Cyclizations

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Reagent-Controlled Switching of 5-*exo* to 6-*endo* Cyclizations in Epoxide Openings**

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Tetrahydrofuran (THF) and tetrahydropyran (THP) rings are ubiquitous structural units that are extensively encountered in a number of biologically active natural products and functional molecules. Therefore, the development of synthetic methods for constructing THF and THP ether rings has attracted much attention from synthetic organic chemists.[1]

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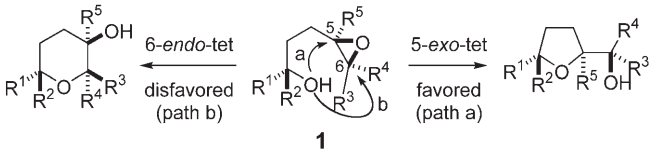
Among the possibilities, the intramolecular cyclization of bishomoepoxy alcohols is intriguing from the point of view of regioselectivity as well as it being one of the most practical and effective methods for the synthesis of both THF and THP cyclic ethers. In general, 5-*exo*-tet cyclizations are preferred to the 6-*endo*-tet variant because of a dominant stereoelectronic effect, which is known as Baldwin's rule.[2] However, the exact mode of cyclization depends on the substrates employed (Scheme 1). Thus, to observe 6-*endo* regioselectivity in opposition to Baldwin's rule a wide variety of methods have been devised, particularly over the last two decades. However, they almost all involve elaborate modifications of the epoxide substrate, for example, by the introduction of a π orbital[3] adjacent to the epoxide or sulfonyl[4] or trimethylsilyl (TMS)[5] substituents on the epoxide to activate the C6 position. There have hitherto been only two exceptions, namely, antibody catalysis[6] and $La(OTf)_3$-catalyzed cyclizations,[7] which overcome the normal preference for 5-*exo*-tet ring formation without the need for modification of the substrate, although in the latter case the substrates are limited to unusual methoxymethyl-substituted epoxides **1** ($R^5 = CH_2OMe$; Scheme 1). Herein, we report the non-enzymatic



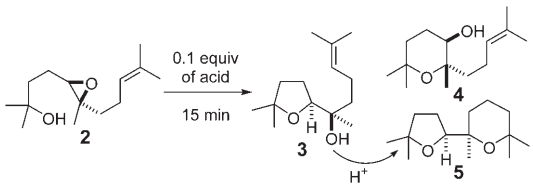
Scheme 1. 5-*Exo* versus 6-*endo* cyclizations of bishomoepoxy alcohols to give THF (path a) and THP derivatives (path b).

reagent-controlled switching of 5-*exo* to 6-*endo* cyclizations using the epoxide substrate **1** (R^1–R^4 = alkyl, R^5 = H), which usually demonstrates 5-*exo* regioselectivity.

In view of our interests in the synthesis of structurally and bioactively unique triterpene polyethers (oxasqualenoids),[8] we chose bishomoepoxy alcohol **2**[9] as the substrate for our investigation of the effective 6-*endo* cyclization. Alcohol **2** was prepared by the Sharpless epoxidation[10] of the corresponding bishomoallylic alcohol precursor.[11] In practice, acid-catalyzed cyclizations of bishomoepoxy alcohols such as **2** predominantly afford 5-*exo*-cyclized products[12] in a stereospecific and stereoselective manner (entry 1, Table 1).[13] First, we examined the solvent effect of the reaction catalyzed by (±)-10-camphorsulfonic acid (CSA). As the polarity of the solvents increased, the ratio of 6-*endo* cyclization increased (entries 2–4, Table 1). A stronger acid than CSA, such as trifluoromethanesulfonic acid (TfOH), further increased the yield of the 6-*endo* product **4** (entries 5–7). Bicyclic ether **5**, which could be generated by further cyclization of **3**,[14] was isolated in 13% yield as a by-product alongside **3** and **4** (entry 7, Table 1). However, we could not alter the preference for 5-*exo*-tet ring formation.

Next, we investigated the use of silyl triflates in the presence of 2,6-lutidine to activate the epoxide (Table 2).[15] Although treatment of **2** with TMSOTf in dichloromethane yielded only undesired diene **8a** (entry 1, Table 2), we were delighted to find that the reaction in acetonitrile provided 6-

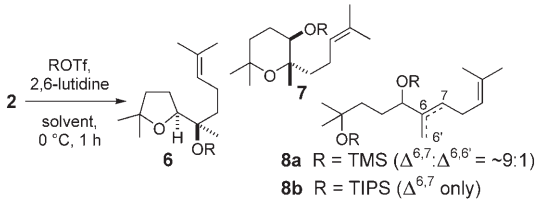
Table 1: Cyclizations of bishomoepoxy alcohol **2** catalyzed by Brønsted acids.



