[Chem. Pharm. Bull. 32(4)1411—1415(1984)]

Stereoselective Reduction of α-Methyl-β-hydroxy Ketones with Zinc Borohydride

TADASHI NAKATA,* YŌICHIRŌ TANI, MASAYOSHI HATOZAKI, and TAKESHI OISHI*

The Institute of Physical and Chemical Research (RIKEN), Wako-shi, Saitama 351, Japan

(Received August 4, 1983)

Zinc borohydride reduction of α-methyl-β-hydroxy ketones **3** produced the *erythro*-2-methyl-1,3-glycol derivatives **4** with high stereoselectivity. The selectivity was particularly high when an olefinic group was conjugated to the carbonyl group. Reduction of the same system with $NaBH_4$ and $LiBH_4$ showed poor selectivity.

Keywords——stereoselective reduction; α-methyl-β-hydroxy ketone; *erythro*-2-methyl-1,3-glycol; zinc-mediated transition state; zinc borohydride; sodium borohydride; lithium borohydride

We recently demonstrated that zinc borohydride [$Zn(BH_4)_2$] reduction of α-methyl-β-keto esters **1** proceeded stereoselectively to give the *erythro* β-hydroxy esters, particularly when an olefinic group was conjugated to the carbonyl group.[1] The α,β-epoxy ketones **2** were also found to give the corresponding *erythro* isomers on $Zn(BH_4)_2$ reduction.[2] In the latter case, excellent stereoselectivity was always obtained regardless of the substitution pattern of the epoxide ring.

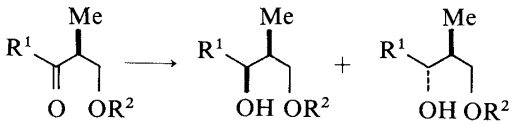
1 2

Chart 1

Based on these findings, we carried out the $Zn(BH_4)_2$ reduction of β-hydroxy and β-alkoxy ketones **3a**—**e**,[3] which are structurally related to the β-keto ester **1**.[4] $NaBH_4$ and $LiBH_4$ were also used to compare the selectivity of the reductions. The results are shown in Table I. As was expected, the selectivity leading to the *erythro* isomers **4** was excellent when R^1 was a phenyl or vinyl group but was almost absent when R^1 was a β-phenethyl group.

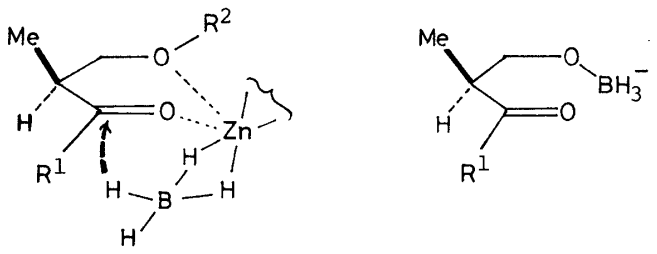
In the case of the β-methoxy ketone **3a**, reduction is expected to proceed through the same transition state ia as suggested for the reduction of **1**[1] or **2**.[2] The rather unsatisfactory selectivity obtained in the reduction of **3b** may be attributable to the unfavorable coordination of the MEM ($CH_3OCH_2CH_2OCH_2$–) group to $Zn(BH_4)_2$. Even in the reduction of **3c** and **3d**, where the β-hydroxyl group is not masked, the same type of transition state ib should be operative. Formation of the borate ester ii or its equivalent may not be involved, since, although $Zn(BH_4)_2$ reduction proceeds quite rapidly and finishes within 5 min, no appreciable hydrogen gas evolution was observed within 5 min when $Zn(BH_4)_2$ was added even in ethanol at the reduction temperature (0 °C).

