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Regioselective Ring Opening and Isomerization Reactions of 3, 4-Epoxyesters Catalyzed by Boron Trifluoride

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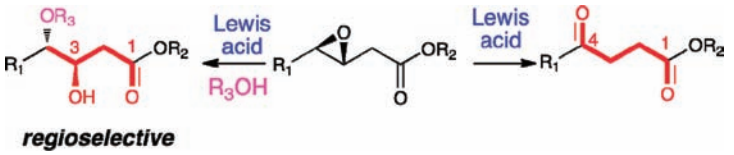
ABSTRACT

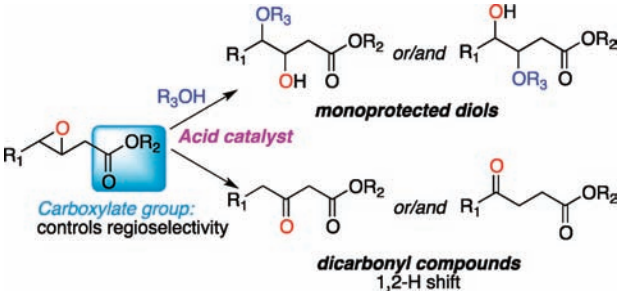


Efficient ring opening of 3,4-epoxyesters with alcohols to produce 4-alkoxy-3-hydroxyesters and their isomerization into 4-ketoesters using boron trifluoride as the catalyst are presented. Both transformations are simple and efficient methods for the synthesis of the above named synthetically useful compounds.

Epoxides are valuable synthetic compounds since they can undergo diverse transformations that give rise to other functionalities. Among these reactions, the ring opening of epoxides with alcohols to give β-alkoxyalcohols[1] and the Meinwald rearrangement reactions[2] to give carbonyl compounds are challenging transformations.

We wanted to study these transformations as applied to 3,4-epoxyesters. The opening of 3,4-epoxyesters with an alcohol would afford monoprotected diols, and the isomerization reaction would give rise to dicarbonyl compounds (Scheme 1). The regioselectivity in both processes would be controlled by the neighboring carboxylate group.[3] The starting epoxyesters can be accessed through asymmetric epoxidation.[4] Then, the synthesis of monoprotected diols as depicted in Scheme 1 represents an easy access to chiral 3,4-dihydroxyesters which are moieties present in the structure of some natural products.[5]

Scheme 1. Derivatizations of 3,4-Epoxyesters



We began our studies of the isomerization of 3,4-epoxyesters by combining epoxide **1a** with a chelating Lewis acid as

(1) (a) Smith, J. G. *Synthesis* **1984**, 629. (b) Barluenga, J.; Vázquez-Villa, H.; Ballesteros, A.; González, J. M. *Org. Lett.* **2002**, *4*, 2817. (c) Torborg, C.; Hughes, D. D.; Buckle, R.; Robinson, M. W. C.; Bagley, M. C.; Graham, A. E. *Synth. Commun.* **2008**, *38*, 205.

(2) (a) House, H. O. *J. Am. Chem. Soc.* **1955**, *77*, 3070. (b) Naqvi, S. M.; Horwitz, J. P.; Filler, R. *J. Am. Chem. Soc.* **1957**, *79*, 6283. (c) Meinwald, J.; Labana, S. S.; Chadha, M. S. *J. Am. Chem. Soc.* **1963**, *85*, 582. (d) Kulasegaram, S.; Kulawiec, R. J. *J. Org. Chem.* **1997**, *62*, 6547.

(3) For carboxylate group as a neighboring group, see: (a) Tomioka, H.; Hirai, K.; Tabayashi, K.; Murata, S.; Izawa, Y.; Inagaki, S.; Okajima, T. *J. Am. Chem. Soc.* **1990**, *112*, 1692. (b) Crich, D.; Hu, T.; Cai, F. *J. Org. Chem.* **2008**, *73*, 8942. (c) Crich, D.; Sharma, I. *J. Org. Chem.* **2010**, *75*, 8383. (d) Wang, H.; Fan, R. *J. Org. Chem.* **2010**, *75*, 6994.

(4) Wang, Z.; Tu, Y.; Frohn, M.; Zhang, J.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224.

