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Regiochemical Control in Intramolecular Cyclization of Methylene-Interrupted Epoxydiols

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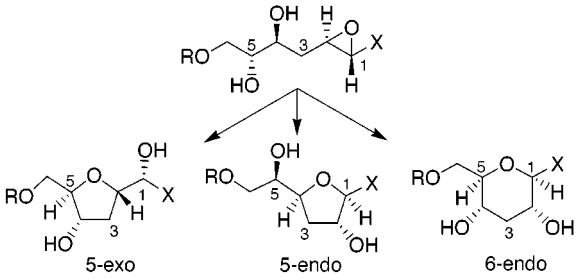
ABSTRACT



Methylene-interrupted epoxydiols have multiple regiochemical routes for cyclization. The 5-exo process is the most prevalent under acidic conditions. However, the regioselectivity can be controlled by the appropriate choice of acid promoter and pendant groups adjacent to the epoxide. The 5-exo product is obtained exclusively without the presence of a carbocation-stabilizing pendant group. Alkenyl and thiophenyl groups adjacent to the epoxide alter the regioselectivity and enable access to the 5-endo tetrahydrofuran and 6-endo tetrahydropyran products.

Regiochemical control in opening of epoxides is paramount in many synthetic strategies. Coupled with excellent methodologies for establishing desired stereogenic centers for epoxides,[1−3] alcohols,[4−7] and diols,[8,9] control of intramolecular regiochemistry in cyclization of epoxyalcohols can lead to versatile strategies for stereodefined syntheses. We are primarily interested in investigating novel metabolites of arachidonic acid, namely, arachidonic acid tetrahydrofuran diols (AA-THF-diols, Scheme 1) which possess 3-oxygenated 2,3,5-trisubstituted THF ring as the core structure. These compounds have exhibited biological activity; however, the exact stereo- and regioisomer(s) responsible for the activity remain to be elucidated.[10] Quantitative structure/activity relationship (QSAR) studies of this class of metabolites will require a straightforward and convenient synthetic strategy of the various stereo- and regioisomers. This method will also be useful for the synthesis of other natural products such

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(1) Jacobson, E. N. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 1993; p 159.
(2) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 1993; p 101.
(3) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224.
(4) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539.
(5) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.
(6) Masamune, S.; Kim, B.-M.; Petersen, J. S.; Sato, T.; Veenstra, S. J. *J. Am. Chem. Soc.* **1985**, *107*, 4549.
(7) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709.
(8) Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.
(9) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 1993; p 227.
(10) Moghaddam, M. F.; Motoba, K.; Borhan, B.; Pinot, F.; Hammock, B. D. *Biochim. Biophys. Acta* **1996**, *1290*, 327.

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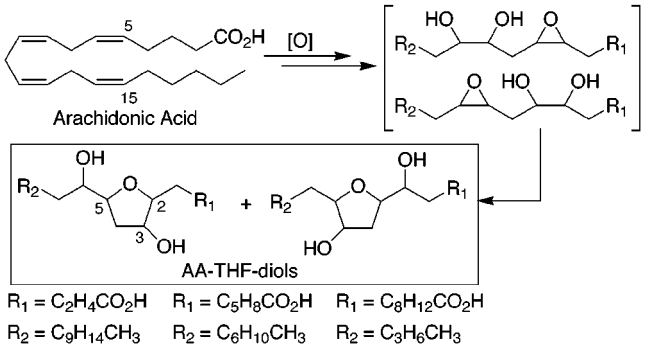
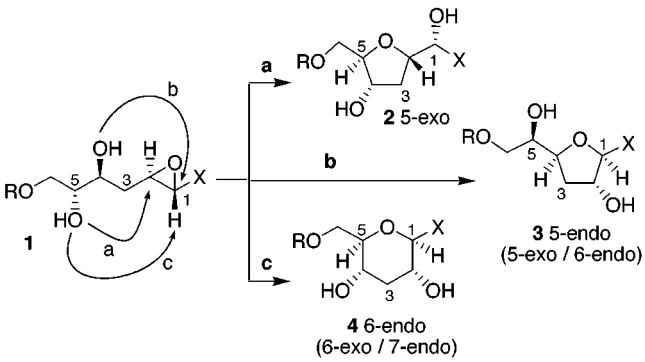
Scheme 1. Proposed Biosynthesis of AA-THF-diols



as the recently discovered nonclassical acetogninns, containing such trisubstituted THF motifs.[11−14]

