REGIOSELECTIVE RING-OPENING OF 2,3-EPOXY ALCOHOLS WITH TETRAMETHYLAMMONIUM TRIACETOXYBOROHYDRIDE

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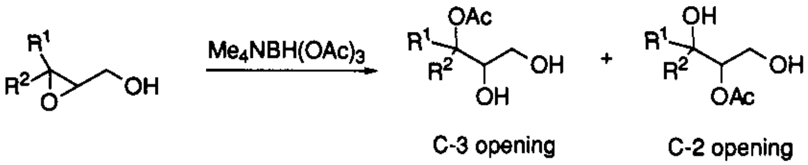
Abstract — Treatment of 2,3-epoxy alcohols with tetramethylammonium triacetoxyborohydride afforded the ring-opening products at the C-3 position, regioselectively, where the presence of $Me_4NBH(OAc)_3$ increased the reaction rate and regioselectivity by forming the chelation intermediate between the metal center and the epoxy alcohol oxygens.

Development of a regioselective ring-opening reaction of 2,3-epoxy alcohols with nucleophiles[1] has been of continuing interest in organic chemistry since the polyfunctional products from this reaction are often convenient building blocks for the synthesis of biologically important compounds including natural products. Regioselectivity in this ring-opening reaction depends on both steric and electronic factors.[1] In 1985, Sharpless and his co-worker reported the metal alkoxide assisted regioselective ring-opening reaction of 2,3-epoxy alcohols, in which titanium tetra-isopropoxide was found to play an important role to exhibit a regioselectivity.[2] Thereafter a number of methods using titanium alkoxides[3] or borane reagents[4] were devised to introduce a various types of nucleophiles to 2,3-epoxy alcohols.

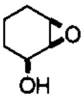
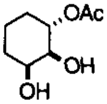
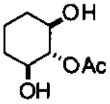
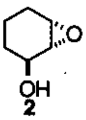
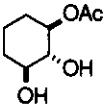
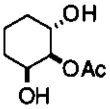
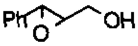
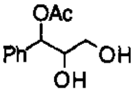
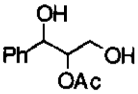
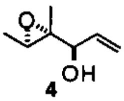
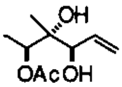
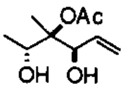
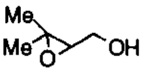
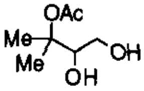
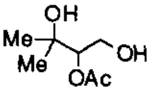
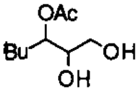
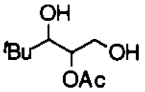
Recently we have been involved in the synthesis of natural products having 2,3-epoxy alcohol function by using the Sharpless asymmetric epoxidation of unsymmetrical divinylcarbinols.[5] In conjunction with this synthetic work, we have been interested in developing an alternative regioselective ring-opening of 2,3-epoxy alcohols. We report here our own successful results, where treatment of 2,3-epoxy alcohols with $Me_4NBH(OAc)_3$,[6] a diastereoselective reducing agent of β-hydroxy ketone, provided acetoxy diols with a high degree of generality and regioselectivity.



Scheme 1

Reaction of the epoxy alcohol (**1**) with a stoichiometric amount of Me$_4$NBH(OAc)$_3$ in THF at 70°C proceeded smoothly to afford the C-3 opening product, as the sole product, in high yield (Table 1, entry 1). When this reaction was applied to the *anti*-epoxy alcohol (**2**) under the same conditions, the reaction was sluggish and none

Table 1. Ring-opening reaction of the epoxy alcohols with Me$_4$NBH(OAc)$_3$[a]

