Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 2189–2193

TETRAHEDRON:
ASYMMETRY

AlEt$_3$-promoted eliminative ring-opening of β-hydroxy epoxides: highly stereoselective synthesis of terminal α-hydroxy olefins

Fei Wang, Shao Hua Wang, Yong Qiang Tu* and Shi Kuo Ren

Department of Chemistry & State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, PR China

Received 5 May 2003; accepted 29 May 2003

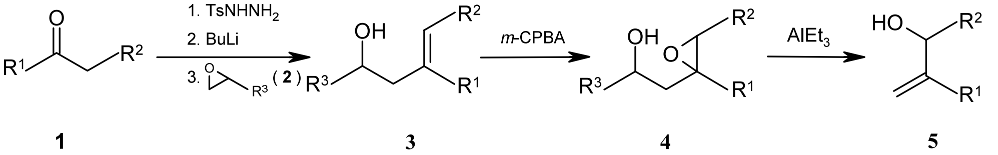
Abstract—AlEt$_3$-promoted eliminative ring-opening of β-epoxy alcohols leading to α-hydroxy olefins is reported. This eliminative ring-opening reaction is shown to be highly stereoselective, thus providing an alternative asymmetric synthesis for α-hydroxy olefins.

1. Introduction

α-Hydroxy epoxides are well recognized as useful building blocks in asymmetric synthesis.[1] Though their homologues, β-hydroxy epoxides, should be similarly valuable, their utility in asymmetric synthesis has been much less demonstrated primarily due to the difficulty in access to the homochiral versions of β-hydroxy epoxides, particularly trisubstituted ones.[2] During our research on the chemistry of β-hydroxy epoxides, we became interested in their reactivity under the influence of Lewis acids. Though a few β-hydroxy epoxides with the particular structures susceptible to a rearrangement under Al(OR)$_3$ promotion, most of the substrates we tested were found to be unaffected by Al(OR)$_3$.[3] Our efforts in this avenue resulted in the observation of AlEt$_3$-mediated eliminative ring-opening reactions of β-hydroxy epoxides leading to a disubstituted terminal α-hydroxy olefins with high stereoselectivity. The synthetic value of this transformation lies in its ability to construct efficiently and highly stereoselectively, from a chiral β-hydroxy epoxide, a chiral disubstituted terminal α-hydroxy olefin unit which has been extensively used as key building blocks in organic synthesis,[4] and is found in many natural products.[5] Herein, we report our results.

2. Results and discussion

We first examined the reactivity of racemic β-hydroxy epoxides towards frequently used Lewis acids. Racemic β-hydroxy epoxide **4** was prepared as one diastereomer (entries 1–5, 7, 8, 11, 12 and 14) or a mixture of two (entries 6, 9, 10 and 13) from ketone **1** by addition of in situ generated vinyl lithium to racemic epoxide **2**[6] followed by an epoxidation with *m*-CPBA in CH_2Cl_2 (Scheme 1).[7] β-Hydroxy epoxide **4a** (entry 1, Table 2) was selected as a model compound and exposed to a series of Lewis acids under various conditions. The results are listed in Table 1. As shown in Table 1, in the presence of AlMe$_3$, AlEt$_3$, Al(*i*-PrO)$_3$ and Zr(*i*-PrO)$_4$ in THF at 40°C, **4b** was surprisingly converted to a terminal α-hydroxy olefin **5a** in good yield. AlEt$_3$ was found to be the best. However, with $SnCl_4$, $ZnCl_2$ et al., either **4a** was converted to an unidentifiable mixture or no reaction occurred. Non-polar solvents such as *n*-hexane or haloalkanes were not suitable for this transforma-



Scheme 1.

---

* Corresponding author. Tel.: 86-931-8912410; fax: 86-931-8912582; e-mail: tuyq@lzu.edu.cn

0957-4166/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0957-4166(03)00457-9

Table 1. Eliminative ring-opening of **4a** by Lewis acid[a]

Entry	Lewis acid	Time (h)	Yield (%)
1	$AlMe_3$	12	90
2	$AlEt_3$	24	96
3	Zr(*i*-PrO)$_4$	36	87
4	Al(*i*-PrO)$_3$	24	70
5	Ti(*i*-PrO)$_2$Cl$_2$	20	40
6	$TiCl_4$	0.5	25
7	SmI_2	CP[b]	–
8	$SnCl_4$	CP	–
9	$AlCl_3$	NR[c]	–
10	$ZnMe_2$	NR	–
11	$ZnEt_2$	NR	–
12	$ZnBr_2$	NR	–
13	Ti(*i*-PrO)$_4$	NR	–

[a] Reaction condition: THF at 40°C.