Entry	Acid	Solvent	*T*	Yield [%][a]		Ratio[b]
				3	**4**	5-*exo*/6-*endo*
1	CSA	CH_2Cl_2	0 °C	86	2	36:1
2	CSA	CH_2Cl_2	RT	77	4	22:1
3	CSA	CH_3CN	RT	70	20	3.5:1
4	CSA	CH_3NO_2	RT	59	18	3.2:1
5	TfOH	CH_2Cl_2	0 °C	76	6	13.3:1
6	TfOH	CH_3CN	0 °C	55	22	2.5:1
7	TfOH	CH_3NO_2	0 °C	33	25	1.9:1[c]

[a] Isolated yield. [b] Based on the isolated yield. [c] The ratio 5-*exo*/6-*endo* is equivalent to **(3+5)**/**4**.

Table 2: Cyclizations of bishomoepoxy alcohol **2** promoted by silyl triflates ROTf.[a]



Entry	ROTf (equiv)	Solvent	Yield [%][b]		Ratio[c]
			6+7	**8**	5-*exo*/6-*endo*
1	TMS (5)	CH_2Cl_2		70	
2	TMS (2)	CH_3CN	63		1:2.6
3	TMS (2)	CH_3NO_2	54		1:3.3
4	TES (2)	CH_3NO_2	59		1:5.8
5	TBS (5)	CH_3NO_2	82		1:12
6	TIPS (5)	CH_3NO_2	83		1:15
7[d]	TIPS (5)	CH_2Cl_2	34	38	1:2.7
8	TIPS (5)	CH_3CN	78		1:6.8

[a] The reaction was carried out at 0 °C for 1 h under a nitrogen atmosphere in the presence of 2,6-lutidine (1.4 equiv based on ROTf). [b] Isolated yield. [c] The ratio was determined by integration of the ^{1}H NMR spectra of the mixture of **6** and **7**. [d] The reaction was performed for 3.5 h. TES = triethylsilyl; TBS = *tert*-butyldimethylsilyl; TIPS = triisopropylsilyl.

endo-cyclized THP **7** in preference to 5-*exo* THF **6** (entry 2, Table 2).[16] The employment of nitromethane as solvent increased the 6-*endo* regioselectivity (entry 3, Table 2). Thus, other commercially available silyl triflates were further examined in nitromethane (entries 4–6, Table 2). The 6-*endo* regioselectivity was found to increase according to the steric bulkiness of the R group in ROTf (TMS < TES < TBS < TIPS). The best result was obtained by treating **2** with 5 equivalents of TIPSOTf in the presence of 7 equivalents of 2,6-lutidine in nitromethane at 0 °C for 1 h to give THP **7** (R = TIPS) in a ratio of 15:1 6-*endo*/5-*exo*. The TIPSOTf-promoted reaction in less-polar solvents led to a decrease in the 6-*endo* regioselectivity (entries 7 and 8, Table 2).

These results may be rationalized as follows: As these reactions are acidic epoxide openings, both S_N1 and S_N2 properties could be incorporated in the transition state (Figure 1). In terms of a stereoelectronic effect, 5-*exo* prod-

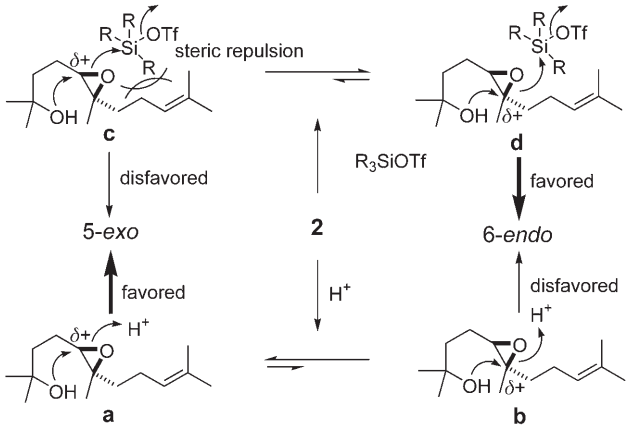


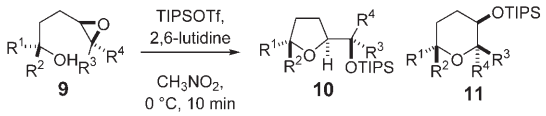
Figure 1. Possible transition states **a**–**d** with both S_N1 and S_N2 properties leading to 5-*exo* and 6-*endo* products.

