Evolution of a Practical Total Synthesis of Ciguatoxin CTX3C

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ABSTRACT

More than 20 000 people suffer annually from ciguatera seafood poisoning in subtropical and tropical regions. The extremely low content of the causative neurotoxins, designated as ciguatoxins, in fish has hampered their isolation, detailed biological study, and preparation of anti-ciguatoxin antibodies for detecting these toxins. Ciguatoxins consist of 12 trans-fused polycyclic ethers, ranging from six- to nine-membered, and include a spirally attached five-membered cyclic ether at one end. The large (3 nm in length) and complicated molecular structure of ciguatoxins has impeded chemists from completing their total synthesis. In 2001, we achieved the first total synthesis of ciguatoxin CTX3C by assembly of four structural fragments. Since then, protocols to combine the fragments have significantly improved in terms of overall stereoselectivity, efficiency, and practicality. In this Account, we describe recently evolved methodologies for the total synthesis of CTX3C.

Introduction

Ciguatera is an important form of human poisoning caused by the consumption of seafood.[1,2] More than 20 000 people suffer annually from ciguatera, making it one of the most common food poisonings of nonbacterial origin. Yasumoto et al. identified an epiphytic dinoflagellate, *Gambierdiscus toxicus*, as the causative organism.[3] The dinoflagellate-derived toxins 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 a month or more or recur periodically. Typical symptoms include a disorder of temperature sensation, diarrhea, vomiting, muscle pain, and itching, while paralysis, coma, and even death may occur in severe cases. Up to now, difficulties in predicting, detecting, and treating ciguatera have had an adverse socioeconomic impact, particularly in developing countries.

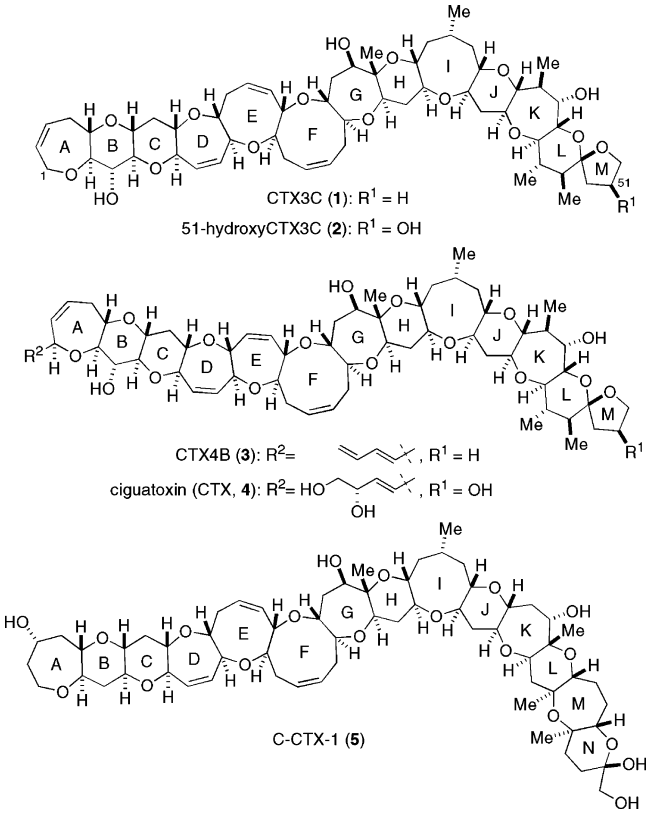

FIGURE 1. Structures of ciguatoxins.

Ciguatoxins are regarded as the principal causative toxins of ciguatera seafood poisoning (Figure 1).[4] In 1989, the Yasumoto group successfully elucidated the structures of ciguatoxin CTX (**4**) and CTX4B (**3**),[5] which were found to be huge ladder-like polycyclic ethers with molecular lengths over 3 nm. Yasumoto and co-workers subsequently isolated other congeners including CTX3C (**1**)[6] and 51-hydroxyCTX3C (**2**).[7] Moreover, Caribbean ciguatoxins (e.g., C-CTX-1, **5**), structurally characterized by Lewis et al., were revealed to have distinct structures from those of Pacific ciguatoxins (**1**−**4**).[8] To date, more than 20 congeners of ciguatoxins have been structurally determined.[9]

The lethal potencies of ciguatoxins (LD_{50} = 0.25−4 μg/kg) by intraperitoneal injection into mice are much greater than the structurally related red-tide toxins, brevetoxins (LD_{50} >100 μg/kg).[10−13] The low fatality rate in ciguatera is due solely to the minute concentration of ciguatoxins

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Masahiro Hirama was born in 1948 in Tokyo. He studied for his Ph.D. at Tohoku University under Prof. Shô Itô in 1977 and completed postdoctoral studies at the University of Pittsburgh with Prof. S. J. Danishefsky and at MIT with Prof. S. Masamune. In 1980, he returned to Japan and joined the Suntory Institute for Bioorganic Research (Nakanishi's Institute). In 1983, he joined Tohoku University as an assistant professor and was promoted first to associate professor in 1986 and then to Professor of Chemistry in 1989. In addition, since 1997 he has been concurrently serving as Director of the CREST and then SORST Projects of Japan Science and Technology Agency (JST). He received the Progress Award in Synthetic Organic Chemistry, Japan, in 1985. Additionally, he was awarded the Inoue Prize for Science in 1998, the Synthetic Organic Chemistry Award, Japan, in 2000, and the Chemical Society of Japan Award in 2004. His current research interests are natural product synthesis, synthetic methods and strategies, and design of bioactive molecules with a special emphasis on protein−ligand complexes.

