

Accounts

Recent Advances in the Synthesis of *trans*-Fused Polycyclic Ethers by Hydroxy-Epoxide-Cyclization and Ether-Ring-Expansion Reactions

Kenshu Fujiwara* **and Akio Murai***,†

Division of Chemistry, Graduate School of Science, Hokkaido University, Sapporo 060-0810

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Natural *trans*-fused polycyclic ethers, produced by marine sources such as dinoflagellates, are hypothesized to be constructed efficiently from the corresponding polyepoxide precursors by a cascade of ring-closure reactions. The efficiency of the biogenetic pathway has been attractive for synthetic chemists and has prompted them to develop new methods for the construction of cyclic ethers from epoxides. In this review, recent advances in the synthesis of *trans*-fused polycyclic ethers by hydroxy-epoxide-cyclization reactions via monocyclic epoxonium ion intermediates and ether-ring-expansion reactions via bicyclic epoxonium ion intermediates are described.

Recently, natural *trans*-fused polycyclic ethers have attracted the attention of many scientists in various research fields because of their potent bioactivities and complex chemical structures.[1] The relationship between polyether structures and bioactivities is a major area of research. However, most of the natural polyethers are limited in amount due to very low natural production, which causes difficulty in their biological study. Thus, chemical synthesis of polyethers has been studied as an alternative way to supply these compounds. Although polyethers provide significant challenges in the construction of such complex structures, several successful synthetic efforts based on *biomimetic* reaction have been made.

Most natural polyethers are produced by marine dinoflagellates. For example, brevetoxins A, B, and hemibrevetoxin B (Fig. 1) are generated as ichthyotoxins by red tide microalga *Gymnodinium breve*.[2] Ciguatoxins (Fig. 1), representative toxins of ciguatera fish poisoning, are also produced originally by dinoflagellate *Gambierdiscus toxicus*.[3] Although exact biosynthesis of these polyethers by dinoflagellates is still unknown, a domino cyclization reaction of a polyepoxide precursor has been proposed as a key process in their biogenesis by Nakanishi and by Shimizu independently (Scheme 1).[4] This hypothesis shows that a poly-*trans*-epoxide precursor (**1** or **2**) would be cyclized from a terminal of the molecule with successive *endo* epoxide-opening reactions to give brevetoxin B. This provides not only an elegant explanation of the biogenesis of brevetoxin B but also new concepts for chemical synthesis. Inspired by the hypothesis, many synthetic chemists have developed efficient new methods for the construction of *trans*-fused cyclic ethers using ring-closure reactions of epoxides.

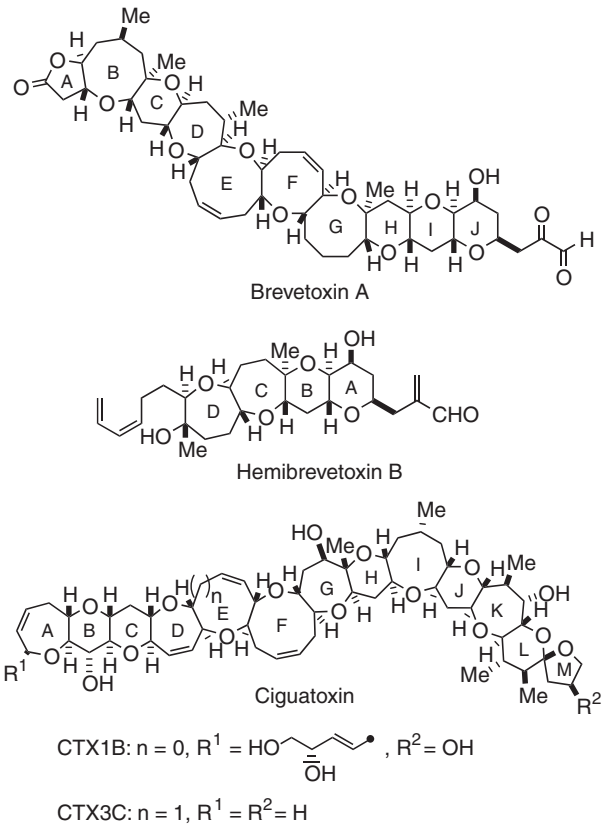

Fig. 1.

The biogenesis can be interpreted in two different ways with detailed considerations in synthetic organic chemistry.[5] For example, cyclization of polyepoxide **3** into poly(tetrahydropyran)

† Present address: Asabu-cho 6-14-44, Kita-ku, Sapporo 001-0045

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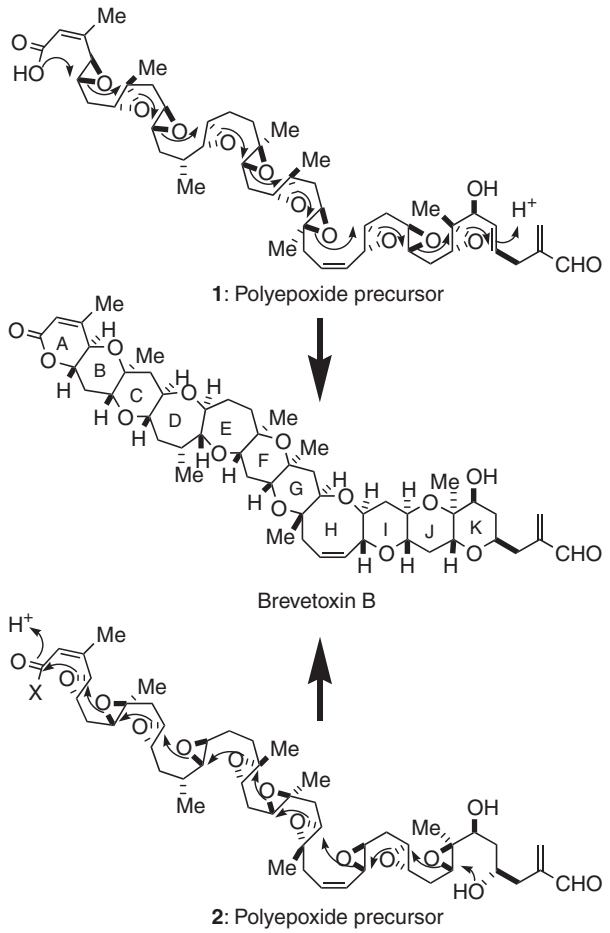


Scheme 1.

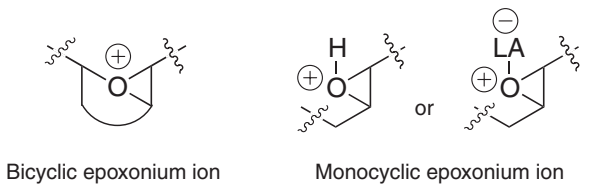
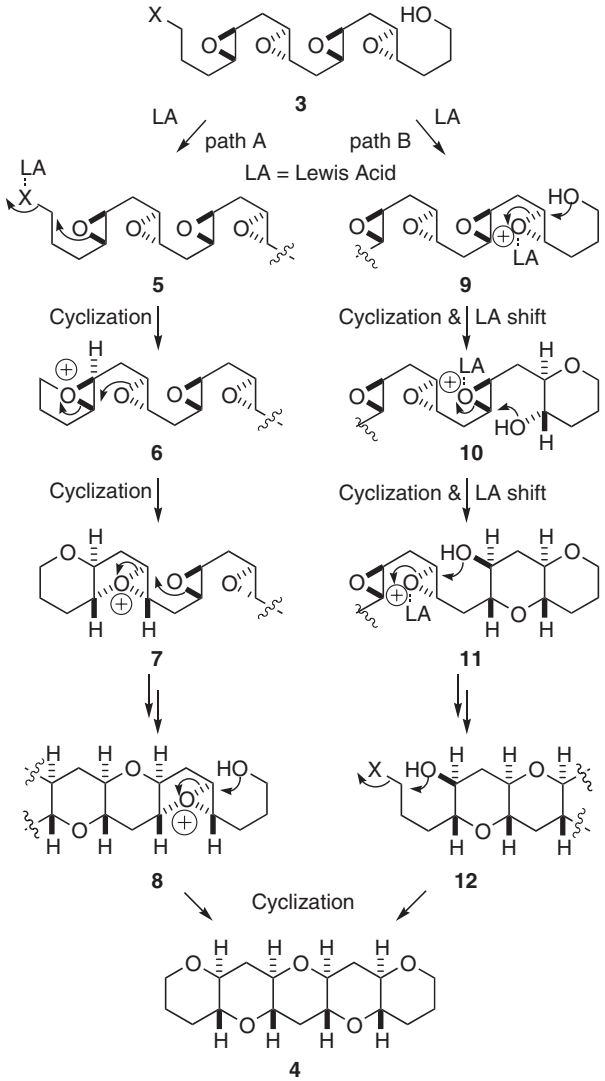


Fig. 2.

4 can be explained by both paths A and B in Scheme 2. Path A is a domino ether-ring-expansion reaction involving *bicyclic epoxonium ion* intermediates; on the other hand, path B is a cascade *endo*-cyclization reaction including *monocyclic epoxonium ion* intermediates (Fig. 2).

The path A process starts when the leaving ability of the terminal leaving group is activated by a Lewis acid (**5** in Scheme 2). Next, the oxygen atom of the first epoxide intramolecularly attacks the terminal electrophilic carbon to produce bicyclic epoxonium ion intermediate **6**. The epoxonium ion part is attacked by the oxygen of the second epoxide, and the C–O bond is cleaved to afford the second bicyclic epoxonium ion **7**. The process is continued until the last bicyclic epoxonium ion **8** is formed. Finally, the last epoxonium ion is attacked by the terminal hydroxy group at the *endo*-site to produce *trans*-fused polycyclic ether **4**.

The process of path B is initiated by the activation of the epoxide near the hydroxy terminal with a Lewis acid to form



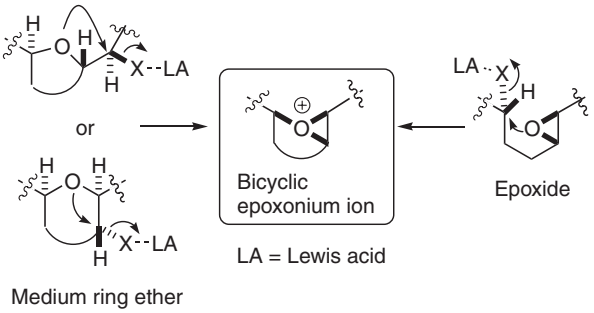
Scheme 2.

monocyclic epoxonium ion intermediate **9**. The epoxonium ion is cleaved in *endo*-mode by the terminal hydroxy group to produce a cyclic ether alcohol. Then the second epoxide is activated with the Lewis acid to provide the second monocyclic epoxonium ion **10**, which is also cyclized into *trans*-fused bicyclic ether **11** by intramolecular attack of the hydroxy group in *endo*-mode. These activation-cyclization steps are repeated until the last epoxide is consumed. The final alcohol **12** is trapped intramolecularly by the terminal electrophile to produce **4**.

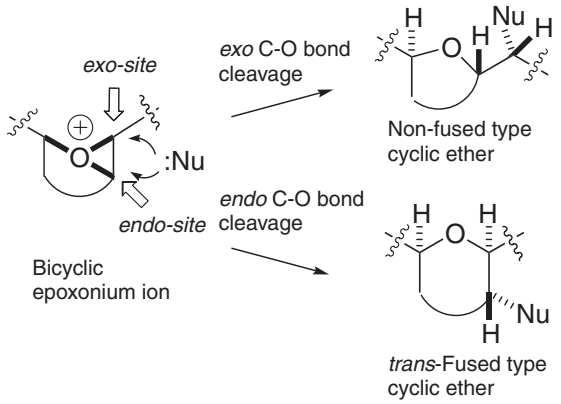
In fact, these two reaction categories are also seen in many chemical syntheses of *trans*-fused cyclic ethers. Here, recent advances in each category of the synthesis are described.

