Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 46 (2005) 89–91

Tetrahedron Letters

$SnCl_4$-promoted rearrangement of 2,3-epoxy alcohol derivatives: stereochemical control of the reaction

Yasuyuki Kita,* Satoshi Matsuda, Ryoko Inoguchi, Jnaneshwara K. Ganesh and Hiromichi Fujioka

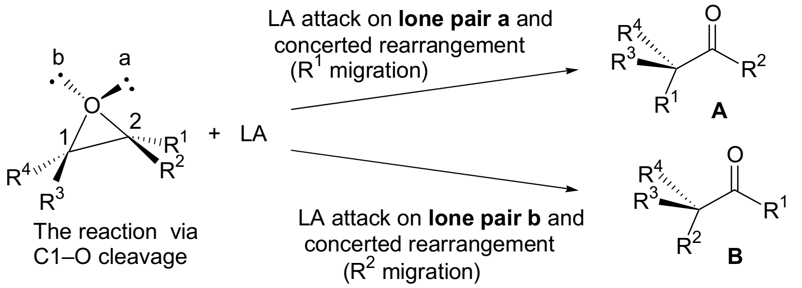
Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565-0871, Japan

Received 4 October 2004; revised 29 October 2004; accepted 4 November 2004

Abstract—The $SnCl_4$-promoted rearrangement of 2,2,3,3-tetrasubstituted-2,3-epoxy-1-alcohol derivatives proceeded in a regio- and stereo-controlled manner to selectively give two types of rearranged products from a single isomer by changing the protecting group of the alcohol.

The rearrangements of epoxides with a Lewis acid (LA) are powerful transformations of carbon skeletons, and have been broadly studied.[1] The structures of the rearranged products depend on the course of the rearrangement, in other words, the stereochemistry of the reactions. The control of the stereochemistry is then very important. The oxygen atom of the oxiran ring has two lone pairs, lone pair a and lone pair b. When the reaction proceeds in a stereoselective manner, the different attacking course of LA to the lone pair gives the different products, product **A** from the lone pair a attack and product **B** from the lone pair b attack (Scheme 1). We present here such examples, that is, remarkable control of the stereochemistry of the rearrangement, for the reactions of the $SnCl_4$–mediated rearrangement of 2,2,3,3-tetrasubstituted-2,3-epoxy-1-alcohols by only changing the protecting group of the alcohol.

The rearrangement of 2,3-epoxy-1-alcohols and their derivatives is one of the most valuable tools for constructing α- or β-hydroxy ketones, via the C3- or the C2-cleavage of the oxiran rings. Most of them are 2,3-disubstituted and 2,2,3- or 2,3,3-trisubstituted epoxides, and the reactions occur via more stable carbocation intermediates.[2] In other words, the reaction occurs through the carbocations on the more substituted carbons, if the epoxides do not have electron-stabilizing substituents such as a phenyl or vinyl group. On the other hand, to the best of our knowledge, the rearrangements of 2,2,3,3-tetrasubstituted epoxy alcohol derivatives are comparatively few.[3] Recently, we studied the rearrangement of 2,2,3,3-tetrasubstituted-2,3-epoxy-1-acylates and 2,2,3,3-tetrasubstituted-2,3-epoxy-1-sulfonates, and succeeded in controlling the regiochemistry of the rearrangements.[4] As an extension of the study,



Scheme 1.

Keywords: $SnCl_4$-promoted rearrangement; Tetrasubstituted-2,3-epoxy alcohol; Stereocontrol; α-Alkoxy ketone; β-Hydroxy ketone.

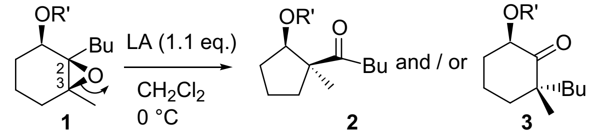
* Corresponding author. Tel.: +81 668798225; fax: +81 668798229; e-mail: kita@phs.osaka-u.ac.jp

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.11.018

we next aimed to control the stereochemistry of the rearrangement. To examine the concept in Scheme 1, we chose six-membered and acyclic 2,2,3,3-tetrasubstituted-2,3-epoxy-1-alcohols and their derivatives for the following reasons: (1) tetrasubstituted epoxides can avoid the difference in the stability of the carbocations on the C2- and C3-carbons, (2) conformationally more flexible substrates, that is, the six-membered rings for cyclic system and acyclic system, have little affect on the two rearrangement courses, and (3) the oxygen atom of the alcohol function can proceed via the chelation transition state by the bidentate LA. We chose $BF_3\cdot Et_2O$, as the representative monodentate LA, and $SnCl_4$, as the representative bidentate LA.

