CHEMICAL REALIZATION OF THE BIOGENETIC PATHWAYS PROPOSED FOR THE FUSED-POLYCYCLIC ETHERS OF MARINE ORIGINS

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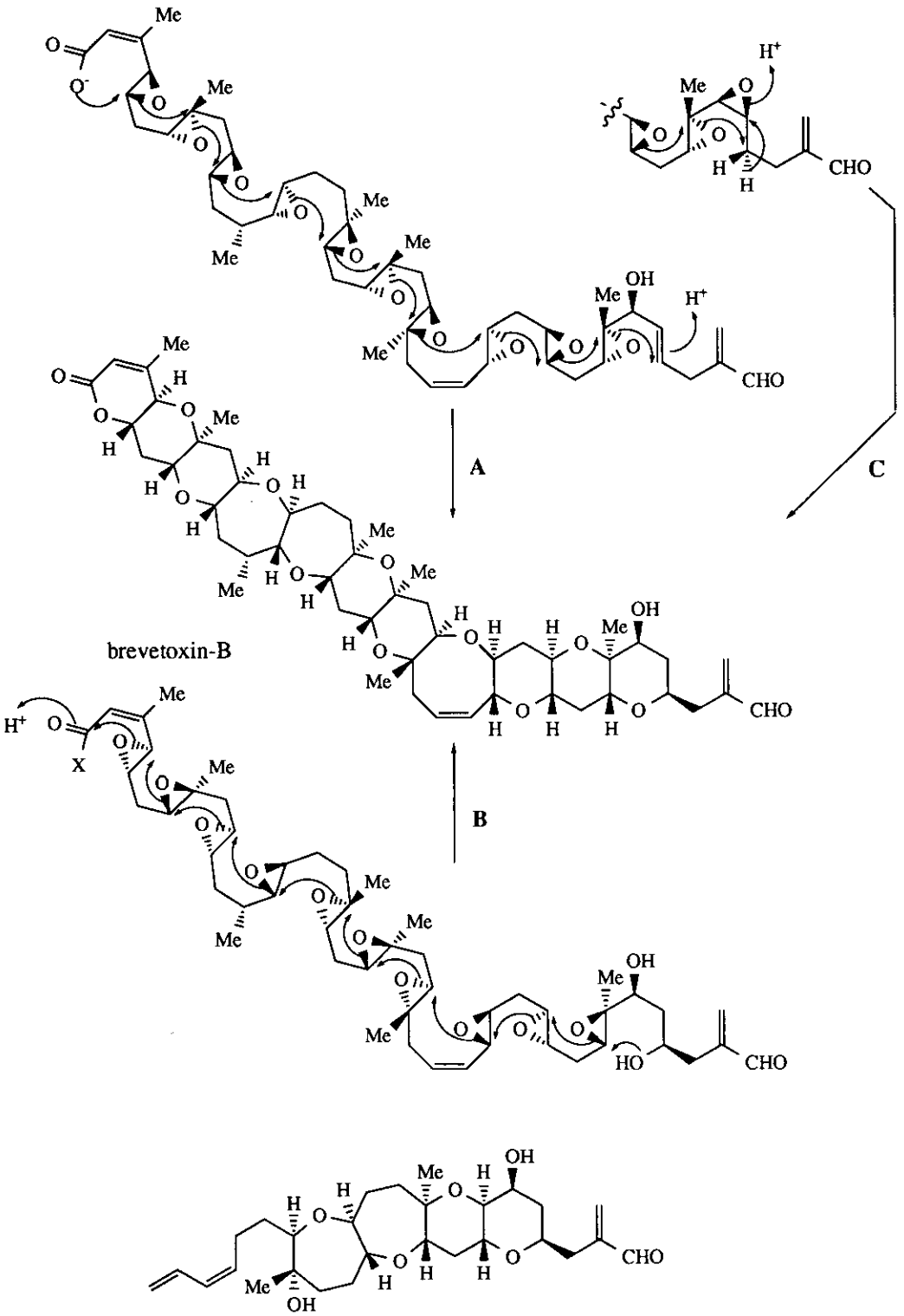
Abstract-The biomimetic constructions of fused polycyclic ethers of marine origins according to the proposals for their biogenetic pathways starting from *trans*-polyepoxide compounds could be realized chemically as the model experiments in two ways: one is regarded epoxy groups as electrophiles and other is those as nucleophiles.

1. Introduction.

Since brevetoxin-B was isolated from the red-tide organism, *Gymnodinium breve*, and the structure was determined by Nakanishi in 1981,[1] isolation of many fused-cyclic polyethers has continued to be reported from marine sources.[2] The representatives are halichondrins,[3] brevetoxin-A,[4] hemibrevetoxin-B,[5] ciguatoxins,[6] and maitotoxin.[7] Halichondrins exhibit remarkable *in vivo* antitumor activity. The other compounds always showed very highly toxic properties and involved in human intoxication. Particularly, the last compound having the molecular weight of 3422 Da (as the disodium salt) has attracted much attention from the various fields and, in 1996, the complete relative stereochemistry has been determined by Tachibana[8] and Kishi groups.[9] Furthermore, the absolute configuration of ciguatoxin has very recently been decided by Yasumoto.[6d] From the view points of their characteristic structures, many synthetic chemists have challenged the total syntheses of these compounds. One of the winners is Kishi, who has succeeded in the first total synthesis of halichondrin-B in 1992.[10] On the other hand, Nicolaou has developed various brilliant new concepts for construction of successively fused polycyclic ether system as the pioneer of this field and eventually accomplished the first total syntheses of hemibrevetoxin-B in 1992,[11] brevetoxin-B in 1995,[12a-12g] and brevetoxin-A[12h] in 1998. The total syntheses of hemibrevetoxin-B have also been achieved by Yamamoto,[13] Nakata,[14] and Mori.[15] We have also completed the whole mother skeleton of the compound[16] by applying our established lactone enol triflate method.[17] At the present time, many groups are now in progress aiming to the synthesis of ciguatoxin.[18]

Concerning the biogenesis of these fused polycyclic ethers represented by brevetoxin-B, Nakanishi[19] had initially speculated the pathway (A) involving successive ring closure of the respective polyepoxide



Scheme 1.

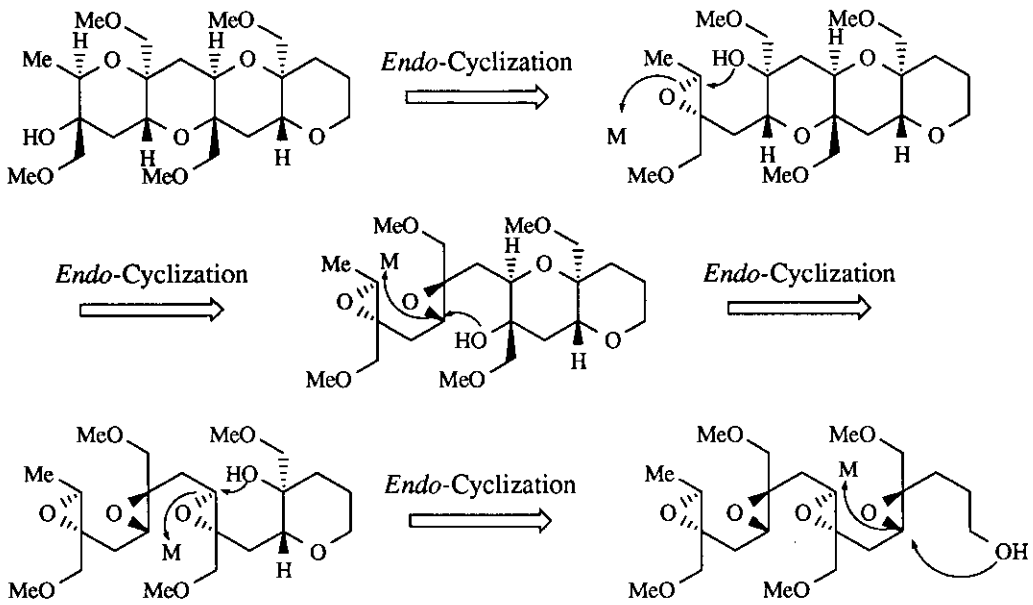
initiated synchronously by attack of the carboxylate ion to the oxirane carbon at the left terminus of the carbon chain as well as protonation at the olefinic double bond at the right terminus (Scheme 1). Shimizu[20a] had proposed an alternate route (**B**) involving amphiphilic intramolecular attack of hydroxyl group of the right site to the near oxirane carbon commencing with protonation to carbonyl oxygen at the left site of the polyepoxy alcohol precursor. After the isolation of hemibrevetoxin-B, Shimizu[20b] had suggested newly another scheme (**C**) by initial opening of the *cis*-epoxide at the right end followed by a hydride ion transfer and consecuitive *trans*-epoxide openings, which seems to be similar to the path **A**, because the structure of hemibrevetoxin-B constitutes essentially the right half of brevetoxin molecules and doesn't involve the lactone part in the left side of brevetoxins.[2a,5] Unfortunately, there have not been any chemical supports for these proposals for the cascade of the epoxide openings. All the routes involve the successive *trans*-epoxide openings in an *endo* fashion against the Baldwin rule.[21] We have attempted to realize such proposals chemically in two ways; one is regarded epoxy groups as electrophiles[22] and other is those as nucleophiles.[23]

2. *Endo*-Selective Ring Closure of Epoxy Alcohols Regarding Epoxy Groups as Electrophiles.

In order to access synthetically the marine polycyclic ether compounds consisting of *cis*- and *trans*-fused tetrahydropyran ring systems, stereoselective and *endo*-selective intramolecular opening of epoxy alcohols would be a most attractive strategy. Four major successful tactics have been developed in line with this strategy: activation of *trans*-epoxides by an adjacent π-donor such as vinyl moiety,[24] palladium-catalyzed procedures,[25] intramolecular Nicholas reactions,[26] and deactivation of oxirane ring system by electron-withdrawing group.[15,27] Furthermore, *endo*-cyclization of epoxy alcohol system has recently been succeeded using catalytic antibody.[28] We have planned the more convergent construction of the fused polycyclic ether systems starting from the polyene epoxides by *stepwise* chelation-controlled *endo*-cyclization by introducing the methoxymethyl groups at the respective epoxide carbon atoms (Scheme 2), while there have been no chemically established evidence involving *successive* or *stepwise endo* cyclization of the epoxy alcohols for the proposed biogenetic pathway. In our plan, the epoxy groups are regarded as electrophiles as the chemically normal species. Although Lewis acid catalyzed intermolecular nucleophilic attacks to C3 position in the 2,3-epoxy-1-ol system have been well known,[29] the corresponding intramolecular version of this type has not been reported yet except the case of C-nucleophiles.[30]

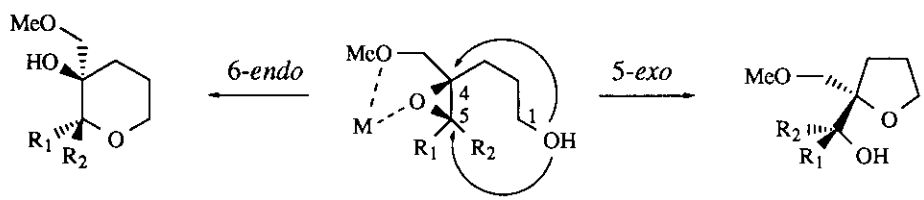
2-1. $La(OTf)_3$-Catalyzed 6-*Endo*-Epoxide Opening of 4,5-Epoxy-4-methoxymethyl-1-hexanols.

