/ Review

Development of New Synthetic Methods Using Oxiranyl Anions and Application in the Syntheses of Polycyclic Ether Marine Natural Products

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This review reports on the development of new synthetic methods using oxiranyl anions and their application to the synthesis of polycyclic ether marine natural products. Novel iterative and convergent methods for large, complex polycyclic ether structures have been devised. In these, the reactions of sulfonyl-stabilized oxiranyl anions were employed to construct *trans*-fused polyether ring systems, along with 6-*endo* cyclization and ring expansion reactions. Total syntheses of polycyclic ether marine toxins, viz. hemibrevetoxin B, gambierol, and gymnocin-A, were achieved based on the oxiranyl anion strategy developed.

Key words oxiranyl anion; polycyclic ether; total synthesis; hemibrevetoxin B; gambierol; gymnocin-A

1. Introduction

Polycyclic ether marine toxins are the secondary metabolites produced by toxic red tide dinoflagellates, which are associated with massive fish kills and human food poisoning.¹⁾ Since the first discovery of brevetoxin B in 1981,²⁾ a number of polycyclic ethers have been isolated from toxic dinoflagellates (Fig. 1). For more than three decades, many chemists have been interested in their potent biological activity such as neurotoxicity and cytotoxicity as well as their characteristic molecular structures involving five- to nine-membered ether rings fused to each other.³⁾

One of the intriguing aspects of these marine toxins is that their polycyclic ether frameworks are constructed in a *trans-syn-trans* manner by an intramolecular epoxide-opening cascade reaction, which is considered to be a key step in their biosynthesis (Chart 1). This hypothesis was first introduced by Nakanishi for brevetoxin B,^{4–6)} and it soon became a topic of discussion because the epoxide-opening cascade is classified as a disfavored *endo* process by Baldwin's rules of ring closure.⁷⁾ The unprecedented structures biosynthesized by the *endo*-selective epoxide-opening cascade as well as their strong biological activities have prompted synthetic chemists to develop efficient new strategies for the synthesis of these marine toxins.^{8–13)}

Over the last two decades, we have been investigating the reaction of oxiranyl anions stabilized by the sulfonyl group. This review summarizes the new synthetic methods developed based on the oxiranyl anion strategy and their application to the synthesis of bioactive polycyclic ether marine natural products.

2. Bioinspired Retrosynthetic Analysis of Polycyclic Ethers

Our strategy is based on the biosynthesis hypothesis of polycyclic ethers. The regio- and stereoselective 6-*endo* mode of ring closure of epoxide **II** may be an attractive approach for polytetrahydropyran **I** (Chart 2), because it is challenging to carry out a reaction that contradicts Baldwin's rule. The next problem is how to synthesize the polyepoxide precursor **II**. In a proposal for the biosynthesis of brevetoxin B, the building block of the tetrahydropyran rings was hypothesized to be a three-carbon unit derived from succinate or its equivalent.⁵⁾ This biosynthetic study inspired us to mimic nature by using the coupling reaction of the oxiranyl anion **III** as a three-carbon synthon. Considering the potential for further chemical transformation, a sulfonyl-stabilized oxiranyl anion of epoxy sulfone **IV** might serve as a synthetic equivalent of **III**. Based on this idea, we have developed a general iterative strategy for constructing a polytetrahydropyran ring system by combining the alkylation of an oxiranyl anion and the subsequent 6-*endo* cyclization as key processes.

3. Reaction of Sulfonyl-Stabilized Oxiranyl Anions

Epoxides are widely recognized as versatile intermediates in organic chemistry because of their enhanced reactivity due to the high degree of ring strain. The reactions of epoxides, which are mostly attributable to their electrophilic nature, involve cleavage of the three-membered ring and include a wide range of nucleophilic ring openings and acid- or base-catalyzed rearrangements. On the other hand, the reaction of an epoxide as a nucleophile, *i.e.*, an oxiranyl anion, is less common and undoubtedly one of the most fascinating aspects of epoxide chemistry (Chart 3). The chemistry of oxiranyl anions was first reported by Eisch and Galle in 1976, where

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Fig. 1. Structures of Representative Marine Natural Products with Polycyclic Ether Structures

an α -lithiated silyl epoxide could be generated and trapped with an electrophile to give a more substituted epoxide.^{14–16} In spite of their pioneering work, however, oxiranyl anions have received little attention from synthetic chemists, mainly because the anions formed were considered to be very unstable and difficult to handle under severe experimental conditions.

