PERSPECTIVE

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Convergent syntheses of polycyclic ethers. Illustrations of the utility of acetal-linked intermediates

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One of the most characteristic and spectacular class of compounds isolated from marine sources is the polycyclic ethers. Following the initial report of the structural determination of brevetoxin B, a variety of novel polycyclic ethers have begun to surface. These natural products include ciguatoxins, gambierol, gambieric acids, yessotoxins and gymnocins, each of which exhibit distinct biological properties such as cytotoxicity and neurotoxicity, as well as antiviral and antifungal activities. Because of these intriguing biological activities and their complex molecular architecture, the total synthesis of these compounds has been pursued by many laboratories over two decades. In particular, the development of novel convergent strategies to assemble the structural fragments is crucial for the successful construction of these nanoscale molecules. This Perspective will focus on a recent convergent methodology using an acetal-linkage as a key motif. Application of this methodology culminated in the total syntheses of gambierol and ciguatoxin CTX3C.

Masayuki Inoue was born in Tokyo in 1971. He received a BSc degree in Chemistry from the University of Tokyo in 1993. In 1998, he obtained his PhD from the same university, working under the supervision of Professors K. Tachibana and M. Sasaki, on synthetic studies of ciguatoxin. After spending highly rewarding years with Professor S. J. Danishefsky at the Sloan-Kettering Institute for Cancer Research (1998–2000), working on the total synthesis of frondosin B and illicinones, he joined the Graduate School of Science at Tohoku University as an assistant professor of Professor Hirama's group. At Tohoku University, he was promoted to lecturer in 2003, and then to associate professor in 2004. There, he completed the total synthesis of ciguatoxin CTX3C, TMC-95A, and merrilactone A. He received both the Young Scientist's Research Award in Natural Product Chemistry and the Chugai Award in Synthetic Organic Chemistry in 2001. His research interests include the synthesis, design and study of biologically important molecules, with a particular emphasis on the total synthesis of structurally complex natural products.

Masayuki Inoue

Introduction

Since brevetoxin B (Fig. 1, **1**) was shown to have an unprecedented polycyclic ether structure by X-ray crystallography in 1981,[1] 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 semi-rigid ladder-like structure. The striking regularity with which the oxygen atoms bridge the polycyclic framework and the all-*trans*/*syn*/*trans* ring fusions are remarkable features of these molecules. Despite this common polycyclic motif, they show diverse biological activities with extreme potency.

Brevetoxins (**1**, **2**[3]) are potent ichthyotoxins (**2**: LC_{100} 4 ng mL^{-1} to guppies), and were isolated from the dinoflagellate *Gymnodinium breve*, a causative organism of the massive "red tide" fish kills. A similar red tide dinoflagellate *Gymnodinium mikimotoi* produces gymnocin-A (**3**).[4] In contrast to brevetoxins, **3** is weakly toxic in fish, but is cytotoxic to P388 mouse leukemia cells.[4] Ciguatoxins (**5**,[5] **6**[6]), potent neurotoxins, were isolated as the toxic principles of the wide-spread seafood poisoning known as ciguatera.[7] These toxins accumulate in fish though the food chain, starting from the dinoflagellate *Gambierdiscus toxicus*.[8] Some strains of this organism produce not only ciguatoxins, but also other polycyclic ethers, such as gambierol (**4**), that exhibit toxicity against mice.[9]

The novel functions of these molecules have attracted interest from both the biological and chemical communities, and many investigations have focused on elucidating their biological targets. However, receptor proteins have only been identified for brevetoxins and ciguatoxins.[10,11] These molecules have been shown to bind strongly with the voltage sensitive sodium channels of excitable membranes, causing them to open, thereby allowing sodium ion influx.

Over the past two decades, a number of laboratories have attempted the chemical construction of these compounds due to their unusual molecular architecture, biological activity and association with important phenomena such as red tide and food poisonings. Their exquisitely complex structures have served as inspiration for the development of new methodologies in organic synthesis, and as an elegant platform for exhibiting the creativity of modern organic chemists.[12] In 1995, Nicolaou, a pioneer in the field of polyether syntheses, reported the first total synthesis of brevetoxin B (**1**).[13] This major advance was followed by the synthesis of brevetoxin A (**2**) by the same laboratory in 1998.[14] In the last five years, even more rapid progress has been made by many laboratories. The efforts culminated in the total syntheses of ciguatoxin CTX3C (**5**) by Hirama *et al.* in 2001,[15,16] gambierol (**4**) by both Sasaki[17] and Kadota and Yamamoto[18] in 2002, brevetoxin B (**1**) by Nakata in 2002,[19] and gymnocin-A (**3**) by Sasaki in 2003.[20] 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 minimum synthetic transformations. Because