We planned to enhance the intramolecular attack of the hydroxy group in 4,5-epoxy-1-hexanol to C5 position rather than to C4 by activating the C5-O bond through chelation of Lewis acid between the oxygen atoms of the epoxide and the methoxymethyl group at C4 as simple ligands (Scheme 3). Based on the above consideration, the stereochemically homogeneous *trans*- (**1a**) and *cis*-epoxides (**1b**) were



Scheme 2.

treated with several Lewis acids in some solvent systems under the conditions as shown in Table 1.[22a] In order to establish the reaction conditions, we initially examined the cyclization of **1a**. In the first place, we anticipated that the 6-*endo* selective ring closure would be achieved by using a bidentate Lewis acid, while the 5-*exo* closure would naturally occur by using a unidentate Lewis acid according to Baldwin's rule.[21] The use of CSA or $BF_3{\cdot}OEt_2$ produced only tetrahydrofuran (**3a**) in 92% and 95% yields, respectively, as expected (Entries 1 and 2). Contrary to our expectation, in the case of bidentate $TiCl_4$, **1a** gave **3a** in 34% yield together with C5 chlorinated **4** in 24% yield (Entry 3). On the other hand, although the reaction with lanthanide Lewis acid $CeCl_3$ afforded **4** as a major product in 69% yield after 13 days, it also gave 6-*endo* cyclic tetrahydropyran (**2a**) stereospecifically along with **3a** as a 1:1 mixture in a 17% combined yield (Entry 5). At this moment, it was postulated that lanthanide Lewis acid might form the same chelation with **1a**, which would make the 5-*exo* cyclization slow enough to



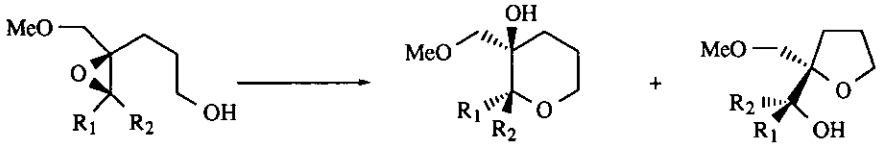
2
Tetrahydropyran

1a: R^1=H, R^2=Me
1b: R^1=Me, R^2=H
M: Lewis acid

3
Tetrahydrofuran

Scheme 3.

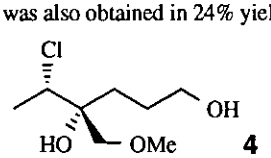
Table 1.



1a: R^1=H, R^2=Me **2a: R^1=H, R^2=Me** **3a: R^1=H, R^2=Me**
1b: R^1=Me, R^2=H **2b: R^1=Me, R^2=H** **3b: R^1=Me, R^2=H**

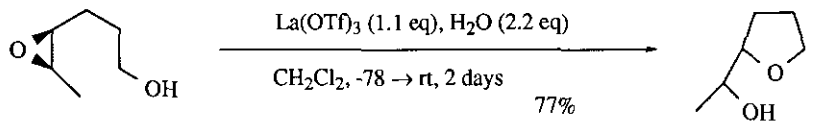
Entry	1	Conditions					Cyclic ethers	
		Lewis acid (eq)	H_2O/eq	Solv.	Temp./°C	Time	Yield/%	Ratio[a]
1	**1a**	CSA (0.1)	0	CH_2Cl_2	20	10 min	92	**2a**:**3a**= 0:100
2		$BF_3{\cdot}OEt_2$ (1.1)	0	CH_2Cl_2	-78 → 20	30 min	95	0:100
3		$TiCl_4$ (1.1)	0	CH_2Cl_2	-70	2 h	34[b]	0:100
4		$Sn(OTf)_2$ (1.1)	0	CH_2Cl_2	-78	30 min	88	0:100
5		$CeCl_3$ (1.2)	0	CH_2Cl_2	20	13 days	17[c]	50: 50
6		$La(OTf)_3$ (1.1)	0	CH_2Cl_2	20	14 h	87	0:100
7		$La(OTf)_3$ (1.1)	1.1	CH_2Cl_2	20	2 days	72	70: 30
8		$La(OTf)_3$ (1.1)	2.2	CH_2Cl_2	20	2 days	68	82: 18
9		$La(OTf)_3$ (1.1)	3.3	CH_2Cl_2	20	2 days	74	82: 18
10		$La(OTf)_3$ (1.1)	0	THF	20	2 days	90	48: 52
11		$La(OTf)_3$ (1.1)	2.2	THF	20	2 days	92	52: 48
12		$La(OTf)_3$ (1.1)	0	Et_2O	20	2 days	75	0:100
13		$La(OTf)_3$ (1.1)	2.2	Et_2O	20	2 days	89	10: 90
14	**1b**	CSA (0.2)	0	CH_2Cl_2	20	10 min	97	**2b**:**3b**= 17: 83
15		$La(OTf)_3$ (1.1)	0	CH_2Cl_2	20	2 days	94	53: 47
16		$La(OTf)_3$ (1.1)	2.2	CH_2Cl_2	20	2 days	96	90: 10

a) Estimated by 400 MHz ^{1}H-NMR. b) **4** was also obtained in 24% yield. c) **4** was also obtained in 69% yield.



4

compete with the intermolecular attack of the nucleophilic ligand of Lewis acid to C5 and with 6-*endo* cyclization. With these thoughts in mind, **1a** was treated with $La(OTf)_3$[31] as a lanthanide Lewis acid having a less nucleophilic ligand under anhydrous conditions in order to prevent the intermolecular nucleophilic attack. However, the reaction gave only **3a** after 14 h (Entry 6), as in the case of $Sn(OTf)_2$ (Entry 4). Fortunately, when we used moist $La(OTf)_3$, **2a** was surprisingly provided together with **3a**. After repeated examination, it was found that the presence of 2 or 3 eq of H_2O in CH_2Cl_2 affords **2a** effectively along with **3a** in the ratio of 82:18, respectively, after 2 days (Entries 7, 8, 9).[32,33] This reaction was then examined in etherial solvents. When the reaction was attempted in THF, **2a** was produced with an equal amount of **3a** whether H_2O was added or not (Entries 10, 11). In the case of Et_2O, the complete 5-*exo* cyclization under anhydrous conditions (Entry 12) and low 6-*endo* selectivity under hydrous conditions (Entry 13) were observed. It seems that both THF and Et_2O might coordinate to the La atom and inhibit coordination of H_2O to La due to the donating properties of etherial oxygens. THF appears to act like H_2O, while Et_2O shows no effect on the enhancement of the 6-*endo* cyclization. Next, we examined the cyclization of *cis*-epoxy alcohol (**1b**) and obtained almost similar data to the cases of **1a**. The reaction mediated by CSA afforded **3b** as a major product along with a small amount of **2b** (Entry 14). $La(OTf)_3$ gave **2b** predominantly (**2b**:**3b** = 90:10) and stereospecifically in the presence of 2 eq of H_2O (Entry 16), while it gave a 1:1 mixture of **2b** and **3b** under anhydrous conditions (Entry 15). When we treated simple epoxy alcohol (**5**) with $La(OTf)_3$ and 2 eq of H_2O under the same conditions as Entry 16, 5-exocyclic **6** was afforded as a sole product (Scheme 4). It is suggested that the methoxymethyl group at C4 of **1** could play an important role in the activation of epoxide with $La(OTf)_3$ as an intramolecular ligand.

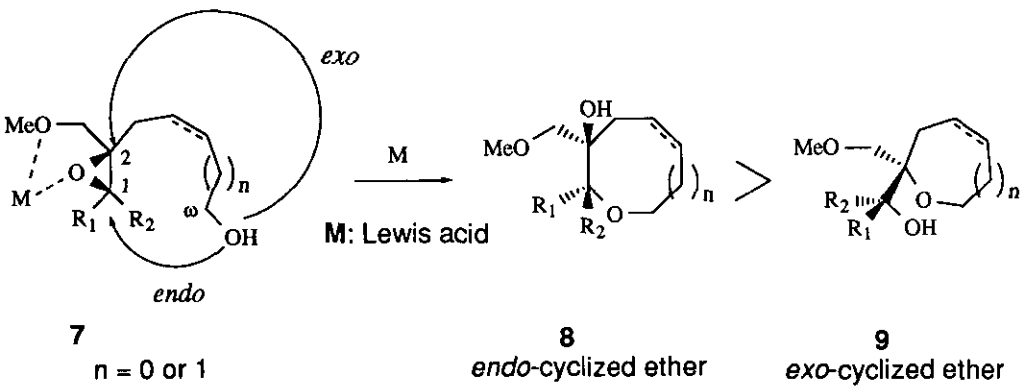


5 **6**

Scheme 4.

2-2. $La(OTf)_3$-Catalyzed 7-*Endo* and 8-*Endo* Selective Cyclizations of Hydroxy Epoxides.

Although many efficient methods which are capable of the 6-*endo* ring closure of hydroxy epoxide rather than the usually favored 5-*exo* mode have been developed until now,[24-28] only a few general methods for the 7-*endo* selective cyclization[18k,34] and none for the 8-*endo* mode have been reported. We have been interested in the possibility of extension of our methodology[22a] to the 7-*endo* and 8-*endo* cyclization which provides a new entry to medium-sized cyclic ethers. We have searched for an effective Lewis acid on *endo*- selective cyclization in a 2-methoxymethyl-1,2-epoxy-ω-ol system (**7**; ω=6 or 7) and achieved the 7-*endo* and the first 8-*endo* selective cyclizations by our methodology using $La(OTf)_3$ (Scheme 5).[22b]



7 n = 0 or 1 **8** *endo*-cyclized ether **9** *exo*-cyclized ether

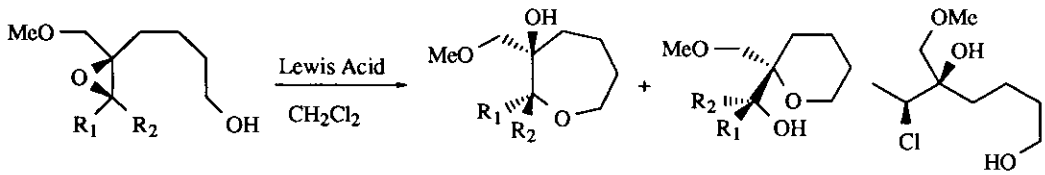
Scheme 5.

At first, *trans*- and *cis*-5,6-epoxy-5-methoxymethylheptan-1-ols (**10a** and **10b**) were treated with each of the single-coordinating [CSA and $BF_3{\cdot}OEt_2$] and multi-coordinating Lewis acids [$TiCl_4$, $Sn(OTf)_2$, $Zn(OTf)_2$, and $La(OTf)_3$] in CH_2Cl_2 under the conditions as shown in Table 2. When CSA was used, 6-*exo* cyclization predominated over 7-*endo* to produce oxanes (**12a**) and (**12b**) selectively from **10a** and **10b**, respectively (Entries 1 and 8). Similar 6-*exo* selection was also observed in the reactions of $BF_3{\cdot}OEt_2$ (Entries 2 and 9). Treatment of **10a** with $TiCl_4$ gave only a chlorohydrin (**13**) in high yield (Entry 3). In both the cases of $Sn(OTf)_2$ or $Zn(OTf)_2$ having a less nucleophilic ligand, **10a** and **10b** gave the respective oxanes mainly (Entries 4, 5, 10, and 11), although some ligand addition reactions could be avoided. In the case of $La(OTf)_3$[31] under anhydrous conditions, the 7-*endo* cyclization of **10a** proceeded to give oxepane (**11a**) mainly (Entry 6, **11a**:**12a**=81:19) in contrast to the 6-*exo* selective cyclization of **10b** (Entry 12, **11b**:**12b**=18:82). The addition of 3 eq of H_2O to $La(OTf)_3$ improved the 7-*endo* opening of epoxide in both the cases of **10a** and **10b** (**11a**: **12a**=92:8; Entry 7 and **11b**:**12b**=86:14; Entry 13), while the reaction rate in **10b** slowed down.

Secondly, we examined the cyclization of *trans*- and *cis*-6,7-epoxy-6-methoxymethyloctan-1-ols (**14a** and **14b**, Table 3). After several attempts, only $Zn(OTf)_2$ and $La(OTf)_3$ gave cyclic ethers (**15** and **16**) along with aldehyde (**17**) albeit in low yields under the conditions shown in Table 3.[35] While $Zn(OTf)_2$ gave oxepane predominantly (Entries 1 and 4), $La(OTf)_3$ effected 8-*endo* cyclization comparably to the *exo* mode (Entries 2, 3, 5, and 6).

Next, *trans*- and *cis*-6,7-epoxy-6-methoxymethyl-3-octen-1-ols (**18a** and **18b**) were investigated (Table 4). Treatment of **18** with CSA at 25 °C for several days produced only a small amount of cyclic ethers along with the recovery of the majority of the starting epoxides. Surprisingly, **18b** gave 8-*endo* cyclized ether mainly under the conditions (**19b**:**20b**=89:11, Entry 7), while **18a** afforded a 44:56 mixture of **19a** and **20a** (Entry 1). The preferential production of the oxocene from **18b** was also observed in the case of $BF_3{\cdot}OEt_2$ under highly diluted conditions (**19b**:**20b**=83:17, Entry 8), although the yield of cyclization was modest (27%) with concomitant production of **22**. On the other hand, the reaction of **18a** under the same conditions gave a mixture of **19a** and **20a** in moderate yield (56%) in the ratio of 22:78, respectively

Table 2.

