Convergent Strategies for Syntheses of *trans*-Fused Polycyclic Ethers

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Received March 1, 2005

Contents

Masayuki Inoue was born in Tokyo in 1971. He received his B.Sc. degree in Chemistry from the University of Tokyo in 1993. In 1998 he obtained his Ph.D. degree from the same university, working under the supervision of Professors K. Tachibana and M. Sasaki on synthetic studies of ciguatoxin. After spending 2 years with Professor S. J. Danishefsky at the Sloan-Kettering Institute for Cancer Research (1998−2000), he joined the Graduate School of Science at Tohoku University as an assistant professor in the research group of Professor M. Hirama. At Tohoku University he was promoted to Lecturer in 2003 and then to Associate Professor in 2004. He has been honored with the Young Scientist's Research Award in Natural Product Chemistry (2001), Chugai Award in Synthetic Organic Chemistry (2001), First Merck-Banyu Lectureship Award (2004), Chemical Society of Japan Award for Young Chemists (2004), and Thieme Journal Award 2005. His research interests include the synthesis, design, and study of biologically important molecules with particular emphasis on the total synthesis of structurally complex natural products.

1. Introduction

The *trans*-fused polycyclic ethers are one of the most characteristic and spectacular classes of compounds isolated from marine sources. These molecules are produced by marine microorganisms, mostly by unicellular flagellated algae called dinoflagellates. The first fused polycyclic ether to be structurally determined was brevetoxin-B (Figure 1, **1**) in 1981.[1] Since then, various natural products with similar skeletons have been structurally elucidated using modern spectroscopic techniques.[2] These molecules are made up of a single carbon chain locked into a long semirigid ladder-like structure. The striking regularity with which the oxygen atoms bridge the nanoscale polycyclic framework is a remarkable feature of these molecules: cyclic ethers of sizes ranging from five- to nine-membered rings all fuse in a trans/syn/trans fashion. Despite this common polycyclic motif, they show diverse biological activities with extreme potency.

Brevetoxins (**1**,[1] **2**[3]) are potent ichthyotoxins (**2**: LC_{100} 4 ng/mL to guppies) and were isolated from the dinoflagellate *Karenia* (formerly *Gymnodinium*) *breve*, blooms of which cause a phenomenon known as "red tide". Red tides giving rise to these toxins have killed great numbers of fish and caused intoxication in humans. These molecules exert their toxicity by binding to the voltage-sensitive sodium channels (VSSC) of excitable membranes, causing them to open, thereby allowing sodium ion influx.[4] Hemibre-

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10.1021/cr0406108 CCC: $53.50
Published on Web 10/22/2005

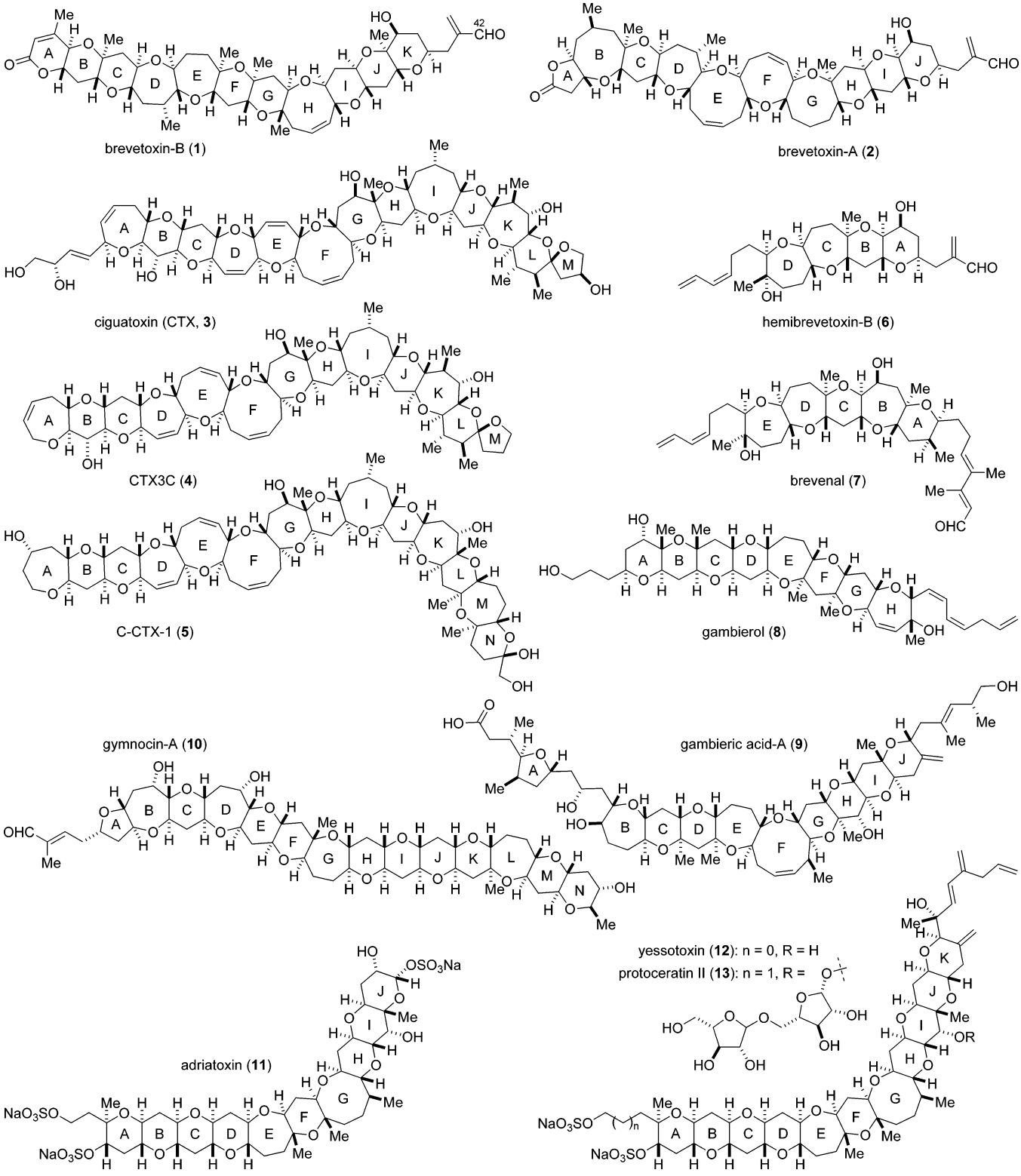


Figure 1. Structure of representative polycyclic ethers.

vetoxin-B (**6**)[5] and brevenal (**7**)[6] were found in the same organism, and their molecular sizes are about one-half of that of brevetoxins. Hemibrevetoxin-B (**6**) was reported to cause the same characteristic rounding of cultured neuroblastoma cells as brevetoxins. Significantly, it was demonstrated that **7** competitively displaced brevetoxin from its binding site on VSSC and antagonized the toxic effect of brevetoxins in fish. Thus, **7** has the potential to serve as a therapeutic agent in the treatment of brevetoxin poisoning.

Ciguatoxins (**3**,[7] **4**,[8] **5**[9])[10] were isolated as the principle toxins in widespread seafood poisoning known as ciguatera.[11] More than 20 000 people suffer annually from ciguatera, making it one of the most common food poisonings of nonbacterial origin. The toxins, generated by the epiphytic dinoflagellate *Gambierdiscus toxicus*,[12] are transferred through the aquatic food chain. Approximately 100 species of fish cause ciguatera; these ciguateric fish look, taste, and smell the same as uncontaminated fish. Ingestion of

affected fish leads to neurological, gastrointestinal, and cardiovascular disorders, which may last up to 1 month or more, or recur periodically. Ciguatoxins and brevetoxins share a specific binding site on VSSC, although ciguatoxins bind 10 times more strongly than brevetoxins.[4,13−15] Moreover, the lethal potencies of ciguatoxins (LD_{50} = 0.25−4 μg/kg), determined by intraperitoneal injection into mice, are much greater than those of brevetoxins (LD_{50} > 100 μg/kg).[14] The low fatality rate in ciguatera is due solely to the minute concentration of ciguatoxins in fish flesh.

Some strains of *Gambierdiscus toxicus* produce not only ciguatoxins, but also other polycyclic ethers such as gambierol (**8**)[16] and gambieric acids (**9**).[17] Gambierol (**8**) exhibits toxicity toward mice (LD_{50} = 50 μg/kg) with symptoms resembling those of ciguatoxins, inferring the possibility that **8** is involved in ciguatera poisoning. Most recently, by using taste cells the molecular target of **8** was identified to be the voltage-sensitive potassium channel.[18] On the other hand, gambieric acid (**9**) is nontoxic to mice; nevertheless, **9** is a potent antifungal. The antifungal activity of **9** is 2000 times greater than that of amphotericin B.

The notorious red tide dinoflagellate *Gymnodinium mikimotoi*, which is representative of the species that causes damage worldwide, produces gymnocin-A (**10**).[19] Gymnocin-A is approximately 250 times less ichthyotoxic than 42-dihydrobrevetoxin-B but is cytotoxic to P388 mouse leukemia cells (ED_{50} = 1.3 μg/mL).

Yessotoxin (**12**) was isolated as one of the causative toxins in diarrheic shellfish poisoning, with *Protoceratium reticulatum* being identified as the biogenetic origin of **12**.[20] The polycyclic skeleton of adriatoxin (**11**) is identical to that of the A−J-ring system of **12** but lacks the K-ring and its side chain.[21] As these toxins have shown potent mouse lethality, contamination of bivalves by **11** and **12** poses a worldwide problem to human health as well as to the shellfish industry. Most recently an extremely potent cytotoxic agent, protoceratin II (**13**), was isolated from the culture broths of *Protoceratium reticulatum* and characterized as having a yessotoxin skeleton substituted with two arabinosides.[22] Remarkably, IC_{50} values of **13** against human cancer cell lines were reported to be less than 0.5 nM.

These polycyclic ethers have attracted intense interest from biologists and chemists alike because the novel and specific activities of these toxins may present a unique opportunity for investigation of the unknown biological events as well as application as important chemotherapeutic agents. Although many investigations have focused on elucidating their biological targets, receptor proteins have only been identified for brevetoxins, ciguatoxins, and gambierol as mentioned above,[4,13−15,18,23] mainly due to their limited availability from natural sources.

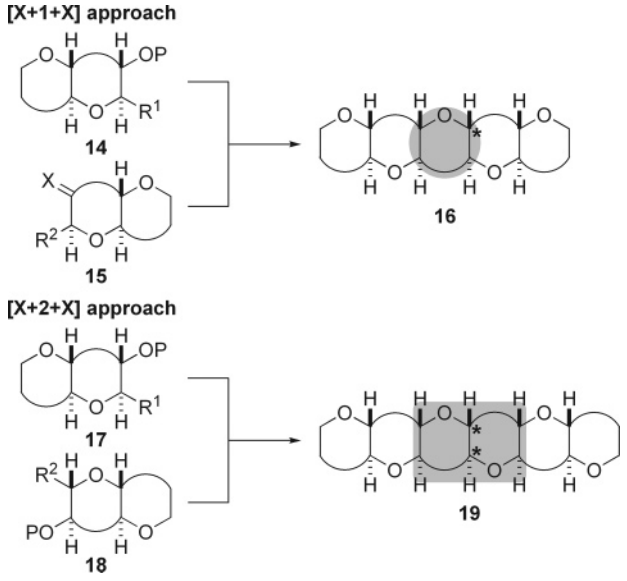
Over the past two decades a number of laboratories have attempted the chemical construction of these compounds, motivated by their unusual molecular architecture, biological activity, and association with the catastrophic effects of red tide phenomena and food poisoning.[24] Their exquisitely complex structures have served as the inspiration for development of new methodologies in organic synthesis and as an elegant platform for exhibiting the creativity of the modern organic chemist. In 1995 Nicolaou, a pioneer in the field of polyether synthesis, reported the first total synthesis of brevetoxin-B (**1**).[25] This major advance was followed by the synthesis of brevetoxin-A (**2**) by the same laboratory in 1998.[26] In the last 5 years many laboratories have contributed to even more rapid progress. These efforts culminated in the total syntheses of ciguatoxin CTX3C (**4**) by Hirama (2001),[27] gambierol (**8**), synthesized independently by Sasaki[28] (2002), Kadota/Yamamoto[29] (2002), and Rainier (2005),[30] brevetoxin-B (**1**) by Nakata (2004)[31] and Kadota/Yamamoto (2005),[32] and gymnocin-A (**10**) by Sasaki (2003).[33] These landmark achievements were made possible by the development of a number of important reactions and methodologies.

The large and complex structures of these molecules necessitate a highly efficient synthetic strategy with excellent material throughput and a minimum number of synthetic transformations. Because the linear construction of the ether rings is virtually impossible due to the size of these molecules, development of an efficient methodology for coupling the fragments, which is suitable for use in the advanced stages of synthesis, has been particularly important for the total synthesis. This review focuses on development and application of various convergent strategies for the assembly of natural polycyclic ethers and their structural fragments.

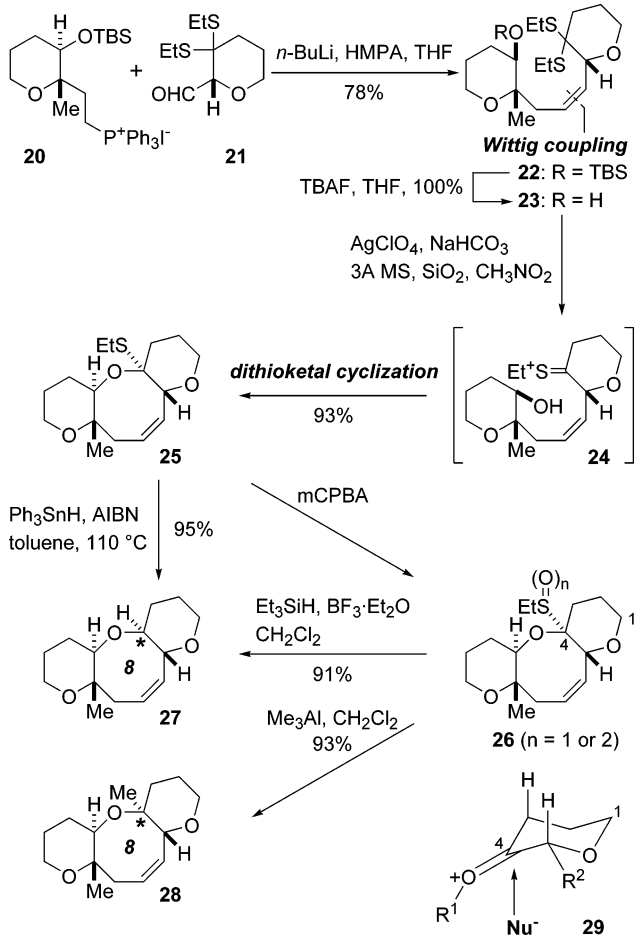
2. Two Convergent Synthetic Strategies for the Construction of Polycyclic Ether Arrays

The existing convergent strategies for the syntheses of *trans*-fused polycyclic ethers can be roughly categorized into two routes as illustrated in Scheme 1. After coupling the structural fragments, the "[X + 1 + X] approach" necessitates cyclization of one ether ring with the introduction of at least one stereocenter to build the fused ether array (**14** + **15** → **16**), whereas the "[X + 2 + X] approach" involves con-

Scheme 1. Two Convergent Strategies for Syntheses of Polycyclic Ethers



Scheme 2. Hydroxy Dithioketal Strategy Developed by Nicolaou (1986, 1989)



struction of the two rings with the formation of two stereocenters (**17** + **18** → **19**). The [*X* + 2 + *X*] approach is more flexible for the design of a synthetic strategy than the [*X* + 1 + *X*] approach but apparently involves more bond-forming reactions as well as the introduction of more stereogenic centers. The challenge in both strategies lies in developing a reaction sequence that links the structural fragments, constructs new ethers having the requisite ring sizes, and controls the bridgehead stereocenters without affecting the preexisting functionalities of these complex molecules. Furthermore, when a medium-sized ring is present between the fragments, unfavorable entropy factors and transannular nonbonding interactions pose further difficulties in effecting ring closure.[34] In sections 3 and 4 of this review the two approaches are further classified into subcategories by the key reactions utilized in the syntheses, and these are discussed separately below. Newly introduced bridgehead stereocenters are marked with an asterisk throughout the manuscript as compounds **16** and **19** in Scheme 1.

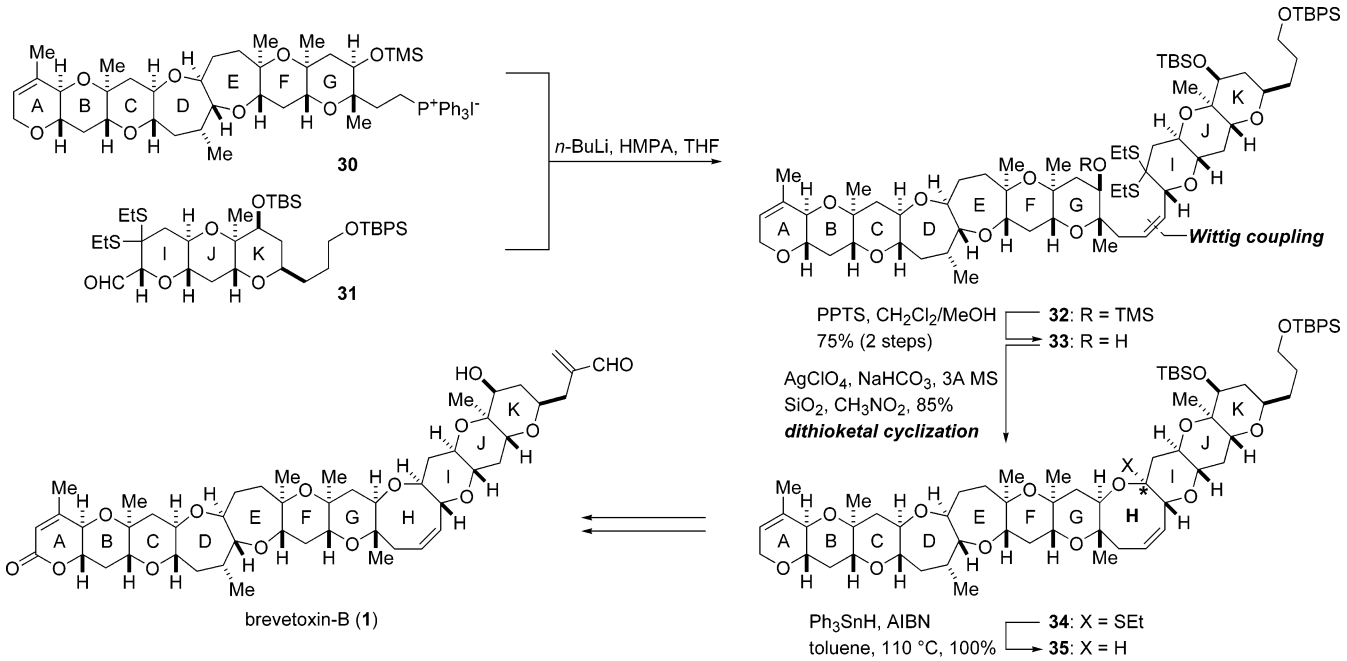
3. [X + 1 + X] Approach

3.1. Wittig Coupling/Hydroxy Dithioketal Cyclization

One of the earliest, yet most powerful, [*X* + 1 + *X*] approaches was developed by Nicolaou in 1986.[35] The hydroxy dithioketal cyclization strategy was specifically designed for the total synthesis of brevetoxins and can be conducted under mild reaction conditions.