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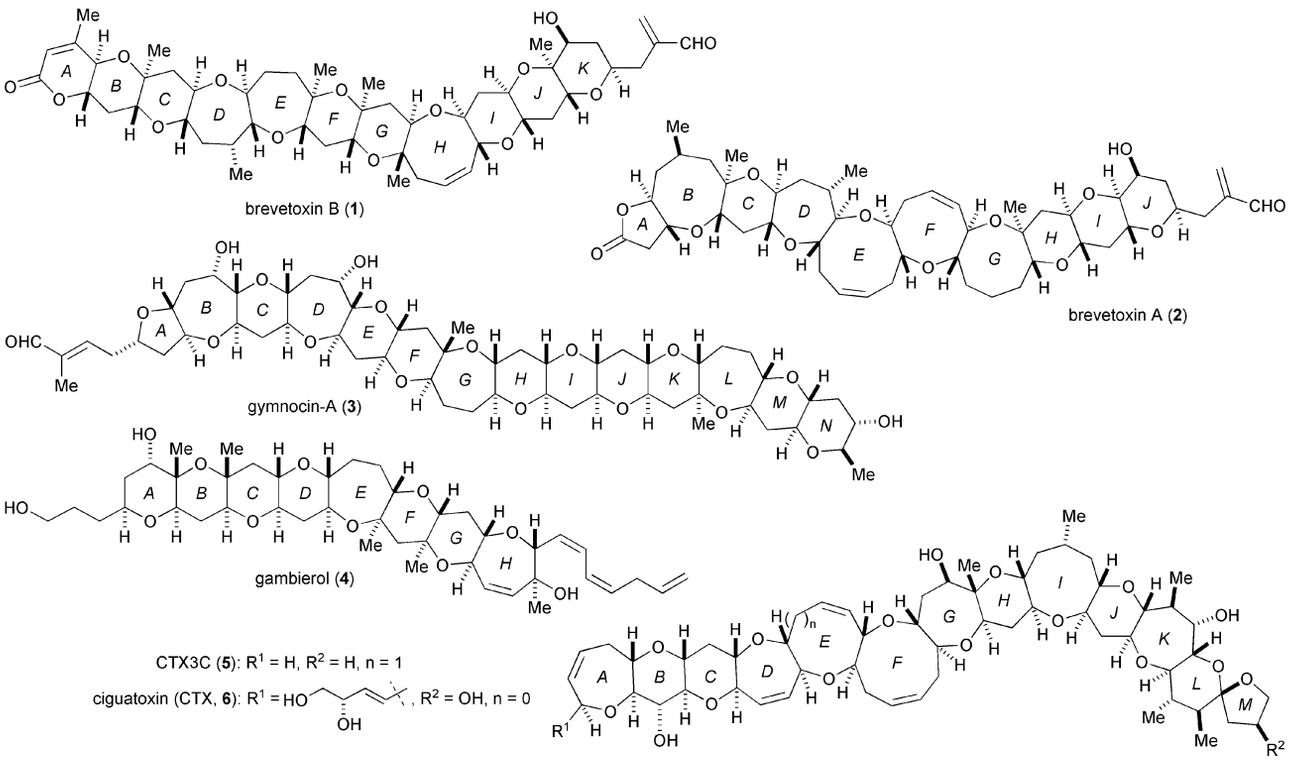
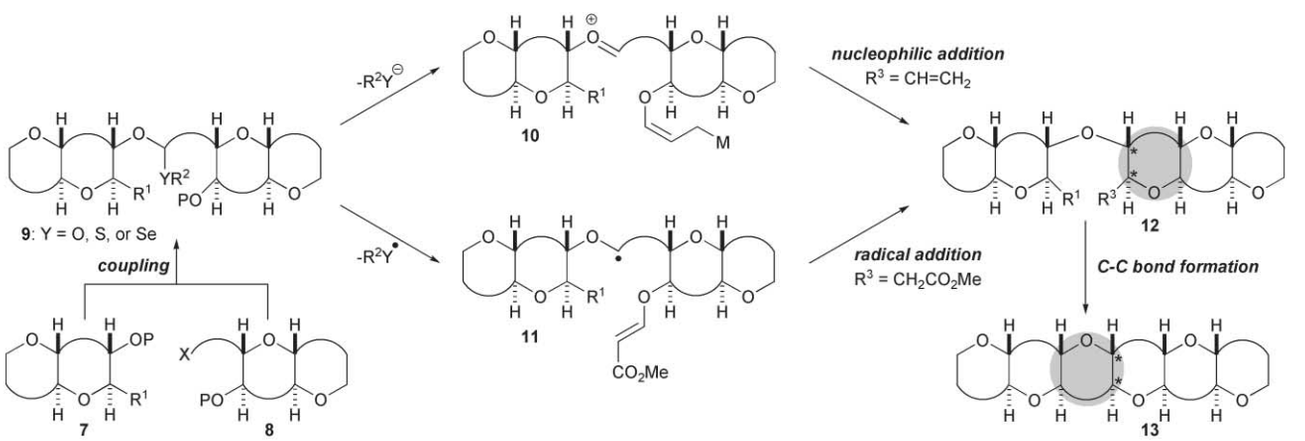


Fig. 1 Structure of representative polycyclic ethers.



Scheme 1 Convergent strategy *via* an acetal-linked intermediate.

linear construction of the ether rings is virtually impossible due to the size of the molecule, development of an efficient methodology for coupling the fragments, suitable for use in the latter stages of synthesis, has been particularly important for the total synthesis. Various convergent strategies have been published, and successfully applied to syntheses of natural products and their structural fragments. Among these, this Perspective will focus on a recent methodology using an acetal-linkage as a key motif. Development of such protocols and their application to the total synthesis of gambierol (**4**) and CTX3C (**5**) will also be discussed in this Perspective.

