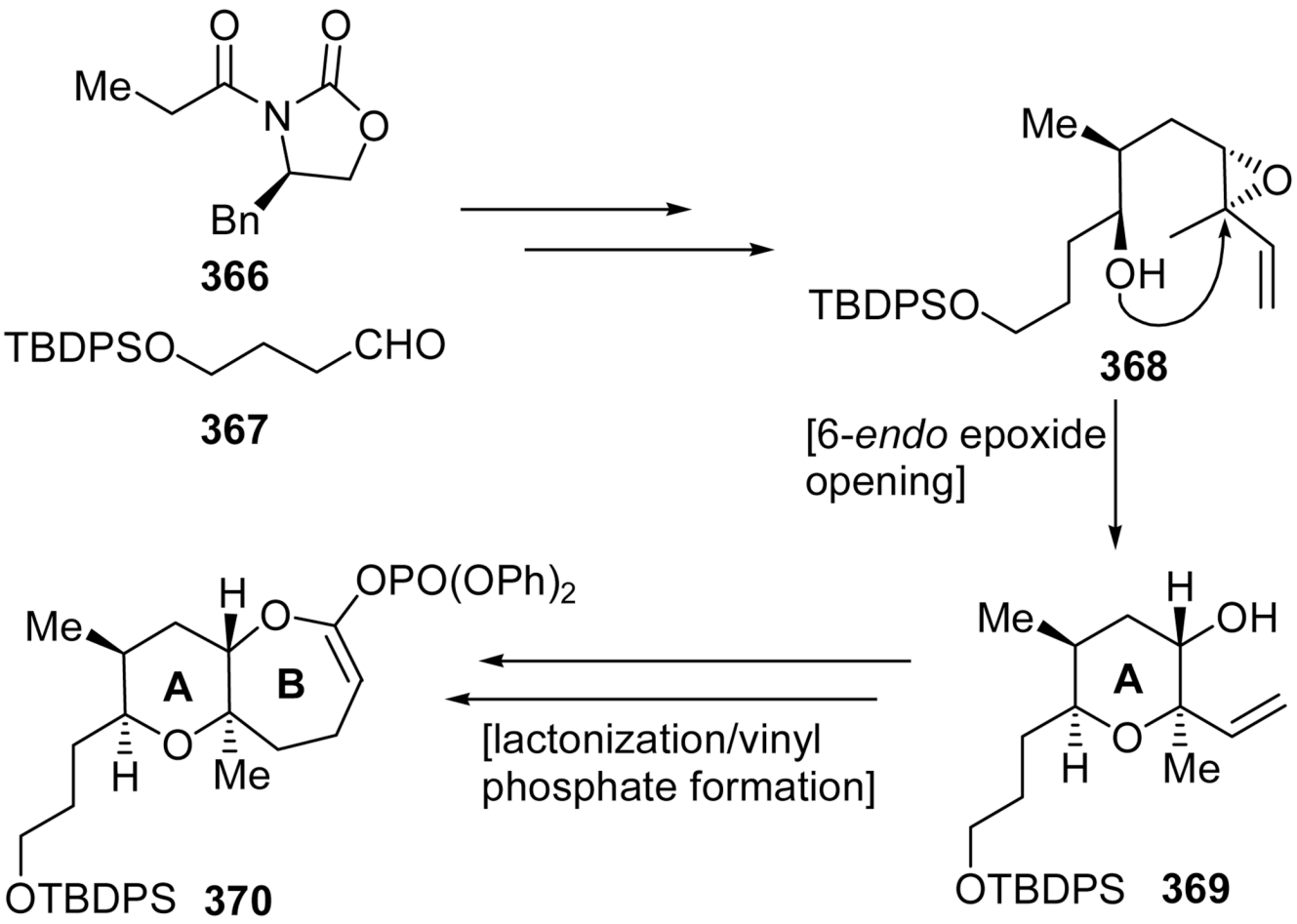
Scheme 59.

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

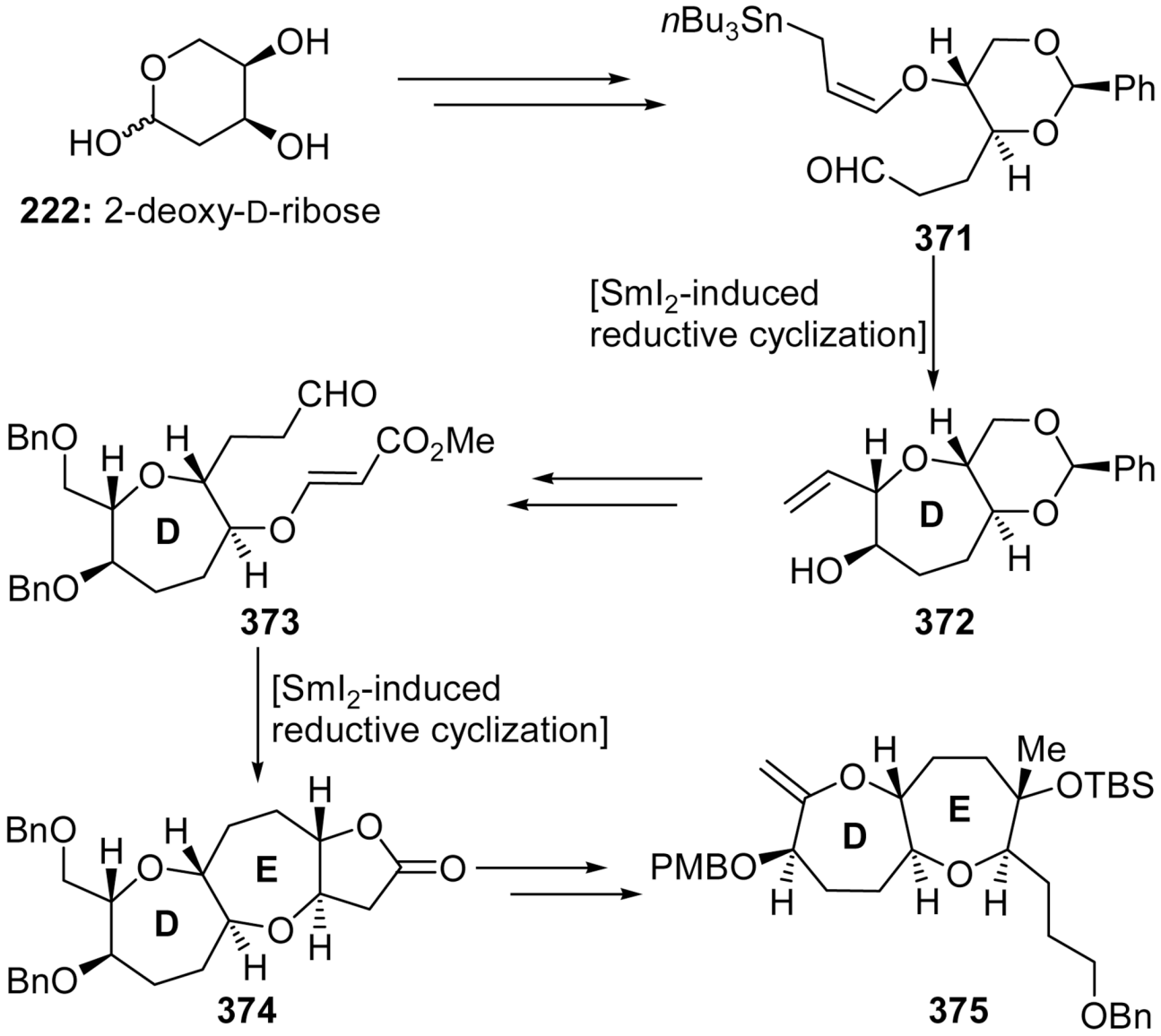


Scheme 60.