The synthetic utility of oxiranyl anions as a nucleophile could be enhanced by introducing an anion-stabilizing group on the lithiated carbon, which enables easier anion formation and prolongs the lifetime of the very fleeting anion. These highly reactive intermediates are particularly useful from the synthetic point of view, and the generation and reactivity of the α -lithiated epoxides with various types of electrophiles have been investigated, as well as their configurational stability and the stereochemistry of the reactions. Previous studies on this topic were comprehensively reviewed by Satoh¹⁷ in

1996, by Mori¹⁸ in 1997, and, more recently, by Hodgson *et al.*,^{19–21} Chemla and Vrancken,²² and the Florio group.²³ However, the synthetic potential of oxiranyl anions, especially in natural product synthesis, has not been explored.

Initial studies on α -lithiated epoxy sulfones were performed by Jackson's group between the late 1980s and early 1990s.^{24–28} We reinvestigated the reaction of the oxiranyl anion of epoxy sulfones because the strong electron-withdrawing nature of the sulfonyl group predicts that it may be a good anion-stabilizing group as well as a good leaving group after reaction with electrophiles, where the sulfonyl group needs to be removed for further elaboration into target molecules.

We first examined the alkylation reaction of the sulfonyl-stabilized oxiranyl anion **2**, generated from the epoxy sulfone **1** with alkyl iodides and alkyl triflates²⁹ (Table 1). The reaction of the oxiranyl anion with electrophiles under normal

Biography

Yuji Mori was born in Gifu, Japan, in 1950. He received his B.Sc. degree from Gifu Pharmaceutical University in 1973 and Ph.D. degree from Kyoto University in 1978. He was appointed as Assistant Professor of Meijo University in 1978. From 1983 to 1985, he worked with Professor Clark Still as a visiting researcher at Columbia University in New York, U.S.A. He was promoted to Associate Professor in 1993 and then to Professor in 2000. He received the Pharmaceutical Society of Japan Award for Young Scientist in 1993 and the Pharmaceutical Society of Japan Award in 2018. He has been the Dean of the Graduate School of Environmental and Human Sciences (2002–2005, 2009–2011, and 2015–2017) and the Director of the Research Institute of Meijo University (2011–2015). His research interests are in the field of organic synthesis, in particular in the development of new synthetic methods and total synthesis of biologically and structurally interesting natural products.

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Chart 1. Hypothetical Biosynthesis of Brevetoxin B via an Epoxide-Opening Cascade

Chart 2. Synthesis Strategy of Polytetrahydropyran Based on Oxiranyl Anion Coupling and 6-Endo Epoxide Opening

quenching conditions (method A) formed the desired products in moderate yields. In order to minimize the decomposition of the unstable oxiranyl anion during the addition of an electrophile, alkylation with alkyl triflate was then performed under *in situ* quenching conditions (method B). Thus, treating a mixture of an epoxy sulfone and a triflate with *n*-BuLi in tetrahydrofuran (THF) in the presence of hexamethylphosphoric triamide (HMPA) at -100°C afforded the coupling product with very high yield.

4. Iterative Synthesis of Polytetrahydropyran Ring Systems by Using the Oxiranyl Anion Strategy

Trans-fused tetrahydropyran rings are the most frequently

Chart 3. Reaction of Epoxides

Table 1. Alkylation of Sulfonyl-Stabilized Oxiranyl Anions with Alkyl Iodides and Triflates

1	2	3		
epoxy sulfone ^a	electrophile ^b	product ^c	method ^d	yield
			A	50%
4	TBSO-alkyl iodide		A	47%
4			A B	84% 98%
5			A B	28% 90%
6			B	82%

^aRacemic epoxy sulfone was used. ^bOptically active compound was used. ^cProduct is a 1:1 mixture of diastereomers. ^dA: normal quenching method. B: *in situ* quenching method.

encountered cyclic units and they form the rigid backbone in polycyclic ether marine toxins. The synthesis of such a ring system is receiving a great deal of attention, and various approaches have been explored with an increasing emphasis on cascade and iterative strategies.^{8,13,30,31} Our method for constructing a tetrahydropyran ring is based on 6-*endo* cyclization (Chart 4). Alkylation of oxiranyl lithium **12** with a triflate would give epoxy sulfone **13**. Theoretically, **13** could undergo ring closure via 5-*exo* or 6-*endo* cyclization, leading to a THF or a tetrahydropyran ring, respectively. However, the strong electron-withdrawing nature of the sulfonyl group would prevent cleavage of the adjacent C–O bond in an acid-catalyzed epoxy ring-opening process and consequently induce 6-*endo* cyclization to generate tetrahydropyranyl ketone **14** after elimination of the sulfonyl group. Conceptually, this is a complementary approach to that of the π -orbital-assisted 6-*endo* cyclization developed by Nicolaou *et al.*³²