(5) (a) Mori, K.; Takigawa, T.; Matsui, M. *Tetrahedron* **1979**, *35*, 833. (b) Kito, K.; Ookura, R.; Yoshida, S.; Namikoshi, M.; Ooi, T.; Kusumi, T. *Org. Lett.* **2008**, *10*, 225. (c) Garbe, L.; Morgenthal, K.; Kuscher, K.; Tressl, R. *Helv. Chim. Acta* **2008**, *91*, 993. (d) Ookura, R.; Kito, K.; Saito, Y.; Kusumi, T.; Ooi, T. *Chem. Lett.* **2009**, *38*, 384.

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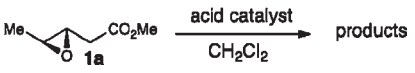
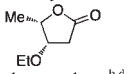
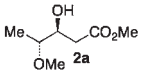
magnesium bromide etherate. The reaction afforded a mixture of bromohydrins (Table 1, entry 1). We then submitted compound **1a** to reaction with magnesium bromide etherate in the presence of ethanol so as to accomplish an opening of the epoxide by the alcohol, but we again obtained a bromohydrin mixture (entry 2).

The use of several Lewis acids in the presence of alcohols in this reaction provided halohydrins or led to the decomposition of the starting material. After extensive investigation, we discovered that the use of boron trifluoride etherate afforded compound **2a** in high regioselectivity and excellent yield (Table 1, entry 5).

We next evaluated the scope of the substrate with a variety of differentially substituted 3-enoates using $BF_3 \cdot Et_2O$ and different alcohols (Table 2).

Table 1. Optimization of Conditions

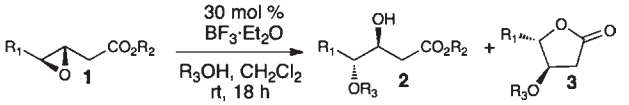


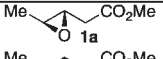
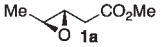
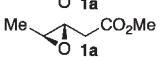
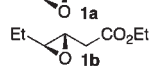
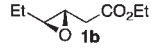
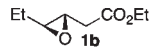
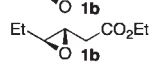
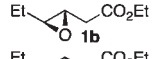
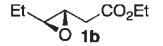
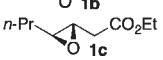
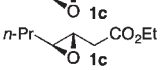
entry	acid[a]	equiv	alcohol	temp / time	products
1	$MgBr_2 \cdot Et_2O$	1.5		rt / 6 h	bromohydrins[b,c]
2	$MgBr_2 \cdot Et_2O$	1.5	EtOH	rt / 12 h	bromohydrins[b,c]
3	CSA	0.3	EtOH	rt / 12 h	 + other products[b,d]
4	$TiCl_4$		MeOH	rt / 16 h	chlorohydrins + traces of **2a**
5	$BF_3 \cdot Et_2O$	1.0	MeOH	0°C / 3.5 h	 (90%)

[a] Reactions performed on a 0.5 mmol scale. [b] Starting material was recovered. [c] A 1:1 mixture of regioisomeric lactones was obtained and the yield was 55%. [d] The stereochemistry for depicted lactone is preliminary, and it was obtained as a minor product (20%) as analyzed by NMR spectroscopy (^{1}H, 500 MHz).

3,4-Epoxyesters **1a**–**e** were treated with a series of alcohols in the presence of boron trifluoride as a catalyst. The regioisomer **2** was obtained as the major product in all cases as a result of the attack of the alcohol to the 4-position.[6] The reaction was quite sensitive to steric hindrance. For example, compound **1a** having a methyl substituent in the 4-position afforded higher regioselectivity than **1b** having an ethyl substituent using the same alcohol (Table 2, entry 1 vs 4). The regioselectivity of the reaction was also dependent on the type of alcohol: primary alcohols gave higher regioselectivity than secondary or tertiary ones. The reaction of **1a** with methanol took place at 0 °C for 3.5 h, while for the rest of assays the best conditions were 18 h at room temperature. The amount of catalyst that afforded the best yield for all cases was 30 mol %. Initially the alcohol was used as a cosolvent in an equal mixture with dichloromethane, but when a stoichiometric amount of alcohol was used (5 equiv) the result was the same (Table 2, entry 5 vs 6). The optimal amount of Lewis acid for obtaining the best yield was also found to be 30 mol %. Lactones **3a**–**e** were obtained as the minor product of the reactions resulting from cyclization of the minor regiomeric 3-alkoxy-4-hydroxyesters.