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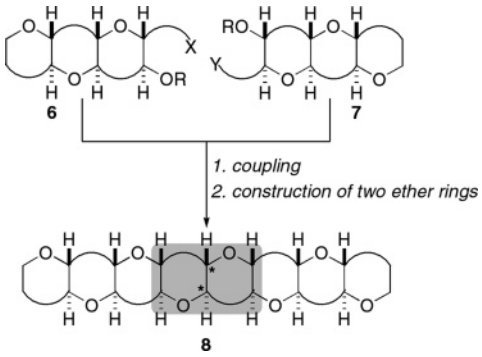


FIGURE 2. Unified convergent strategy to build the fused ether array.

in fish flesh. To detect such small amounts of ciguatoxins prior to ingestion of fish, highly sensitive antibody-based immunoassays have been necessitated; however, a reliable and easy-to-use assay kit is not currently available.

Pharmacological studies have established that ciguatoxins exert their potent toxicities by binding to the voltage-sensitive sodium channels (VSSC) of excitable membranes, which results in persistent activation of the channel.[14] Ciguatoxins and brevetoxins share a specific binding site on VSSC, although ciguatoxins bind 10 times more strongly than brevetoxins.[15−18] The site specificity and selective function of these toxins may present an opportunity for investigation into the activation and gating mechanisms of the channel itself.

However, the potential biological applications of ciguatoxins have been impeded by the extreme difficulty in isolating ciguatoxins. Thus, chemical synthesis has been the sole realistic solution available to obtain sufficient quantities of ciguatoxins for studying sodium channels, as well as for developing immunochemical methods. In addition to these rationales, the fascinating molecular architecture of ciguatoxins strongly attracted us to study their synthetic construction. In the opening phase of this program, we focused on ciguatoxin CTX3C, **1**.

Plan of Convergent Strategy

The synthetic challenge posed by **1** reflects its highly complex nanoscale structure: 13 oxygen atoms and 52 carbon atoms coiled in a polycyclic macromolecule that includes 30 stereogenic centers.[19−24] The 12 ether rings, ranging from six- to nine-membered, are fused in a trans/syn manner, and the five-membered ring is spirally attached at the end. Owing to the size and complexity of the molecule, efficient assembly of the structural fragments is crucial for its successful construction. Our synthesis employed a unified strategy to obtain this fused ether array: (i) the coupling of the synthetic fragments **6** and **7** (Figure 2) and then (ii) the construction of the two rings with introduction of two stereocenters (**8**). The challenge lies in developing a reaction sequence that constructs the new ethers of requisite ring sizes in a stereoselective manner without affecting the preexisting functionalities.

In applying this concept to **1**, we designed an optimally convergent route in which four simple units (**9**, **10**, **11**, and **12**, Figure 3) were to be coupled and further modified to form the CD-, FG-, and JK-rings. The comparably complex ABCDE- and HIJKLM-ring systems were aimed to be synthesized prior to the final coupling on the central region of the molecule, that is, the FG-ring system.

