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Chemo- and Stereoselective Reduction of α,β -Epoxyketones with Diisopropoxytitanium(III) Tetrahydroborate

K.S. Ravikumar^{a,b} and Srinivasan Chandrasekaran^{*a}

^a Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India. ^b IDL-Nitro Nobel Basic Research Institute, Sankey Road, Malleswaram, Bangalore 560 003, India.

Abstract: Reduction of α,β -epoxyketones with diisopropoxytitanium(III) tetrahydroborate in dichloromethane under mild conditions (-78° - -20°C) provides anti- (or erythro-) α,β -epoxy alcohols in high yields with high degree of chemo- and stereoselectivity. Copyright © 1996 Elsevier Science Ltd

The chemo- and stereoselective reduction of α,β -epoxyketones is a challenging problem in organic synthesis and the α,β -epoxyalcohols that are formed are versatile intermediates which can be elaborated efficiently into polyhydroxy compounds with multiple chiral centers.¹ A few reports are available for the stereoselective reduction of α,β -epoxyketones.² While the reduction of α,β -epoxyketones with NaBH₄ leads to the corresponding α,β -epoxyalcohols with modest stereoselectivity.^{2a} the reduction with NaBH₄ in the



presence of CaCl₂ or LaCl₃ in methanol,^{2f} NaBH₄/CeCl₃/MeOH^{2d} and Zn(BH₄)₂/Et₂O^{2e} have been reported to give high *anti*-stereoselectivity. Shibata reported a highly stereoselective reduction of α , β -epoxyketones with halodibutyltinhydride^{2e} and Hosomi showed divergent stereoselectivity using hydridosilicates.^{2g}

Recently, we demonstrated that diisopropoxytitanium(III) tetrahydroborate, $(>-O)_2$ TiBH₄, <u>1</u> is a useful reagent for the highly chemoselective 1,2-reduction of α , β -unsaturated carbonyl compounds to the

Entry	Substrate	Time (min)	Product ^a (a,ß-epoxyalcohol) syn : anti	Yield ^b (%)
1.		20	<u>10</u> ²ª 18 : 82	86
2.		45	<u>11</u> ^{2b} 2 : 98	93
3.		45	<u>12</u> ⁹ 1 : 99	91
4.		90	<u>13</u> ²ª 1 : 99	73°
5.		45	<u>14</u> ^{8c} 3 : 97	92
6.	Ph O Z	45	<u>15</u> ^{2e} 23 : 77	88
7.	Ph O Ph O <u>8</u>	90	<u>16</u> ^{2e,8d} 25 : 75	90
8.	O O O <u>9</u>	90	<u>17</u> ^{2e} 31 : 69	93

Table 1.

a. Ratio determined by GC (<u>10</u> - <u>14</u>) or ¹H NMR (<u>15</u> - <u>17</u>). b. Isolated yield. c. Yield based on recovered starting material.

corresponding allylic alcohols.³ In continuation of our work in this area, we report that the use of titanium(III) tetrahydroborate <u>1</u> for the reduction of acyclic and cyclic α,β -epoxy ketones constitutes a highly chemo- and stereoselective method for the synthesis of *anti-\alpha,\beta*-epoxy alcohols (eq. 1.).

The tetrahydroborate, 1 was generated *in situ* from diisopropoxytitanium dichloride⁴ and benzyltriethylammonium borohydride⁵ in dry CH₂Cl₂ at -20°C and was allowed to react with a number of acyclic and cyclic α,β -epoxy ketones in CH₂Cl₂ (-78° \rightarrow -20°C; 20-90 min) and the corresponding *anti*- α,β epoxy alcohols are obtained with high degree of stereoselectivity. The results are summarized in **Table 1**. While the reaction of 1 with unsubstituted cyclic α,β -epoxy ketone 2 gave the *anti*- α,β -epoxy alcohol 10 with 82% stereoselectivity, the substituted epoxy ketones 3, 4, and 5 afforded the *anti*- α,β -epoxy alcohols 11, 12, and 13 respectively in >98% stereoselectivity. Even the acyclic α,β -epoxy ketone 6 on reaction with 1 provided the *anti*- α,β -epoxy alcohol 14 with excellent selectivity (>97%). However, the phenyl substituted epoxy ketones 7 and 8 gave the *anti*- α,β -epoxy alcohols 15 and 16 respectively in 75-77% stereoselectivity.



Interestingly the methyl substituted epoxy ketone 2 on reaction with 1 gave the epoxy alcohol 17 with only moderate *anti*- selectivity (69%). The *anti*- selective reduction with titanium(III) tetrahydroborate 1 can be explained in terms of Cram's chelation model⁶ (Fig. 1). Titanium forms a tightly coordinated chelate with the epoxy ketone and subsequent intramolecular hydride transfer from the less hindered side to the carbonyl carbon affords the expected *anti*-isomer.

