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Eu(OTf)$_3$-Catalyzed Highly Regioselective Nucleophilic Ring Opening of 2,3-Epoxy Alcohols: An Efficient Entry to 3-Substituted 1,2-Diol Derivatives

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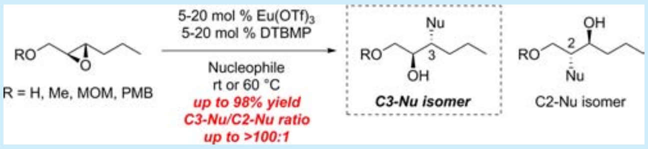
Supporting Information

ABSTRACT: In our study of the total synthesis of (+)-irciniastatin A, we found a need to develop a method that enables a C3-selective nucleophilic ring opening of 2,3-epoxy alcohol by MeOH, by which we found that the use of combined catalytic amounts of Eu(OTf)$_3$ and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) enables the intended transformation to obtain 3-methoxy-1,2-diol efficiently. Promising features of a protocol that effects a highly regioselective nucleophilic ring opening of 2,3- and 3,4-epoxy alcohols using various nucleophiles including alcohols, thiols, and unprotected amines are described.



A strategy employing the asymmetric epoxidation of allylic alcohols[1] followed by the stereoselective modification of an epoxide product[2] provides chemists with a reliable latitude for the design and synthesis of optically active compounds with multiple stereogenic centers. The Ti(O-*i*-Pr)$_4$-mediated nucleophilic ring opening of the glycidol (2,3-epoxyl alcohol) unit, developed by Sharpless and co-workers, provides many applications for realizing a regio- and diastereocontrolled introduction of various substituents including ethers, esters, amino groups, chalcogens, and halogens at position C3.[3] Some other conditions have also been reported over the past decades.[4−6] However, we have recently realized that there is still room for developing effective conditions for this kind of transformation. For example, in our efforts to realize the total synthesis of (+)-irciniastatin A,[7] we were unable to achieve a C3 epoxide opening of 2,3-epoxy alcohol by MeOH using the preexisting protocols (Figure 1). In addition, literature survey revealed that most of the reported methods require stoichiometric amounts of Lewis acids to achieve regioselective ring opening, and thus, an effective catalytic method is desired.[8]

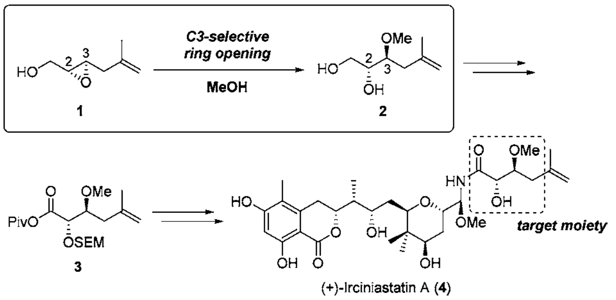


Figure 1. Outline of our synthesis of (+)-irciniastatin A.

We therefore developed an efficient and catalytic protocol to effect the C3-selective epoxide opening of 2,3-epoxy alcohol using various nucleophiles. Herein, we report a protocol for Eu(OTf)$_3$-catalyzed regioselective nucleophilic ring opening of diverse 2,3-epoxy alcohols and their derivatives using alcohols, thiols, and amines. This reagent system is also applicable to the C4-selective epoxide opening of 3,4-epoxy alcohols.

First, we screened Lewis acid conditions that led to the C3-selective ring opening of 2,3-epoxy alcohol **1** with MeOH (Table 1). The treatment of **1** with BF$_3$·OEt$_2$ in MeOH at 0 °C yielded the desired 1,2-diol **2** and the undesired 1,3-diol **5** in a 1:1 ratio, indicating that the stereoelectronic requirements for epoxide opening at C2 and C3 are essentially identical (entry 1). The Sharpless conditions[3] using Ti(O-*i*-Pr)$_4$ gave an inseparable 3:1 mixture of **2** and **5** in 54% yield after refluxing in MeOH for 5 days (entry 2).[9] The unexpectedly slow reaction would be due to the formation of Ti(OMe)$_4$ or Ti(OMe)$_n$(O-*i*-Pr)$_{4-n}$ in MeOH, as indicated by the formation of a white precipitate in the reaction mixture. The Crotti conditions[4] using LiClO$_4$ resulted in low conversion even after 3 days (entries 3 and 4). In contrast, a promising reactivity was observed in the case of using 1.2 equiv of Yb(OTf)$_3$, although the selectivity was moderate (3:1, entry 5).[10] We assumed that the generation of the undesired isomer (C2-Nu isomer) **5** was caused by TfOH, which was generated in small amounts from Yb(OTf)$_3$ during the reaction. Considering this hypothesis, several bases for scavenging TfOH were examined, and the addition of 1.0 equiv of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) was found to improve the regioselectivity (>20:1, entry 6). We then sought for the optimal catalytic conditions. Decreasing the amount of Yb(OTf)$_3$ to 30 mol % required an