TABLE I. Reduction of β-Alkoxy or β-Hydroxy Ketones **3** with $Zn(BH_4)_2$, $NaBH_4$, and $LiBH_4$



	Ketone **3**		Alcohol; *erythro*-**4** : *threo*-**5** (yield)[a]		
	R^1	R^2	$Zn(BH_4)_2$[b]	$NaBH_4$[c]	$LiBH_4$[b]
a:	Ph	Me	33 : 1[d] (99%)	1.8 : 1[d] (97%)	3 : 1[d] (95%)
b:	Ph	MEM	8.9 : 1[d] (98%)	1.5 : 1[d] (96%)	2.3 : 1[d] (99%)
c:	Ph	H	25 : 1[e] (95%)	3.5 : 1[e,f] (98%)	6 : 1[e] (97%)
d:	Me	H	25 : 1[e] (91%)	—	—
	CH_2				
e:	$PhCH_2CH_2$	H	1.3 : 1[g] (97%)	—	—

a) Combined isolated yield.
b) In ether at 0 °C.
c) In MeOH at 0 °C.
d) Ratio determined after separation by preparative TLC.
e) Ratio determined by NMR (C-3 H signal).
f) **4**:**5**=2.5:1 (reflux in EtOH)[5].
g) Ratio determined from the NMR data of the isopropylidene derivative.[1]



ia : R^2=Me
ib : R^2=H

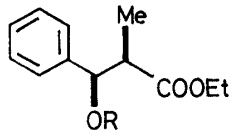
ii

Chart 2

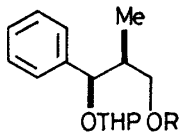
The selectivity was almost lost when the reduction was carried out using $NaBH_4$ in methanol (Table I). In order to avoid the suspected unfavorable solvent effect due to methanol, ether-soluble $LiBH_4$ was used in place of $NaBH_4$. However, the selectivity was not significantly improved. This supports the previous suggestion that the zinc-mediated transition state i is the major contributor to the *erythro* selective reduction.

Materials

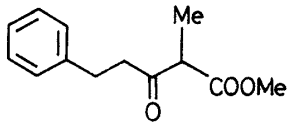
Authentic samples of the *erythro* alcohols **4a**—**c** were all derived from the known *erythro*-2-methyl-3-hydroxy ester **6**.[1] Tetrahydropyranylation of **6** followed by $LiAlH_4$ reduction afforded **8**. Methylation of **8** with MeI and KH, followed by acid-catalyzed deprotection, yielded **4a**. The same ester **6** was reduced with $LiAlH_4$ to yield **4c**, whose primary hydroxyl group was selectively converted to the MEM ether to afford **4b**. Preparation of the authentic *erythro* glycols **4d**[6] and **4e**[1] has already been reported. The ketones **3a** and **3d** were prepared by Jones and pyridinium dichromate (PDC) oxidations of *erythro*-**4a** and *erythro*-**4d**, respectively. Reformatsky reaction of benzaldehyde and ethyl α-bromopropionate[7] followed by $LiAlH_4$ reduction afforded a mixture of **4c** and **5c**. The ketone **3c** was prepared from this mixture by selective oxidation of the secondary alcohol in the presence of the primary alcohol with



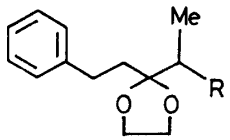
6 : R=H
7 : R=THP



8 : R=H
9 : R=Me



10



11 : R=COOMe
12 : R=CH_2OH

Chart 3

bis(tri-*n*-butyltin) oxide.[8] The ketone **3b** was obtained by protection of **3c** with MEMCl. The ketone **3e** was prepared from **10**[1] by acetalization, $LiAlH_4$ reduction, and acid-catalyzed deacetalization.

Experimental

Infrared (IR) spectra were measured on a JASCO A-102 spectrometer, nuclear magnetic resonance (NMR) spectra on JEOL JNM-PLX 60, JNM-FX 60, and JNM-FX 400 instruments with tetramethylsilane as an internal standard, and mass spectra (MS) on Hitachi RMU-6M and M-80 double-focusing spectrometers.

Preparation of $Zn(BH_4)_2$–Ether Solution——Gensler's procedure[9] for the preparation of $Zn(BH_4)_2$–ether solution was slightly modified as follows. $ZnCl_2$ (*ca.* 10 g) in a 200 ml flask was fused 3 or 4 times under reduced pressure and then anhydrous ether (*ca.* 100 ml) was added. The mixture was refluxed for 1—2 h under argon and allowed to stand at 23 °C. The supernatant sat. solution of $ZnCl_2$ (0.69 M)[10] in ether (80 ml; 55 mmol) was added to a stirred suspension of $NaBH_4$ (4 g; 106 mmol) in anhydrous ether (300 ml). The mixture was stirred for 2 d and stored at room temperature under argon. The supernatant solution was used for reduction.