We attempted 6-*endo* cyclization of epoxy sulfones **15a** and

15b and **16a** and **16b**, which were obtained by separation of the diastereoisomers of **9** and **10** followed by the removal of the *tert*-butyldimethylsilyl (TBS) group (Chart 5). Cyclization of the *trans*-isomers **15a** and **15b** and *cis*-isomer **16a** did not occur under a wide range of conditions, whereas only the *cis*-isomer **16b** afforded a 6-*endo* cyclization product **18** upon treatment with *p*-toluenesulfonic acid (TsOH) in 89%

Chart 4. General Strategy for Constructing a Tetrahydropyran Ring by 6-*Endo* Cyclization

Chart 5. 6-*Endo* and Formal 6-*Endo* Cyclization of Epoxy Sulfones

yield. As expected, the sulfonyl group on the epoxide **16b** favors the 6-*endo* mode pathway to yield tetrahydropyranone **18**. The reason for this striking difference in cyclization is that only the *cis*-isomer **16b** can adopt a chair-like transition state with no serious steric interactions compared with other isomers. The attempted cyclization of **15a**, **15b**, and **16a** using the Lewis acid $\text{MgBr}_2 \cdot \text{OEt}_2$ afforded only the bromoketone **17** rather than the expected cyclic product. Fortunately, the exposure of **17** to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) led to clean cyclization to give the desired product **18** as an 85:15 separable mixture of diastereomers.³³ This overall transformation from **15a**, **15b**, and **16a** to **18** is a formal 6-*endo* cyclization and it offers a practical method to synthesize *trans*-fused tetrahydropyrans using racemic epoxy sulfones, which are easily prepared by the epoxidation of vinyl sulfones.

The success of 6-*endo* cyclization of the epoxy sulfone **16b** led us to develop an iterative method for constructing polytetrahydropyrans using the optically active epoxy sulfone **21**³⁴ (Chart 6). The synthesis started from the diol **19**, which was converted to the triflate **20** by selective triflation of the primary alcohol and silylation of the secondary alcohol in a one-pot procedure. Treatment of the optically active epoxy sulfone **21** with *n*-BuLi in the presence of triflate **20** at -100°C led to smooth oxiranyl anion formation and alkylation to give the epoxy sulfone **22** in high yield. The exposure of **22** to *p*-TsOH afforded bicyclic ketone **24** by 6-*endo* cyclization of hydroxy epoxy sulfone **23**. Reduction followed by desilylation provided the bicyclic diol **25**, from which point the original steps (**19** to **25**) can be repeated. The second cycle of the five-step sequence afforded the tricyclic diol **29** in 52% overall yield. The above sequence was reiterated to construct the all-*trans*-*syn*-*trans* tetracyclic polyether **32** with 54% overall yield for the four steps. The advantages of using the sulfonyl-stabilized oxiranyl anion are the high efficiency of C–C bond formation and the promotion of 6-*endo* cyclization.

As an extension of the above oxiranyl anion strategy, we further investigated the synthesis of tetrahydropyran deriva-

Chart 6. Iterative Synthesis of Polytetrahydropyrans Based on the Oxiranyl Anion Strategy

tives **33–35** containing an angular methyl group adjacent to the ring oxygen (Chart 7). These ring systems are often encountered as structural units in polycyclic ether marine toxins. An attractive feature of our approach is that the suitable precursors **39a–c** for 6-*endo* cyclization could be easily accessed by the combinations of triflates **36** and **37** and epoxy sulfones **21** and **38**. Reaction conditions for the 6-*endo* cyclization of **39a–c** depend on the nature of the alcohol and epoxide moieties present in the substrate. For example, the 6-*endo* cyclization of **39c** between a sterically hindered tertiary alcohol and a more reactive methylated epoxide was problematic because of 1,2-migration of the sulfonyl group to an α -sulfonyl ketone. This problem was solved by trapping the eliminating sulfonic acid with $\text{Ti}(\text{TFA})_3$ as an insoluble salt before migration occurs, and **40c** was obtained in good yield.^{35,36)}

5. Synthesis of Seven-Membered Ether Ring Systems by Ring Expansion

The keto tetrahydropyrans synthesized *via* oxiranyl anion coupling and the 6-*endo* cyclization strategy are amenable to single-carbon homologation by the ring expansion reaction to produce seven-membered ether rings. Reaction of the conformationally fixed keto tetrahydropyran **41** with diazomethane and substituted diazomethanes was therefore examined (Chart 8). The reaction of trimethylsilyldiazomethane (TMSCHN₂)³⁷⁾ in the presence of BF₃·OEt₂ proved to be superior to diazomethane in forming the desired seven-membered ketone **42** as a major product, and the process was explained by an equatorial attack of TMSCHN₂ on the ketone. Density functional theory (DFT) calculations indicated that an equatorial attack is more favorable by 3.2 kcal/mol than the axial attack.³⁸⁾ The regioselectivity of the homologation is explained based on the steric interaction between the silyl group of the diazo compound and the α -substituent of the starting ketone.