Convergent synthetic strategy *via* acetal-linked intermediate

The generalized route to the fused ether array through the acetal-linked intermediate is illustrated in Scheme 1. Firstly, acetal **9** is synthesized through coupling of the synthetic fragments **7** and **8**. Construction of the ether ring from **9** *via* intramolecular C–C bond formation would then give *O*-linked oxacycle **12**, of which cyclization *via* another C–C bond formation would afford fused ether array **13**. Formidable challenges lie in the construction of the first ring with the introduction of the two stereocenters of **12** and efficient cyclization of the second medium-sized ether ring (**12** → **13**). Generally, construction of medium ring structures has been hampered by difficulties in effecting ring closure due to unfavorable entropy factors as well as transannular nonbonding interactions. One of the advantages of this strategy is that the carbon chains of *O*-linked oxacycle **12** are in close proximity in the global minimum conformer, as indicated by molecular modeling studies of **14** (Fig. 2), and thus **12** has the appropriate conformation for cyclization through C–C bond formation.

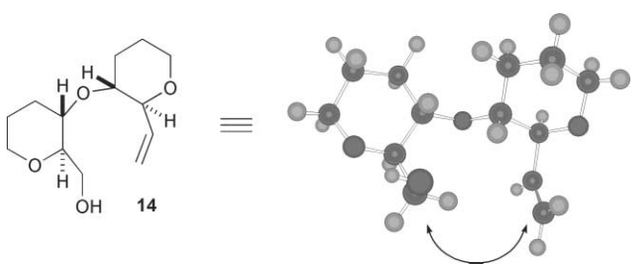


Fig. 2 Minimized structure of *O*-linked oxacycle **14** (MacroModel Ver. 8.0, MM2*).

There are two possible reaction courses for the first intramolecular ether ring formation (Scheme 1): (i) nucleophilic addition to the acetal carbon (**10** ⟶ **12**) and (ii) addition of the α-oxyradical to the olefin (**11** ⟶ **12**). In both cases, development of stereoselective methods to control the two bridgehead stereocenters is the critical issue, and will be the particular focus of this Perspective.

Nucleophilic addition of γ-alkoxyallylsilane to cyclic acetal

In the early 1990s, Yamamoto's group published a series of papers on the intramolecular Lewis acid-mediated reaction of γ-alkoxyallylmetals with acetals to obtain cyclic ethers (**15** ⟶ **16** or **17**, Fig. 3).[21] This pioneering work was extended to convergent methodologies to assemble polycyclic ethers by Martín[22] and Tachibana.[23]

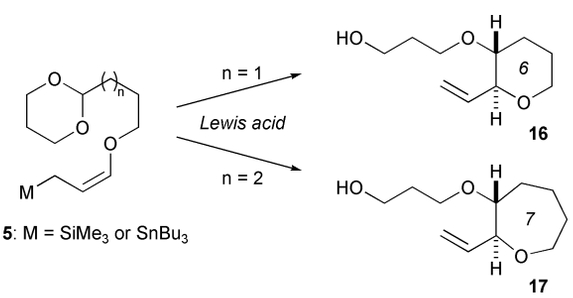


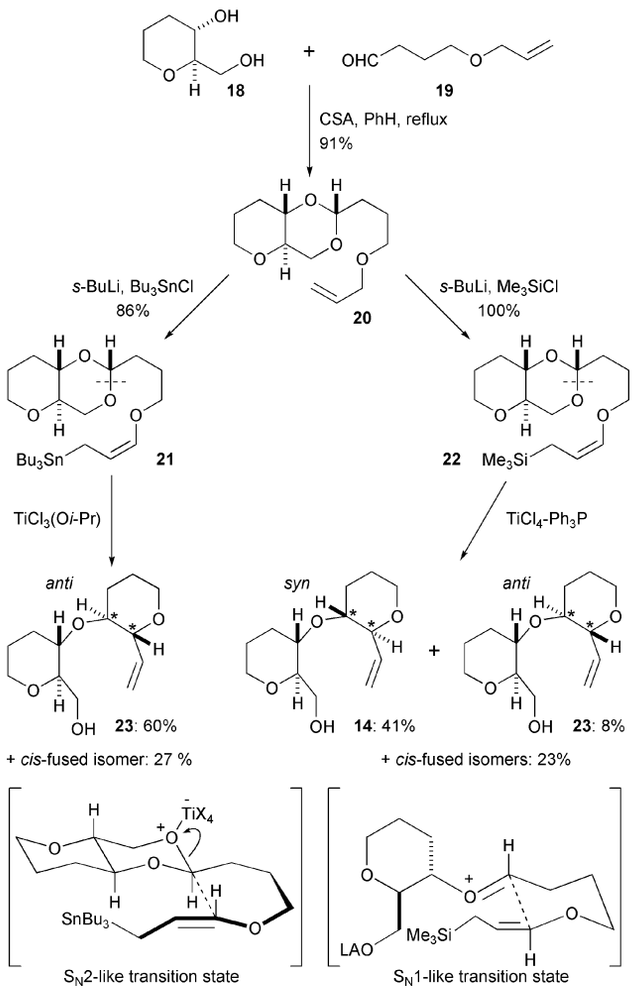
Fig. 3 Intramolecular cyclization of γ-alkoxyallylmetal with acetal developed by Yamamoto.[21]

