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Fused Cyclic Ether Formations from Bromo-Diepoxides by AgOTf-Promoted Successive Ring Expansion Reactions

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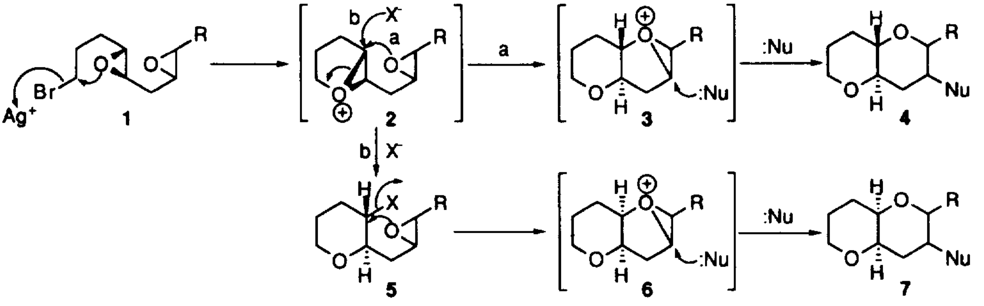
***Abstract*:** The one-pot successive ring expansion reactions of 1-bromo-9-*tert*-butyldiphenylsilyloxy-4,5,7,8-diepoxynonanes promoted by AgOTf were investigated. The *syn-trans*-derivative was treated with AgOTf in dry CH_2Cl_2 to give the *cis*-fused perhydrotriflyloxypyranopyran as the major product. On the other hand, the corresonding *anti-trans*-isomer was transformed into the *cis*-fused perhydrotriflyloxypyranofuran under the same conditions. Copyright © 1996 Elsevier Science Ltd

The extension of an epoxy compound into a cyclic ether is a very versatile synthetic strategy. Although an extensive work has been reported on endo-cyclization of epoxy alcohols,[1] the ring expansion reaction of an epoxy group has been little investigated. Recently, we have reported the novel synthesis of the tetrahydropyran ring by the expansion of the oxirane ring on an acyclic system without directing groups regarding the epoxy group as a nucleophile.[2] We describe herein the application of this methodology to formation of fused cyclic ethers by successive ring expansion reactions starting from the bromo-diepoxides.



Scheme 1.

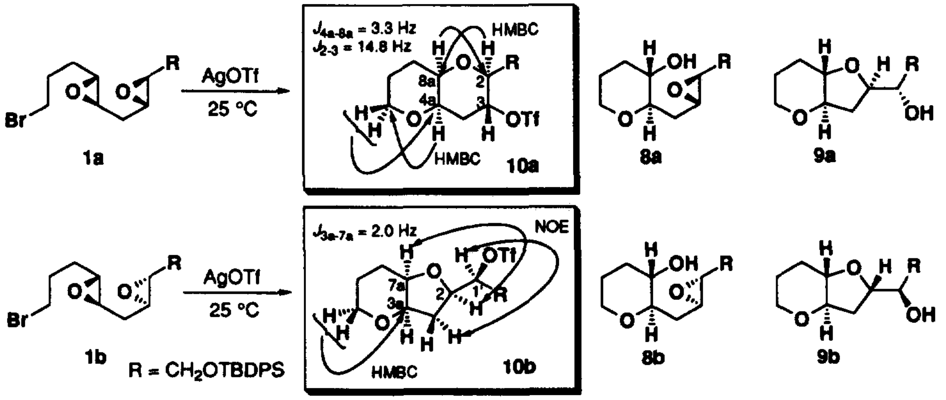
The proposed reaction mode of the successive ring expansion is illustrated in Scheme 1. The first step is the process in which the first bridged oxonium ion **2** would be formed by the intramolecular nucleophilic attack of the first epoxy group to the cationic site.[2] In the next step, if the intramolecular 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 **3**, and the successive ring expansion would be terminated by the intermolecular nucleophilic attack to produce the *trans*-fused bicyclic ether **4**. 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 **5**. If the X group is a poor leaving group, the reaction would be completed at this stage. On 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 **7** *via* the second oxonium ion **6**. We attempted to investigate how the successive ring expansion reactions of the *syn-trans*- and *anti-trans*-bromo-diepoxides (**1a** and **1b**) could occur.[3]