The combination of TMSCHN₂ and BF₃·OEt₂ has been applied to the synthesis of tricyclic 6-7-7 and 6-7-6 fused ring systems³⁹⁾ (Chart 9). The bicyclic ketone **24** underwent smooth ring expansion to produce the bicyclic seven-membered ketone

Chart 7. Synthesis of Angular Methyl-Substituted Tetrahydropyrans by 6-*Endo* Cyclization

Chart 8. Ring Expansion of **41** with Silylated Diazomethanes

Chart 9. Synthesis of Polycyclic Ethers Containing Seven-Membered Rings

Chart 10. Retrosynthetic Analysis of Hemibrevetoxin B

Chart 11. Formal Total Synthesis of Hemibrevetoxin B

44 in good yield. In an effort to extend the oxiranyl anion strategy to oxepane-containing polyether systems, the keto oxepane 44 was elaborated to triflates 46a and 46b. Thus, the stereocontrolled reduction of ketone 44 to 45a was accomplished in two steps: hydroxy-directed reduction with $\text{Me}_4\text{NBH}(\text{OAc})_3$ after removal of the *t*-butyldiphenylsilyl (TBDPS) group. In contrast, the stereoselective synthesis of the tertiary alcohol 45b required four-step elaboration: 1) methylation with Tebbe reagent; 2) epoxidation with *m*-chloroperoxybenzoic acid (*m*-CPBA); 3) reduction with LiEt_3BH ; and 4) desilylation with tetrabutylammonium fluoride (TBAF).³⁵ Subsequent one-pot *O*-triflation and *O*-

silylation of the diols gave triflates 46a and 46b. Reactions of 46a and 46b with oxiranyllithiums generated from 21 and 38 followed by the exposure to TsOH and $\text{BF}_3 \cdot \text{OEt}_2$ afforded the 6-7-6 tricyclic ketones 48 and 52, respectively. Further homologation of the ketone 48 with TMSCHN_2 led to the 6-7-7 fused ring system 49. A limitation of this approach is the inability of ring expansion for ketone 52, presumably due to severe steric congestion of the 1,3-diaxial methyl groups.⁴⁰ These results demonstrate the synthetic utility of the oxiranyl anion strategy combined with the ring expansion reaction in the synthesis of polycyclic ether natural products.

Chart 12. Retrosynthesis of Gambierol

Chart 13. Synthesis of the ABCD Ring System of Gambierol

6. Synthesis of Polycyclic Ether Marine Natural Products by an Iterative Approach

6.1. Formal Total Synthesis of Hemibrevetoxin B The Florida red tide dinoflagellate *Karenia brevis* produces a group of potent neurotoxic brevetoxins, which are linked to marine mortalities and human illness by acting to open voltage-gated sodium ion channels in cell membranes.⁴¹⁾ Hemibrevetoxin B (**53**), isolated from the cultured cell of *K. brevis* by Shimizu and Prasad in 1989,⁴²⁾ causes the same characteristic rounding of cultured mouse neuroblastoma cells as brevetoxins A and B and shows cytotoxicity at a concentration of 5 μmol . Its smallest 6-6-7-7 tetracyclic structure among marine polycyclic ethers makes **53** an ideal total synthetic target to test the applicability and scope of newly developed methodologies.^{43–51)}

Retrosynthetic analysis of **53** illustrates our oxiranyl anion

approach, where a hypothetical polyepoxide precursor **54** was disconnected into the A ring unit **55** and the three oxiranyl anion synthons **56**, **57**, and **58** for which the synthetic equivalents are the epoxy sulfones **38**, **21**, and **59**, respectively, as shown in Chart 10.