[b] CP: complex products.

[c] NR: no reaction.

tion, even at refluxing temperatures. On the basis of these results, we then expanded the scope of this transformation to a series of β-hydroxy epoxides using $AlEt_3$ as the Lewis acid and THF as the solvent, and the results were summarized in Table 2.

As expected, all the β-hydroxy epoxides were transformed to terminal α-hydroxy olefins in high yields. The best results were obtained when excess $AlEt_3$ (5 equiv.) was used. Use of a catalytic amount of $AlEt_3$ only led to a partial conversion. It is noteworthy that both of the diastereomers of β-hydroxy epoxide were converted to the same terminal α-hydroxy olefin (entries 6, 9, 10 and 13, Table 2). This reaction is applicable to a wide range of β-hydroxy epoxides bearing various R^1, R^2 and R^3 substitutent. For example, R^1 and R^2 could be two aliphatic (entries 1 and 2), one aliphatic and one aromatic (entries 3–5 and 12) or linked cyclic groups (entries 6–11), whereas R^3 could be an aliphatic (entries 1–3, 6 and 9–14) or an aromatic substituent (entries 4 and 7), or a hydrogen (entries 5 and 8).

With these successful results in hand, we then turned our attention to the non-racemic version of such an eliminative ring-opening. Enantiomerically pure β-hydroxy epoxides were prepared from the cheap and naturally abundant (*S*)-(−)-ethyl lactate **6**, as shown in Scheme 2. Reduction of **6** with $NaBH_4/AlCl_3$ followed by tosylation of the primary hydroxyl group and cyclization with BuLi afforded (*S*)-propylene oxide. Reaction of (*S*)-propylene oxide with an in situ prepared vinyl lithium reagent from ketone **1** at −15°C gave homochiral β-hydroxy olefin **7**. Epoxidation of **7** with *m*-CPBA yielded homochiral epoxide **8** (**8a**–**d**) as one isomer. It should be mentioned that a highly stereoselective epoxidation of **8c** and **8d** required a low temperature (−78→0°C). These results indicated that the β-hydroxy function could effectively direct the epoxidation of a trisubstituented β-hydroxy olefin in terms of face selectivity. **8e**–**h**, enantiomers of **8a**–**d**, were similarly prepared from (*R*)-propylene oxide generated from reduction of **6**, tosylation of the 2-hydroxy group, cyclization and epoxidation. When **8** was treated with $AlEt_3$ in THF, it was converted to terminal α-hydroxy olefin **9** efficiently in a high enantiomeric purity (ee >99%), indicating that the eliminative ring-opening is highly stereoselective. The results were listed in Table 3.

To determine the stereoselectivity of the rearrangement, we studied the stereochemistry of the epoxy function in **4k** and the hydroxy group in **5k** (entry 11, Table 2) using 2D NMR spectrum. The 2D NMR spectra showed the epoxy function in **4k** and the hydroxy group in **5k** both are α-oriented (*trans* to the β-oriented methyl group), implying this $AlEt_3$-promoted eliminative ring-opening proceeds with retention of configuration. The absolute configuration of the newly generated stereogenic center in **9c** was assigned as *R* by Mosher's method,[8] indicating that the absolute configuration of the epoxy function in **8c** is (1*R*,2*R*). We tentatively assume the hydroxy-directed *m*-CPBA epoxidation of **7** has the same face selectivity regardless of R^1 and R^2. Based on this assumption, we tentatively assigned the absolute configurations of **8** and **9** as shown in Table 3. A possible mechanism is outlined in Scheme 3. Reaction of $AlEt_3$ with the hydroxyl group and subsequent coordination to the epoxy function converts **8** to a six-membered intermediate **a**; the epoxy group is thus activated by the coordination leading to an eliminative ring-opening with the formation of aluminium allylic hydroxide **b**; hydrolysis of **b** finishes the transformation with the release of a terminal α-hydroxy olefin and an aldehyde. This mechanism is supported by the following observations. (a) GC–MS analysis of the reaction mixtures from **4d** and **4g** proved the presence of benzaldehyde; (b) no eliminative ring-opening occurred when the hydroxy function in **8** was blocked by acetyl group.