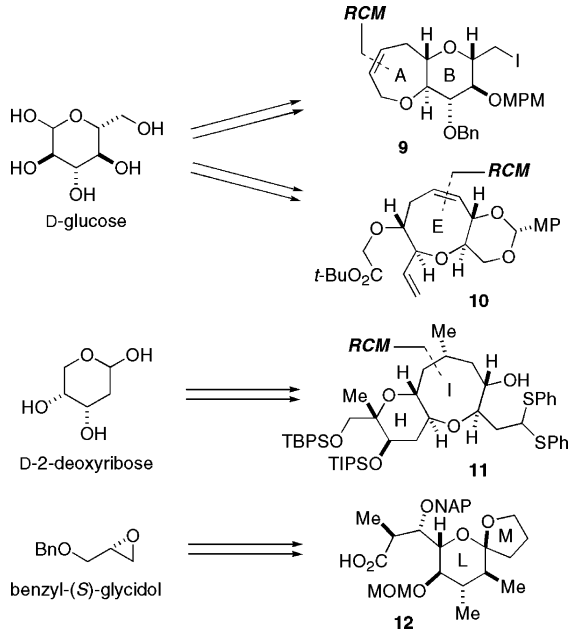


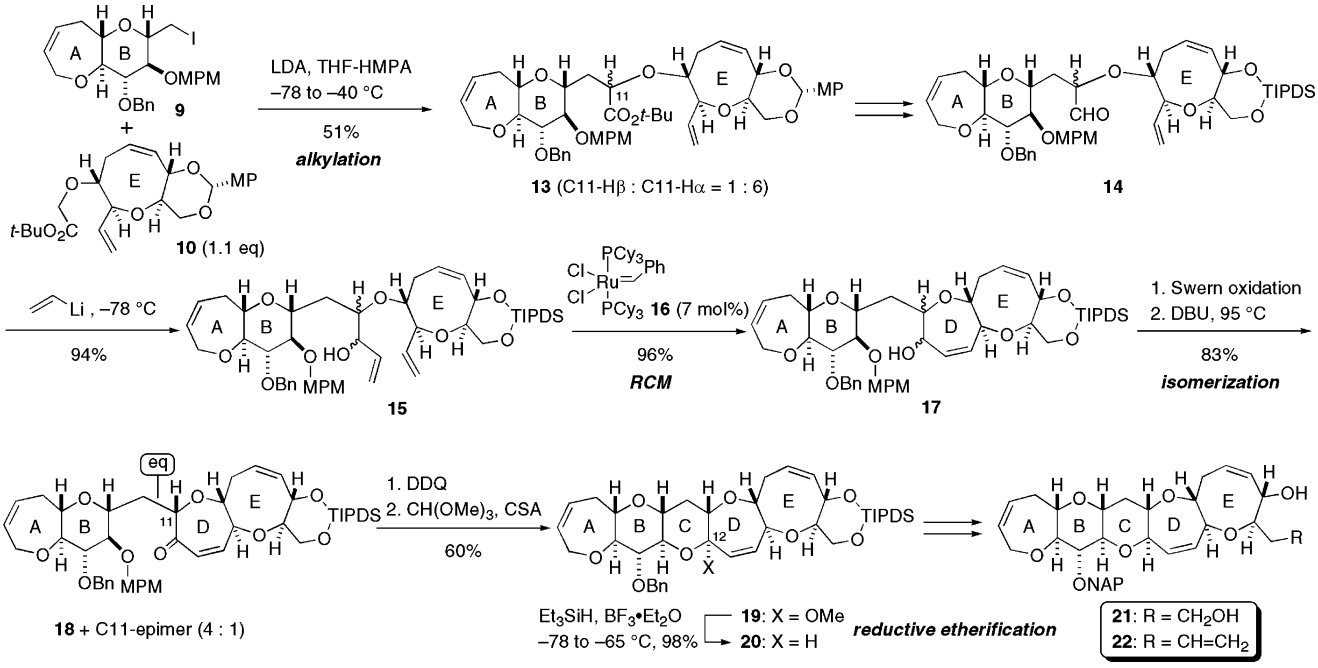
FIGURE 3. Four fragments for total synthesis of CTX3C.

Four structural fragments (**9**−**12**) were prepared from the simple starting materials D-glucose (**9**, **10**), D-2-deoxyribose (**11**), and benzyl-(*S*)-glycidol (**12**), as shown in Figure 3.[25] The medium-sized ether rings, A-, E-, and I-rings, were cyclized using the ring-closing olefin metathesis reaction (RCM),[26,27] which greatly simplified synthesis of the fragments. This Account focuses on the coupling strategies for combining these structures en route to CTX3C with particular emphasis on methodologies evolved after 2001.