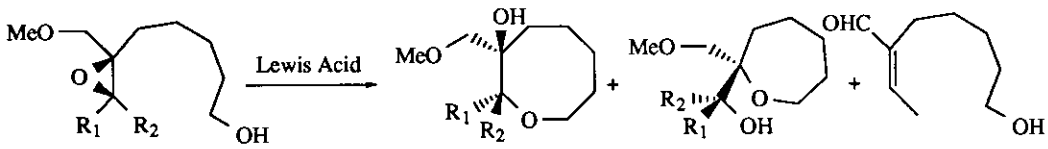


10a: R^1=H, R^2=Me **11a: R^1=H, R^2=Me** **12a: R^1=H, R^2=Me**
10b: R^1=Me, R^2=H **11b: R^1=Me, R^2=H** **12b: R^1=Me, R^2=H** **13**

Entry	10	Conditions				Cyclic ethers		Recovery of 10/%
		Lewis acid (eq)	H_2O/eq	Temp./°C	Time	Yield/%	Ratio[a]	
1	**10a**	CSA[b] (0.1)	0	20	24 h	90	**11a**:**12a**= 5: 95	**10a**= 0
2		BF_3·OEt_2[c] (1.1)	0	20	1 h	61	3: 97	0
3		$TiCl_4$[b] (1.1)	0	-78	1 h	0[f]	—	0
4		$Sn(OTf)_2$[b] (1.1)	0	20	1 h	64	5: 95	0
5		$Zn(OTf)_2$[b] (1.1)	0	20	3 h	70	21: 79	0
6		$La(OTf)_3$[d,e] (1.1)	0	20	3 days	73	81: 19	21
7		$La(OTf)_3$[b,e] (1.1)	3.3	20	3 days	74	92: 8	10
8	**10b**	CSA[b] (0.1)	0	20	3 h	82	**11b**:**12b**=11: 89	**10b**= 0
9		BF_3·OEt_2[b] (1.1)	0	20	1.5 h	73	3: 97	0
10		$Sn(OTf)_2$[b] (1.1)	0	20	1 h	74	8: 92	0
11		$Zn(OTf)_2$[b] (1.1)	0	20	2 h	81	8: 92	0
12		$La(OTf)_3$[b,e] (1.1)	0	25	5 days	100	18: 82	0
13		$La(OTf)_3$[b,e] (1.1)	3.3	25	5 days	46	86: 14	34

a) Estimated by GLC. b) The concentration of substrate was 80 mM. c) The concentration of substrate was 50 mM. d) The concentration of substrate was 60 mM. e) La_2O_3 was contained [molar ratio La_2O_3:$La(OTf)_3$=1:4]. f) 82% production of **13**.

Table 3.



14a: R^1=H, R^2=Me **15a: R^1=H, R^2=Me** **16a: R^1=H, R^2=Me**
14b: R^1=Me, R^2=H **15b: R^1=Me, R^2=H** **16b: R^1=Me, R^2=H** **17**

Entry	14	Conditions				Cyclic ethers		Yield of 17/%
		Lewis acid (eq)	Solvent[a)]	Temp./°C	Time	Yield/%	Ratio[b)]	
1	**14a**	$Zn(OTf)_2$ (1.1)	CH_2Cl_2	25	5 days	trace	**15a**:**16a**=33: 66	25
2		$La(OTf)_3$[c)] (1.1)	CH_3CH_2CN	55	3 days	2	63: 37	0
3		$La(OTf)_3$[c)] (1.1)	$(CH_2Cl)_2$	55	6 days	7	56: 44	8
4	**14b**	$Zn(OTf)_2$ (1.0)	CH_2Cl_2	20	7 days	14	**15b**:**16b**=33: 66	6
5		$La(OTf)_3$[c)] (1.1)	CH_3CH_2CN	60	6 days	23	43: 57	7
6		$La(OTf)_3$[c)] (1.1)	$(CH_2Cl)_2$	55	6 days	10	47: 53	24

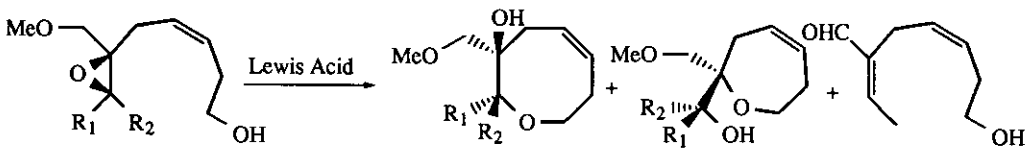
a) The concentration of substrate was 50 mM. b) Estimated by 300 MHz ^{1}H-NMR. c) La_2O_3 was contained [molar ratio La_2O_3:$La(OTf)_3$=1:4].

(Entry 2). The use of $Sn(OTf)_2$ gave only complex by-products, probably due to its strong Lewis acidity. When $Zn(OTf)_2$ was used, the 8-*endo* selective cyclization of **18a** was observed to give an 84:16 mixture of **19a** and **20a** in 49% yield (Entry 3). Even under the same conditions, **18b** afforded cyclic ethers only in low yield and selectivity. In both the reactions of **18a** and **18b** with $La(OTf)_3$, exclusive 8-*endo* cyclization was effected, although prolonged reaction time needed for consumption of the starting material in each case (Entries 4 and 10). The addition of H_2O lowered the activity of the catalyst and 8-*endo* selectivity (Entry 5). Acetonitrile as a solvent was also useful in the reaction of **18a** and heightened the yield of the oxocene from **18b** (Entries 6 and 12). Heating was effective for increase of the reaction rate without reduction of the *endo* selectivity (Entries 11 and 13).

2-3. Discussion.

We could find a new 6-*endo* ring closure reaction of *trans*- and *cis*-4,5-epoxy-4-methoxymethyl-1-hexanols rather than the usually favored 5-*exo* mode by the chelation of $La(OTf)_3 \cdot nH_2O$ between the oxygen atoms of the epoxide and the methoxymethyl groups. From the fact that the reaction under hydrous conditions took longer than under anhydrous conditions and that lanthanoid metal has a large ionic

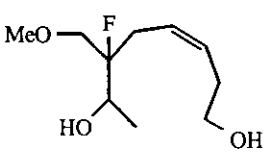
Table 4.



18a: R^1=H, R^2=Me **19a: R^1=H, R^2=Me** **20a: R^1=H, R^2=Me**
18b: R^1=Me, R^2=H **19b: R^1=Me, R^2=H** **20b: R^1=Me, R^2=H** **21**

Entry	**18**	Conditions				Cyclic ethers		Yield of **21**/%
		Lewis acid (eq)	Solvent[a]	Temp./°C	Time	Yield/%	Ratio[a]	
1	**18a**	CSA (0.1)	CH_2Cl_2[d]	25	11 days	4	**19a**:**20a**=44: 56	trace
2		$BF_3{\cdot}OEt_2$ (1.1)	CH_2Cl_2[e]	5	17 h	56	22: 78	8
3		$Zn(OTf)_2$ (1.1)	CH_2Cl_2[d]	20	3 days	49	84: 16	1
4		$La(OTf)_3$[b] (1.1)	CH_2Cl_2[f]	25	6 days	42	96: 4	0
5		$La(OTf)_3$[b,c] (1.1)	CH_2Cl_2[f]	25	8 days	3	91: 9	0
6		$La(OTf)_3$[b] (1.1)	CH_3CN[f]	25	7 days	40	98: 2	0
7	**18b**	CSA (0.1)	CH_2Cl_2[d]	25	5 days	8	**19b**:**20b**=89: 11	4
8		$BF_3{\cdot}OEt_2$ (1.1)	CH_2Cl_2[e]	5	6 h	27[g]	83: 17	8
9		$Zn(OTf)_2$ (1.1)	CH_2Cl_2[d]	20	23 h	12	50: 50	19
10		$La(OTf)_3$[b] (1.1)	CH_2Cl_2[f]	25	8 days	55	100: 0	0
11		$La(OTf)_3$[b] (1.1)	$(CH_2Cl)_2$[f]	50	6 days	56	99: 1	0
12		$La(OTf)_3$[b] (1.1)	CH_3CN[f]	25	8 days	69	98: 2	0
13		$La(OTf)_3$[b] (1.1)	CH_3CN[f]	45	3 days	71	98: 2	0

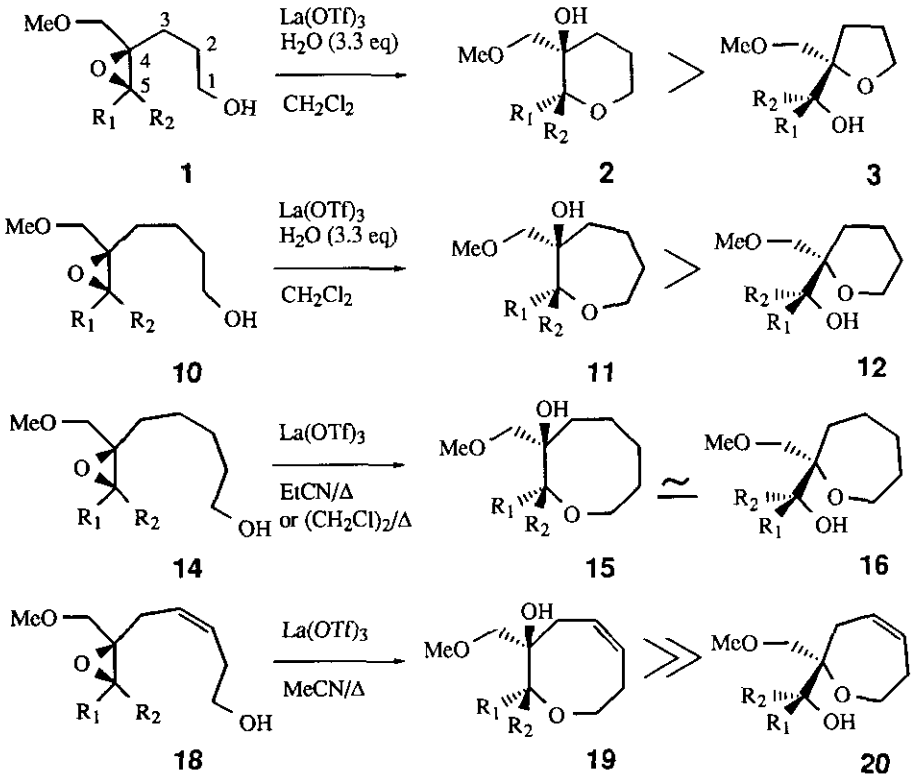
a) Estimated by 300 MHz ^{1}H-NMR. b) La_2O_3 was contained [molar ratio La_2O_3:$La(OTf)_3$=1:4]. c) H_2O (3.3 eq) was contained. d) The concentration of substrate was 25 mM. e) The concentration of substrate was 4 mM. f) The concentration of substrate was 50 mM. g) Fluoride (**22**) was also given (28%).



22

radius[36] and varies its coordination number within the range from 3 to 12 (generally from 7 to 9),[36] our 6-*endo* selectivity might be attributable to the structural factor of coordination rather than the acidity of Lewis acid. The coordination of H_2O to La changes not only the angle ∠O (epoxide)-La-O (methoxymethyl) to be suitable for activation of the bond between C5 and the epoxide oxygen, but also the angle ∠C5-C4-C3 to fit the conformation for the intramolecular attack of the hydroxy group to C5 in the transition state.