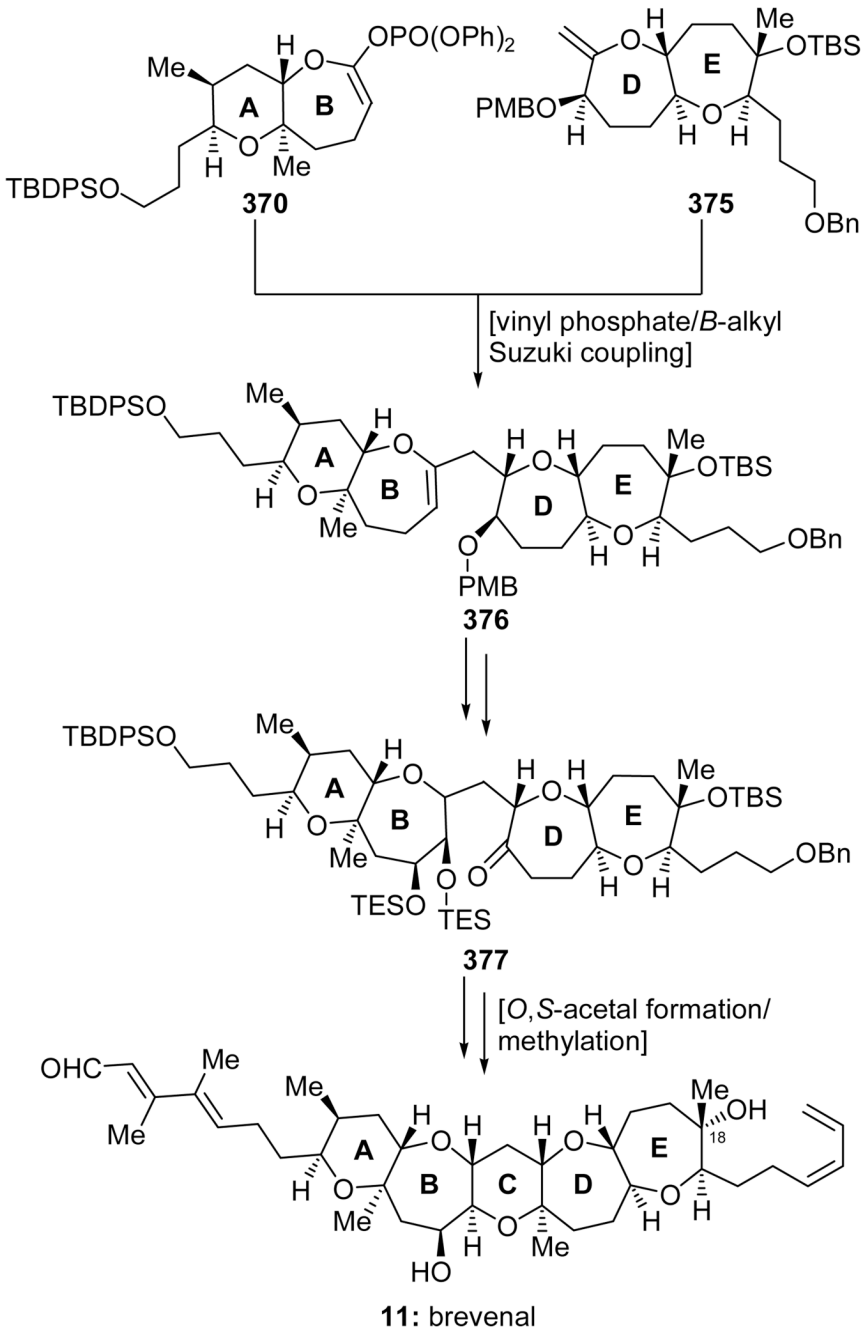
Total synthesis of gymnocin A (**12**). Final stages of the synthesis (Sasaki et al., 2003).[110]



Scheme 61.
Total synthesis of brevenal (**11**). Construction of the AB ring system (**370**) (Sasaki et al., 2006). [114]

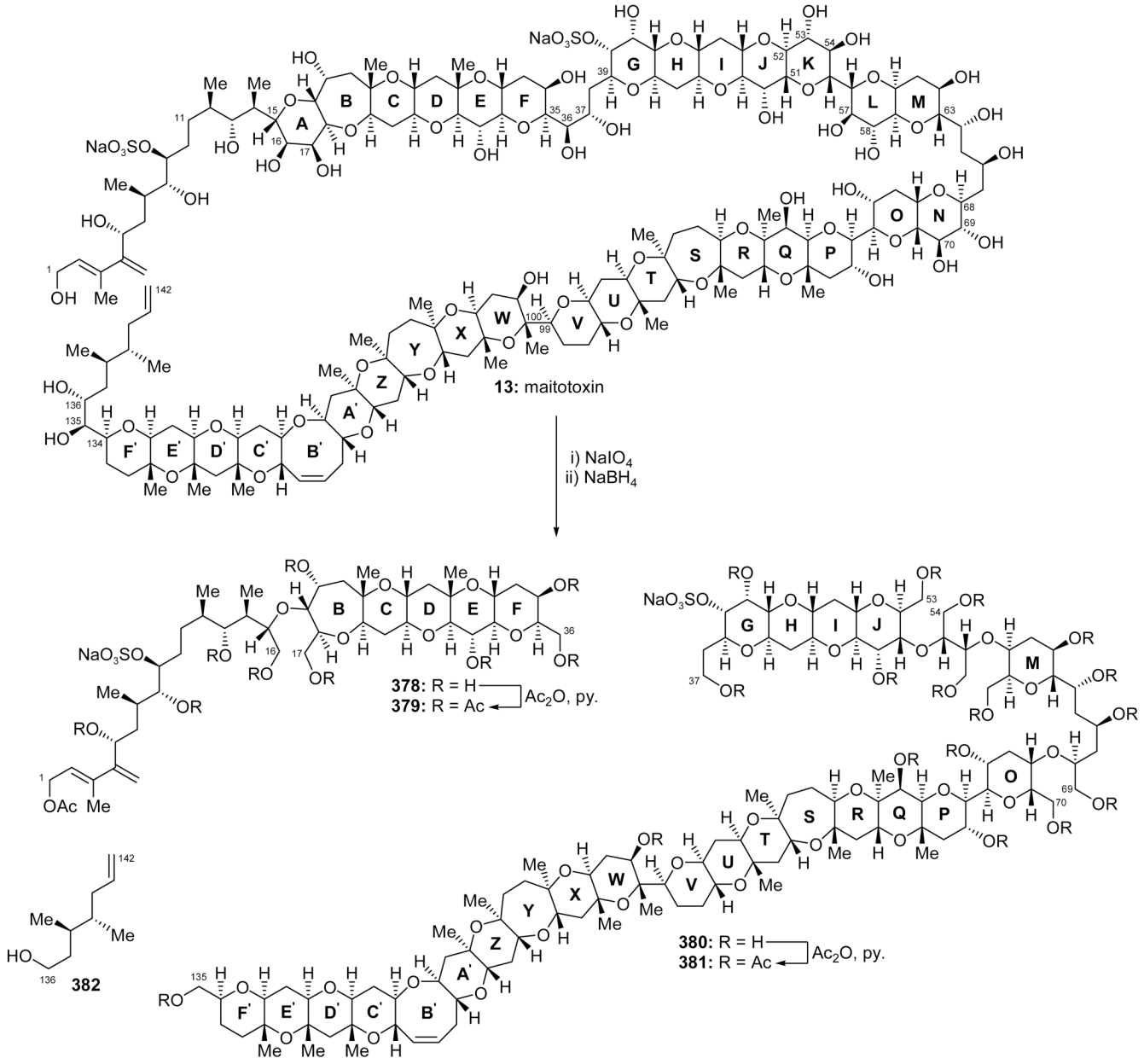


Scheme 62.
Total synthesis of brevenal (**11**). Construction of the DE ring system (**375**) (Sasaki et al., 2006). [114]