A commonly used approach for the synthesis of substituted cyclic ether units is the intramolecular epoxide opening, first reported by Kishi.[15,16] Most systems studied in this context have a single hydroxyl group acting as the nucleophile;[17−22] however, epoxydiols such as **1** where both hydroxyl groups can participate in the cyclization event (paths **a**, **b**, and **c**, Scheme 2) have not been studied. Path **a** is the typical 5-exo

Scheme 2. Possible Modes of Cyclization (See Ref 25 for Definitions of Hybrid Nomenclature in Parentheses)



ring opening process. Paths **b** and **c** (Scheme 2) can be labeled as endo processes based on Baldwin nomenclature[23] or a hybrid exo/endo process following Warren's terminology.[24,25] Herein, we report our initial results in investigating control elements for regiospecific intramolecular cyclization of methylene-interrupted epoxydiols. With the appropriate choice of the pendant functional group (X, Scheme 2) and reaction conditions, we have been able to access different reaction pathways to secure regioisomeric THF and THP rings.

2-Deoxy-D-ribose was utilized as the entry point to obtain the common structural motif represented in **1**. Epoxydiol precursors (**5a**−**g**) were synthesized using routine transformations (see Supporting Information for details). Table 1 lists the results obtained upon treatment of **5a**−**g** with various acidic conditions. Exposure of these compounds to both protic acid (AcOH:H_2O:THF (6:3:1)) and Lewis acid (BF_3·Et_2O) led to selective desilylation of the TMS ether protecting groups and intramolecular epoxide opening in the same step. The cyclization products were peracetylated for ease of NMR characterization, and their structures were established by 2D-COSY and NOE experiments.

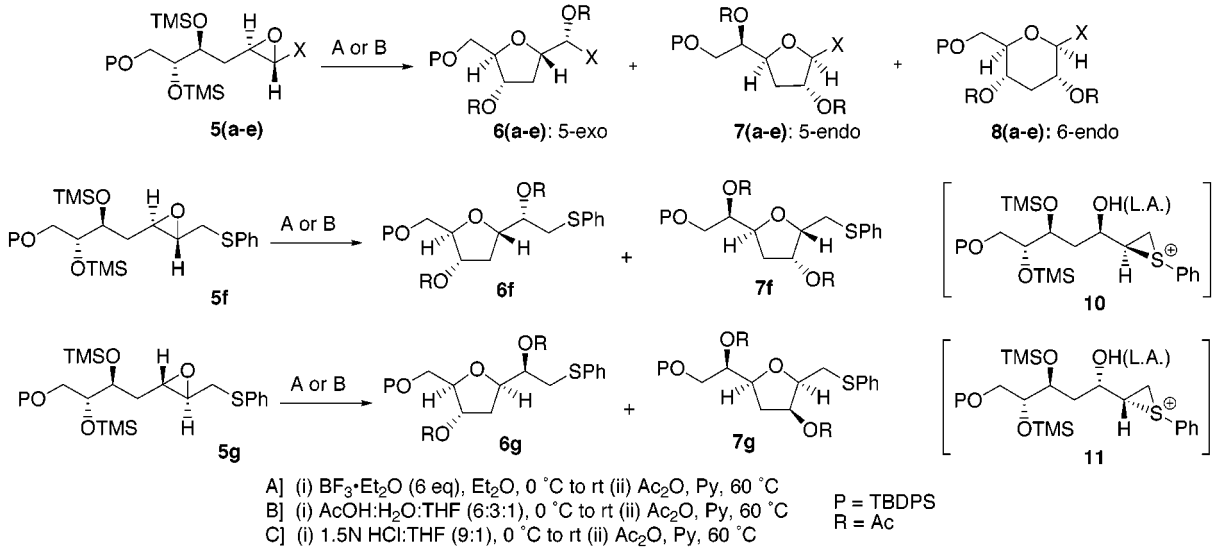
On the basis of the better alignment of the newly forming and rupturing bonds[23] and the electron-withdrawing inductive effect of the pendant groups (except alkyl group in **5d**), we expected that the 5-exo cyclization (path **a**, Scheme 2) would be favored for compounds **5a**,**b**,**d**,**e**. As shown in Table 1, the expected 5-exo product was obtained in each of these cases as a single diastereomer. Complete stereochemical inversion was observed at C-2, which is consistent with a concerted mechanism of epoxide opening. The same regioselectivity of epoxide opening was observed with the diastereomer of **5a** (epimeric at both epoxidic carbons), thus indicating that the stereochemical relationship between the diol and the epoxide is not of any consequence for this system.