3. Conclusion

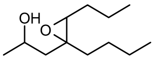
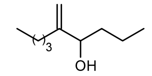
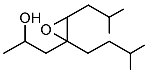
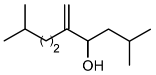
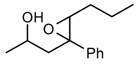
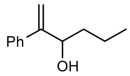
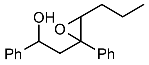
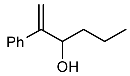
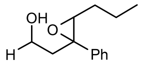
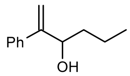
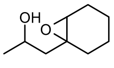
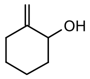
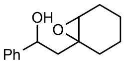
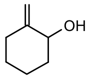
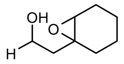
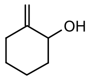
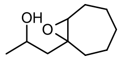
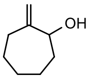
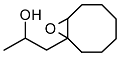
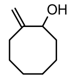
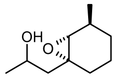
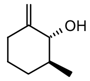
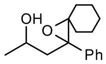
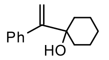
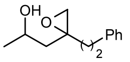
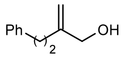
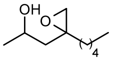
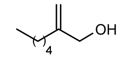
We have discovered a $AlEt_3$-mediated eliminative ring-opening reaction of β-hydroxy epoxides. This eliminative ring-opening has been demonstrated to be a highly stereoselective asymmetric synthesis for terminal α-hydroxy olefins. Further studies on the application of this methodology in the synthesis of natural products are in progress.

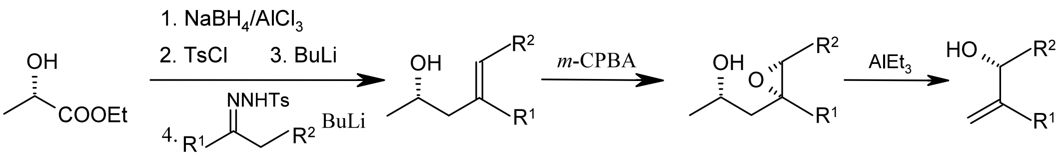
4. Experimental

4.1. General

THF was freshly distilled from a deep-blue solution of sodium-benzophenone ketyl under argon. Column chromatography was performed on silica cartridges. ^1H and ^{13}C NMR spectra were recorded on an Avance DRX-200 MHz (^1H: 100 MHz, ^{13}C: 50 MHz) or a Bruker AM 400 MHz (^1H: 400 MHz, ^{13}C 100 MHz) instrument with TMS as internal standard. MS data were measured with EI (70 eV) and HRMS data were

Table 2. Eliminative ring-opening of β-hydroxy epoxide by $AlEt_3$

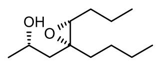
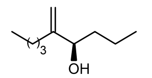
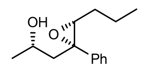
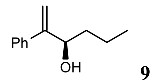
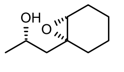
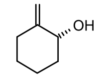
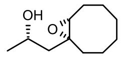
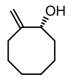
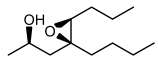
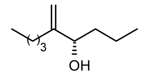
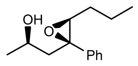
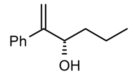
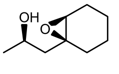
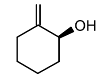
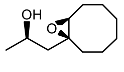
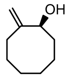
Entry	Substrate **4** (Diasteroisomeric ratio)	Product **5**	Yield (%)
1	 **4a**	 **5a**	96
2	 **4b**	 **5b**	90
3	 **4c**	 **5c**	95
4	 **4d**	 **5c**	97
5	 **4e**	 **5c**	95
6	 **4f** (61:39)	 **5f**	89
7	 **4g**	 **5f**	90
8	 **4h**	 **5f**	88
9	 **4i** (59:41)	 **5i**	92
10	 **4j** (62:38)	 **5j**	93
11	 **4k**	 **5k**	92
12	 **4l**	 **5l**	97
13	 **4m** (63:37)	 **5m**	67
14	 **4n**	 **5n**	45



6 **7** **8** **9**

Scheme 2.

Table 3. Eliminative ring-opening of optically active β-hydroxy epoxides

Entry	Substrate **8**	Product **9**	% ee
1	 **8a**	 **9a**	> 99
2	 **8b**	 **9b**	> 99
3	 **8c**	 **9c**	> 99
4	 **8d**	 **9d**	> 99
5	 **8e**	 **9e**	> 99
6	 **8f**	 **9f**	> 99
7	 **8g**	 **9g**	> 99
8	 **8h**	 **9h**	> 99

measured with EI or ESI techniques (Bruker ApexII). Enantiomeric determination was accomplished by Agilent 1100 HPLC using Chiralcel OD or OB column.