As shown in Scheme 2, the coupling of **20** and **21** by Wittig reaction led to selective formation of *cis*-olefin **22**, the TBS group of which was removed using TBAF to give **23**. Treatment of **23** with silver salt in the presence of 3 Å molecular sieves (3A MS) and silica gel led to oxocene cyclization in high yield, despite the strain and entropic barrier encountered during the cyclization. In this reaction it is presumed that the action of $AgClO_4$ on **23** induces the formation of a transitory hydroxy thionium ion **24**, a highly reactive species that undergoes facile ring closure to oxocene **25**. The cis double bond of **23** plays a crucial

Scheme 3. Total Synthesis of Brevetoxin-B (Nicolaou, 1995)



role in the cyclization event by reducing rotational freedom in the cyclization substrate; in the absence of a cis double bond, ring closure does not occur.

Treatment of **25** with triphenyltin hydride and a catalytic amount of the radical initiator 2,2′-azobisisobutyronitrile (AIBN) accomplished a homolytic cleavage of the C−S bond and furnished oxocene **27** in diastereomerically pure form with retention of stereochemistry. On the other hand, oxidation of **25** with mCPBA and treatment of the resultant **26** with BF_3·Et_2O and Et_3SiH furnished **27** exclusively. Trimethylaluminum also reacted with intermediate **26** to afford the methylated compound **28**. The stereochemical outcome of the reduction (**26** → **27**) can be explained by the less congested transition state in the α-attack of the nucleophile onto **29**. This is also in accord with the Cieplak effect,[36] which favors axial attack at a "cyclohexane-like" region. The attack of tin hydride reagents on the intermediate radical should encounter similar stereoelectronic interactions.

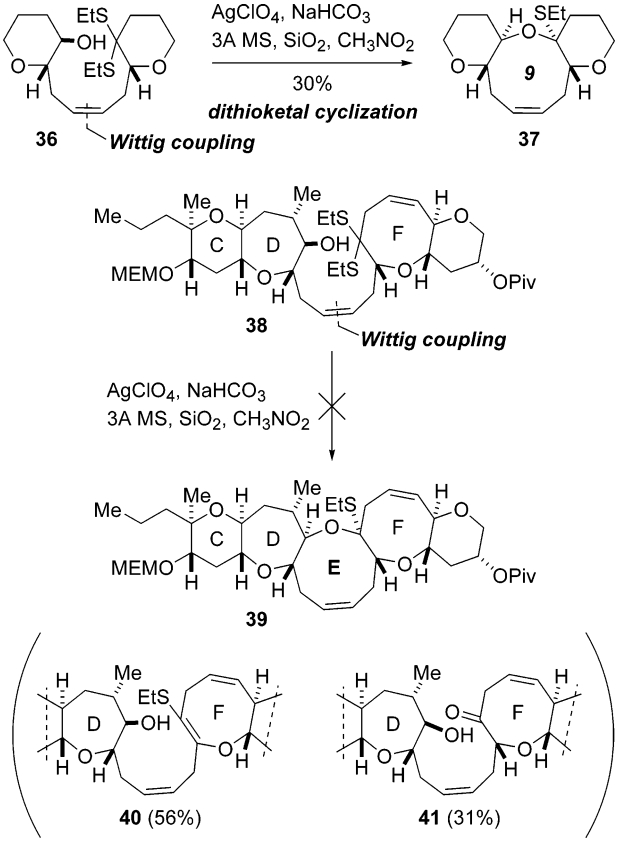
This reaction sequence was successfully applied to the last stage of the total synthesis of brevetoxin-B (Scheme 3).[25,37,38] Wittig reaction achieved the coupling of heptacyclic **30**[39] and tricyclic **31** to provide the desired coupling product **32**, the TMS group of which was removed under acidic conditions to afford **33**. Ag^+-induced hydroxy dithioketal cyclization of **33** and the subsequent radical reduction of the C−S bond of **34** gave rise to the entire polycyclic framework **35**. A short sequence of reactions from **35** completes the first total synthesis of brevetoxin-B (**1**).

Not only the oxocene ring, but also the nonacene ring can be cyclized by the same reaction conditions, albeit in modest yield (**36** → **37**, Scheme 4).[35] However, the more complex substrate **38**, which corresponds to the central region of brevetoxin-A (**2**), failed to give the cyclized product **39** under the optimized conditions.[40] Only the elimination product **40** and the hydrolysis product **41** were obtained. These studies clarified that nine-membered ring formation using hydroxy dithioketal cyclization was not suitable for assembling the structure of **2**.

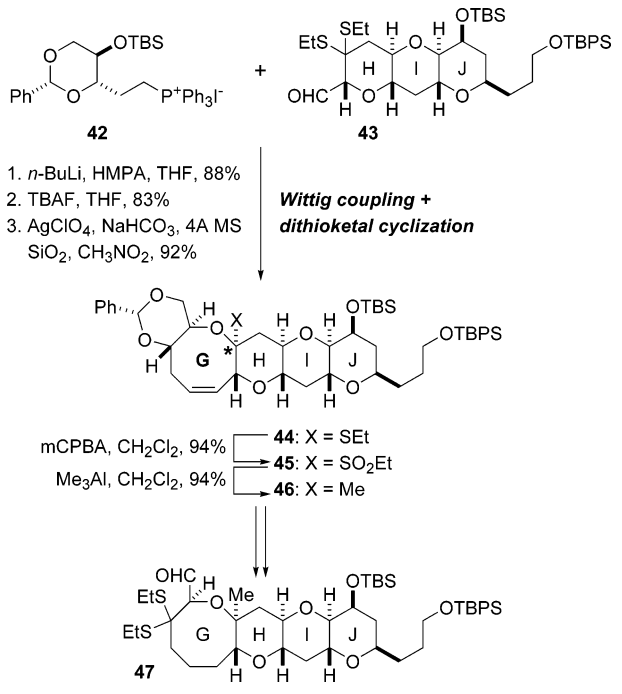
In response to these negative data, the highly reliable oxocene cyclization was fully exploited in the alternative route to brevetoxin-A (**2**) (Scheme 5).[26,41] Attachment of the eight-membered G-ring to the HIJ-ring system **43** was realized through Wittig coupling, hydroxy dithioketal cyclization (**42** + **43** → **44**), and angular methyl introduction (**44** → **45** → **46**). Subsequent transformations from **46** provided GHIJ-ring fragment **47**.

As illustrated in Scheme 6, further Wittig coupling between **47** and **48** proved unsuccessful, presumably because of the steric hindrance of aldehyde **47** and the relatively bulky ylide generated from **48**.[26b] Interestingly, when phosphorane **49** was used as a less hindered equivalent of **48**, the coupling adduct **53** was obtained in high yield after base treatment of the resulting hydroxyphosphine oxides **50** and **51**. Protecting-group removal and Ag^+-induced cyclization furnished the eight-membered mixed thioketal **55**. Oxidation of **55** with mCPBA led to the corresponding sulfone, which upon exposure to BF_3·Et_2O

Scheme 4. Attempted Cyclization of the Nine-Membered E-Ring of Brevetoxin-A



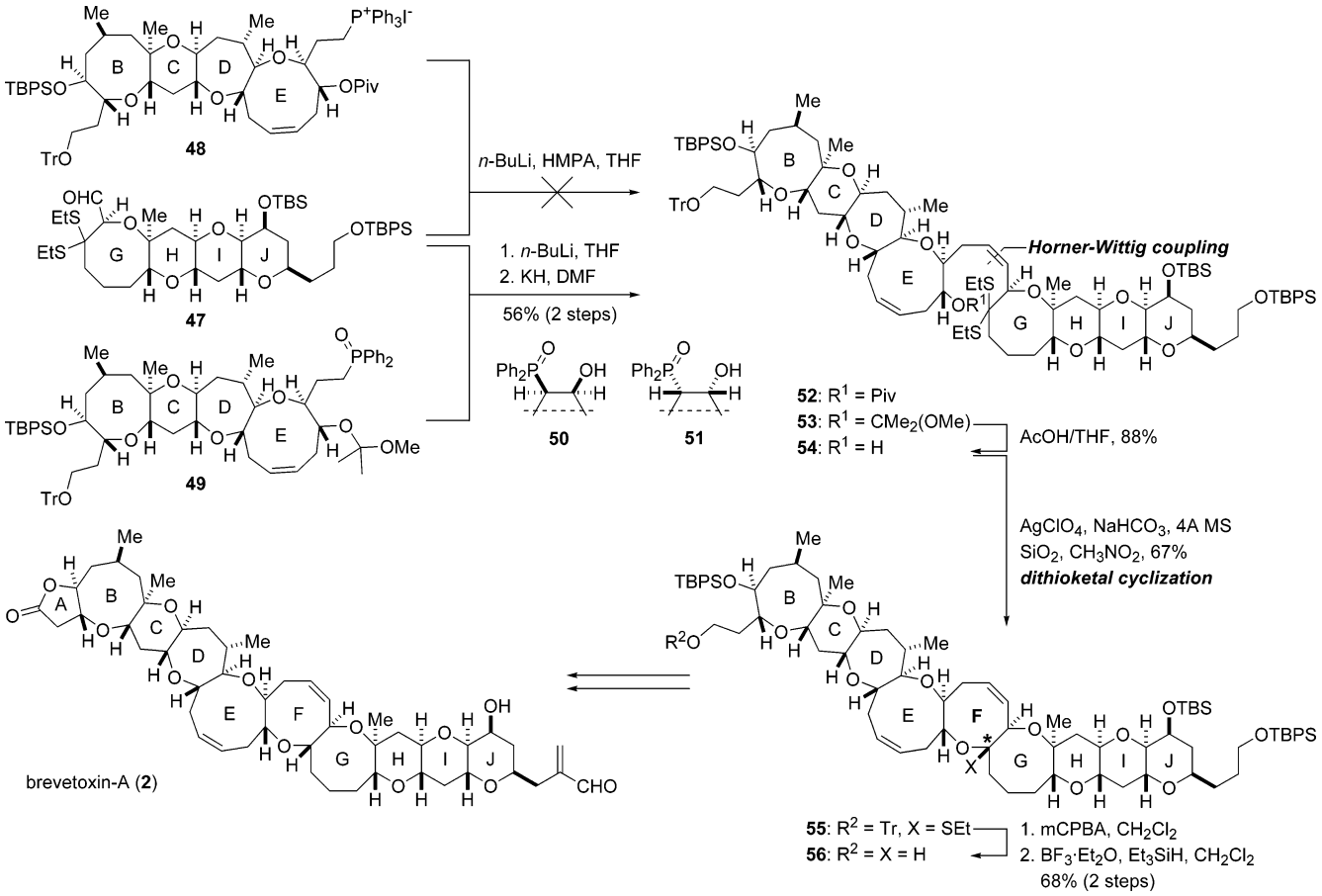
Scheme 5. Synthesis of the GHIJ-Ring System of Brevetoxin-A



in the presence of Et_3SiH furnished the BCDEF-GHIJ-ring skeleton **56** with the concomitant reductive cleavage of the trityl ether. Several further synthetic operations from **56** led to the total synthesis of brevetoxin-A (**2**).

It is worth mentioning the unique transannular reaction of the medium-sized rings of brevetoxin-A

Scheme 6. Total Synthesis of Brevetoxin-A (Nicolaou, 1998)



(**2**) (Scheme 7).[26b] The radical-based reduction of the eight-membered mixed thioketal of the EFGHIJ system **57** resulted in the undesired spiro structure **61**. Apparently, the double bond of ring F interfered with the radical of **58,** initiating a cascade that eventually leads to **61**. On the other hand, the oxonium cation-based reduction of **62** was cleanly effected by the action of Lewis acid and silane, and this reaction sequence was applied for the total synthesis of **2** (**55** → **56**, Scheme 6).

In summary, the dithioketal cyclization strategy was a major driving force enabling the first total syntheses of both brevetoxin-A and -B. These are also the first syntheses of highly complex *trans*-fused polycyclic ethers of such sizes.

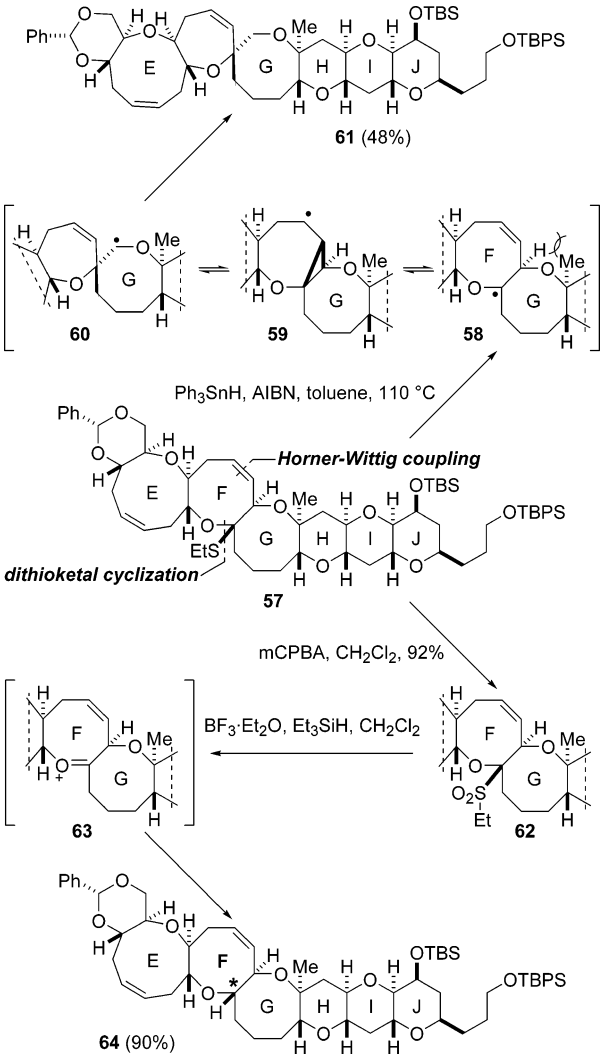
3.2. Suzuki Coupling/Reductive Etherification

B-Alkyl Suzuki coupling has proven to be a powerful tool for the total synthesis of complex natural products.[42] In 1998 Sasaki and co-workers reported the application of the Suzuki reaction to the convergent syntheses of polycyclic natural products (Scheme 8).[43,44] Hydroboration of the exocyclic enol ether **65** with 9-BBN set the desired stereochemistry via axial hydride delivery to give **67**, which reacted with ketene acetal triflate **68** under Suzuki-coupling conditions to afford the cross-coupled product **69**. The second stereoselective hydroboration of **69** with thexylborane also occurred via axial attack, and the obtained alcohol **71** was oxidized to ketone **72**. Exposure of **72** to acidic methanol and acetylation gave hemiacetal **73**, which was subjected to reductive etherification using $Et_3SiH/BF_3{\cdot}Et_2O$ to furnish pentacyclic ether **74**.[45] Remarkably, after the coupling only five synthetic manipulations were required for construction of the polycyclic ether array.

As outlined in Scheme 9, Sasaki's group utilized this methodology for the synthesis of the ABCDE system of ciguatoxin CTX3C (**4**).[46] AB-ring olefin **75** was treated with 9-BBN to deliver the corresponding alkylborane, which was reacted in situ with **76** in the presence of Pd(0), giving rise to **77**. Because of the chemical lability of medium-sized ketene acetal triflate, phosphate **76** was used as a stable alternative to the triflate. Subsequently four synthetic steps from **77** construct the D-ring of **78**, then the cyclization of the C-ring as methylacetal **79**, followed by Lewis-acid-mediated silane reduction, providing the pentacyclic ring system **80**. Finally, generation of the olefins of the A- and E-rings from **80** delivered the ABCDE-ring system **81** of CTX3C (**4**).

The FGHIJKLM system of ciguatoxin (**3**) was synthesized from three subunits (**82**, **83**, and **90**, Scheme 10).[47] First, FG-ring exo-olefin **82** and eight-membered enol phosphate **83** were successfully coupled using the procedure developed, affording **84**. Oxidation of **84** with dimethyldioxirane (DMDO) followed by in-situ S_N1-type stereoselective reduction of the resultant epoxide gave alcohol **85**, which was further elaborated to mixed thioketal **86**. Oxidation of sulfide **86** to the sulfone and in-situ methylation using Me_3Al generated the desired product **87** along

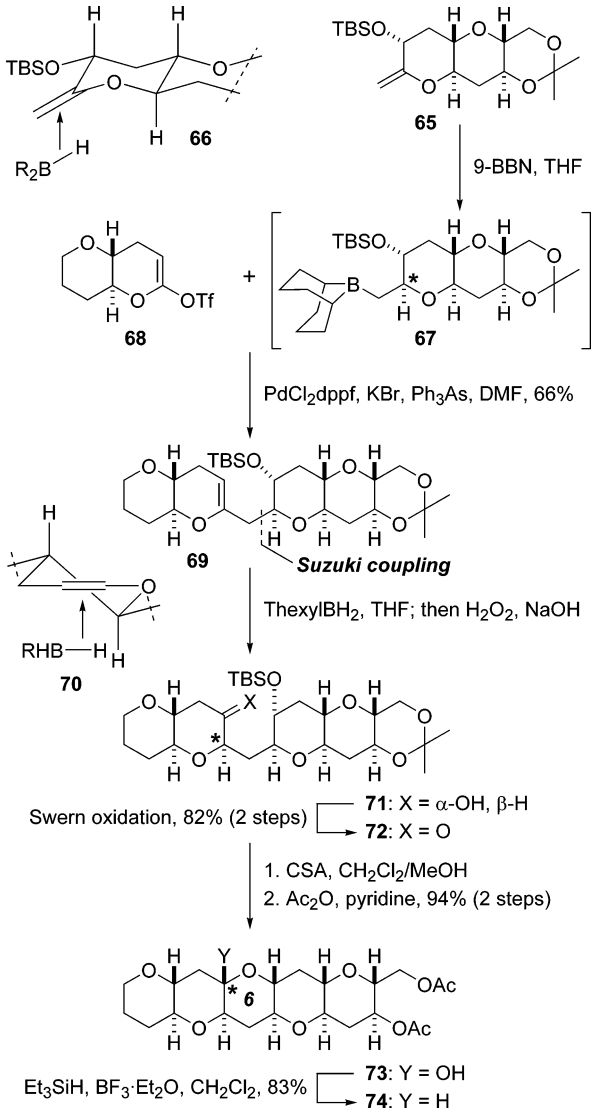
Scheme 7. Reduction of the Mixed Ketals



with the isomer **88**.[35] Then the FGHI exo-enol ether **89** was prepared through subsequent functional-group manipulations of **87**. A second coupling was realized using the seven-membered triflate **90** as a substrate. Hydroboration of **89**, followed by Suzuki cross-coupling with **90** and a second hydroboration using BH_3, delivered alcohol **91**. Conversion of **91** into mixed thioketal **92** and then radical reduction gave rise to octacyclic ether **93**. Regeneration of the olefin of the F-ring from diol **93** was realized in two steps, furnishing the targeted FGHIJKLM-ring fragment **94**.