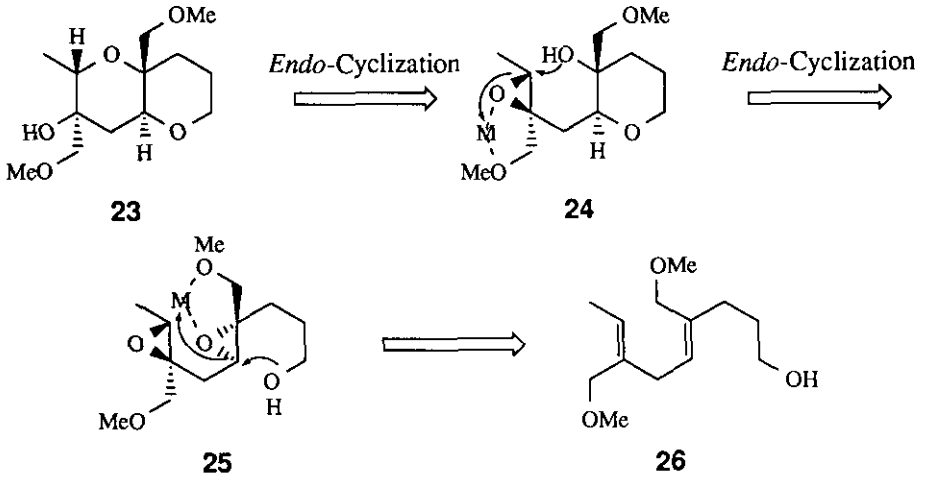
Furthermore, the use of $La(OTf)_3$ could achieve the 7-*endo* and 8-*endo* selective cyclizations of *trans*- and *cis*-5,6-epoxy-5-methoxymethylheptan-1-ols (**10**) and *trans*- and *cis*- 6,7-epoxy-6-methoxymethyl-3-octen-1-ols (**18**), respectively. The yield of cyclization products and the rate of the reaction decreased with increasing distance between the hydroxyl and epoxide groups of the substrate in the order of **10<18<14**. In the cases of **18** and **14**, unfavorable side reactions, such as rearrangement of the epoxide moiety, led to the formation of enals (**17** and **21**) and other undesirable products, and such formation increased as the strength of Lewis acidity increased. The success with $La(OTf)_3$ in these cases might be attributed to not only its ability to chelate rigidly between the oxygen atoms of the epoxide and methoxymethyl groups but also its Lewis acidity which is adequate for the cyclization but not so high as to induce such side reactions. Our results were summarized in Scheme 6.



Scheme 6.

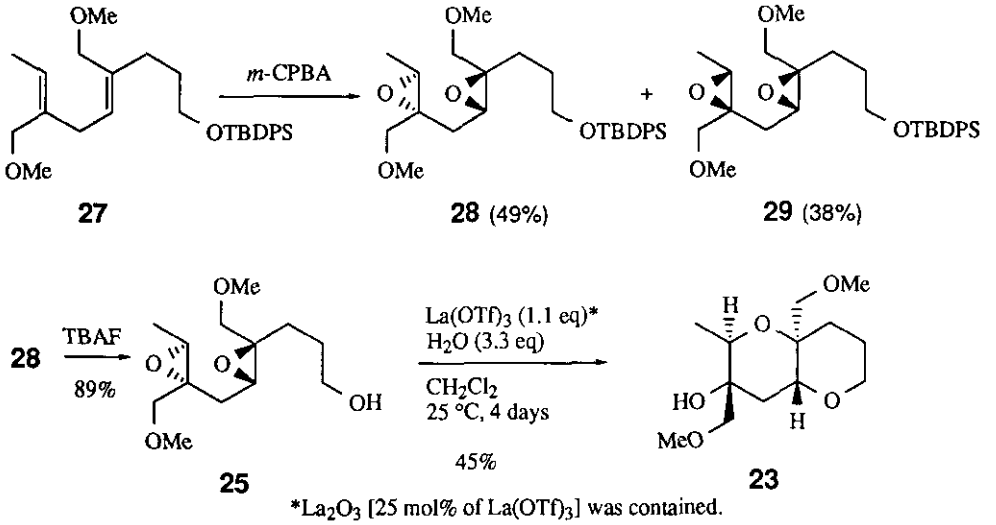
2-4. Extension of Our Established 6-*Endo*-Selective Ring Closure Reaction to Bisepoxy Bismethoxymethyl Alcohol.

As a model experiment concerning biomimetic realization of biogenesis proposed for fused polycyclic ethers starting from polyepoxy alcohol, we have planned to extend our established reaction to intramolecular construction of bicyclic ring system (**23**). Our strategy is shown in Scheme 7. We have expected the *endo*-cyclization of bisepoxide (**25**) to proceed stepwise *via* monocyclic ether (**24**). In order to prepare **25**, it would be more straightforward to epoxidize directly bisolefin alcohol (**26**), which could be prepared



23 **24** **25** **26**

Scheme 7.



27 **28** (49%) **29** (38%) **25** **23**

*La_2O_3 [25 mol% of $La(OTf)_3$] was contained.

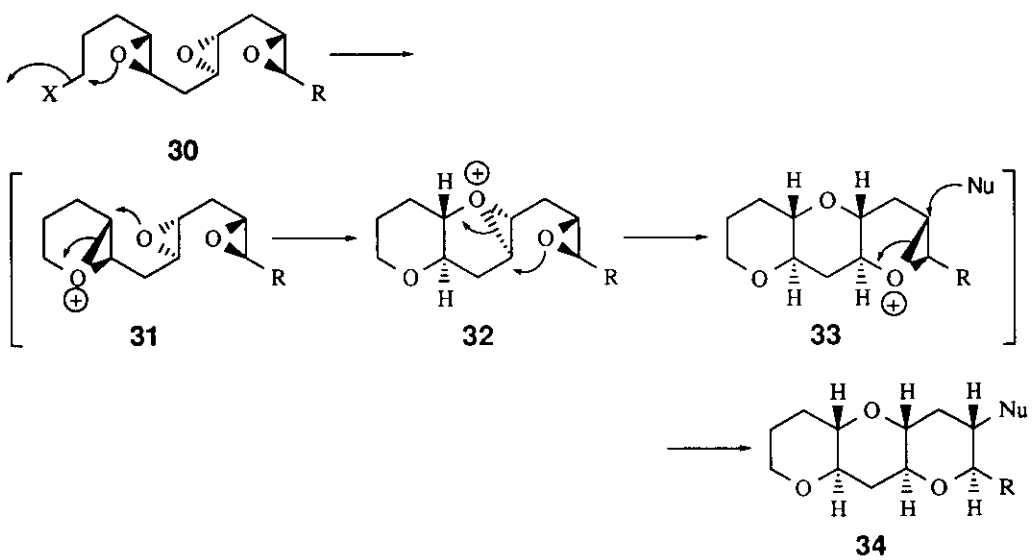
Scheme 8.

stereoselectively involving the boron-mediated aldol reaction developed by Abiko and Masamune[37] followed by DCC dehydration of the resulting *syn*-aldol. Although several research groups have developed the direct asymmetric epoxidation of unfunctionallized olefins,[38] we prepared and treated **27** tentatively with *m*-CPBA to afford **28** and **29** in 49% and 38% yields, respectively (Scheme 8).[39] The silyl group of **28** was detached to **25**. When racemic **25** was reacted with $La(OTf)_3$ (1.1 eq) and H_2O (3.3 eq) in CH_2Cl_2 at 25 °C for 4 days, the desired fused bicyclic ether (**23**) was provided in 45% yield along with 21% of three unidentified products.[39]

These results might enable to develop our idea to construct further fused polycyclic ether system starting from the corresponding opened polyepoxide. The problem of the asymmetric epoxidation from the polyolefin compound could be solved by application of the published epoxidation reactions using chiral dioxirane agents.[38] It would be clarified in the near future whether our reaction (**25** → **23**) shown in Scheme 8 proceeded successively or stepwise.

3. *Endo*-Selective Ring Closure of Epoxy Bromides Regarding Epoxy Groups as Nucleophiles.

As another way for chemical realization of biomimetic construction of fused polycyclic ethers, we have investigated the successive ring-expansion reactions of bromo polyepoxides by regarding the epoxy groups as the nucleophiles for the intramolecular cationic carbons. We wanted to develop the biomimetic synthesis in a simple model system without any directing groups by using the property of the molecular itself and adopted the method by the ring-expansion reaction, which would utilize the structural strain in a bridged oxonium ion intermediate. Our working hypothesis is illustrated in Scheme 9. The first step



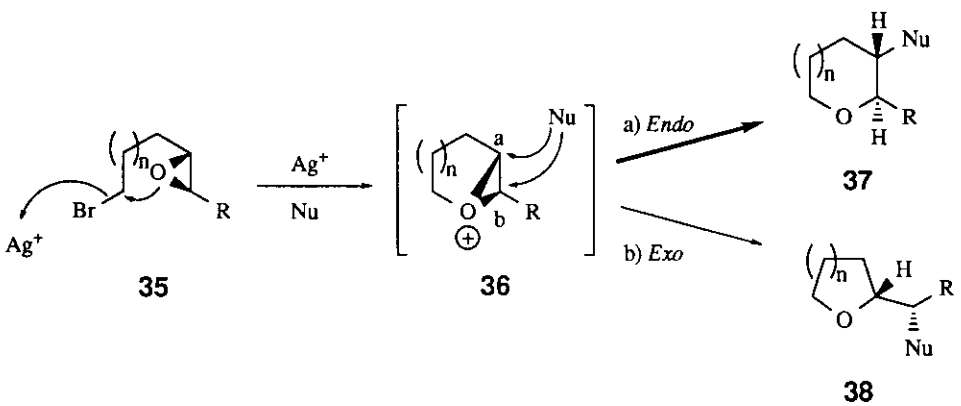
Scheme 9.

(the initiation step) is the process in which the first bridged oxonium ion (**31**) would be formed by the intramolecular nucleophilic attack of the first epoxy group to the cationic site. The next is the propagation step, in which the second epoxy group attacks the first oxonium ion (**31**) to generate the second oxonium ion (**32**). It is assumed that the target molecule (**34**) could be synthesized, if the same successive reactions of the third, fourth...epoxy groups are followed by trapping of the last oxonium ion by the intermolecular or intramolecular attack of some nucleophile (the termination step).

Concerning the formation of only a single cyclic ether *via* the bridged oxonium ion, some related approaches have been reported. Martín has demonstrated the intramolecular nucleophilic attack of an epoxy group to the iodonium cation on a carbocyclic framework.[40] However, the problems of low regioselectivity and the participation of the neighboring group still remained. The application to acyclic systems of its reaction described in the proposed biosynthetic process has been unknown. Kishi[41] and Martín[18l] have reported the ring expansion of oxolane to oxane *via* the bridged oxonium ions. However, the net difference in the reactivity between the two reactive positions of the bridged oxonium ion is unclear, because of the difference in the chemical environment of the electrophilic site (the difference between the secondary and tertiary carbons of the oxonium ion), or the effects of the neighboring group and the complicated conformational factors. Therefore, in the investigation of the successive ring expansion of epoxy groups, the problems to be clarified are as follows: 1) the nucleophilic ability of an epoxy group in simple acyclic systems; 2) the directionality of the ring expansion on the systems without any directing groups (*endo* or *exo*);[42] 3) the possibility of the successive ring expansion. We have attempted to solve these problems.[23]

3-1. Single Ring Expansion Reactions; the Simplest Initiation and Termination Model.

In order to examine the nucleophilic ability of an epoxy group and the directionality of the ring expansion on an acyclic epoxide without any directing groups, the conversion of 1-bromo epoxide (**35**) into the cyclic ethers (**37** or **38**) was attempted. This system could be regarded as both the simplest initiation and



Scheme 10.

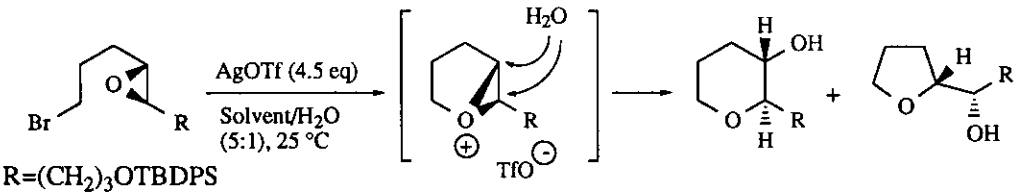
termination model for the intermolecular attack of a nucleophile in the biomimetic synthesis. The working hypothesis is shown in Scheme 10. Initially, the epoxy group in **35** would attack intramolecularly the electrophilic center, which could be generated by the activated bromo group with a silver cation, to form the bridged oxonium ions (**36**). The next step is divided into two intermolecular attacks of the external nucleophiles (Nu) to the oxonium ions (**36**); the attack to the site-a would produce **37** (*endo*-mode), whereas the attack to the site-b, **38** (*exo*-mode).[42]

3-1-1. AgOTf-Promoted Conversion of *trans*-1-Bromo-4,5-epoxide into Oxane.

