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Regiochemical control in intramolecular cyclizations of 2,3-epoxysulfides mediated by solvent effects

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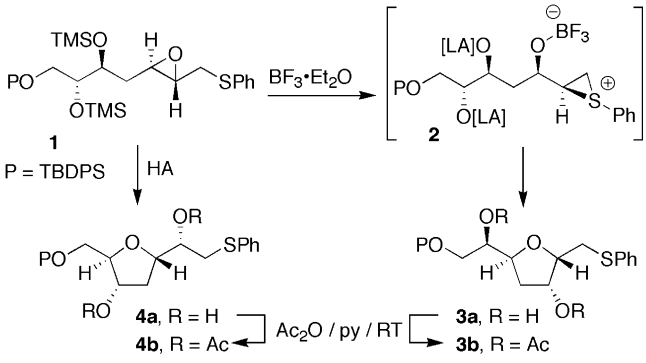
Abstract—The regioselectivity of cyclization in methylene-interrupted epoxydiols with a thiophenyl ether group adjacent to the epoxide can be controlled by the appropriate choice of reaction conditions. Thus, while the 5-*exo* mode of cyclization is observed under protic conditions with polar solvents, the intermediacy of an episulfonium ion generated in non-polar solvents lead to a regioisomeric THF product. © 2003 Elsevier Science Ltd. All rights reserved.

Neighboring group participation in the regioselective opening of epoxides with internal or external nucleophiles is an important transformation and is widely used in organic synthesis. Many of these regioselective ring opening reactions are based on oxygen directing interactions via chelation[1–3] or oxonium ion formation,[4,5] sulfur directed interactions via episulfonium[6–13] or sulfoxonium ion intermediates,[14] or presence of suitable groups such as double bonds to stabilize developing charged intermediates.[15,16] These regioselective openings have been successfully translated into construction of medium sized cyclic ethers found as a part of many natural products.[2–4,15–19]

Episulfonium ions are synthetically useful intermediates.[20–22] Their formation for use in synthetic applications has been well studied by Warren and co-workers[10–13] and Rayner's group.[21,22] They are particularly attractive in ring opening strategies as the resulting products have a net retention of configuration at the site of nucleophilic attack (double inversion) as compared to other directing groups where a complementary inversion ensues.

Our own interest in the synthesis and biological activity of 2,3,5-trisubstituted tetrahydrofuran (THF) diols derived from arachidonic acid had prompted us to investigate regiochemical determinants in the intramolecular cyclizations of methylene-interrupted epoxydiols.[19,23] During the course of our work, we observed that the appropriate choice of acid can lead to regioisomeric THF systems in the cyclization of methylene-interrupted epoxydiols with a pendant thiophenyl group neighboring the oxirane. As illustrated in Scheme 1, cyclization of **1** promoted by $BF_3{\cdot}OEt_2$ led to the isolation of **3b** (after acetylation with acetic anhydride) obtained via the intermediacy of the episulfonium ion **2**. On the other hand, use of protic acids yielded the 5-*exo* product **4b**.

Although the latter statement is generally true for most protic acids investigated, we were puzzled by the fact that with $AcOH{:}H_2O{:}THF$ (6:3:1) solvent system the observed product ratio was a mixture of **3b** and **4b**. Our studies had clearly shown that this ratio was not a result of equilibration between the regiosomeric THF products **3a** and **4a** under our reaction conditions, thus suggesting that both the 5-*exo* and the episulfonium mechanisms were operational. This also suggests that



Scheme 1. Different modes of cyclization of **1** with protic and Lewis acids.

Keywords: epoxysulfides; episulfonium; regiochemical control; epoxide opening; tetrahydrofuran rings.

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Table 1. Cyclization of **1** with Lewis and protic acid

	Conditions	Yield (%)	**3b**:**4b**
1	$BF_3{\cdot}Et_2O$–Et_2O	65	>99:1
2	10% HCl–THF (9:1)	74	7:93
3	AcOH–H_2O–THF (6:3:1)	75	30:70

either product could be obtained selectively with protic acids if the conditions for each are optimized.

We felt that these selectivities were due to the formation or lack of formation of episulfonium ion intermediates and are dependent on the reaction conditions. This prompted us to investigate conditions to obtain regioisomeric THF products from a common precursor under non-aqueous protic acid conditions.