Table 2. 3,4-Epoxyesters into 4-Alkoxy-3-hydroxyesters



entry	substrate[a]	R_3	**2**/**3**[b]	yield (%)
1	 **1a**	Me[c]	25 / 1	99
2	 **1a**	*i*-Pr	7 / 1	70
3	 **1a**	*t*-Bu	8 / 1	77
4	 **1b**	Me	6 / 1	97
5	**1b**	Et	4 / 1	98
6	 **1b**	Et[d]	4 / 1	98
7	 **1b**	*i*-Pr	3.4 / 1	98
8	 **1b**	*t*-Bu	3 / 1	99
9	**1b**	Bn[d]	10 / 1	96
10	 **1c**	Me	8 / 1	88
11	 **1c**	Bn[d]	5 / 1	73
12	 **1d**	Me	3 / 1	78[e]
13	 **1e**	Me	4 / 1	95

[a] R_2 = Et for all substrates except for **1a** (R_2 = Me). [b] The ratio was measured from ^{1}H NMR spectroscopy (500 MHz) of the unpurified mixture. [c] The reaction was peformed at −5 °C for 3.5 h. [d] 5 equiv of the alcohol were used. [e] Lactone **5** was also isolated (20%).

When 3,4-epoxyesters **1a**–**c** were treated with boron trifluoride without any alcohol at room temperature for 18 h of reaction time, 4-ketoesters **4a**–**c** were obtained as the only products of the reaction in excellent yields (Scheme 2). The isomerization of 3,4-epoxyesters into 4-ketoesters implies that a 1,2-shift of a hydrogen from the 4-position

(6) The structure of the major regioisomer **2** was confirmed by NMR techniques.

(7) (a) Cardellach, J.; Font, J.; Ortuno, R. M. *J. Heterocycl. Chem.* **1984**, *21*, 327. (b) Ohkuma, T.; Kitamura, M.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 5509. (c) Frenette, R.; Monette, M.; Bernstein, M. A.; Young, R. N.; Verhoeven, I. R. *J. Org. Chem.* **1991**, *56*, 3083. (d) Short, K. M.; Mjalli, M. M. A. *Tetrahedron Lett.* **1997**, *38*, 359. (e) Vaishali, M. S.; Mark, R. H.; Leah, M. S.; Alexander, J. S. *J. Org. Chem.* **2001**, *66*, 7283. (f) Cristina, F.; Raffaella, G.; Francesco, M.; Patrizia, N.; Giuliana, P.; Ennio, V. *Tetrahedron: Asymmetry* **2001**, *12*, 1039.

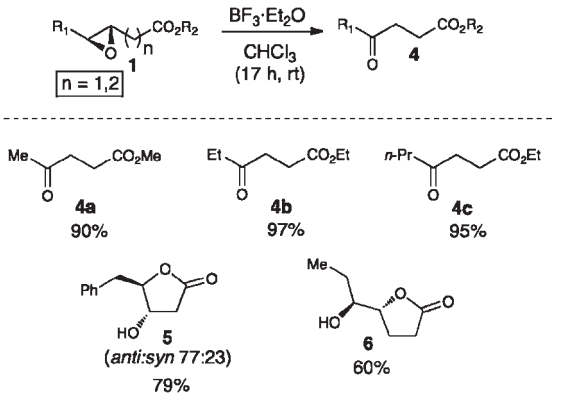
(8) (a) Seto, H.; Sato, T.; Urano, S.; Uzawa, J.; Yonehara, H. *Tetrahedron Lett.* **1976**, 4367. (b) Kosuge, T.; Tsuji, K.; Hirai, K.; Yamaguchi, K.; Okamoto, T.; Iitaka, Y. *Tetrahedron Lett.* **1981**, *22*, 3417. (c) Li, S.-H.; Wang, J.; Niu, X.-M.; Shen, Y.-H.; Zhang, H.-J.; Sun, H.- D.; Li, M.-L.; Tian, Q.-E.; Lu, Y.; Cao, P.; Zheng, Q.-T. *Org. Lett.* **2004**, *6*, 4327.

to the 3-position took place. The resulting 4-ketoesters are intermediates for preparation of a large number of five-membered cyclic compounds,[7] and the 4-ketoester moiety is ubiquitous within complex natural products.[8] Although several reactions have been reported for the preparation of 4-ketoesters[9] and other 1,4-dicarbonyl compounds,[10] new approaches are welcomed.