The reactions were initially attempted in the presence of H_2O as the external nucleophile. As shown in the Table, the *syn*-bromo-diepoxide **1a** was treated with AgOTf (10 eq) in THF/H_2O (5:1) at 25 °C for 1 h to give **8a** (31%) and **9a** (11%) along with the corresponding epoxy tetrahydrofuran isomer (1%) (entry 1). From the *anti*-bromo-diepoxide **1b**, **8b** (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 **9a** and **9b** were afforded in 53 and 46% yield, respectively (entries 2 and 5). In these reactions, the respective clear conversions of **8a** and **8b** into **9a** and **9b** were observed by TLC analyses; that is, these results indicate that **9a** and **9b** were produced not by the successive ring expansion of two epoxy groups, but by 5-exo-cyclizations of mono-epoxy alcohols (**8a** and **8b**) promoted by the acid in the systems. From these results, it was suggested that the intermolecular nucleophilic attack of H_2O to the first activated epoxy group was faster than the intramolecular attack by the second epoxy group.

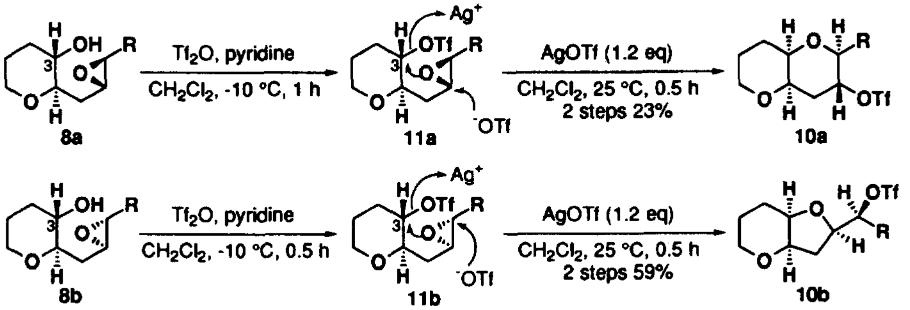
Next, the reactions were carried out under anhydrous conditions in which a triflate ion (a poor nucleophilic but a very good leaving group) would be expected to act as the external nucleophile. A mixture of **1a** and **1b** was, however, treated with AgOTf (1.2 equiv) in dry THF to obtain the higher polar products, which probably were formed on the reaction of the activated substrates with THF (entry 7). In dry CH_2Cl_2, **1a** was transformed into the *cis*-fused perhydrotriflyloxypyranopyran **10a** (39%) (entry 3), while **1b** was led to the *cis*-fused perhydrotriflyloxypyranofuran **10b** (29%) (entry 6). 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. The respective structures of **10a** and **10b** were determined by NMR (H-H coupling constants, NOEs, and HMBC revealed in Table), IR, and MS spectra.[4] Judging from the *cis*-junctures of **10a** and **10b**, it was suggested that the reactions proceeded through path **b** illustrated in Scheme 1. In order to confirm involvement of the intermediate such as 5, the compounds **11a** and **11b**, prepared from **8a** and **8b** with Tf_2O and pyridine in CH_2Cl_2, were converted on treatment with AgOTf under the same conditions as above into the *cis*-fused bicyclic ethers (**10a** and **10b**), respectively (Scheme 2).

From the above results, we can make the following comments: 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

Table. Ring Expansion of *syn*- and *anti*-Diepoxides.



Entry	Substrate	Solvent	AgOTf/eq.	Time/h	Products (Yield/%)	Recovery (%)
1	**1a**	THF/H_2O (5/1)	10	1	**8a** (31) + **9a** (11)	**1a** (24)
2	**1a**	THF/H_2O (5/1)	10	4	**9a** (53)	**1a** (0)
3	**1a**	CH_2Cl_2	1.2	0.5	**10a** (39)	**1a** (0)
4	**1b**	THF/H_2O (5/1)	10	1.5	**8b** (41)	**1b** (12)
5	**1b**	THF/H_2O (5/1)	10	23	**9b** (46)	**1b** (0)
6	**1b**	CH_2Cl_2	1.2	0.5	**10b** (29)	**1b** (0)
7	**1a**+**1b**	THF	1.2	0.5	high polar products	0



Scheme 2.

