CHEMISTRY LETTERS, pp. 967-970, 1992.

Stereoselective Reduction of α,β-Epoxy Ketones into erythro-α,β-Epoxy Alcohols with Sodium Borohydride in the Presence of Calcium Chloride

Hideaki FUJII, Koichiro OSHIMA,* and Kiitiro UTIMOTO*
Department of Industrial Chemistry, Faculty of Engineering, Kyoto University, Sakyo-ku, Kyoto 606-01

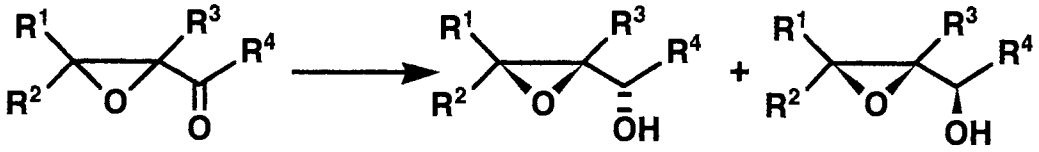
erythro-α,β-Epoxy alcohols were prepared with high stereoselectivity by sodium borohydride reduction of the corresponding α,β-epoxy ketones in the presence of calcium chloride or manganese(II) chloride regardless of the substituents on the epoxide ring.

Recently we have reported that erythro-3-hydroxy-2-methyl amides were prepared with high stereoselectivity by $NaBH_4$ reduction of the corresponding β-keto amides in the presence of a catalytic amount of $MnCl_2$ or $CaCl_2$.[1] Here we wish to describe further extension of this method to the stereoselective reduction of α,β-epoxy ketones into erythro-α,β-epoxy alcohols with $NaBH_4$ in the presence of $CaCl_2$. Oishi and Nakata have reported[2] highly stereoselective synthesis of erythro-α,β-epoxy alcohols by the reduction of α,β-epoxy ketones with zinc borohydride and our new method would provide an effective alternative procedure for the same transformation.

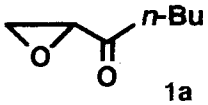
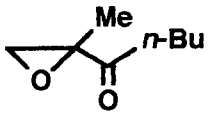
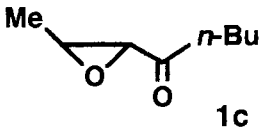
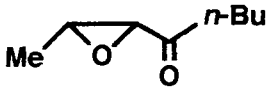
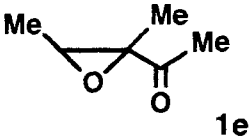
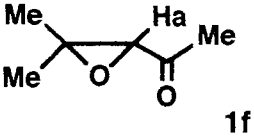
The α,β-epoxy ketone **1c** was chosen as a substrate and the stereoselectivity of the reduction of **1c** (1.0 mmol) with $NaBH_4$ was examined in the presence of various metal chlorides (2.0 mmol). The respective metal chloride and the isomeric ratio of the reduction products (erythro-epoxy alcohol **2c** : threo isomer **3c**) were as follows: None, **2c**:**3c** = 66:34; $MgCl_2$, 70:30; $MnCl_2$, 86:14; $CaCl_2$, 88:12; $SrCl_2$, 89:11; $BaCl_2$, 91:9. Lanthanoids metal chlorides such as $CeCl_3$, $SmCl_3$, or $YbCl_3$ were also effective for the stereoselective reduction of **1c** and gave erythro-α,β-epoxy alcohol **2c** as a major product (**2c**:**3c** = 85:15-90:10).[3] Calcium chloride was selected among the effective metal chlorides because of the availability. The reduction of **1c** with $NaBH_4$ in the presence of $CaCl_2$ at various temperature was studied and reaction temperature proved to affect the isomeric ratio of **2c** and **3c** slightly. The ratios of **2c** and **3c** were **2c**:**3c** = 87:13 at 25 °C, 88:12 at 0 °C, 89:11 at -24 °C, and 91:9 at -78 °C. The reduction of various α,β-epoxy ketones with $NaBH_4$ in the presence of $CaCl_2$ or $MnCl_2$ at 0 °C in methanol was examined and the results are shown in Table 1. In order to make a comparison with these data, the results of the reduction with $NaBH_4$[4] or *n*-Bu_4NBH_4 are also shown in the Table.