General Procedure for $Zn(BH_4)_2$ Reduction of the Ketones 3——A solution of $Zn(BH_4)_2$ in ether (6 ml) was added to a solution of the ketone **3** (100—130 mg) in ether (5 ml) at 0 °C and the mixture was stirred for 1 h at this temperature. The reduction was almost completed within 5 min. The reaction was quenched by the successive addition of water and 10% aq. HCl, and the mixture was extracted with ether. The extract was washed with sat. aq. $NaHCO_3$ and sat. aq. NaCl, then dried over $MgSO_4$, and concentrated. The crude product was purified by preparative silica gel thin layer chromatography (TLC). Yields and *erythro/threo* ratios are shown in Table I.

***erythro*-3-Methoxy-2-methyl-1-phenyl-1-propanol 4a**——A mixture of ethyl *erythro*-3-hydroxy-2-methyl-3-phenylpropionate **6**[1] (3.0 g), 2,3-dihydropyran (1.7 ml) and *p*-TsOH (120 mg) was stirred for 70 min at room temperature. The mixture was diluted with ether and washed with 10% aq. Na_2CO_3 and then sat. aq. NaCl. The ether solution was dried over $MgSO_4$ and concentrated to give an oil, which was chromatographed on silica gel. Elution with hexane–ether afforded **7** (3.3 g; 78% yield). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720. NMR ($CDCl_3$) δ: 1.04 (t, J=7 Hz, $COOCH_2C\underline{H}_3$), 1.35 (d, J=7 Hz, Me), 3.94 (q, J=7 Hz, $COOC\underline{H}_2CH_3$), 4.88 (d, J=7.7 Hz, C$\underline{H}$–OTHP). $LiAlH_4$ (500 mg) was added to a solution of **7** (3.3 g) in ether (30 ml) under ice-cooling. After the mixture had been stirred at room temperature overnight, water (0.5 ml), 15% aq. NaOH (0.5 ml), and water (1.5 ml) were succesively added. The mixture was stirred for *ca.* 15 min and then $MgSO_4$ was added. The resulting suspension was filtered and the filtrate was concentrated to give an oil, which was chromatographed on silica gel. Elution with hexane–ether afforded **8** (2.8 g; 99% yield). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3475. NMR ($CDCl_3$) δ: 0.72 (d, J=7 Hz; Me), 4.01 (d, J=4.3 Hz; C$\underline{H}$–OTHP). A solution of **8** (1.387 g) in THF (6 ml) was added to a suspension of excess KH (washed with hexane) in THF (10 ml). Then, MeI (0.42 ml) was added to the mixture at 0 °C. After 1 h of stirring, water was added and the mixture was extracted with ether. The extract was washed with sat. aq. NaCl, dried over $MgSO_4$, and concentrated to give **9** (1.355 g; 93% yield). NMR ($CDCl_3$) δ: 1.05 (d, J=7 Hz, Me), 3.26 (s, OMe), 4.69 (d, J=6.5 Hz, C$\underline{H}$–OTHP). The methoxy ether **9** (1.355 g) was dissolved in a mixture of methanol (55 ml), water (11 ml), and 10 drops of conc. HCl. The mixture was stirred at room temperature overnight and then concentrated. The residue was dissolved in ether and the ether solution was washed with sat. aq. NaCl, then dried over $MgSO_4$, and concentrated to give an oil, which was subjected to preparative TLC [silica gel, hexane–ether (1 : 1)] to afford **4a** (742 mg; 80% yield). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3630,

3520. NMR ($CDCl_3$) δ: 0.85 (d, $J=7$ Hz, Me), 3.37 (s, OMe), 4.88 (t, $J_{1,2}=J_{1,OH}=4$ Hz, CHOH). High resolution MS Calcd for $C_{11}H_{16}O_2$: 180.1150. Found: 180.1164 (M^+).

