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Stereoselective Synthesis of Six- and Seven-Membered Ether Rings Based on the Ring Expansion

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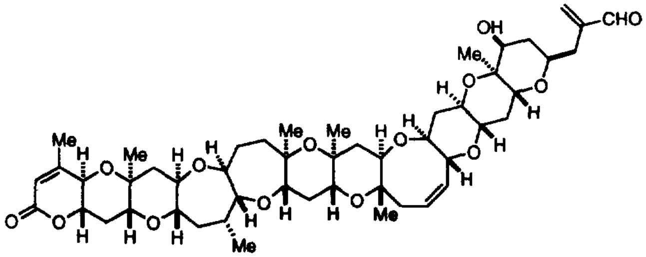
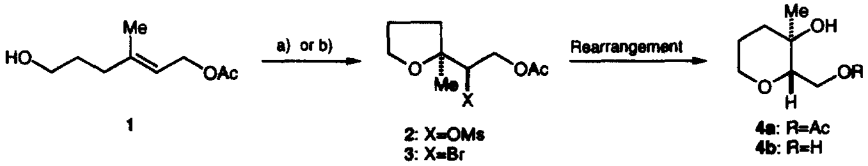
Abstract: Six- and seven-membered ether rings were stereoselectively synthesized based on the rearrangement of the cyclic ether with the simultaneous ring expansion. Treatment of ether having a mesylate or bromide group as the leaving group on the side chain with $Zn(OAc)_2$ or AgOAc stereoselectively produced the ring expanded ether in good yield.

Recently, marine polycyclic ethers exemplified by brevetoxin B[2] have attracted the attention of synthetic organic chemists due to their unusual structural framework, novel functionalities, and potent biological activities. The most characteristic feature of this class of marine natural products is that they have fused polycyclic ether ring systems. Thus, development of efficient methods for constructing these systems have been reported by several groups.[3] During the total synthesis of lasalocid A, the construction of the tetrahydropyran ring system was accomplished by a novel rearrangement of the corresponding tetrahydrofuran having the mesylate as the leaving group on the side chain.[4] This rearrangement might be expected to be very effective for the synthesis of the cyclic ether rings found in marine natural products such as brevetoxins and maitotoxin. Thus, the reaction was further investigated using five- and six-membered ethers having the leaving group on the side chain. We now report an efficient method for the synthesis of six- and seven-membered ether ring systems based on the rearrangement of the cyclic ether with the simultaneous ring expansion.



Brevetoxin B

The rearrangement of five-membered ethers having a mesylate or bromide group as the leaving group on the side chain was examined.[5,6] The five-membered ethers **2** and **3** as the substrates for the rearrangement were synthesized starting from allyl acetate 1,[7] prepared from geraniol, as follows. Epoxidation of 1 with m-chloroperbenzoic acid (MCPBA) followed by treatment with dl-camphorsulfonic acid (CSA) produced the cyclic ether which was treated with MsCl to give the required mesylate **2** (56% in 3 steps). The cyclic ether **3** having a bromide group on the side chain was synthesized in 74% yield by the reaction of **1** with N-bromosuccinimide (NBS). Several reaction conditions for the rearrangement were investigated and the results are shown in Table 1. The rearrangement was first investigated under the original conditions used in the synthesis of lasalocid A (run 1); upon treatment with Ag_2CO_3 in acetone-H_2O at reflux, the rearrangement of the mesylate **2** took place giving the ring expanded ether **4a** in 46% yield along with the recovered starting material **2** (39%). AgOTf was not effective for the rearrangement of the mesylate **2** (run 2), although it was quite effective for the bromo derivative **3** even at room temperature to give **4a** (run 6). Treatment of **2** with AgOAc in AcOH-H_2O at reflux produced **4a** in 51% yield (run 3). The best result was obtained by treatment of **2** with 4 equiv of $Zn(OAc)_2$ in AcOH-H_2O (1:1) at reflux giving **4a** in 75% yield (run 4). In the case of the bromo derivative **3**, treatment with AgOAc gave the best yield of **4** in 75% yield (run 8).[5] The reported conditions[6] using $AgBF_4$ gave **4** in 51% yield (run 7).



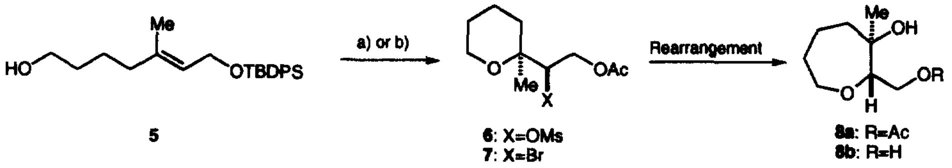
a) (i) MCPBA, CH_2Cl_2, rt; (ii) CSA, CH_2Cl_2, rt; (iii) MsCl, Et_3N, CH_2Cl_2, rt (56%, 3 steps); b) NBS, MeCN, rt, (74%).

Table 1. Rearrangement of five-membered ether, **2** or **3**, to six-membered ether **4**

Run	Substrate	Reagent[a]	Reaction Conditions	Yield of Product 4	
1	2: X=OMs	Ag_2CO_3	acetone-H_2O, reflux, 24hr	46% (**4a**)	(39%)[c]
2		AgOTf	acetone-H_2O, rt, 17hr	---	(97%)[c]
3		AgOAc	AcOH-H_2O, reflux, 2hr	51% (**4a**)[b]	
4		$Zn(OAc)_2$	AcOH-H_2O, reflux, 6hr	75% (**4a**)[b]	
5	3: X=Br	Ag_2CO_3	acetone-H_2O, reflux, 16hr	38% (**4a**)	(24%)[c]
6		AgOTf	acetone-H_2O, rt, 18hr	58% (**4a**)	
7		$AgBF_4$	DMF, 70°C, 4hr	51% (**4a**: 23%, formate of **4a**: 28%)	
8		AgOAc	AcOH-H_2O, reflux, 2hr	75% (**4a**: 62%, **4b**: 13%)	
9		$Zn(OAc)_2$	AcOH-H_2O, reflux, 8hr	61% (**4a**: 33%, **4b**: 28%)	

a) Four equiv of reagent was used.
b) The products were acetylated with Ac_2O in pyridine after the rearrangement.
c) Yield of the recovered starting material **2** or **3**.