First of all, the conversion of *trans*-1-bromo-4,5-epoxide (n=1 in Scheme 10) into an oxane was examined under the conditions in which an external nucleophile was added into the system. AgOTf was adopted as a silver cation source, because AgOTf was more soluble in various organic solvents than other silver cation sources. As the nucleophile, we chose water as a neutral molecule, since we supposed that the soft nucleophiles might form some complexes with silver cation to deactivate it. Thus, we treated bromo epoxide (**39**) with AgOTf in various aqueous organic solvents. The results are shown in Table 5.[23a] In heterogeneous solvent systems (CH_2Cl_2, benzene, and Et_2O), the reaction proceeded with difficulty, though Et_2O gave the best *endo*/*exo* selectivity (94:6) (Entries 1, 2, and 3). In the cases of THF/H_2O (5:1), 1,4-dioxane/H_2O (5:1), and acetone/H_2O (5:1), the *trans*-3-hydroxy oxane derivative (**41**) was obtained as the major product in high stereoselectivities in 72%, 49%, and 55% yields, respectively (Entries 4, 5, and 6). It seems that the best yield in THF/H_2O was due to the effect of THF as the proton scavenger which prevented cleavage of the TBDPS group. Actually, TBDPSOH was isolated in 18% and 6% yields in dioxane/H_2O and acetone/H_2O, respectively. In MeCN/H_2O or DMSO/H_2O, the *endo*/*exo* selectivity was lowered (Entries 7 and 8). The activity of the silver cation might be lowered in MeCN/H_2O, because it might form probably an inert complex with the silver cation.

It is presumed that the pathways in Table 5 are not necessarily common under aqueous conditions. Alternate pathways (paths **c**, **e**, **f**, **g**, **h**, **i**, and **j**) are possible as shown in Scheme 11.[23d] These pathways mean the following; paths **c** and **e** are the reverse processes of paths **b** and **d**, respectively; path **f** is hydrolysis of the epoxy group of **39** under acidic conditions; paths **g** and **h** are the cyclizations of bromo diol (**44**) to **41** and **42**, respectively; path **i** is the nucleophilic substitution of Br with H_2O molecule; path **j** is the 5-*exo*-cyclization of the hydroxy epoxide (**43**), to be exact, whose product is the enantiomer of **42**. We investigated whether these possible pathways participated in the generation of **41** and **42** (Scheme 12). When the olefin bromide (**45**) treated with AgOTf (4.5 eq) in THF/H_2O (5:1) at 25 °C for 6.5 h, the starting material (**45**) was recovered in 99%. Accordingly, the terminal bromo group was not displaced by the hydroxy group. Therefore, paths **i** and **j** were excluded. Next, racemic **46** was treated under the same conditions as above to recover the starting material in 92%, while, on exposure to trifluoromethanesulfonic acid (TfOH) (1.0 eq) in THF/H_2O (5:1) at 25 °C for 6.5 h, compound (**46**) afforded the *anti*-diol (**47**) (5%) in company with **42** (50%). These results revealed that the hydrolysis (path **f**) of the epoxy group of **39** might occur, though it was slow. The *anti*-diol (**44**) was newly

Table 5.



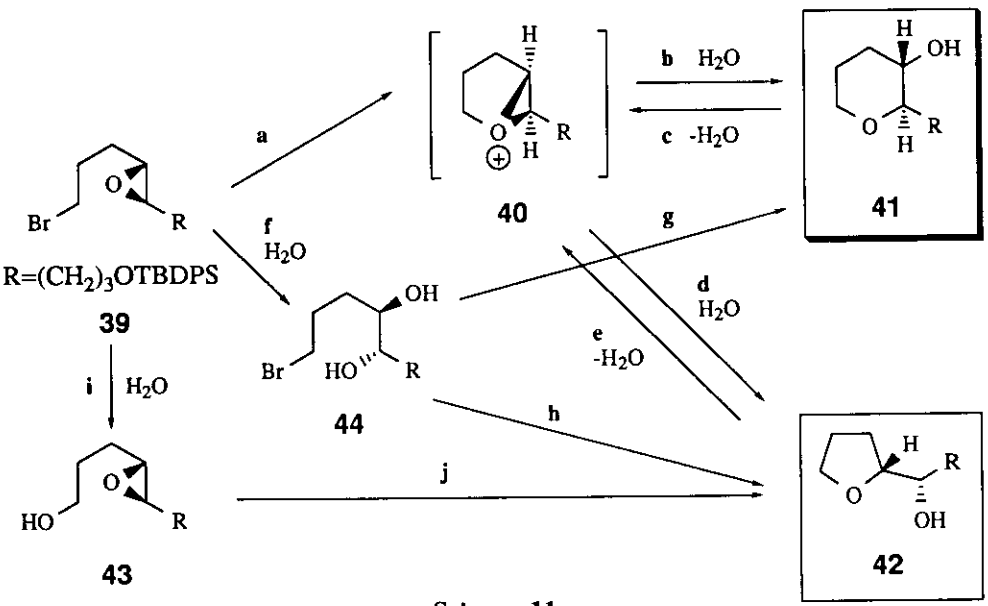
R=$(CH_2)_3$OTBDPS

39 **40** **41** **42**

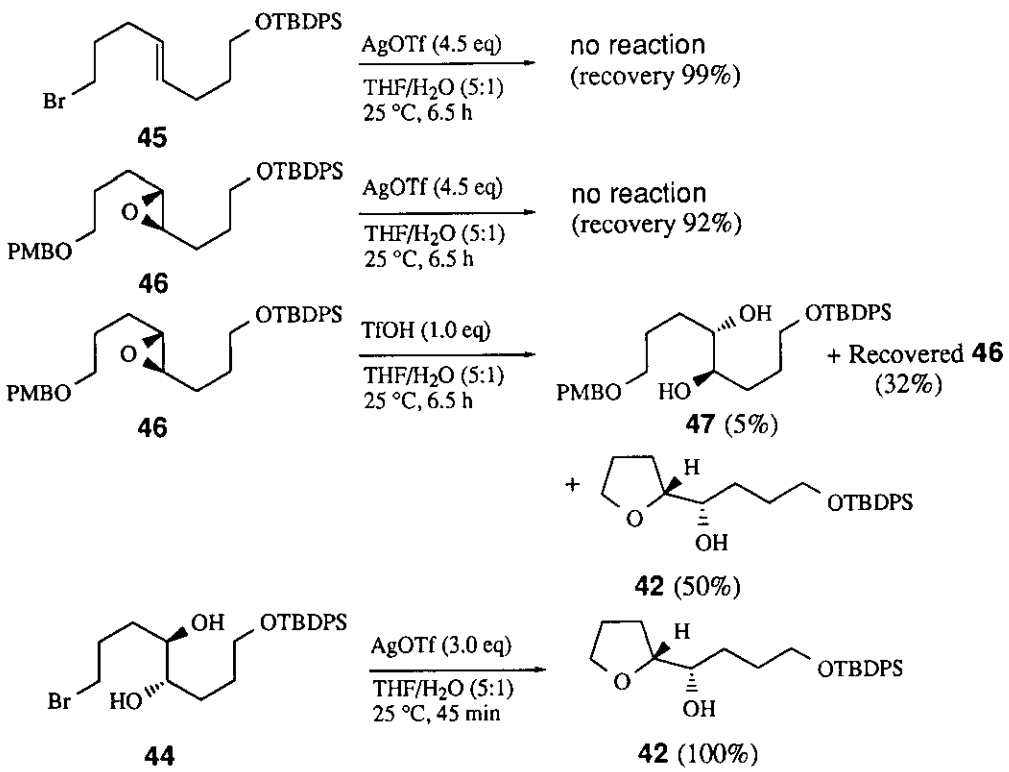
Entry	Conditions		Products		Recovery of **39**/%
	Solvent	Time	Yield/% (**41**+**42**)	Ratio (**41**:**42**)[a]	
1	CH_2Cl_2	8 h	0	—	92
2	benzene	8 h	3	79: 21	89
3	Et_2O	8 h	5	94: 6	82
4	THF	6.5 h	91	79: 21	6
5	1,4-dioxane	8 h	61	80: 20	6
6	acetone	6.5 h	70	78: 22	0
7	CH_3CN	8 h	21	60: 40	57
8	DMSO	8 h	48	71: 29	7

a) The ratio of **41**:**42** was determined by ^{1}H-NMR after acetylation.

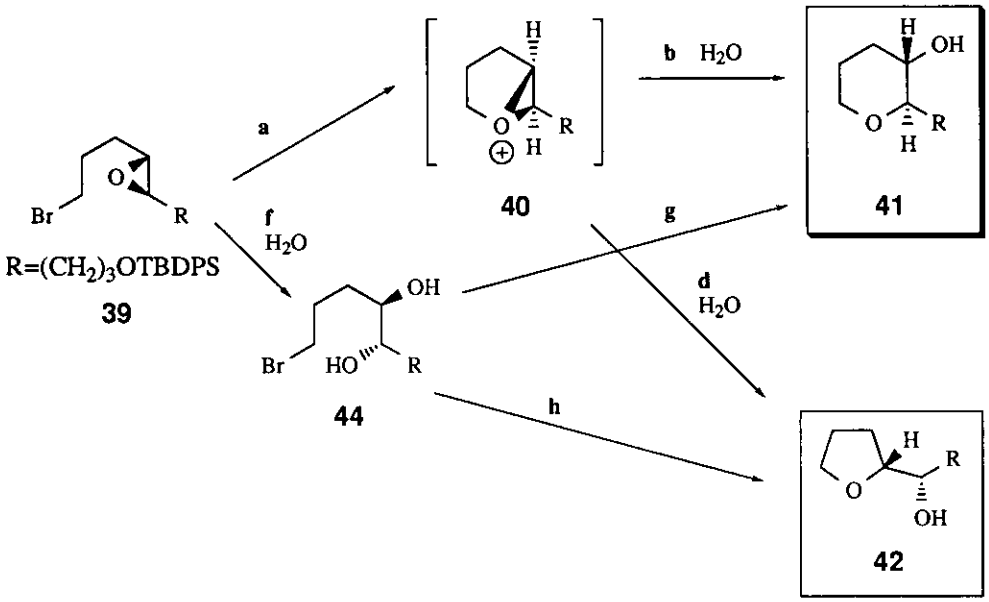
prepared and reacted with AgOTf in THF/H_2O (5:1) to provide only the hydroxy oxolane (**42**). Consequently, it was clarified that path **h** was present, but path **g** was not. Lastly, the rearrangement between **41** and **42** (path **c** → path **d**, and path **e** → path **b**) was examined. The respective compounds (**41**) and (**42**) were subjected to AgOTf (4.5 eq) and TfOH (1.0 eq) in THF/H_2O (5:1) at 25 °C for 6.5 h to only recover unchanged **41** and **42** in 94% and 99%, respectively. Therefore, path **c** and path **e** were ruled out. These results could conclude, as summarized in Scheme 13, that the hydroxy oxane (**41**) was produced by only the processes through paths **a** and **b**. On the other hand, two possibilities were present with regard to generation of the hydroxy oxolane (**42**). One is the pathway through path **a** and path **d**. The other is through path **f** and path **h**, though it seemed that this pathway did not much participate in the formation of **42** because of the slow process of path **f**. It is thus concluded that *the hydroxy oxane **41** is the kinetic product in the ring expansion reaction under aqueous conditions*, whose net *endo*-selectivity was estimated to be higher than the results shown in Table 5.



Scheme 11.