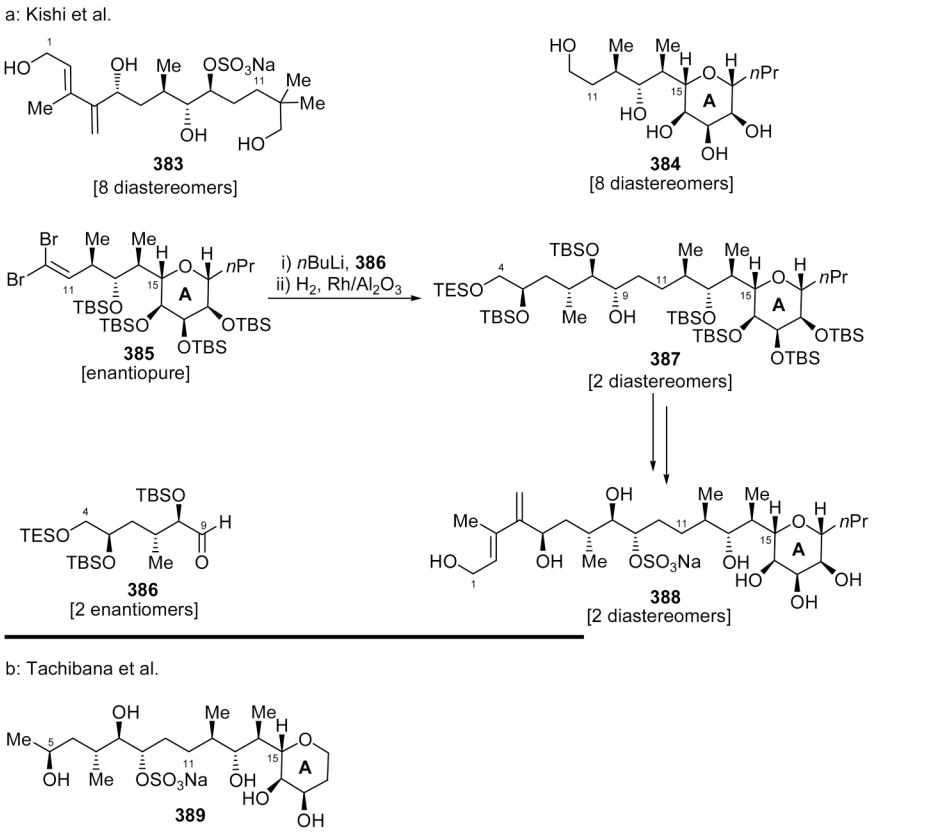


Scheme 63.

Total synthesis of brevenal (**11**). Final stages of the synthesis (Sasaki et al., 2006).[114]

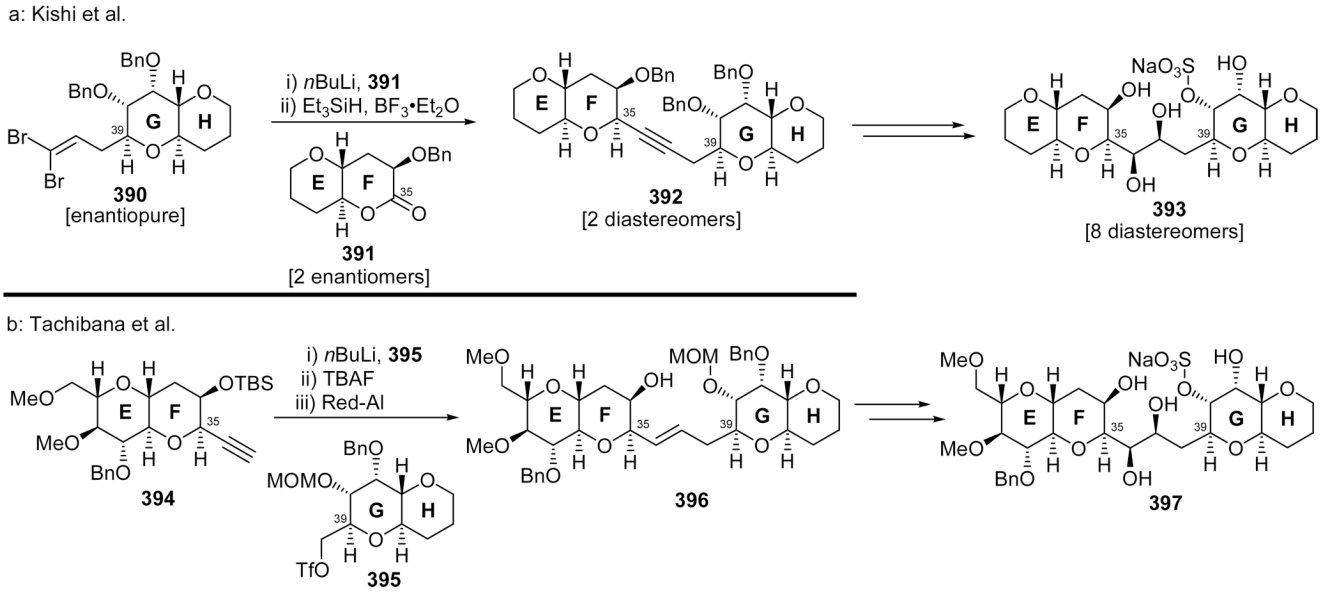


Scheme 64.
Degradation of maitotoxin (**13**) (Yasumoto et al., 1992).[118]



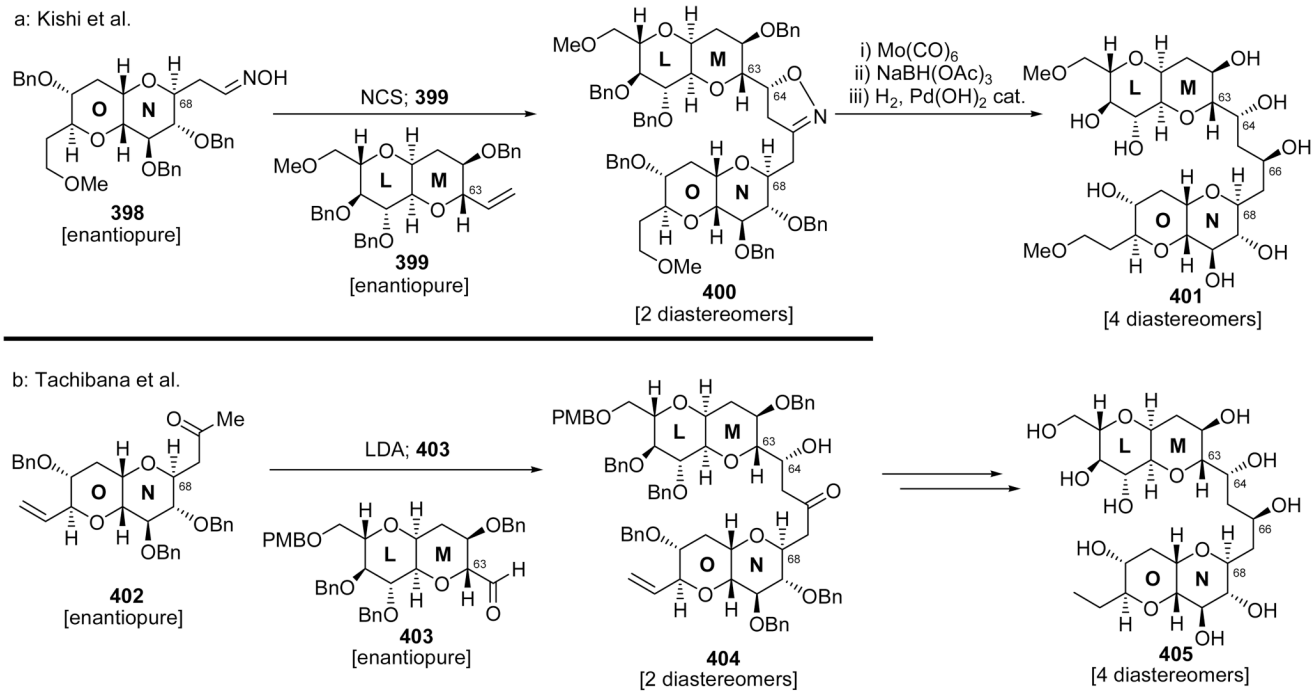
Scheme 65.