Approaches to *trans*-Fused Cyclic Ethers by Ether-Ring-Expansion Reactions via Bicyclic Epoxonium Ion Intermediates

There are also two modes in the formation of bicyclic epoxonium ion intermediates, as follows (Scheme 3): (1) In the case of *a medium ring ether having a leaving group at a carbon next to an ether carbon*, when a Lewis acid activates



Scheme 3.



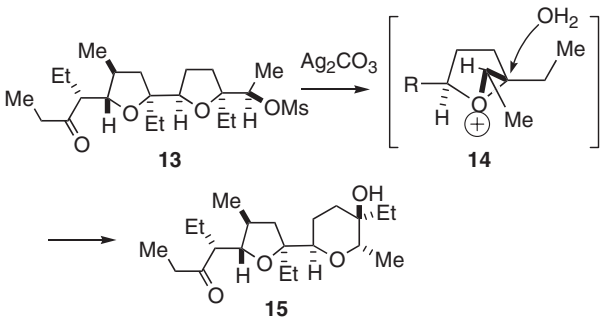
Scheme 4.

the leaving group, the oxygen of the ether attacks the carbon adjacent to the activated leaving group to form a bicyclic epoxonium ion intermediate. (2) In the case of *an epoxide possessing a leaving group at a carbon which is 3 or 4 bonds apart from the epoxide*, when the leaving group is activated by a Lewis acid, the oxygen of the epoxide attacks the carbon to produce a bicyclic epoxonium ion intermediate.

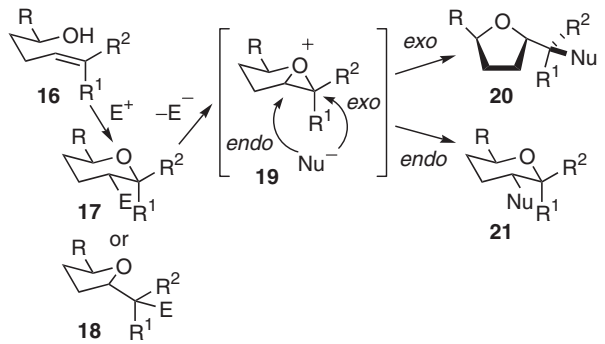
Experimental facts show that most of the intermediates react at two carbon centers on the three-membered ring (Scheme 4). Here, we would like to call the site at the reactive bridgehead carbon in the bicyclic system "*endo*-site" and call the site at the other reactive carbon on the three-membered ring "*exo*-site", for convenience. There are also two modes in the reaction of bicyclic epoxonium ion intermediates with nucleophiles: (1) When a nucleophile attacks the "*endo*-site", "*endo* C–O bond cleavage" in the bicyclic epoxonium ion occurs to give a *trans*-fused type cyclic ether. (2) On the other hand, the "*exo*-site" attack of a nucleophile produces a non-fused type cyclic ether via "*exo* C–O bond cleavage". In order to synthesize *trans*-fused cyclic ethers selectively, several approaches to increase the *endo*-site attack of the nucleophiles have been developed.

From Medium Ring Ethers. A pioneering work in this field was reported by Kishi in 1978. An ether-ring-expansion reaction via a bicyclic epoxonium ion intermediate was applied to the total synthesis of lasalocid A (Scheme 5).[6] It was explained that bicyclic epoxonium ion **14**, resulting from the activation of mesylate **13** with $AgCO_3$, was attacked by H_2O at the *endo*-site in an S_N2 fashion to produce **15**.

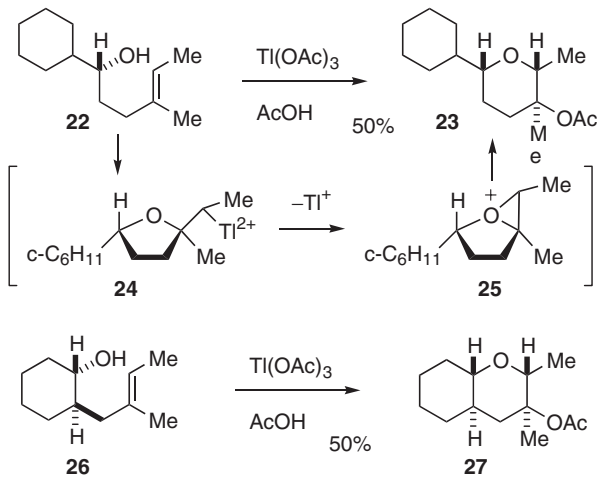
Bartlett has developed a methodology for the synthesis of an oxane or oxolane system from a 4-pentenol system by a two-



Scheme 5.



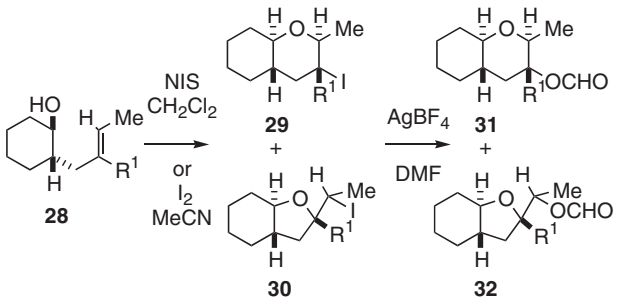
Scheme 6.



Scheme 7.

step process (Scheme 6):[7] the first step is activation of the double bond of **16** with an electrophile (E^+), followed by intramolecular nucleophilic attack of the hydroxy group to form oxane **17** and/or oxolane **18**, and the second step is rearrangement of the ether ring of **17** and/or **18** via the substitution reaction of epoxonium ion intermediate **19** with an oxygen nucleophile to give oxolane **20** and/or oxane **21**. The selectivity of *endo*/*exo*-cleavage was affected by the substitution pattern of the double bond in **16**.

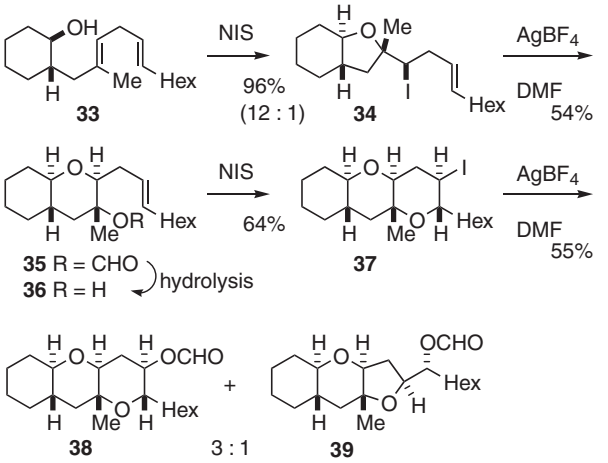
When $Tl(OAc)_3$ was used as an electrophile, the reaction of **22** in AcOH gave *trans*-fused type cyclic ether **23** selectively (Scheme 7).[7a] This was explained by a sequence of reactions including cyclization to the oxolane **24**, the subsequent formation of **25** along with elimination of Tl^+, and ring-expansion of



	29 + 30		31 + 32	
R^1	Yield	29 : 30	Yield	31 : 32
Me	80%	1 : 10	60%	1 : 0
H	90%	1 : 0	72%[a]	1 : 0

a) The yield includes an alcohol corresponding to **31**.

Scheme 8.



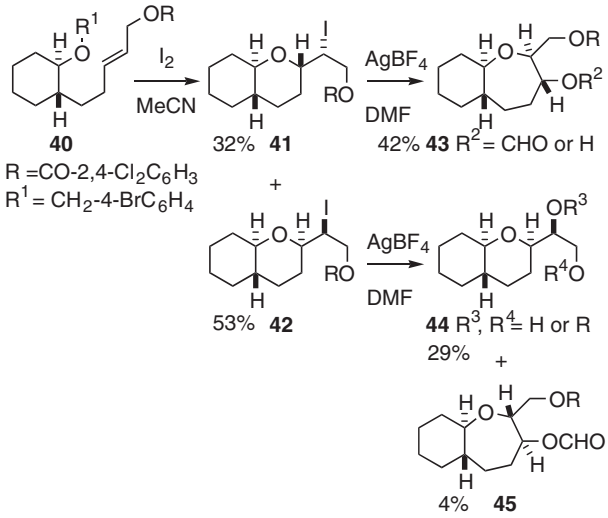
Scheme 9.

25. The reaction of cyclic alcohol **26** with $Tl(OAc)_3$ also produced bicyclic compound **27** selectively.

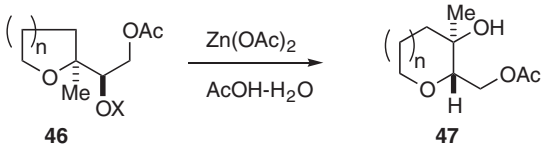
Bartlett also found that a reaction process involving iodoetherification and $AgBF_4$-mediated ring-expansion was available for the synthesis of *trans*-fused cyclic ethers (Scheme 8).[7b] Iodoetherification of **28** with NIS or I_2 gave selectively iodooxane **29** (R^1 = Me) or iodooxolane **30** (R^1 = H). Both of the iodoethers **29** and **30** were transformed into oxane **31** selectively when they were treated with $AgBF_4$.

Successful application of this method in an iterative manner to a *trans*-fused tricyclic system was also reported (Scheme 9).[7b] Treatment of diene alcohol **33** with NIS gave selectively iodooxolane **34** in high yield; this was converted by $AgBF_4$ to oxane **35** predominantly. The same process was repeated after hydrolysis of **35** to produce *trans*-fused tricyclic compound **38** as a major isomer. It should be noted that a bicyclic epoxonium ion intermediate having a rigid fused ring framework derived from **37** retained high *endo*-site reactivity to form **38**.

Construction of 7-membered cyclic ethers was also examined by this methodology (Scheme 10).[7b] Iodoetherification of **40** produced two diastereomeric oxanes, **41** and **42**



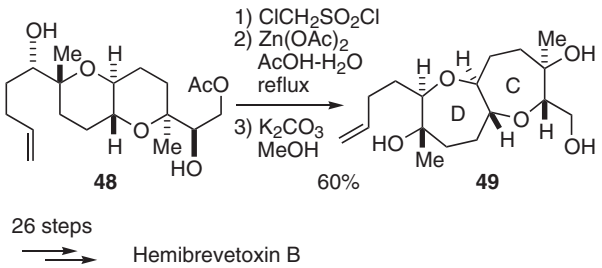
Scheme 10.



	Temp.	Time	Yield of **47**
n = 1, X = SO_2Me	reflux	6 h	75%[a]
n = 1, X = SO_2CH_2Cl	50 °C	4 h	85%[b]
n = 2, X = SO_2Me	reflux	8 h	95%[b]
n = 2, X = SO_2CH_2Cl	reflux	0.5 h	89%[b]

a) Yield after acetylation of the rearranged product.
b) Including hydrolysis product of **47**.

Scheme 11.

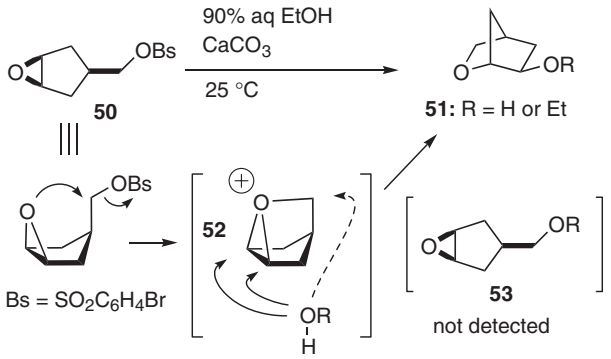


Scheme 12.