4.2. General procedure for rearrangement of β-epoxy alcohols

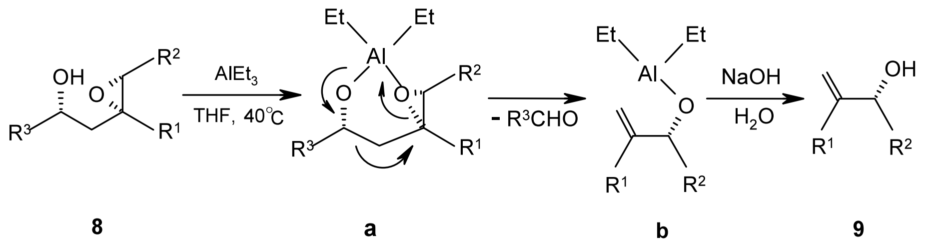
To a stirred solution of β-hydroxy epoxide (1 mmol) in THF (10 ml) was added dropwise a THF solution of $AlEt_3$ (3 mol/L, 5 mmol, 1.67 ml). The reaction mixture was stirred at 40°C. Upon disappearance of the starting material as monitored by TLC, the reaction was quenched with a 10% NaOH solution. The resulting mixture was diluted with diethyl ether, washed with brine and dried over Na_2SO_4. Purification by neutral silica-gel column chromatography (petrol ether/ethyl acetate) gave the corresponding product.

Acknowledgements

We thank the NSFC (No. 29972019, 29925205 and QT program), FUKTME of China, and the Fund of Ministry of Education (No. 99209) for support of this work.

References

1. (a) Dehoux, C.; Fontaine, E.; Escudier, J. M.; Baltas, M.; Gorrichon, L. *J. Org. Chem.* **1998**, *63*, 2601–2608; (b) Liu, D. G.; Wang, B.; Lin, G. Q. *J. Org. Chem.* **2000**, *65*, 9114–9119; (c) Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 4970–4982; (d) Morimoto, Y.; Shirahama, H. *Tetrahedron* **1996**, *52*, 10631–10652; (e) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1987**, *52*, 3337–3342.
2. (a) Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.* **1984**, *49*, 3707–3711; (b) Wang, Z. X.; Tu, Y.; Frohn, M.; Zhang, J. R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224–11235; (c) Okachi, T.; Murai, N.; Onaka, M. *Org. Lett.* **2003**, *5*, 85–87.
3. (a) Holton, R. A.; Kennedy, R. M. *Tetrahedron Lett.* **1984**, *25*, 4455–4458; (b) Waddell, T. G.; Ross, P. A. *J. Org. Chem.* **1987**, *52*, 4802–4804; (c) Wender, P. A.; Mucciaro, T. P. *J. Am. Chem. Soc.* **1992**, *114*, 5878–5879; (d) Holton, R. A.; Somoza, C.; Kim, H.-B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C. L.; Vu, P.; Tang, S. H.; Zhang, P. S.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597–1598.
4. (a) Hara, R.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **1996**, *118*, 9186–9187; (b) Corey, E. J.; Guzman-Perez, A.; Lazerwith, S. E. *J. Am. Chem. Soc.* **1997**, *119*, 11769–11776.
5. (a) Fraga, B. M. *Nat. Prod. Rep.* **2000**, *17*, 483–504; (b) Perry, N. B.; Burgess, E. J.; Baek, S.; Weavers, R. T. *Org. Lett.* **2001**, *3*, 4243–4245.



8 **a** **b** **9**

Scheme 3.

6. (a) Shapiro, R. H.; Heath, M. J. *J. Am. Chem. Soc.* **1967**, *89*, 5734–5735; (b) Kaufman, G.; Cook, F.; Shechter, R.; Bayless, J.; Friedman, L. *J. Am. Chem. Soc.* **1967**, *89*, 5736–5737; (c) Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147–154.
7. (a) Magnusson, G.; Thorén, S. *J. Org. Chem.* **1973**, *38*, 1380–1384; (b) Fringuelli, F.; Germani, R.; Pizzo, F.; Santinelli, F.; Savelli, G. *J. Org. Chem.* **1992**, *57*, 1198–1202.
8. (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549; (b) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143–2147; (c) Oh, S. S.; Butler, W. M.; Koreeda, M. *J. Org. Chem.* **1989**, *54*, 4499–4503.