In 2002 Sasaki reported the first total synthesis of gambierol (**8**, Scheme 11).[28,48] The last stage of the synthesis involved the convergent union of two complex fragments **95** and **96**[49] via Suzuki-coupling chemistry. Hydroboration of **95** with 9-BBN and cross coupling with **96** afforded **97**, which was subjected to hydroboration and then oxidation to give ketone **99**. Deprotection of the *p*-methoxybenzyl (MPM) group of **99** using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and cyclization of the D-ring gave mixed thioketal **100** after acetylation. Subsequent radical reduction of **100** yielded the octacyclic polyether core **101**. Finally, the total synthesis of **8** was accomplished through a sequence of careful trans-

Scheme 8. *B*-Alkyl Suzuki Coupling-based Strategy Developed by Sasaki (1998)

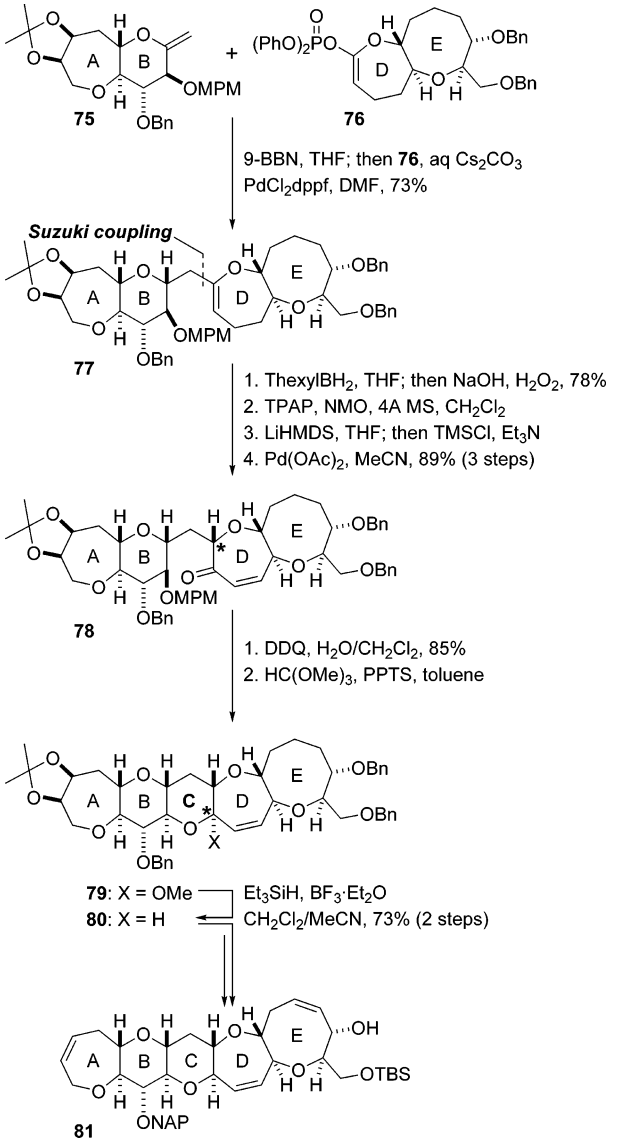


formations from **101** involving attachment of the chemically sensitive triene side chain.[50]

An even more complex natural polyether was synthesized by the same research group. Gymnocin-A (**10**, Scheme 12) is characterized by 14 contiguous and saturated ether rings, including two repeating 6/6/7/6/6 ring systems (the EFGHI- and JKLMN-rings). The total synthesis of **10** relied heavily upon the Suzuki-coupling strategy and was accomplished in 2003.[33]

BD-ring system **104** was synthesized by coupling the alkylborane, derived from **102**, with enol phosphate **103** and subsequent hydroboration.[51] Sequential construction of the C- and A-rings from **104** completed the synthesis of the ABCD exocyclic enol ether **105**. The GHI- (**112**) and KLMN-ring fragments (**111**) were prepared from the common intermediate **110**.[52] The coupling protocol was applied to **106** and **107**, and the adduct obtained was subjected to hydroboration to give **108** and **109** as a mixture. The poor stereoselectivity of the hydroboration, which contrasts with the high selectivity generally observed for this reaction, is presumably due to the steric hindrance of the pseudoaxial methyl group on the

Scheme 9. Synthesis of the ABCDE-Ring Fragment of CTX3C (Sasaki, 2004)



seven-membered G/L-ring. Both **108** and **109** were converted to **110**, which was further elaborated to the two fragments **111** and **112**. Again, hydroboration of **112** with 9-BBN and the following reaction with **111** using Pd(0) proceeded smoothly to give the cross-coupled product, hydroboration of which stereoselectively installed the angular hydrogen and the alcohol, generating **113**. Construction of the six-membered J-ring from **113** and fabrication of the enol triflate structure led to the FGHIJKLMN-ring fragment **114**. A final cross coupling between exo-enol ether **105** and triflate **114**, followed by hydroboration, resulted in formation of intermediate **115** with 13 ether rings in high yield. Protective-group manipulation (**115** → **116**) and following oxidation produced ketone **117**. An OTIPS group was then introduced at the α-position of **117** in three steps to afford **118**. Internal mixed thioketalization from **118** and reprotection with TBS led to **119**. Finally, reductive desulfurization of **119** furnished the tetradecacyclic polyether core **120**, and further elaboration from **120** gave rise to gymnocin-A (**10**).

In this methodology two stereoselective hydroboration reactions and the reductive etherification of the six-membered acetal reliably control the newly formed stereocenters in the desired fashion. Overall, the above syntheses proved the methodology developed by Sasaki to be highly general, powerful processes for the assembly of complex polycyclic ethers.

3.3. SmI_2-Promoted Coupling/Reductive Etherification

In 2005 Oguri/Hirama reported the convergent synthetic route to *trans*-fused 6/6/6/6/6 pentacyclic ether skeleton using the SmI_2-promoted Reformatsky-type reaction (Scheme 13).[53−55] Treatment of a mixture of tricyclic aldehyde **121** and α-ketosulfone **122** with SmI_2, followed by acetylation, led to the coupling adduct **123** as a 1:1 diastereomeric mixture. Exposure of **123** to CSA in $MeOH/CH_2Cl_2$ and acetylation resulted in methylacetal **124**, which was transformed to pentacyclic ether **125** via reductive etherification. Similar convergent couplings utilizing the anomeric carbon as a nucleophile have been reported by Nicolaou[39b] and Yamamoto[56] in the context of the polyether synthesis.[57]

4. [X + 2 + X] Approach

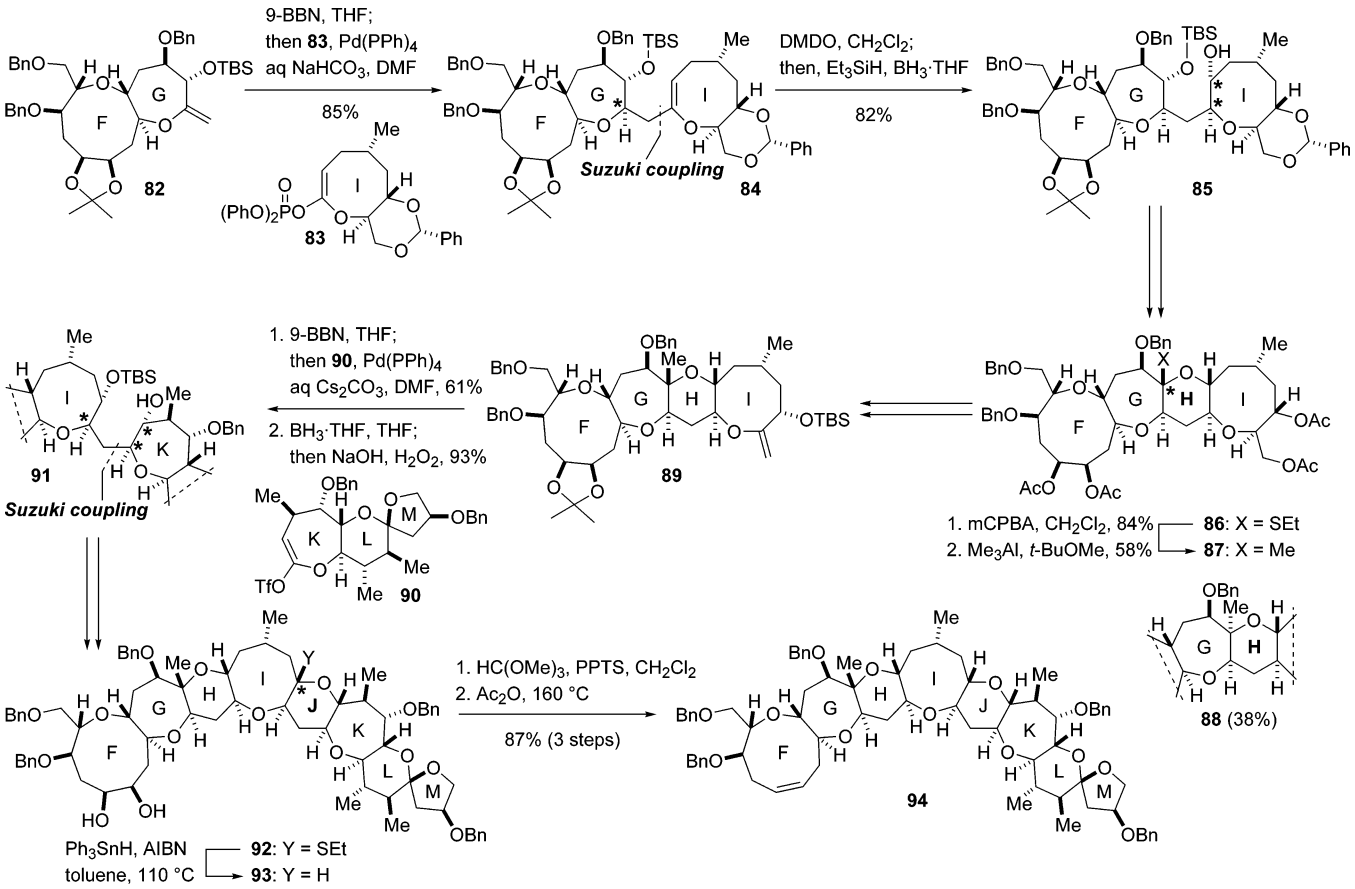
4.1. Di(thioester) Bridging/Hydroxyketone Cyclization

One of the most salient and synthetically challenging substructural features of brevetoxin-B (**1**) is the *trans*-fused bis(oxepane) ring system. In 1989 Nicolaou reported an ingenious solution for the construction of this structure by the stepwise cyclization of two oxepane rings between the structural fragments.[58,59]

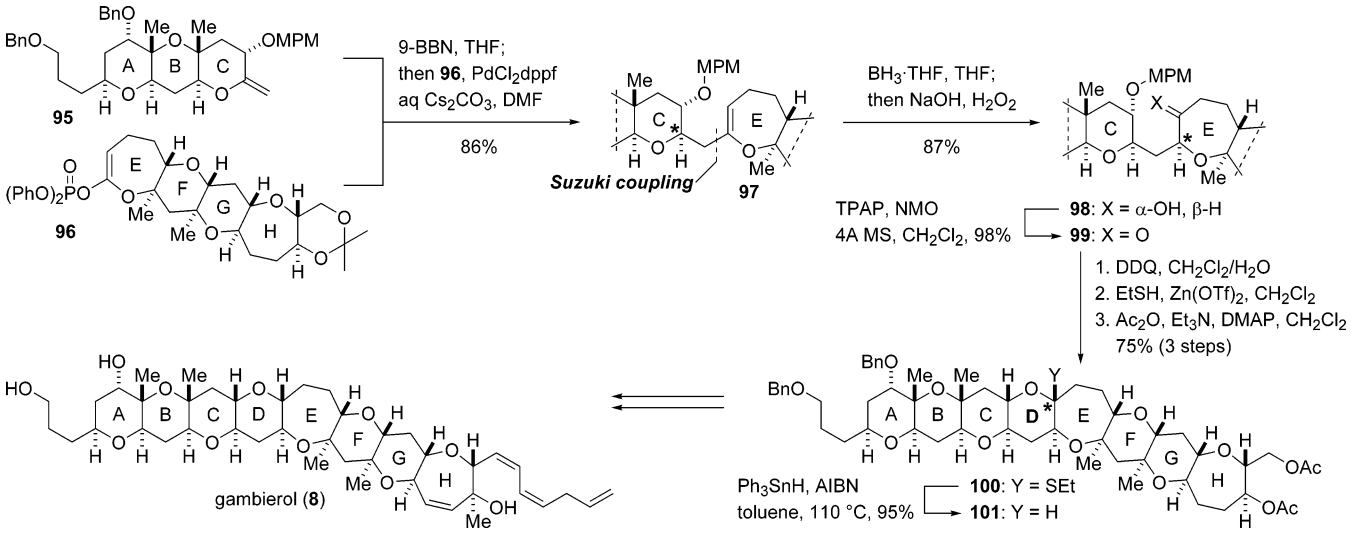
As shown in Scheme 14, coupling of alcohol **126** with carboxylic acid **127** followed by thionation using Lawesson's reagent gave rise to dithionoester **129** via **128**. Then photolysis of **129** led to oxepene system **132** through C−C bond formation. Irradiation of **129** presumably generates the radical species **130** and hence 1,2-dithietane system **131**, which loses sulfur to afford **132**. The obtained **132** was exposed to TBAF, furnishing oxepanone **133** as a single diastereomer. Finally, reductive cyclization of hydroxyketone **133** using TMSOTf and Ph_2MeSiH resulted in the selective formation of the BCDE framework **136** of brevetoxin-B (**136**:**137** = 6:1). In this stereoselective cyclization intramolecular ketalization and subsequent expulsion of the silicon−oxygen group of the silylated lactol **134** would generate oxonium species **135**, which is reduced through pseudoaxial delivery of a hydride.

This highly promising protocol was tested for the construction of the bis(oxepane) region of **1** (Scheme 15).[59] Application of the same reaction sequence to **126** and **138** as that in Scheme 14 (**126** + **127** → **133**) successfully produced hydroxyketone **139,** which is only one C−O bond away from the skeleton of brevetoxin-B (**1**). However, hydroxyketone **139** failed to cyclize under the reductive conditions, and the observed main product in this reaction was the reduced, open-chain diol **141**.

Scheme 10. Synthesis of the FGHIJKLM-Ring System of Ciguatoxin (Sasaki, 2002)



Scheme 11. Total Synthesis of Gambierol (Sasaki, 2002)



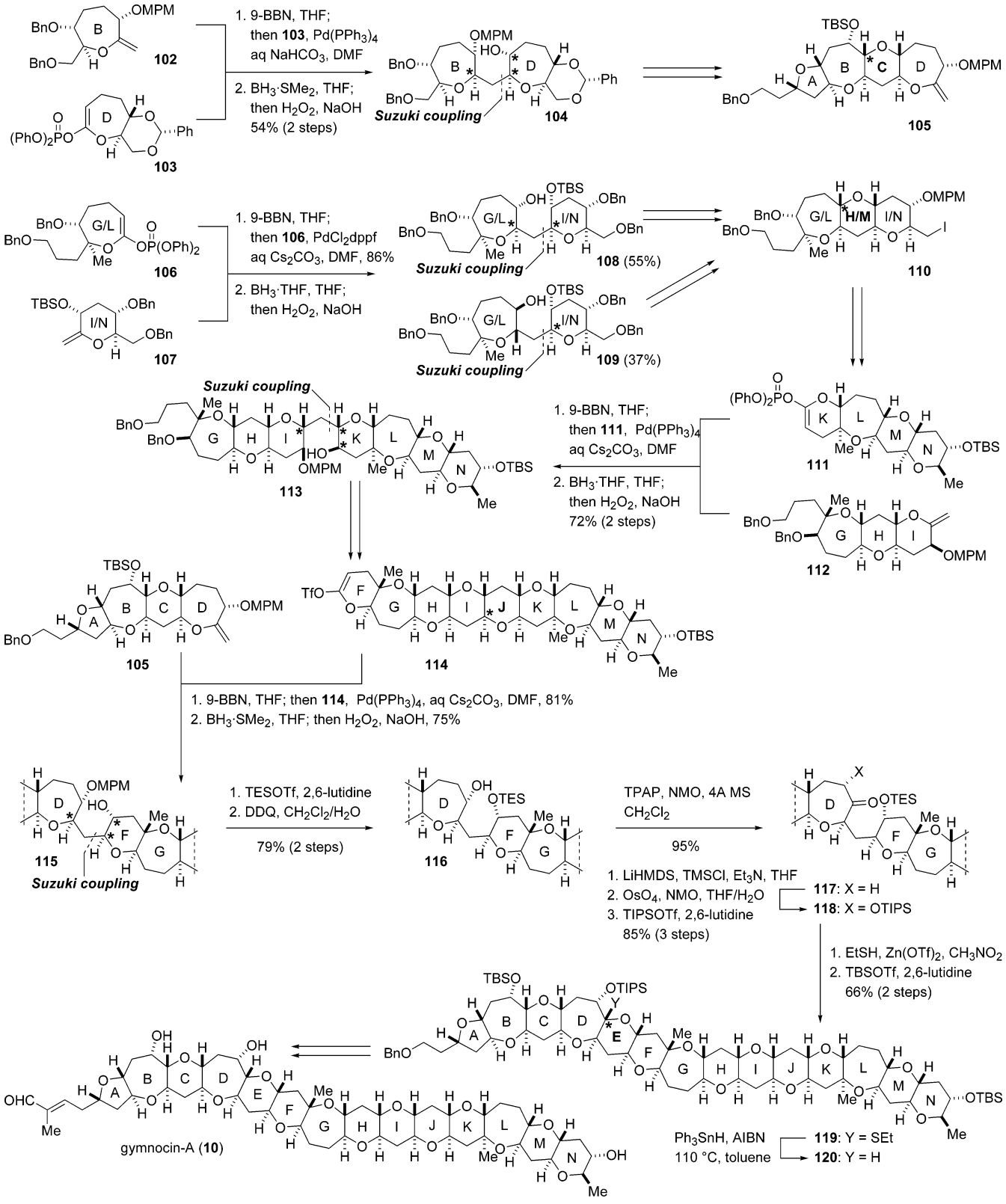
Despite this unsuccessful attempt, the present strategy is the first highly efficient [$X + 2 + X$] approach for the assembly of polycyclic ethers and inspired numerous new methods described below. Moreover, the total synthesis of **1** was eventually accomplished by the Nicolaou group through an alternative synthetic scheme (Scheme 3).[25,37]

4.2. Esterification/Intramolecular Enol Formation with RCM or Related Reactions

Ring-closing olefin metathesis (RCM) is rapidly emerging as a powerful tool in organic synthesis.[60] In 1996 Nicolaou and co-workers reported the formation of cyclic enol ether from an olefinic ester by means of RCM (Scheme 16).[61,62]

Olefinic ester **142**, prepared from two bicyclic ethers through esterification, was converted to six-membered enol ether **146** by the action of the Tebbe reagent.[63] The reaction proceeded through the initial formation of enol ether **143**. Compound **143** reacted with a second molecule of the Tebbe reagent to afford the titanium alkylidene **144**, intramolecular reaction of which then led to the desired cyclic enol ether **146** via the fragmentation of titanacyclobutane **145**. The

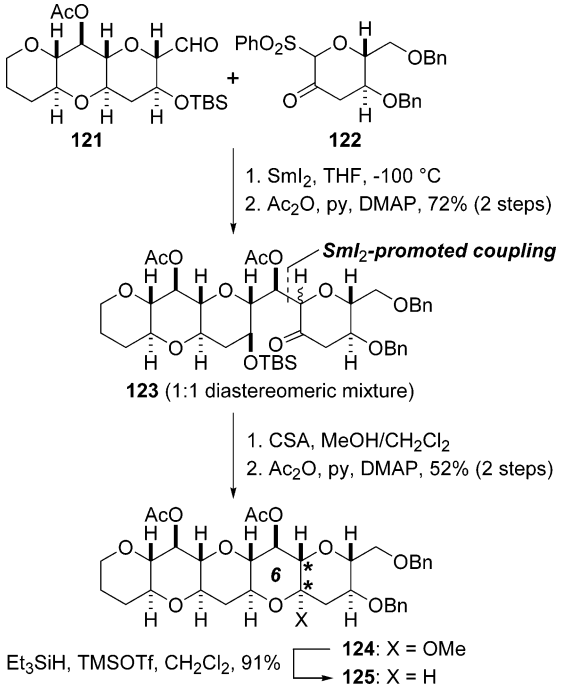
Scheme 12. Total Synthesis of Gymnocin-A (Sasaki, 2003)



obtained molecule **146** was successfully transformed to the hexacyclic framework **149** in four steps; stereoselective hydroboration, Dess−Martin oxidation (**146** → **147**), TBS removal (**147** → **148**), and stereoselective reductive etherification (**148** → **149**).