Determination of the relative stereochemistry of the C_1–C_{15} domain of maitotoxin (a: Kishi et al., 1996;[120] b: Tachibana et al., 1996[121]).



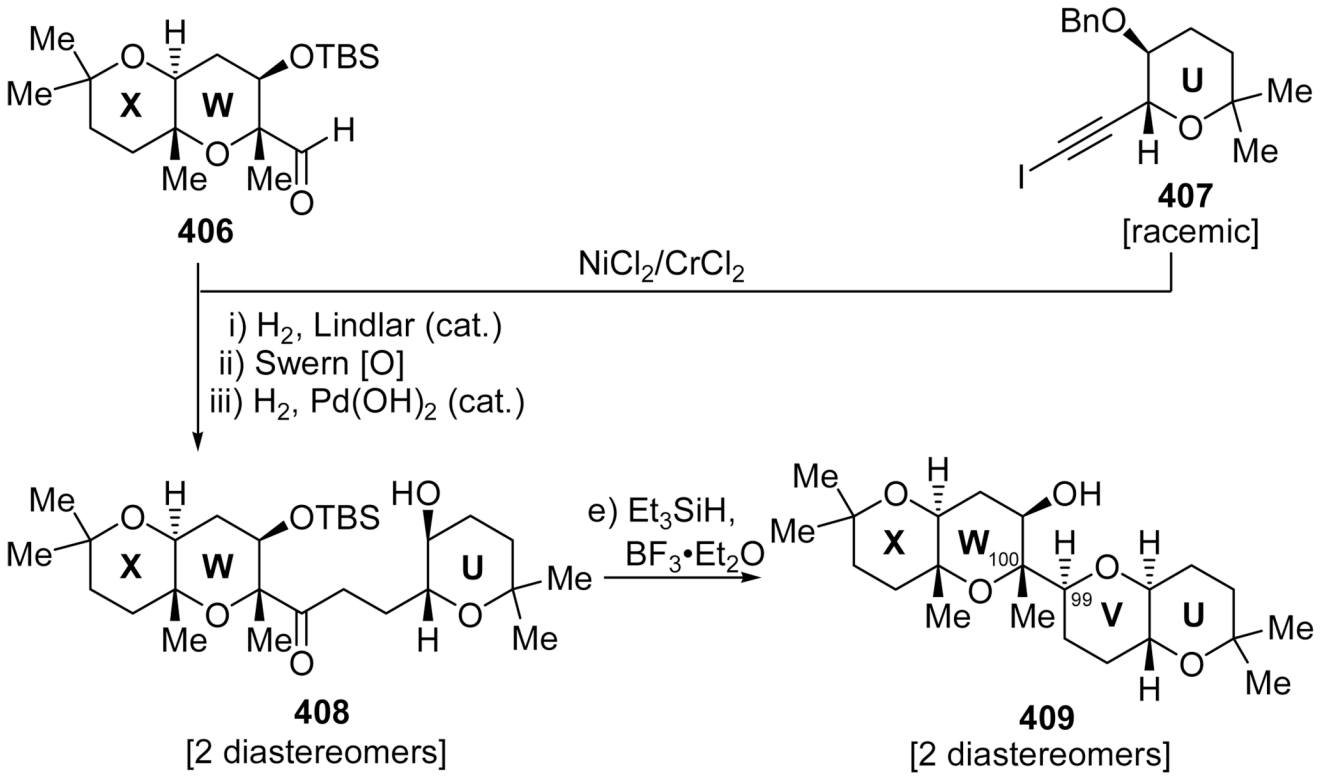
Scheme 66.

Determination of the relative stereochemistry of the C_{35}–C_{39} domain of maitotoxin (**13**) (a: Kishi et al., 1996;[120] b: Tachibana et al., 1995[122]).



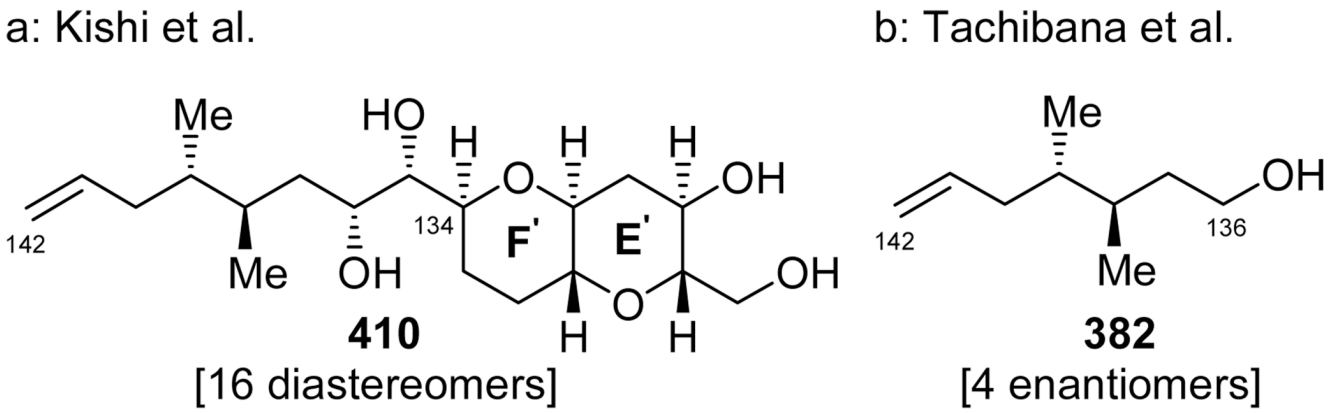
Scheme 67.

Determination of the relative stereochemistry of the C_{63}–C_{68} domain of maitotoxin (**13**) (a: Kishi et al., 1996;[120] b: Tachibana et al., 1995[123]).