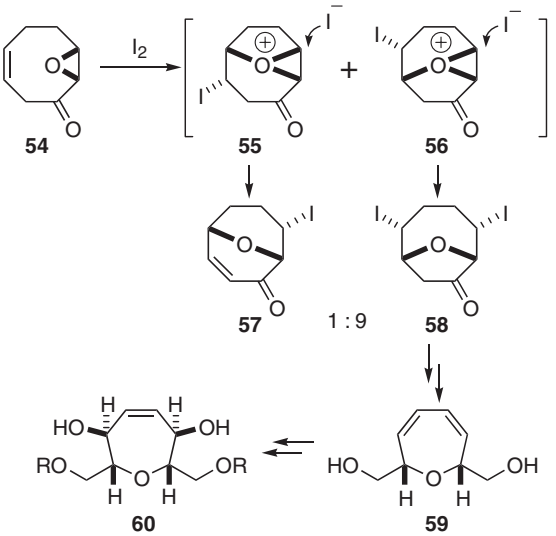
(1:1.6). While treatment of *cis*-oxane **42** with $AgBF_4$ gave *cis*-oxane **44** selectively, the same treatment of *trans*-oxane **41** afforded *trans*-fused type oxepane **43** in 42% yield.

The Kishi method has been refined into a more practical procedure by Nakata.[8] It was found by Nakata that the ring-expansion reaction of **46** efficiently proceeded with $Zn(OAc)_2$ in aqueous acetic acid to give **47** exclusively, and that a monochloromethanesulfonate (monochlate) group acted as a better leaving group in **46** than a mesylate group (Scheme 11).[9]

Nakata also applied this method to the total synthesis of hemibrevetoxin B (Scheme 12).[10] Bicyclic ether **49** corresponding to the CD ring part was efficiently synthesized from



Scheme 13.



Scheme 14.

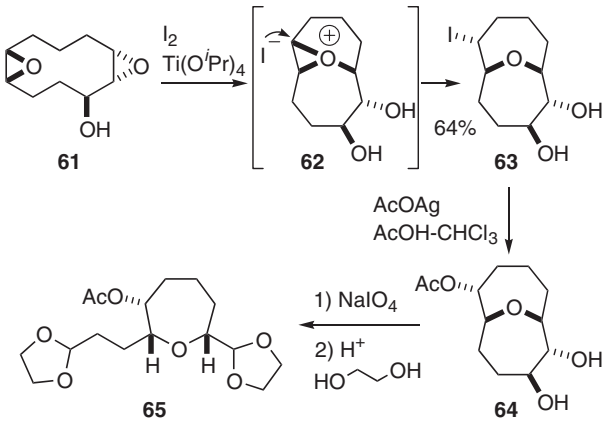
48 by a double ring-expansion manner.[11]

From Epoxides. Generation of an epoxonium ion from an epoxide has been known since the 1960s.[12] More recently, David reported ring enlargement of epoxide **50**, giving exclusively **51** without **53**, where epoxonium ion **52** was thought to be an intermediate (Scheme 13).[13] This was a clear example in which the oxygen of an epoxide could act as a nucleophile.

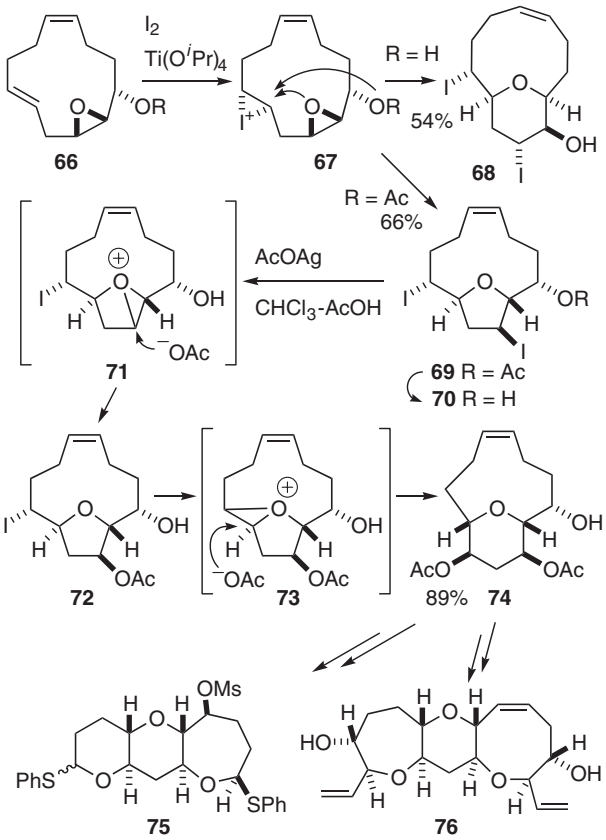
Martín developed a novel method based on epoxide-ring-enlargement on a carbocyclic framework, in which an electrophilic carbon generated on the framework was captured by the oxygen of an epoxide on the same framework to produce a bridged oxabicyclic system via a tricyclic epoxonium ion.[14]

Epoxycyclooctenone **54** was reacted with iodine to give mainly bicyclic ether **58** along with **57** (**58**:**57** = 9:1) (Scheme 14).[14d,e,h] Selective production of **58** was accounted for by the selective formation of intermediate **56** and the regioselective C–O bond cleavage with an iodide ion. The bicyclic ether **58** was converted through several steps via **59** to unsaturated 7-membered cyclic ether **60**, the structure of which was seen in ciguatoxins.

When cyclodecane-1,2:6,7-diepoxide derivative **61** was treated with $Ti(O^iPr)_4/I_2$, bicyclic 7-membered ether **63** was afforded (Scheme 15).[14f] This could also be explained by the site-selective attack of the iodide ion to epoxonium ion **62**, which would be generated in the following way: the epoxide



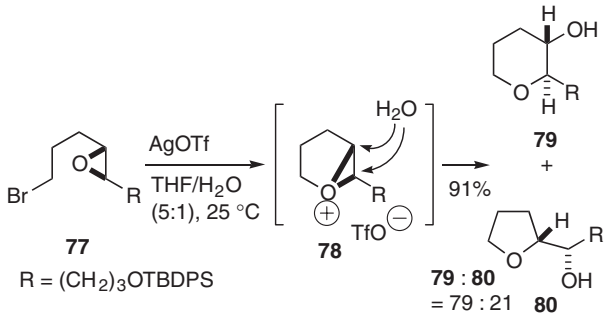
Scheme 15.



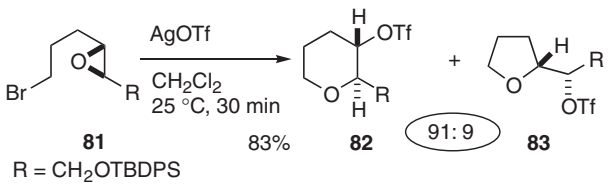
Scheme 16.

nearby the hydroxy group of **61** was initially activated by a Lewis acid with anchimeric regiocontrol, and reacted with another nucleophilic epoxy oxygen to generate **62**. An acetate substitution reaction of **63** with AgOAc gave selectively **64**, of which the retained stereochemistry could be attributable to intermediate **62**. The bicyclic ether **64** led to 7-membered cyclic ether **65**.

In the ring-expansion reaction of epoxy cyclododecadiene derivative **66** with $Ti(O^iPr)_4/I_2$, the R group of **66** determined the ring size of the product (Scheme 16).[14c,g,h] When R was H, the OR (OH) group of **67** attacked the iodonium ion intramolecularly to give oxane **68**. On the other hand, changing R to Ac resulted in predominant attack of the epoxide of **67** to



Scheme 17.



Scheme 18.

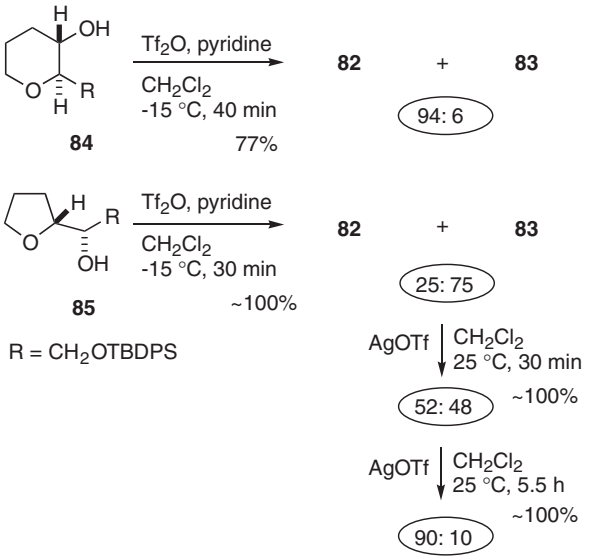
the iodonium ion to afford oxolane **69**. Treatment of **70** with AgOAc induced ring-expansion via epoxonium ion intermediates **71** and **73** to produce *trans*-fused type 6-membered cyclic ether **74**, which successfully led to *trans*-fused tricyclic ethers **75** and **76**.

While the ring-expansion of carbocyclic epoxides has been extensively studied by Martín as above, that of acyclic epoxides was rarely investigated. It is important to understand the mode of ring-expansion in acyclic epoxides in order to achieve biomimetic chemical synthesis of fused polyethers through path A of the Nakanishi–Shimizu hypothesis (Scheme 2). Thus, we started to examine the reaction of a simple acyclic epoxide system.[15]

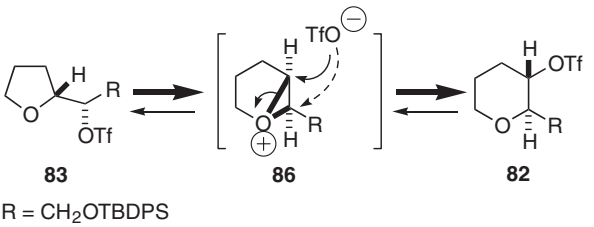
First, a simple epoxide having a bromo-substituent at the terminal site was used as a substrate (**77**) (Scheme 17).[15] When the epoxide **77** was treated with AgOTf in the presence of H_2O as an external nucleophile in THF at ambient temperature, a 79:21 mixture of oxane **79** and oxolane **80** was produced in good yield. This result clearly showed that the oxygen of an epoxide was able to react with an intramolecular electrophilic site even in an acyclic system. The product ratio could be reflected in the reactivity of bicyclic epoxonium intermediate **78**, in which the *endo*-site was more reactive to H_2O than the *exo*-site in spite of the absence of methyl-substitution at the *endo*-site.

Next, a similar substrate **81** was treated with AgOTf in dry CH_2Cl_2 to produce a 91:9 mixture of triflyloxy substituted oxane **82** and oxolane **83** (Scheme 18).[15] It was noted that a triflate ion acted as a nucleophile in this reaction in spite of its high leaving ability, and that the *endo*-site selectivity of this reaction was higher than that of the above reaction with H_2O.

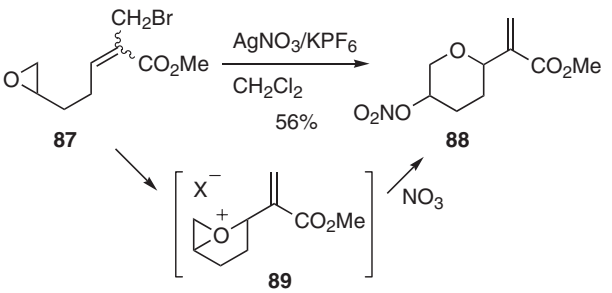
When the triflates **82** and **83** were prepared for the confirmation of their structure, interesting results that suggested interconversion of **82** and **83** were obtained (Scheme 19).[15] The reaction of pure **84** with Tf_2O in the presence of pyridine in CH_2Cl_2 surprisingly produced a 94:6 mixture of **82** and **83** in spite of the absence of AgOTf. Pure **85** also gave a 25:75



Scheme 19.



Scheme 20.