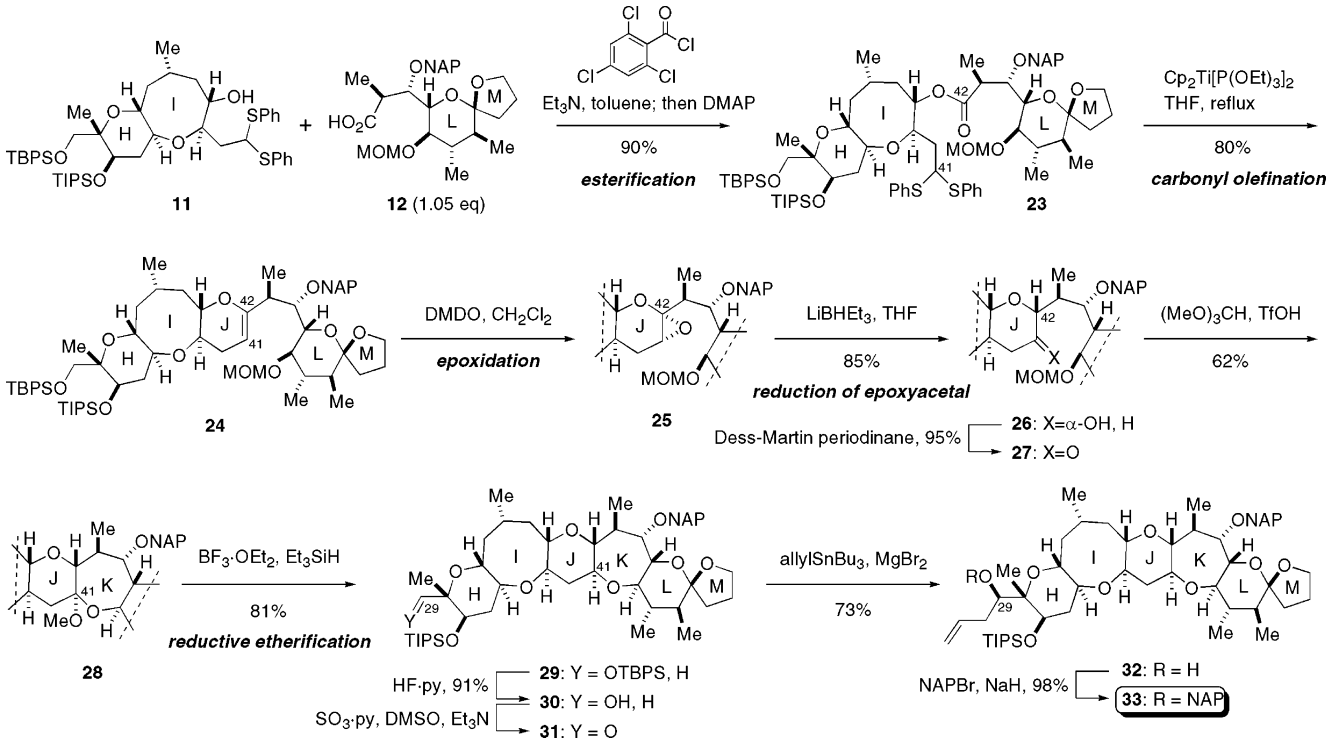
Synthesis of the Left Wing Fragment

The left wing fragment was synthesized[28] from AB- and E-rings (**9**, **10**) with construction of the CD-ring using an alkylation/metathesis sequence[29] (Scheme 1). Attack of the lithium enolate of **10** on iodide **9** led to alkylated adduct **13** as an inseparable mixture of C11-epimers favoring the undesired stereoisomer. Thus, to obtain sufficient amounts of the correct stereoisomer, epimerization of C11 was deemed necessary. Several synthetic steps transformed **13** to aldehyde **14**, to which addition of vinyl lithium afforded diene **15**. Tetraene **15** was smoothly cyclized using Grubbs reagent **16**[30] to provide the seven-membered D-ring **17**. Swern oxidation of the secondary alcohol of **17** to its ketone and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) mediated isomerization of the C11-stereocenter produced the more thermodynamically stable pseudoequatorial **18** as the major isomer. Removal of the *p*-methoxybenzyl (MPM) group in **18** using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), followed by methyl acetalization under acidic conditions, afforded pentacycle **19**. The hydride attacked from the α-face of **19** in the reductive etherifi-

Scheme 1. Synthesis of the Left Wing Fragment of CTX3C



Scheme 2. Synthesis of the Right Wing Fragment of CTX3C



cation,[31] thus setting the C12-stereocenter and providing ABCDE-ring fragment **20**. Finally, subsequent functional group manipulations of **20** yielded the 2-naphthylmethyl (NAP)-protected left wing fragments **21** and **22**.

Synthesis of the Right Wing Fragment

A different methodology was applied to the synthesis of the right wing fragment (Scheme 2).[32,33] Condensation of alcohol **11** and carboxylic acid **12** using the Yamaguchi protocol produced the corresponding ester **23**.[34] Construction of the J-ring from **23** through C−C bond formation was not easy due to the steric hindrance at C42.[35] Thus, we utilized powerful intramolecular carbonyl olefination developed by Takeda and co-workers;[36] treatment of **23** with $Cp_2Ti[P(OEt)_3]_2$ under refluxing THF successfully closed the six-membered J-ring to afford pentacycle **24** in high yield.

The next stage of the synthesis involved the stereoselective introduction of hydrogen at C42 and oxygen functionality at C41. After some experiments, it became clear that **24** has a strong conformational bias and accepts the reagent mainly from the α-face (Figure 4). Observed

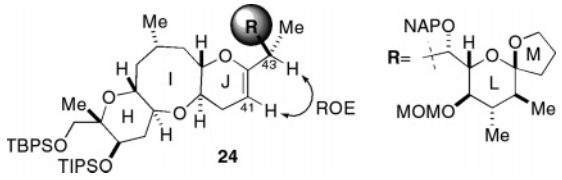


FIGURE 4. Observed ROE and probable local conformation of enol ether **24**.

rotating-frame Overhauser enhancement (ROE) data indicated that the sterically demanding LM-ring portion projects toward the β-face of **24** and blocks attack of the reagent. For instance, hydroboration of **24** led predominantly to the undesired stereoisomer with an α-hydrogen at C42.

To introduce the β-hydrogen at C42, it was necessary to develop a method with complementary stereoselectivity to that of hydroboration. The new method employed was a two-step protocol based on the stereoselective reduction of an epoxyacetal. First, α-epoxide **25** was synthesized from **24** as a sole isomer using dimethyldioxirane (DMDO). After many unsuccessful attempts, S_N2-type hydride delivery to the C42-acetal epoxide was realized by treating **25** with $LiBHEt_3$. In this way, the desired product **26** was obtained as an exclusive diastereomer.