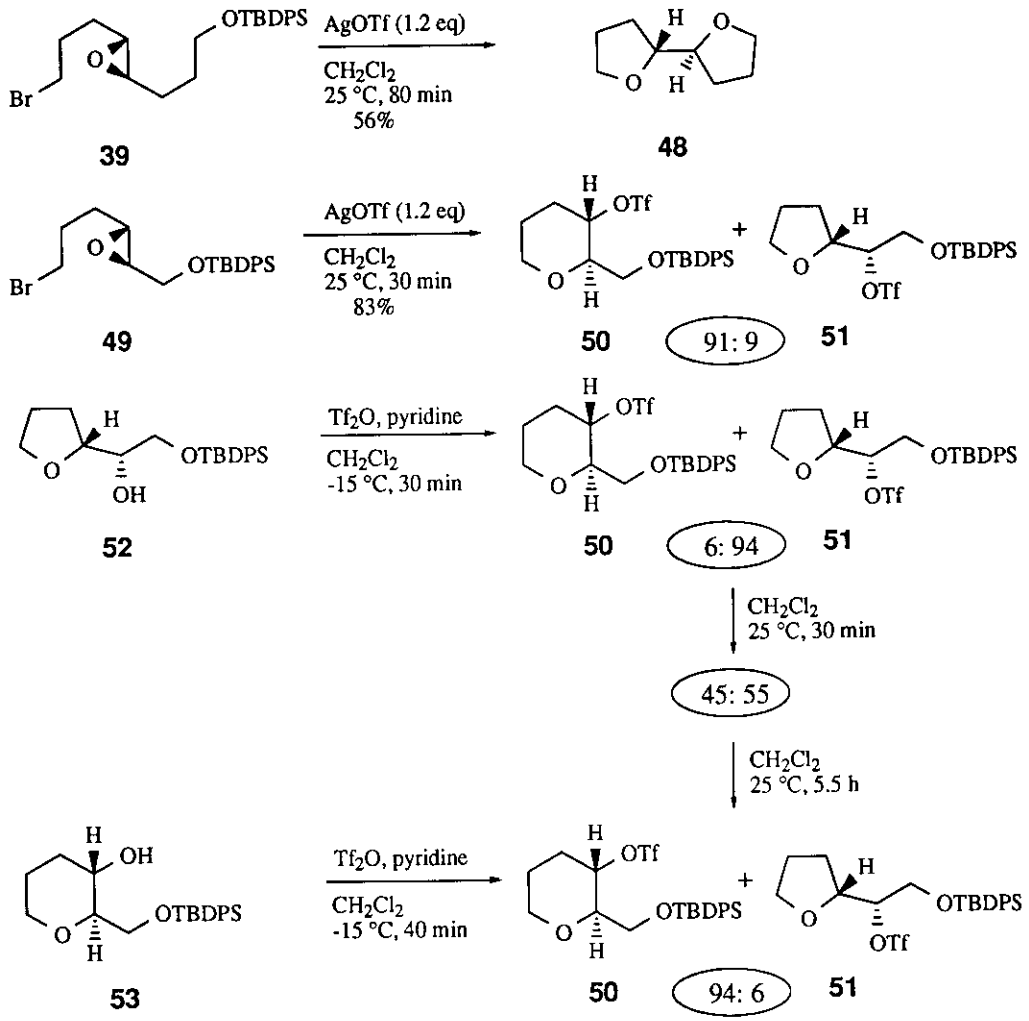


Scheme 12.

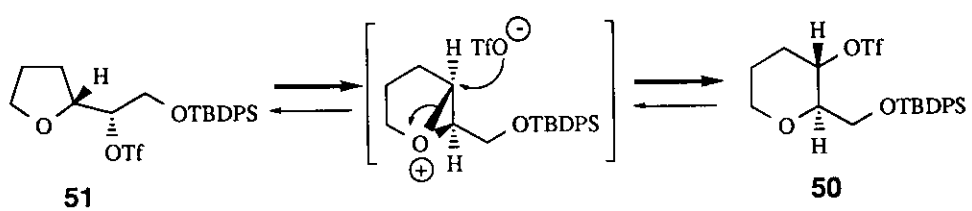


Scheme 13.

Next, the convertsion of *trans*-1-bromo-4,5-epoxide into an oxane was attempted under the conditions without any additive external nucleophiles (Scheme 14).[23c] When **39** was treated with AgOTf in dry CH_2Cl_2 at 25 °C for 80 min, the oxolane rings-assembled bicyclic ether (**48**) as a single product in 56% yield. This result indicates the participation of the oxygen atom on the side chain to the activated site. It would be necessary to furnish some new substrate in order to investigate the reaction under anhydrous conditions. We prepared the substrate (**49**) having a shorter side chain and subjected to the reaction with AgOTf (1.2 eq) in dry CH_2Cl_2 at 25 °C for 30 min to obtain a 91:9 inseparable mixture of the *trans*-3-triflyloxy oxane (**50**) and its oxolane isomer (**51**) in 83% combined yield.[43] Although the regioselectivity of products was excellent, it was clarified from the following experiments that the excellent *endo*-selectivity did not necessarily reflect the kinetically controlled ratio. Thus, the pure hydroxy oxolane (**52**) was prepared and then esterified with Tf_2O and pyridine in CH_2Cl_2 at -15 °C for 30 min to obtain a 6:94 mixture of **50** and **51** (Scheme 14). In spite of the absence of AgOTf, **51** was converted into **50** in CH_2Cl_2. On further reaction at 25 °C for 30 min, the ratio of the mixture of **50**:**51** amounted to 45:55. After 5.5 h, it was changed to 94:6. In contrast, when the pure hydroxy oxane (**53**) was treated under the same conditions as above, a 94:6 mixture of **50**:**51** was obtained. The reversible rearrangement of the skeletons undoubtedly takes place between the oxane (**50**) and the oxolane (**51**) as illustrated in Scheme 15. The equilibrium seems to lie in favor of formation of the oxane (**50**). Therefore, it is pointed out that *the oxane (50) was thermodynamically more stable than its oxolane isomer (51).*



Scheme 14.

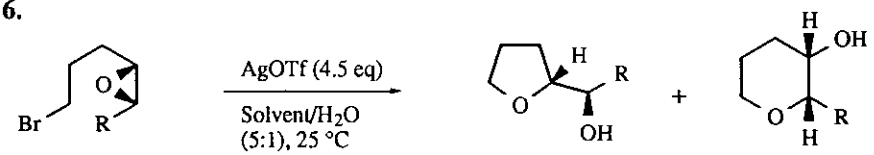


Scheme 15.

3-1-2. The Ring Expansion of *cis*-1-Bromo-4,5-epoxide.

In order to examine the generality of the reaction, it was attempted to apply our new ring-expansion reaction to *cis*-1-bromo-4,5-epoxide (**54**).[23a] The results on the ring expansion reaction of **54** are shown in Table 6. The solvents used for the reaction were aqueous THF, 1,4-dioxane, and acetone, which were the solvents giving the good results in the case of *trans*-epoxide (**39**). The reaction of *cis*-epoxide (**54**) proceeded more slowly than that of its *trans*-isomer (**39**). In every case, the hydroxy oxolane (**55**) was generated as a single product, and no trace amount of **56** was detected.

Table 6.



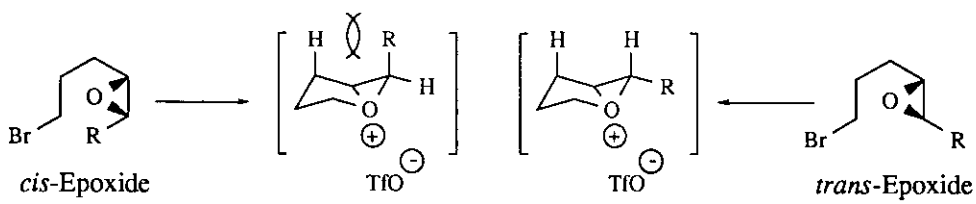
R=$(CH_2)_3$OTBDPS

54 **55** **56**

Entry	Conditions		Products[a)]		Recovery of **54**/%
	Solvent	Time	Yield/% (**55**)	Yield/% (**56**)	
1	THF	19 h	54	0	6
2	1,4-dioxane	19 h	52	0	5
3	acetone	19 h	49	0	7

a) TBDPSOH was isolated in 9, 27, and 21% yields in Entries 1, 2, and 3, respectively.

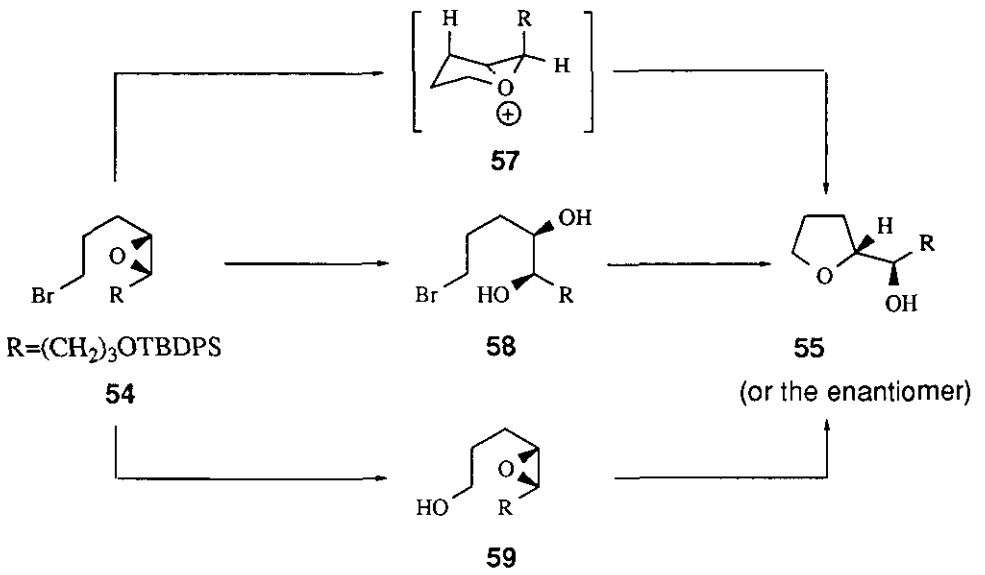
If the bridged oxonium ion would be formed in the case of *cis*-epoxide (**54**), the 1, 3-steric interaction shown in Figure 1 could exist between the side chain and the C-H bond. Such an interaction is absent in its *trans*-isomer. However, it is not clear from only these results which pathways in Scheme 16 caused **55** to produce, though the small reaction rate suggests the difficulty of the intramolecular nucleophilic attack of the epoxy group.



cis-Epoxide *trans*-Epoxide

R=$(CH_2)_3$OTBDPS

Figure 1.



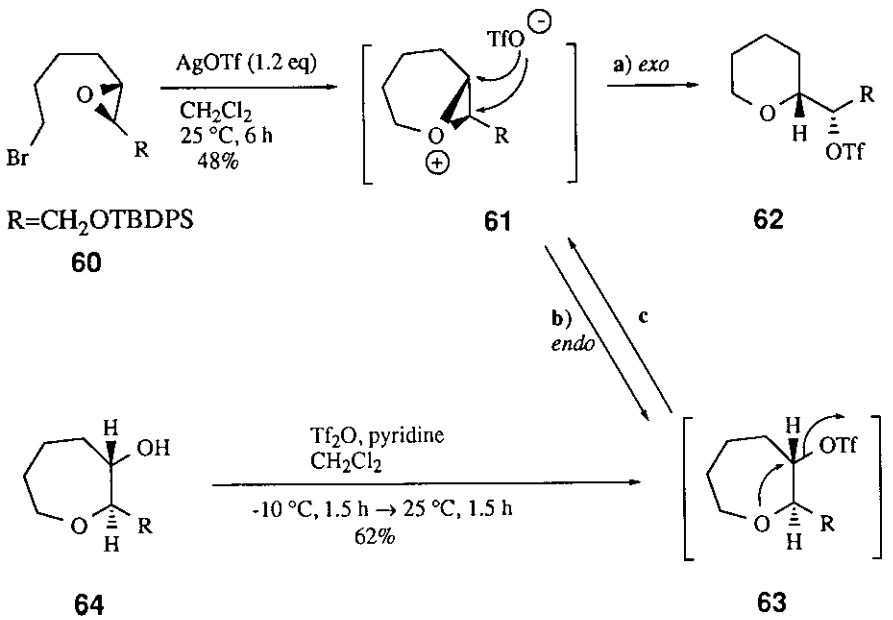
Scheme 16.

3-1-3. AgOTf-Promoted Conversion of *trans*-1-Bromo-5,6-epoxide into Oxepane.