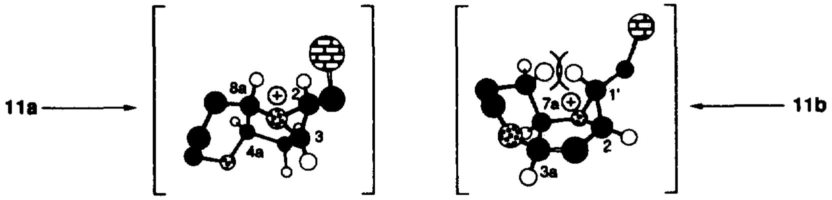


Figure. (The numberings correspond to those of **10a** and **10b**, respectively.)

triflate ion in these systems; 2) when the triflate ion was used as the external nucleophile, the formations of **11a** and **11b** were 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 inversions of the stereochemistries of the C3 in **11a** and **11b**; 3) the directions of the ring expansions of the second epoxy groups depended on the relations of the stereochemistries of the two epoxy groups. Though the reason why the pyranofuran skeleton (not the pyranopyran) was generated from the *anti*-diepoxide **1b** was not clarified from the experimental results, the reaction might proceed as the strain attributed to the steric repulsion in the structure of the second oxoniumion formed from **11b** was defused (Figure).

In this paper, we examined the AgOTf-promoted one-pot successive ring expansion reactions on the bromo-diepoxides. The *syn-trans*-derivative **1a** was reacted with AgOTf in dry CH_2Cl_2 to give **10a**, while the *anti-trans*-isomer **1b** was transformed into **10b** under the same conditions. It is strongly suggested that both *cis*-fused **10a** and **10b** would be produced *via* **11a** and **11b**, respectively.

References and Notes

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3. Diepoxides (**1a** and **1b**), prepared as a 1:1 mixture of two diastereomers in 12 steps and a 31% overall yield from the 4-pentyn-1-ol, were separated by HPLC. The structures of **1a** and **1b** were determined by NMR analyses (H-H coupling constants and NOEs) of the acetates of **9a** and **9b**, respectively.
4. ^1H NMR and HR-MS spectra of compounds **10a** and **10b**. **10a**: ^1H NMR ($CDCl_3$), δ 1.07 (9H, s), 1.30 (C_7H, m), 1.59-1.69 (C_8H, m), 1.89-2.01 (C_4H, C_7H, C_8H, m), 2.58 (C_4H, ddd, J = 3.3, 5.1, 12.8 Hz), 3.40 (C_6H, dt, J = 2.4, 12.5 Hz), 3.47 ($C_{8a}H$, t, J = 3.3 Hz), 3.48 (C_2H, ddd, J = 2.2, 3.5, 14.8 Hz), 3.61 ($C_{4a}H$, t, J = 3.3 Hz), 3.87 ($C_{1'}H$, dd, J = 2.2, 11.7 Hz), 3.91 ($C_{1'}H$, dd, J = 3.5, 11.7 Hz), 3.96 (C_6H, dt, J = 12.5, 2.8 Hz), 5.44 (C_3H, ddd, J = 5.1, 9.7, 14.8 Hz), 7.35-7.44 (6H, m), 7.73 (2H, dd, J = 1.7, 7.9 Hz), and 7.81 (2H, dd, J = 1.5, 7.9 Hz); HR-MS (FD), found, m/z 559.1752. Calcd for $C_{26}H_{34}O_6F_3SiS(M^++H)$, 559.1798. **10b**: ^1H NMR ($CDCl_3$), δ 1.07 (9H, s), 1.20 (C_6H, m), 1.53 (C_6H, tq, J = 4.2, 13.4 Hz), 1.66 (C_7H, ddt, J = 3.5, 4.6, 13.4 Hz), 1.92 (C_3H, dd, J = 3.7, 14.5 Hz), 1.98-2.06 (C_7H, m), 2.22 (C_3H, ddd, J = 5.0, 9.5, 14.5 Hz), 3.23 (C_5H, dt, J = 1.8, 13.4 Hz), 3.68 (C_5H, dt, J = 13.4, 2.0 Hz), 3.69 ($C_{7a}H$, m), 3.87 ($C_{3a}H$, dd, J = 2.0, 5.0 Hz), 4.00 ($C_{2'}H$, dd, J = 5.7, 12.6 Hz), 4.05 ($C_{2'}H$, dd, J = 2.8, 12.6 Hz), 4.30 (C_2H, ddd, J = 3.7, 5.7, 9.5 Hz), 5.12 ($C_{1'}H$, dt, J = 2.8, 5.7 Hz), 7.37-7.46 (6H, m), and 7.68-7.73 (4H, m); HR-MS (FD), found, m/z 559.1768. Calcd for $C_{26}H_{34}O_6F_3SiS$ (M^++H), 559.1798.

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