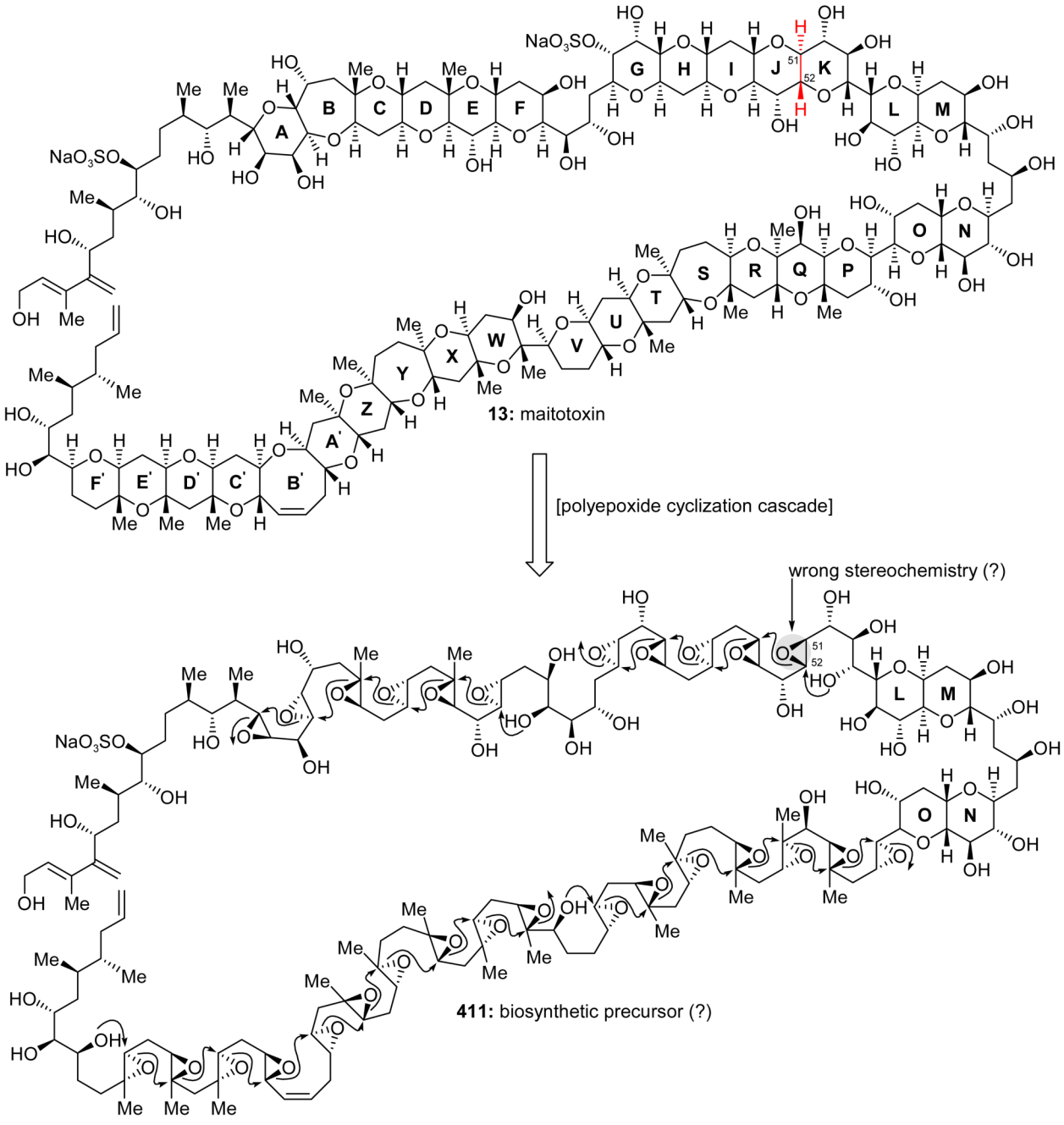
Scheme 68.

Confirmation of the relative stereochemistry of the C_{99}–C_{100} junction of maitotoxin (**13**) (Kishi et al., 1996).[124]



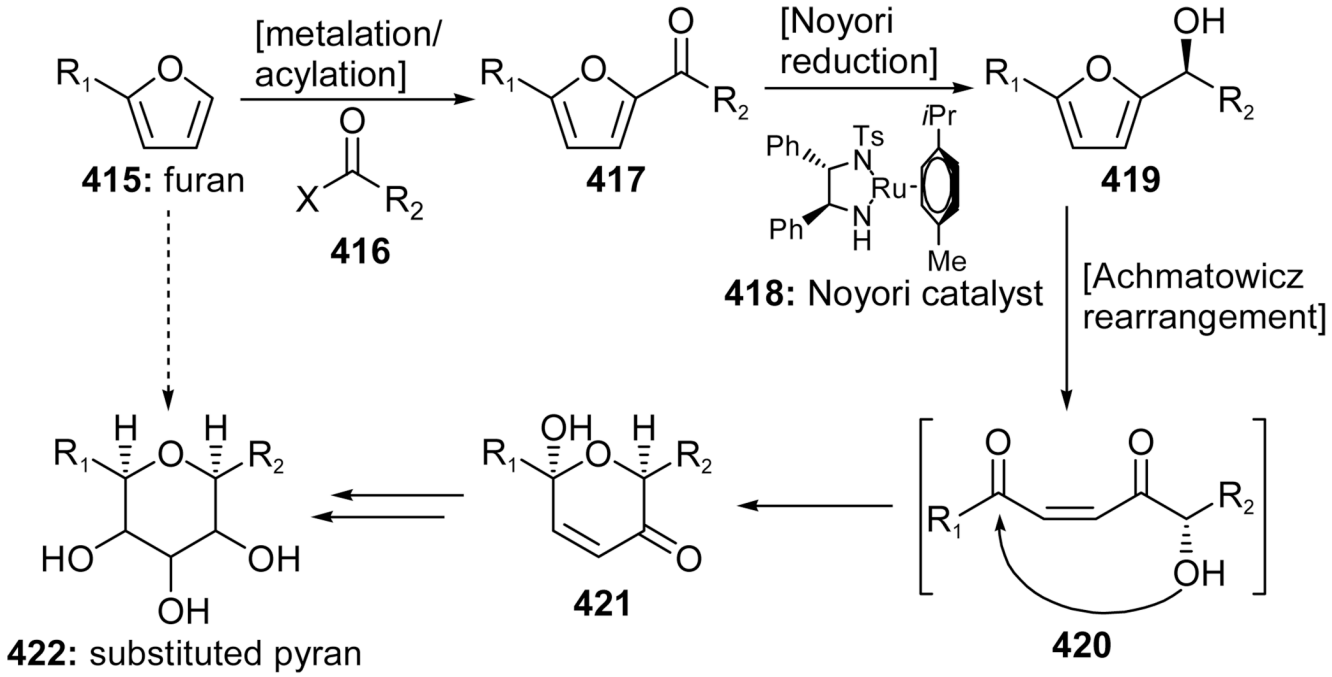
Scheme 69.

Determination of the relative stereochemistry of the C_{134}–C_{142} domain (a: Kishi et al., 1996) [120] and of the absolute stereochemistry of maitotoxin (**13**) (b: Tachibana et al., 1996).[125]