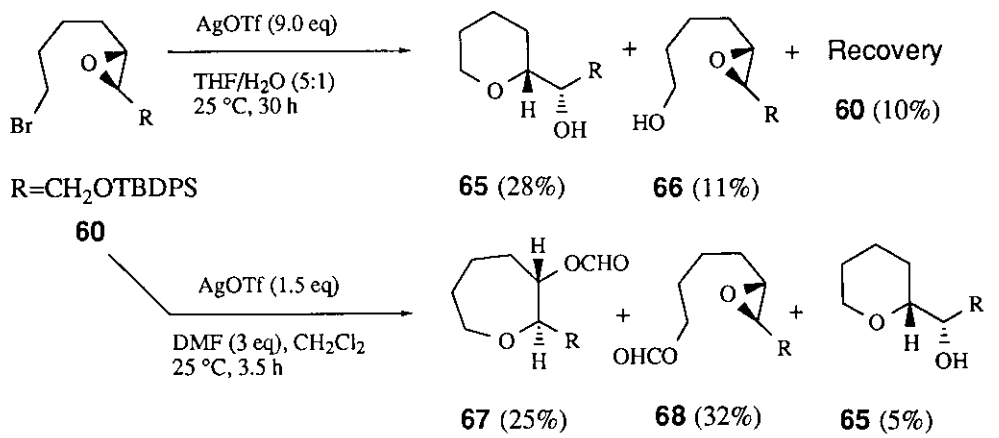
The methodology of our epoxy group's ring-expansion was also applied to *trans*-1-bromo-5,6-epoxide (n=2, Scheme 10).[23c,23d] Firstly, the results of the thermodynamic control were examined. The reaction of **60** was carried out under conditions without any additives to obtain the triflyloxy oxane (**62**) (48%) (Scheme 17). The longer reaction time as compared with **49** suggested that the intramolecular nucleophilic attack of the epoxy group was difficult owing to the elongation of the carbon chain. Because the oxepane isomer (**63**), the product in an *endo*-mode, was not detected at all, it was examined whether **63** could be rearranged into **62** (path **c** → path **a** illustrated in Scheme 17). The hydroxy group in **64** was then esterified with Tf_2O and pyridine in CH_2Cl_2 to provide the oxane (**62**) only. This result revealed that the intermediate (**63**) must be labile and rearranged easily into **62**, which could be, therefore, regarded as *a thermodynamic product* in the reaction of **60**.

Next, for examining the results of the kinetic control, the reaction using **60** was carried out in the presence of an additive external nucleophile (Scheme 18). In aqueous THF (THF/H_2O = 5:1), the products consisted of three components: the hydroxy oxane (**65**) (28%), the hydroxy epoxide (**66**) (11%), and a high polar compound, which was assumed to be the coupling product between the activated substrate and THF molecule. The compound (**65**) seemed to be formed by the 6-*exo*-cyclization of **66**. In order to avoid the substitution of the bromo group with the hydroxy group, the additive external nucleophile was exchanged with dimethylformamide (DMF). The bromo epoxide (**60**) was treated with AgOTf in the presence of 3.0 eq of DMF in CH_2Cl_2 to obtain the formyloxy oxepane (**67**) in 25% yield. However, the reaction was accompanied by a considerable amount of by-products; one was the formyloxy

epoxide (**68**), another was hydroxy oxane (**65**) which was presumably produced by hydrolysis of **62** in the purification with PTLC, and the others were a complex mixture. There still remains a possibility that compound (**67**) might be produced by the skeletal rearrangement of **62** which was perhaps formed more rapidly. In order to circumvent this possibility, **62** was treated with DMF (3.0 eq) and AgOTf (1.5 eq) under the same conditions. Nothing was generated with recovery of the starting material (**62**) in 95%. Namely, *the formyloxy oxepane (**67**) was the kinetic product on the ring-expansion reaction of **60**.*



Scheme 17.

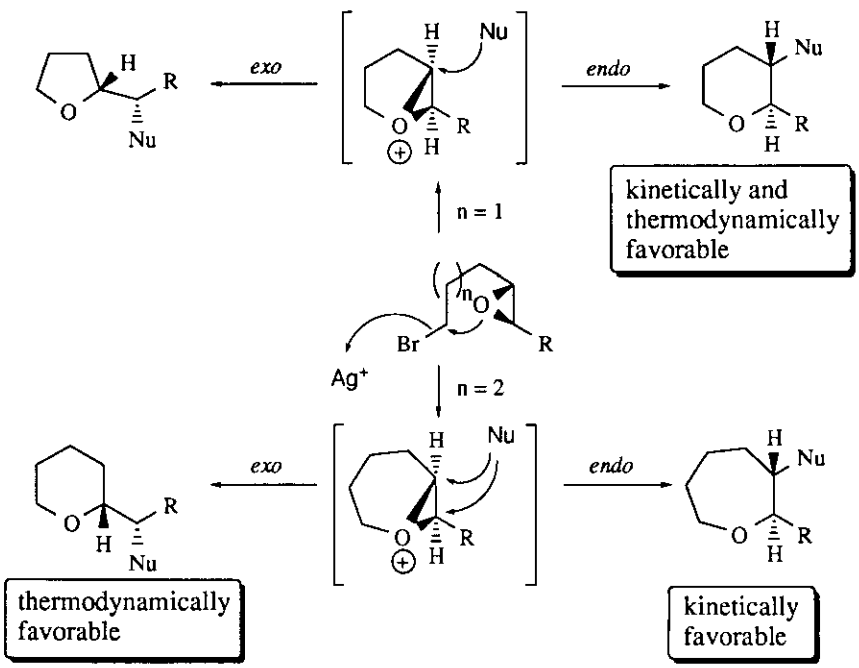


Scheme 18.

In summary, of the two possible ring-expanded compounds, the oxepane and oxane derivatives, obtained from the reaction of the *trans*-1-bromo-5,6-epoxide (**60**), the kinetically favorable compound was the former, while the thermodynamically more stable compound was the latter. It was very interesting that the kinetically controlled direction of the ring expansion reactions was prefentially in an *endo* fashion on both *trans*-1-bromo-4,5-epoxide (**39**) and *trans*-1-bromo-5,6-epoxide (**60**).

3-1-4. Summary.

In this chapter, the following facts were clarified as shown in Scheme 19. The *trans*-epoxy groups acted as nucleophiles to attack the intramolecular electrophilic centers. In the systems without any directing groups, *the direction of the ring-expansion reaction on the system producing the oxane or the oxolane skeleton could be both kinetically and thermodynamically controlled in an endo-mode. The direction on the system forming the oxepane or the oxane skeleton could be endo-fashion under kinetically controlled conditions, while it could be thermodynamically controlled in an exo-mode.*

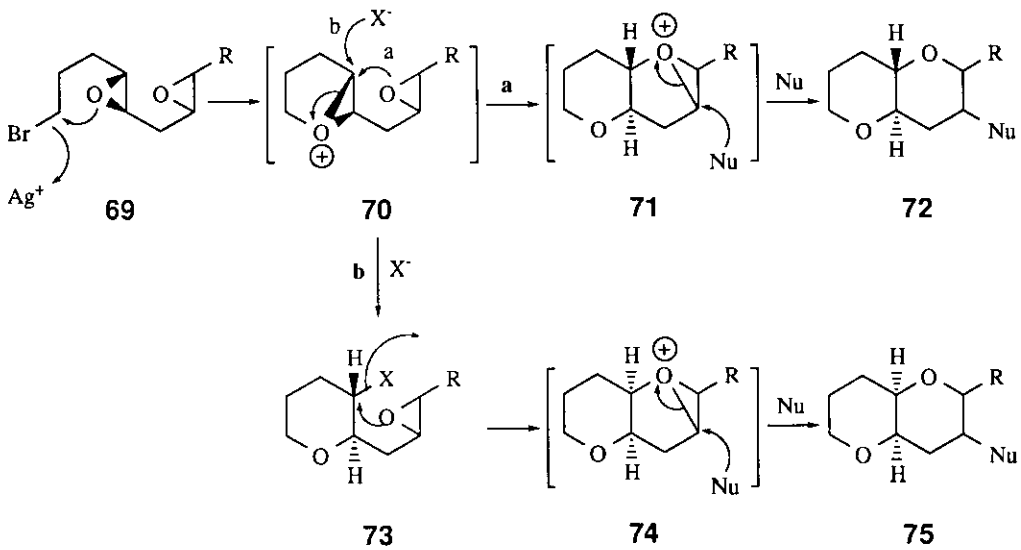


Scheme 19.

3-2. The Successive Ring-Expansion Reactions; the Simplest Propagation Model.

We investigated the successive ring-expansion reactions of the *trans,trans*-diepoxides (**69**).[23b,23d] Various factors were estimated for these reactions. The proposed reaction mode of the successive ring expansion is illustrated in Scheme 20. The first step is the process in which the first bridged oxonium ion (**70**) would be formed by the intramolecular nucleophilic attack of the first epoxy group to the cationic site.

In the next step, if the intramolecular attack of the second epoxy group is a faster process than the intermolecular attack of the external nucleophile (X^-), the reaction would proceed through path **a** to form the second oxonium ion (**71**), and the successive ring expansion would be terminated by the intermolecular nucleophilic attack to produce the *trans*-fused bicyclic ether (**72**). On the other hand, if the intramolecular attack of the second epoxy group could proceed more slowly than the intermolecular attack of X^-, the reaction would go through path **b** to form the epoxy tetrahydropyran (**73**). If the X group is a poor leaving group, the reaction would be completed at this stage. To the contrary, when the X group works as a good leaving group, the second epoxy group would attack further the back side of the X group to provide the *cis*-fused bicyclic ether (**75**) *via* the second oxonium ion (**74**).

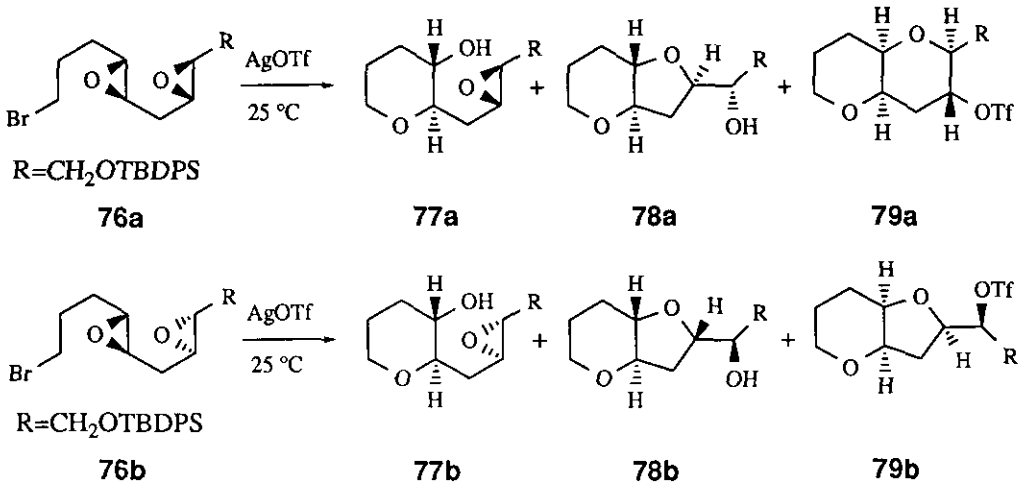


Scheme 20.

3-2-1. Ring Expansion Reactions of *syn*- (76a) and *anti*-Diepoxides (76b).[23b]

It was attempted to investigate how the successive ring-expansion reactions of the *syn-trans,trans*-diepoxide (**76a**) (an unnatural type) and *anti-trans,trans*-diepoxide (**76b**) (a natural type) could occur. These systems could be regarded as the simplest propagation models in the cascade reaction. Thus, we prepared the requisite optically active *syn-trans,trans*-diepoxide (**76a**) and *anti-trans,trans*-diepoxide (**76b**) starting from 4-pentyn-1-ol PMB-ether in 10 steps.[23b] The reactions were initially attempted in the presence of H_2O as the external nucleophile. As shown in Table 7, the *syn*-diepoxide (**76a**) was treated with AgOTf (10 eq) in THF/H_2O (5:1) for 1 h to give **77a** (31%) and **78a** (11%) along with the corresponding epoxy tetrahydrofuran isomer (1%) (Entry 1). From the *anti*-diepoxide (**76b**), **77b** (41%) was obtained with the corresponding epoxy tetrahydrofuran isomer (1%) under almost the same conditions (at 25 °C for 1.5 h) (Entry 4). When the reaction time was extended to 4 h and 23 h in the respective cases, the *trans*-fused bicyclic ethers (**78a**) and (**78b**) were afforded in 47 and 46% yields, respectively

Table 7.