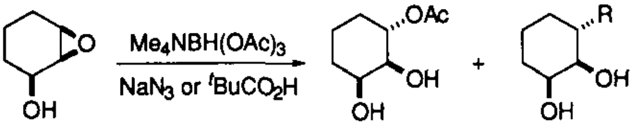
entry	epoxy alcohol	time (h)	products (yield, %)			
			C-2 opening		C-3 opening	
1[b]	 **1**	1.5		(94%)		(0%)
2[b]	 **2**	72		(—%)[c]		(—%)[c]
3[b]	 **3**	1.5		(83%)		(9%)
4	 **4**	2		(91%)		(0%)
5[b]	 **5**	3		(32%)		(21%)
6[b]	 **6**	5		(0%)		(91%)

[a] All reactions were carried out with Me$_4$NBH(OAc)$_3$ (1.1 mol equiv.) in THF (5 mL / 1 mmol of epoxy alcohol) at 70°C. [b] Racemate was used. [c] Not isolated. The product is a complex mixture with reducing products

of the acetoxy introduced products could be isolated.[7] These results were rationalized by assuming that the presence of $Me_4NBH(OAc)_3$ increased the reaction rate and regioselectivity by forming the chelation intermediate between the metal center and the epoxy alcohol oxygens as proposed by Sharpless.[2] The ring-opening reaction is also applicable to linear epoxy alcohols. For example, treatment of the epoxy alcohols (**3**) and (**4**) under the same conditions gave the C-3 acetoxy diols with high regioselectivity (Table 1, entries 3 and 4). On the other hand, the similar treatment of the sterically hindered epoxy alcohol (**5**) having two alkyl substituents at the C-3 position, gave the C-3 opening product and C-2 isomer in a ratio of 1.5:1 (Table 1, entry 5). Furthermore, the same reaction of the epoxy alcohol (**6**) bearing *tert*-butyl group at the C-3 position, afforded the C-2 opening product with the converse regioselectivity (Table 1, entry 6). This fact clearly suggested that acetoxy ligand on borane could not attack the C-3 position because of steric hindrance.

We have also examined the epoxy ring-opening reaction for **1** with the other nucleophiles, such as NaN_3 or $^tBuCO_2H$ under the same reaction conditions.

Refluxing THF solution of **1** in the presence of 1.1 equiv. of $Me_4NBH(OAc)_3$ and 1.5 or 5.0 equiv. of NaN_3 as the nucleophile gave 61% or 75% yield of the azido diol (**8a**) and 22% or 17% yield of the acetoxy diol (**7**). Using 5.0 equiv. of $^tBuCO_2H$ as the nucleophile, **1** provided 14% of **7** and 63% of pivaloxy diol (**8b**). Although the acetoxy-introduced product was always observed as a minor product in these reactions, none of C-2 isomers could be isolated.



1

7

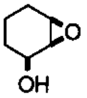
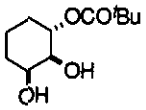
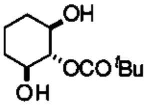
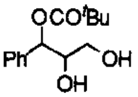
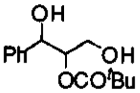
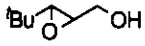
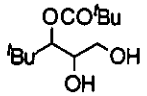
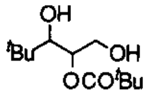
8a : R = N_3
8b : R = OCO^tBu

NaN_3 (1.5 eq.) : **7** (22%) / **8a** (61%)
NaN_3 (5.0 eq.) : **7** (17%) / **8a** (75%)
$^tBuCO_2H$ (5.0 eq.) : **7** (14%) / **8b** (63%)

Scheme 2

In order to prevent the attack of acetoxy group, an alternative reaction condition employing ^{t}BuCO$_2$H and Me$_4$NBH$_4$ was investigated and the results were summarized in Table 2. Ring-opening reaction of both epoxy alcohols (**1**) and (**3**) with pivalic acid in the presence of Me$_4$NBH$_4$ proceeded smoothly to give C-3 pivaloxy diols with high regioselectivity (Table 2, entries 1 and 2). Again, the reaction of the sterically hindered **6** gave 94% yield of C-2 pivaloxy diol with converse regioselectivity (Table 2, entry 3).