In studies toward the total synthesis of ciguatoxin, Tachibana and co-workers developed a method for the synthesis of 6/9/6-tricyclic system in 1997.[23] Their synthesis started with coupling between diol **18** and aldehyde **19** by acetalization (Scheme 2). Lithiation of allylic ether **20** with *s*-BuLi and *in situ* trapping of the resulting anion with either *n*-Bu_3SnCl or Me_3SiCl gave γ-alkoxyallylmetal **21** or **22**. Interestingly, Lewis acids cleaved the same less-hindered C–O acetal bonds of **21** and **22**, but generated different stereoisomers. Whereas cyclization of allylstannane **21** exclusively formed the undesired *trans*/*anti*/*trans*-isomer **23**, allylsilane **22** led to selective formation of the desired *trans*/*syn*/*trans*-isomer **14**.

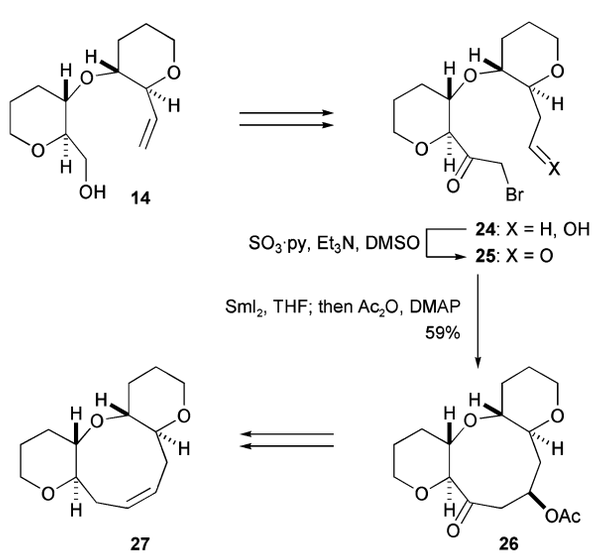
The mechanistic rationale for these cyclizations is shown in Scheme 2. The reactive allylstannane in **21** would react in an S_N2-like manner; cleavage of the C–O bond of acetal would take place simultaneously with the C–C bond formation between the γ-allylic and acetal carbons. Therefore, cyclization would selectively produce the undesired **23**. On the other hand, it was assumed that alternative use of the significantly less reactive γ-alkoxyallylsilane **22**[24] would enable the reaction to take place *via* an S_N1-like transition state. In this pathway, the memory of chirality of the acetal carbon would disappear to give an oxonium cation, which would react with allylsilane in order to minimize unfavorable steric interactions to afford the desired isomer **14**.

Compound **14** was then converted to α-bromoketone **25** (Scheme 3), which was smoothly cyclized to 9-membered ring **26** by the action of SmI_2.[25] Thus, *O*-linked oxacycle **25** proved to be suitable for medium-sized ether ring formation as indicated by the molecular mechanics in Fig. 2. Finally, the targeted 6/9/6-ring system **27** was synthesized from **26** in several functional group manipulations.

Sasaki and Tachibana exploited this strategy for the synthesis of decacyclic ciguatoxin model **34** in 1998 (Scheme 4).[26] Their preliminary model experiments revealed that the seven-membered acetal was more reactive toward intramolecular nucleophilic addition than the six-membered counterpart.[27] Thus, 1,4-diol **29** was selected as a structural fragment in anti-

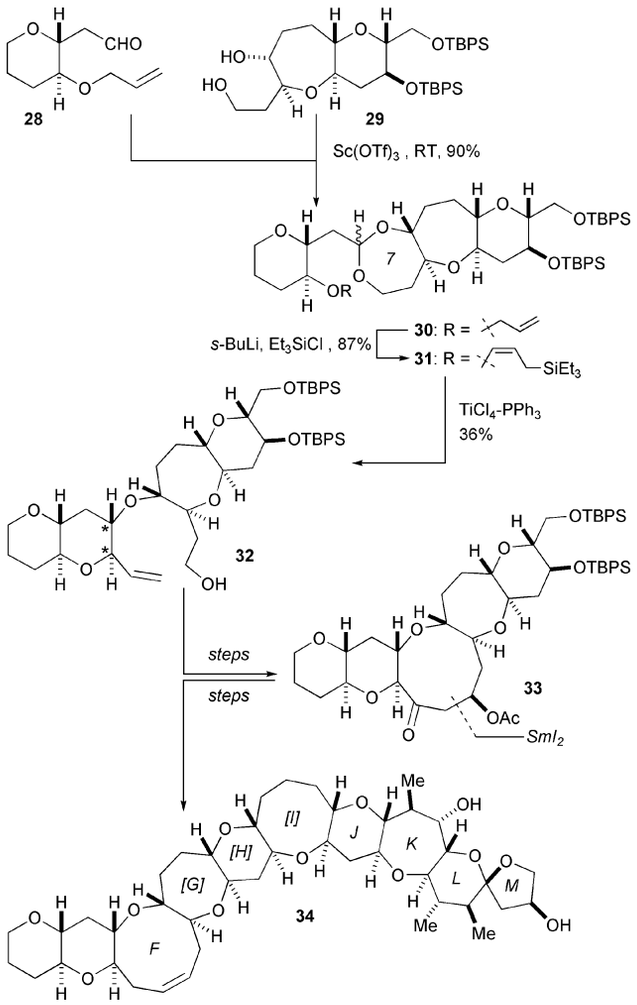


Scheme 2 Tachibana's construction of *O*-linked oxacycle through γ-alkoxyallylmetal-acetal cyclization (1997).[23]