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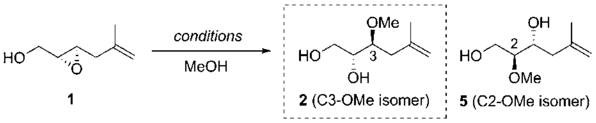
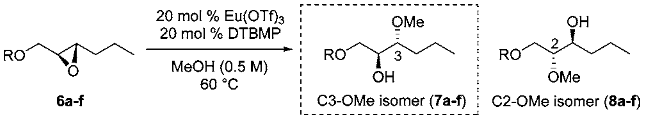
Table 1. Optimization of Regioselective Ring-Opening Reaction of Epoxy Alcohol 1

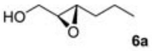
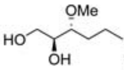
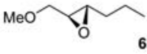
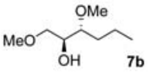
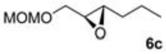
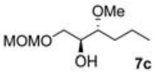
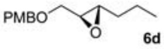
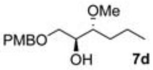
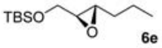
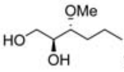
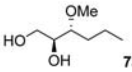


entry	Lewis acid (equiv)	base (equiv)	temp	time	yield[a]	selectivity[b] 2 / 5
1	$BF_3 \cdot OEt_2$ (1.5)	—	0 °C	6 h	65%	1:1
2	$Ti(OiPr)_4$ (1.5)	—	reflux	5 days	54%	3:1
3	$LiClO_4$ (2.0)	—	reflux	3 days	trace	—
4	$LiClO_4$ (10 M)	—	reflux	3 days	10%	6:1
5	$Yb(OTf)_3$ (1.2)	—	rt	18 h	70%	3:1
6	$Yb(OTf)_3$ (1.0)	DTBMP (1.0)	rt	8 h	64%	>20:1
7	$Yb(OTf)_3$ (0.3)	DTBMP (1.2)	reflux	18 h	82%	8.3:1
8	$Sc(OTf)_3$ (0.2)	DTBMP (0.8)	reflux	10 h	87%	4:1
9	$La(OTf)_3$ (0.2)	DTBMP (0.8)	reflux	10 h	90%	17:1
10	$Eu(OTf)_3$ (0.2)	DTBMP (0.8)	reflux	13 h	92%	18:1
11	$Eu(OTf)_3$ (0.2)	DTBMP (0.2)	reflux	4.5 h	86%	18:1

[a] Combined yields of the isolated C3 and C2 regioisomers. [b] All ratios were determined by ^1H spectroscopy.

Table 2. Regioselective Ring-Opening Reactions of 2,3-Epoxy Alcohol Derivatives with MeOH

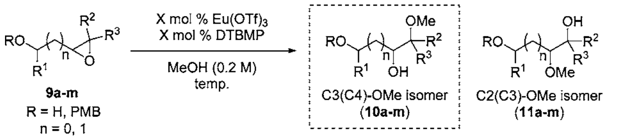


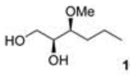
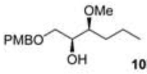
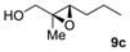
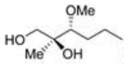
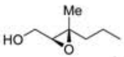
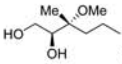
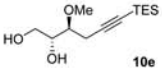
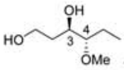
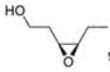
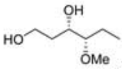
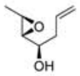
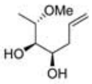
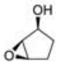
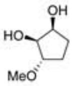
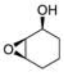
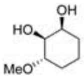
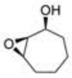
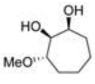
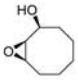
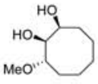
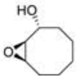
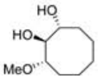
entry	substrate	product	time	yield	selectivity C3 / C2
1	 **6a**	 **7a**	1 h	93%	C3 only
2	 **6b**	 **7b**	7 h	85%	C3 only
3	 **6c**	 **7c**	9 h	83%	C3 only
4	 **6d**	 **7d**	13 h	88%	C3 only
5	 **6e**	 **7a**	6 h	83%	ND[a]
6	 **6f**	 **7a**	16 h	59%	ND[a]