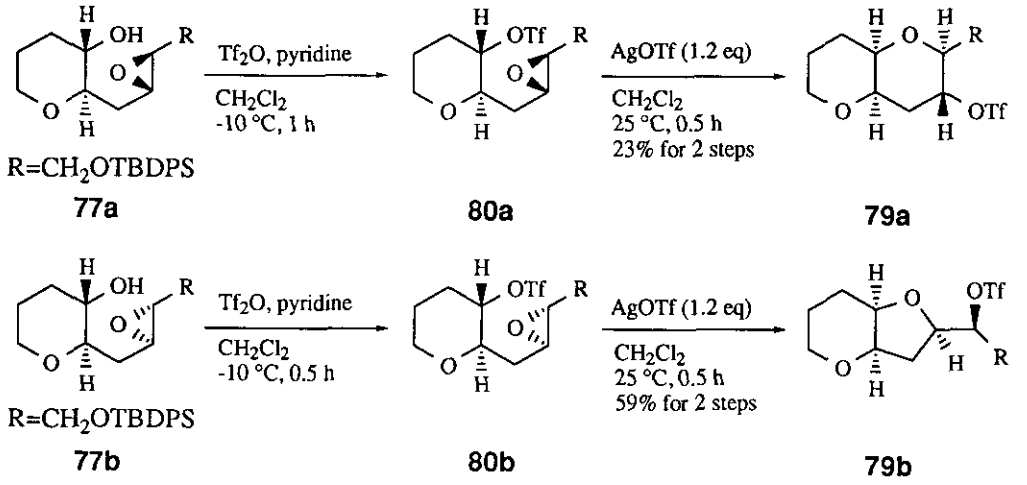


Entry	Substrate	Solvent	AgOTf (eq)	Time	Products (%)	Recovery (%)
1	**76a**	THF/H_2O (5:1)	10	1 h	**77a** (31) + **78a** (11)	**76a** (24)
2	**76a**	THF/H_2O (5:1)	10	4 h	**78a** (47)	**76a** (0)
3	**76a**	CH_2Cl_2	1.2	0.5 h	**79a** (39)	**76a** (0)
4	**76b**	THF/H_2O (5:1)	10	1.5 h	**77b** (41)	**76b** (12)
5	**76b**	THF/H_2O (5:1)	10	23 h	**78b** (46)	**76b** (0)
6	**76b**	CH_2Cl_2	1.2	0.5 h	**79b** (29)	**76b** (0)

(Entries 2 and 5). In these reactions, the respective clear conversions of **77a** and **77b** into **78a** and **78b** were observed by TLC analyses; that is, these results indicate that **78a** and **78b** were produced not by the successive ring expansions of two epoxy groups, but by 5-*exo*-cyclizations of the hydroxy epoxides (**77a** and **77b**) promoted by the acid in the systems. From these results, it was suggested that the intermolecular nucleophilic attack of H_2O to the first oxonium ion was faster than the intramolecular attack by the second epoxy group.

Next, the reactions were carried out under conditions without any additives, in which a triflate ion (a poor nucleophilic but a very good leaving group) would be expected to act as the external nucleophile. In dry CH_2Cl_2, **76a** was transformed into the *cis*-fused perhydrotriflyloxypyranopyran (**79a**) (39%) (Entry 3), while **76b** was led to the *cis*-fused perhydrotriflyloxypyranofuran (**79b**) (29%) (Entry 6). These rather low yields were attributed to the decomposition of these products in the purification stages. It is to be noted that the sizes of the second ring in the products depend on the stereochemistries of the

diepoxides. The other products consisted of a complex mixture in both cases. Judging from the *cis*-junctures of **79a** and **79b**, it was suggested that the reactions proceeded through path **b** illustrated in Scheme 20. However, the intermediate such as **73** was not isolated, because the conversion of **73** to **74** was presumably the fast process. In order to confirm involvement of the intermediates, the respective triflates (**80a**) and (**80b**), prepared from **77a** and **77b** with Tf_2O and pyridine in CH_2Cl_2, were subjected to the same conditions as the above successive ring-expansion reactions to afford the *cis*-fused bicyclic ethers (**79a** and **79b**), respectively (Scheme 21).



Scheme 21.

3-2-2. Discussion.

From the results described in 3-2-1, the following comments could be made. 1) Independently of the stereochemistries of the two epoxy groups, the direct intramolecular nucleophilic attacks of the second epoxy groups to the first activated epoxy groups were slower than the attack of the external nucleophiles such as the triflate ion in these systems. 2) When the triflate ion was used as the external nucleophile, formation of **80a** and **80b** was followed by the intramolecular nucleophilic attacks of the second epoxy groups, respectively, with the activation of the triflyloxy group owing to the silver ion. The *cis*-junctures were eventually formed by the double inversion in the stereochemistries of the C3 in **80a** and **80b**. 3) The direction of the ring expansion of the second epoxy group depends on the relative configurations of two epoxy groups. It has not been clarified at the present stage from the experimental results whether the difference in ring sizes between **79a** and **79b** resulted from the kinetic or the thermodynamic control. Because bicyclic systems possess the more rigid conformations, the skeletal rearrangement does not necessarily exist. However, in any event, the reasons why the second epoxy group of **76b** was expanded in *exo*-mode could be explained as follows. If the reaction was kinetically controlled, the regioselectivity of product depends on the activation energies of the transition states led from the second oxonium ion

(**81b**) shown in Figure 2. If the structures of transition states were reactant-like, it is presumed that the activation energy to the *exo*-transition state is lower than that to the *endo*-transition state in the system of **76b**, because of the steric repulsions in **81b**. In the case of the product-like structures of transition states, also, the same result is obtained, because the steric repulsion in **79b** is less than that of its pyranopyran

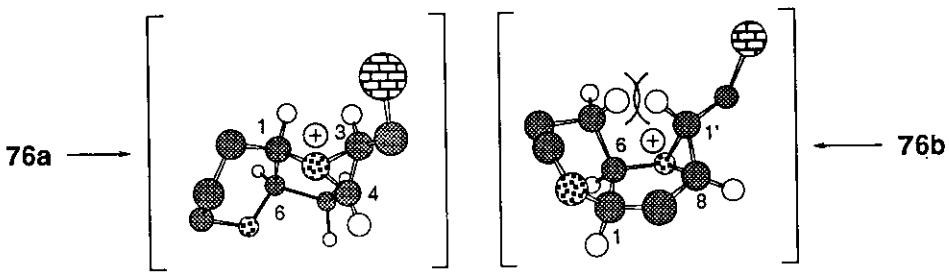


Figure 2.

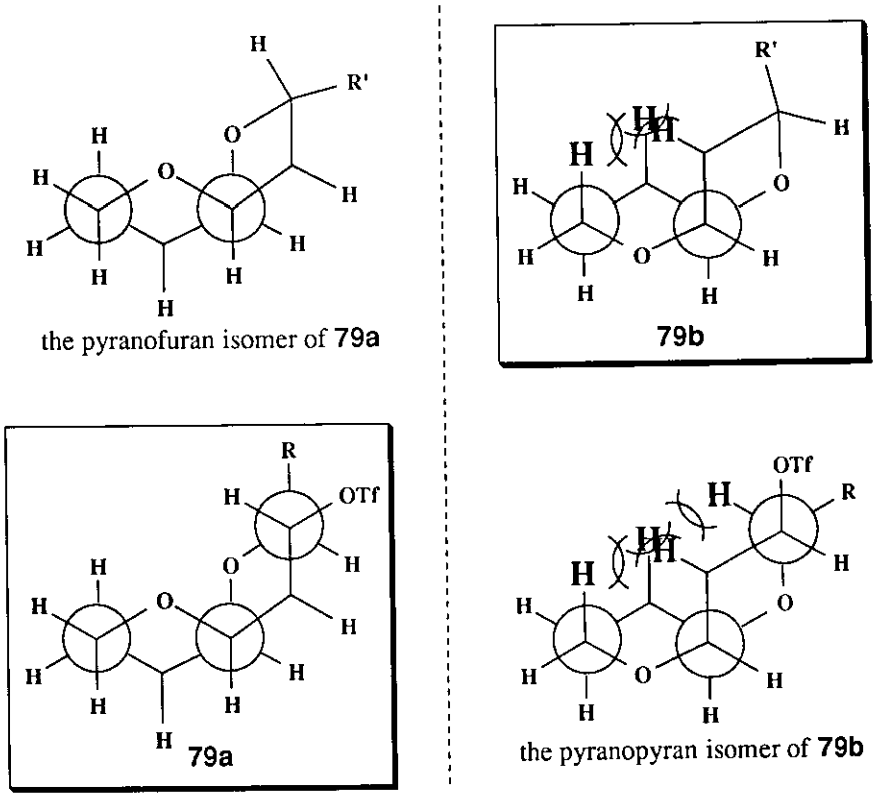


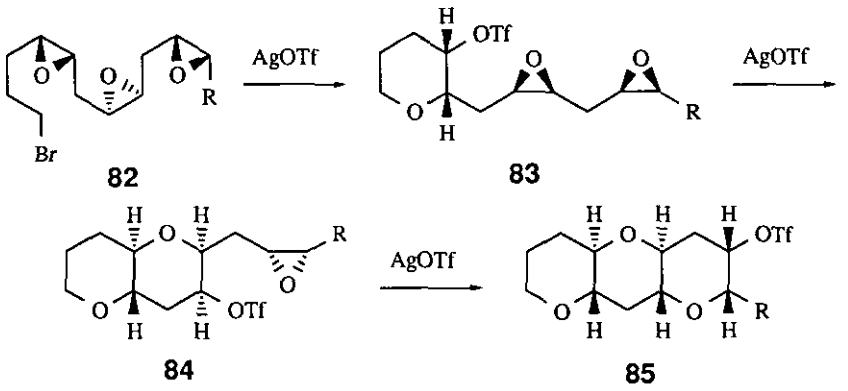
Figure 3.

isomer as shown in Figure 3. If the reactions were thermodynamically controlled, the regioselectivity of product depends on the stability of each product. In the case of the system of **76b**, **79b** is expected to be thermodynamically more stable than its pyranopyran isomer, because of the lower steric repulsion as shown in Figure 3. It seems that the second epoxy group of **76a** was expanded in the essential direction, that is, *endo*, because of the absence of the above effects.

4. Conclusion.

We described our attempted chemical realization of the proposed biogenetic pathway for the fused polycyclic ether systems by using two procedures. In the Section 2, we have succeeded in the construction of the *trans*-fused bicyclic oxane system using a bisepoxy bismethoxymethyl alcohol system as indicated in Scheme 8. In order to develop this reaction further, there seem to be some problems: 1) Is it possible to extend to construct the more elongated *trans*-fused polycyclic ether systems? 2) How do we convert the methoxymethyl group of the product into methyl group or hydrogen atom, because almost all natural fused-polycyclic products have methyl groups or hydrogen atoms on their ring junctures? 3) Is it possible to apply the reaction to the construction of successively fused oxepane or oxocane type compounds? 4) Is the present conditions using $La(OTf)_3$ the really best way for the desired chelation-controlled reaction? 5) Are there any other functional groups to be chelated with some Lewis acids for the endocyclic ring closure of the corresponding epoxy alcohol?...These are the notable problems to be solved in future.

On the other hand, in the Section 3, the AgOTf-promoted formation of fused cyclic ether systems by the successive ring-expansion reactions of bromo epoxides has been discussed from the two following points: 1) conversion of the oxiranes into the oxane or the oxepane (the initiation and termination model); 2) the successive ring-expansion reactions of diepoxides (the propagation model). From these examination, the following facts were clarified. 1) The *trans*-epoxy groups acted as nucleophiles to attack the intramolecular electrophilic centers. In the systems without any directing groups, the direction of the ring-expansion reaction on the system producing the oxane or the oxolane skeleton could be either kinetically or thermodynamically controlled in an *endo*-mode. The direction on the system forming the oxepane or the oxane skeleton could be an *endo*-fashion under kinetically-controlled conditions, while it could be thermodynamically controlled in an *exo*-mode. 2) In the one-pot successive ring-expansion reaction of the *trans,trans*-diepoxides, the products are the *cis*-fused bicyclic ethers regardless of the relative configurations between both epoxy groups. It is demonstrated that the *cis*-juncture was formed by the double inversion of the stereochemistry on the juncture's carbon atom *via* the alkyl triflate intermediate in each case. It seems that the last results (2) suggest the higher possibility of ring-expansion reactions. For example, if the reaction starts from the *cis*-epoxide (**82**), the desired *trans*-fused cyclic ether (**85**) could be obtained by the successive double inversion on the juncture's carbon atoms *via* the alkyl triflate intermediates (**83** and **84**) (Scheme 22). We expect strongly that the formation of the *trans*-fused polycyclic ether system could be realized by this modified method.



Scheme 22.

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42. In the Section 3 of this review, the reaction which gives the *endo* (*exo*) adduct of the external nucleophile is defined as an *endo* (*exo*)-mode.

43. The ratio of the products was determined by ^{1}H-NMR.

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