Compound **5c** with the olefinic appendage was designed in order to stabilize a developing positive charge at C-1 during activation and epoxide opening, thus leading to the 5-endo product **7c** (path **b**, Scheme 2). This strategy has been successfully used by others with monohydroxy epoxy systems.[17,21,22] We examined the possibility of extending the same idea to our epoxydiol system to selectively generate 2,3,5-trisubstituted THF units. Treatment of **5c** with BF_3·Et_2O led to the isolation of **7c** after peracetylation via the 5-endo pathway, thus securing a regiochemically distinct trisubstituted THF unit. Interestingly, cyclization of **5c** with aqueous acetic acid yielded only THP **8c** (Table 1) via the 6-endo route (path **c**, Scheme 2).

Cyclization of **5c** was also triggered with 10% aqueous HCl in THF (9:1). THP **8c** was again obtained as the sole product in 75% yield, indicating that the strength of the aqueous acid is not the determining factor in the process.

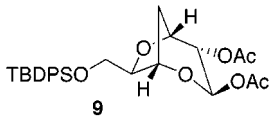
(11) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504.
(12) Capon, R. J.; Barrow, R. A.; Rochfort, S.; Jobling, M.; Skene, C. *Tetrahedron* **1998**, *54*, 2227.
(13) Kempf, A. J.; Wilson, K. E.; Hensens, O. D.; Monaghan, R. L.; Zimmerman, S. B.; Dulaney, E. L. *J. Antibiot.* **1986**, *39*, 1361.
(14) Robinson, N.; Gibson, T. M.; Chicarelli-Robinson, M. I.; Cameron, L.; Hylands, P. J.; Wilkinson, D. *J. Nat. Prod.* **1997**, *60*, 6.
(15) Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1978**, *31*, 2745.
(16) Nakata, T.; Schmid, G.; Vranesic, M.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2933.
(17) Evans, P. A.; Murthy, V. S. *Tetrahedron Lett.* **1999**, *40*, 1235.
(18) Fujiwara, K.; Tokiwano, T.; Murai, A. *Tetrahedron Lett.* **1995**, *36*, 8063.
(19) Fujiwara, K.; Mishima, H.; Amano, A.; Tokiwano, T.; Murai, M. *Tetrahedron Lett.* **1998**, *39*, 393.
(20) Mukai, C.; Ikeda, Y.; Sugimoto, Y.; Hanaoka, M. *Tetrahedron Lett.* **1994**, *35*, 2179.
(21) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C. K. *J. Am. Chem. Soc.* **1989**, *111*, 5330.
(22) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C. K. *J. Am. Chem. Soc.* **1989**, *111*, 5335.
(23) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
(24) McIntyre, S.; Warren, S. *Tetrahedron Lett.* **1990**, *31*, 3457.
(25) A hybrid notation of Baldwin's terminology, used by Warren and co-workers, and relevant to our work is included in the Supporting Information.

Table 1. Acid-Promoted Cyclization of Methylene-Interrupted Epoxydiols



compound	condition	yield (%)[a]	product[b]
5a, X = CH_2OH	A	75	**6a**[c]
	B	72	**6a**[c]
5b, X = CHO	A	17[d]	**9**[e]
	B	20[d]	**9**[e]
5c, X = $CHCH_2$	A	82	**7c**
	B	80	**8c**
5d, X = CH_2CH_3	A	80	**6d**
	B	78	**6d**
5e, X = OCH_3	A	60	**6e**
	B	75	**6e**
5f	A	65	**7f**
	B	75	**6f**:**7f** (70:30)
	C	74	**6f**:**7f** (97:3)
5**g**	A	70	**6g**:**7g** (3:97)
	B	78	**6g**:**7g** (80:20)
	C	74	**6g**:**7g** (95:5)

[a] All reported isolated yields are over the two steps described in conditions A, B, and C. [b] In each case, the indicated products are the only observed and isolated products. None of the other possible regioisomers were detectable by TLC, crude GC, or NMR analysis. [c] Hydroxyl in X is acetylated. [d] A complex mixture of products was obtained possibly due to rearrangement and polymerization of aldehyde under acidic conditions. The only isolable product after acetylation was **9**. [e] Product obtained is due to the 5-exo opening (via **7c**) of the epoxide, which underwent intramolecular hemiacetylation. **9** was identified after peracetylation.