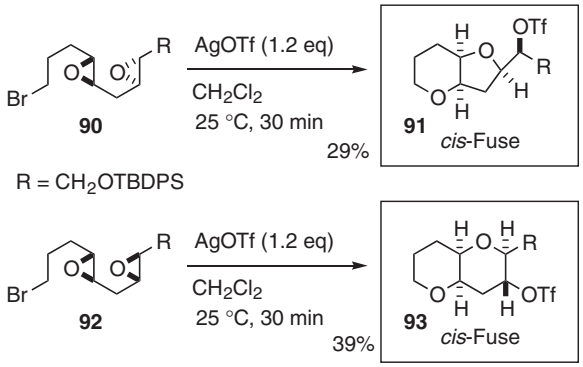
Scheme 21.

mixture of **82** and **83** under the same conditions. When the 25:75 mixture was reacted with AgOTf, the ratio was changed into 52:48 after 30 min and into 90:10 after 5.5 h.

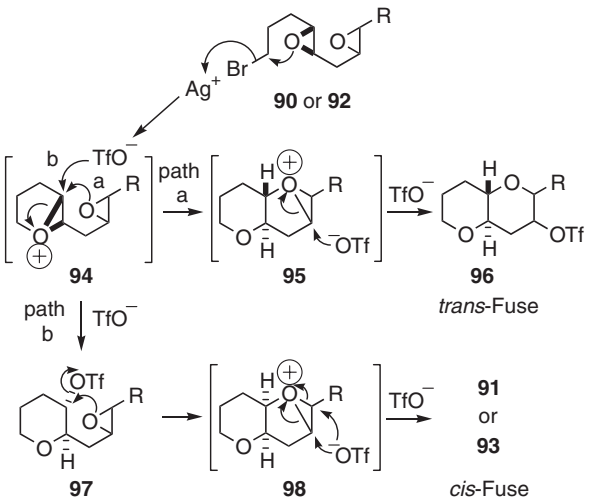
From these results, it was clear that there was an equilibrium between **82** and **83** in the presence of a protonic or Lewis acid, which would be mediated by bicyclic epoxonium ion **86** (Scheme 20).[15] Accordingly, the product ratio of the ring-expansion reaction of **81** with AgOTf in CH_2Cl_2 would result from the thermodynamic stability of **82** and **83**. On the other hand, the product ratio of the reaction of **77** with AgOTf in the presence of H_2O could be kinetically controlled.

Ohkata also reported the formation of oxane **88** from acyclic epoxide **87** via the *endo*-site cleavage of bicyclic epoxonium ion **89** (Scheme 21).[16]

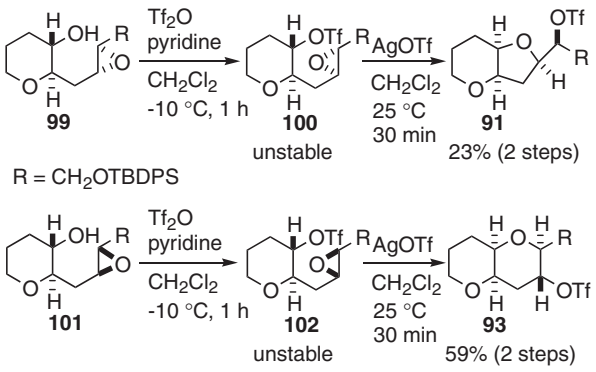
Successive epoxide-ring-expansion reaction providing fused bicyclic ethers was further examined by our group



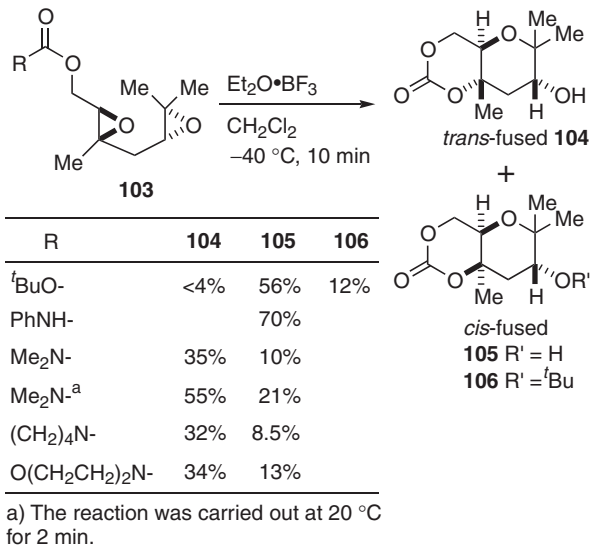
Scheme 22.



Scheme 23.



Scheme 24.



R	104	105	106
^{t}BuO-	<4%	56%	12%
PhNH-		70%	
Me_2N-	35%	10%	
Me_2N-[a]	55%	21%	
$(CH_2)_4N$-	32%	8.5%	
$O(CH_2CH_2)_2N$-	34%	13%	

a) The reaction was carried out at 20 °C for 2 min.

Scheme 25.

(Scheme 22).[15] When diepoxide **90** was treated with AgOTf in CH_2Cl_2, only *cis*-fused bicyclic ether **91** was produced in 29% yield. Diastereomeric **92** also provided *cis*-fused **93** exclusively in 39% yield under the same conditions. The low yields were attributed to the decomposition of the products during purification.

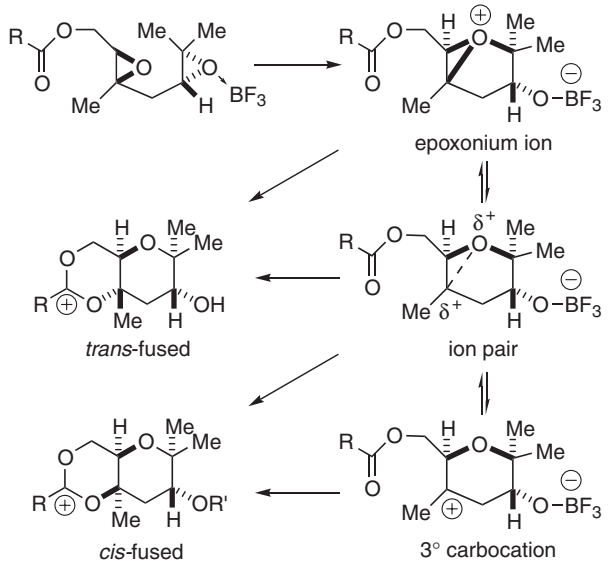
Production of the *cis*-fused compounds could be explained as illustrated in Scheme 23.[15] After generation of first epoxonium ion **94** from **90** or **92**, a triflate ion would attack the *endo*-site of **94** to afford oxane **97**. The triflate part of **97** would be activated by Ag^+ and produce *cis*-fused epoxonium ion **98**, which would be transformed into **91** or **93** via cleavage of the *exo* or *endo* C–O bond.

Although all attempts to isolate triflate intermediates **100** and **102** from the reaction media to support the above assumption were in vain, these triflates could be synthesized alternatively from **99** and **101** (Scheme 24). Both of these triflates gave the same *cis*-fused products as those from diepoxide **90** and **92**.

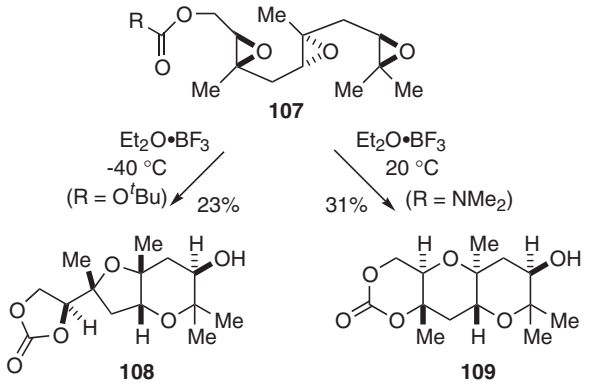
The reaction rate of intramolecular nucleophilic attack of the epoxide to the bicyclic epoxonium ion in **94** (path a) seems to be slower than that of intermolecular attack of the triflate ion (path b) (Scheme 23). Therefore, accomplishment of the successive ring-expansion reaction of a polyepoxide obviously requires a new design for the reaction system, in which the influence of external nucleophiles has to be ruled out completely.

McDonald accomplished tandem cyclization of polyepoxides, which would be categorized into ring-expansion via the bicyclic epoxonium ion intermediates.[17] His reaction system was well devised in order to exclude external nucleophiles, and had an internal nucleophile-controlling regio- and stereoselectivity of the ring-expansion reaction. When a variety of terminal functional groups were examined in the reaction of diepoxide **103** with $Et_2O•BF_3$, it was found that an *N*,*N*-dimethylcarbamate group was superior to a *t*-butyl carbonate or an *N*-phenylcarbamate group in the production of *trans*-fused compound **104** (Scheme 25).[17c]

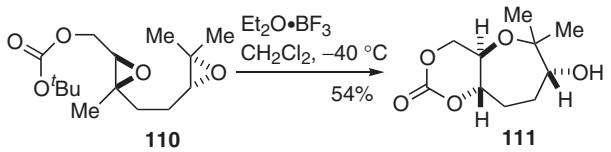
This selectivity was explained by McDonald as the mechanism shown in Scheme 26, in which the internal nucleophile was intercepted at different points in the continuum between the epoxonium ion at one extreme and the tertiary carbocation at the other.[17c] He proposed that the less nucleophilic *t*-butyl carbonate provided *cis*-fused products through nucleophilic addition in the continuum closer to the tertiary carbocation, whereas a better nucleophile, such as the tertiary carbamate, preferred to produce the *trans*-fused products by intercepting a tight ion-pair intermediate nearer in structure to the epoxonium ion.



Scheme 26.



Scheme 27.



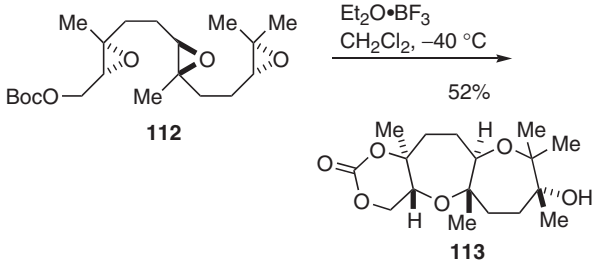
Scheme 28.

The tandem cyclization of triepoxide **107** was also examined (Scheme 27).[17a,b] Although the substrate having a carbonate terminal afforded *cis*-fused compound **108**, the *N*,*N*-dimethylcarbamate derivative of **107** successfully produced *trans*-fused cyclic ether **109**.

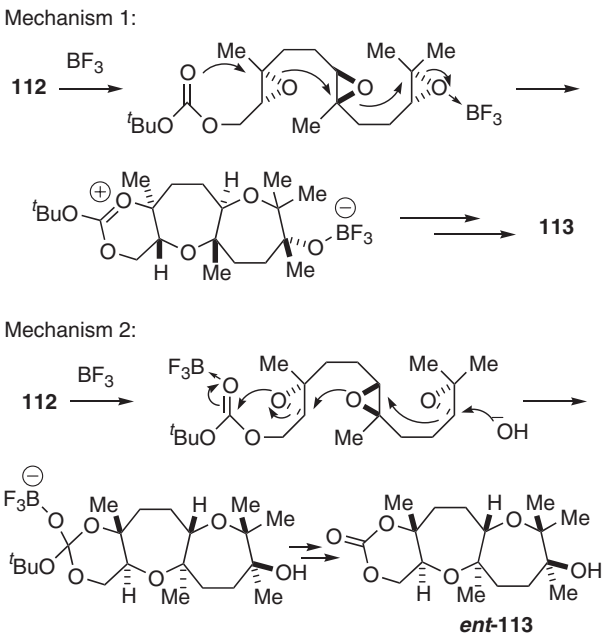
Further, the *trans*-fused 7-membered cyclic ether **111** was synthesized from diepoxide **110** by the same method, in which the terminal *t*-butyl carbonate acted as a good internal nucleophile (Scheme 28).[17a,b]

Optically active triepoxide **112** produced tricyclic **113** under the same conditions in good yield (Scheme 29).[17a,b]

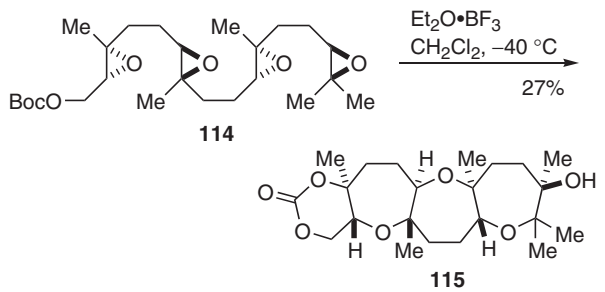
The absolute stereochemistry of **113** determined was explained as Mechanism 1 in Scheme 30 by McDonald. Here, initial activation of the terminal epoxide by BF_3 induced the cascade cyclization of **112** to afford **113**. The pathway starting from activation of the carbonate with BF_3 (Mechanism 2), thought to produce the enantiomer of **113**, was ruled out.[17b]



Scheme 29.



