

Illinois Wesleyan University

From the Selected Works of Ram S. Mohan

2005

A Study of Epoxyolefin Cyclizations Catalyzed by Bismuth Trifluoromethanesulfonate and Other Metal Triflates

Ram S. Mohan, *Illinois Wesleyan University*

Joshua R. Lacey

Peter W. Anzalone

Christopher M. Duncan

Matthew J. Hackert



Available at: https://works.bepress.com/ram_mohan/5/

A Study of Epoxyolefin Cyclizations Catalyzed by Bismuth Trifluoromethanesulfonate and Other Metal Triflates

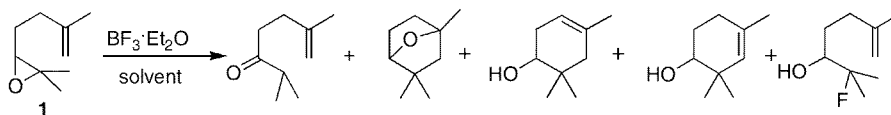
Joshua R. Lacey, Peter W. Anzalone, Christopher M. Duncan,
Matthew J. Hackert and Ram S. Mohan

Abstract—Epoxyolefin cyclizations have attracted considerable interest due to their importance in biosynthetic pathways. Bismuth trifluoromethanesulfonate as well as several other metal triflates are shown to be highly effective (0.1 mol %) catalysts for the cyclization of geraniolene oxide. The product composition is found to be more dependent on solvent and substrate concentration than on the nature of the metal triflate. Cyclization products are favored in CH_2Cl_2 and under high dilution conditions. Ether solvents favored acyclic products.

The cyclization of epoxyolefins has been the subject of intense study ever since the discovery that these reactions are involved in the biosynthesis of many terpenes, including cholesterol. An early example is the cyclization of geraniolene oxide **1** using $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to give a mixture of acyclic and cyclic products (Scheme 1).¹

A classic example of such a cyclization was first reported by van Tamelen who demonstrated that squalene 2,3-epoxide is an intermediate in the enzymatic cyclization of squalene to lanosterol and cholesterol.² Several non-enzymatic conditions have been reported to effect epoxyolefin cyclizations. The non-enzymatic cyclizations of (\pm)-10,11-oxidofarnesyl acetate, methyl farnesate, methyl (\pm)-10,11-oxidofarnesate, and 14,15-geranylgeranyl acetate have been studied using several catalysts such as BF_3 , H_3PO_4 , and SnCl_4 .³ Johnson and co-workers have elegantly demonstrated epoxide-initiated olefin cyclizations.⁴ The Lewis acid induced cyclization of

vinyl ether-epoxides has also been studied.⁵ Lewis acid mediated epoxy alcohol rearrangements have been shown to be directed by the hydroxy group.⁶ The potential of the epoxy furan cyclization for the formation of six- and seven-membered rings has been well demonstrated.⁷ The Friedel–Crafts cyclic alkylations of several epoxides have been studied using AlCl_3 and SnCl_4 .⁸ The utility of epoxyolefin cyclizations in the construction of carbocycles has been used to advantage in the synthesis of natural products such as *d,l*-malabaracenediol,^{9a} (\pm)-martinol,^{9b} (\pm)-karakana ether,^{9c} and (+)-aphidicolin.^{9d} The cyclization of epoxy-silanes has been investigated using TiCl_4 .¹⁰ Epoxyolefin cyclizations have also been initiated by MeAlCl_2 ^{1b} and bis(4-bromo-2,6-di-*tert*-butylphenoxide).¹¹ However, most of the catalysts that have been used for epoxyolefin cyclizations are highly corrosive, toxic, and difficult to handle.¹² In addition, few of them have been employed under highly catalytic conditions (ca. 0.1 mol % catalyst). An added



Scheme 1.