[a] Not determined.

increase in the reaction temperature to reflux for completion and reduced the regioselectivity (8.3:1, entry 7). Further screening of lanthanoid triflates eventually led to the identification of $Eu(OTf)_3$ as the ideal catalyst for this particular substrate (entries 8–11).

Table 3. Regioselective Ring-Opening Reactions of Epoxy Alcohol Derivatives with MeOH

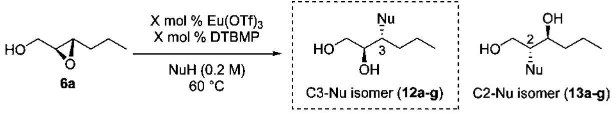


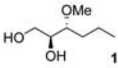
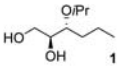
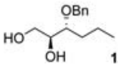
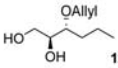
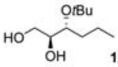
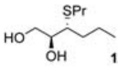
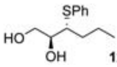
entry	epoxide	product	temp	time	yield	selectivity C3 / C2
1[a]	 **9a**	 **10a**	60 °C	3 h	88%	12:1
2[a]	 **9b**	 **10b**	60 °C	12 h	86%	25:1
3[a]	 **9c**	 **10c**	30 °C	11 h	74%	C3 only
4[a]	 **9d**	 **10d**	30 °C	4 h	87%	C3 only
5[a]	 **9e**	 **10e**	60 °C	5 h	90%	4:1
6[a]	 **9f**	 **10f**	rt	18 h	92%	14:1[d]
7[a]	 **9g**	 **10g**	rt	9 h	90%	12:1[d]
8[b]	 **9h**	 **10h**	60 °C	12 h	96%	C3 only
9[c]	 **9i**	 **10i**	30 °C	24 h	64%	C3 only
10[c]	 **9j**	 **10j**	rt	1 h	97%	C3 only
11[a]	 **9k**	 **10k**	60 °C	6 h	85%	39:1
12[a]	 **9l**	 **10l**	60 °C	44 h	65%	43:1
13[a]	 **9m**	 **10m**	60 °C	44 h	NR[e]	ND[f]

[a] 20 mol % $Eu(OTf)_3$/DTBMP was used. [b] 10 mol % $Eu(OTf)_3$/DTBMP was used. [c] 5 mol % $Eu(OTf)_3$/DTBMP was used. [d] Selectivity of C4/C3 regioisomer. [e] No reaction. [f] Not determined.

Encouraged by the high reactivity and regioselectivity of the $Eu(OTf)_3$-catalyzed, DTBMP-assisted epoxide ring opening reaction with MeOH, we examined the compatibility of this catalytic system using protected 2,3-epoxy-1-hexanols **6b–f** (Table 2). Fortunately, methyl-, MOM-, and PMB-protected substrates gave the corresponding C3-methoxylated products as the sole detectable products.[11] However, TBS- and Ac-protected substrates resulted in the detachment of the

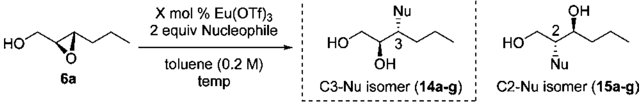
Table 4. Ring-Opening Reactions with Various Alcohol/Thiol Nucleophiles

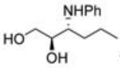
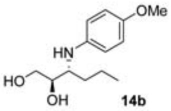
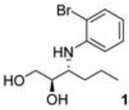
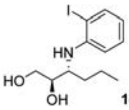
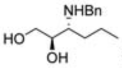
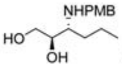
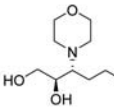