Tri-*O*-acetyl-D-glucal was used as the chiral pool material for the synthesis of the A ring triflate **55** (Chart 11). This triflate and the epoxy sulfone **38** were united by the oxiranyl anion method to afford the product **60**. The exposure of **60** to TsOH led to 6-*endo* epoxide opening to give the bicyclic ketone **61**, which was converted into the aldehyde **62** in five steps. The reaction of the oxiranyl anion generated from **21** with the aldehyde by an *in situ* trapping method afforded the epoxy alcohol **63** in good yield. Treatment of **63** with $\text{BF}_3 \cdot \text{OEt}_2$ caused 6-*endo* cyclization to provide a tricyclic

Chart 14. Synthesis of the ABCDEFG Ring System of Gambierol

α -hydroxy ketone, which was further transformed into the ketone **64** by reductive removal of the hydroxyl group with SmI₂. This ketone is the substrate for ring expansion using TMSCHN₂ that produced the ABC ring system **65**. The third nucleophilic substitution of triflate **66** by the oxiranyl anion of **59** followed by 6-*endo* cyclization proceeded smoothly to form ketone **68** in good yield, which required the second ring expansion and methylation to reach tetracyclic core **69** of the target molecule. The protecting group manipulation furnished the advanced intermediate **70**, which was previously elaborated into hemibrevetoxin B (**53**) by the Yamamoto group,⁴⁵⁾ thus completing the formal total synthesis of hemibrevetoxin B.^{52,53)} This is the first example of the successful application of unstable oxiranyl anions in complex natural product synthesis.

6.2. Total Synthesis of Gambierol Gambierol (**71**) was isolated in 1993 as a neurotoxin from the cultured cells of the ciguatera-causative dinoflagellate *Gambierdiscus toxicus*.^{54,55)} The octacyclic toxin exhibits potent toxicity in mice at LD₅₀ = 50 μ g/kg (intraperitoneally (i.p.)), and its symptoms in mice resemble those shown for ciguatoxins, indicating that gambierol is also responsible for ciguatera seafood poisoning.^{56,57)} The unique structure and biological properties as well as the scarce amount of gambierol from natural sources make it an attractive target for total synthesis.^{58–61)} Our synthesis

proceeded through the advanced intermediate **72** and the two epoxy sulfones **73** and **21**, which were coupled iteratively and elaborated to produce gambierol (Chart 12).

The construction of the ABCD fragment **72** commenced with the oxiranyl anion coupling of racemic *trans*-epoxy sulfone **75** with the monocyclic D ring triflate **74** (Chart 13). The treatment of **76** with TsOH followed by MgBr₂·OEt₂ led to the formation of bromoketone **77**, which underwent intramolecular etherification upon exposure to DBU to form the C ring ketone **78** with a 94:6 diastereoselectivity. This method for forming the tetrahydropyran ring has a great advantage that the stereochemistry of bromoketone **77** and in turn that of epoxy sulfone **75** are irrelevant, because the initial cyclization products undergo facile DBU-catalyzed equilibration to afford a thermodynamically more stable isomer possessing an equatorial side chain.³³⁾ Construction of the B ring having 1,3-diaxial methyl groups proceeded with complete stereoselectivity through a six-step sequence involving methylation of **78** with Et₃Al and Nicolaou's 6-*endo* hydroxy epoxide opening³²⁾ of **81** to form the tricyclic system **82**. The homoallylic hydroxy-directed epoxidation of **82** to **83**, followed by the addition of a dithioacetal unit and removal of the dithioacetal group, furnished the dihydroxy ketone **85**, which was converted into the ABCD fragment **72** by reductive etherification followed by protecting group adjustments.⁶²⁾

Chart 15. Completion of the Total Synthesis of Gambierol

Construction of the right half ring system onto the ABCD fragment was achieved by using our iterative tetrahydropyran synthesis (Chart 14). The first coupling of the optically active epoxy sulfone **73** with the left half tetracyclic triflate **72**, followed by the BF_3 -promoted 6-*endo* cyclization of **87** and ring expansion with TMSCHN_2 , afforded the pentacyclic ketone **89**. A four-step sequence was employed to transform the ketone into the vinyl ether **90**, which was subjected to SmI_2 -induced reductive cyclization⁶³ to form the F ring **91** having 1,3-diaxial methyl groups. The ester **91** was further converted into triflate **94** through a sequence involving diisobutylaluminum hydride (DIBALH) reduction of ester, dehydration using the Grieco protocol,⁶⁴ OsO_4 - NaIO_4 oxidation, NaBH_4 reduction, and triflation. The second oxiranyl anion coupling between triflate **94** and epoxy sulfone **21** and an iteration of our tetrahydropyran synthesis afforded the ABCDEFG triflate **97**.