Hirama et al. applied the Tebbe reagent in the synthesis of the IJKLM system of CTX3C (**4**) (Scheme 17).[64] However, the yield of the desired cyclic enol ether **153** varied, and in the low-yield reactions significant amounts of exo-enol ethers (**151**, **152**) were produced. Treatment of the resultant mixture of exo-enol ethers **151** and **152** with the Tebbe reagent did not give the cyclized product **153**, indicating that these RCM catalysts could not induce the cyclization, presumably because of steric hindrance around the exo-enol ether.

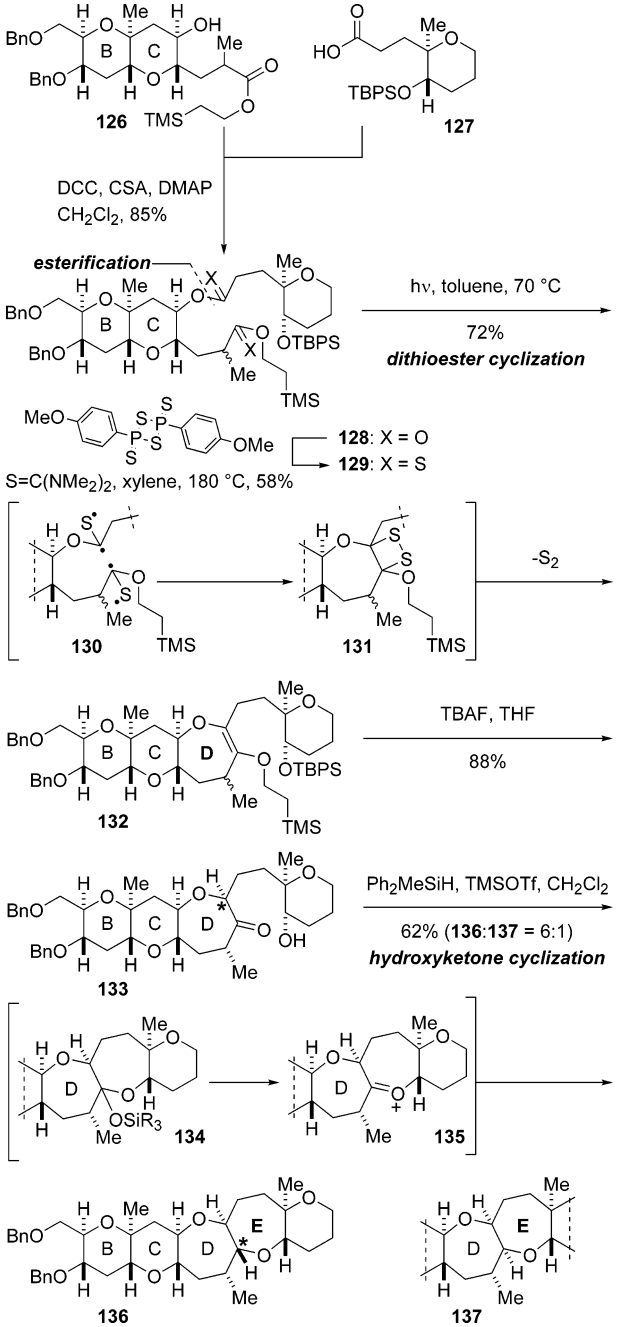
Scheme 13. SmI_2-Promoted Coupling Strategy (Oguri/Hirama, 2005)



As an alternative, Hirama adopted the direct carbonyl olefination reaction of bis(phenylthio)acetals developed by Takeda.[65] Treatment of **155** with the low-valent titanium complex $Cp_2Ti[P(OEt)_3]_2$ generated the desired enol ether **153** in a reproducible manner. In this reaction the strong affinity between the titanium and the carbonyl oxygen in **156** could favorably drive the reaction to give the oxatitanacyclobutane **157**, despite the steric hindrance, leading to product **153**. Thus, intramolecular carbonyl olefination acted as a powerful alternative to RCM-mediated enol ether formation.

The right wing fragment of CTX3C was synthesized by the group of Inoue/Hirama (Scheme 18).[66] Yamaguchi esterification of alcohol **158** with carboxylic acid **159** produced **160**,[67] treatment of which with $Cp_2Ti[P(OEt)_3]_2$ successfully closed the six-membered J-ring to afford pentacycle **161**. Because conventional hydroboration of **161** led predominantly to the undesired stereoisomer with α-C42−H, a new two-step protocol based on the S_N2-type reduction of an epoxyacetal was employed. First, α-epoxide **162** was synthesized from **161** using DMDO. S_N2-type hydride delivery to **162** was realized by treating **162** with $LiBHEt_3$, leading to the desired product **163** exclusively as a single diastereomer. Alcohol **163** was then oxidized with Dess−Martin periodinane to afford **164**. Upon exposure of **164** to triflic acid and $(MeO)_3CH$, the seven-membered methylacetal **165** was formed directly with concomitant loss of the MOM group. Finally, reductive etherification of acetal **165** constructed the final ether ring with complete stereocontrol, affording **166**. Thus, the JK-ring was assembled from the fragments in only seven synthetic operations. Introduction of the carbon chain corresponding to the G-ring completed the synthesis of the targeted right wing fragment (**167** and **168**).

Scheme 14. Construction of the Dioxepane Model of Brevetoxin-B (Nicolaou, 1989)

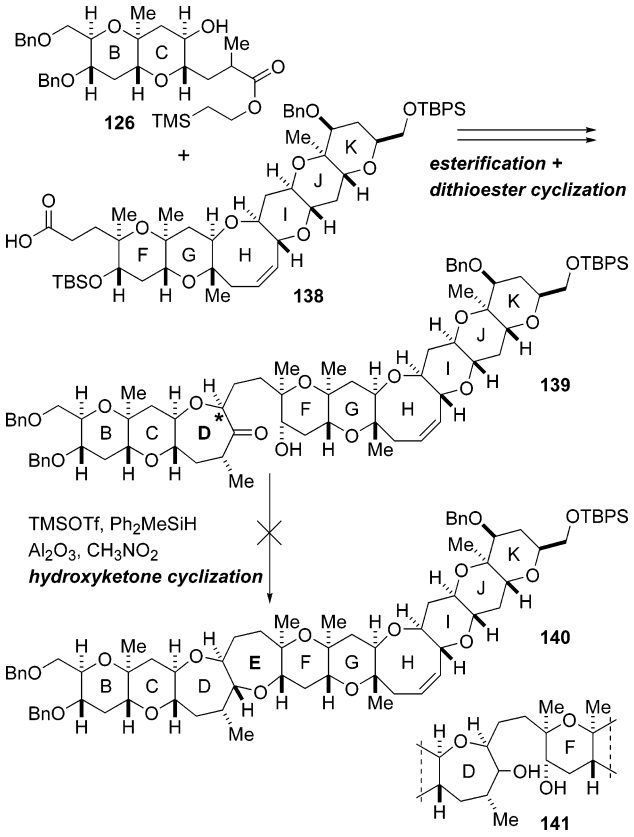


In 2005 Rainier accomplished the total synthesis of gambierol (**8**) by the successful implementation of enol ether-olefin RCM for the fragment assembly (Scheme 19).[30] Condensation of **169** and **170** provided ester **171**,[68] which was converted to the seven-membered enol ether **172** using the Takai−Utimoto titanium methylidene protocol.[69] It is worth noting that the choice of both substrate and reagent significantly affected the yield of the cyclization. After this powerful cyclization reaction, compound **172** was transformed into natural product **8** in only 11 steps.

4.3. Esterification/Intramolecular SmI_2-Promoted Cyclization

In 2003 Nakata reported the efficient convergent synthesis of polycyclic ethers using SmI_2-promoted

Scheme 15. Unsuccessful Attempt to Close the E-Ring by Hydroxyketone Cyclization

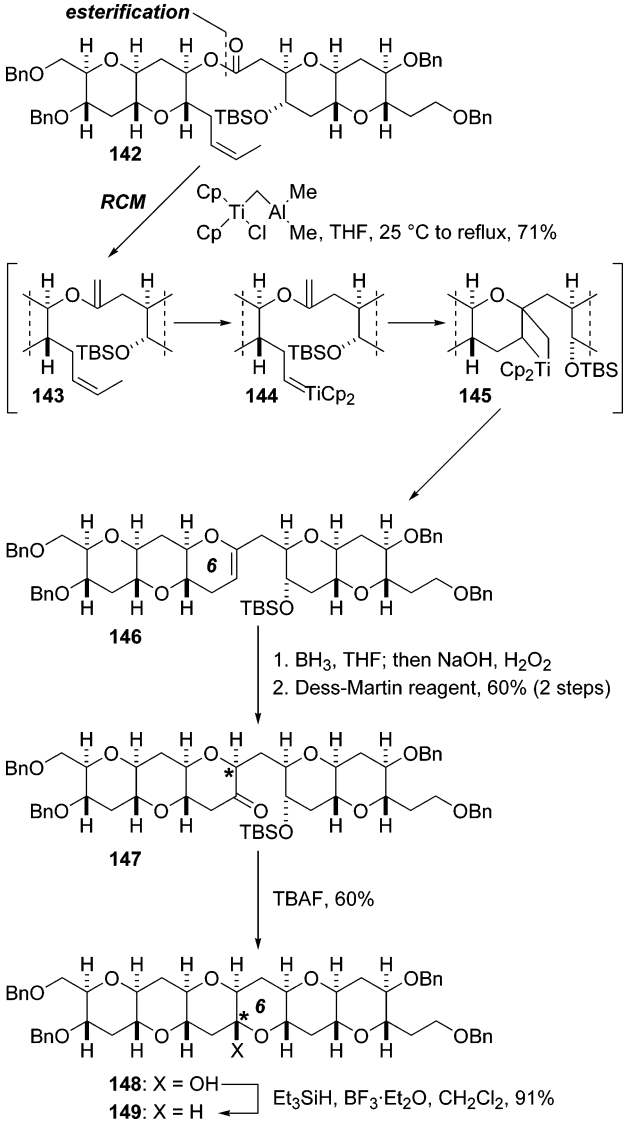


intramolecular cyclization as a key reaction (Scheme 20).[70] After esterification of monocyclic ethers **173** and **174**, treatment of iodo ester **175** with SmI_2 in the presence of catalytic NiI_2 smoothly gave the six-membered hemiacetal **176**.[55,71] PPTS-mediated dehydration of **176** led to dihydropyran **177**, which was stereoselectively converted to the *trans*-fused tetracyclic ether **178** in a four-step sequence including hydroboration and reductive etherification.

4.4. Acetylide–Triflate Coupling/Double-Reductive Etherification

In 2000 three independent groups (Fujiwara/Murai, Nakata, and Mori) developed a new methodology by which a 6/6-bicyclic system could be constructed between fragments in only four steps.[72−74] Scheme 21 shows Nakata's synthesis of a tetracyclic ether.[73] A coupling reaction between triflate **180** and the lithium acetylide of **179**[75] provided the symmetrical alkyne **181**, which was oxidized with $RuO_2/NaIO_4$ to furnish α-diketone **182**.[76] Acetalization using CSA and $HC(OMe)_3$ led to six-membered diacetal **183** with complete regio- and stereocontrol. The predominant formation of the desired product **183** in the double-acetalization process was supported by the calculated stability of the isomers: **183** was found to be more stable than five-membered diacetal **185** and isomeric six-membered diacetals **186** and **187**. The last reaction in this methodology was the double-stereoselective reduction of **183** using TMSOTf and Et_3SiH, giving rise to tetracyclic ether **184** as the sole product with retention of the stereochemistry.

Scheme 16. Titanium-Mediated Metathesis Strategy Developed by Nicolaou (1996)

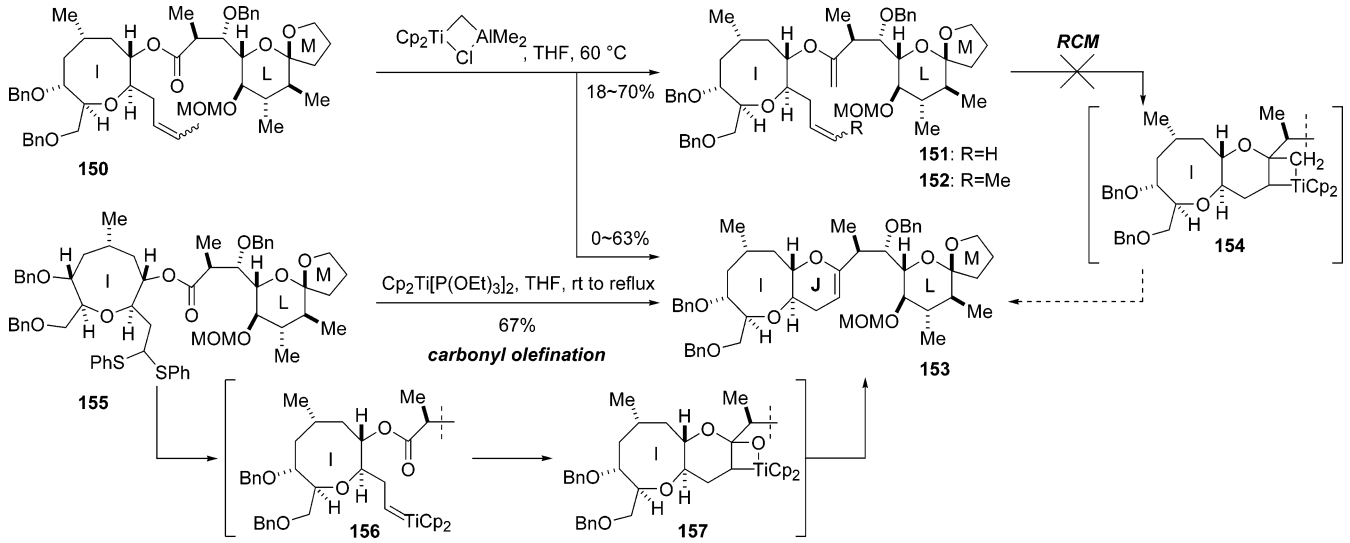


The present methodology was then independently applied to the convergent synthesis of the ABCDE-ring system of yessotoxin (**12**) and adriatoxin (**11**) by the groups of Nakata (2002)[77] and Mori (2003).[78] The coupling sequence of Mori's synthesis is summarized in Scheme 22. Treatment of a mixture of acetylene **188** and triflate **189** with *n*-BuLi gave **190**, which was oxidized to the 1,2-diketone using $RuO_2/NaIO_4$, affording **191**. Stereoselective double acetalization and reduction were realized with $CSA/HC(OMe)_3$/MeOH and $TMSOTf/Et_3SiH$, respectively, resulting in the ABCDEF-ring fragment **193**.

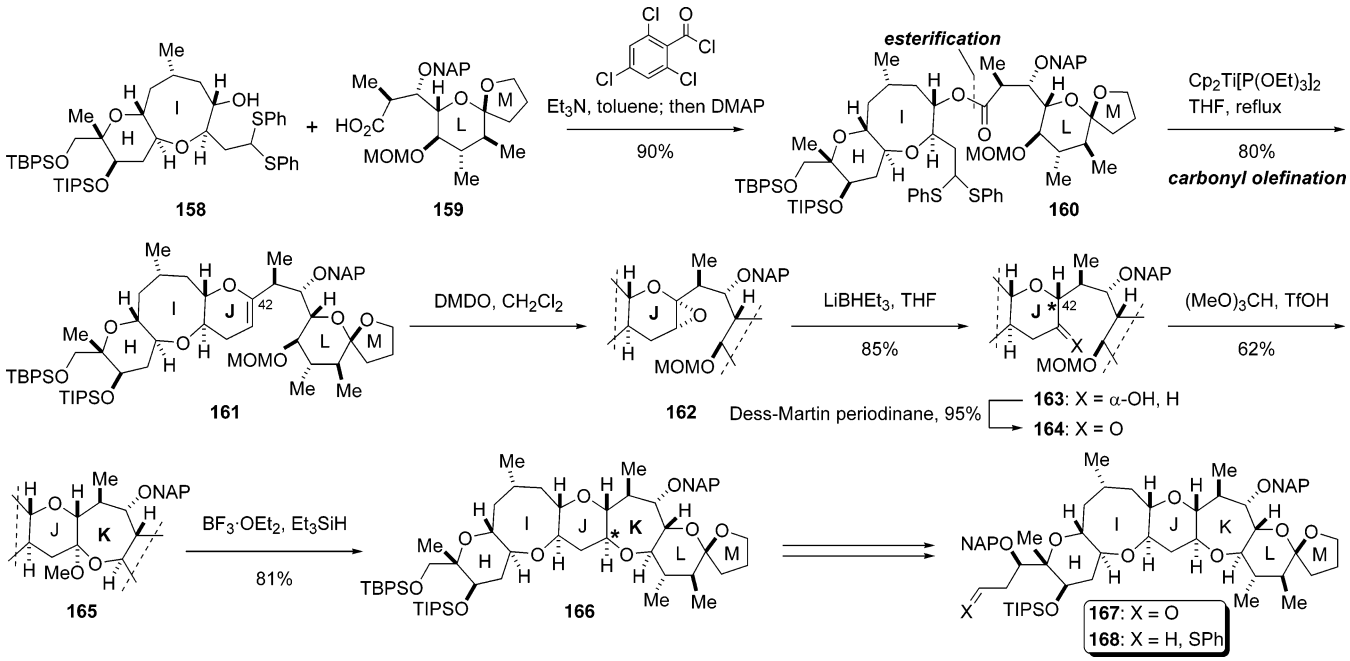
4.5. Acetylide–Aldehyde Coupling/Hetero-Micheal Cyclization

Nakata reported the synthesis of the 6/6/6/6-tetracyclic ring system based on the acetylide–aldehyde coupling and the subsequent hetero-Micheal cyclization (Scheme 23).[79] The reaction of the lithium acetylide, derived from **195**, with **194** gave secondary alcohol, which was oxidized to provide ynone **196**. Introduction of β-methoxy group to **196** using MeONa/MeOH, followed by removal of the TBS group,

Scheme 17. Construction of the J-Ring of CTX3C via Direct Carbonylolefination (Hirama, 2001)



Scheme 18. Synthesis of the Right Wing Fragment of CTX3C (Inoue/Hirama, 2004)



produced **197**. Then acidic treatment of **197** effected the hetero-Michael reaction, leading to six-membered enone **198**. Compound **198** was converted to tetracyclic ether **199** through the stereoselective hydroboration and the reductive six-membered ether ring formation.