ucts would predominate by way of transition states **a** and **c** (Baldwin's rule). On the other hand, if an incipient partial positive charge upon the epoxide opening is considered, then 6-*endo* products would predominate because tertiary carbocations **b** and **d** are more stable than the secondary ones **a** and **c**. In the case of Brønsted acids as shown in Table 1, the stereoelectronic effect overcomes the electrostatic one; therefore, 5-*exo* THF **3** was overwhelmingly produced in dichloromethane (entry 1, Table 1). However, the factors that favored transition state **b**, namely, more-polar solvents and a stronger acid, relatively increased the production of 6-*endo* THP **4** (entry 7, Table 1). In the case of trialkylsilyl triflates (Table 2), steric repulsion between alkyl groups on the silicon and in the substrate occurs in transition state **c** leading to 5-*exo* THF **6** with a sterically encumbered acyclic tertiary silyl ether. Then, as the disadvantageous steric repulsion overcomes the advantageous stereoelectronic effect, 6-*endo* THP **7** with a cyclic secondary silyl ether would predominate by way of transition state **d** without such a steric repulsion. In practice, the factors that destabilize **c** and stabilize **d**, that is, sterically bulkier silyl triflates and more-polar solvents, respectively, impart a greater 6-*endo* regioselectivity.

The TIPSOTf-promoted cyclization was also investigated for substrates **9a**–**f** (Table 3). Good 6-*endo* regioselectivities were observed for all except **9d** (entry 4, Table 3). It was also seen that the cyclization proceeds in a stereospecific manner (entry 6, Table 2; and entries 1–3, Table 3) and displays 6-*endo* regioselectivity regardless of the relative configuration of the tertiary alcohol and epoxide substrates (entry 5, Table 3).

In conclusion, we have demonstrated the TIPSOTf-promoted switching of 5-*exo* to 6-*endo* cyclizations in nitro-

Table 3: Cyclizations of bishomoepoxy alcohols **9a–f** promoted by TIPSOTf.[a]



Entry	9	R^1, R^2, R^3, R^4	Yield [%][b] 10 + 11	Ratio[c] 5-*exo*/6-*endo*
1	**a**	$R^1 = R^2 = R^4 = Me$, $R^3 = (CH_2)_2CH{=}CMe_2$	9 + 71	1:8
2	**b**	$R^1 = R^2 = R^3 = Me$, $R^4 = (CH_2)_3CHMe_2$	72	1:17
3	**c**	$R^1 = R^2 = R^4 = Me$, $R^3 = (CH_2)_3CHMe_2$	7 + 60	1:8
4	**d**	$R^1 = R^2 = R^3 = R^4 = Me$	86	1:3
5	**e + f**[d]	$R^1 = Ph$, $R^2 = R^3 = R^4 = Me$ (**e**), $R^2 = Ph$, $R^1 = R^3 = R^4 = Me$ (**f**)	79	1:8

[a] The reaction of **9** with TIPSOTf (5 equiv) in CH_3NO_2 was carried out in the presence of 2,6-lutidine (7 equiv) at 0 °C for 10 min under a nitrogen atmosphere. [b] Isolated yield. [c] Ratios were either determined by integration of the ^{1}H NMR spectra of the mixture of **10** and **11** or based on isolated yields. [d] As a mixture in a ratio of 1:1.4.

methane without the need for modification of the substrate, which normally shows a preference for 5-*exo*-tet ring formations. It is noteworthy that this sterically controlled switching by TIPSOTf (Figure 1) forms a contrast to the chelation-controlled switching in $La(OTf)_3$-catalyzed cyclizations.[7] Thus, a THF or THP ring can be formed from the same substrate by changing only the reagent, which would make possible the straightforward approach to bioactive oxasqualenoids.[8] Clarification of the details of the reaction mechanism and applications of this cyclization to natural products synthesis are in progress.

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[16] Desilylation of the mixture of silyl ethers **6** and **7** with tetrabutylammonium fluoride provided THF **3** and THP **4**, respectively, in almost the same ratios as those reported in Table 2.