erythro-α,β-Epoxy alcohols were produced with high stereoselectivity by $NaBH_4$ reduction in the presence of $CaCl_2$ irrespective of the substitution pattern of the epoxide. Treatment of a THF solution of **1b** (1.0 mmol) with $Ca(BH_4)_2$ (1.0 mmol), which was prepared from $CaCl_2$ and $NaBH_4$ according to the literature,[5] provided slightly inferior selectivity (**2b**:**3b** = 88:12) compared to the method described in this paper (Entry 9 in Table 1). The reduction of **1b** (1.0 mmol) could be conducted in the presence of a catalytic

Table 1. Reduction of α,β-Epoxy Ketones[a)]



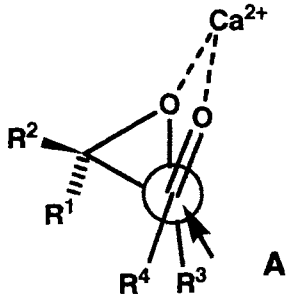
1 2 3

Entry	Epoxy ketone	Reagent	Product ratio of **2** : **3**
1	 **1a**	*n*-Bu_4NBH_4	60 : 40
2		$NaBH_4$	65 : 35
3		$NaBH_4$-$MnCl_2$	81 : 19
4		$NaBH_4$-$CaCl_2$	85 : 15
5	 **1b**	*n*-Bu_4NBH_4	55 : 45
6		$NaBH_4$	70 : 30
7		$NaBH_4$-$ZnCl_2$	89 : 11
8		$NaBH_4$-$MnCl_2$	92 : 8
9		$NaBH_4$-$CaCl_2$	95 : 5
10	 **1c**	*n*-Bu_4NBH_4	50 : 50
11		$NaBH_4$	66 : 34
12		$NaBH_4$-$MnCl_2$	86 : 14
13		$NaBH_4$-$CaCl_2$	88 : 12
14	 **1d**	*n*-Bu_4NBH_4	90 : 10
15		$NaBH_4$	90 : 10
16		$NaBH_4$-$MnCl_2$	97 : 3
17		$NaBH_4$-$CaCl_2$	98 : 2
18	 **1e**	*n*-Bu_4NBH_4	48 : 52
19		$NaBH_4$	42 : 58
20		$NaBH_4$-$MnCl_2$	85 : 15
21		$NaBH_4$-$CaCl_2$	92 : 8
22	 **1f**	*n*-Bu_4NBH_4	83 : 17
23		$NaBH_4$	88 : 12
24		$NaBH_4$-$MnCl_2$	95 : 5
25		$NaBH_4$-$CaCl_2$	97 : 3

a) Isolated yields were 75-85%. Epoxy ketone (1.0 mmol), $NaBH_4$ (or *n*-Bu_4NBH_4, 1.0 mmol), and metal chloride (2.0 mmol) were employed. Reactions were performed at 0 °C.

amount of $CaCl_2$ (0.2 mmol) with small loss of stereoselectivity (**2b**:**3b** = 89:11).

The chelated model A[6] should be considered for the transition state and the selective formation of the erythro product can be rationalized by assuming that hydride attacks the carbonyl carbon from the less hindered side shown by the arrow in a similar fashion as shown in a previous report.[2] The ^1H NMR spectral properties of the $CaCl_2$ complex of α,β-epoxy ketone **1f** were investigated in CD_3OD in order to substantiate the metal chelation. Upon addition of $CaCl_2$, the signal of the methine proton (Ha) was moved downfield. The chemical shift for Ha varied with increasing concentration of $CaCl_2$. Chemical shift and concentration (molar ratio of **1f**/$CaCl_2$) were as follows: δ 3.60, without $CaCl_2$; δ 3.62, 2/1; δ 3.68, 1/2; δ 3.75, 1/4. Small downfield shifts (Δδ 0.01-0.07) were also observed for protons of three methyl groups. For instance, chemical shift of methyl protons of MeC=O group (and concentration) were δ 2.23 (without $CaCl_2$), δ 2.24 (2/1), δ 2.26 (1/2), and δ 2.30 (1/4). These specta changes indicate coordination of the calcium ion with epoxy ketone **1f** even in such a polar solvent as methanol.