In summary, it has been demonstrated that diisopropoxytitanium(III) tetrahydroborate 1 is a convenient reagent for the stereoselective reduction of both cyclic and acyclic α,β -epoxy ketones to the corresponding *anti*- α,β -epoxy alcohols in very good yields.

EXPERIMENTAL SECTION

General Remarks. ¹H NMR spectra were recorded at 90 MHz and 300 MHz in CDCl₃. TLC were performed on 0.25-mm precoated silica plates (60F-254). Gas chromatographic (GLC) analyses of product mixtures and purified samples were performed on SE-30 on chromosorb W-HW 80/100 (3 mm x 2 m) column. All the reduction experiments were carried out under nitrogen. All α , β -epoxy ketones were prepared according to the literature procedures.⁷ The diastereomeric mixture of products were purified and isolated by flash chromatography on silica gel (tlc grade). A stock solution of diisopropoxytitanium dichloride in dry CH₂Cl₂ (11.8% w/v) was used.⁴ The ratio of diastereomers^{2.8} was determined by GLC (10 - 14) or ¹H NMR (15 - 17).

General Procedure for the Preparation of Diisopropoxytitanium(III) Tetrahydroborate, 1.

To a stirred solution of diisopropoxytitanium dichloride (2 mL, 1 mmol) was slowly added benzyltriethylammonium tetrahydroborate (0.414 g, 2 mmol) in dry CH_2Cl_2 (4 mL) under N₂ at -20°C, and the reaction mixture was stirred for 30 min and used as such for reductions.

General Procedure for the Reduction of α , β -Epoxyketones.

The solution of tetrahydroborate 1 obtained as above was cooled to -78°C and the α,β -epoxyketone, 2 (0.224 g, 2 mmol) in dry CH₂Cl₂ (2 mL) was added. The reaction mixture was brought to -20°C over a period of 15 min and stirred for 30 min. A solution of saturated K₂CO₃ (5 mL) was added and stirred for an additional 15 min (25°C). The reaction mixture was extracted with ether (3x20 mL) and it was washed with brine and dried (Na₂SO₄). Removal of solvent followed by flash chromatography on silica gel (tlc grade; ether-petroleum ether, 30:70) afforded the diastereomeric mixture of *syn* and *anti-\alpha,\beta-epoxyalcohol* 10 as an oil^{2e} (0.196 g, 86%). GC analysis of the purified product indicated the presence of *syn/anti* alcohols in a ratio of 18:82. IR (neat): ν 3450, 830 cm⁻¹; ¹H NMR (CDCl₃) δ 3.9 (m, CHOH, *syn-*), 4.15 (m, CHOH, *anti-*).

anti-2,3-Epoxy-3-methylcyclohexanol, <u>11</u>.^{2b} Yield: 93%; IR (neat): ν 3420, 845 cm⁻¹; ¹H NMR (CDCl₃): δ 1.4 (s, 3H), 1.45-2.10 (m, 6H), 2.3 (br, 1H, exchangeable, **OH**), 2.95 (s, 1H), 4.0 (t, J = 6.4 Hz, 1H).

anti-3,5,5-Trimethyl-2,3-epoxycyclohexanol, <u>12</u>.⁹ Yield: 91%; IR (neat): ν 3380, 825 cm⁻¹; ¹H NMR (CDCl₃): δ 0.9 (s, 3H), 0.95 (s, 3H), 1.35 (s, 3H), 1.95 (br, 1H, exchangeable OH), 2.95 (s, 1H), 4.15 (t, J = 6.4 Hz, 1H).

anti-1,2-Epoxy-p-menth-6-ol, 13.24 Yield: 73% (based on the starting material recovered); IR (neat): v 3380,

835 cm⁻¹; ¹H NMR (CDCl₃): δ 0.9 (d, J = 5.5 Hz, 6H), 1.4 (s, 3H), 3.1 (s, 1H), 3.5-4.1 (br m, 2H).

anti-3,4-Epoxy-4-methyl-2-pentanol, <u>14</u>.^{8c} Yield: 92%; IR (neat): ν 3350, 835 cm⁻¹; ¹H NMR (CDCL₃): δ 1.28 (br s, 6H), 1.35 (d, J = 6.3 Hz, 3H), 2.6 (d, 1H, OH), 3.45 (m, 1H).