The epoxysulfide **1** was synthesized as reported previously.[19] Our earlier results are summarized in Table 1 (entries 1–3). $BF_3{\cdot}OEt_2$ cyclizations of epoxysulfide **1** yielded THF **3b** via the intermediacy of an episulfonium ion while 10% aqueous HCl afforded THF **4b** from a direct 5-*exo* cyclization of epoxysulfide **1**. The immediate products of the reaction (**3a** and **4a**) were acetylated to aid in purification and structural determination. Presumably, either through protonation of the thiophenyl moiety or rapid 5-*exo* cyclization of the activated epoxide with strong acids the episulfonium ion is not a predominant species in the latter reaction. However, aqueous acetic acid furnished a mixture of **3b** and **4b** in a 30:70 ratio. This led us to believe that possibly the strength of the acid and/or the polarity of the solvent were important factors in determining the amount of episulfonium ion intermediate formed, and therefore dictate the product ratio of **3a** versus **4a**.

A series of experiments were performed to delineate the roles of acid strength and solvent polarity in the formation of the episulfonium ion intermediates with protic acids (Table 2).[24] The contribution from the strength of various acids as a function of polar and non-polar solvents (EtOH and CH_2Cl_2) was investigated. A solvent of even lesser polarity such as benzene could not be used since the TMS groups could not be deprotected with weak acids other than HF·pyridine. As can be seen from Table 2, THF **4b** was obtained as the major product of the reactions performed in EtOH, irrespective of the acid used to promote the cyclization (Table 2, entries 1–5). Use of the weak acid PPTS in EtOH yielded a 3:97 ratio of **3b**:**4b**, an even higher selectivity than the stronger *p*TSA in the same solvent (Table 2, entry 5). This is not surprising and stands to reason that weaker acids are not capable of promoting the episulfonium ion formation as easily as stronger acids, and therefore the 5-*exo* product predominates.

In contrast, the product ratios were dictated by the strength of the acid used to promote the cyclizations in the less polar CH_2Cl_2. Thus, while good selectivity was obtained with a strong acid such as *p*TSA (Table 2, entry 6), the selectivity was progressively lost with the weaker acids (Table 2, entries 7 and 8). These results indicate that in a polar solvent such as EtOH the strength of the acid is not crucial in determining the product ratios. It also shows that unlike in polar solvents, the amount of episulfonium ion formed in non-polar solvents does depend on the strength of the acid.

Table 2. Cyclizations with different acids in EtOH and CH_2Cl_2

	Conditions[a]	Time (h)	Yield (%)[b]	**3b**:**4b**[c]
1	H_2SO_4–EtOH	1	81	8:92
2	*p*TSA–EtOH	2	83	6:94
3	AcOH–EtOH	6	82	8:92
4	HF·py–EtOH	0.5	95	9:91
5	PPTS–EtOH	12	73	3:97
6	*p*TSA–CH_2Cl_2	4	95	95:5
7	TFA–CH_2Cl_2	2	89	90:10
8	HF·py–CH_2Cl_2	0.5	80	78:22

[a] 0.02 M reactions were carried out at 50°C, except for HF·py which was kept at rt. 3 equiv. of acid was added in each reaction.
[b] Yields are reported over two steps (cyclization and acetylation) and refer to isolated quantities.
[c] Ratio of **3b**:**4b** was determined by GC analysis.

These observations were further confirmed when the cyclizations were performed with the same acid (*p*TSA) in solvents of different polarities (Table 3).[24] Acids weaker than *p*TSA (such as AcOH and PPTS) were not used since they were not able to deprotect the silyl ethers in some of the more non-polar solvents, and therefore did not promote cyclizations. Even with *p*TSA the reactions had to be carried out at 50°C to effect clean desilylations. Use of EtOH as the solvent led to the isolation of **4b** as the major product (Table 3, entry 1). The selectivity of the reaction slightly eroded in DMF to yield **3b** and **4b** in a 10:90 ratio. The loss of selectivity continued as the amount of episulfonium ion intermediate increased with decreased solvent polarity. Thus, THF and Et_2O afforded higher ratios of **3b** (Table 3, entries 3 and 4) as compared to the reaction in EtOH. Gratifyingly, use of CH_2Cl_2 as the solvent led to the isolation of THF **3b** as the major product (entry 5), thus reversing the selectivity of the same reaction per-

Table 3. Role of solvent polarity

	Conditions[a]	Time (h)	Yield (%)[b]	**3b**:**4b**[c]
1	*p*TSA–EtOH	2	83	6:94
2	*p*TSA–DMF	2	75	10:90
3	*p*TSA–THF	3	83	28:72
4	*p*TSA–Et_2O	3	89	34:66
5	*p*TSA–CH_2Cl_2	4	95	95:5
6	*p*TSA–EtOH (10 equiv.)–CH_2Cl_2	4	70	75:25
7	*p*TSA–PhH	24	40	60:40
8	H_2SO_4–PhH	12	83	88:12