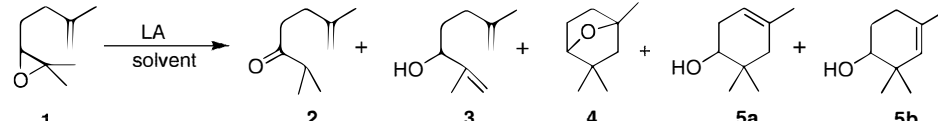
problem with Lewis acids containing a nucleophilic anion is that products can arise from attack by the anion on the epoxide. For example, when geraniolene oxide **1** is treated with $\text{BF}_3 \cdot \text{Et}_2\text{O}$, a significant amount of the fluorohydrin (Scheme 1) is obtained.^{1a} In spite of their demonstrated versatility, metal triflates have not been used as catalysts for epoxyolefin cyclizations. Our continued interest in bismuth compounds, due primarily to their remarkably low toxicity, ease of handling, and low cost prompted us to study epoxyolefin cyclizations catalyzed by bismuth triflate.^{13,14} Herein we report a study of the reactions of geraniolene oxide **1** in the presence of a variety of metal triflates, including bismuth triflate, under highly catalytic conditions (0.1 mol % catalyst). To the best of our knowledge, this is the first example of a metal triflate catalyzed cyclization of an epoxyolefin.¹⁵

Geraniolene oxide **1** was treated with $\text{Bi}(\text{OTf})_3 \cdot x\text{H}_2\text{O}$ (0.1 mol %) in a variety of solvents including CH_2Cl_2 , DME, dioxane, pentane, THF, and toluene. These results are compared with those obtained with other

metal triflates such as $\text{Ga}(\text{OTf})_3$, $\text{In}(\text{OTf})_3$, KOTf , $\text{La}(\text{OTf})_3$, LiOTf , $\text{Sc}(\text{OTf})_3$, and $\text{Yb}(\text{OTf})_3 \cdot x\text{H}_2\text{O}$. In addition, the cyclization of **1** was carried out with $\text{CF}_3\text{SO}_3\text{H}$ in CH_2Cl_2 and TMSOTf in an ionic liquid, $[\text{bmim}][\text{OTf}]$. These results are summarized in Table 1. Metal triflates derived from $\text{Bi}(\text{III})$, $\text{Ga}(\text{III})$, $\text{In}(\text{III})$, and $\text{Sc}(\text{III})$ were the most effective catalysts (0.1 mol %) while $\text{La}(\text{III})$ triflate (entry 12), $\text{Yb}(\text{III})$ triflate (entries 15 and 16) as well as the alkali metal triflates (entries 11 and 13) proved less efficient. Due to its low cost, ease of handling, and relative insensitivity to moisture, $\text{Bi}(\text{OTf})_3 \cdot x\text{H}_2\text{O}$ was found to be the metal triflate of choice for the reaction. We initially carried out the reactions of geraniolene oxide **1** at ca. 0.36 M concentrations (typically 0.20 g of the epoxide was dissolved in 4.0 mL of the solvent). Under these conditions, in addition to the cyclization products **4**, **5a**, and **5b**, two acyclic products, **2** and **3** were also formed in significant amounts.¹⁶

The reaction was also catalyzed by 0.10 mol % triflic acid (entry 17) and the ratio of products was essentially

Table 1. Results of the reaction of geraniolene oxide **1** with various metal triflates^a

									
Entry	Catalyst	Mol %	Solvent	<i>t</i> ^b	Ratio of products ^{c,d}				Yield ^e
					2 ²¹	3 ²²	4 ^{1a}	(5a ²³ + 5b ²⁴)	
1	Bi(OTf) ₃ ·xH ₂ O	0.10	CH ₂ Cl ₂	5 min	22	29	13	36 (82:18)	95
2	Bi(OTf) ₃ ·xH ₂ O, Proton sponge [®]	0.10 1.0	CH ₂ Cl ₂	24 h	NR				—
3	Bi(OTf) ₃ ·xH ₂ O, K ₂ CO ₃	0.10 40	CH ₂ Cl ₂	5 min	19	31	11	39	95
4	Bi(OTf) ₃ ·xH ₂ O	1.0	Pentane	10 min	57	20	6.0	17	—
5	Bi(OTf) ₃ ·xH ₂ O	0.10	Toluene	45 min	25	50	9.0	16	—
6	Bi(OTf) ₃ ·xH ₂ O	1.0	THF	10 min	55	39	0	6.0	72
7	Bi(OTf) ₃ ·xH ₂ O	0.10	Dioxane	10 min	49	43	2.0	6.0	—
8	Bi(OTf) ₃ ·xH ₂ O	0.10	DME	20 min	59	36	1.0	4.0	—
9	Ga(OTf) ₃	0.10	CH ₂ Cl ₂	10 min	22	32	11	35	85
10	In(OTf) ₃	0.10	CH ₂ Cl ₂	40 min	20	37	10	33	90
11	KOTf	5.0	CH ₂ Cl ₂	17 h	23	31	10	36	79
12	La(OTf) ₃	5.0	CH ₂ Cl ₂	5.5 h	22	31	11	36	94
13	LiOTf	5.0	CH ₂ Cl ₂	5.5 h	NR				—
14	Sc(OTf) ₃	0.10	CH ₂ Cl ₂	35 min	20	31	10	39	80
15	Yb(OTf) ₃ ·xH ₂ O	1.0	CH ₂ Cl ₂	17 h	11	22	8.0	59	79
16	Yb(OTf) ₃ ·xH ₂ O	1.0	THF (dry)	18 h	41	54	0	5.0	80
17	CF ₃ SO ₃ H	0.10	CH ₂ Cl ₂	20 min	21	33	10	36	88
18	CF ₃ SO ₃ H, K ₂ CO ₃	0.10 40	CH ₂ Cl ₂	16 h	NR				—
19	TMSOTf	3.0	[bmim][OTf]	30 min	74	15	0	11	75