In the first place, we studied the reaction of the cyclic six-membered compounds **1** (Table 1). Every reaction proceeded via the C3-carbocation intermediate. Since we already concluded the reason for the reactions of epoxy acylates via the C3-carbocation intermediates due to destabilization of the C2-carbocation by the electron-withdrawing nature of the acyloxy group,[4] the result can be rationalized by the fact that the electron-withdrawing nature of the LA-coordinated alcohol unit makes the C2-carbocation unstable. When an acyl function (PNB: *p*-nitrobenzoyl) was used as a protecting group of the alcohol, the difference in the ratio of the two products depending on the kind of LA ($SnCl_4$ and $BF_3\cdot Et_2O$) was not observed (entries 1 and 8). However, $SnCl_4$ tended to afford the products in two ways. In the reactions of epoxy alcohols and alkyl ether derivatives, the six-membered α-hydroxy ketones **3** were obtained as major products (entries 2–4). On the other hand, the compounds with the trialkylsilyl group gave the ring-contracted five-membered products **2** in good yields (entries 5–7). These phenomena might be rationalized by a chelation and nonchelation transition state as will be discussed later (Scheme 2). However, for the reactions using $BF_3\cdot Et_2O$, a monodentate LA, every epoxy alcohol derivative gave the ring-contracted five-membered product **2** without depending on the protecting group (entries 8–11).

Table 1.

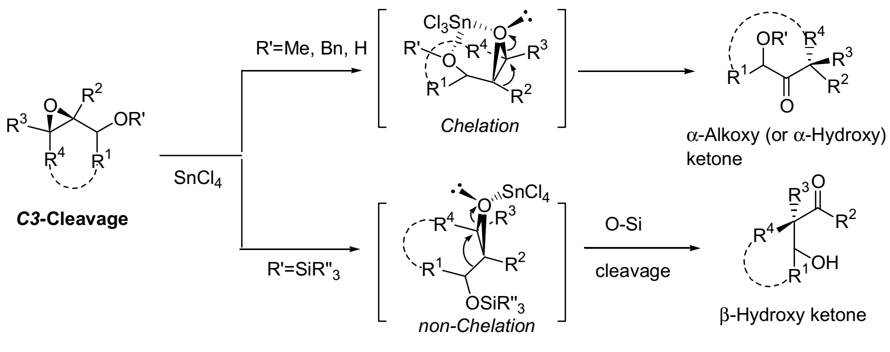


Entry	1	R′	LA	Yield (%)	
				2	3
1	**1a**	PNB	$SnCl_4$	26	46
2	**1b**	H	$SnCl_4$	—	**98**
3	**1c**	Me	$SnCl_4$	8	**59**
4	**1d**	Bn	$SnCl_4$	20	**44**
5	**1e**	*t*-BuMe$_2$Si	$SnCl_4$	**94**[a]	—
6	**1f**	Et$_3$Si	$SnCl_4$	**71**[a]	—
7	**1g**	Me$_3$Si	$SnCl_4$	**39**[a]	—
8	**1a**	PNB	$BF_3\cdot Et_2O$	24	34
9	**1b**	H	$BF_3\cdot Et_2O$	47	—
10	**1d**	Bn	$BF_3\cdot Et_2O$	81	—
11	**1e**	*t*-BuMe$_2$Si	$BF_3\cdot Et_2O$	34[a]	—

[a] Hydroxy compound (R′ = H) was obtained.