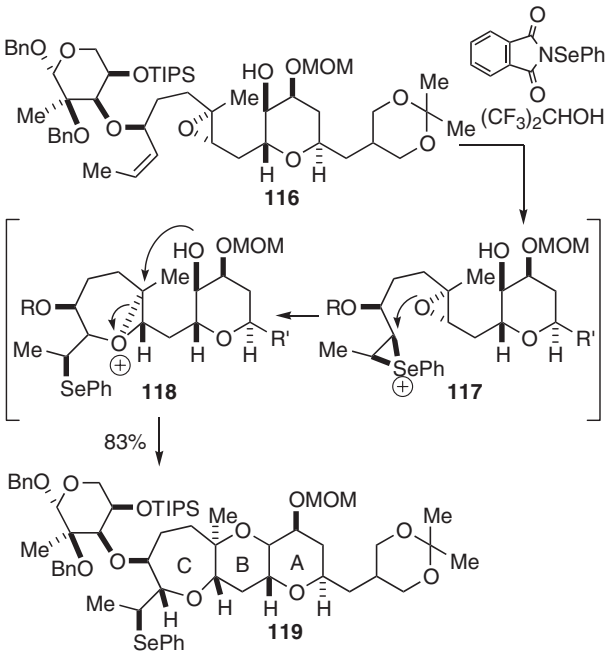
Scheme 30.



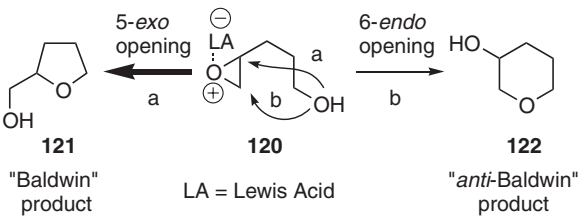
Scheme 31.

After all, McDonald achieved a landmark tandem cyclization of tetraepoxide **114** to produce *trans*-fused tetracyclic compound **115** in 27% yield (Scheme 31).[17b]

Recently, Holton achieved concise total synthesis of hemibrevetoxin B, in which the cascade cyclization of hydroxy epoxide **116** into **119** was performed as a key step (Scheme 32).[18] This transformation might be explained as follows: after initial formation of episelenonium ion **117**, the episelenonium ion



Scheme 32.



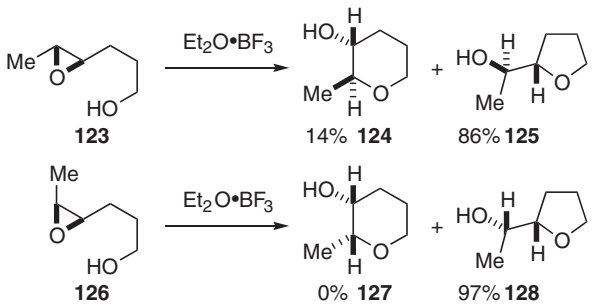
Scheme 33.

part would be attacked by the epoxide oxygen in **117** to give bicyclic epoxonium ion intermediate **118**, which would be attacked at the *endo*-site by the intramolecular hydroxy group to produce **119**.

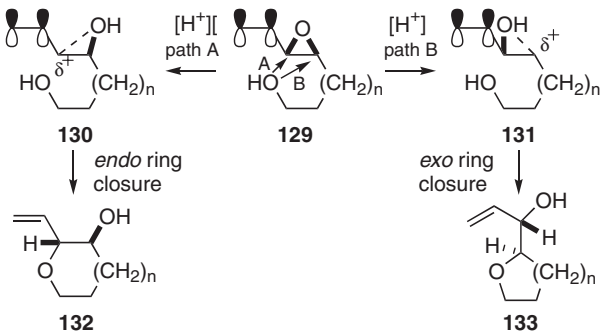
Approaches to *trans*-Fused Cyclic Ethers by Hydroxy-Epoxide-Cyclization Reactions via Monocyclic Epoxonium Ion Intermediates or Activated Epoxides

A major problem in the synthesis of *trans*-fused cyclic ethers via monocyclic epoxonium ion intermediates (activated epoxides) is to control the mode of epoxonium-ring-opening into *endo*-mode. Cyclization of simple hydroxy epoxides producing 5 to 7-membered rings normally prefers *exo*-mode ring-opening in accordance with Baldwin's rule.[19] In the case of activated hydroxy epoxide **120**, 5-*exo*-opening mode giving hydroxy oxolane **121** is normally favored rather than 6-*endo*-opening mode providing hydroxy oxane **122** (Scheme 33). For example, Coxon reported that both *trans*- and *cis*-4,5-epoxyhexanols **123** and **126** were cyclized with $Et_2O \cdot BF_3$ to produce oxolanes **125** and **128** predominantly (Scheme 34).[20] In order to solve the problem, many synthetic methodologies have been developed to date.[21]

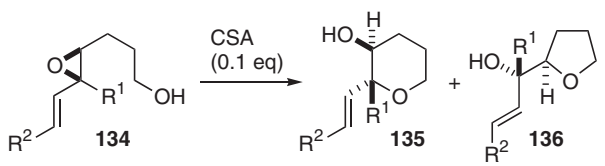
Nicolaou reported a practical method for selective *endo*-opening of hydroxy epoxides.[22] In order to activate *endo*-opening, a vinyl group was placed adjacent to the *endo*-site of the



Scheme 34.



Scheme 35.



R^1	R^2	Yield	**135** : **136**
H	CO_2Me	96%	60 : 40
H	H	95%	100 : 0
Me	CO_2Me	92%	66 : 34
Me	H	96%	100 : 0

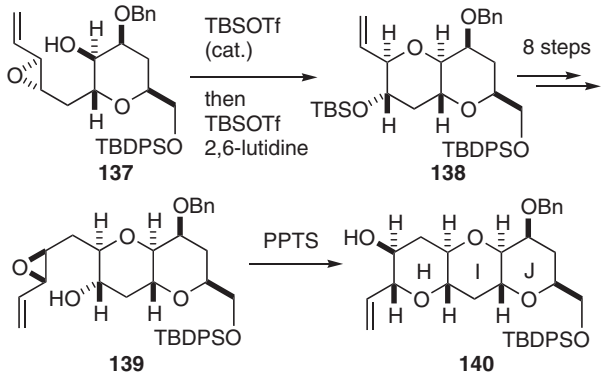
Scheme 36.

epoxide. The vinyl group could stabilize the developing electron-deficient orbital at the *endo*-site in the transition state by π-electron donation, which makes *endo*-cyclization favorable (Scheme 35). In fact, vinyl derivatives of epoxide **134** produced oxanes exclusively (Scheme 36). On the other hand, the presence of an electron-withdrawing methoxycarbonyl group gave reduced selectivity.

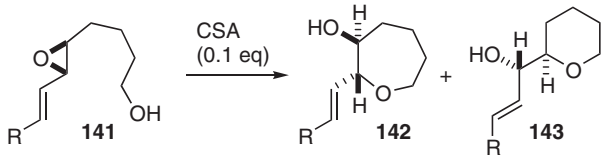
Moreover, iterative use of this method was effective for the construction of a *trans*-fused poly(tetrahydropyran) system. For example, the HIJ ring part of brevetoxin A was efficiently synthesized by the iterative use (Scheme 37).[23]

This method was also applied to the synthesis of 7-membered monocyclic ether, in which a 2-chlorovinyl group gave better selectivity than a vinyl or a 2-methoxycabonylvinyl group (Scheme 38).[24]

The hydroxy-vinyl-epoxide-cyclization sometimes showed low *endo* selectivity in the construction of a fused bicyclic system having an angular methyl group. Nakata reported that a

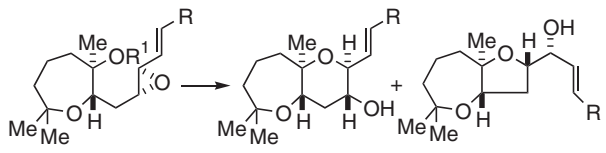


Scheme 37.



	Yield	142 : 143
R = CO_2Me	75%	22 : 78
R = H	75%	82 : 18
R = Cl	75%	92 : 8

Scheme 38.



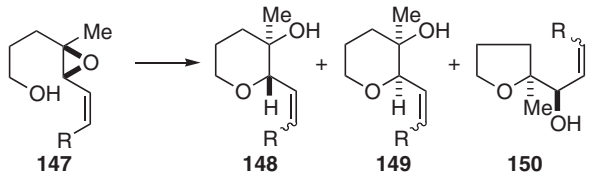
144	Conditions	Yield	145 : 146
R = H	TBAF; PPTS	86%	1 : 1
R = H	AcOH-H_2O (10:1)	78%	3.8 : 1
R = Ph (*E*:*Z* = 8:1)	TBAF; PPTS	86%	only **145**

Scheme 39.

styryl epoxide gave higher selectivity than the vinyl epoxide in such cases (Scheme 39).[25] The styryl group allowed exclusive *endo*-cyclization of **144** possessing a tertiary alcohol as an internal nucleophile.

The styryl group was also effective for the 6-*endo*-cyclization of epoxide **147** having a methyl group at the opposite side to the styryl group (Scheme 40).[26] When protonic acids were used for activation of the epoxide, considerable inversion of stereochemistry was observed during cyclization. This problem was completely solved when the reaction carried out under basic conditions using NaH in DMSO.

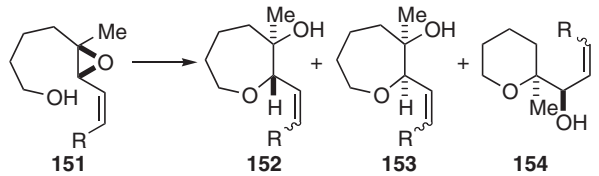
In the case of ring-opening of trisubstituted epoxide **151** under the acidic conditions, the styryl group gave better *endo*-selectivity than the vinyl group, though significant epimerization was observed (Scheme 41). On the other hand, basic treatment of the styryl derivative showed perfect regio- and stereoselectivity, although the conversion was low.



147	Conditions	Yield	148 : 149 : 150
R = H	PPTS (cat.), CH_2Cl_2, rt	NR[a]	49 : 0 : 51
R = Ph	PPTS (cat.), CH_2Cl_2, rt	97%	65 : 35 : 0
R = Ph	CSA (cat.), CH_2Cl_2, -78 °C	100%	90 : 10 : 0
R = Ph	NaH, DMSO, rt	97%	100 : 0 : 0

a) NR: not reported.

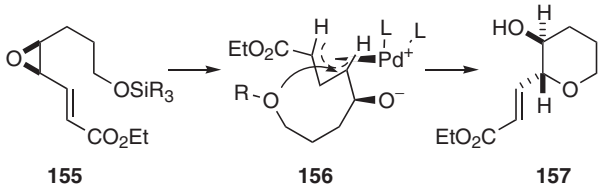
Scheme 40.