Table 2. Ring-opening reaction of the epoxy alcohols with Me$_4$NBH$_4$ in the presence of ^{t}BuCO$_2$H^a

entry	epoxy alcohol	time (h)	products (yield, %)			
			C-2 opening		C-3 opening	
1	 **1**	12		(96%)		(trace)
2	 **3**	15		(79%)		(14%)
3	 **6**	20		(trace)		(94%)

^{a} All reactions were carried out with Me$_4$NBH$_4$ (1.1 mol equiv.) and ^{t}BuCO$_2$H (5.0 mol equiv.) in THF (5 mL / 1 mmol of epoxy alcohol) at 70°C.

In summery, we have demonstrated a regioselective ring-opening reaction of 2,3-epoxy alcohols in the presence of tetramethylammonium borane reagent with the various types of nucleophiles. This ring-opening reaction proceeded without Payne rearrangement and an acetyl migration. The method under mild conditions provides an attractive alternate for the formation of the protected triol system in combination with the Sharpless asymmetric epoxidation.

ACKNOWLEDGEMENT

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REFERENCES AND FOOTNOTES

1. C. H. Behrens, S. Y. Ko, K. B. Sharpless, and F. J. Walker, *J. Org. Chem.*, 1985, **50**, 5687; C. H. Behrens and K. B. Sharpless, *Pure & Appl. Chem.*, 1983, **55**, 589.
2. M. Caron and K. B. Sharpless, *J. Org. Chem.*, 1985, **50**, 1557.
3. Introduction of an oxygen function: (a) E. Alvarez, M. T. Nuñez, and V. S. Martín, *J. Org. Chem.*, 1990, **55**, 3429. (b) Y. E. Raifeld, A. Nikitenko, and B. M. Arshava, *Tetrahedron:Asymmetry*, 1991, **2**, 1083. (c) Y. E. Raifeld, A. Nikitenko, and B. M. Arshava, *Tetrahedron*, 1990, **49**, 2509. (d) J. M. Palazon, B. Aññorbe, and V. S. Martín, *Tetrahedron Lett.*, 1986, **27**, 4987. (e) S. Y. Ko and K. B. Sharpless, *J. Org. Chem.*, 1986, **51**, 5413; Introduction of a halogen atom: see (3a) and (f) K. S. Kirshenbaum and K. B. Sharpless, *Chemistry Lett.*, 1987, 11; Introduction of a nitrogen function: see (3e) and (g) M. Canas, M. Poch, X. Verdaguer, A. Moyano, M. A. Paricás, and A. Riera, *Tetrahedron Lett.*, 1991, **32**, 6931. (h) M. Caron, P. R. Carlier, and K. B. Sharpless, *J. Org. Chem.*, 1988, **53**, 5185. (i) T. K. Chakraborty and G. V. Reddy, *Tetrahedron Lett.*, 1990, **31**, 1335; Introduction of s sulfide group: see (3e) and (3g); Introduction of hydride: (j) L. -x. Dai, B. -l. Lou, Y. -z. Zhang, and G. -z. Guo, *Tetrahedron Lett.*, 1986, **27**, 4343.
4. Introduction of a halogen atom was reported using monochloroborane-dimethyl sulfide: P. Bovicelli, P. Lupattelli, M. T. Bersani, and E. Mincione, *Tetrahedron Lett.*, 1992, **33**, 6181.
5. T. Honda, M. Ohta, and H. Mizutani, *Heterocycles*, 1997, **46**, 137.
6. D. A. Evans, K. T. Chapman, and E. M. Carreira, *J. Am. Chem. Soc.*, 1988, **110**, 3560.
7. A formation of the hydride attacked-reduction products was observed in the ^{1}H NMR spectrum.

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