entry	NuH	product	time	yield	selectivity C3 / C2
1^{a,b,c}	MeOH	 **12a**	1 h (5 h)^{b} (3.5 h)^{c}	93% (87%)^{b} (81%)^{c}	C3 only (20:1)^{b} (45:1)^{c}
2^{a,b,c}	*i*PrOH	 **12b**	1 h (4 h)^{b} (4 h)^{c}	93% (83%)^{b} (83%)^{c}	25:1 (12:1)^{b} (25:1)^{c}
3^{a,b,c}	BnOH	 **12c**	1 h (4 h)^{b} (4 h)^{c}	91% (88%)^{b} (78%)^{c}	25:1 (12:1)^{b} (30:1)^{c}
4^{a,c}	allyl alcohol	 **12d**	1 h (4 h)^{c}	98% (83%)^{c}	25:1 (25:1)^{c}
5^{a,c}	*t*BuOH	 **12e**	3 h (4 h)^{c}	48% (50%)^{c}	13:1 (10:1)^{c}
6^{a,c}	PrSH	 **12f**	2 h (3 h)^{c}	91% (85%)^{c}	C3 only (C3 only)^{c}
7^{a,c}	PhSH	 **12g**	1.5 h (3 h)^{c}	80% (78%)^{c}	15:1 (25:1)^{c}

[a] 20 mol % Eu(OTf)$_3$/DTBMP was used. [b] 5 mol % Eu(OTf)$_3$/DTBMP was used. [c] 5 equiv of NuH was added. (Toluene was used as the solvent.)

Table 5. Ring-Opening Reactions with Various Amine Nucleophiles



entry	product	temp	time	yield	selectivity C3 / C2
1^{a}	 **14a**	rt	7 h (7 h)^{b}	90% (90%)^{b}	25:1 (10:1)^{b}
2^{a,b}	 **14b**	rt	5 h (5 h)^{b}	93% (90%)^{b}	33:1 (18:1)^{b}
3^{a}	 **14c**	rt	6 h	88%	20:1
4^{a}	 **14d**	rt	6 h	87%	26:1
5^{a,c}	 **14e**	60 °C	2 h	88%	9:1
6^{a,c}	 **14f**	60 °C	3 h	85%	7:1
7^{a,d}	 **14g**	60 °C	40 min	81%	3.6:1

[a] 20 mol % Eu(OTf)$_3$ was used. [b] 10 mol % Eu(OTf)$_3$ was used in toluene (0.5 M). [c] The ratio was determined after Boc protection. [d] The ratio was determined after acetylation.

protecting group together with nucleophilic ring opening (entries 5 and 6).

Next, we explored the scope and limitations of the catalytic system using various epoxy alcohols (Table 3). *cis*-2,3-Epoxy alcohol **9a** gave the corresponding C3 adduct **10a** with sufficient regioselectivity of 12:1. Interestingly, the PMB-protected *cis*-epoxide **9b** showed higher regioselectivity (entry 2). Importantly, this method was also found to be applicable to the trisubstituted epoxides **9c** and **9d** to provide the corresponding C3-methoxylated products **10c** and **10d**, respectively (entries 3 and 4). The substrate **9e** with an alkyne moiety provided moderate C3 selectivity (entry 5). Note that the catalytic system could be used for the C4-selective opening of 3,4-epoxy alcohols: 3,4-epoxy-1-alcohols **9f** and **9g**, respectively, gave **10f** and **10g** in good yields with sufficient C4 regioselectivities (entries 6 and 7). Various cyclic substrates were found to undergo a C3-selective nucleophilic ring opening with high regioselectivity (entries 9–12). Cyclic *cis*-epoxy alcohols gave the corresponding C3 adducts, whereas *anti*-epoxy alcohol **9m** was recovered unreacted (entry 13).

After screening the reaction with MeOH, we became interested in the regioselective epoxide ring opening reaction using other nucleophiles. We thus explored the scope of the reaction using other solvents (Table 4). We confirmed that various alcohols attack at the C3 position with high regioselectivity (entries 1–5). In addition, thiol nucleophiles can also be used with high regioselectivity (entries 6 and 7). It should be stressed that these nucleophiles can be applied not only as solvents but also as reagents at several equivalents.

Furthermore, we found that various amines can be used as nucleophiles for the system (Table 5). Some types of aniline nucleophile were successfully employed to achieve excellent yields and regioselectivities, even at room temperature (entries 1–4). Note that the addition of DTBMP is not necessary in the case of amine nucleophiles.[12] Moreover, the use of some aliphatic amines as nucleophiles resulted in the formation of the corresponding 3-amino-1,2-diols with good selectivity (entries 5–7). These results strongly indicate that this method can be applied to the synthesis of nitrogen-containing natural products.