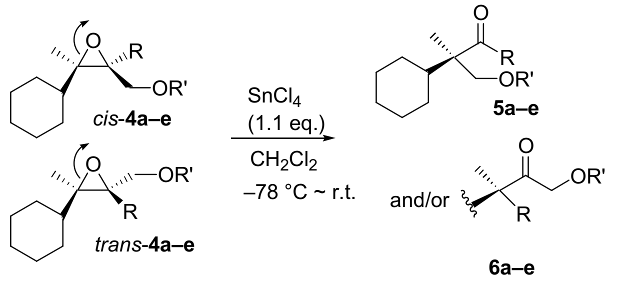
For the bidentate LA, $SnCl_4$ also showed a similar reactivity in acyclic systems (Table 2). Treatment of the epoxy alcohols (*cis*- and *trans*-**4a**) with $SnCl_4$ generated the bidentate chelation transition state between Sn metal and two oxygen atoms (hydroxy and epoxide oxygens), which selectively led to the formation of the α-hydroxy ketone **6a**. Similarly, the epoxy benzyl ethers, *cis*-**4b**,**c**, and *trans*-**4b**,**c** selectively afforded the α-benzyloxy ketones **6b**,**c** by the migration of the alkyl groups via the C3-carbocation intermediate (entries 2 and 3 for *cis*-isomer and entries 7 and 8 for *trans*-one).[5] On the other hand, the epoxy *tert*-butyldimethylsilyl (TBS) ethers, *cis*-**4d**,**e**, and *trans*-**4d**,**e**, gave the β-hydroxy ketones, *cis*-**5d**,**e** by the migration of silyloxymethyl groups via the C3-carbocation (entries 4 and 5 for *cis*-isomer and entries 9 and 10 for *trans*-one).

The above results are rationalized as follows: the alkyl ether compounds can form the bidentate chelation transition state between two oxygen atoms and Sn metal. This decreases the migratory aptitude of the alkyloxy methyl group, and then the alkyl group opposite to the benzyloxy methyl group selectively migrates to produce the α-alkoxy ketones. On the other hand, the bulky trialkylsilyl group inhibits the formation of the chelation intermediate and makes the LA attack opposite-side lone pair of the oxygen atom. A stereoselective rearrangement of the trialkylsilyloxy group in the *anti*-periplaner position then occurs. For the trialkylsilyloxy



Scheme 2.

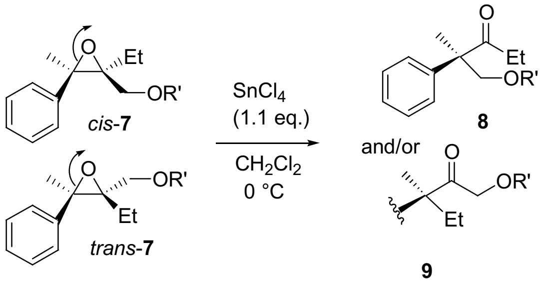
Table 2.



Entry	4	R	R′	Yield (%)	
				5	6
1	*cis*-**4a**	Et	R′ = H	—	**76**
2	*cis*-**4b**	Me	R′ = Bn	—	**91**
3	*cis*-**4c**	Et	R′ = Bn	—	**94**
4	*cis*-**4d**	Me	R′ = TBS	**90**[a]	—
5	*cis*-**4e**	Et	R′ = TBS	**65**[a]	—
6	*trans*-**4a**	Et	R′ = H	27	**56**
7	*trans*-**4b**	Me	R′ = Bn	11	**76**
8	*trans*-**4c**	Et	R′ = Bn	—	**55**
9	*trans*-**4d**	Me	R′ = TBS	**100**[a]	—
10	*trans*-**4e**	Et	R′ = TBS	**47**[a]	—

[a] Hydroxy ketone (**5**: R′ = H) was obtained.

Table 3.



Entry	Substrate	Yield (%)	
		8	9
1	*cis*-**7a** (R′ = Bn)	13	**68**
2	*trans*-**7a** (R′ = Bn)	11	**80**
3	*cis*-**7b** (R′ = TBS)	**78**[a]	—
4	*trans*-**7b** (R′ = TBS)	**89**[a]	—

[a] Hydroxy ketone (**8**: R′ = H) was obtained.

compounds, every reaction afforded the β-hydroxy ketone possibly obtained by desilylation after the rearrangement because the products are completely different from those derived from epoxy alcohols without protecting group.

The above phenomenon was also observed in the reactions of the compounds with the C3–phenyl group **7**. The rearrangement reactions of **7** must proceed via the more stable C3-carbocation than those of compounds **1** and **4**. In these cases, the control of the stereochemistry was also achieved to give the β-hydroxy ketones **8** and the α-benzyloxy ketones **9** depending on the protecting group. These results are also rationalized as shown in Scheme 2. This result shows that the concept in Scheme 1 has a generality for conformationally flexible compounds (Tables 2 and 3).