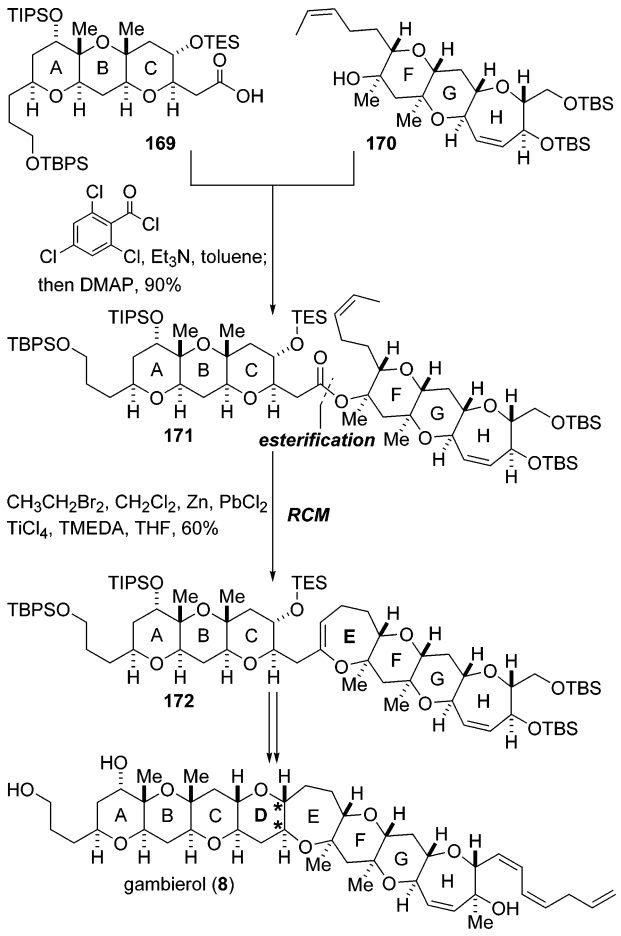
4.6. NHK Coupling/Double-Reductive Etherification

A similar methodology to that of the previous section (section 4.4) was developed by Martín utilizing the Ni/Cr-mediated Nozaki−Hiyama−Kishi (NHK) reaction[80] for fragment coupling (Scheme 24).[81] The coupling of alkenyl iodide **200** and aldehyde **201** by the action of $CrCl_2$ and catalytic $NiCl_2$ yielded the allylic alcohols, which were oxidized to α,β-unsaturated ketone **202**. Subsequent ozonolysis of **202** afforded diketone **203**. Stepwise removal of two protective groups (Ac and Bn) and then *O*-methylation of the resulting bis-hemiacetal delivered methyl diacetal **204**, which was doubly reduced by silane−Lewis-acid treatment to give tetracyclic diol **205** with concomitant loss of acetonide.

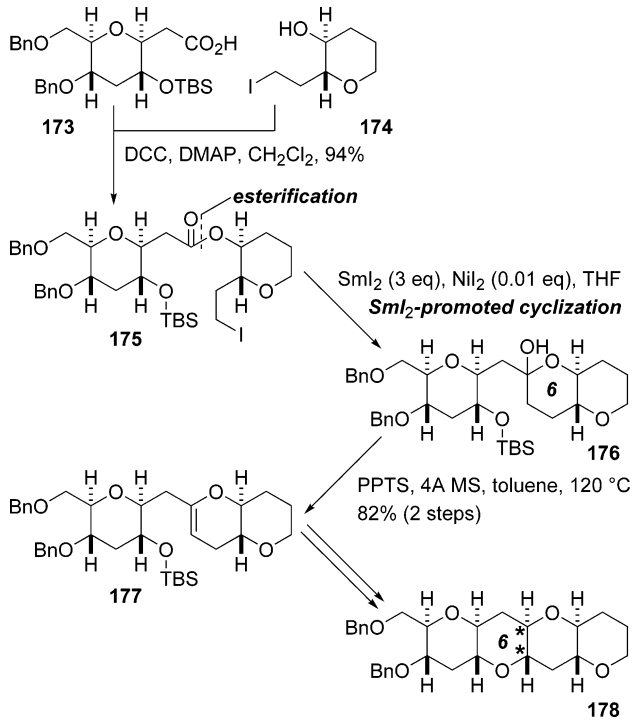
4.7. Dithioacetal *S*-Oxide Coupling/Stepwise Reductive Etherification

In 1999 Fujiwara/Murai developed a convergent approach based on dithioacetal *S*-oxide-aldehyde condensation and subsequent stepwise reductive etherification (Scheme 25).[82] Deprotonation of **207** with LDA followed by addition of aldehyde **206** provided coupling adduct **208**. Desilylation of **208** and subsequent acid treatment in MeOH/$HC(OMe)_3$ produced the tricyclic compound **209**, which was reduced with Et_3SiH in the presence of $SnCl_4$ to give **210**. Swern oxidation of **210** and hydrogenolysis of Bn, followed by the second reductive etherification of **211**, gave rise to tetracyclic ether **184**.

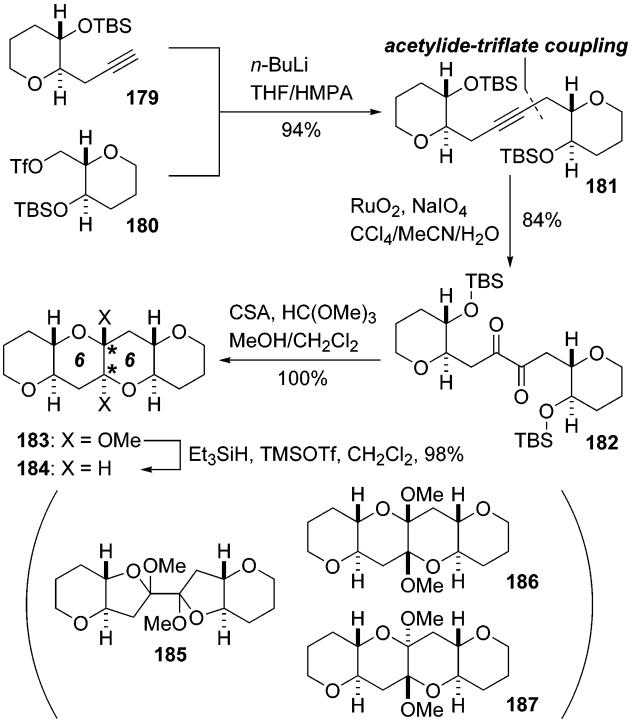
Scheme 19. Total Synthesis of Gambierol (Rainier, 2005)



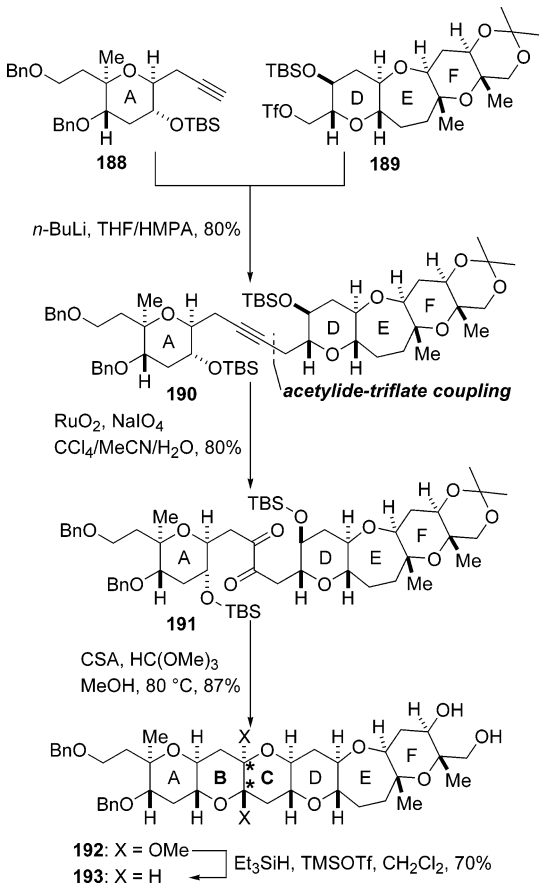
Scheme 20. SmI_2-Promoted Cyclization Strategy Developed by Nakata (2003)



Scheme 21. Acetylide−Triflate Coupling Strategy Developed by Three Independent Groups (Fujiwara/Murai, Nakata, Mori, 2000)

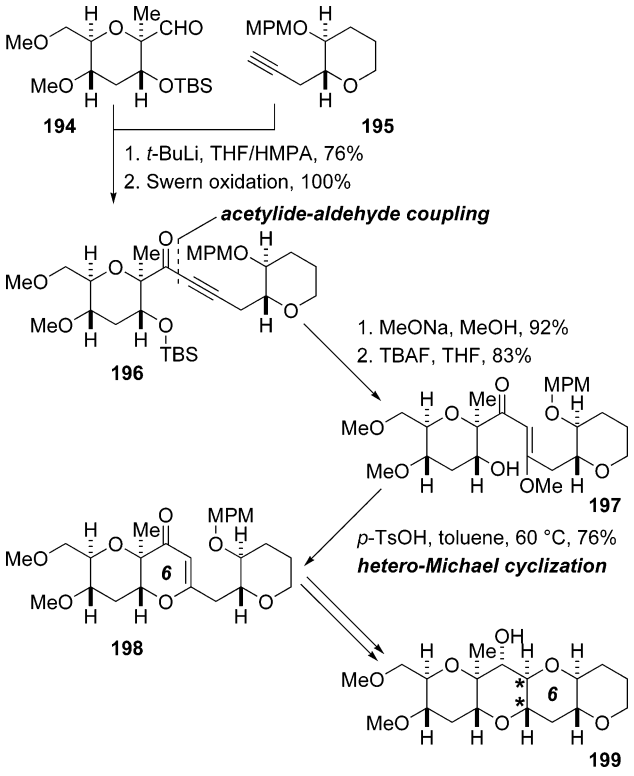


Scheme 22. Synthesis of the ABCDEF-Ring System of Yessotoxin (Mori, 2003)

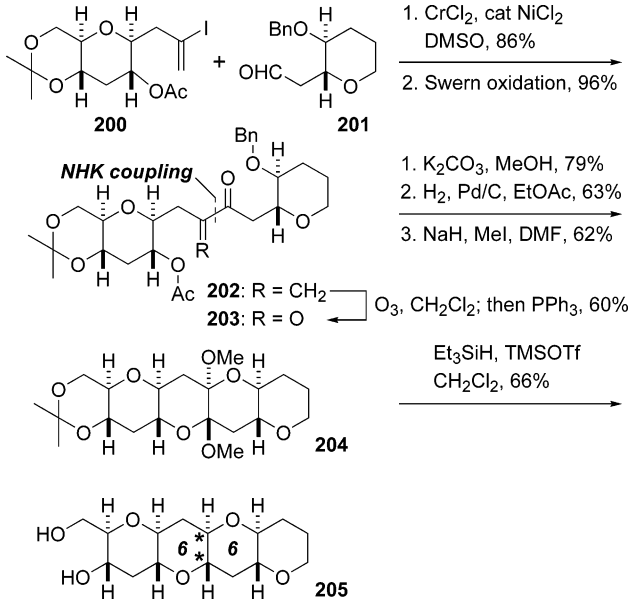


The Fujiwara group further applied this strategy to the formal total synthesis of hemibrevetoxin-B (**6**, Scheme 26).[83] The coupling of **212** and **213** under basic conditions produced **214**. Acidic removal of the TBS and methylthio methylsulfinyl acetal groups of **214**, followed by Lewis-acid-mediated hydroxyketone

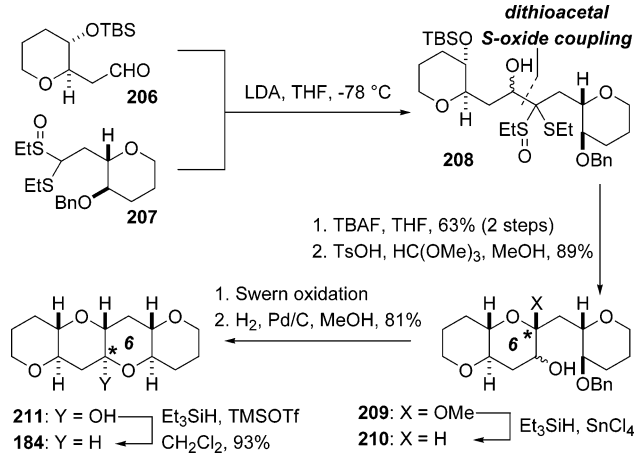
Scheme 23. Hetero-Michael Cyclization Strategy Developed by Nakata (2002)



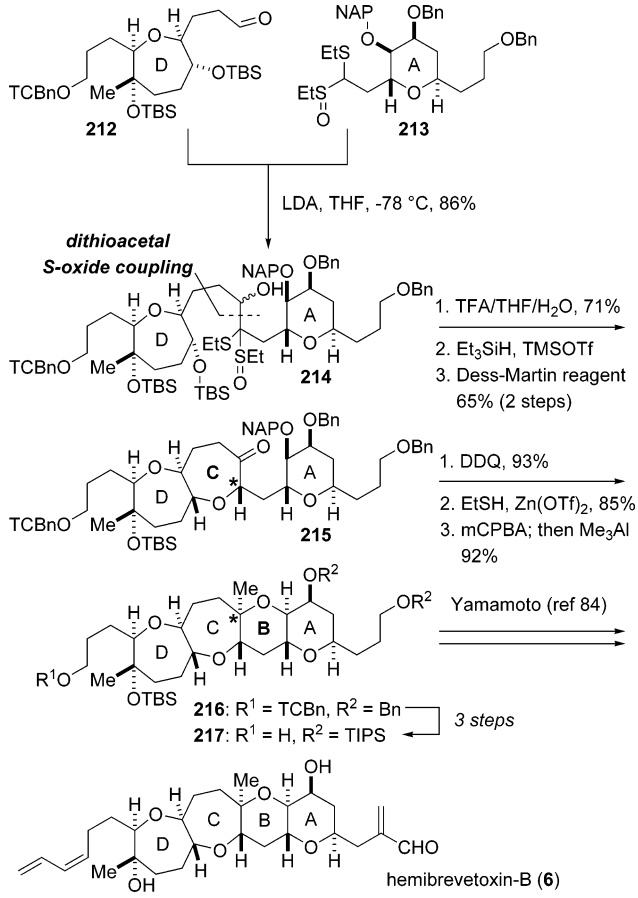
Scheme 24. Convergent Strategy Based on Ni/Cr-Mediated Cross-Coupling Reaction (Martin, 2001)



Scheme 25. Convergent Strategy Based on Dithioacetal *S*-Oxide Coupling (Fujiwara/Murai, 1999)



Scheme 26. Formal Total Synthesis of Hemibrevetoxin-B (Fujiwara, 2004)[a]

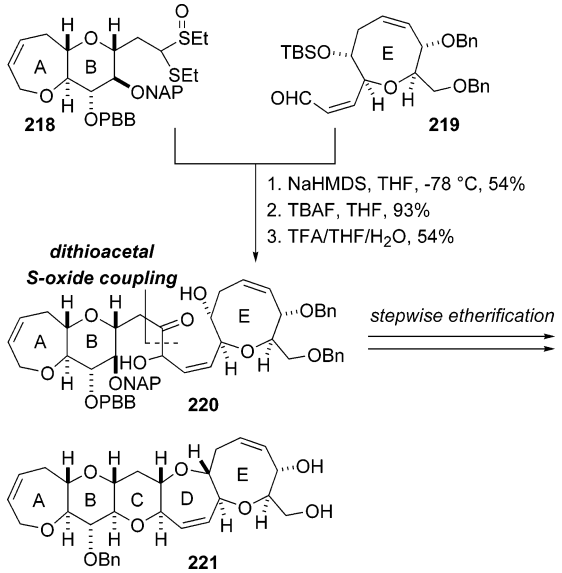


[a] TCBn = 2,4,6-trichlorobenzyl.

cyclization and Dess−Martin oxidation, afforded seven-membered ether **215**. After 2-naphthylmethyl (NAP) deprotection of **215** and intramolecular mixed thioketal formation, a subsequent two-step procedure for angular methyl introduction resulted in hemibrevetoxin framework **216**. Compound **217**, prepared from **216** via protective-group manipulations, was previously converted to hemibrevetoxin-B (**6**) by the Yamamoto group;[84] thus, the formal total synthesis was accomplished.