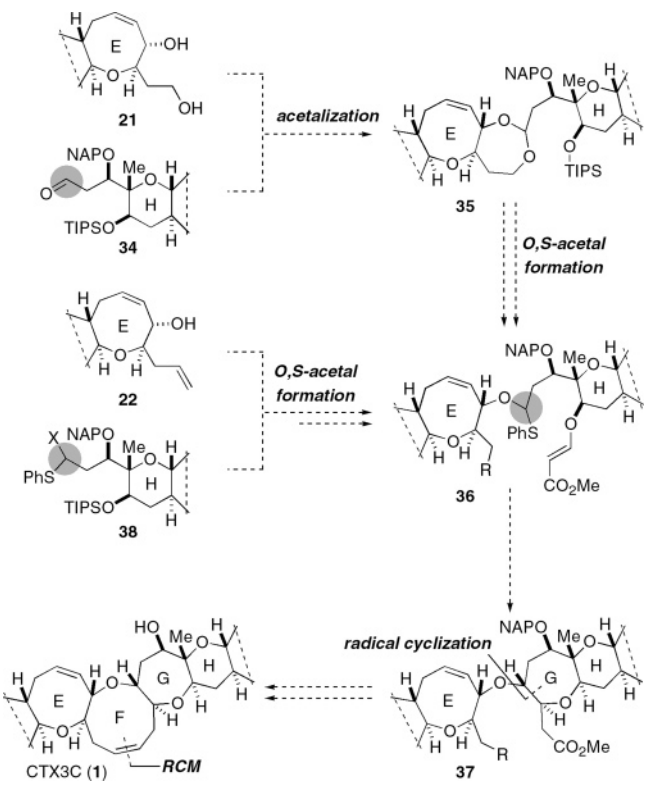
Once the correct C42-isomer **26** was successfully obtained, the remaining tasks for synthesis of the right wing were formation of the K-ring and extension of the carbon chain to the left side. Alcohol **26** was oxidized with Dess−Martin periodinane to afford **27**. When **27** was exposed to triflic acid and $(MeO)_3CH$ in hexane, the seven-membered methyl acetal **28** was directly formed with concomitant loss of the methoxymethyl (MOM) group. Finally, reductive etherification of acetal **28** constructed the final ether ring with complete stereocontrol at C41, affording HIJKLM-ring system **29**. Thus, the JK-ring was assembled from fragment **11** in only seven synthetic operations.

The carbon chain corresponding to the G-ring was then introduced. HF·pyridine selectively removed the primary *tert*-butyldiphenylsilyl (TBPS) of **29** without removal of the secondary triisopropylsilyl (TIPS) to afford **30**, which was in turn oxidized with SO_3·pyridine to provide **31**. Aldehyde **31** was subjected to $MgBr_2$-promoted allylation using allyltributyltin to generate β-alcohol **32**. Finally, NAP protection of **32** gave rise to the targeted right wing fragment **33**.

First-Generation Total Synthesis of Ciguatoxin CTX3C

The third coupling to unify the left and right wing fragments is far more challenging than the previous two couplings, because of the increased complexity of the substrates. To attain the target structure, the reaction sequences need to be mild and concise. Our first-generation strategy for the total synthesis of CTX3C[25,37−39] employed five key transformations as shown in Scheme 3: (i) acetalization between 1,4-diol **21** and aldehyde **34**; (ii) regioselective introduction of the PhS group (**35** → **36**);