Scheme 3 Tachibana's synthesis of 6/9/6-tricyclic ring system (1997).[23]

cipation of the high yield and diastereoselectivity of Lewis acid-mediated cyclization. Acetal formation between β-alkoxy aldehyde **28** and 1,4-diol **29** was realized in the presence of a catalytic amount of $Sc(OTf)_3$.[28] The reaction took place at room temperature and produced seven-membered acetal **30** in 90% yield. Lithiation of **30** followed by treatment with Et_3SiCl gave γ-alkoxyallylsilane **31**. Upon treatment of **31** with $TiCl_4$–PPh_3, the desired *O*-linked **32** was obtained as a major product in 36% yield, together with three other stereoisomers. Similarly



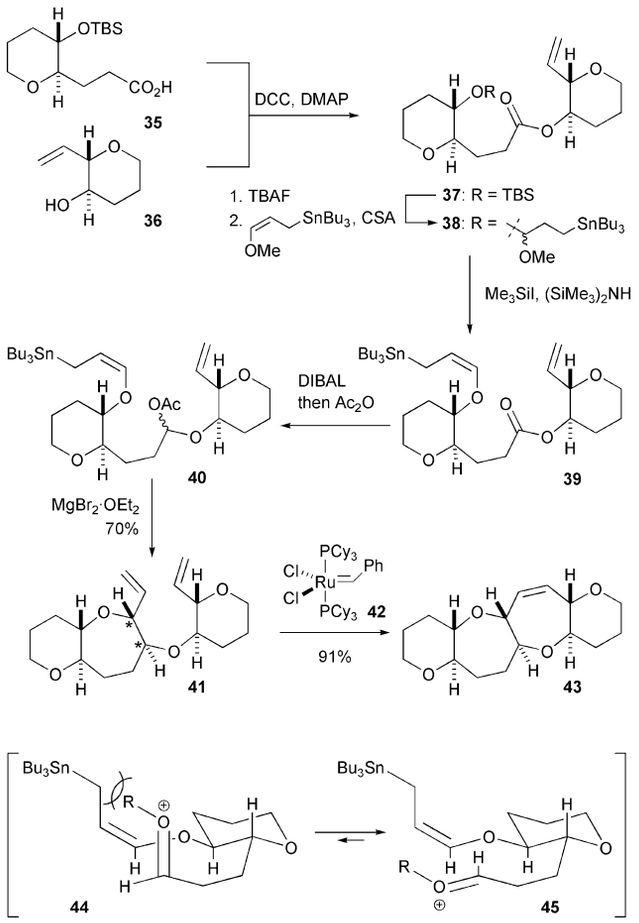
Scheme 4 Synthesis of decacyclic ciguatoxin model by Sasaki and Tachibana (1998).[26]

to the synthesis of the previous compound, **32** was converted to 6/9/7/6-ring system **33**, which was further converted to decacyclic ciguatoxin model **34** through coupling with the JKLM ring fragment. 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 stereochemistries.

Nucleophilic addition of γ-alkoxyallylstannane to α-acetoxy ether

In 2001, Kadota and Yamamoto developed a stereoselective approach to polycyclic ring systems using the intramolecular cyclization of γ-alkoxyallylstannanes to α-acetoxy ethers (Scheme 5).[29] Carboxylic acid **35** and alcohol **36** were coupled through esterification to afford **37**. After deprotection of the silyloxy group of **37**, the alcohol was converted to allylstannane **39** *via* **38**. α-Acetoxy ether **40** was then prepared from ester **39** according to Rychnovsky protocol:[30] (i) reduction of **39** with DIBAL and (ii) *in situ* trapping of hemiacetal with acetic anhydride. Treatment of mixed acetal **40** with $MgBr_2{\cdot}OEt_2$ resulted in the intramolecular cyclization to give seven-membered ring **41** as an exclusive isomer (>95 : 5), which was transformed to 6/7/7/6-ring system **43** by the ring-closing olefin metathesis reaction (RCM).[31]

The stereochemical outcome of the reaction of allylstannane **40** did not reflect the chirality at the α-acetoxy group, presumably because of its facile formation of the oxonium cation in



Scheme 5 Yamamoto's intramolecular cyclization of γ-alkoxyallylstannane with α-acetoxy ether (2001).[29]