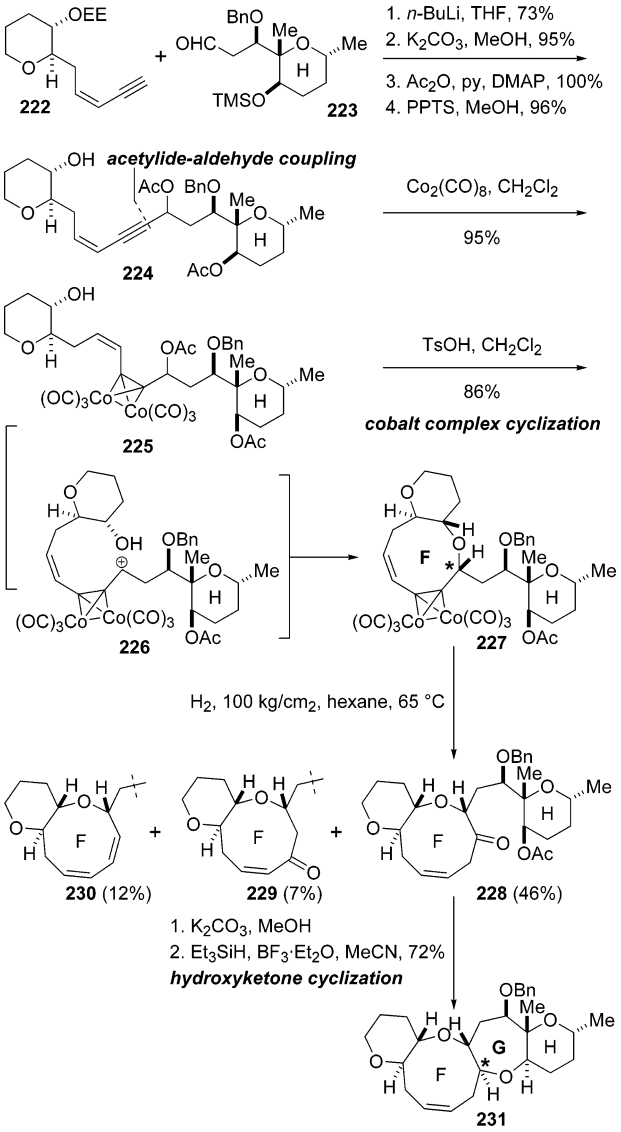
The synthesis of the ABCDE-ring fragment of ciguatoxin CTX3C (**4**) was achieved by means of the above methodology (Scheme 27).[85] Deprotonation of AB-ring segment **218** with NaHMDS followed by reaction with E-ring aldehyde **219** gave the adduct, which was transformed to α-hydroxy ketone **220** in two steps. Stereoselective construction of the CD-ring system from **220** was achieved through stepwise reductive etherification, giving rise to ABCDE-ring fragment **221**.

Scheme 27. Synthesis of the ABCDE-Ring System of CTX3C (Fujiwara, 2004)[a]

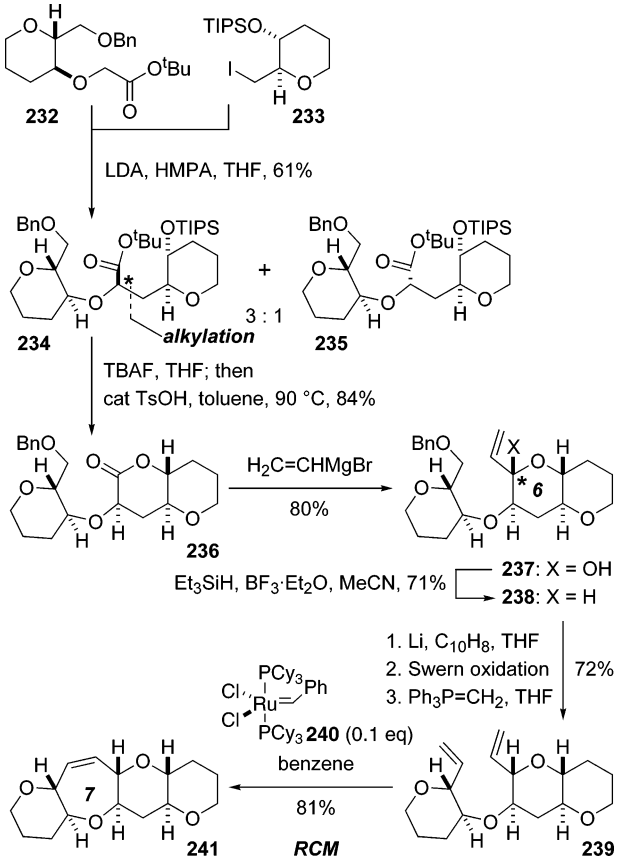


[a] PBB = *p*-bromobenzyl.

Scheme 28. Synthesis of the FGH-Ring Fragment of Ciguatoxin (Isobe, 2002)



Scheme 29. Alkylation–Metathesis Strategy Developed by Hirama (1998)



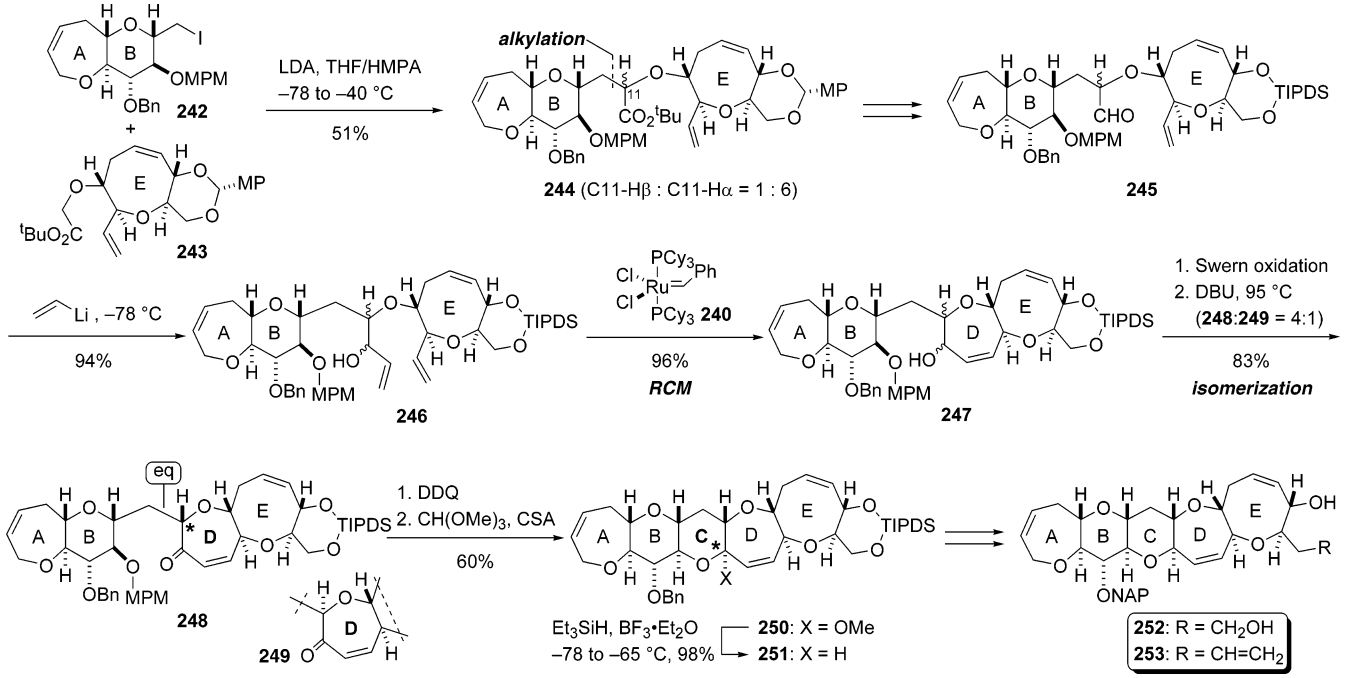
4.8. Acetylide–Aldehyde Coupling/Cyclization of Acetylene Cobalt Complex

In 1994 Isobe reported a novel approach for the cyclization of medium-sized rings via acetylene cobalt complexes.[86,87] This innovative methodology was applied to the convergent synthesis of the central region of ciguatoxin (**3**) (Scheme 28).[88] Assembly of the ciguatoxin FGH-ring system **231** started with a condensation between aldehyde **223** and acetylide prepared from **222**, and the adduct was converted to **224** by protective-group manipulations. Cyclization substrate **225** was then prepared by the formation of the cobalt complex of **224**. Remarkably, treatment of **225** with TsOH gave nine-membered ether ring **227** in a completely stereoselective fashion, presumably proceeding via the cobalt-complex-stabilized propargylic cation **226**.[89] Then the obtained tricyclic compound **227** was subjected to hydrogenation without any catalyst, delivering ketone **228** along with conjugated enone **229** and diene **230**. This unusual decomplexation reaction installed the oxygen functionality at the desired position. After deacetylation of **228**, the resultant hydroxyketone was treated with $BF_3{\cdot}Et_2O$ in the presence of Et_3SiH to accomplish the stereoselective construction of FGH-ring system **231**. The new approach developed by Isobe can be used in the last stage of the total synthesis of ciguatoxins (**3**–**5**).

4.9. Intermolecular Alkylation/RCM Reaction

In 1998 Hirama introduced a new technique for synthesizing 6/*n*/6/6-tetracyclic systems (n = 7–10)

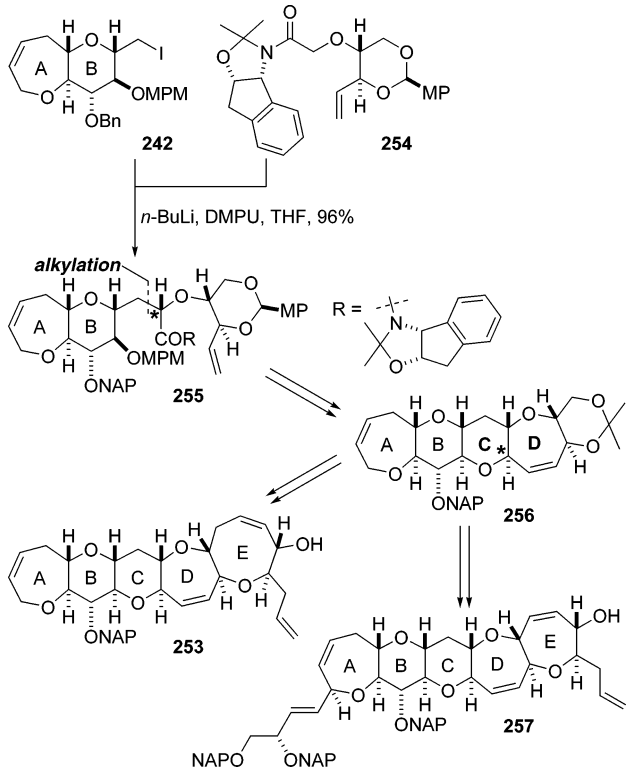
Scheme 30. Synthesis of the Left Wing Fragments of CTX3C (Hirama, 2002)



using alkylation and RCM as key reactions (Scheme 29).[90] Coupling of *tert*-butyl ester **232** with iodide **233** using LDA in the presence of HMPA gave desired compound **234** as the major isomer. Removal of the TIPS group of **234** followed by acid treatment provided six-membered lactone **236**. Then addition of vinylmagnesium bromide to **236** gave the hemiacetal, which was stereoselectively reduced with Et_3SiH/BF_3·Et_2O to afford *O*-linked oxacycle **238**. A subsequent three-step sequence converted the benzyloxymethyl moiety of **238** to the terminal olefin of **239**, treatment of which with Grubbs catalyst **240**[60,91] delivered 6/7/6/6 tetracyclic ring system **241**. Use of the RCM reaction with the Grubbs catalyst proved to be a general method for the cyclization of medium-sized ether rings in this and other studies (see sections 4.10−4.14) and has become the most important technology for the building of seven- to nine-membered ether rings from *O*-linked oxacycles.

The versatility of the alkylation−metathesis strategy was exemplified by the synthesis of the left wing fragment of CTX3C (**4**), which was achieved by the same group (Scheme 30).[92] In contrast to the model study in Scheme 29, intermolecular alkylation afforded the undesired stereoisomer as the major isomer (**242** + **243** → **244**). Several synthetic steps transformed **244** to aldehyde **245**, the addition of vinyllithium to which afforded **246**. Tetraene **246** was smoothly cyclized using Grubbs reagent **240** to provide the seven-membered D-ring **247**. Swern oxidation of the secondary alcohol of **247** to its ketone and DBU-mediated epimerization produced the more thermodynamically stable pseudoequatorial **248** as the major isomer. Removal of the MPM group in **248** using DDQ, followed by methyl acetalization under acidic conditions, afforded pentacycle **250**. The hydride selectively attacked from the α-face of **250** in the reductive etherification, thus providing ABCDE-ring fragment **251**. Finally, subsequent functional-

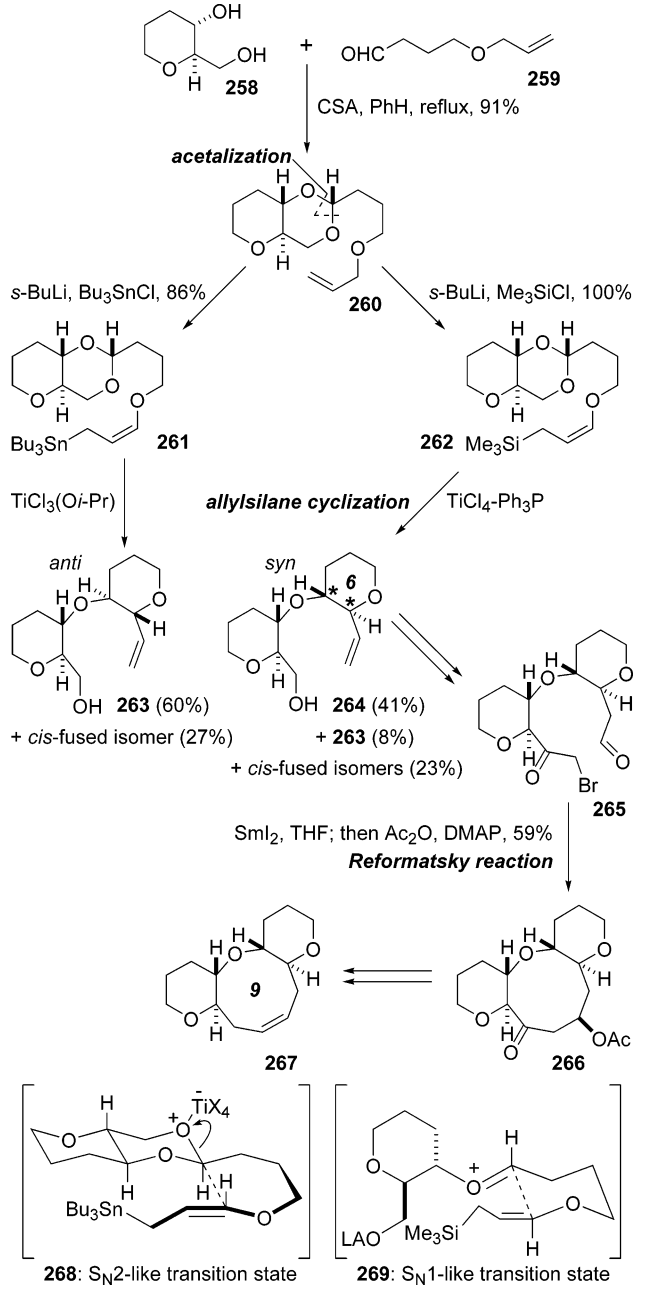
Scheme 31. Synthesis of the ABCDE-Ring Systems of CTX and CTX3C (Hirama, 2004)



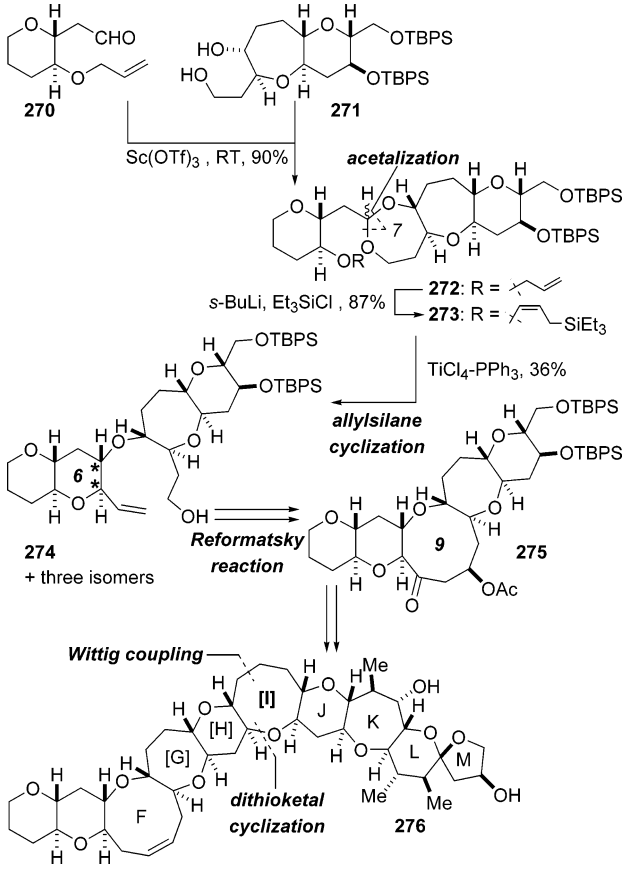
group manipulations of **251** yielded the left wing fragments (**252**, **253**) of CTX3C (**4**).

To avoid the base-mediated epimerization, Hirama developed an alternative approach (Scheme 31).[93] Stereoselectivity of the alkylation step was successfully controlled by attaching a chiral aminoindanol derivative[94] to the substrate. Namely, the coupling reaction between **242** and **254** exclusively afforded the desired isomer **255**. After derivatization of **255** to ABCD-ring system **256**, **256** was successfully

Scheme 32. Tachibana's Synthesis of the 6/9/6-Tricyclic Ring System (1997)



Scheme 33. Synthesis of the Decacyclic Ciguatoxin Model by Sasaki/Tachibana (1998)



utilized as a common intermediate for syntheses of **253**[93b] and **257**,[95] which correspond to the left wings of CTX3C (**4**) and CTX (**3**), respectively.

4.10. *O,O*-Acetalization/Nucleophilic Addition of γ-Alkoxyallylsilane to Cyclic Acetal

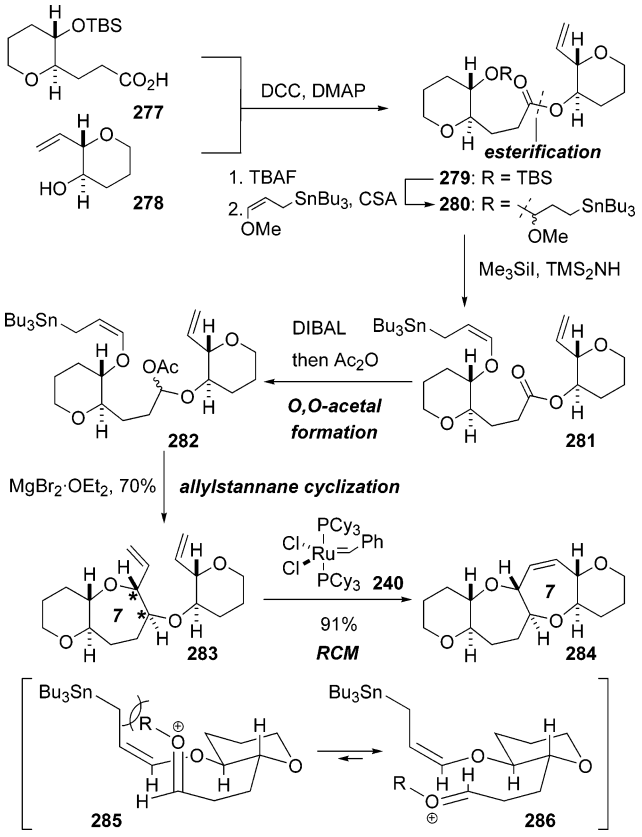
Convergent synthetic strategies via acetal-linked intermediates have recently emerged from several laboratories and proved to be one of the most powerful methodologies for the assembly of polycyclic structures.[24f] The development of such protocols and their application to total syntheses are discussed in sections 4.10−4.14.