[a] 0.02 M reactions were carried out at 50°C. 3 equiv. of acid was added in each reaction.
[b] Yields are reported over two steps (cyclization and acetylation) and refer to isolated quantities.
[c] Ratio of **3b**:**4b** was determined by GC analysis.

formed in EtOH. Therefore, it seems that the equilibrium between the activated epoxide leading to **4a** and the episulfonium ion yielding **3a** could be dictated by the polarity of the solvent used for the reaction. This was further demonstrated by attempting the cyclization of **1** with *p*TSA in CH_2Cl_2 doped with EtOH (Table 3, entry 6). As expected, the selectivity was reduced owing to the higher polarity of the mixed solvent yielding a 75:25 ratio of **3b** and **4b**.

The reaction of **1** in benzene with *p*TSA was slow and produced many side products (Table 3, entry 7). More surprisingly, in contrast to what we would have predicted based on the non-polar nature of the solvent, the reaction was not very selective. The lack of selectivity may be due to the weak acidity of *p*TSA in benzene as suggested by the sluggish reaction, hence the competing direct 5-*exo* process could occur to a greater extent. This was corroborated by the use of a strong acid in benzene (H_2SO_4), where it was found that the reaction was faster and a product ratio of 88:12 was obtained (Table 3, entry 8).

The concern over the possible sluggish deprotection of the bis-TMS protecting groups in **1** with weak acids, in particular in non-polar solvents prompted us to investigate the selectivity of the reaction initiated with HF·pyridine. The deprotection of the silyl groups with HF·pyridine is rapid, and at the same time the pyridinium ion supplies the reaction with a weak acid. Also, the reactions could be carried out at room temperature even with non-polar solvents such as benzene (Table 4).[24] Cyclization of **1** in EtOH with HF·pyridine yielded the 5-*exo* product **4b** as the major product. Use of less polar solvents THF and Et_2O yielded higher ratios of **3b**:**4b** (16:84 and 22:78, respectively), thus following the same trend as observed before with the change in solvent polarity.

The selectivity was once again reversed with CH_2Cl_2 (Table 4, entry 4), yielding THF **3b** as the major product, although not with the same high selectivity as was observed with *p*TSA (Table 2, entry 6). This could be due to either the higher polarity of HF·pyridine as compared to *p*TSA, or the fact that the rapid deprotection of the TMS groups could lead to a more nucleophilic alkoxide-like intermediate that promotes faster 5-*exo* cyclizations. However, the reaction in benzene yielded clean conversion to **3b** as the major product. Thus, the trend of increasing episulfonium ion derived product with decreasing solvent polarity continues to hold for the HF·pyridine initiated reactions as well. The results tabulated in Tables 3 and 4 demonstrate that it is possible to control the regiochemistry of epoxide opening with a neighboring thiophenyl group in the presence of protic acids. This allows either regioisomeric product to be obtained selectively from a common precursor by simply choosing the correct combination of acid promoter and solvent.

Our observations suggest that under protic acid conditions epoxysulfides and their corresponding episulfonium ions exist in equilibrium with each other. The

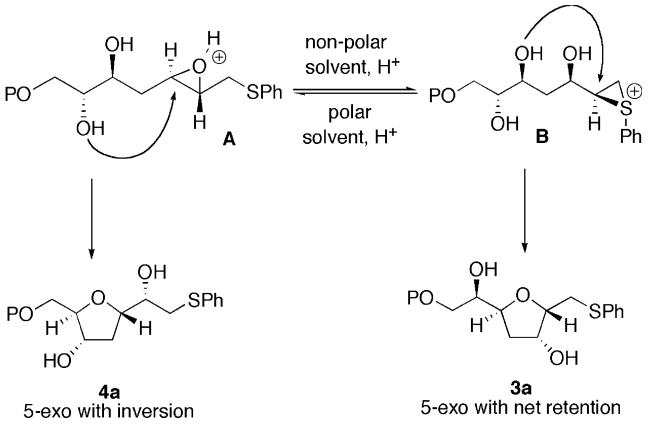
Table 4. Cyclizations of **1** with HF·pyridine in various solvents

	Conditions[a]	Time (h)	Yield (%)[b]	**3b**:**4b**[c]
1	HF·py–EtOH	0.5	95	9:91
2	HF·py–THF	0.5	88	16:84
3	HF·py–Et_2O	0.5	88	22:78
4	HF·py–CH_2Cl_2	0.5	85	77:23
5	HF·py–PhH	0.5	75	91:9