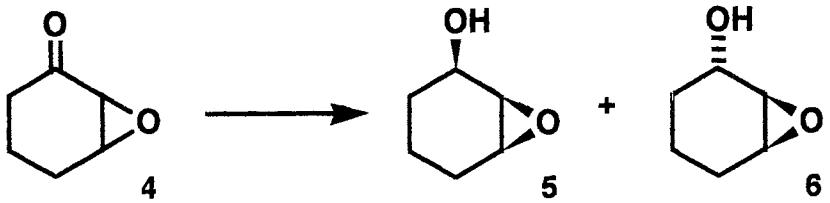


A typical experiment is as follows. Calcium chloride[7] (0.22 g, 2.0 mmol) was added to a methanol (10 ml) solution of α,β-epoxy ketone **1d** (0.14 g, 1.0 mmol) at 25 °C and the resulting clear solution was stirred for 30 min at 25 °C. The mixture was cooled to 0 °C and $NaBH_4$ (40 mg, 1.0 mmol) was added. Vigorous gas evolution occurred. After stirring for 10 min at 0 °C, the reaction mixture was poured into aq. NaCl[8] and extracted with ethyl acetate (10 ml x 2). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The isomeric ratio of the product was determined by capillary gas chromatography (Silicone OV-17, 50 m, 0.32 mm i.d., 110°C, **2d** : **3d** = 98 : 2).[9] Purification of the product by silica-gel column chromatography gave **2d** in 75% yield.

Financial support by the Ministry of Education, Science and Culture of Japan (Grant-in-Aid for Scientific Research #03650700) is acknowledged.

References

1) H. Fujii, K. Oshima, and K. Utimoto, *Tetrahedron Lett.*, **32**, 6147 (1991).
2) T. Oishi and T. Nakata, *Acc. Chem. Res.*, **17**, 338 (1984); T. Nakata, T. Tanaka, and T. Oishi, *Tetrahedron Lett.*, **22**, 4723 (1981).
3) In the case of the reduction in the presence of lanthanoids metal chlorides, the product was contaminated by unidentified complex byproducts and the combined yields of epoxy alcohol were 60-70%.
4) The reported data for $NaBH_4$ reduction by P. Chautemps and J.-L. Pierre (*Tetrahedron*, **32**, 549 (1976)) are considerably different from our own results which are shown in the Table.
5) A. Pelter, K. Smith, and H. C. Brown, "Borane Reagents," Academic Press, London (1988), p. 414.
6) Following experiment also supports the chelated model for the transition state. Reduction of 2,3-epoxy



cyclohexanone **4** with $NaBH_4$ afforded a mixture of *cis*-2,3-epoxycyclohexanol **5** and its *trans* isomer **6** in 52:48 ratio. An addition of various metal chlorides to the reaction mixture could not improve the selectivity so much ($MnCl_2$, **5**:**6** = 40:60; $CaCl_2$, 43:57; $BaCl_2$, 46:54; $SrCl_2$, 46:54). The results might be ascribed to the fact that coordination of the metal ion with **4** is difficult because of its rigid conformation.

7) Calcium chloride was purchased from Wako pure chemical industries, Ltd. and used without further purification.

8) Epoxy alcohols were sensitive to acidic conditions and the use of 1 M HCl (1 M = 1 mol dm^{-3}) to quench the reaction caused partial decomposition of the product.