In 1997 Tachibana and co-workers developed a method for the synthesis of the 6/9/6-tricyclic system[96] utilizing the intramolecular Lewis-acid-mediated reaction of γ-alkoxyallylmetals with acetals (Scheme 32).[97,98] Their synthesis started with the coupling of diol **258** and aldehyde **259** by acetalization. Lithiation of allylic ether **260** with *s*-BuLi and in-situ trapping of the resulting anion with either *n*-Bu_3SnCl or Me_3SiCl gave γ-alkoxyallylmetal **261** or **262**. Interestingly, allylsilane **262** led to the selective formation of the desired *trans*/*syn*/*trans*-isomer **264**, while cyclization of allylstannane **261** exclusively formed the undesired *trans*/*anti*/*trans*-isomer **263**. The reactive allylstannane of **261** would react from the S_N2-like intermediate **268**; cleavage of the C−O bond of the acetal would take place simultaneously with the C−C bond formation, producing the undesired compound **263**. On the other hand, it was assumed that the alternative use of the significantly less reactive γ-alkoxyallylsilane **262**[99] would enable the reaction to take place via the S_N1-like transition state **269** in which unfavorable steric interactions are minimized. This latter transition state would afford **264** with the introduction of the two bridgehead stereocenters in the desired manner.

Compound **264** was then converted to α-bromoketone **265**, which was smoothly cyclized to nine-membered ring **266** by the action of SmI_2.[55,100] Finally, the targeted 6/9/6-ring system **267** was synthesized from **266** through functional-group manipulations.

Sasaki/Tachibana exploited this strategy for the synthesis of decacyclic ciguatoxin model **276** in 1998 (Scheme 33).[101] 1,4-Diol **271** was selected as a structural fragment instead of the corresponding 1,3-diol because preliminary model experiments revealed that

Scheme 34. Yamamoto's Intramolecular Cyclization of γ-Alkoxyallylstannane with α-Acetoxy Ether (2001)



the seven-membered acetal was more reactive toward nucleophilic addition than its six-membered counterpart. Acetal formation between chemically sensitive β-alkoxy aldehyde **270** and diol **271** was realized in the presence of a catalytic amount of $Sc(OTf)_3$,[102] producing seven-membered acetal **272** in high yield. Lithiation of **272** followed by treatment with Et_3SiCl gave γ-alkoxyallylsilane **273**. Upon treatment of **273** with $TiCl_4-PPh_3$ the desired *O*-linked compound **274** was obtained as the major product together with three other stereoisomers. Similarly to the synthesis of the previous compound **266**, **274** was converted to the 6/6/9/7/6-ring system **275** though SmI_2-promoted ring formation. Finally, coupling of **275** and the JKLM-ring fragment using Nicolaou's hydroxy dithioketal strategy[35] (see section 3.1) delivered decacyclic ciguatoxin model **276**.

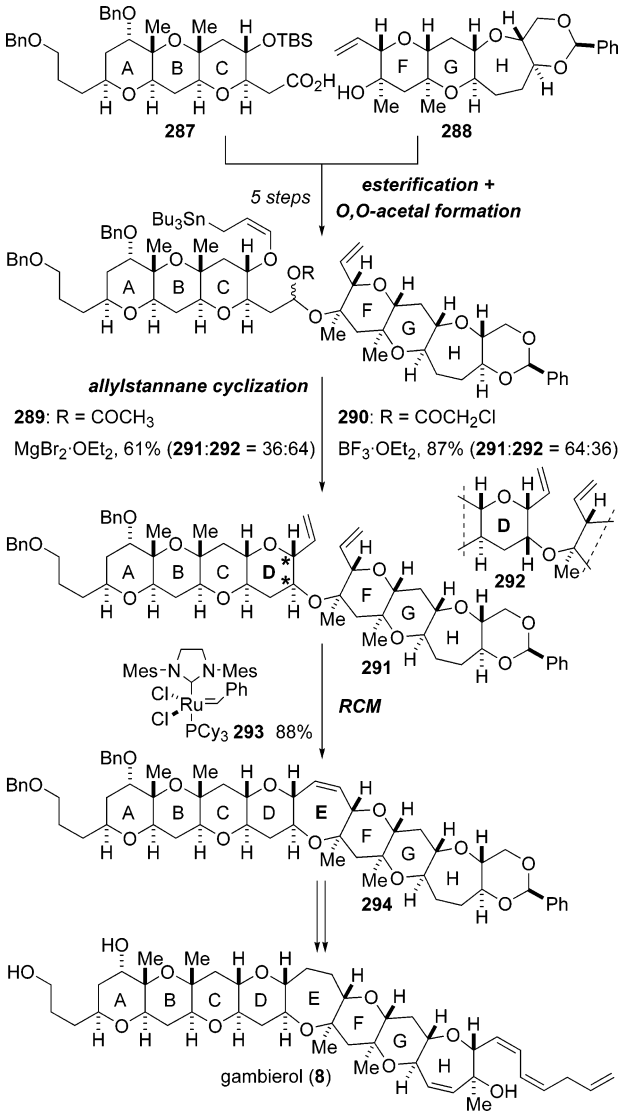
These studies clearly demonstrated that the acetal-based convergent strategy provided a general and powerful method for the construction of complex *trans*-fused ether polycycles. Furthermore, tuning the reactivity of both the acetals and nucleophiles was shown to be important in obtaining *O*-linked oxacycles with the desired stereochemistry.

4.11. Esterification/Nucleophilic Addition of γ-Alkoxyallylstannane to α-Acetoxy Ether

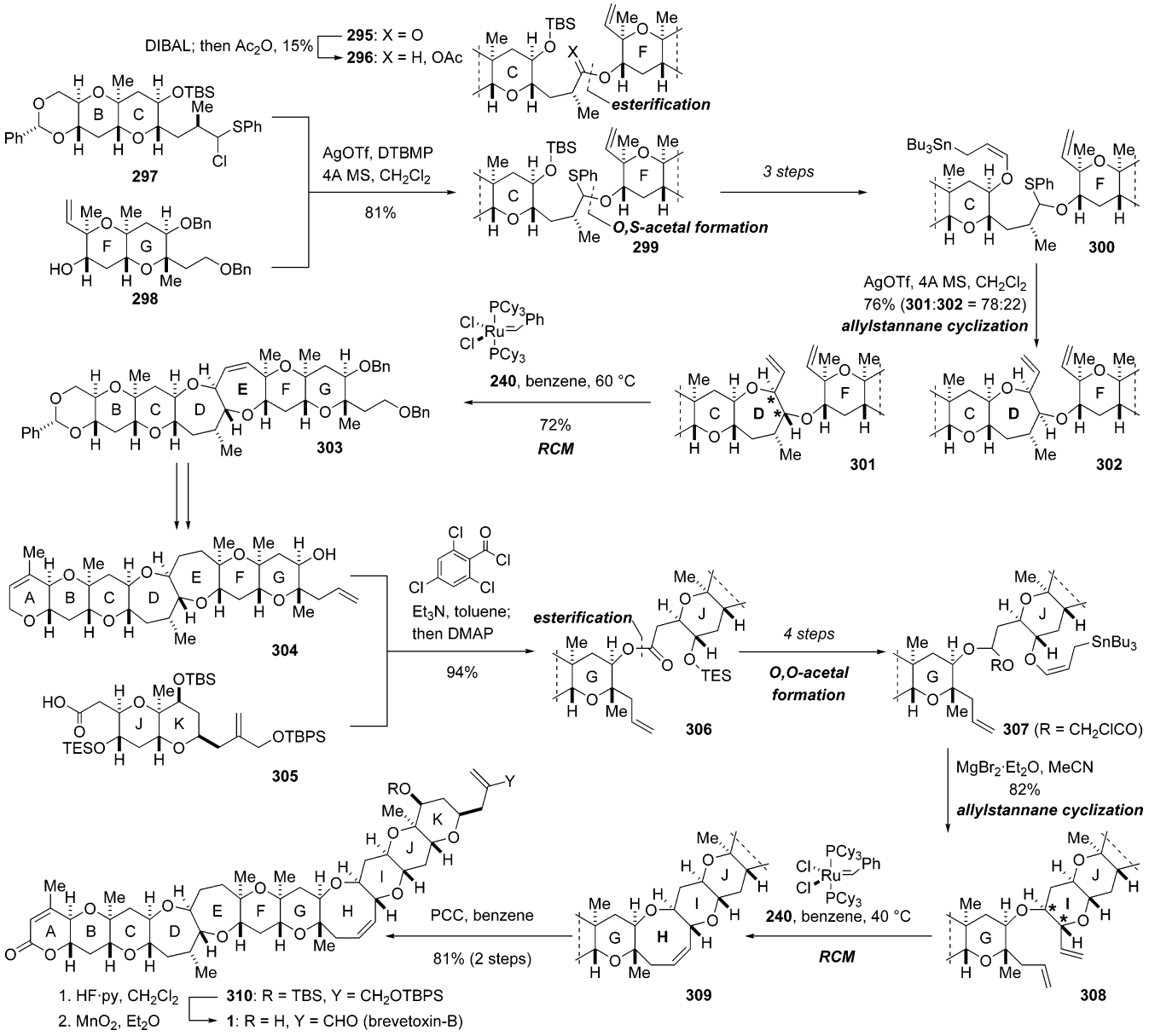
In 2001 Kadota/Yamamoto developed a stereoselective approach to polycyclic ring systems using the intramolecular cyclization of γ-alkoxyallylstannanes to α-acetoxy ethers (Scheme 34).[103] Carboxylic acid **277** and alcohol **278** were coupled through esterification to afford **279**. After deprotection of the silyloxy group of **279**, the alcohol was converted to allylstannane **281** via **280**. α-Acetoxy ether **282** was then prepared from ester **281** according to the Rychnovsky protocol:[104] (i) reduction of **281** with DIBAL and (ii) in-situ trapping of hemiacetal with acetic anhydride. Treatment of mixed-acetal **282** with $MgBr_2·OEt_2$ resulted in intramolecular cyclization to give seven-membered ring **283** as the exclusive isomer, which was then transformed to the 6/7/7/6-ring system **284** by the RCM reaction.

The stereochemical outcome of the reaction of allylstannane **282** did not reflect the chirality at the α-acetoxy group, presumably because of the facile formation of its oxonium cation, in contrast to cyclic acetal **261** in Scheme 32. Thus, the observed stereoselectivity can be explained by the S_N1-like transition-state model. The allylic stannane moiety is oriented in a pseudoequatorial position in order to avoid 1,3-diaxial repulsion. The oxonium cation moiety, which bears a substituted tetrahydropyranyl group R, also prefers a pseudoequatorial position, as depicted by the transition-state structure **286**, which leads to **283**.

Scheme 35. Total Synthesis of Gambierol (Kadota/Yamamoto, 2002)



Scheme 36. Total Synthesis of Brevetoxin-B (Kadota/Yamamoto, 2005)

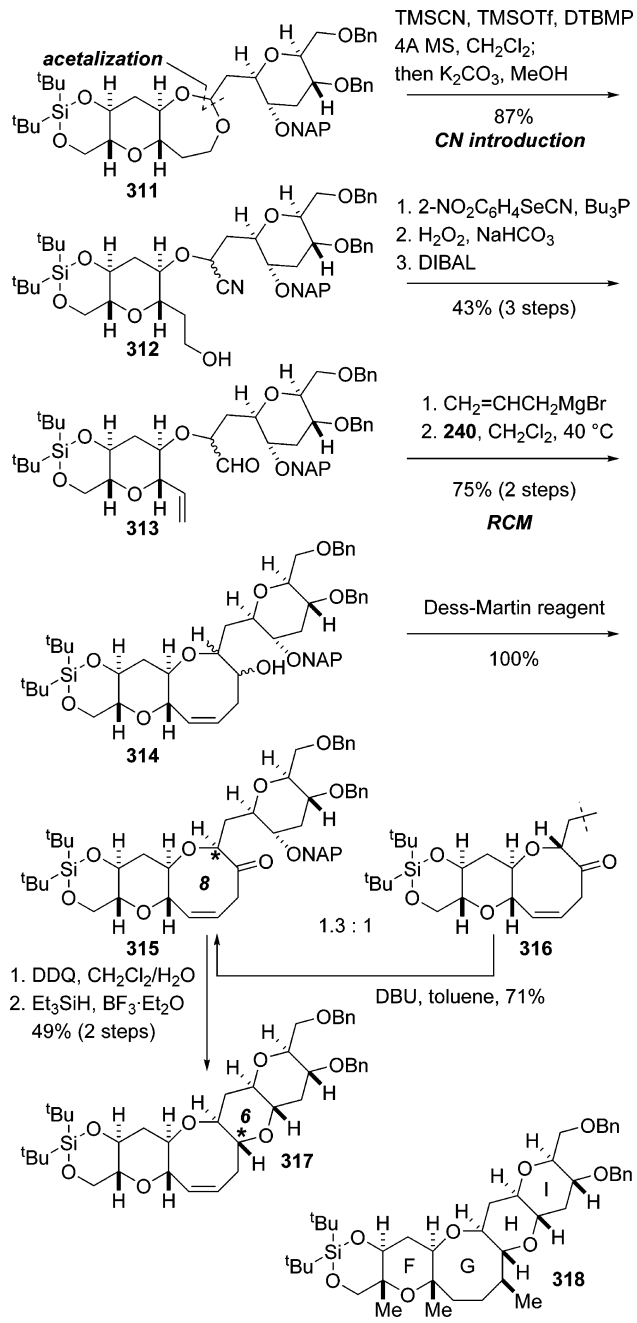


It should be emphasized that use of an esterification reaction for segment coupling and the seven-step construction of the two fused ring system makes the present methodology highly efficient and practical. This was clearly demonstrated by the following two convergent total syntheses.

Kadota et al. accomplished the total synthesis of gambierol in 2002 (**8**, Scheme 35).[29] ABC-segment **287** and FGH-segment **288** were condensed, and then a series of reactions including desilylation, attachment of the allylic stannane moiety, and subsequent application of the Rychnovsky protocol gave α-acetoxy ether **289**. In contrast to the model experiments, treatment of **289** with $MgBr_2 \cdot OEt_2$ afforded the undesired stereoisomer **292** as the major component. Interestingly, $BF_3 \cdot Et_2O$-mediated cyclization of α-chloroacetyl **290** led to the selective formation of **291**. This improved diastereoselectivity is presumably due to the more facile formation of the oxonium cation intermediate from the chloroacetyl group than from the acetyl group. The resultant diene **291** was subjected to cyclization by action of the second-generation Grubbs catalyst **293**,[105] leading to octacyclic gambierol skeleton **294**. Finally, **294** was successfully converted to the natural product **8** through functional-group modification, side-chain introduction, and last deprotection.

The highly convergent total synthesis of brevetoxin-B (**1**) was achieved by the same group in 2005 (Scheme 36).[32] Since, due to over-reduction of the hemiacetal intermediate, the DIBAL reduction of BCFG-ring ester **295** gave the desired α-acetoxy ether **296** only in low yield, the modified protocol was applied to build BCDEFG-ring segment **303**. According to the method developed by Inoue/Hirama (see section 4.14),[106,107] chlorosulfide **297** was coupled with alcohol **298** using AgOTf in the presence of 2,6-di-*tert*-4-methylpyridine (DTBMP) to provide *O*,*S*-acetal **299** to which was attached the γ-alkoxyallylstannane moiety to afford **300** in three steps. Cyclization of **300** was again promoted by AgOTf, leading selectively to oxepane **301**. Stepwise con-

Scheme 37. Convergent Synthesis of 6/*n*/6/6-Tetracyclic Systems via α-Cyano Ethers (Oishi, 2003, 2005)



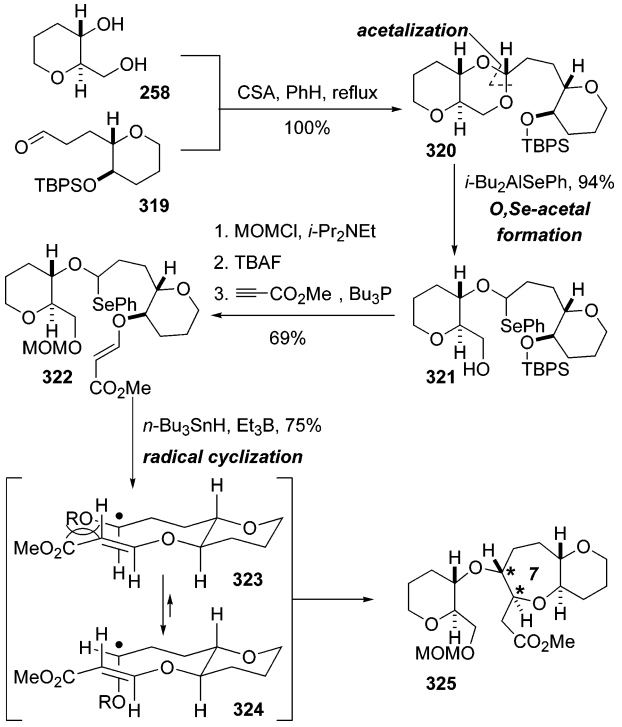
struction of the E- and A-rings by RCM from **301** gave rise to the ABCDEFG-ring system (**301** → **303** → **304**).

Esterification of alcohol **304** with carboxylic acid **305** and a subsequent three-step sequence produced *O*,*O*-acetal **307**. The Lewis-acid-promoted cyclization of **307** afforded the six-membered I-ring **308**.[108] RCM cyclization of **308** formed the undecacyclic ether skeleton **309**, and finally, the successful functional-group transformations from **309** resulted in the total synthesis of brevetoxin-B (**1**).