Scheme 3. First- and Second-Generation Strategy for Total Synthesis of CTX3C



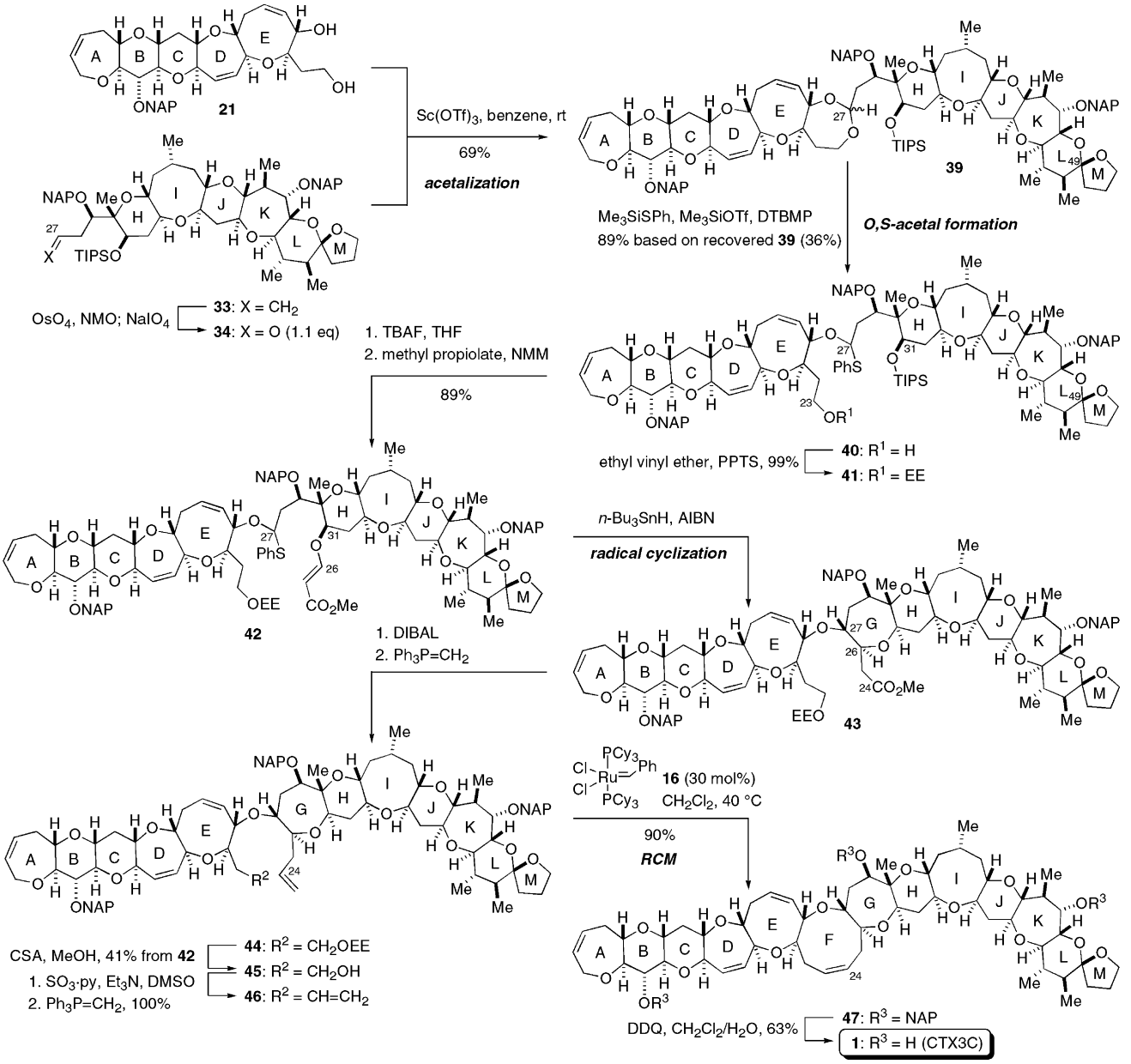
(iii) radical cyclization to form the seven-membered G-ring (**36** → **37**); (iv) RCM reaction to build the nine-membered F-ring; and (v) final removal of NAP group from the molecule (**37** → **1**).[40,41]

First, the terminal olefin of **33** was oxidatively cleaved to produce aldehyde **34** (Scheme 4). Condensation of 1,4-diol **21** and aldehyde **34** using catalytic $Sc(OTf)_3$ successfully delivered seven-membered acetal **39**.[42] Then, a reagent combination of Me_3SiOTf and Me_3SiSPh in the presence of 2,6-di-*tert*-butyl-4-methyl pyridine (DTBMP) cleaved the acetal of **39** to form *O*,*S*-acetal **40**.[43] Importantly, the C49-spiroacetal was left intact in this acetal cleavage reaction.

Stereoselective construction of the G-ring was then investigated. The primary alcohol of **40** was protected as the ethoxyethyl (EE) ether to give **41**. Removal of the TIPS group from **41** followed by treatment with methyl propiolate and *N*-methylmorpholine (NMM) afforded β-(*E*)-alkoxyacrylate **42**. Compound **42** was then subjected to radical cyclization using *n*-Bu_3SnH and 2,2′-azobisisobutyronitrile (AIBN), giving rise to the desired oxepane **43**. For this step, the generated C27-radical added to the α,β-unsaturated ester in a completely stereo- and chemoselective manner.

The stereoselectivity of the cyclization is explained as indicated in Figure 5.[44] Initially the stereochemical information of the acetal carbon is lost upon formation of the radical intermediate **48**. The β-(*E*)-alkoxyacrylate favors the extended *s*-trans over the *s*-cis conformation. Furthermore, the steric interactions between the bulky alkoxy group and the *s-trans*-alkoxyacrylate of pseudoequatorial

Scheme 4. First-Generation Total Synthesis of CTX3C



48eq results in the preference of pseudoaxial **48ax**, from which the desired isomer **43** is the only possible outcome among the four possible isomers. Hence, an important aspect of this strategy is that stereoselective synthesis of the *O*,*S*-acetal is not necessary, yet the two stereogenic centers of **43** (C26 and C27) are controlled by conformation of the transition state.

The remaining tasks for total synthesis were construction of the F-ring by RCM reaction and subsequent deprotection (Scheme 4). Diisobutylaluminum hydride (DIBAL) reduction of ester **43** to the aldehyde, followed by Wittig methylenation and acidic removal of the EE group, produced primary alcohol **45**. Oxidation of **45** with SO_3·pyridine−DMSO and subsequent Wittig reaction afforded olefin **46**. Grubbs reagent **16** effectively induced cyclization of pentaene **46** to produce NAP-protected CTX3C, **47**. This remarkable transformation clearly demonstrated the high specificity of **16** to terminal olefins, even in an elaborate substrate with multiple olefins.