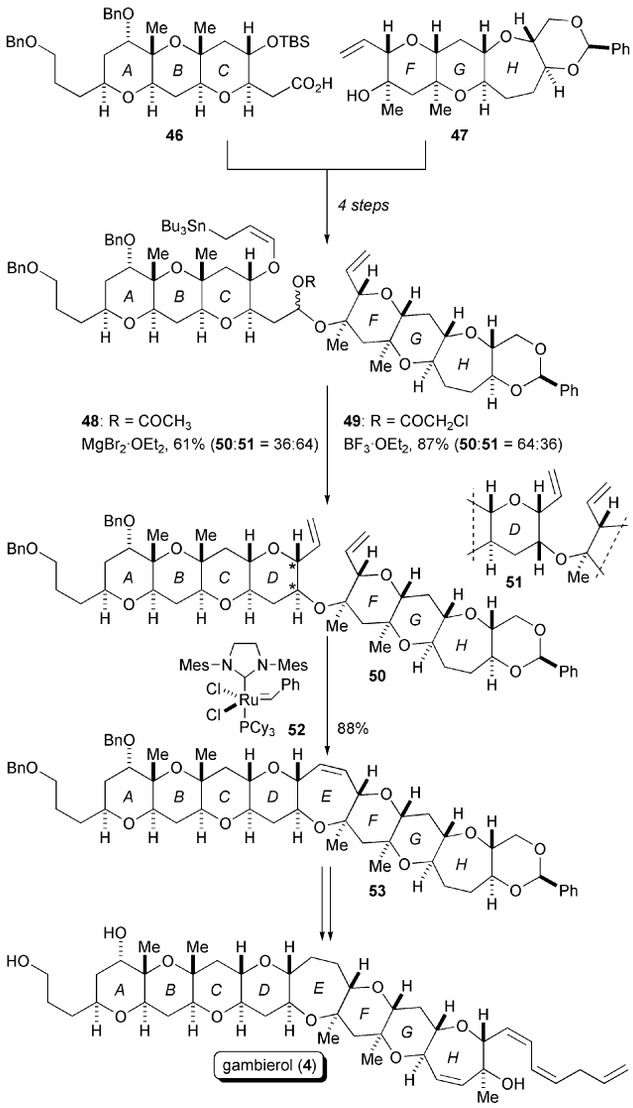
contrast to cyclic acetal **21** in Scheme 2. Thus, the observed stereoselectivity can be explained by the S_N1-like transition state model. The allylic stannane moiety is oriented to a pseudo-equatorial position in order to avoid 1,3-diaxial repulsion, and the oxonium cation moiety bearing a substituted tetrahydropyranyl group R also prefers a pseudo-equatorial position as depicted by the transition state structure **45**, which leads to **41**.

Kadota *et al.* accomplished the highly convergent total synthesis of gambierol (**4**) by exploiting newly developed technology (Scheme 6).[18] ABC-segment **46** and FGH segment **47** were condensed, and then a series of reactions including desilylation, attachment of allylic stannane moiety and subsequent Rychnovsky protocol gave α-acetoxy ether **48**. In contrast to the model experiments, treatment of **48** with $MgBr_2{\cdot}OEt_2$ afforded the undesired stereoisomer **51** as the major component. Interestingly, $BF_3{\cdot}Et_2O$-mediated cyclization of α-chloroacetyl **49** led to the selective formation of **50**. This improved diastereoselectivity is presumably due to more facile formation of the oxonium cation intermediate from the chloroacetyl group than from the acetyl group.

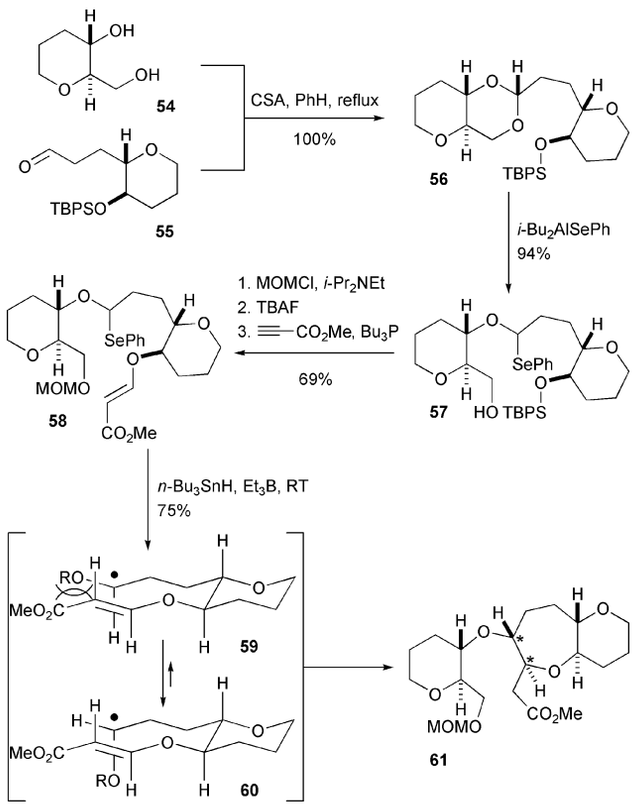
The obtained diene **50** was subjected to RCM, leading to octacyclic gambierol skeleton **53**. Finally, **53** was successfully converted to the natural product **4** through functional group modification, side chain introduction and final deprotection. It should be emphasized that the use of an esterification reaction for segment coupling and the seven-step construction of the two fused ring system makes the present methodology highly efficient and practical.