syn- and anti-3,4-Epoxy-4-phenylbutan-2-ol, <u>15</u>.²⁶ Yield: 88%; IR (thin film): ν 3400, 900 cm⁻¹; ¹H NMR (CDCl₃): δ 1.32 (d, J = 6.4 Hz, 3H, CH₃, syn-), 1.36 (d, J = 6.6 Hz, 3H, CH₃, anti-), 3.87 (d, J = 2.3 Hz, 1H, PhCH, anti-), 3.96 (d, J = 2.1 Hz, 1H, PhCH, syn-).

syn- and anti-2,3-Epoxy-1,3-diphenylpropan-1-ol, <u>16</u>.^{2e,8d} Yield: 90%; IR (thin film): ν 3400, 900 cm⁻¹; ¹H NMR (CDCl₃): δ 4.00 (d, J = 2.1 Hz, 1H, PhCH, syn-), 4.14 (d, J = 2.1 Hz, 1H, PhCH, anti-), 4.70 (d, J = 4.9 Hz, 1H, CHOH, syn-), 4.98 (d, J = 2.9 Hz, 1H, CHOH, anti-).

syn- and anti-2, 3-Epoxy-1-phenylbutan-1-ol, <u>17</u>.^{2e} Yield: 93%; IR (neat): ν 3440, 835 cm⁻¹; ¹H NMR (CDCl₃): δ 1.26 (d, J = 5.1 Hz, CH₃, anti-), 1.31 (d, J = 5.1 Hz, CH₃, syn-), 4.50 (d, J = 5.4 Hz, CHOH, syn-), 4.74 (d, J = 3.4 Hz, CHOH, anti-).

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References

- 1. Oishi, T.; Nakata, T. Acc. Chem. Res., 1984, 17, 338.
- (a) Chautemps, P.; Pierre, J.-L. Tetrahedron, 1976, 32, 549. (b) Rucker, G.; Horster, H.; Cajewski, W. Synth. Commun., 1980, 10, 623. (c) Nakata, T.; Tanaka, T.; Oishi, T. Tetrahedron Lett., 1981, 22, 4723. (d) Li, K.; Hamann, L.G.; Koreeda, M. Tetrahedron Lett., 1992, 33, 6569. (e) Kawakami, T.; Shibata, I.; Baba, A.; Matsuda, H. J. Org. Chem., 1993, 58, 7608. (f) Taniguchi, M.; Fujii, H.; Oshima, K.; Utimoto, K. Tetrahedron, 1995, 51, 679. (g) Hojo, M.; Fujii, A.; Murakami, C.; Aihara, H.; Hosomi, A. Tetrahedron Lett., 1995, 36, 571.

- 3. Ravikumar, K.S.; Baskaran, S.; Chandrasekaran, S. J. Org. Chem., 1993, 58, 5981.
- 4. (a) Dijkgraaf, C.; Rousseau, J.P.G. Spectrochim. Acta., 1968, 24A, 1213.
 (b) Reetz, M.T.; Steinbach, R.; Kebeler, K. Angew. Chem., Suppl. 1982, 1899.
- (a) Brandstrom, A.; Junggren, U. Lamm, B. *Tetrahedron Lett.*, **1972**, 3173.
 (b) Ravikumar, K.S.; Chandrasekaran, S. J. Org. Chem., **1996**, 61, 826.
- 6. Cram, D.J.; Elhafez, F.A.A. J. Am. Chem. Soc., 1952, 74, 5828.
- (a) Cowper, R.M.; Davidson, L.H. Org. Synth. Coll. Vol. II, 1943, 480. (b) Wasson, R.L.; House, H.O. Org. Synth., 1957, 37, 58. (c) Noma, Y.; Nonomura, S.; Ueda, H.; Tatsumi, C. Agr. Biol. Chem., 1974, 38(4), 735. (d) Julia, S.; Guixer, J.; Masana, J.; Rocas, J.; Colonna, S.; Annuziata, R.; Molinari, H. J. Chem. Soc., Perkin Trans. I, 1982, 1317.
- (a) Takai, K.; Oshima, K.; Nozaki, H. Bull. Chem. Soc. Jpn., 1983, 56, 3791.(b) Grandi, R.; Pagnoni, U.M.; Trave, R.; Garanti. L. Tetrahedron, 1974, 30, 4037. (c) Pierre, J.-L.; Chautemps, P.; Arnaud, P. Bull. Soc. Chim. Fr., 1969, 1317. (d) Dickinson, J.M.; Murphy, J.A.; Patterson, C.W.; Wooster, N.F. J. Chem. Soc., Perkin Trans. I, 1990, 1179.
- 9. Magnusson, G.; Thoren, S. J. Org. Chem., 1973, 38(7), 1380.

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