***erythro*-2-Methyl-3-phenyl-1,3-propanediol 4c**——A suspension of **6** (16.4 g) and $LiAlH_4$ (2.3 g) in ether (250 ml) was stirred at room temperature overnight. After the successive addition of water (2.3 ml), 15% aq. NaOH (2.3 ml), and water (6.9 ml), $MgSO_4$ was added. The resulting dried suspension was filtered and the filtrate was concentrated to give **4c** (13.89 g). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3620, 3530, 3400. NMR ($CDCl_3$) δ: 0.79 (d, $J=7$ Hz, Me), 4.87 (d, $J=4$ Hz, CHOH). High resolution MS Calcd for $C_{10}H_{14}O_2$: 166.0994. Found: 166.0998 (M^+).

***erythro*-2-Methyl-3-phenyl-1,3-propanediol 1-MEM Ether 4b**——Diisopropylethylamine (186 μl) and β-methoxyethoxymethyl chloride (MEMCl) (122 μl) were added to a solution of **4c** (89 mg) in CH_2Cl_2 (3 ml). The mixture was stirred for 1 h at room temperature and then diluted with ether. The solution was washed with 10% aq. HCl, sat. aq. $NaHCO_3$ and sat. aq. NaCl, then dried over $MgSO_4$, and concentrated. The residual oil was subjected to preparative TLC [silica gel, hexane–ether (1 : 10)] to afford **4b** (53 mg; 39% yield). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600, 3480. NMR ($CDCl_3$) δ: 0.84 (d, $J=6.1$ Hz, Me), 3.34 (s, OMe), 4.72 (s, $-OCH_2O-$). High resolution MS Calcd for $C_{10}H_{13}O_3$: 165.0915. Found: 165.0960 (M^+-MEM).

3-Methoxy-2-methylpropiophenone 3a——Jones reagent (2 ml) was added to a solution of **4a** (618 mg) in acetone (10 ml) under ice-cooling. After 8 min of stirring, isopropanol was added to the mixture to decompose excess Jones reagent, then the solvent was removed. Water was added to the residue and the mixture was extracted with ether. The extract was washed with sat. aq. $NaHCO_3$ and sat. aq. NaCl, then dried over $MgSO_4$, and concentrated to give an oil, which was subjected to preparative TLC [silica gel, hexane–ether (1 : 1)] to afford **3a** (559 mg; 91% yield). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1685. NMR ($CDCl_3$) δ: 1.21 (d, $J=6.6$ Hz; Me), 3.32 (s, OMe). High resolution MS Calcd for $C_{11}H_{14}O_2$: 178.0994. Found: 178.0992 (M^+).

2,4-Dimethyl-3-oxo-4-penten-1-ol 3d——A mixture of the diol **4d**[6] (355 mg) and pyridinium dichromate (PDC, 1.5 g) in CH_2Cl_2 (10 ml) was stirred for 1 h at room temperature. The resulting mixture was diluted with ether and passed through a Florisil column. The eluate was evaporated, and the residue was subjected to preparative TLC [silica gel, hexane–ether (1 : 4)] to afford **3d** (133 mg; 38% yield). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600, 3525, 1665. NMR ($CDCl_3$) δ: 1.13 (d, $J=7$ Hz, Me), 1.90 (br s, C-4 Me), 5.83 (br, C-5 Ha), 6.00 (s, C-5 Hb). MS *m/z*: 128 (M^+).

3-Hydroxy-2-methylpropiophenone 3c——Bis(tri-*n*-butyltin) oxide[8] [$(n\text{-}Bu_3Sn)_2O$] (15.65 ml) and a solution of bromine (1.98 ml) in CH_2Cl_2 (50 ml) were added successively to a solution of a mixture of **4c** and **5c** (4.946 g) (prepared from benzaldehyde and ethyl α-bromopropionate by means of the Reformatsky reaction[7] followed by $LiAlH_4$ reduction) in CH_2Cl_2 (50 ml). The mixture was stirred for 3.5 h at room temperature under argon. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel. Elution with hexane–EtOAc (1 : 1) afforded **3c** (3.42 g; 70% yield). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600, 3530, 1675. NMR ($CDCl_3$) δ: 1.23 (d, $J=7$ Hz, Me). High resolution MS Calcd for $C_{10}H_{12}O_2$: 164.0837. Found: 164.0861 (M^+).