Intramolecular radical cyclization from mixed-acetal

In 1998, Sasaki and Tachibana reported the convergent synthesis of *O*-linked oxepane based on the intramolecular radical



Scheme 6 Total synthesis of gambierol by Kadota *et al.* (2002).[18]



Scheme 7 Intramolecular radical cyclization developed by Sasaki (1998).[32]

reaction (Scheme 7).[32] Acetalization between **54** and **55** led to six-membered acetal **56**, which was converted to *O*,*Se*-acetal **57** through the regioselective cleavage of the less hindered C–O bond using *i*-$Bu_2AlSePh$.[33] Protection of the primary hydroxyl group in **57**, subsequent removal of the silyl group and attachment of β-(*E*)-alkoxyacrylate afforded **58**. Treatment of **58** with *n*-Bu_3SnH in the presence of Et_3B[34] resulted in formation of the desired *O*-linked oxepane **61** as a single diastereomer in high yield.

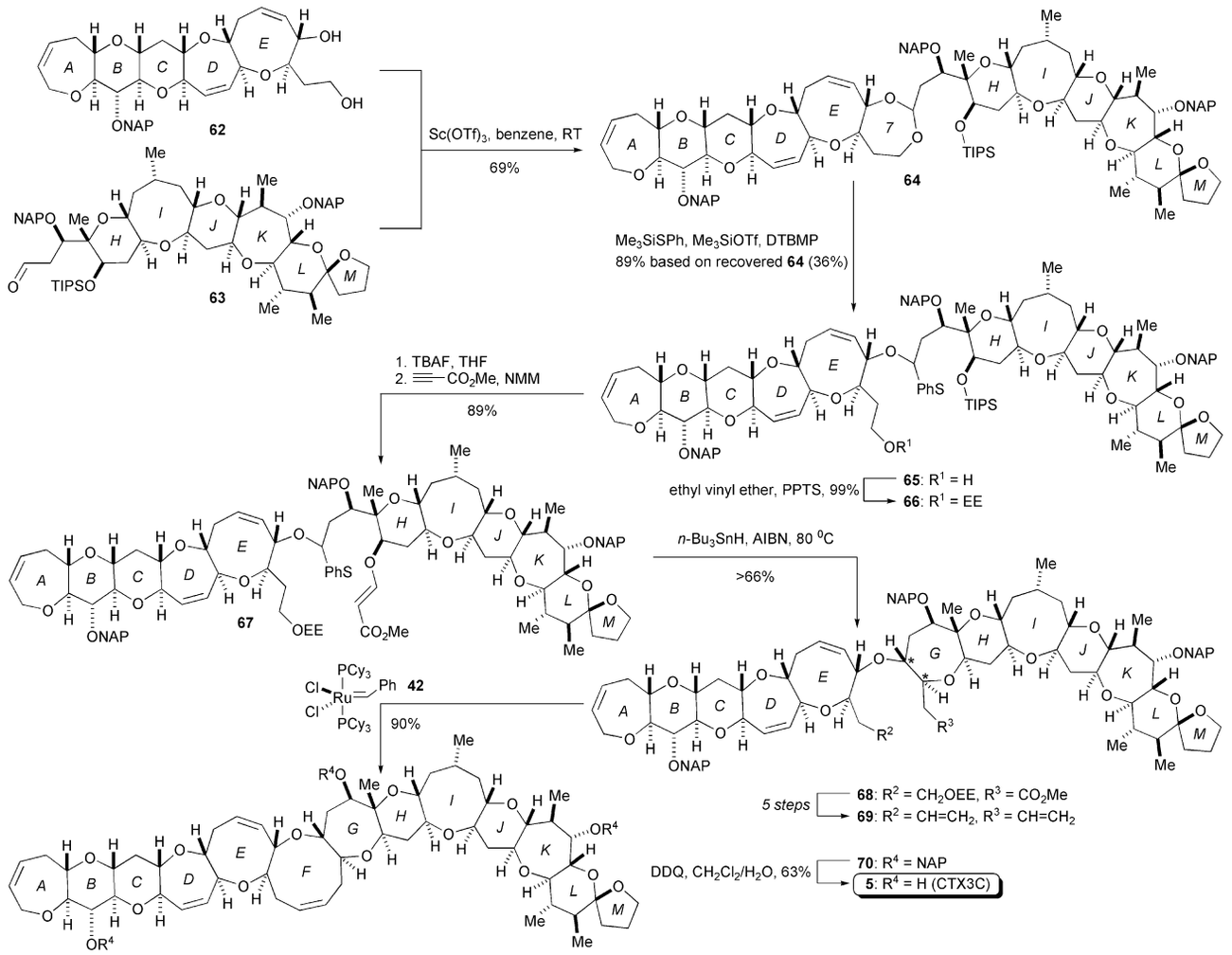
The stereoselectivity of the cyclization is explained as indicated in Scheme 7. Initially, the stereochemical information of the acetal carbon was lost upon formation of the radical intermediate. The β-alkoxyacrylate favored the extended s-*trans*- over s-*cis*-conformation in order to avoid the 1,3-diaxial-like interactions.[35] Furthermore, the steric interactions between the bulky alkoxy group and the s-*trans*-alkoxyacrylate of the pseudo-equatorial **59** resulted in preference for the pseudo-axial **60**, from which the desired isomer **61** 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, which culminated in their total synthesis of ciguatoxin CTX3C (**5**, Scheme 8).[15,16] $Sc(OTf)_3$-promoted coupling of diol **62** and aldehyde **63** delivered seven-membered acetal **64**. 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.[36] Indeed, the acetal cleavage reaction of **64** was realized using Me_3SiOTf and Me_3SiSPh,[37] which led to *O*,*S*-acetal **65** without affecting the potentially reactive C49-spiroacetal. After three synthetic steps from **65**, β-alkoxyacrylate **67** was then subjected to radical cyclization using *n*-Bu_3SnH and 2,2′-azobisisobutyronitrile (AIBN), giving rise to the desired oxepane **68** as the sole isomer. For this step, the generated C27-radical added to the α,β-unsaturated ester in a completely stereo- and chemoselective manner. To prepare for cyclization of the last remaining F-ring, the carbon chains of **68** were transformed to the terminal olefins of **69** in six steps. The RCM reaction of **69** using Grubbs catalyst **42** provided the protected CTX3C **70**, which was converted to the target CTX3C (**5**) through global deprotection. Hence, this total synthesis of CTX3C proved the power and reliability of the *O*,*S*-acetal strategy to build complex polyether structures.