151	Conditions	Yield	152 : 153 : 154
R = H	PPTS (cat.), CH_2Cl_2, rt	NR[a]	23 : 0 : 77
R = Ph	PPTS (1 eq.), CH_2Cl_2, rt	80%	16 : 84 : 0
R = Ph	NaH, DMSO, rt	10%[b]	100 : 0 : 0

a) NR: not reported. b) **151** was recovered (60%).

Scheme 41.

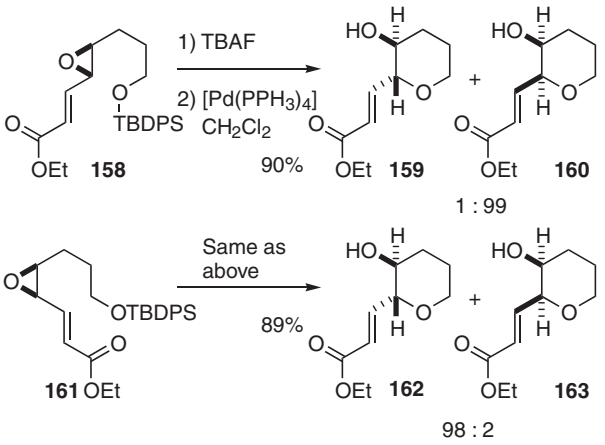


Scheme 42.

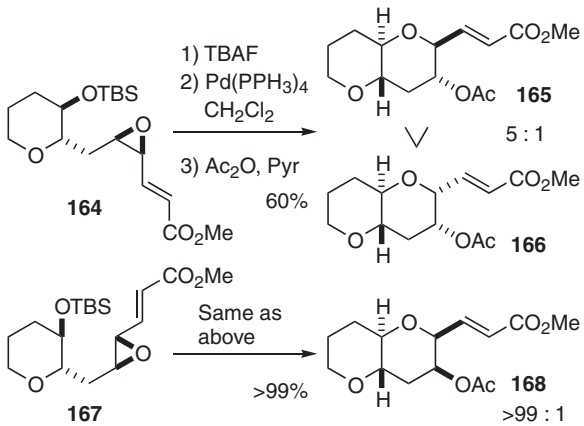
Hirama reported the palladium-catalyzed cyclization reaction of 4,5-epoxy-8-trialkylsilyloxy-2-octenoate **155** into hydroxy oxane **157** in high yield and selectivity, in which activation of the trialkylsilyloxy group by a fluoride ion was important for increasing reactivity and stereoselectivity. The stereochemistry of the reaction was explained by the double inversion mechanism including the formation of π-allyl palladium intermediate **156** (Scheme 42).[27] For example, *trans*-epoxide **158** mainly produced *cis*-disubstituted oxane **160**, while *cis*-epoxide **161** gave *trans*-disubstituted oxane **162** predominantly (Scheme 43).

This method was also applied to the construction of fused bicyclic compounds **165** and **168** from the corresponding epoxides **164** and **167** (Scheme 44).[28]

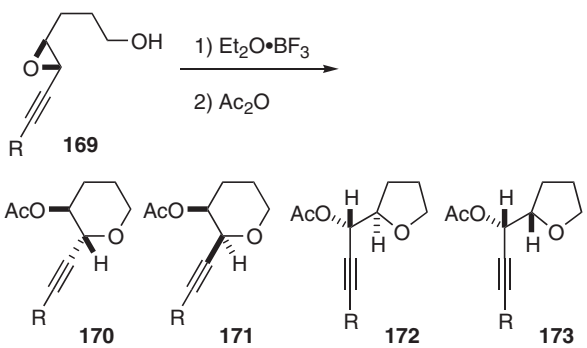
Regio- and stereoselectivity in the ring-opening reaction of alkyne-substituted *trans*-epoxide **169** were studied by Mukai (Scheme 45).[29] The electronic nature of the terminal substituent of the alkyne mainly affected the selectivity. Electron-de-



Scheme 43.



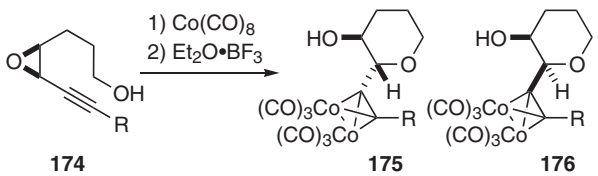
Scheme 44.



R	Yield	170 : 171 : 172 : 173
H	92%	10 : 0 : 90 : 0
TMS	91%	61 : 1 : 34 : 4
Bu	96%	95 : 0 : 5 : 0
Ph	94%	96 : 4 : 0 : 0
p-MePh	96%	83 : 17 : 0 : 0
PhCO	96%	1 : 0 : 99 : 0

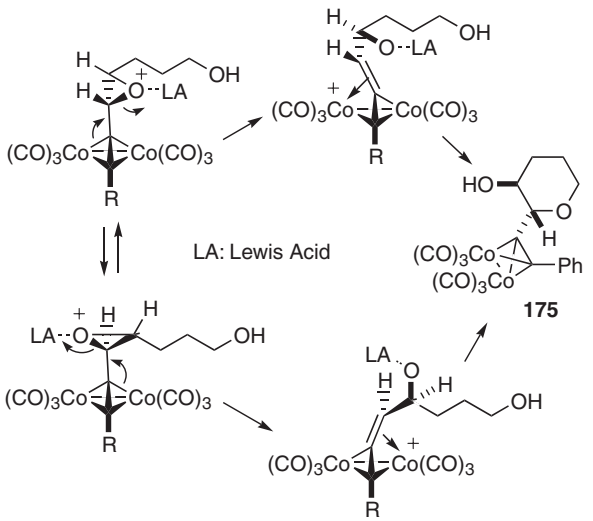
Scheme 45.

ficient groups preferred 5-*exo*-opening of **169**. Conversely, electron-donating groups showed high 6-*endo*-cyclization to give *trans*-hydroxy oxanes predominantly.

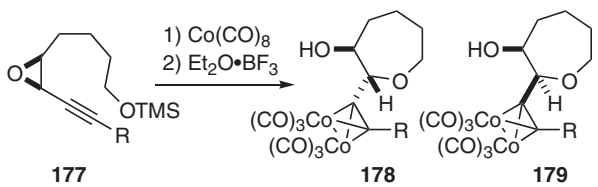


	Yield	175 : 176
R = TMS	88%	100 : 0
R = Ph	93%	99 : 1

Scheme 46.



Scheme 47.



	Yield	178 : 179
R = TMS	76%	69 : 31
R = Ph*	56%	78 : 22

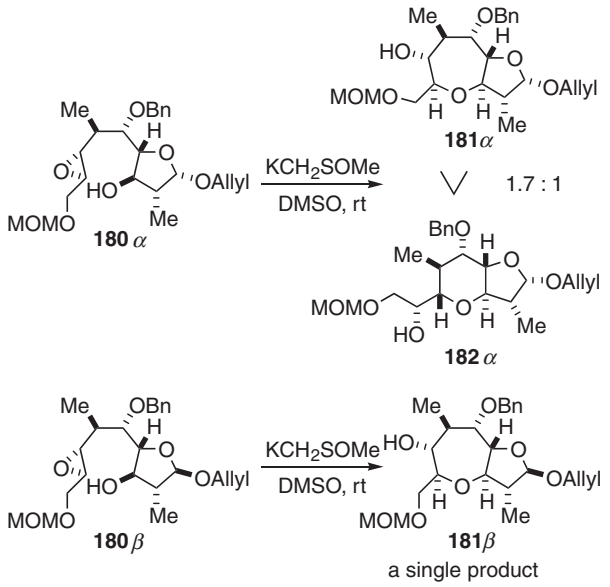
* A mixture (*cis*:*trans* = 93:7) was used.

Scheme 48.

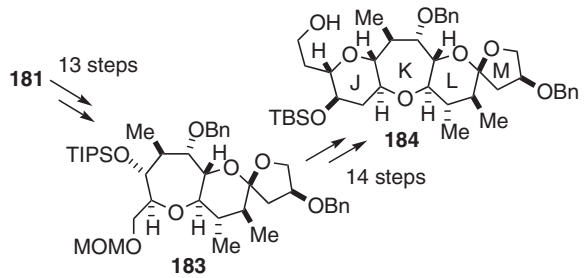
Mukai also reported 6-*endo*-cyclization of hydroxy epoxides having a cobalt-complexed alkyne group (Scheme 46).[30,31] Complexation of *cis*-epoxide **174** with octacarbonyldicobalt followed by the treatment with $Et_2O \cdot BF_3$ exclusively produced *endo*-opening product **175**. The stereochemistry of **175** suggested that the reaction proceeded in a double inversion manner by the anchimeric assistance of the cobalt–alkyne complex part (Scheme 47).

In the case of 7-*endo*-cyclization of **177**, although the stereoselectivity was lower than that of **174**, complete *endo*-selectivity was observed (Scheme 48).[32] Similar methodologies using the cobalt–alkyne complex have been developed for the synthesis of fused polycyclic ethers by Isobe[33] and Martín.[34]

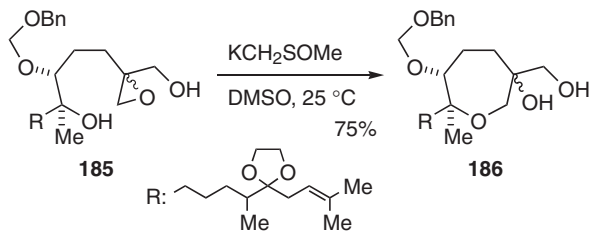
Sasaki and Tachibana found 7-*endo*-cyclization of hydroxy



Scheme 49.



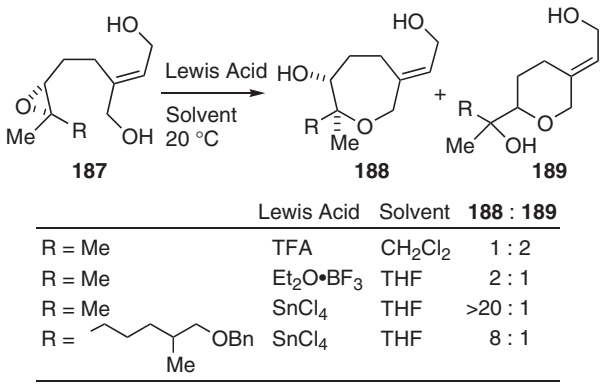
Scheme 50.



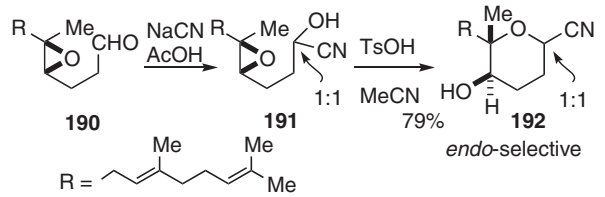
Scheme 51.

epoxides without any directing group in their synthesis of the K-ring part of CTX1B (Scheme 49).[35] When hydroxy epoxide **180α**, which had a 5-membered cyclic acetal, was treated with methylsulfinylmethylpotassium, 7-membered cyclic ether **181α** was produced as a major product. The anomeric isomer **180β** was cyclized under the same conditions to give only the 7-membered ring ether **181β**. Suitable conformational preorganization of **180β** for 7-*endo*-cyclization was suggested by conformational analysis using NMR and molecular mechanics calculations. The bicyclic ethers **181α** and **β** were further transformed into the JKLM-ring part **184** (Scheme 50).[35]

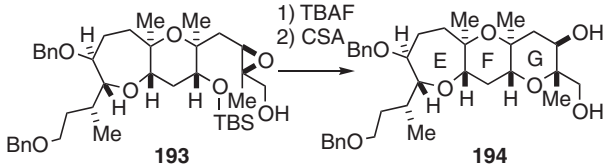
Nicolaou reported 7-*endo*-cyclization of a simple hydroxy epoxide under basic conditions in the total synthesis of zoapatanol, in which the epoxide **185** was readily converted to **186** with methylsulfinylmethylpotassium in high yield



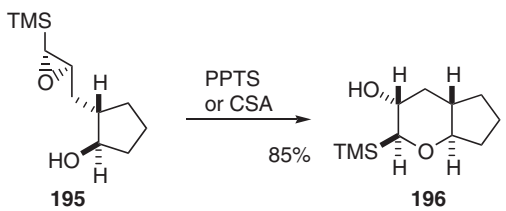
Scheme 52.