3-Hydroxy-2-methylpropiophenone MEM Ether 3b——Diisopropylethylamine (0.83 ml) and MEMCl (0.54 ml) were added to a solution of **3c** (518 mg) in CH_2Cl_2 (5 ml), and the mixture was stirred for 20 h at room temperature. After the same work-up as described for the preparation of **4b**, the residue was subjected to preparative TLC (silica gel, hexane–EtOAc (1 : 1)] to give **3b** (683 mg; 86% yield). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1685. NMR ($CDCl_3$) δ: 1.21 (d, $J=7$ Hz, Me), 3.36 (s, OMe), 4.67 (s, $-OCH_2O-$). High resolution MS Calcd for $C_{11}H_{13}O_2$: 177.0915. Found: 177.0924 ($M^+-OCH_2CH_2OMe$).

2-Methyl-3-oxo-5-phenyl-1-pentanol 3e——Ethylene glycol (1 ml) and a trace of *p*-TsOH were added to a solution of **10**[1] (352 mg) in benzene (15 ml) and the mixture was refluxed overnight using a Dean–Stark apparatus. The mixture was diluted with ether and the organic layer was washed with 10% aq. Na_2CO_3 and sat. aq. NaCl, then dried over $MgSO_4$, and evaporated. The residue was subjected to preparative TLC [silica gel, hexane–ether (1 : 1)] to afford **11** (206 mg; 48% yield). NMR ($CDCl_3$) δ: 1.22 (d, $J=7$ Hz, Me), 3.67 (s, COOMe), 4.00 (s, $-OCH_2CH_2O-$). A suspension of $LiAlH_4$ (200 mg) and **11** (206 mg) in ether (15 ml) was stirred at room temperature overnight. After the successive addition of water (0.2 ml), 15% aq. NaOH (0.2 ml), water (0.6 ml), and $MgSO_4$, the suspension was filtered and the filtrate was concentrated. The residue was subjected to preparative TLC (silica gel, ether) to afford **12** (124 mg; 67% yield). NMR ($CDCl_3$) δ: 0.98 (d, $J=7$ Hz, Me), 4.00 (s, $-OCH_2CH_2-$). A mixture of **12** (50 mg) and *p*-TsOH (a trace) in acetone (10 ml) was stirred for 3 h at room temperature. The solvent was removed and the residue was dissolved in ether. The ether solution was washed with 10% aq. Na_2CO_3 and sat. aq. NaCl, then dried over $MgSO_4$, and concentrated to give an oil, which was subjected to preparative TLC [silica gel, hexane–ether (1 : 3)] to afford **3e** (26 mg; 63% yield). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3550, 1700. NMR ($CDCl_3$) δ: 1.08 (d, $J=7$ Hz; Me), 2.86 (s, CH_2CH_2Ar). High resolution MS Calcd for $C_{12}H_{16}O_2$: 192.1150. Found: 192.1164 (M^+).

Acknowledgement This work was supported in part by a Grant-in-Aid (No. 557495) for Scientific Research from the Ministry of Education, Science and Culture.

References and Notes

1) T. Nakata and T. Oishi, *Tetrahedron Lett.*, **21**, 1641 (1980).

2) T. Nakata, T. Tanaka, and T. Oishi, *Tetrahedron Lett.*, **22**, 4723 (1982).
3) This work was presented at the 101st Annual Meeting of the Pharmaceutical Society of Japan at Kumamoto, April, 1981. Abstracts of Papers, p. 452. This work was also presented at the 41st Symposium on the Synthetic Organic Chemistry at Tokyo, June, 1982. Proceeding, p. 29.
4) Reduction of α-hydroxy ketones with $Zn(BH_4)_2$ has also been extensively studied in this laboratory. T. Nakata, T. Tanaka, and T. Oishi, *Tetrahedron Lett.*, **24**, 2653 (1983).
5) S. Yamada and K. Koga, *Tetrahedron Lett.*, **1967**, 1711.
6) T. Nakata, M. Fukui, H. Ohtsuka, and T. Oishi, *Tetrahedron Lett.*, **24**, 2661 (1983); *Tetrahedron*, in press.
7) R. L. Shriner, "Organic Reactions," Vol. 1, John Wiley & Sons, Inc., New York, 1942, p. 1.
8) K. Saigo, A. Morikawa, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **49**, 1656 (1976).
9) W. J. Gensler, F. Johnson, and A. D. B. Sloan, *J. Am. Chem. Soc.*, **82**, 6074 (1960).
10) H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. Am. Chem. Soc.*, **95**, 3310 (1973).