In contrast, compound **1d** having a benzyl group furnished lactone **5**[11] as a mixture of *syn* and *anti* isomers, with the *anti* form predominating. Compound **1e** having a phenyl group gave a complex mixture of reaction products (Scheme 2).

We also wanted to apply the same reactions to a 4,5-epoxyester and to compare the outcome with the 3,4-epoxyesters. We readily prepared a 4,5-epoxyester (**1f** being $n = 2$, $R_1 = Et$ in Scheme 2) (see Supporting Information), treated it with boron trifluoride, and obtained γ-butyrolactone **6**. This product was obtained even in the presence of an alcohol. Compound **6** is an intermediate for the synthesis of the communiol natural products.[12]

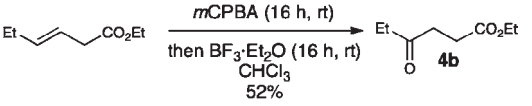
Scheme 2. Isomerization of 3,4-Epoxyesters into 4-Ketoesters



A one-pot procedure for the conversion of 3-enoates into 4-ketoesters was also evaluated. Ethyl 3-hexenoate was directly converted into dicarbonyl compound **4b** through treatment with peracid followed by addition of boron trifluoride (Scheme 3).

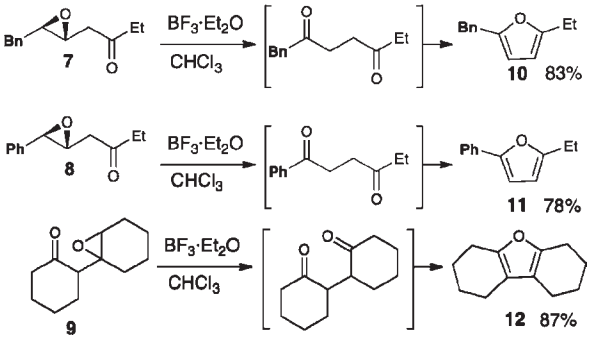
We also wanted to extend our study to 3,4-epoxyketones. However, when compounds **7**, **8**, and **9** were treated with boron trifluoride, furans **10**, **11**, and **12**, respectively, were

Scheme 3. One-Pot Procedure

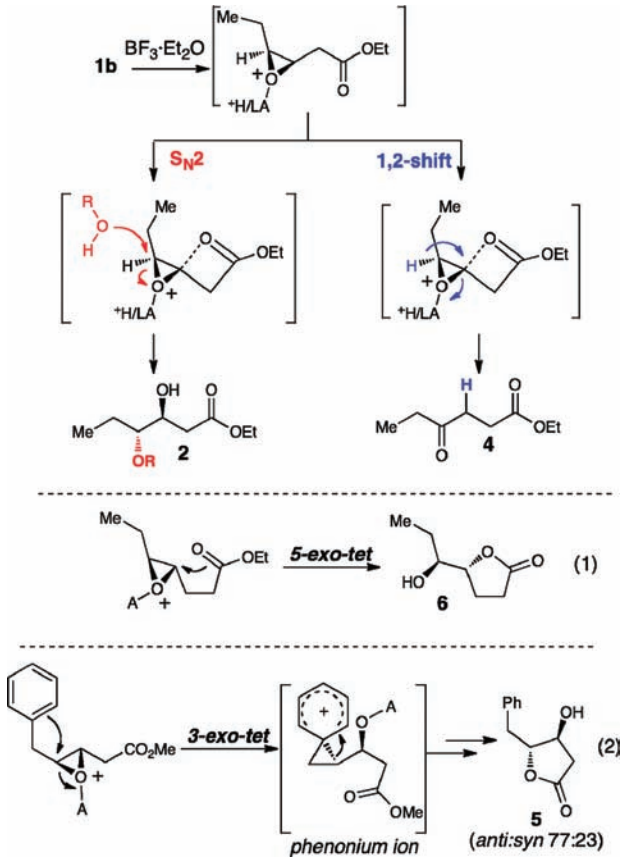


the only isolated products (Scheme 4). Even in the presence of an alcohol or using other catalysts (tris(perfluorophenyl)-borane, or PPTS), the epoxyketones gave the furan