Scheme 53.



Scheme 54.



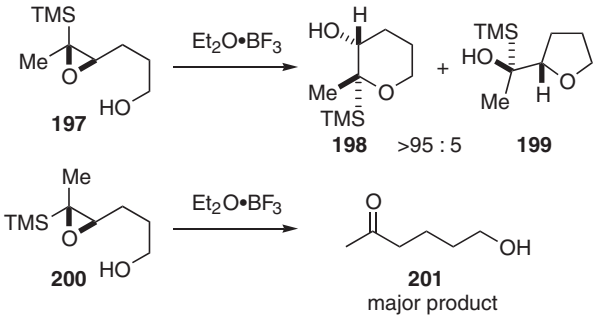
Scheme 55.

(Scheme 51).[36]

Alternative selective 7-*endo*-cyclization reactions in zoapatanol synthesis were also achieved under acidic conditions (Scheme 52). Treatment of **187** with $SnCl_4$ in THF gave excellent 7-*endo* selectivity.[37]

Selective 6-*endo*-cyclization reactions of hydroxy epoxides without any activator groups were reported by Corey[38] and Nakata[39] (Schemes 53 and 54, respectively). The preferential cleavage of the *endo* C–O bond under the acidic conditions may be attributable to the methyl substitution at the *endo*-site, which would stabilize cationic polarization at the *endo*-carbon by electron donation in the transition state of the *endo*-cyclization.

The α-opening of α,β-epoxy silanes by a variety of nucleophiles is a preferred process.[40] The α-site activation of a trialkylsilyl group was applied to 6-*endo*-cyclization of hydroxy epoxides by Schaumann (Scheme 55).[41] The acid-catalyzed



Scheme 56.

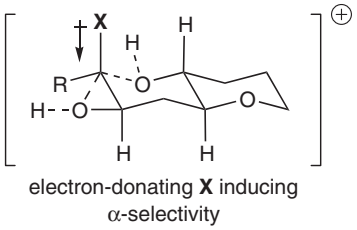


Fig. 3.

cyclization of 1,4-*anti* hydroxy epoxy silanes, such as **195**, showed high *endo* selectivity though 1,4-*syn* isomers gave *exo*-cyclized products under the same conditions.

Jamison studied a similar cyclization of trisubstituted α,β-epoxy silanes in view of the construction of a multicyclic system. When *cis*-epoxide **197** was catalyzed by $Et_2O{\cdot}BF_3$, *endo*-cyclized product **198** was selectively produced (Scheme 56).[42] On the other hand, *trans*-isomer **200** gave ketone **201** as a major product under the same conditions. The geometrical requirement for the *endo*-cyclization, which arranged the large TMS group in an axial position in the transition state (Fig. 3), was adequate for his multi-ring synthesis.

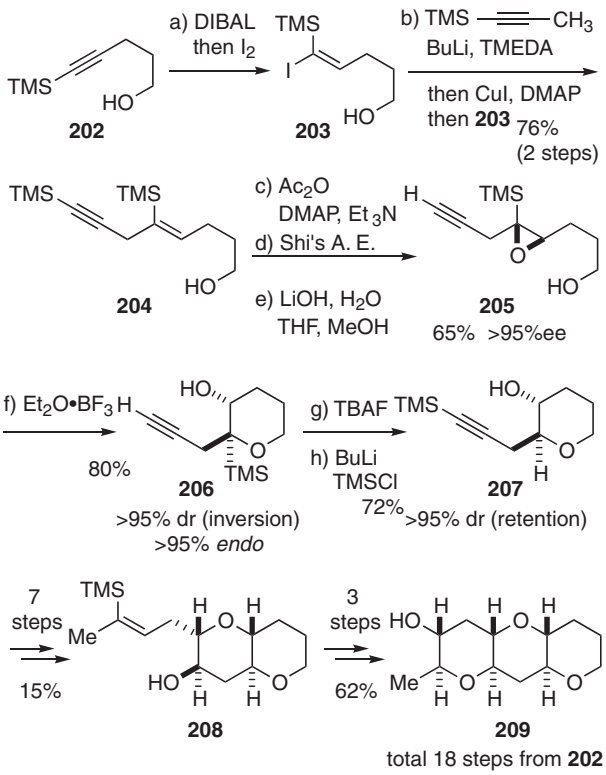
Jamison also developed a method for enantioselective preparation of hydroxy epoxy silanes, which was linked to the above *endo*-cyclization reaction to provide an efficient iterative process for the synthesis of *trans*-fused poly(tetrahydropyran)s (Scheme 57).[42]

Mori established a unique method for *endo*-selective cleavage of hydroxy epoxide **212** giving oxanone **213**, based on inactivation of *exo*-cleavage by an electron-withdrawing sulfone group at the *exo*-site (Scheme 58).[43] This idea was complementary to that of the π-orbital-assisted cyclizations. The substrate **212** was readily prepared from an anion of optically active epoxy sulfone **211** and triflate **210**.

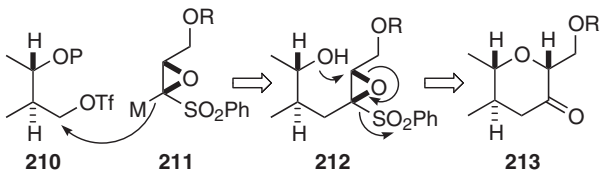
The *endo*-cyclization method was also available for sterically more crowded oxanes (Scheme 59).[44] Indeed, formation of di-*t*-alkyl ether **215** ($R^1 = R^2 = Me$) was achieved by use of a combination of two Lewis acids ($Et_2O{\cdot}BF_3/Tl(TFA)_3$).

The iterative use of the method was demonstrated to show its effectiveness for a *trans*-fused polycyclic ether system, in which a tetrahydropyran ring was constructed in only 5 steps (Scheme 60).[43] It was also applied to efficient total synthesis of hemibrevetoxin B.[45]

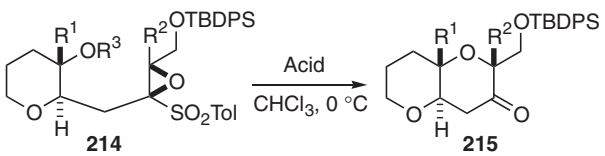
We designed an alternative hydroxy epoxide system for 6-*endo*-selective cyclization, in which a methoxymethyl group was employed at the C4 position of a 4,5-epoxy-1-ol unit



Scheme 57.



Scheme 58.

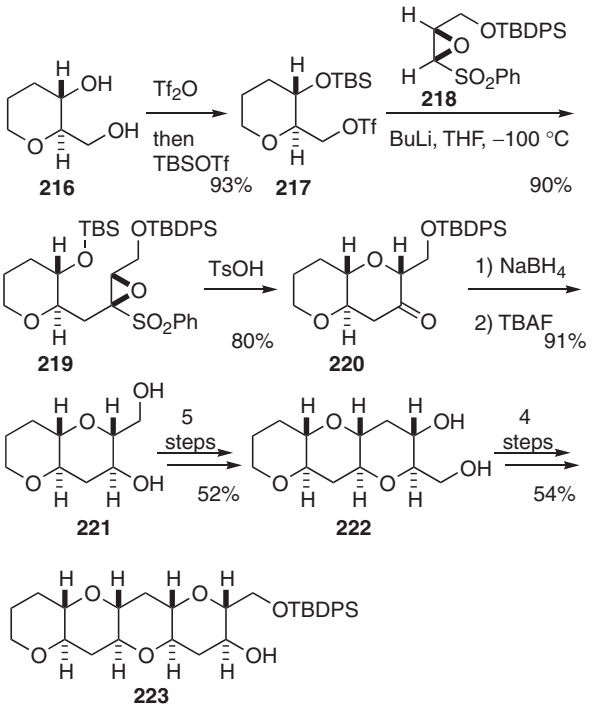


R^1	R^2	R^3	Acid	Yield
H	Me	TES	$TsOH{\cdot}H_2O$ (1.5 eq)	90%
Me	H	TMS	$Et_2O{\cdot}BF_3$ (5 eq)	89%
Me	Me	TMS	$Et_2O{\cdot}BF_3/Tl(TFA)_3$ (1.0/3.0 eq)	62%

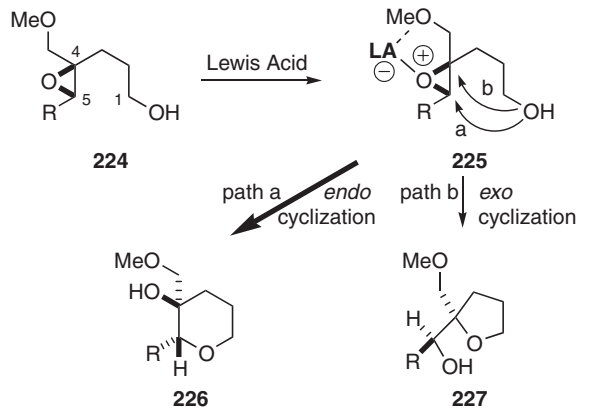
Scheme 59.

(**224**) (Scheme 61).[46] The *endo*-cyclization would be enhanced by activating the C5–O bond through coordination of a Lewis acid between the oxygens of the epoxides and the methoxymethyl group.

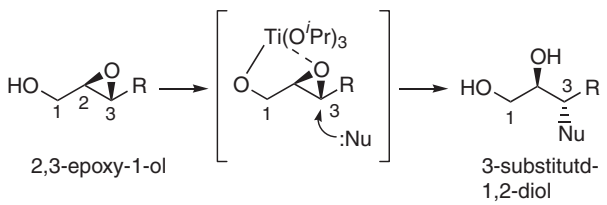
So far, such site-selective epoxide-cleavage by anchimeric assistance under Lewis acidic conditions has been well known in intermolecular nucleophilic reactions. For example, Sharpless reported that the reactions of a 2,3-epoxy-1-ol system with several nucleophiles selectively produced C3-substituted products in the presence of titanium (IV) isopropoxide



Scheme 60.



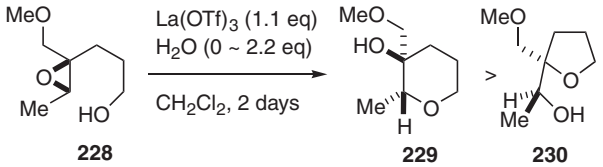
Scheme 61.



Scheme 62.

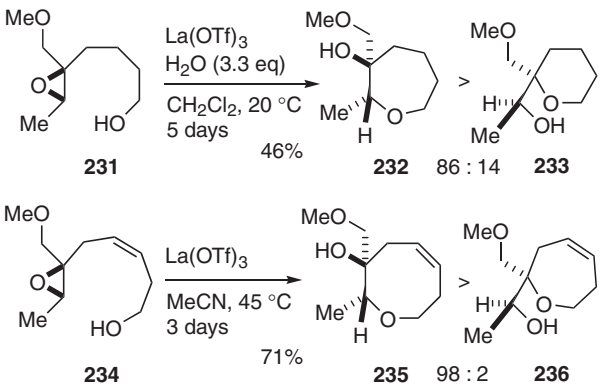
(Scheme 62).[47] On the other hand, the corresponding intramolecular epoxide cleavage with an oxygen nucleophile has not been reported yet. Thus, we first examined the cyclization of simple *cis*-4-methoxymethyl-4,5-epoxy-1-hexanol **228** (Scheme 63).