The final global deprotection of **47** to yield the target product, CTX3C, was accomplished by treating a solution of **47** with DDQ. We were pleased that the standard workup and column chromatography afforded synthetic CTX3C, **1**, and that the potentially oxidizable allylic ether of the A-ring was untouched. The synthetic CTX3C was determined to be identical to the naturally occurring form in all physical data, and our study also confirmed the absolute stereochemistry of ciguatoxins.[45]

Development of Second-Generation Strategy

The first-generation total synthesis demonstrated the power of the *O*,*S*-acetal strategy to build complex polyether structures. With the intention of synthesizing CTX

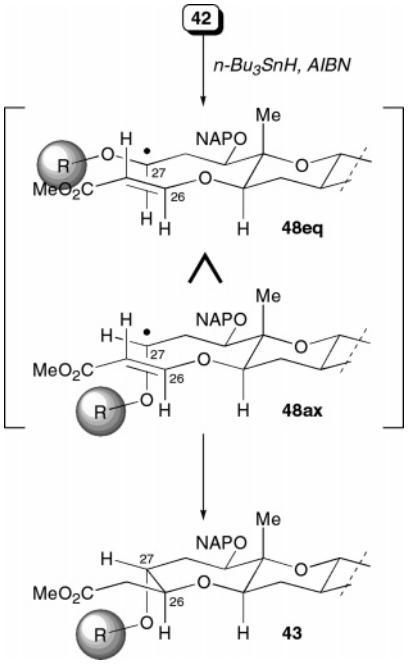


FIGURE 5. Mechanistic rationale of the radical cyclization.

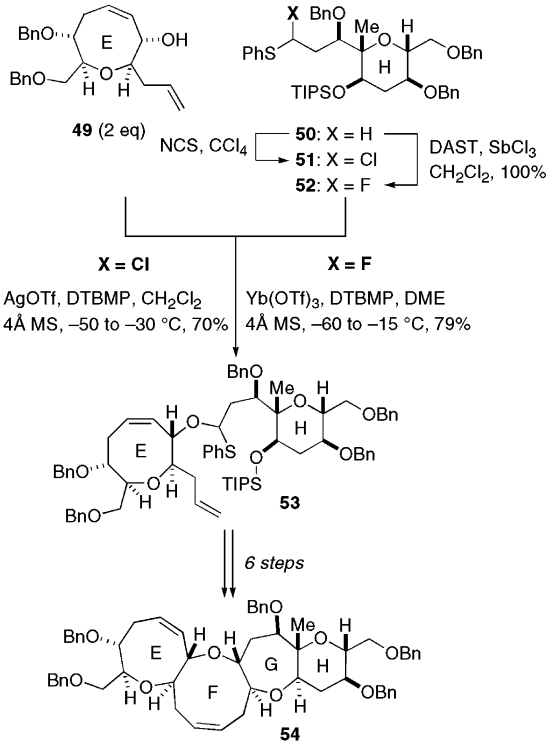
congeners (Figure 1), as well as other natural and artificial polyethers, we have become interested in further expanding the applicability of the strategy using alternative methods. In particular, to synthesize the structures with acid-sensitive functionalities, we seek development of a alternative, milder route to the *O*,*S*-acetal without the need for highly acidic conditions such as in the acetalization (**21** + **34** → **39**, Scheme 4) and PhS introduction (**39** → **40**).

Our alternative synthetic strategy relied on the direct construction of *O*,*S*-acetal **36** by coupling secondary alcohol **22** and α-halosulfide **38** (Scheme 3). The obtained **36** would be readily subjected to the radical cyclization to form the seven-membered ring (**36** → **37**). Generally, halophilic activators for coupling are highly chemoselective and nonacidic, allowing the use of a wide variety of protective groups in multifunctional systems. In addition, fewer synthetic steps are required from the coupling reaction compared with the previous method because it is not necessary to proceed via *O*,*O*-acetal **35**.

To develop such a coupling protocol, the EFGH-ring fragment **54**, which represents the central region of the molecule, was selected as a synthetic target (Scheme 5).[46,47] When H-ring sulfide **50** 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 **51**, which was unstable and was used for the next coupling reaction without purification. Activation of **51** by silver triflate (AgOTf) in the presence of E-ring alcohol **49**, DTBMP, and 4 Å molecular sieves (MS) resulted in the formation of the desired *O*,*S*-acetal **53**.[48,49] The thioalkyl group of **53**, which could also be activated by silver salt, was stable under the coupling conditions.

More recently, we applied α-fluorosulfide **52** to the coupling reaction.[50] A reagent combination of (diethylamino)sulfur trifluoride (DAST) and catalytic $SbCl_3$ in CH_2Cl_2 quantitatively converted **50** to α-fluorosulfide **52**.[51] In contrast to the corresponding chloride **51**, fluoride **52** was chemically stable and isolable in pure form using silica gel chromatography. Interestingly, it was found that Yb(OTf)$_3$ effectively induced coupling of the stable fluoride **52**, even at low temperatures. *O*,*S*-acetal **53** was produced by treating fluoride **52** with Yb(OTf)$_3$ in the presence of alcohol **49**, DTBMP, and 4 Å MS in 1,2-dimethoxyethan (DME).