Scheme 4. Conversion of 3,4-Epoxyketones into Furans



Scheme 5. Proposed Reaction Pathways



(9) (a) Parker, K. A.; Kallmerten, J. K. *J. Org. Chem.* **1980**, *45*, 2614. (b) Kunz, T.; Janowitz, A.; Reissig, H. U. *Synthesis* **1990**, 43. (c) Fujimura, T.; Aoki, S.; Nakamura, E. *J. Org. Chem.* **1991**, *56*, 2809. (d) Reissig, H. U.; Reichelt, I.; Kunz, T. *Org. Synth.* **1992**, *71*, 189. (e) Brogan, J. B.; Zercher, C. K. *J. Org. Chem.* **1997**, *62*, 6444. (f) Ballini, R.; Barboni, L.; Bosica, G.; Fiorini, D. *Synthesis* **2002**, 2725. (g) Huang, D.; Yan, M.; Zhao, W.; Shen, Q. *Synth. Commun.* **2005**, *35*, 745.

(10) (a) Mattson, A. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 2314. (b) Avetta, C. T.; Konkol, L. C., Jr.; Taylor, C. N.; Dugan, K. C.; Stern, C. L.; Thomson, R. J. *Org. Lett.* **2008**, *10*, 5621. (c) DeMartino, M. P.; Chen, K.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 11546. (d) Shen, Z.; Goh, K. K. K.; Cheong, H.; Wong, C. H. A.; Lai, Y.; Yang, Y.; Loh, T. *J. Am. Chem. Soc.* **2010**, *132*, 15852.

(11) Stereochemistry of lactone **5** was confirmed by comparison with spectra from: Harcken, C.; Brückner, R. *Synlett* **2001**, *5*, 718.

(12) Enomoto, M.; Kuwahara, S. *J. Org. Chem.* **2006**, *71*, 6287.

compounds as the only products of the reaction in excellent yield.

According to Baldwin's rules, a 4-exotet cyclization is favored, but a 5-endotet is not. We postulate that the carbonyl oxygen stabilizes the positive charge at the 3-position of the oxirane ring in a 4-exotet mode, inducing the hydrogen to migrate from C-4 to C-3. On the other hand, if an alcohol is present, then an intermolecular attack of the alcohol at the less hindered 4-position occurs (Scheme 5). In the case of compound **1f**, a 5-exotet cyclization occurred to give lactone **6** (reaction 1 in Scheme 5). Finally, the formation of compound **5** can be explained through two consecutive cyclizations: first, a 3-exotet cyclization occurs, where the phenyl ring opens the oxirane ring to afford a phenonium intermediate[13] which then undergoes a cyclopropane–homobenzylic cation rearrangement[14] (reaction 2 in Scheme 5) that would furnish the lactone **5**, with the *anti* configuration as the major product.

In summary, 3,4-epoxyesters are opened with alcohols in the presence of boron trifluoride to give 4-alkoxy-3-hydroxyesters in a highly regioselective fashion. 3,4-Epoxyesters having an alkyl group furnish 1,4-dicarbonyl compounds as a single product when treated with boron trifluoride in a nonhydroxylic solvent. We believe both transformations are simple and efficient methods for the synthesis of monoprotected diols and 1,4-dicarbonyl compounds and will find synthetic applications. The application of these results to the synthesis of new proteases inhibitors is ongoing, and further results will be reported in due course.

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

(13) (a) Cram, D. J. *J. Am. Chem. Soc.* **1949**, *71*, 3863. (b) Cram, D. J. *J. Am. Chem. Soc.* **1952**, *74*, 2129. (c) Sieber, S.; Schleyer, P. V. *J. Am. Chem. Soc.* **1993**, *115*, 6987.

(14) For similar reactions (cyclopropane–homoallylic cation rearrangement), see: (a) Marshall, J. A.; Ellison, R. H. *J. Org. Chem.* **1975**, *40*, 2070. (b) Marshall, J. A.; Ellison, R. H. *J. Am. Chem. Soc.* **1976**, *98*, 4312.