We then examined the rearrangement of the six-membered ether to the seven-membered ether. The six-membered ethers **6** and **7** were synthesized starting from alcohol **5**[8] by the same procedure mentioned above. Epoxidation of **5** with MCPBA followed by CSA treatment gave the cyclic ether (97%) which was mesylated (74%). Upon treatment of the mesylate with AcCl-$ZnCl_2$,[9] deprotection of the silyl group and acetylation took place simultaneously giving the required mesylate **6** (98%). On the other hand, successive treatment of **5** with n-Bu_4NF (90%), NBS (71%), and Ac_2O (95%) produced the six-membered ether **7**. Rearrangement of **6** and **7** was carried out under the same conditions as the five-membered ethers and the results are shown in Table 2. Although treatment of **6** with Ag_2CO_3 in EtCOMe-H_2O at reflux produced **8a** in only 17% yield along with the recovered starting material **6** (48%) (run 1), the reaction with AgOAc in AcOH-H_2O at reflux produced **8** in 84% yield (run 2). The best result was again obtained by treatment with 4 equiv of $Zn(OAc)_2$ in AcOH-H_2O (1:1) at reflux giving the ring expanded ether **8** in 95% yield (run 3). In the case of the bromo compound **7**, treatment with AgOAc gave the best yield (55%) of **8** (run 6).



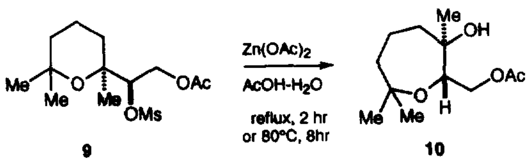
a) (i) MCPBA, CH_2Cl_2, 0°C; (ii) CSA, CH_2Cl_2, rt (97%, 2 steps); (iii) MsCl, Et_3N, CH_2Cl_2, rt (74%); (iv) AcCl, $ZnCl_2$, MeCN, rt (98%);
b) (i) n-Bu_4NF, THF, rt (90%), (ii) NBS, MeCN, rt (71%); (iii) Ac_2O, pyridine, rt (95%).

Table 2. Rearrangement of six-membered ether, **6** or **7**, to six-membered ether **8**

Run	Substrate	Reagent[a]	Reaction Conditions	Yield of Product 8	
1	**6**: X=OMs	Ag_2CO_3	MeCOEt-H_2O, reflux, 38hr	17% (**8a**)	(48%)[b]
2		AgOAc	AcOH-H_2O, reflux, 8hr	84% (**8a**: 47%, **8b**: 37%)	
3		$Zn(OAc)_2$	AcOH-H_2O, reflux, 8hr	95% (**8a**: 53%, **8b**: 42%)	
4	**7**: X=Br	Ag_2CO_3	acetone-H_2O, reflux, 13hr	---	(65%)[b]
5		AgOTf	acetone-H_2O, rt, 29hr	38% (**8a**: 31%, **8b**: 7%)	(6%)[b]
6		AgOAc	AcOH-H_2O, reflux, 4hr	55% (**8a**: 49%, **8b**: 6%)	
7		$Zn(OAc)_2$	AcOH-H_2O, reflux, 8hr	31% (**8a**: 16%, **8b**: 15%)	(32%)[b]

a) Four equiv of reagent was used except for run 1 (8 equiv).
b) Yield of the recovered starting material **6** or **7**.

The rearrangement of the α,α,α',α'-tetrasubstituted ether **9** with $Zn(OAc)_2$ in AcOH-H_2O was completed within 2 hr at reflux giving 7-membered ether **10** in 90% yield or almost proceeded even at 80°C for 8 hr. The 1,3-diaxial repulsion by the dimethyl groups would cause an acceleration of this rearrangement.[10]



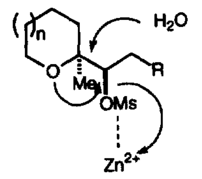


Fig. 1 n = 0 or 1

The present rearrangement took place with complete stereoselectivity giving a single isomer,[11] which suggests that this reaction should proceed concertedly as shown in Fig 1.

The effective method for the stereoselective synthesis of six- and seven-membered ethers was developed. Especially, rearrangement of cyclic ethers having the mesylate as the leaving group might effectively afford the required ring expanded ether, which has some advantages because the key intermediate epoxide could be synthesized with high stereo- and enantio-selectivities by the Sharpless asymmetric epoxidation. Application of the present method to natural product synthesis is now in progress and the scope and limitations of this rearrangement are also under investigation.

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8. The alcohol **5** was synthesized from **1** as follows; 1) TsCl, pyridine, CH_2Cl_2, rt (75%); 2) NaCN, DMSO, 80-85°C (100%); 3) K_2CO_3, MeOH, rt (76%); 4) TBDPSCl, imidazole, DMF, rt (100%); 5) DIBAH, CH_2Cl_2, -78°C; 6) $NaBH_4$, MeOH, rt (75%, 2 steps).
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10. The same behavior was observed on the same type of $\alpha,\alpha,\alpha',\alpha'$-tetrasubstituted ethers, which will be reported elsewhere.
11. The stereostructures of **4a**, **8a**, and **10** were confirmed by their NMR (NOE and/or HMBC) analyses.

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