Semiempirical calculations (PM3 force field, Spartan V. 5.1.3) suggest that **8c** is slightly more stable than **7c** (by about 2 kcal/mol). This prompted us to investigate the possibility that **7c** might have been produced under aqueous acidic conditions but was then isomerized to yield the more stable product **8c**. However, treatment of **7c** with 10% HCl in THF did not lead to any isomerization product and starting material was recovered. We also were not able to isomerize **8c** into **7c** under reaction conditions that led to the isolation of **7c** (BF_3·EtO_2). The regioselectivity observed in ring opening of **5c** might be due to differential rates of silyl deprotection or different transition state energies in the ring opening for a given substrate under different reaction conditions in the cases that lead to **8c**. We are presently investigating these possibilities.

We next studied the cyclization reactions of epoxysulfides **5f** and **5g**, anticipating that under acid conditions these cyclizations would involve the intermediacy of episulfonium ions **10** and **11**, respectively (Table 1). Warren and coworkers have extensively studied the selective synthesis of THF and THP systems with and without 1,2-phenylthio migrations via episulfonium ion intermediates.[26−28] Epoxysulfides are known to undergo rearrangement to form

(26) Fox, D. J.; House, D.; Kerr, F.; Warren, S. *J. Chem. Soc., Chem. Commun.* **2000**, 1781.

episulfonium ion under acidic conditions.[29−31] In light of the results with **5c**, we believed that the use of thiophenyl ether as the neighboring group should enable us to direct the regiochemistry of cyclization by both strategies discussed above, that is by the dual use of functional group participation as well as the choice of the reagent used to trigger the functional group participation.

Results of acid-promoted cyclizations of epoxysufide **5f** and **5g** are summarized in Table 1. Attack at the less substituted end of the episulfonium ion was not observed experimentally. Formation of **7f** and **7g** involves net retention of configuration at C-1, thus providing a set of products complementary to THF systems obtained with **5e**; i.e., in this case net retention at point of attack furnishes the epimer of the 5-endo cyclization product analogue reported above. Treatment of **5f** with $BF_3{\cdot}Et_2O$ yielded the 5-exo cyclized product **7f** as a single diastereomer. The observed NOEs confirmed a net retention of configuration at C-1, thus suggesting the formation of episulfonium ion prior to cyclization.

Exposure of epoxysulfide **5f** to aqueous acetic acid furnished a mixture of THF products **6f** and **7f**. However, when epoxysulfide **5f** was treated with 1.5 N HCl, **6f** was isolated as the major product. While **7f** is the 5-exo cyclization product resulting from an episulfonium ion intermediate, **6f** is the 5-exo product resulting from direct cyclization of the epoxysulfide. Semiempirical calculations (Spartan 5.1.3, AM1 force field) show **6f** to be more stable than **7f** by about 2 kcal/mol. To examine if the product ratio observed with acetic acid is due to slow equilibration to the more stable isomer, the reaction was continued for extended periods. However, the ratio of isomers was not significantly different even after 24 h. Also, when the product obtained from the $BF_3{\cdot}Et_2O$ reaction (**7f**) was submitted to acetic acid and 1.5 N HCl conditions separately, no equilibration was observed. These results suggest that in acetic acid the cyclization probably occurs through two pathways, one involving an episulfonium ion intermediate and the other by direct cyclization of the epoxysulfide. On the other hand, under strong protic acid conditions (HCl), the thio group could be solvated, thereby disfavoring formation of the episulfonium ion. Unlike that in the case of epoxy alkene **5c**, no THP products were observed. The regioselectivity observed in the cyclizations of epoxysulfide remains constant even with a change in the epoxide stereochemistry, as is evident from the cyclization of **5g** (Table 1) using the same set of conditions to yield **6g** and **7g**.

In summary, we have demonstrated that regioselectivity in epoxide opening in case of methylene-interrupted epoxy-diol system **1** can be controlled with appropriate pendant groups (X) and the acid promoter. We have obtained five stereoisomeric 3-oxygenated 2,3,5 trisubstituted THF rings from a common precursor without the need for orthogonal protection of the diol functionality. Total synthesis of AA-THF-diols using this methodology is currently underway.

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Supporting Information Available: Detailed experimental procedures and tabulated spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) House, D.; Kerr, F.; Warren, S. *J. Chem. Soc., Chem. Commun.* **2000**, 1779.
(28) House, D.; Kerr, F.; Warren, S. *J. Chem. Soc., Chem. Commun.* **2000**, 1783.
(29) Gill, M. D.; Pegg, N. A.; Rayner, M. C. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1371.
(30) Gill, M. D.; Pegg, N. A.; Rayner, C. M. *Tetrahedron* **1996**, *52*, 3609.
(31) Miyauchi, H.; Nakamura, T.; Ohashi, N. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1731.