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

Yuji Mori
Faculty of Pharmacy, Meijo University; 150 Yagotoyama, Tempaku-ku, Nagoya 468–8503, Japan.
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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,\(^4\) 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 polypeoxide 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
an α-lithiated silyl epoxide could be generated and trapped with an electrophile to give a more substituted epoxide. 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 Satoh in 1996, by Mori in 1997, and, more recently, by Hodgson et al., Chemla and Vrancken, and the Florio group. 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. 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 triflates (Table 1). The reaction of the oxiranyl anion with electrophiles under normal

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

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.
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 hexamethylphosphoramide (HMPA) at \(-100^\circ\text{C}\) 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 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 oxiranylthium 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-butylidimethylsilyl (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% 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 MgBr₂·OEt₂ 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 2134) (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 destyration 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-
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 sulfinic acid with Tl(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) 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 systems 39 (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
In good yield. In an effort to extend the oxiranyl anion strategy to oxepane-containing polyether systems, the keto oxepane \( \text{44} \) was elaborated to triflates \( \text{46a} \) and \( \text{46b} \). Thus, the stereocontrolled reduction of ketone \( \text{44} \) to \( \text{45a} \) was accomplished in two steps: hydroxy-directed reduction with \( \text{Me}_4\text{NBH(OAc)}_3 \) after removal of the \( t \)-butyldiphenylsilyl (TBDPS) group. In contrast, the stereoselective synthesis of the tertiary alcohol \( \text{45b} \) required four-step elaboration: 1) methylenation with Tebbe reagent; 2) epoxidation with \( m \)-chloroperoxybenzoic acid (\( m \)-CPBA); 3) reduction with \( \text{LiEt}_3\text{BH} \); and 4) desilylation with tetrabutylammonium fluoride (TBAF). \(^{35}\) Subsequent one-pot \( O \)-triflation and \( O \)-silylation of the diols gave triflates \( \text{46a} \) and \( \text{46b} \). Reactions of \( \text{46a} \) and \( \text{46b} \) with oxiranyllithiums generated from \( \text{21} \) and \( \text{38} \) followed by the exposure to \( \text{TsOH} \) and \( \text{BF}_3\cdot\text{OEt}_2 \) afforded the 6-7-6 tricyclic ketones \( \text{48} \) and \( \text{52} \), respectively. Further homologation of the ketone \( \text{48} \) with TMSCHN\(_2\) led to the 6-7-7 fused ring system \( \text{49} \). A limitation of this approach is the inability of ring expansion for ketone \( \text{52} \), 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.

\[\text{Hemibrevetoxin B (53)}\]
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 polyeoxide 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 unit 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 BF₃·OEt₂ caused 6-endo cyclization to provide a tricyclic

![Chart 12. Retrosynthesis of Gambierol](image)

![Chart 13. Synthesis of the ABCD Ring System of Gambierol](image)
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, 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 µg/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 14. Synthesis of the ABCDEFG Ring System 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 BF₃-promoted 6-endo cyclization of 87 and ring expansion with TMSCHN₂, afforded the pentacyclic ketone 89. A four-step sequence was employed to transform the ketone into the vinyl ether 90, which was subjected to SmI₂-induced reductive cyclization 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, OsO₄–NaIO₄ oxidation, NaBH₄ 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 BF₃·OEt₂ followed by ring expansion with TMSCHN₂ (Chart 15). Installation of the double bond and methyl group on the H ring was carried out through the Saegusa oxidation 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).

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...
medium ring ethers toward marine toxins.

The strategy we pursued was an \([X + 2 + Y]\) convergent approach, 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 \(6/6/6/6\) 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 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 (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 BF\(_3\)-OEt\(_2\) at \(-80^\circ\)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 (\(-40^\circ\)C). Sequential cleavage of the TBS group and acetalization of ketones 115, 116, and 117 with TsOH in CHCl\(_3\)/MeOH and reductive etherification of the resulting acetals with Et\(_3\)SiH in the presence of trimethylsilyl triflate (TMSOTf) afforded the tetracyclic ethers 118, 119, and 120, respectively. The power of this \([X + 2 + Y]\)-type convergent 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) and adriatoxin (122) (Fig. 2), were synthesized from the key intermediate 127 (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-
mediated cyclization furnished the key ketone 127. Desilylative acetalization followed by reductive etherification of the resulting methyl acetal 128 with Et$_3$SiH 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 presence of Zn(OTf)$_2$. Oxidation of the sulfide 130 with m-CPBA 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
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 [X + 2 + 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. This complex polyether exhibits potent cytotoxicity (IC$_{50} = 1.3$ µg/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
system among known polycyclic ethers after brevisulcenal-F\(^7\(^6\)\) and gymnocin-B.\(^7\(^6\)\(^7\(^7\)\) The total synthesis of gymnocin-A has only been achieved by Tsukano and Sasaki\(^7\(^8\)\(^–\(^8\(^0\)\) 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 oxirananyl 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 \(^1\(^4\(^0\)\(^,\)\(^1\(^4\(^1\)\(^,\)\(^1\(^4\(^2\)\)\) 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 tetracyclic system of gymnocin-A could be constructed through five iterations of oxirananyl 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 oxirananyl anion coupling of 143 and 144 to afford the product 148\(^8\)\(^1\) (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\(_2\) 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 \(\alpha\)-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
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 (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-ribose 83 (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 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-ribose 83 (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 156, which was subjected to acetalization followed by reductive etherification, desilylation, and triflation to afford the desired FGH triflate 157.

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 yield (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 diethylisopropylsilyl (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 tetradecacyclic 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 debenzylation 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. Finally,
9. Conclusion

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 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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