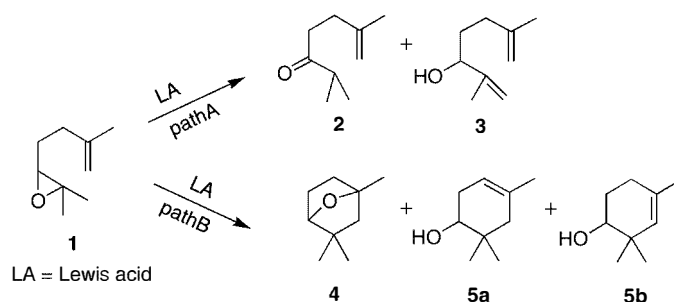
^a All reactions were carried out in reagent grade solvents at room temperature unless otherwise mentioned. The ionic liquid was dried at 70 °C under vacuum (0.1 mmHg) for 12 h prior to use.

^b Reaction progress was followed by GC.

^c Ratios are normalized to 100% and were determined by GC analysis of the crude reaction product mixture. The average of 2–6 runs is reported for each entry. Ratios obtained by GC analysis agree closely with those obtained by integration of appropriate peaks in the ¹H NMR spectrum. The relative ratio of **5a** and **5b** was obtained by ¹H NMR spectroscopy. The ratio of **5a:5b** was the same with all the metal triflates.

^d Superscript against product refers to literature reference for the compound.

^e Refers to isolated yield of crude product mixture. The products shown typically comprised 85–90% of the crude mixture. Isolated yields of purified products were low due to the laborious chromatography required to separate products with similar *R*_f values. Products were characterized by IR and NMR spectroscopy as well as by comparison of their spectral data with those reported in the literature.



Scheme 2.

Table 2. Effect of epoxide **1** concentration (M) on product composition using $\text{Bi}(\text{OTf})_3 \cdot x\text{H}_2\text{O}$ as the catalyst

Entry	Mol % $\text{Bi}(\text{OTf})_3 \cdot x\text{H}_2\text{O}$	Epoxide 1 concentration (M)	Solvent	Ratio of products ^a		Yield ^b
				2+3 path A	4+5a/b path B	
1	0.10	0.357	CH_2Cl_2 , rt	51	49	95
2	1.0	0.357	CH_2Cl_2 , -78°C	40	60	83
3	1.0	0.0713	CH_2Cl_2 , rt	26	74	70
4	1.0	0.0285	CH_2Cl_2 , rt	15	85	79
5	1.0	0.00713	CH_2Cl_2 , rt	8	92	79

^a Ratios are normalized to 100% and were determined by GC analysis of the crude reaction product mixture.

^b Refers to isolated yield of crude product mixture. The products shown typically comprised 85–90% of the crude mixture.

the same as that obtained with the metal triflates. This observation raised the possibility that the reactions in the presence of metal triflates are actually catalyzed by triflic acid, released in situ by hydrolysis of the metal triflates by any water present in the solvent, especially since anhydrous solvents were not used. In order to test this hypothesis, the $\text{Bi}(\text{OTf})_3 \cdot x\text{H}_2\text{O}$ catalyzed reaction of geraniolene oxide was carried out in the presence of solid K_2CO_3 as well as proton-sponge[®] (*N,N,N',N'*-tetramethyl-1,8-naphthalenediamine)[®].¹⁷ It was found that no reaction occurred even after 24 h (Table 1, entry 2) in the presence of proton sponge[®] while the addition of K_2CO_3 had no effect on the reaction (Table 1, entry 3). In order to test the efficacy of K_2CO_3 in neutralizing any triflic acid generated in situ, geraniolene oxide **1** was treated with 0.1 mol % $\text{CF}_3\text{SO}_3\text{H}$ in the presence of K_2CO_3 (entry 18). In this case, no reaction was observed and the starting material was recovered. These observations suggest that bismuth triflate is indeed acting as a Lewis acid and presumably initiates the reaction by complexing with the epoxide oxygen.¹⁸ The inactivity of bismuth triflate in the presence of proton sponge[®] is due likely to the complexation of bismuth to the amine nitrogens.