The final H ring was also constructed by the oxiranyl anion strategy with compounds **97** and **21** to afford the seven-membered ketone **99** after 6-*endo* cyclization of **98** with $\text{BF}_3 \cdot \text{OEt}_2$ followed by ring expansion with TMSCHN_2 (Chart 15). Installation of the double bond and methyl group on the H ring was carried out through the Saegusa oxidation⁶⁵ of ketone **99** to an α,β -unsaturated ketone, followed by the stereoselective addition of MeMgBr to yield the *tert*-alcohol **100**, which was converted to aldehyde **101** over four steps. Side-chain elaboration involving the *cis*-selective Wittig reaction and global deprotection afforded trihydroxy (*Z*)-vinyl iodide **102**. Finally, Stille coupling of **102** with (*Z*)-dienyl stannane **103** completed the total synthesis of gambierol (**71**).^{66,67}

Chart 16. Divergent [X + 2 + Y] Convergent Strategy for Polycyclic Ethers

7. Convergent Strategy for the Synthesis of Polycyclic Ethers

Ladder-shaped polyether marine toxins such as brevetoxins, ciguatoxins, and gymnocins have more than 10 fused rings, and their molecular mass typically ranges between 800 and 1200 Da. The synthesis of such large, complex molecules requires the development of a high-performance assembly technique that enables the construction of fused polyethers of various ring sizes. We have endeavored to develop a convergent method for the synthesis of polycyclic ethers containing

Chart 17. Divergent-Convergent Synthesis of Tetracyclic Ethers

medium ring ethers toward marine toxins.

The strategy we pursued was an $[X + 2 + Y]$ convergent approach,⁸⁾ where the oxiranyl anion **104** and triflate **105** were employed as coupling partners (Chart 16, step 1). Intramolecular hydroxy-epoxide cyclization of the product **106** forms the six-membered ketone **107** (step 2), while an ensuing ring expansion reaction yields the seven-membered ketone **109** (step 3). Construction of the second fused ring is achieved by reductive etherification of these hydroxy ketones to afford *trans*-fused 6/6/6/6 and 6/6/7/6 ring systems **108** and **110**, respectively (step 4). This new approach has the flexibility to generate two different-sized ring systems **108** and **110** from the same intermediate **107**, which would be useful for building up various analogs of natural toxins with different ring sizes for biological studies.

To evaluate our idea, we implemented a series of experiments starting from the monocyclic epoxy sulfone **111** and triflate **112**⁶⁸⁾ (Chart 17). The reaction of oxiranyl anion generated from **111** with **112** afforded the epoxy sulfone **113**. Removal of the triethylsilyl (TES) group with TsOH followed by exposure to MgBr_2 produced the bromoketone **114** as a mixture of two diastereoisomers. DBU-mediated cycloetherification afforded ketone **115** as the sole product. The initial cyclization products underwent facile DBU-promoted equilibration to yield a thermodynamically more stable isomer that has an equatorial substituent.⁶²⁾ The six-membered ketone was then subjected to the ring expansion reaction with TMSCHN_2 in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ at -80°C to furnish the seven-membered ketone **116** in 74% yield over two steps. Further ring expansion of **116** into the eight-membered ketone **117** required a higher temperature (-40°C). Sequential cleavage of the TBS group and acetalization of ketones **115**, **116**, and **117** with TsOH in $\text{CHCl}_3/\text{MeOH}$ and reductive etherification of the resulting acetals with Et_3SiH in the presence of trimethylsilyl triflate (TMSOTf) afforded the tetracyclic ethers **118**, **119**, and **120**, respectively. The power of this $[X + 2 + Y]$ -type conver-

Fig. 2. Structures of Yessotoxin and Adriatoxin

gent method is its simplicity to obtain *trans*-fused polycyclic ethers containing six-, seven-, and eight-membered ethers from the same intermediate.

To demonstrate the utility of our divergent and convergent method, we turned to systems with more fused rings. Thus, five different octacyclic ethers, including the CDEFGHIJ-ring system of yessotoxin (**121**)^{69,70)} and adriatoxin (**122**)⁷¹⁾ (Fig. 2), were synthesized from the key intermediate **127**⁷²⁾ (Chart 18). Thus, tetracyclic triflate **124** prepared from **119** was subjected to reaction with the oxiranyl anion of **125** to afford the epoxy sulfone **126**. Subsequent bromoketone formation and DBU-

Chart 18. Divergent Synthesis of Octacyclic Polyethers

mediated cyclization furnished the key ketone **127**. Desilylative acetalization followed by reductive etherification of the resulting methyl acetal **128** with Et_3SiH and TMSOTf gave the octacyclic ether **129**. An angular methyl group was introduced at the acetal carbon atom *via* formation of a mixed thioacetal **130**, which was prepared by reaction with EtSH in the pres-

ence of $\text{Zn}(\text{OTf})_2$. Oxidation of the sulfide **130** with *m*-CPBA followed by methylation with AlMe_3 ⁷³ allowed the stereoselective introduction of the angular methyl group to yield the cyclic ether **131** as a single isomer. The ring expansion approach allowed access to other octacyclic derivatives containing seven- and eight-membered ether rings at the center of the