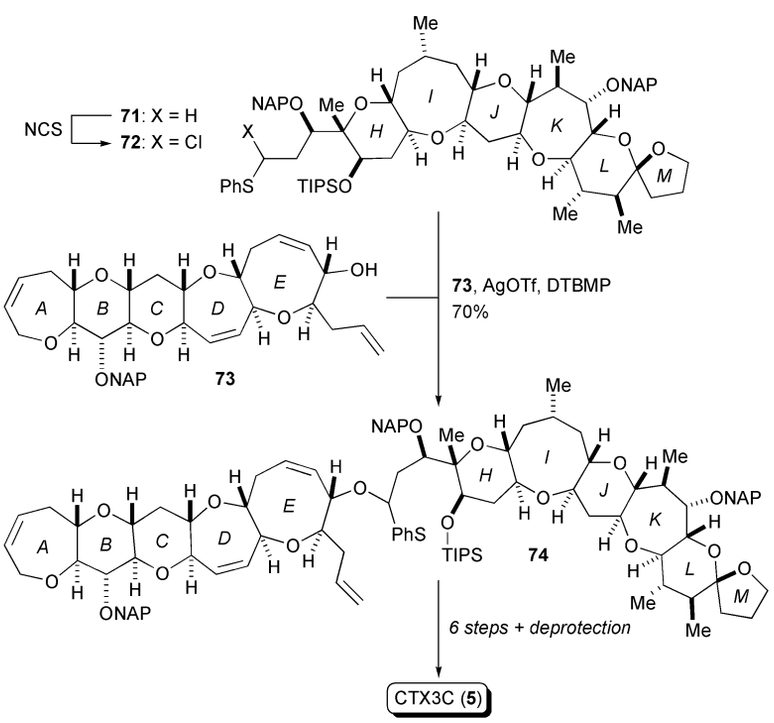
In 2004, Inoue and Hirama reported their second-generation total synthesis of CTX3C (**5**), which is more concise, efficient and applicable (Scheme 9).[38] The alternative synthetic strategy relied on the direct construction of the key *O*,*S*-acetal **74** under mild conditions.[39] The α-chloride was installed on to right wing sulfide **71** using NCS, leading to α-chlorosulfide **72**. The obtained **72** and left wing alcohol **73** were coupled by the action of AgOTf in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) and 4 Å MS.[40] In this way, *O*,*S*-acetal **73** was obtained in high yield, thus accomplishing direct construction of the key intermediate. The F- and G-rings were then constructed from **73** similarly to the first-generation synthesis, which resulted in their second-generation total synthesis of **5**. Importantly, halophilic silver salt, used in the coupling, is highly chemoselective, and allows the use of various functional groups, and this method installed two rings in only eight synthetic transformations.

Conclusion and perspectives

As a result of rapid progress over the last five years, convergent strategies utilizing acetal-linked intermediates have been improved and polished up to a satisfactory level in terms of



Scheme 8 Total synthesis of ciguatoxin CTX3C by Hirama (2001 and 2002).[15,16]



Scheme 9 Second generation total synthesis of CTX3C by Inoue and Hirama (2004).[38]

overall stereoselectivity, efficiency and practicability. A number of the developed synthetic technologies are at the cutting edge of contemporary organic chemistry, particularly the various methods used to prepare key acetal-linked intermediates, the subsequent highly stereoselective constructions of the ether rings, and the RCM reaction to build medium-sized ethers from *O*-linked oxacycles. Importantly, these reaction sequences only require 7–8 synthetic transformations to construct two new

rings, and proved to be highly applicable to complex polycyclic structures, such as gambierol and ciguatoxin CTX3C. It is anticipated that the materials generated through these total syntheses will help to better understand their detailed biological mechanisms of action.

However, *de novo* chemical synthesis of polycyclic ethers has not yet become a routine preparative method to obtain natural products and their analogs. The existing total syntheses typically require more than 100 total steps. Although such syntheses represent impressive contributions to organic chemistry, development of even more practical and general synthetic routes remains a key challenge for the future.

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