In Scheme 2, two possible pathways to the products obtained from the reaction of geraniolene oxide **1** are outlined. Presumably, products **2** and **3** arise via some very short-lived intermediate or via a concerted pathway (Scheme 2, path A). The acid-catalyzed cyclization of geraniolene oxide **1** has been studied in ClCH_2COOH , and it has been proposed that the cyclization products formed via a pathway in which the epoxide C–O bond formation and C–C bond formation are concerted (Scheme 2, path B).¹⁹ We found that the product composition was much more sensitive to the solvent than the Lewis acid.

As can be seen from the results in Table 1, the overall ratio of acyclic products to cyclization products (**2+3**):(**4+5a/b**) remained unchanged with the nature of the metal triflate for a given solvent. With metal triflates, the greatest amounts of cyclized products were obtained in CH_2Cl_2 as the solvent and the least amounts were formed in ether solvents such as THF, dioxane, and DME as well as in the ionic liquid, $[\text{bmim}][\text{OTf}]$.²⁰ We next examined the effect of temperature and substrate concentration on product composition. With $\text{Bi}(\text{OTf})_3 \cdot x\text{H}_2\text{O}$ as the Lewis acid, it was found that the amount of cyclization product was concentration dependant (Table 2). When the reaction is carried out under high dilution conditions, greater percentages of cyclized products **4** and **5a/b** are obtained (Table 2, entries 3–5). A lower reaction temperature (Table 2, entry 2) however, only marginally favors the cyclization products.

In summary, the utility of metal triflates in catalyzing epoxyolefin cyclizations has been demonstrated. Product composition is influenced more by the nature of the solvent and substrate concentration than by the choice of metal triflate. Bismuth triflate is an especially attractive catalyst for these reactions due to the low toxicity, ease of handling, and low cost of bismuth(III) compounds.

Acknowledgments

We are grateful to the National Science Foundation for an RUI (Research at An Undergraduate Institution) grant (# 0350216). We also wish to acknowledge Research Corporation for a Cottrell College Science Award. R.M. wishes to thank The Camille and Henry Dreyfus Foundation for a Henry Dreyfus Teacher Scholar Award. We also wish to thank Dr. Dale Whalen

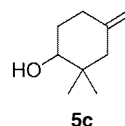
(University of Maryland Baltimore County) for useful discussions.

Supplementary data

General experimental section, representative procedures, isolation, and characterization of all reaction products. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.10.013.