In conclusion, we have found that the Lewis acid promoted rearrangement reaction of the 2,2,3,3-tetrasubstituted-2,3-epoxy-1-alcohol derivatives, which are supposed to have only a slight difference in the stability between the C2- and C3-carbocation, proceed via the C3-carbocation, and furthermore, the reactions using $SnCl_4$ as a Lewis acid can proceed in a stereoselective manner by controlling the chelation and nonchelation transition state only by changing the protecting group. This method could produce two types of rearranged products from the single carbon skeleton. Studies on the stereocontrol of the rearrangement reactions of epoxy alcohol derivatives are rare. Only two papers, to the best of our knowledge, have reported this matter using trisubstituted epoxides and rather special Lewis acids such as high-valent metalloporphyrin complex,[2a] MABR and SbF_5.[2g] Our method here uses a common Lewis acid, $SnCl_4$, which can be a very useful tool in the organic synthetic field.

References and notes

1. For reviews on the Lewis acid-mediated rearrangement of epoxides, see: (a) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737; (b) Rickborn, B. In *Comprehensive Organic Synthesis, Carbon–Carbon-Bond Formation*; Pattenden, G., Ed.; Pergamon: Oxford, 1991; Vol. 3, Chapter 3.3, p 733.
2. For examples, see: (a) Suda, K.; Kikkawa, T.; Nakajima, S.; Takanami, T. *J. Am. Chem. Soc.* **2004**, *126*, 9554; (b) Jeon, S.; Walsh, P. *J. Am. Chem. Soc.* **2003**, *125*, 9544; (c) Marson, C. M.; Walker, A. J.; Pickering, J.; Hobson, A. D. *J. Org. Chem.* **1993**, *58*, 5944; (d) Marson, C. M.; Harper, S.; Oare, A. *J. Org. Chem.* **1998**, *63*, 3798; (e) Marson, C. M.; Khan, A.; Porter, R. A.; Cobb, A. J. A. *Tetrahedron Lett.* **2002**, *43*, 6637; (f) Marson, C. M.; Oare, C. A.; McGregor, J.; Walsgrove, T.; Grinter, T. J.; Adams, H. *Tetrahedron Lett.* **2003**, *44*, 141; (g) Maruoka, K.; Murase, N.; Bureau, R.; Ooi, T.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 3663; (h) Jung, M. E.; Lee, W. S.; Sun, D. *Org. Lett.* **1999**, *1*, 307; (i) Jung, M. E.; Heuvel, A. V. D. *Tetrahedron Lett.* **2002**, *43*, 8169; (j) Jung, M. E.; Hoffmann, B.; Rausch, B.; Contreras, J. M. *Org. Lett.* **2003**, *5*, 3159; (k) Zhu, Y.; Shu, L.; Tu, Y.; Shi, Y. *J. Org. Chem.* **2001**, *66*, 1818; (l) Ranu, B. C.; Jana, U. *J. Org. Chem.* **1998**, *63*, 8212; (m) Bhatia, K. A.; Eash, K. J.; Leonard, N. M.; Oswald, M. C.; Mohan, R. S. *Tetrahedron Lett.* **2001**, *42*, 8129.
3. There is only one example for practical level except our work (Ref. 4), see: Abad, A.; Agulló, C.; Arnó, M.; Cuñat, A. C.; Zaragozá, R. J. *Synlett* **1993**, 895.
4. For recent examples, see: (a) Kita, Y.; Furukawa, A.; Futamura, J.; Ueda, K.; Sawama, Y.; Hamamoto, H.; Fujioka, H. *J. Org. Chem.* **2001**, *66*, 8779; (b) Kita, Y.; Futamura, J.; Ohba, Y.; Sawama, Y.; Ganesh, J. K.; Fujioka, H. *J. Org. Chem.* **2003**, *68*, 5917; (c) Fujioka, H.; Yoshida, Y.; Kita, Y. *J. Synth. Org. Chem. Jpn.* **2003**, *61*, 133; (d) Kita, Y.; Futamura, J.; Ohba, Y.; Sawama, Y.; Ganesh, J. K.; Fujioka, H. *Tetrahedron Lett.* **2003**, *44*, 411.
5. Benzyl ether was chosen because of its easier deprotection than that of methyl ether.