After extensive exploration for an effective Lewis acid to the *endo*-cyclization of **228**, it was found that partially hydrated $La(OTf)_3$, prepared from anhydrous $La(OTf)_3$ and 2–3

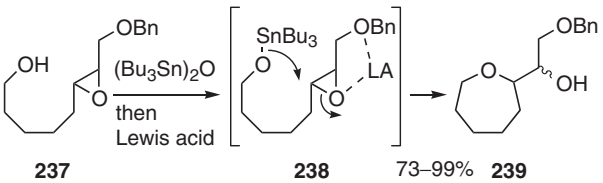


H_2O (eq)	Yield	**229** : **230**
0	94%	53 : 47
2.2	96%	90 : 10

Scheme 63.



Scheme 64.

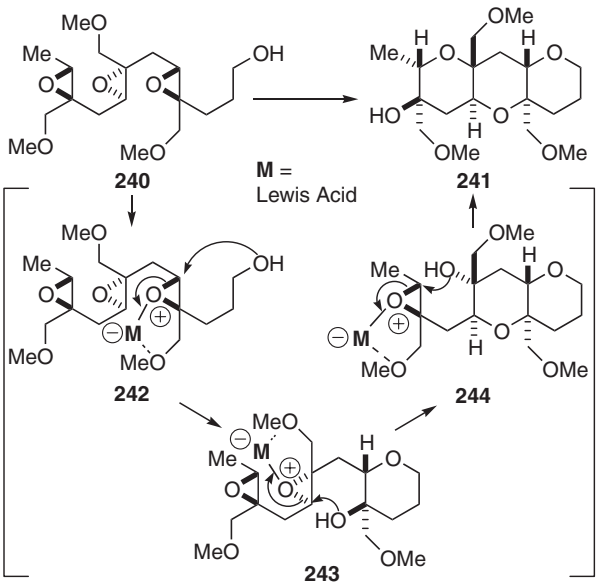


Scheme 65.

equiv. of water before use, efficiently catalyzed *endo*-cyclization to produce **229** predominantly (Scheme 63). The combination of $La(OTf)_3$ and the methoxymethyl group adjacent to the epoxide part was also effective in 7-*endo*-cyclization of **231** as well as in 8-*endo*-cyclization of **234** (Scheme 64).[48]

At almost the same time, Suzuki reported similar anchimeric assistance in his synthesis of medium ring ethers. He achieved Lewis acid-catalyzed selective 7-*exo* and 8-*exo* cyclization of hydroxy epoxides having a benzyloxymethyl group adjacent to the epoxide part (Scheme 65).[49] The enhanced substrate reactivity and *exo*-selectivity were explained by coordination of a Lewis acid between the benzyloxymethyl and epoxide groups. He also applied the method to total synthesis of natural medium ethers.[50]

Next, we planned a cascade 6-*endo*-cyclization reaction of triepoxide **240** based on our established method (Scheme 66). After the first *endo*-cyclization induced by the coordination of a Lewis acid to the first epoxide (**242**), the Lewis acid was expected to move to the next epoxide and to induce the next *endo*-cyclization (**243**). The catalytic process was anticipated to repeat until the last *endo*-cyclization was finished



Scheme 66.

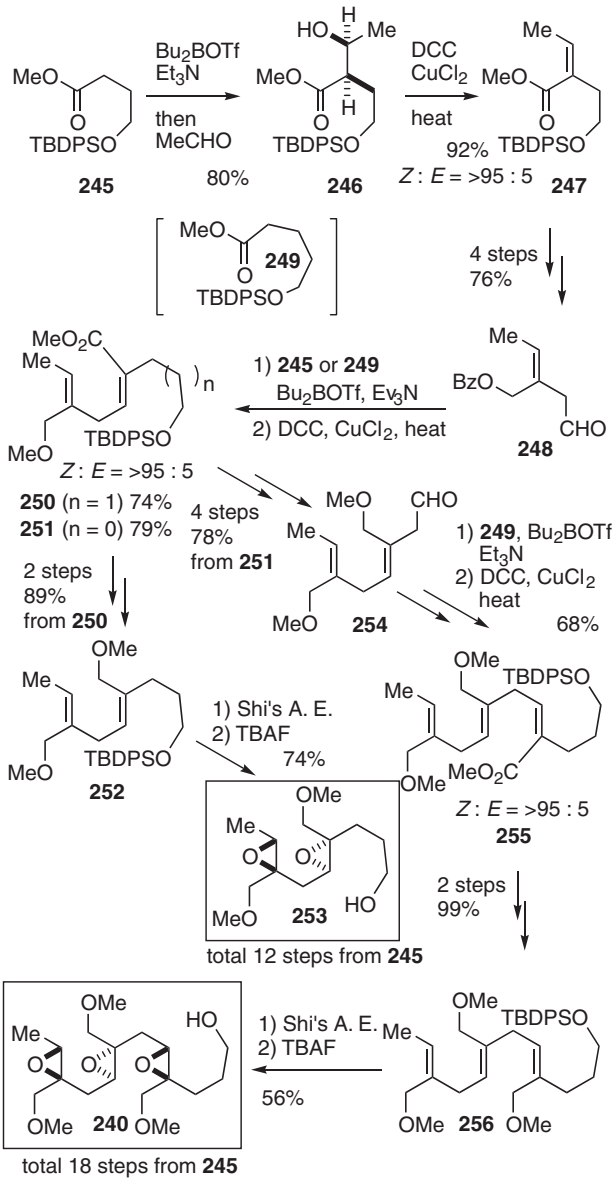
(**244** → **241**).

Synthesis of di- and tri-epoxide substrates **253** and **240** was based on *Z*-selective trisubstituted-olefin-formation followed by the Shi asymmetric epoxidation (Scheme 67).[51,52] Diene and triene precursors **252** and **256** were prepared from esters **245** and **249** through a process including *syn*-selective Abiko–Masamune-ester-boron-aldol-reaction[53] and the subsequent *syn*-elimination of water.[54] The precursors **252** and **256** were successfully epoxidized by Shi's method[51] to produce **253** and **240** stereoselectively.

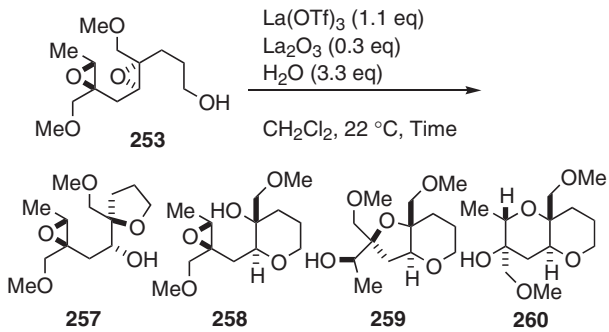
When diepoxide **253** was treated with partial hydrated $La(OTf)_3$ in the presence of a small amount of La_2O_3 for 24 h, *trans*-fused bicyclic ether **260** was produced as a major component along with bicyclic **259** and monocyclic **257** and **258** (Scheme 68).[5b] In this reaction, time-dependence of the product distribution was also observed. Prolonged reaction time (48 h) provided a significant decrease of **258** and increases of **260** and **259**. On the other hand, the two product ratios of *endo*/*exo* corresponding to the first and the second cyclization steps did not change independently of the reaction time. This suggested that the cyclization reaction of **253** proceeded in a stepwise manner as we expected.

Finally, the cyclization of triepoxide **240** was examined under similar conditions (Scheme 69).[52] Treatment of **240** with $La(OTf)_3$–H_2O (a 1:5 molar ratio) in the presence of La_2O_3 in CH_2Cl_2 produced *trans*-fused tricyclic ether **241** in 9.3% yield along with monocyclic ether **261** in 15%. Other products were given as an inseparable complex mixture. Thus, the first biomimetic cascade *endo*-cyclization of hydroxy triepoxide **240** via the monocyclic epoxonium ion intermediate corresponding to path B in Scheme 2 was achieved.

The facts that the *endo*-selectivity of the first cyclization was low and the reaction rate was slower than that of **253** might suggest insufficient catalytic activity of $La(OTf)_3$ for the polyepoxide cyclization. Searching for more active catalysts is a future issue for achieving more efficient cascade *endo*-cyclization of this polyepoxide system.

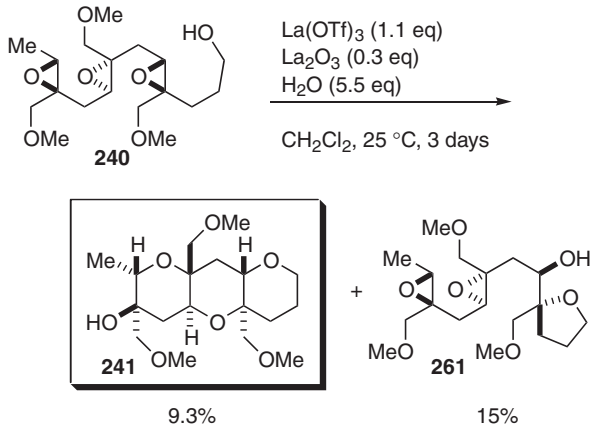


Scheme 67.



Time	257	258	259	260	1st cyclization (*exo* / *endo*)	2nd cyclization (*exo* / *endo*)
24 h	14%	14%	3.5%	40%	(20 / 80)	(8 / 92)
48 h	15%	0.3%	4.5%	52%	(21 / 79)	(8 / 92)

Scheme 68.



Scheme 69.

Conclusion

Natural polyethers, produced by marine dinoflagellates, are hypothesized to be biosynthesized through a domino cyclization reaction of a polyepoxide precursor. The hypothesis provides not only an elegant explanation for the biogenesis of polyethers but also new concepts for chemical synthesis. The hypothesis is interpreted in two different modes in synthetic organic chemistry, one of which is domino epoxide-ring-expansion including *bicyclic epoxonium ion intermediates* and the other is cascade *endo*-cyclization of a hydroxy polyepoxide via *monocyclic epoxonium ion intermediates*. This review has shown that these two reaction modes are also seen in many chemical syntheses of *trans*-fused cyclic ethers. Both types of chemical reactions have provided brilliant total syntheses of natural polyethers as well as efficient biomimetic cascade polyether-formation reactions from polyepoxide precursors.

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Kenshu Fujiwara, Associate Professor at Hokkaido University, was born in Nemuro, Japan, in 1963. He graduated from Tohoku University in 1986 and received his Ph.D. in 1991 under the supervision of Professor Masahiro Hirama. After he worked at Tohoku University as a JSPS postdoctoral fellow for 1991–1992 and at Banyu Pharmaceutical Co. Ltd. as a research scientist for 1992–1993, he joined Professor Akio Murai's group at Faculty of Science, Hokkaido University in 1993 as Research Associate. Then, he worked at Graduate School of Science, Hokkaido University as Research Associate for 1995–1998, as Lecturer for 1998–2000, and as Associate Professor from 2000. He is currently interested in the synthesis of marine natural products, represented by fused-polycyclic ethers, halogenated medium ring ethers, and polyether macrolides.

Akio Murai, Professor Emeritus of Hokkaido University, was born in Sapporo, Japan, in 1938. He graduated from Faculty of Agriculture, Hokkaido University in 1963, and received his Ph.D. in 1966 under the supervision of Tadashi Masamune at Graduate School of Science, Hokkaido University. He worked at Faculty of Science, Hokkaido University as Research Associate for 1966–1976, as Lecturer for 1976–1980, as Associate Professor for 1980–1988, and as Professor for 1988–1995. Then, he worked as Professor at Graduate School of Science, Hokkaido University for 1995–2002. In 2002, he retired and became Professor Emeritus of Hokkaido University. During 1972–1974 he joined Professor James P. Kutney's group at British Columbia University as a Postdoctoral Fellow. His awards include Matsunaga Research Fellowship Award in 1969, the Prize of Organic Chemistry Division of the Chemical Society of Japan in 1987, and 1997–1998 Eli Lilly Lectureship Award in 1998. He has been interested in isolation, total synthesis, and biosynthesis of natural products.