AgOTf-Promoted Conversion of 4,5-Epoxy-1-bromide into Tetrahydropyran Ring

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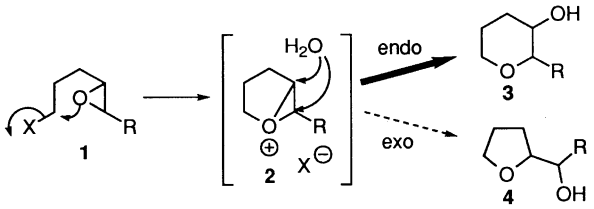
trans-1-Bromo-8-*t*-butyldiphenylsiloxy-4,5-epoxyoctane was treated with AgOTf in THF/H_2O (5:1) to give *trans*-3-hydroxytetrahydropyran derivative as the major product (72%) by the expansion of the oxirane ring.

The conversion of epoxy compound to cyclic ether is a very useful synthetic strategy. It has been known that, in a cyclization of epoxy alcohol, a reaction proceeds preferentially with an exo-mode.[1] Though a great deal of efforts have been made towards the preference of endo-fashion, all endo-cyclization methods have necessitated some directing groups near the epoxy group in the substrates.[2]

In such a cyclization reaction, the epoxy groups have played a role as electrophiles. To the contrary, we have studied on formation of cyclic ethers regarding the epoxy group of a starting material as a nucleophile. Our working hypothesis is shown in Scheme 1. Initially, the epoxy group would attack the



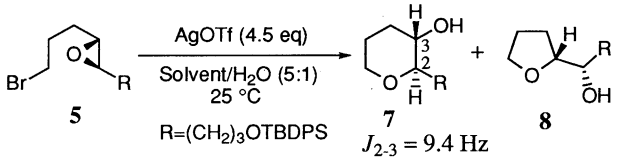
Scheme 1.

intramolecular electrophilic center to form the bridged oxonium ion **2**.[3] The second step is the intermolecular attack of nucleophile to the oxonium ion; the endo-attack would produce a tetrahydropyran derivative **3**, whereas the exo-attack a tetrahydrofuran **4**. We have attempted to control the endo-selectivity of the nucleophilic attack to **2** without any directing group. In this report, we describe the preferential formation of a tetrahydropyran by the ring expansion starting from the simple 4,5-epoxy-1-bromide.

Some ring expansion reactions *via* the bridged oxonium ion have been reported.[4,5] However, in their cases the net differences of reactivity between the two reactive positions on the bridged oxonium ion are unclear. In order to investigate these problems, the simple acyclic substrates, racemic *trans*- and *cis*-epoxides (**5** and **6**, respectively), were prepared.

At first, we examined the ring expansion of *trans*-1-bromo-8-*t*-butyldiphenylsiloxy-4,5-epoxyoctane **5**. Compound **5** was treated with AgOTf[6] in various aqueous organic solvents. The results are shown in Table 1. In heterogeneous solvent systems (Et_2O, benzene, and CH_2Cl_2), the reaction proceeded hardly, though Et_2O gave the best endo/exo selectivity (17/1). In the cases of THF/H_2O (5:1), 1,4-dioxane/H_2O (5:1), and acetone/H_2O (5:1), *trans*-3-hydroxytetrahydropyran derivative **7**[7] was obtained as a major product in high-stereoselectivities in 72%, 49%, and 55% yields, respectively. The stereochemistry of **7** was determined by ^{1}H-NMR analysis ($J_{2\text{-}3}$ = 9.4 Hz) after acetylation. It seems that the best yield in THF/H_2O was due to

Table 1.

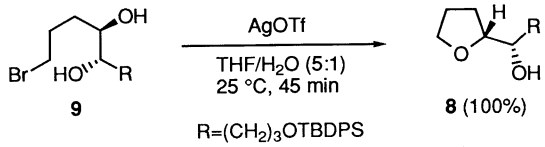


Entry	Solvent	Time/h	Yield/% 7+8	Ratio[a] (7/8)	Recovery/% 5
1	CH_2Cl_2	8.0	0	–	92
2	benzene	8.0	3	3.8/1	89
3	Et_2O	8.0	5	17/1	82
4	THF	6.5	91	3.8/1	6
5	1,4-dioxane	8.0	61	4.0/1	6
6	$(CH_3)_2CO$	6.5	70	3.6/1	0
7	CH_3CN	8.0	21	1.5/1	57
8	DMSO	8.0	48	2.4/1	7

a) The ratio of **7**/**8** was determined by ^{1}H-NMR after acetylation.

the effect of THF as the proton scavenger which prevented TBDPS group from cleavage. Actually, TBDPSOH was isolated in 18% and 6% yields in dioxane/H_2O and acetone/H_2O, respectively. In DMSO/H_2O or CH_3CN/H_2O, the endo/exo selectivity was lowered. The activity of silver cation might be lowered in CH_3CN/H_2O, because it formed the inert complex with silver cation.