References and notes

- (a) Goldsmith, D. J. *J. Am. Chem. Soc.* **1962**, *84*, 3913; More recently the cyclization of geraniolene oxide has been investigated using MeAlCl_2 , see: (b) Corey, E. J.; Sodeoka, M. *Tetrahedron Lett.* **1991**, *32*, 7005.
- (a) van Tamelen, E. E.; Storni, A.; Hessler, E. J.; Schwartz, M. *J. Am. Chem. Soc.* **1963**, *85*, 3295; (b) van Tamelen, E. E.; Willett, J. D.; Clayton, R. B.; Lord, K. E. *J. Am. Chem. Soc.* **1966**, *88*, 4752; (c) van Tamelen, E. E.; McCormick, J. P. *J. Am. Chem. Soc.* **1969**, *91*, 1847; (d) van Tamelen, E. E.; Sharpless, K. B. *J. Am. Chem. Soc.* **1969**, *91*, 1848; (e) van Tamelen, E. E.; Murphy, J. W. *J. Am. Chem. Soc.* **1972**, *92*, 7204; (f) van Tamelen, E. E.; Anderson, R. J. *J. Am. Chem. Soc.* **1970**, *94*, 8225; (g) van Tamelen, E. E. *Acc. Chem. Res.* **1974**, *8*, 152; (h) van Tamelen, E. E.; Leiden, T. M. *J. Am. Chem. Soc.* **1982**, *104*, 2061.
- (a) van Tamelen, E. E.; Storni, A.; Hessler, E. J.; Schwartz, M. A. *Bioorg. Chem.* **1982**, *11*, 133; (b) van Tamelen, E. E.; Nadeau, R. G. *Bioorg. Chem.* **1982**, *11*, 197.
- (a) Fish, P. V.; Sudhakar, A. R.; Johnson, W. S. *Tetrahedron Lett.* **1993**, *34*, 7849; (b) Fish, P. V.; Johnson, W. S. *Tetrahedron Lett.* **1994**, *35*, 1469; (c) Fish, P. V.; Johnson, W. S. *J. Org. Chem.* **1994**, *59*, 2324.
- Boeckman, R. K.; Bruza, K. J.; Heinrich, G. R. *J. Am. Chem. Soc.* **1978**, *100*, 7101.
- Morgan, D. J.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 462.
- Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.* **1983**, *48*, 4572.
- (a) Taylor, S. K.; Hockerman, G. H.; Karrick, G. L.; Lyle, S. B.; Schramm, S. B. *J. Org. Chem.* **1983**, *48*, 2449; (b) Taylor, S. K.; Davisson, M. E.; Hissom, R. B.; Brown, S. L.; Pristach, H. A.; Schramm, S. B.; Harvey, S. M. *J. Org. Chem.* **1987**, *52*, 425; (c) Taylor, S. K.; Blankespoor, C. L.; Harvey, S. M.; Richardson, L. J. *J. Org. Chem.* **1988**, *53*, 3309; For a review see: (d) Taylor, S. K. *Org. Prep. Proc. Int.* **1992**, *24*, 245; (e) Taylor, S. K.; May, S. A.; Hopkins, J. A. *Tetrahedron Lett.* **1993**, *34*, 1283.
- (a) Sharpless, K. B. *J. Am. Chem. Soc.* **1970**, *92*, 6999; (b) van Tamelen, E. E.; Carlson, J. G.; Russell, R. K.; Zawacky, S. R. *J. Am. Chem. Soc.* **1981**, *103*, 4615; (c) Armstrong, R. J.; Weiler, L. *Can. J. Chem.* **1986**, *64*, 584; (d) Tanis, S. P.; Chuang, Y.-H.; Head, D. B. *J. Org. Chem.* **1988**, *53*, 4929.
- (a) Procter, G.; Russell, A. T.; Murphy, P. J.; Tan, T. S.; Mather, A. N. *Tetrahedron* **1988**, *44*, 3953; (b) Pettersson, L.; Frejd, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 789.
- Maruoka, K.; Murase, N.; Ooi, T.; Yamamoto, H. *Synlett* **1991**, 857.
- One example of an easy-to-handle reagent to promote epoxy olefin cyclization is Nafion[®]-H, see: Taylor, S. K.; Dickinson, M. G.; May, S. A.; Pickering, D. A.; Sadek, P. C. *Synthesis* **1998**, 1133.
- (a) Reglinski, J. In *Chemistry of Arsenic, Antimony and Bismuth*; Norman, N. C., Ed.; Blackie Academic and Professional: New York, 1998; pp 403–440; (b) *Organobismuth Chemistry*; Suzuki, H., Matano, Y., Eds.; Elsevier: Amsterdam, 2001.
- For recent reviews on use of bismuth(III) compounds in organic synthesis see: (a) Leonard, N. M.; Wieland, L. C.; Mohan, R. S. *Tetrahedron* **2002**, *58*, 8373; (b) Antoniotti, S. *Synlett* **2003**, 1566; (c) Gaspard-Iloughmane, H.; Le Roux, C. *Eur. J. Org. Chem.* **2004**, 2517; For some recent applications of $\text{Bi}(\text{OTf})_3 \cdot x\text{H}_2\text{O}$ as a catalyst in organic synthesis, see: (d) Anderson, E. A.; Ernat, J. J.; Nguyen, M. P.; Palma, A. C.; Mohan, R. S. *Tetrahedron Lett.* **2005**, *46*, 7747; (e) Anzalone, P. A.; Baru, A. R.; Danielson, E. M.; Hayes, P. D.; Nguyen, M. P.; Panico, A. F.; Smith, R. C.; Mohan, R. S. *J. Org. Chem.* **2005**, *70*, 2091; (f) Sreedhar, B.; Swapna, V.; Sridhar, Ch.; Saileela, D.; Sunitha, A. *Synth. Commun.* **2005**, *35*, 1177; (g) Sreedhar, B.; Swapna, V.; Sridhar, Ch. *Catal. Commun.* **2005**, *6*, 293; (h) Khodaei, M.; Khosropur, A. R.; Kookhazadeh, M. *Can. J. Chem.* **2005**, *83*, 209; (i) Kamal, A.; Ahmed, S. K.; Sandbhor, M.; Khan, M. N. A.; Arifuddin, M. *Chem. Lett.* **2005**, *34*, 1142; (j) Yadav, J. S.; Reddy, B. V. S.; Swamy, T.; Rao, R. K. *Tetrahedron Lett.* **2004**, *45*, 6037; (k) Yadav, J. S.; Reddy, B. V. S.; Premalatha, K. *Synlett* **2004**, 963; (l) Matsushita, Y.; Sugamoto, K.; Matsui, T. *Tetrahedron Lett.* **2004**, *45*, 4723; (m) Arnold, J. N.; Hayes, P. D.; Kohaus, R. L.; Mohan, R. S. *Tetrahedron Lett.* **2003**, *44*, 9173.
- We have previously reported a highly catalytic method for the rearrangement of aryl-substituted epoxides to aldehydes and ketones using bismuth triflate, see: (a) Bhatia, K. A.; Eash, K. J.; Leonard, N. M.; Oswald, M. C.; Mohan, R. S. *Tetrahedron Lett.* **2001**, *42*, 8129; For other examples of activation of epoxides by bismuth triflate see: (b) Ollevier, T.; Lavie-Compin, G. *Tetrahedron Lett.* **2004**, *45*, 49; (c) Yadav, J. S.; Reddy, B. V. S.; Sateesh, G. *Tetrahedron Lett.* **2003**, *44*, 6501.
- Based on ^1H NMR analysis of the crude reaction product, we did not observe the formation of any of the cyclized product **5c**. A control experiment with an authentic sample mixture of **5a/b** ruled out the possibility that **4** might form from either **5a** or **5b**. A similar control experiment has been carried out with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as the catalyst.^{8c}