Chart 19. Retrosynthetic Analysis of Gymnocin-A

Chart 20. Synthesis of ABC Fragment 140

molecule. Thus, treatment of **127** with TMSCHN_2 followed by removal of the TMS group with acid gave the seven-membered ketone **132**. The one-pot removal of the TBS group and cyclic acetal formation was followed by reductive etherification to afford the seven-membered G-ring derivative **133** in good yield. A second BF_3 -mediated ring expansion reaction of **132** with TMSCHN_2 afforded the eight-membered ketone **134**. Cyclic acetal formation and subsequent reductive etherification gave the octacyclic ether **135**, which corresponds to the CDEFGHIJ-ring core of yessotoxin (**121**) and adriatoxin (**122**) which were isolated from scallops and mussels, respectively.

The flexibility of the present divergent approach was further demonstrated by repositioning the carbonyl group in **127** to the I-ring ketone **136** through a conventional four-step manipulation. Ring expansion of **136** was then accomplished using

the same conditions as those employed for **132**, giving the seven-membered ketone **137**. Cyclic methyl acetal formation and reductive etherification afforded the octacycle **138**, a positional isomer of the seven-membered ring of **133**. Therefore, the present $[\text{X} + 2 + \text{Y}]$ convergent method provides a flexible, divergent synthetic route to polycyclic ethers consisting of six-, seven-, and eight-membered ether rings.

8. Total Synthesis of Gymnocin-A

Gymnocin-A (**139**) is a polycyclic ether isolated from cultured cells of the red-tide dinoflagellate *Karenia mikimotoi* by Satake *et al.*⁷⁴ This complex polyether exhibits potent cytotoxicity ($\text{IC}_{50} = 1.3 \mu\text{g/mL}$) against mouse leukemia P388 cells. A characteristic feature is the linear array of 14 contiguous *trans*-fused rings, which is the third-longest fused ring

Chart 21. Synthesis of FGH Fragment **157** Chart 22. Synthesis of KLMN Fragment **142**

system among known polycyclic ethers after brevisulcenal- $F^{75)}$ and gymnocin-B. $^{76,77)}$ The total synthesis of gymnocin-A has only been achieved by Tsukano and Sasaki $^{78-80)}$ using an $[X + 1 + Y]$ approach $^{8)}$ via the *B*-alkyl Suzuki–Miyaura cross coupling. Our successful total synthesis of gymnocin-A highlights the efficient assembly of polyether units by the iterative use of the $[X + 2 + Y]$ convergent method based on the oxiranyl anion strategy.

8.1. Retrosynthetic Analysis of Gymnocin-A The structural homology of the partial ring sequences of the BC and DE ring systems and as well as the FGH and KLM ring systems led us to disassemble gymnocin-A (**139**) into ABC, FGH, and KLMN fragments **140**, **141**, and **142** (Chart 19). Considering the optimum convergency and flexibility, further disassembly of these fragments afforded building blocks **143**–**147**, where the F and K ring units are identical (**145**). Thus, the *trans*-fused tetradecacyclic system of gymnocin-A could be constructed through five iterations of oxiranyl anion

coupling.

8.2. Synthesis of ABC, FGH, and KLMN Fragments

The synthesis of the ABC fragment started from construction of the BC ring by the oxiranyl anion coupling of **143** and **144** to afford the product **148** $^{81)}$ (Chart 20). Removal of the TES group followed by treatment with $MgBr_2$ and exposure to DBU led to smooth bromoketone formation and cyclization to give the thermodynamically stable ketone **149** as the sole product. Ring enlargement of the ketone with TMSCHN $_2$ in the presence of $BF_3 \cdot OEt_2$ followed by TES enol ether formation and osmium-mediated dihydroxylation afforded the hydroxyl ketone **150**, which was transformed into the BC ring unit **151** by a five-step sequence involving cyclic acetal formation, acetylation, and reductive etherification of an α -acetoxy methyl acetal. Further elaboration of the BC unit to the tricyclic ABC ring system **140** involved a radical cyclization of **153**, which was prepared from **151** through seven steps. The A ring was constructed by tributyltin-mediated radical

Chart 23. Synthesis of FGHIJKLMN Fragment 170

cyclization of **153** in high yield, and the resulting product was transformed into the ABC fragment triflate **140** in four steps.