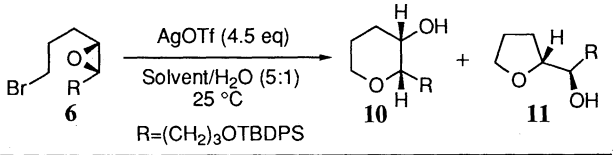
There remains a possibility that compound **7** might be produced by the cyclization of *anti*-diol **9** which was formed by the hydrolysis of the epoxy group in **5**, because the reaction system was acidic. In order to exclude the possibility, racemic *anti*-diol **9** was treated under the same conditions as above using THF to afford tetrahydrofuran derivative **8**[7] as a single product (Scheme 2). It reveals that **7** was not produced from *anti*-diol **9**,



Scheme 2.

but by the intramolecular nucleophilic attack of the epoxy group in **5**. On the other hand, it is not obvious whether the route leading to **8** proceeded by the *anti*-diol pathway or not in the reaction of **5**. The preference for tetrahydropyran derivative **7** would be presumably due to the higher reactivity of the endo-site because

Table 2.



Entry	Solvent	Time/h	Yield/%[a] 10	11	Recovery/% 6
1	THF	19	0	54	6
2	1,4-dioxane	19	0	52	5
3	$(CH_3)_2CO$	19	0	49	7

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

of the ring strain of the bridged oxonium ion.

This new reaction was also applied to racemic *cis*-1-bromo-8-*t*-butyldiphenylsiloxy-4,5-epoxyoctane **6** in aqueous THF, 1,4-dioxane, and acetone (Table 2). The reaction of **6** was slower than that of *trans*-isomer **5**. The reaction gave a tetrahydrofuran **11**[7,8] as a single product, and no trace amount of **10**. If the bridged oxonium ion is formed in the case of *cis*-isomers, the 1,3-steric interaction shown in Figure 1 could exist between the

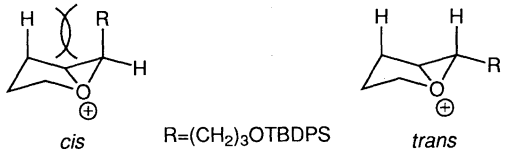


Figure 1.

side chain and the C-H bond. Such an interaction is absent in the *trans*-isomer. However, it is not clear whether **11** was produced through the bridged oxonium ion pathway (the exo-mode, preferentially) or the *cis*-diol one (the oxonium ion could not be formed).

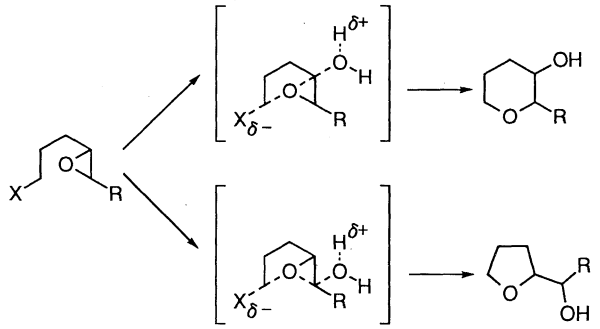
In conclusion, it was found that the *trans*-epoxy group in the simple acyclic substrate **5** could act as an intramolecular nucleophile to form the bridged oxonium ion,[3] which was converted into a tetrahydropyran **7** indicating the preference of the intermolecular endo-attack of nucleophile to the oxonium ion. Application of this new reaction to natural product synthesis is in progress in our laboratory.

References and Notes

1 J. E. Baldwin, *J. Chem. Soc. Chem. Comm.*, **1976**, 734.

2 a) K. C. Nicolaou, C. V. C. Prasad, P. K. Somers, and C.-K. Hwang, *J. Am. Chem. Soc.*, **111**, 5330 (1989). b) K. C. Nicolaou, C. V. C. Prasad, P. K. Somers, and C.-K. Hwang, *J. Am. Chem. Soc.*, **111**, 5335 (1989). c) T. Suzuki, O. Sato, and M. Hirama, *Tetrahedron Lett.*, **31**, 4747 (1990). d) C. Mukai, Y. Ikeda, Y. Sugimoto, and M. Hanaoka, *Tetrahedron Lett.*, **35**, 2179 (1994). e) C. Mukai, Y. Sugimoto, Y. Ikeda, and M. Hanaoka, *Tetrahedron Lett.*, **35**, 2183 (1994).

3 A concerted process might be alternatively assumed on this reaction mechanism as shown in Scheme 3. However, the concept of the bridged oxonium ion seems to explain the experimental results more facilely. Therefore, in this report, the bridged oxoniumion pathway was adopted. The true reaction mechanism could not be clarified from the obtained experimental results.



Scheme 3.

4 E. Alvarez, M. T. Diaz, R. Perez, J. L. Ravelo, A. Regueiro, J. A. Vera, D. Zurita, and J. D. Martin, *J. Org. Chem.*, **59**, 2848 (1994).

5 a) T. Nakata, G. Schmid, B. Vranesic, M. Okigawa, T. Smith-Palmer, and Y. Kishi, *J. Am. Chem. Soc.*, **100**, 2933 (1978); see also: b) T. Nakata, S. Nomura, and H. Matsukura, *Tetrahedron Lett.*, **37**, 213 (1996). c) T. Nakata, S. Nomura, H. Matsukura, and M. Morimoto, *Tetrahedron Lett.*, **37**, 217 (1996).

6 AgOTf was used, because it was more soluble in various organic solvents than other silver cation sources.

7 Satisfactory ^{1}H-NMR, IR, and mass spectral data were provided for compounds **7**, **8**, and **11** after acetylation.

8 The stereochemistry of **11** was determined by the conversion to the acetate of **8** by Mitsunobu reaction.