- Brezinski, B.; Grech, E.; Malarski, Z.; Sobczyk, L. *J. Chem. Soc., Perkin Trans. 2* **1991**, *2*, 857.
- We have previously reported that when the rearrangement of *trans*-stilbene oxide was carried out with $\text{CF}_3\text{SO}_3\text{H}$, the solution turned red and the product diphenylacetaldehyde was less pure than that obtained with bismuth triflate.^{15a} This observation points to the role of bismuth(III) triflate as a Lewis acid in the rearrangement of epoxides and not to protic acid catalysis by triflic acid released by hydrolysis of bismuth triflate. For a discussion on the role of triflic acid in the metal triflate catalyzed acylation of alcohols, see: (a) Dumeunier, R.; Markó, I. E. *Tetrahedron Lett.* **2004**, *45*, 825; (b) Carrigan, M. C.; Freiberg, D. A.; Smith, R. C.; Zerth, H. M.; Mohan, R. S. *Synthesis* **2001**, 2091.
- Corey, E. J.; Staas, D. D. *J. Am. Chem. Soc.* **1998**, *120*, 3526, Under the acidic conditions employed, the authors

report only the cyclic alcohols **5a-c** (52%) as products in addition to the product resulting from ring opening of the epoxide by ClCH_2COOH (48%). None of the ketone **2**, acyclic alcohol **3**, or bicyclic ether **4** were reported to form.

20. Goldsmith and co-workers (see Ref. 1a) who carried out the rearrangement of geraniolene oxide **1** in benzene using ca. 11.0 mol % $\text{BF}_3 \cdot \text{Et}_2\text{O}$ report that significant amounts of fluorohydrin was also obtained (Scheme 1).

21. Alder, A. P.; Wolf, H. R.; Jeger, O. *Helv. Chim. Acta.* **1981**, *64*, 198.
22. Salomon, R. G.; Coughlin, D. J.; Ghosh, S.; Zagorski, M. G. *J. Am. Chem. Soc.* **1982**, *104*, 998.
23. Masamune, T.; Fukuzawa, A.; Furusaki, A.; Ikura, M.; Matsue, H.; Kaneko, T.; Abiko, A.; Sakamoto, N. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1001.
24. Danheiser, R. L.; Martinez-Davila, C.; Sard, H. *Tetrahedron* **1981**, *37*, 3943.