The synthesis of the FGH fragment **157**, a bridging unit of the ABC and KLMN domains, commenced with the alkylation of the epoxy sulfone **146** with triflate **145** to afford product **154**⁸²⁾ (Chart 21). The product was converted to bicyclic ketone **155** in three steps involving selective removal of the TMS group, epoxide opening with MgBr₂, and intramolecular Williamson etherification of the resulting hydroxy bromoketone. This cycloetherification of the tertiary alcohol only proceeded under the developed conditions with 1 M aq. NaOH in the presence of 18-crown-6 in THF. Ring expansion of the ketone with TMSCHN₂ gave the seven-membered ketone **156**, which was subjected to acetalization followed by reductive etherification, desilylation, and triflation to afford the desired FGH triflate **157**.

The synthesis of the KLMN fragment was achieved by union of the K-ring triflate **145** and the N-ring epoxy sulfone **147**, both of which were prepared from 2-deoxy-D-ribose⁸³⁾ (Chart 22). The conversion of epoxy sulfone **158** to the KLMN tribenzyl ether **161** was accomplished through the standard sequence employed for the transformation of **154** to the FGH fragment **157**, except for the last two steps. After exchange of the protecting groups of **161**, the resulting primary alcohol **162** was elaborated to the target KLMN epoxy sulfone fragment **142** through a three-step sequence of Dess–Martin oxidation, Horner–Wadsworth–Emmons olefination with TsCH₂P(O)(OEt)₂, and epoxidation with *t*-BuOOK. An improved route to the KLMN fragment **162** from the FGH fragment **157** was also developed by taking advantage of the same structural motif of FGH and KLM ring systems.⁸⁴⁾

8.3. Completion of the Total Synthesis of Gymnocin-A

In the coupling stage of the three fragments **140**, **157**, and **142**, the order of assembly was designed to avoid the formation of

the unstable triflate of a large polycyclic ether. Thus, we first united the middle FGH triflate **157** with the right KLMN fragment **142** by treating their mixture with *n*-BuLi to afford the coupling product **164** in high yield⁸²⁾ (Chart 23). The product was subjected to a three-step operation involving TES-deprotection, bromoketone formation, and DBU-mediated cyclization to give the ketone **165** as a single isomer. Treatment of **165** with acid followed by reductive etherification afforded the nonacyclic product **166** in high yield. The exchange of protecting groups followed by Dess–Martin oxidation provided aldehyde **168**, which was converted to the epoxy sulfone **170** by the same procedure employed for the synthesis of the KLMN epoxy sulfone **142**.

The final coupling reaction between the tricyclic ABC triflate **140** and the nonacyclic epoxy sulfone **170** proceeded smoothly to afford **171** with excellent yield (Chart 24). It should be emphasized that the oxiranyl anion of the large polyoxygenated molecule **170** still has very high reactivity even at very low temperatures. The product **171** was transformed into ketone **172** through a three-step sequence involving selective deprotection of the TES group in the presence of diethyisopropylsilyl (DEIPS) and TBS groups, transformation of the epoxy sulfone moiety to a bromoketone, and cycloetherification with DBU. Ketone **172** was subjected to ring expansion with TMSCHN₂ to afford the seven-membered ketone, which was transformed to the hydroxy ketone **173** through enol silylation followed by OsO₄ oxidation. Acetalization to **174** followed by reductive etherification provided the desired tetracyclic diol **175** after deacetylation. In the last stage of the synthesis, we directly installed an α,β -unsaturated aldehyde moiety onto the trihydroxy aldehyde **176**, which was obtained by debenzoylation of **175** and the subsequent selective oxidation of the primary alcohol with 1,5-dimethyl-9-azanoradamantane *N*-oxyl (DMN-AZADO) and PhI(OAc)₂.⁸⁵⁾ Finally,

toxin B, gambierol, and gymnocin-A. We are still far from understanding the mode of action of polycyclic ether marine toxins at the molecular level. Further investigation into how the sizes of the ether rings and substituents and side chains on them will result in continuous impetus for developing highly efficient and shorter routes to synthesize such valuable marine natural products.

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The discovery of marine polycyclic ethers with new structures and strong biological activities provided a stimulus for synthetic chemists to discover new synthetic strategies and challenges. The biosynthesis hypothesis proposed for brevetoxin B inspired us to develop new methods using an oxiranyl anion strategy for the synthesis of marine polycyclic ethers. The oxiranyl anion was a very uncommon nucleophile in organic synthesis when we started our project in 1995. The sulfonyl-stabilized oxiranyl anion is a very useful nucleophile and building block, and the sulfonyl group is amenable to further synthetic elaboration for complex polycyclic ether marine toxins, as demonstrated by the total synthesis of hemibrevetoxin A.

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Conflict of Interest The author declares no conflict of interest.

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