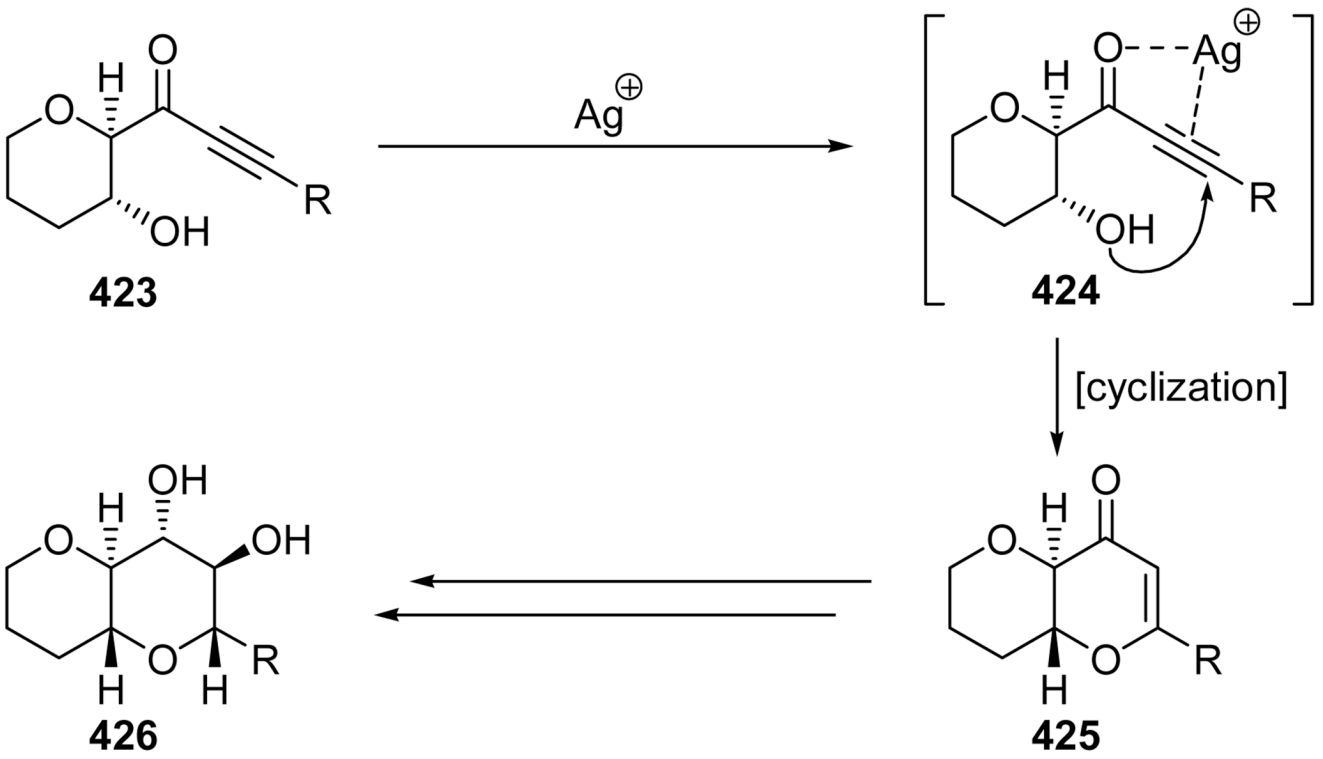


Scheme 70.

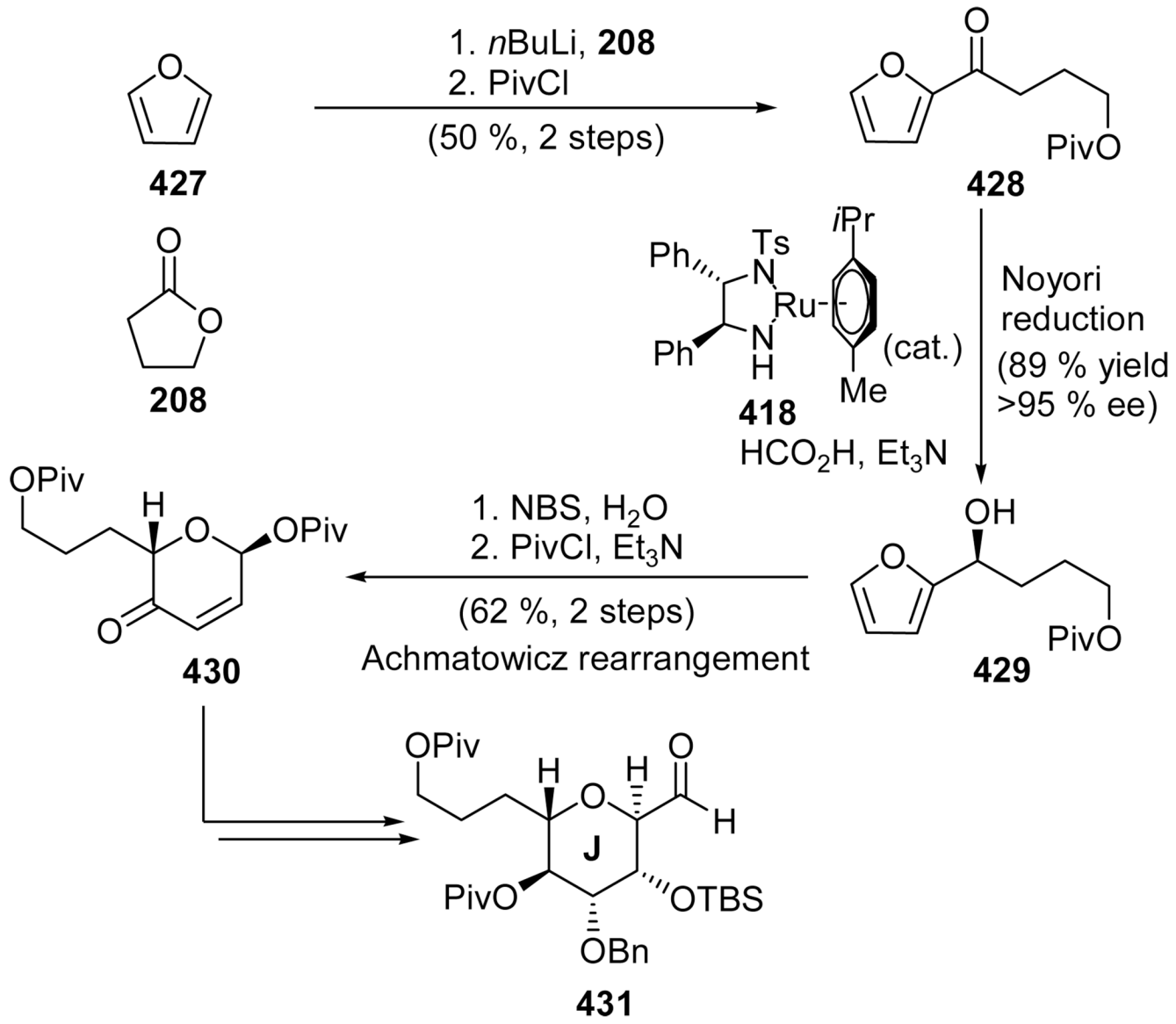
The Nakanishi/Gallimore–Spencer postulated hypothesis for the biosynthesis of maitotoxin (**13**) that brings into question the JK ring junction (C_{51} and C_{52}).



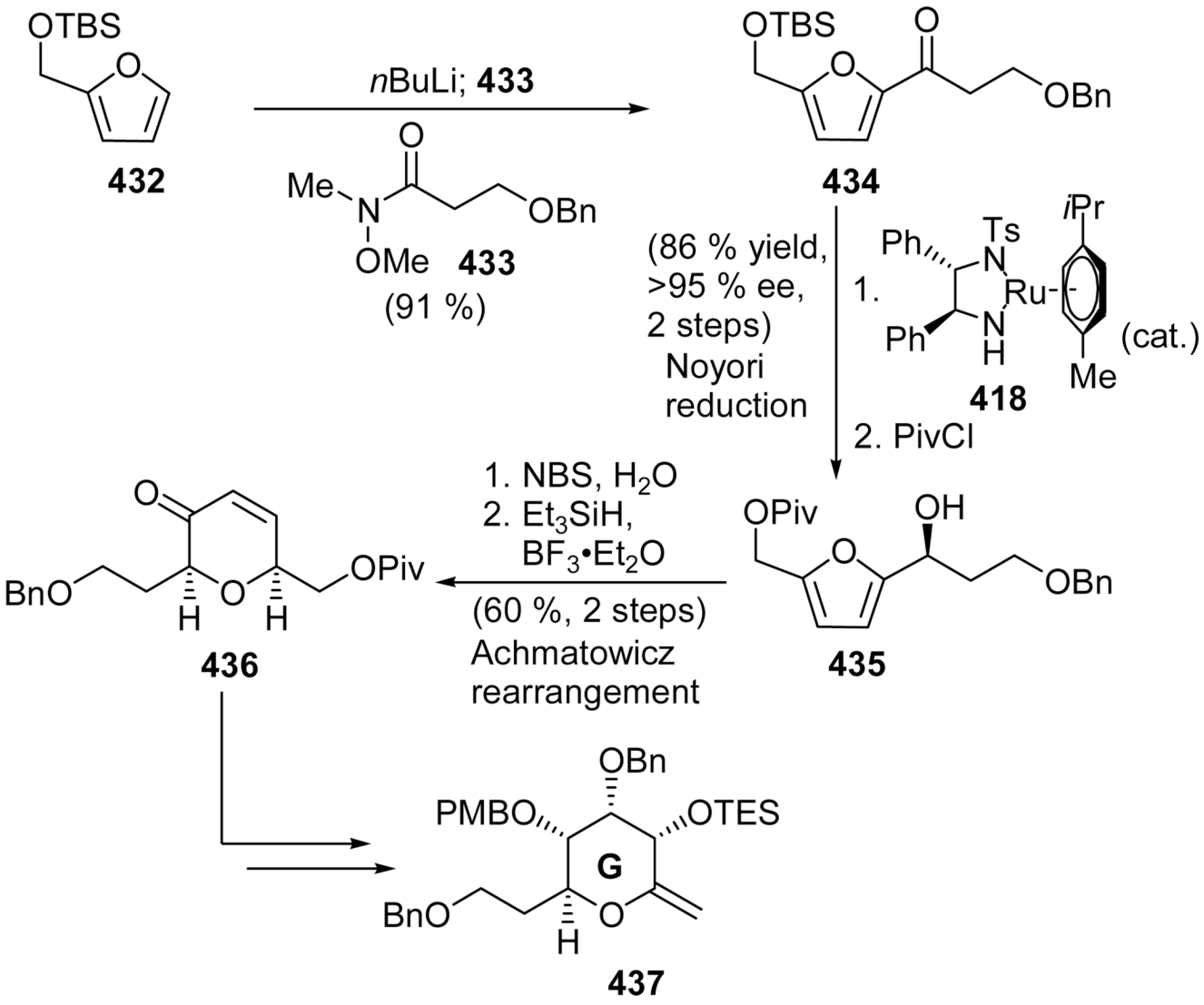
Scheme 71.
Furan-based asymmetric synthesis of substituted pyrans through the Noyori reduction/ Achmatowicz rearrangement sequence method (Nicolaou et al., 2007).[127]