4.12. *O*,*O*-Acetalization/Nucleophilic Addition of Cyanide to Cyclic Acetal

Oishi reported a convergent method for synthesizing 6/*n*/6/6 ($n = 7, 8$) tetracyclic ether systems using

Scheme 38. Intramolecular Radical Cyclization Developed by Sasaki (1998)

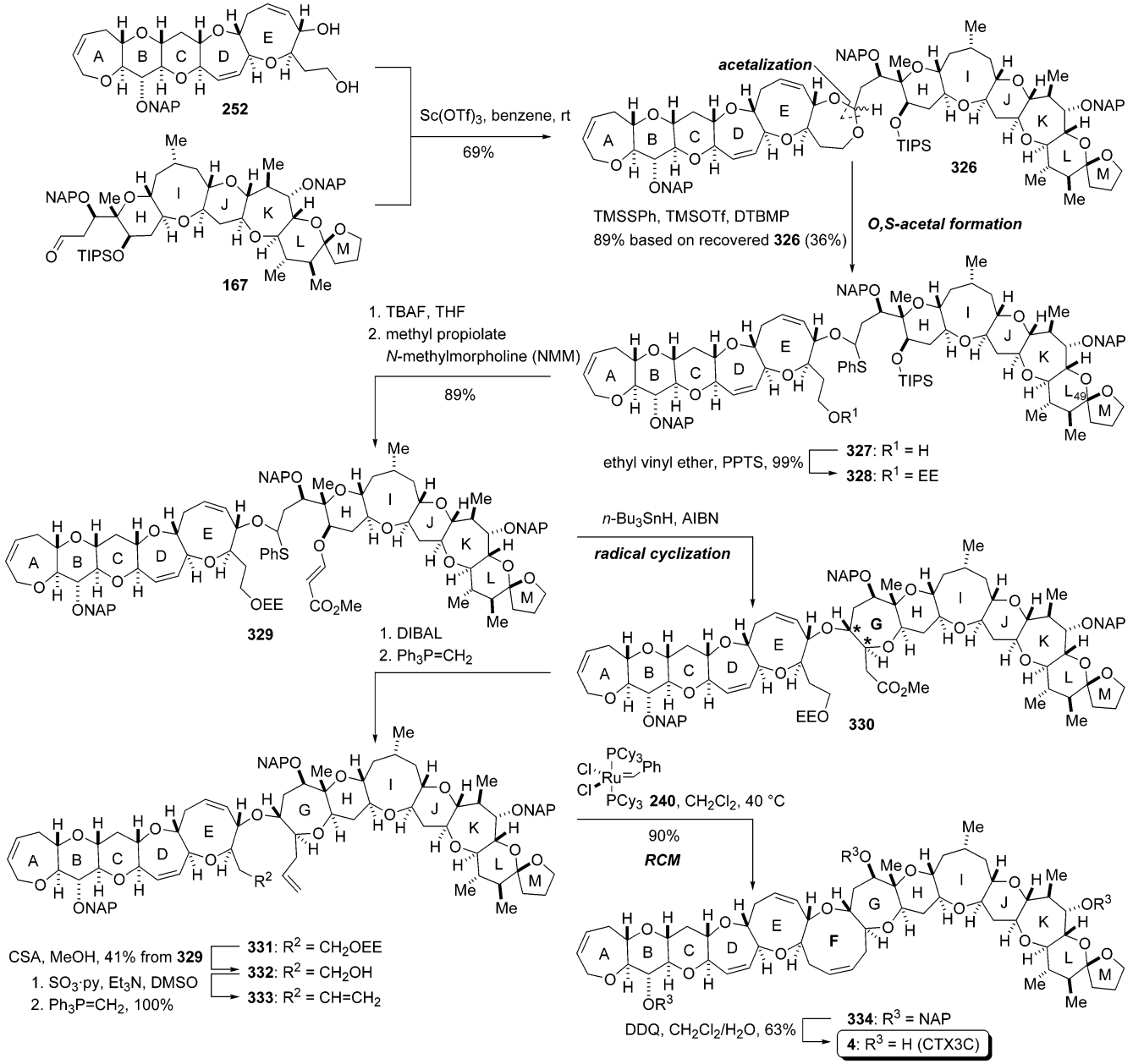


the regioselective introduction of cyanide to cyclic acetals as a key reaction (Scheme 37).[109] After unification of the two fragments through acetal formation, regioselective cleavage of **311** was achieved using TMSCN and TMSOTf to afford nitrile **312**. Subsequently, **312** was converted to aldehyde **313** in three steps. Treatment of **313** with allylmagnesium bromide, followed by the RCM reaction, gave the eight-membered rings as four isomers (**313** → **314**). Oxidation of alcohol **314** gave ketone **315** along with **316**, which was isomerized to **315** using DBU. Finally, the six-membered ring was constructed from **315** through reductive etherification, affording 6/8/6/6-ring system **317**. This methodology was recently applied to the synthesis of the FGHI-ring fragment of yessotoxin **318**.[109b] In addition, a similar strategy using α-cyano ether as an intermediate was applied to the synthesis of the structural fragment of gambieric acid-A (**9**) by Sasaki.[110]

4.13. *O*,*O*-Acetalization/Intramolecular Radical Cyclization from Mixed Acetal

In 1998 Sasaki and Tachibana reported the convergent synthesis of *O*-linked oxepane based on the intramolecular radical reaction.[111] Acetalization between **258** and **319** led to six-membered acetal **320**, which was converted to *O*,*Se*-acetal **321** by the regioselective cleavage of the less hindered C−O bond using *i*-$Bu_2AlSePh$.[112] Protection of the primary hydroxyl group in **321**, subsequent removal of the silyl group, and attachment of β-(*E*)-alkoxyacrylate afforded **322**. Treatment of **322** with *n*-Bu_3SnH in the presence of Et_3B[113] resulted in the formation of the desired *O*-linked oxepane **325** as a single diastereomer in high yield.[114]

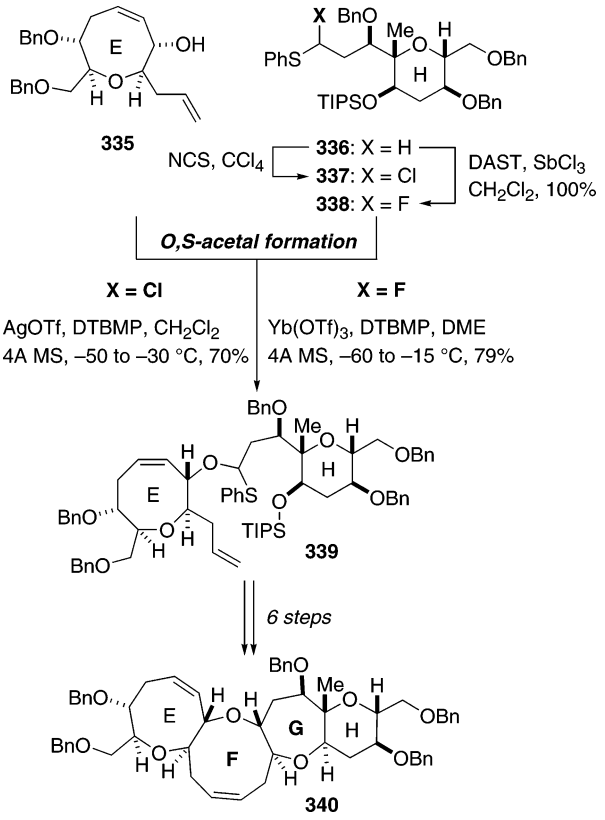
Scheme 39. First-Generation Total Synthesis of CTX3C (Hirama, 2001, 2002)



Scheme 38 explains the stereoselectivity of this cyclization. Initially, the stereochemical information of the acetal carbon was lost upon formation of the radical intermediate. To avoid the 1,3-diaxial-like interactions, the β-alkoxyacrylate favored the extended *s-trans*- over the *s-cis*-conformation. Furthermore, steric interactions between the bulky alkoxy group and the *s-trans*-alkoxyacrylate of the pseudoequatorial **323** resulted in a preference for the pseudoaxial **324**, from which the desired isomer **325** was the only possible outcome among the four possible isomers.

This remarkable protocol based on radical cyclization was further modified and refined by Hirama's laboratory, culminating in their total synthesis of ciguatoxin CTX3C (**4**, Scheme 39).[27,115] $Sc(OTf)_3$-promoted coupling of 1,4-diol **252** and aldehyde **167** delivered seven-membered acetal **326**. The seven-membered acetal was selected over the six-membered counterpart based on their model experiments, which again indicated the superior reactivity of the seven-membered acetal.[101,116] Indeed, the acetal cleavage reaction of **326** was realized using TMSOTf and TMSSPh,[117] which led to *O*,*S*-acetal **327** without affecting the potentially reactive C49-spiroacetal. After three synthetic steps from **327**, β-alkoxyacrylate **329** was then subjected to radical cyclization using n-Bu_3SnH and AIBN, giving rise to the desired oxepane **330** as the sole isomer. For this step the generated radical added to the α,β-unsaturated ester of **329** in a completely stereo- and chemoselective manner. To prepare for cyclization of the last remaining F-ring, the carbon chains of **330** were transformed to the terminal olefins of **333** in five steps. The RCM reaction of **333** using Grubbs catalyst **240** provided the protected CTX3C **334**, which was converted to the target CTX3C (**4**) through global deprotection. This total synthesis of CTX3C proved the power and reliability of the *O*,*S*-acetal strategy in the construction of complex polyether structures.

Scheme 40. Direct Formation of *O,S*-Acetals from α-Halosulfides (Inoue/Hirama, 2002)

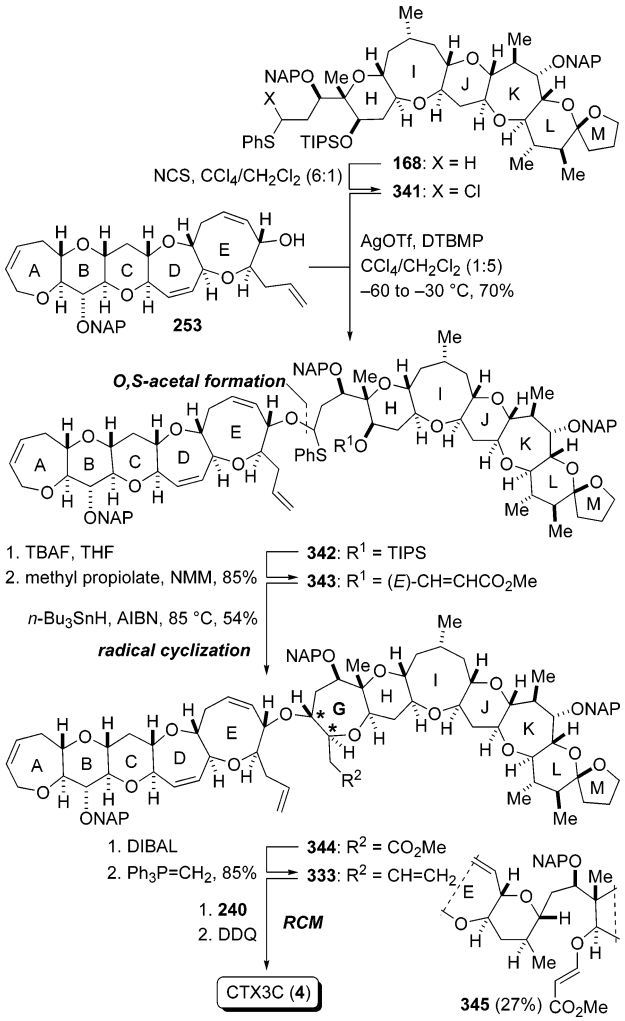


4.14. Direct *O,S*-Acetal Formation/Intramolecular Radical Cyclization

In 2002 Inoue and Hirama developed an alternative, mild route to *O,S*-acetals, which relied on the direct coupling of secondary alcohols and α-halosulfides.[106,107] The EFGH-ring fragment **340**, which represents the central region of CTX3C, was first selected as a synthetic target (Scheme 40). When H-ring sulfide **336** was treated with *N*-chlorosuccinimide (NCS) in CCl_4, the chloride was installed at the α-position of the sulfide under neutral conditions to give chlorosulfide **337**. Activation of **337** by AgOTf in the presence of E-ring alcohol **335** resulted in the formation of the desired *O,S*-acetal **339**.[118,119] The same group applied the chemically stable α-fluorosulfide **338** to the coupling reaction.[120] A combination of the reagents (diethylamino)sulfur trifluoride (DAST) and catalytic $SbCl_3$ in CH_2Cl_2 quantitatively converted **336** to α-fluorosulfide **338**.[121] *O,S*-Acetal **339** was effectively produced by treating fluoride **338** with $Yb(OTf)_3$ in the presence of alcohol **335**. The key intermediate **339** was then converted to the targeted model compound **340** in six synthetic steps, which included radical cyclization and RCM reaction, to give the FG-ring system.

In 2004 Inoue and Hirama reported their second-generation total synthesis of CTX3C (**4**) using the method described above (Scheme 41).[122,123] α-Chlorosulfide **341**, prepared from **168**, and alcohol **253** were coupled by the action of AgOTf. In this way, *O,S*-acetal **342** was obtained in high yield, thus accomplishing direct construction of the key intermediate. The F- and G-rings were then constructed

Scheme 41. Second-Generation Total Synthesis of CTX3C (Inoue/Himara, 2004)



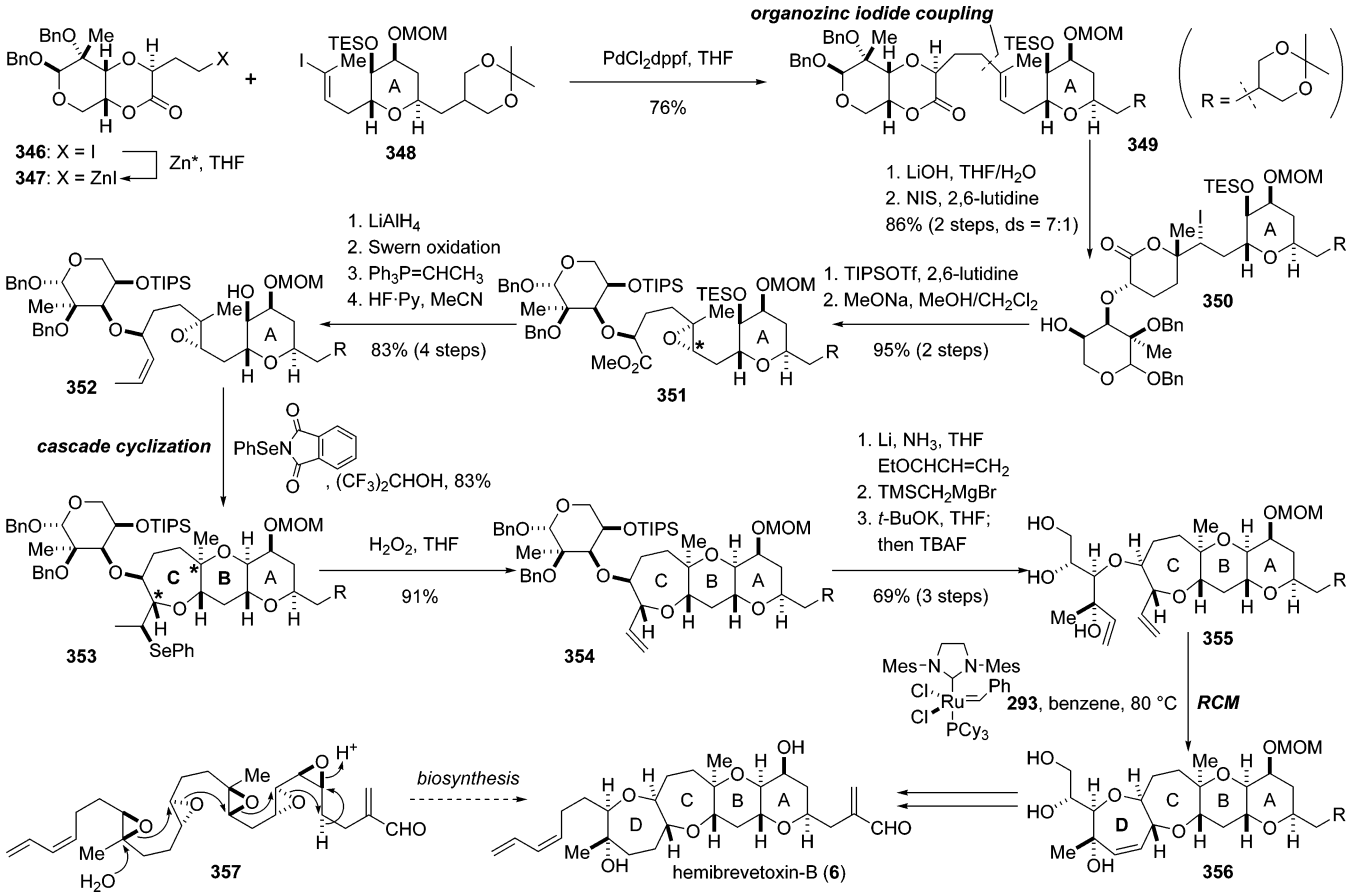
from **342** in a manner similar to the first-generation synthesis, which resulted in their second-generation total synthesis of **4**. Importantly, the halophilic silver salt used in the coupling is highly chemoselective and allows the use of various functional groups. In addition, this method installed two rings in only eight synthetic transformations (12 steps were required in the first-generation synthesis, see Scheme 39).

5. Convergent Strategy Utilizing a Biomimetic Cascade Reaction

It is hypothesized that the biosynthesis of fused polycyclic ethers occurs through the domino *endo*-cyclization of the polyepoxide precursor (see **357** → **6**, Scheme 42).[5,124] This proposed pathway prompted synthetic chemists to develop new biomimetic cascade reactions, which have been indeed realized as exemplified by the work of the McDonald and Fujiwara groups.[125,126] The present review illustrates Holton's total synthesis of hemibrevetoxin-B (**6**) in which the biomimetic approach was successfully combined with the convergent strategy.[127]

The coupling of the two fragments was achieved by the Pd(0)-catalyzed reaction of organozinc iodide **347** with vinyl iodide **348** to produce **349** (Scheme 42).[128] Hydrolysis of lactone **349**, followed by diaste-

Scheme 42. Total Synthesis of Hemibrevetoxin-B (Holton, 2004)



reoselective iodolactonization, provided **350**. Protection of the hydroxyl group of **350** and methanolysis generated epoxide **351**, which was converted to the cascade cyclization substrate **352** in four steps. Upon treatment with *N*-(phenylseleno)phthalimide in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), **352** underwent smooth cyclization to give **353** as a single diastereomer. Thus, two ether rings of **353** were assembled in a single operation.

Oxidation−elimination of the selenide of **353** produced olefin **354**, which was transformed to diene **355** through Bn removal and Peterson olefination. The RCM reaction of **355** cyclized the seven-membered ring of **356**, and finally, the functional-group transformation from **356** completed the total synthesis of hemibrevetoxin-B (**6**).

6. Conclusion

The foregoing work demonstrates the rapid progress that has been made in the field of the convergent synthesis of *trans*-fused polycyclic ethers. Notably, most of these efforts have been concentrated over the last 5 years. A number of the synthetic technologies developed are at the cutting edge of contemporary organic chemistry and have proved to be highly applicable to complex polycyclic natural products, such as hemibrevetoxin-B, brevetoxins, gambierol, gymnocin-A, and ciguatoxin CTX3C. It is anticipated that the materials generated through these total syntheses will further the understanding of their detailed biological mechanisms of action.

However, the chemical synthesis of polycyclic ethers has not yet become a routine preparative method for obtaining natural products and their analogues. The existing total syntheses typically require more than 100 steps in total. In addition, the yields and stereoselectivities of the most powerful methodologies described in this review depend on the local structures of the molecules. There is still no universal convergent strategy that is applicable to all ether ring systems with their diverse functional-group patterns. Therefore, the development of even more practical, concise, and general synthetic routes remains a key challenge for the future.

7. References

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CR0406108