[a] 0.02 M reactions were carried out at rt. 3 equiv. of acid was added in each reaction.
[b] Yields are reported over two steps (cyclization and acetylation) and refer to isolated quantities.
[c] Ratio of **3b**:**4b** was determined by GC analysis.

position of this equilibrium depends on the solvent and the acid used to promote the reaction. For a polar solvent, irrespective of the acid used, the equilibrium is shifted towards the epoxysulfide **A** (Scheme 2), therefore, leading to the 5-*exo* derived product **4a**. On the other hand, for a less polar solvent, the position of this equilibrium favors the formation of the episulfonium ion intermediate **B**, and thus product **3a** with net retention of stereochemistry at point of ring closure is obtained. Weak acids that cannot promote episulfonium ion formation, regardless of the solvent used will naturally yield higher levels of the 5-*exo* product.

Alternatively, it is possible that instead of an equilibrium process, the ratio of products obtained reflect the rate of episulfonium ion formation versus the 5-*exo* cyclization, and that the rate is dependent on the polarity of the solvent. Thus, a suitably positioned diol protected as their TMS ethers are nucleophiles within the system. Here, the acid and polarity of solvent will not only determine the amount of episulfonium ion formed but also determine the rate of desilylation and consequent cyclization. Hence, the observed selectivity of a direct 5-*exo* cyclization may be a combined effect of the polar solvent and the strong acid promoting a rapid desilylation and subsequent cyclization. One could also consider the fact that transilylation is expected to be rapid in ethanol but not likely in CH_2Cl_2, thus leading to the observed product ratios.



Scheme 2.

Experiments delineated in Table 4 were performed to investigate these questions. Treatment with HF·pyridine rapidly yields the unprotected diol,[25] and therefore, removes from consideration rates of desilylation and/or transilylation. The dependence of product ratio on solvent polarity is still evident (Table 4).

In summary we have shown that the regioselectivity in the ring openings of epoxysulfides can be efficiently controlled by the solvent system to promote or prevent the formation of an intermediate episulfonium ion. In turn, this can be utilized to access regioisomeric THF rings with stereochemical control of the newly formed center from a common precursor. Use of a polar solvent will lead to the 5-*exo* product, while a non-polar solvent will yield products via the episulfonium intermediate, the extent of which depends on the strength of the protic acid utilized.

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24. *General procedure for the cyclizations in ethanol and dichloromethane with different acids* (Table 2). The appropriate acid (0.09 mmol, Table 2) was added to a solution of epoxide **1** (20 mg, 0.03 mmol) in anhydrous solvent (2 mL) and heated at 50°C for the specified time. The reactions in ethanol were concentrated under reduced pressure to dryness and the residue was dissolved in ethyl acetate prior to further work-up. The reactions in dichloromethane were directly diluted with ethyl acetate (10 mL) and washed with $NaHCO_3$ (satd, 5 mL). The aqueous layer was then extracted with ethyl acetate (2×10 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The crude product was subjected to acetylation prior to purification. Full spectroscopic data for products reported herein can be found in Ref. 19.
General procedure for the pTSA cyclizations in different solvents (Table 3). *p*TSA (17 mg, 0.09 mmol) was added to a solution of epoxide **1** (20 mg, 0.03 mmol) in an appropriate anhydrous solvent (2 mL, Table 3) and heated at 50°C for the specified time. The reaction in ethanol was concentrated under reduced pressure to dryness and the residue was dissolved in ethyl acetate prior to further work-up. All other reactions were directly diluted with ethyl acetate (10 mL) and washed with $NaHCO_3$ (satd, 5 mL). The aqueous layer was then extracted with ethyl acetate (2×10 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The crude product was subjected to acetylation prior to purification.
General procedure for the HF·pyridine cyclizations in different solvents (Table 4). HF·pyridine (0.09 mmol) was added to a solution of epoxide **1** (20 mg, 0.03 mmol) in an appropriate anhydrous solvent (2 mL,

Table 4) and stirred at room temperature for 30 min. The reaction in ethanol was concentrated under reduced pressure to dryness and the residue was dissolved in ethyl acetate prior to further work-up. All other reactions were directly diluted with ethyl acetate (10 mL) and washed with $NaHCO_3$ (satd, 5 mL). The aqueous layer was then extracted with ethyl acetate (2× 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The crude product was subjected to acetylation prior to purification.

25. This was demonstrated by rapidly quenching the reaction of **1** with HF·pyridine in ethanol after 2 min and acetylating the resulting product. The major isolated product (along with **4b**) was the acetylated epoxydiol which would originate from the desilylation of **1** prior to cyclization.