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

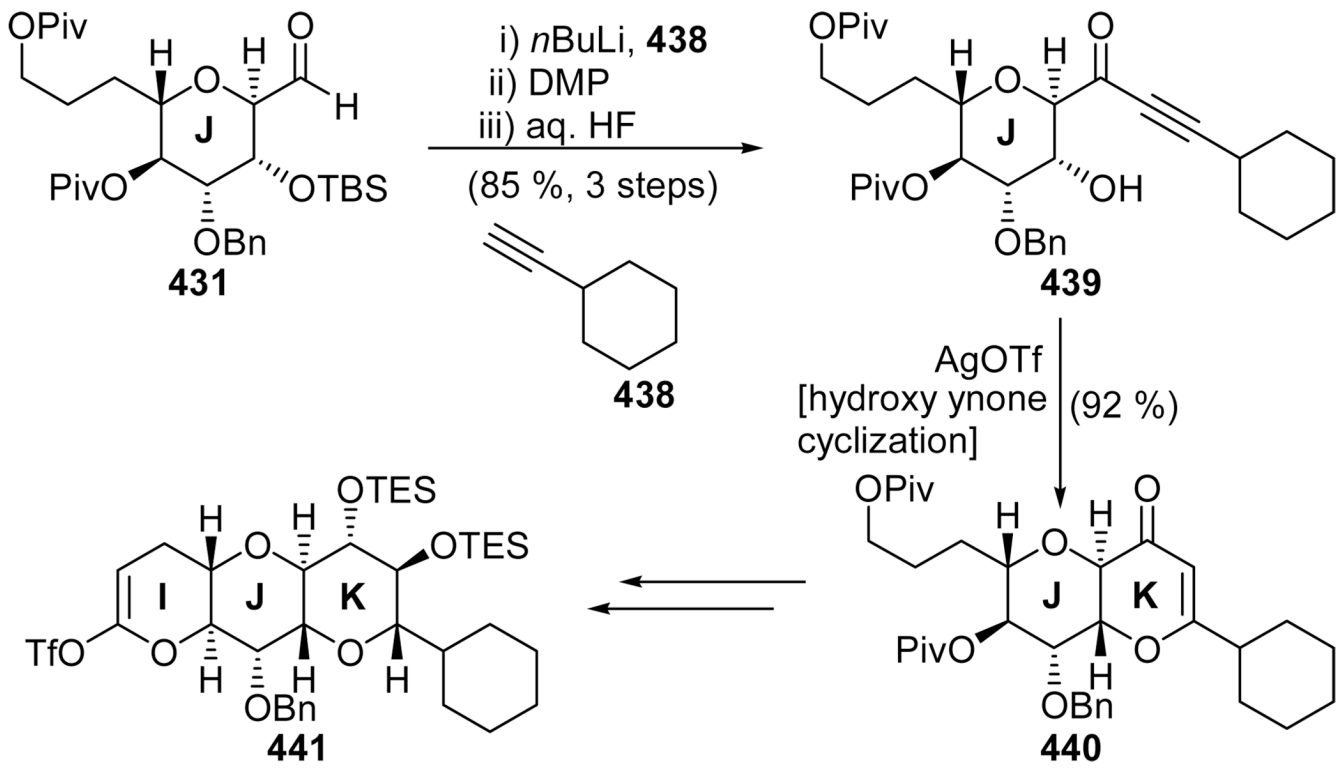


Scheme 73.
Construction of the maitotoxin J ring fragment **431** through the Noyori reduction/Achmatowicz rearrangement sequence method (Nicolaou et al., 2007).[127a]



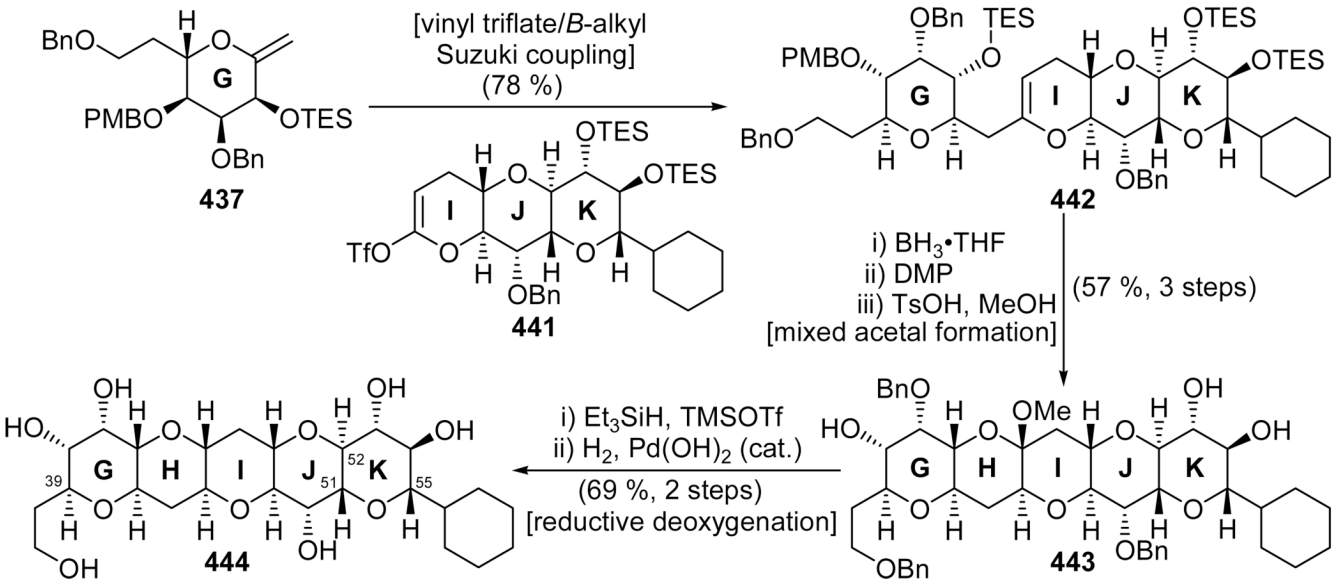
Scheme 74.