In summary, we have developed a highly stereo- and regioselective ring-opening reaction of epoxy alcohols and their derivatives using catalytic amounts of Eu(OTf)$_3$ and DTBMP. This method has the following advantages: (1) excellent regioselectivities are achieved with various epoxides, including unprotected and protected 2,3-epoxy alcohols, 3,4-epoxy alcohols, and cyclic epoxy alcohols; (2) various *O*-, *S*-, and *N*-nucleophiles can be used; (3) the reaction conditions are not sensitive to water or air; (4) the reaction is induced using commercially available europium salt. The present protocol can therefore be widely applied to the synthesis of complex molecules with continuous stereocenters.

ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922. (c) Zhang, W.; Basak, A.; Kosugi, Y.; Hoshino, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 4389. (d) Egami, H.; Ogama, T.; Katsuki, T. *J. Am. Chem. Soc.* **2010**, *132*, 5886. (e) Olivares-Romero, J. L.; Li, Z.; Yamamoto, H. *J. Am. Chem. Soc.* **2013**, *135*, 3411. (f) Wang, C.; Yamamoto, H. *J. Am. Chem. Soc.* **2014**, *136*, 1222.

(2) For synthetic applications of chiral epoxy alcohols, see: Riera, A.; Moreno, M. *Molecules* **2010**, *15*, 1041.

(3) (a) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557. (b) Chong, J. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560. (c) Behrens, C. H.; Ko, S. Y.; Sharpless, K. B.; Walker, F. J. *J. Org. Chem.* **1985**, *50*, 5687. (d) Behrens, B. H.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 5696.

(4) Chini, M.; Crotti, P.; Flippin, L. A.; Gardelli, C.; Giovani, E.; Macchia, F.; Pineschi, M. *J. Org. Chem.* **1993**, *58*, 1221.

(5) For examples of the regioselective ring opening of 2,3-epoxy alcohols with *O*-, *S*-, and halide nucleophiles, see: (a) Onaka, M.; Sugita, K.; Takeuchi, H.; Izumi, Y. *J. Chem. Soc., Chem. Commun.* **1988**, 117. (b) Narender, M.; Reddy, M. S.; Nageswar, Y. V. D.; Rao, K. R. *Helv. Chim. Acta* **2007**, *90*, 1107.

(6) For examples of the regioselective ring opening of 2,3-epoxy alcohols with *N*-nucleophiles, see: (a) Maruoka, K.; Sano, H.; Yamamoto, H. *Chem. Lett.* **1985**, *14*, 599. (b) Onaka, M.; Sugita, K.; Izumi, Y. *Chem. Lett.* **1986**, *15*, 1327. (c) Caron, M.; Carlier, P. R.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 5185. (d) Canas, M.; Poch, M.; Verdaguer, X.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1991**, 32, 6931. (e) Benedetti, F.; Berti, F.; Norbedo, S. *Tetrahedron Lett.* **1998**, *39*, 7971. (f) Martín, R.; Islas, G.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron* **2001**, *57*, 6367. (g) Pastó, M.; Rodríguez, B.; Riera, A.; Pericás, M. A. *Tetrahedron Lett.* **2003**, *44*, 8369. (h) Surendra, K.; Krishnaveni, N. S.; Rao, K. R. *Synlett* **2004**, *36*, 506.

(7) Watanabe, T.; Imaizumi, T.; Chinen, T.; Nagumo, Y.; Shibuya, M.; Usui, T.; Kanoh, N.; Iwabuchi, Y. *Org. Lett.* **2010**, *12*, 1040.

(8) Very recently, Yamamoto and Wang have reported an effective catalytic system using a tungsten salt that has high regioselectivity. Wang, C.; Yamamoto, H. *J. Am. Chem. Soc.* **2014**, *136*, 6888.

(9) For some "unexpected" results using reported methods, see: (a) Alegret, C.; Santacana, F.; Riera, A. *J. Org. Chem.* **2007**, *72*, 7688. (b) Tan, L.; Ma, D. *Angew. Chem., Int. Ed.* **2008**, *46*, 3614.

(10) (a) Meguro, M.; Asao, N.; Yamamoto, Y. *Tetrahedron Lett.* **1994**, *35*, 7395. (b) Meguro, M.; Asao, N.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1995**, 1021.

(11) Under Sharpless conditions, epoxide opening reaction did not proceed using methyl ether **6b** (see ref 3a).

(12) For details of the reaction conditions, see the Supporting Information.