9) NMR data of products in $CDCl_3$ are as follows. **2a**: ^1H NMR δ 0.89-0.96 (m, 3H), 1.27-1.67 (m, 6H), 1.75-1.80 (bs, 1H, OH), 2.74 (dd, J = 4.1, 5.0 Hz, 1H), 2.82 (dd, J = 2.3, 5.0 Hz, 1H), 3.00-3.05 (m, 1H), 3.81-3.89 (bs, 1H); ^{13}C NMR δ 13.91, 22.65, 27.36, 33.07, 43.41, 54.57, 68.34. **3a**: ^1H NMR δ 0.89-0.96 (m, 3H), 1.28-1.67 (m, 6H), 1.73-1.86 (bs, 1H, OH), 2.73 (dd, J = 2.7, 4.9 Hz, 1H), 2.83 (dd, J = 4.9, 7.0 Hz, 1H), 2.96-3.01 (m, 1H), 3.40-3.48 (m, 1H); ^{13}C NMR δ 13.94, 22.62, 27.39, 33.97, 45.20, 55.46, 71.73. **2b**: ^1H NMR δ 0.88-0.96 (m, 3H), 1.20-1.76 (m, 6H), 1.35 (s, 3H), 2.03-2.12 (bs, 1H, OH), 2.61 (d, J = 4.8 Hz, 1H), 2.91 (d, J = 4.8 Hz, 1H), 3.61-3.68 (m, 1H); ^{13}C NMR δ 14.01, 18.16, 22.75, 27.75, 32.58, 50.22, 59,18, 71.48. **3b**: ^1H NMR δ 0.83-0.99 (m, 3H), 1.20-1.78 (m, 6H), 1.33 (s, 3H), 1.81-1.95 (bs, 1H, OH), 2.67 (d, J = 4.7 Hz, 1H), 2.78 (dd, J = 4.7, 0.6 Hz, 1H), 3.23-3.36 (m, 1H); ^{13}C NMR δ 15.49, 18.16, 22.67, 27.74, 32.85, 52.70, 59.64, 71.34. **2c**: ^1H NMR δ 0.85-1.01 (m, 3H), 1.25-1.96 (m, 7H including OH), 1.34 (d, J = 5.3 Hz, 3H), 2.75 (dd, J = 2.5, 3.2 Hz, 1H), 3.09 (dq, J = 2.5, 5.3 Hz, 1H), 3.73-3.84 (m, 1H); ^{13}C NMR δ 13.93, 17.20, 22.68, 27.35, 33.16, 50.98, 61.92, 68.55. **3c**: ^1H NMR δ 0.85-1.01 (m, 3H), 1.23-1.74 (m, 6H), 1.34 (d, J = 5.2 Hz, 3H), 1.82-2.00 (bs, 1H, OH), 2.71 (dd, J = 2.3, 5.2 Hz, 1H), 3.00 (dq, J = 2.3, 5.2 Hz, 1H), 3.39-3.52 (m, 1H); ^{13}C NMR δ 13.94, 17.20, 22.62, 27.36, 33.97, 52.86, 62.80, 71.32. **2d**: ^1H NMR δ 0.85-0.98 (m, 3H), 1.23-1.32 (m, 7H including OH), 1.40 (d, J = 5.6 Hz, 3H), 2.84 (dd, J = 4.1, 7.6 Hz, 1H), 3.12 (dq, J = 4.1, 5.6 Hz, 1H), 3.56 (dt, J = 4.7, 7.6 Hz, 1H); ^{13}C NMR δ 13.28, 13.94, 22.64, 27.19, 34.99, 52.78, 59.06, 68.97. **3d**: ^1H NMR δ 0.86-0.99 (m, 3H), 1.13-1.73 (m, 6H), 1.33 (d, J = 5.6 Hz, 3H), 1.99-2.42 (bs, 1H, OH), 2.89 (dd, J = 4.4, 8.0 Hz, 1H), 3.19 (dq, J = 4.4, 5.6 Hz, 1H), 3.44-3.56 (m, 1H); ^{13}C NMR δ 13.83, 13.91, 22.65, 27.03, 33.45, 53.66, 60.84, 69.62. **2e**: ^1H NMR δ 1.21 (d, J = 6.4 Hz, 3H), 1.28 (s, 3H), 1.33 (d, J = 5.5 Hz, 3H), 2.12-2.20 (bs, 1H, OH), 3.18 (q, J = 5.5 Hz, 1H), 3.79 (q, J = 6.4 Hz, 1H); ^{13}C NMR δ 13.66, 14.04, 18.35, 54.54, 63.60, 68.52. **3e**: ^1H NMR δ 1.22 (d, J = 6.6 Hz, 3H), 1.26 (s, 3H), 1.31 (d, J = 5.6 Hz, 3H), 1.87-1.93 (bs, 1H, OH), 3.05 (q, J = 5.6 Hz, 1H), 3.48 (q, J = 6.6 Hz, 1H); ^{13}C NMR δ 11.14, 13.58, 18.75, 57.23, 63.96, 72.01. **2f**: ^1H NMR δ 1.36 (d, J = 6.3 Hz, 3H), 1.36 (s, 3H), 1.39 (s, 3H), 1.57-1.78 (bs, 1H, OH), 2.65 (d, J = 7.8 Hz, 1H), 3.71 (dq, J = 7.8, 6.3 Hz, 1H); ^{13}C NMR δ 18.63, 20.86, 24.77, 59.28, 66.12, 67.03. **3f**: ^1H NMR δ 1.26 (d, J = 6.5 Hz, 3H), 1.32 (s, 3H), 1.34 (s, 3H), 1.86-2.40 (bs, 1H, OH), 2.71 (d, J = 7.9 Hz, 1H), 3.65 (dq, J = 7.9, 6.5 Hz, 1H); ^{13}C NMR δ 19.04, 19.19, 24.89, 59.32. 66.94, 68.48.

(Received March 12, 1992)