Construction of the maitotoxin G ring fragment **437** through the Noyori reduction/ Achmatowicz rearrangement sequence method (Nicolaou et al., 2007).[127a]

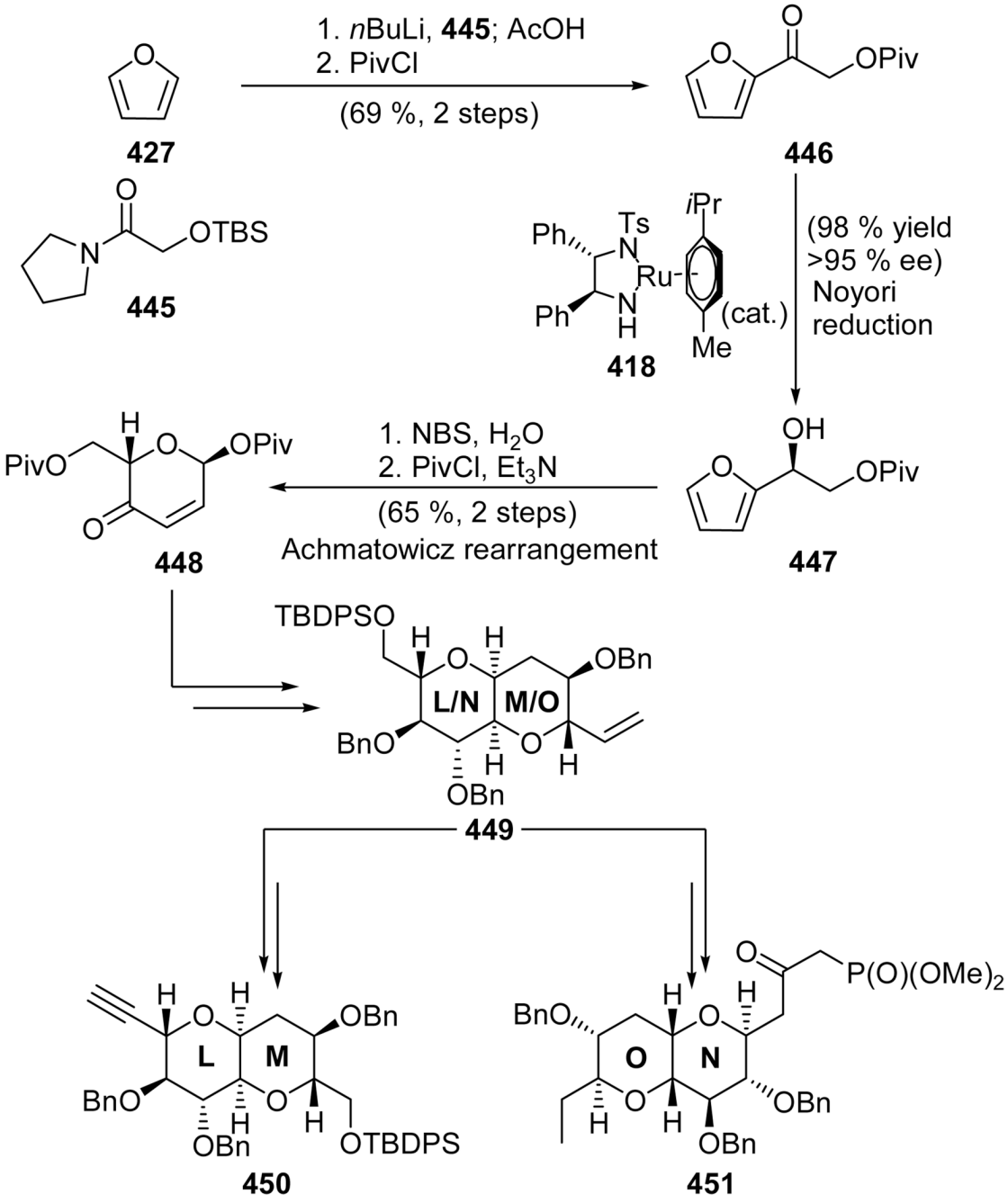


Scheme 75.

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

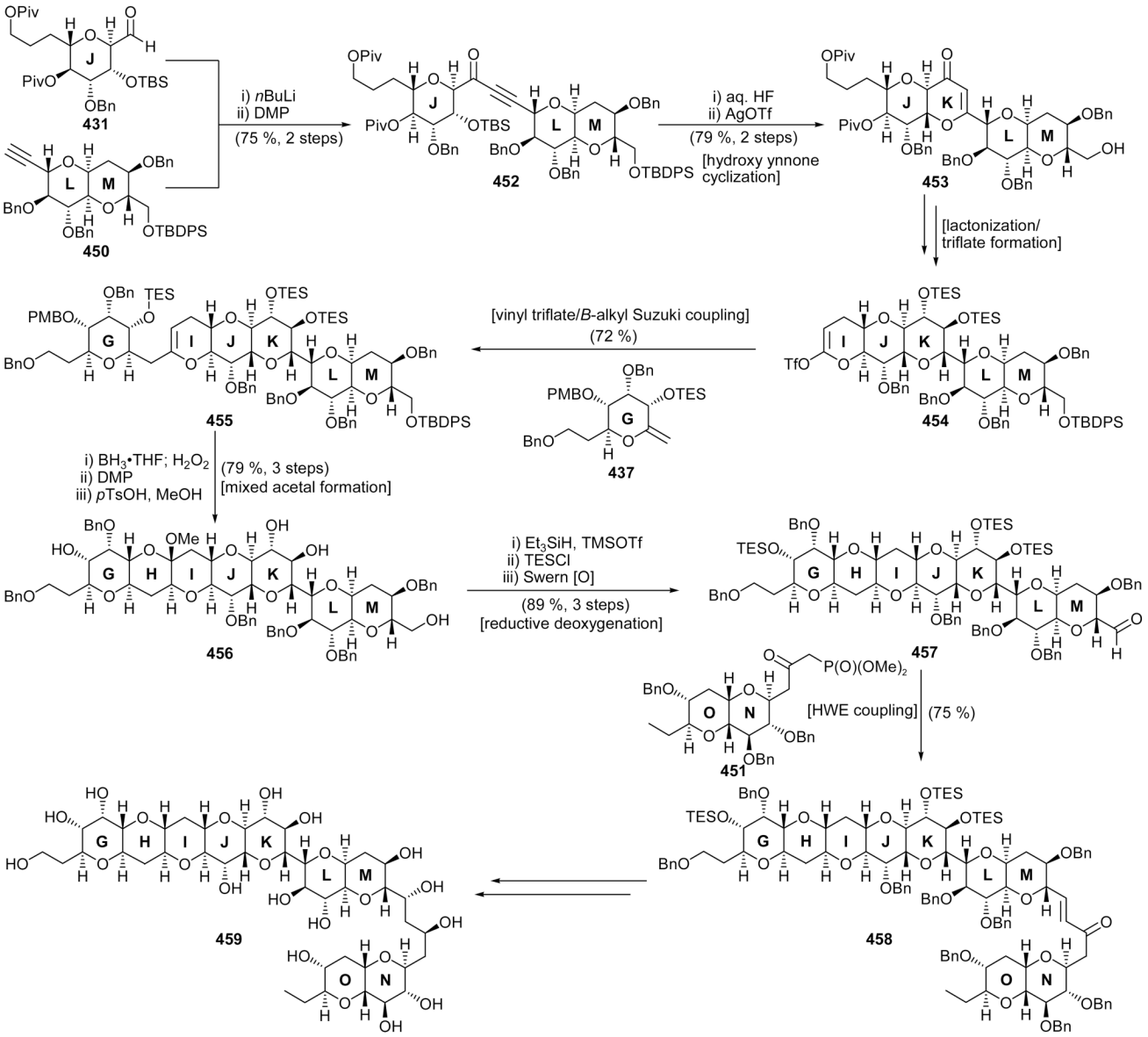


Scheme 76.
Synthesis of the maitotoxin GHIJK fragment **444** (Nicolaou et al., 2007).[127a]



Scheme 77.

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



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