Scheme 5. Direct Formation of *O,S*-Acetal from α-Halosulfide



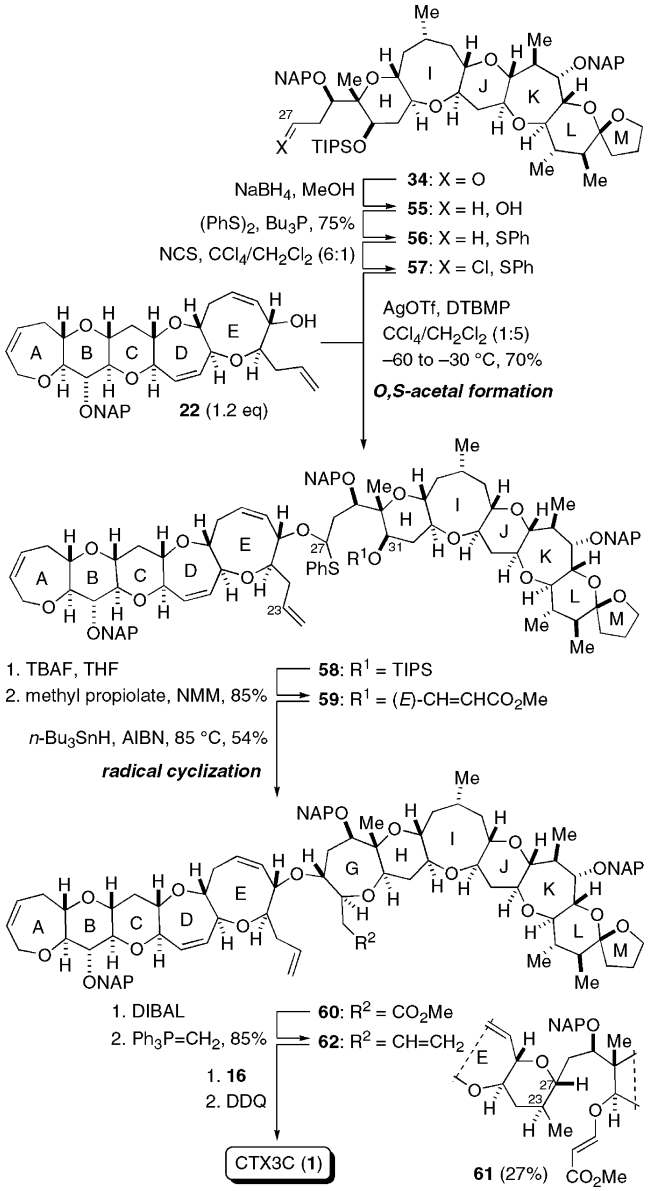
The key intermediate **53** was converted to the targeted model compound **54** in six synthetic steps including radical cyclization and RCM reaction to construct the FG-ring system. Thus, by careful selection of reagents and conditions, we developed two new protocols for direct synthesis of *O*,*S*-acetal **53**.

Second-Generation Total Synthesis of Ciguatoxin CTX3C

The second-generation total synthesis was achieved by this new methodology (Scheme 6).[39] To prepare for the coupling reaction, the right wing sulfide **56** was synthesized from aldehyde **34** in two steps. The α-chloride to sulfide **56** was installed using NCS, leading to α-chlorosulfide **57**. The obtained solution of **57** was introduced to a CH_2Cl_2 solution of alcohol **22** and AgOTf in the presence of DTBMP and 4 Å MS. In this way, *O*,*S*-acetal **57** was obtained in high yield, thus accomplishing direct construction of the key intermediate.

Similarly to the first-generation synthesis, the G-ring was cyclized. Initially, the TIPS group of **58** was removed with tetrabutylammonium fluoride (TBAF) to obtain the secondary alcohol, which was converted to β-alkoxyacrylate **59** using methyl propiolate and NMM. By subjecting

Scheme 6. Second-Generation Total Synthesis of CTX3C



59 to radical cyclization, the G-ring of **60** was constructed stereoselectively along with by-product **61** arising from 6-exo cyclization to the terminal olefin.

Although it is desirable to optimize the regioselectivity of the radical cyclization, the presence of the terminal olefin in **60** facilitated the synthesis of the substrate for the final RCM reaction. Only two steps involving DIBAL reduction of **60** and subsequent methylenation were required to obtain tetraene **62**. Finally, RCM reaction of **62** and following global deprotection provided the targeted CTX3C, **1**. The new improved approach delivers **1** in only nine steps from right and left fragments (previously 13 steps were required).

Conclusions

The highly convergent total synthesis of CTX3C has been improved and refined to a satisfactory level in terms of overall stereoselectivity and efficiency. A number of synthetic technologies developed in this program have high utility, particularly the RCM reaction to construct the medium-sized ethers and the powerful convergent methodologies to assemble the complex polycyclic structures. Remarkably, distinct coupling methods are employed for each local structure of the molecule, and the two new rings (CD- FG-, and JK-rings) are constructed in a concise fashion with stereoselective introduction of two stereocenters. The new synthetic route described here provides access to the supply of sufficient amounts of material for further biological studies. Very recently, we developed an immunoassay method to detect CTX3C using the intermediates, proving the utility of our synthesis in a biomedical application.[52] Therefore, the molecules synthesized here and in the future will accelerate development of strategies to control ciguatera and lead to the creation of VSSC probes that may elucidate VSSC–ligand interactions at the molecular level and the activation and gating mechanisms.

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