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Highly *syn*-Selective Reduction of α-Phenylthio-β-methoxy Ketones with Super-hydride

MASAYUKI SHIMAGAKI,* ATSUSHI SUZUKI, TADASHI NAKATA,
and TAKESHI OISHI*

*RIKEN (The Institute of Physical and Chemical Research)
Wako-shi, Saitama 351-01, Japan*

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Reduction of α-phenylthio-β-methoxy ketones **3a**—**c** with Super-hydride gave *syn*-**4a**—**c**, key intermediates to the thermodynamically less stable (*Z*)-allyl alcohol derivatives **5** and *cis*-epoxides **6**, with high stereoselectivity.

Keywords——*syn*-selective reduction; α-phenylthio-β-methoxy ketone; *syn*-α-phenylthio-β-methoxy alcohol; Super-hydride; chelation model; Felkin–Anh model; (*Z*)-allyl alcohol; *cis*-epoxide

In the previous paper,[1] we reported that the reduction of α-methylthio- or α-phenylthioketones **1** with L-Selectride (LiBH(*sec*-Bu)$_3$) afforded *syn*-alcohols **2** with high selectivity, while reduction with Zn(BH$_4$)$_2$ gave *anti*-alcohol **2** when R^1 was a phenyl or a cinnamyl group. This paper deals with the reduction of ketones **3** having another oxygen function at the β-position with respect to the keto group in **1**. This work was undertaken with the aim of obtaining *syn*-**4** which would be convertible stereoselectively to (*Z*)-allyl alcohols **5**[2] or the corresponding *cis*-epoxides **6**,[3] potential synthons in organic synthesis. Several metal hydrides were used in the present reduction. The results are summarized in Table I.

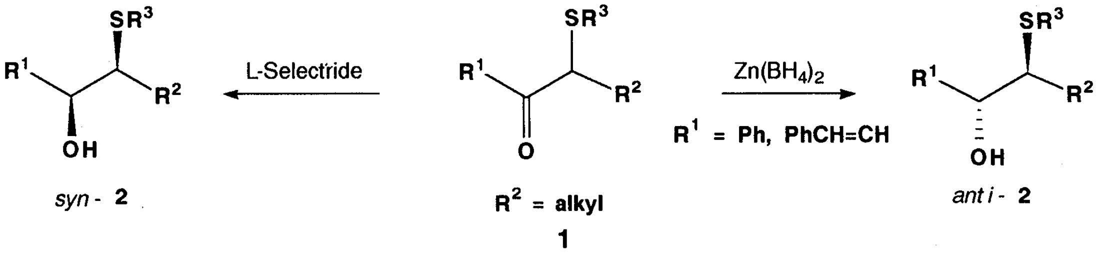

Chart 1

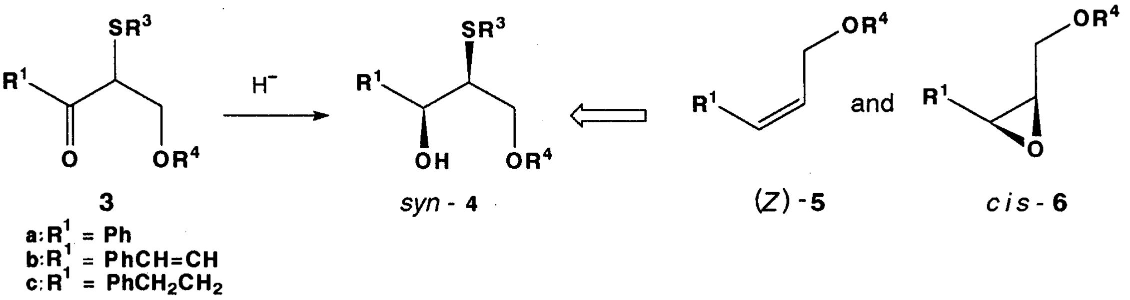

Chart 2

Table I. Reduction of α-Phenylthio-β-methoxy Ketones **3a**—**c** to α-Phenylthio-β-methoxy Alcohols **4a**—**c**

R^1	Ph (**4a**)		PhCH=CH (**4b**)		$PhCH_2CH_2$ (**4c**)	
	syn:*anti*	(yield, %)	*syn*:*anti*	(yield, %)	*syn*:*anti*	(yield, %)
$Zn(BH_4)_2$/ether	97: 3[a]	(87)	87:13[a]	(73)	74:26[a]	(64)
$Ca(BH_4)_2$/MeOH	92: 8	(49)	89:11	(55)	85:15	(74)
$Ca(BH_4)_2/CH_2Cl_2$	89:11	(78)	68:32	(66)	69:31	(73)
L-Selectride/THF	81:19	(41)	99: 1	(52)	95: 5	(59)
Super-hydride/THF	>99: 1	(80)	97: 3	(57)	92: 8	(58)

a) The ratio was determined by 400 MHz NMR spectroscopy.

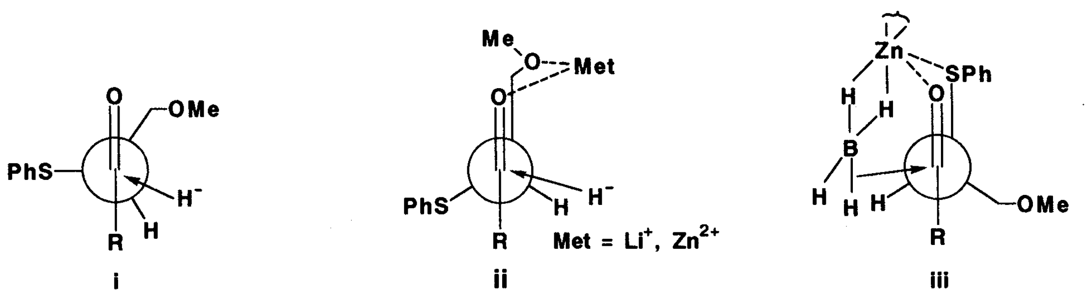

Chart 3

Reduction of **3a**—**c** with $Zn(BH_4)_2$ produced *syn*-**4a**—**c** as a main product, but the selectivity was unsatisfactory except when R^1 is a phenyl group. Comparable results were obtained in the reduction with $Ca(BH_4)_2$.[4] On the other hand, reduction with L-Selectride or Super-hydride ($LiBHEt_3$) produced *syn*-compounds with high selectivity in most cases.[5]

The transition state leading to *syn*-**4** may be illustrated as either Felkin–Anh model i or metal-mediated six-membered cyclic model ii. The metal-mediated sulfur-containing five-membered transition state iii would afford the undesired *anti*-isomers.

In the reduction with L-Selectride or Super-hydride, the transition states i and ii may both contribute, but participation of the transition state iii may not be important in these cases since the coordinating ability of a Li cation to a divalent sulfide is known to be weak. On the other hand, in the reduction with $Zn(BH_4)_2$ the contribution of the transition state iii leading to the *anti*-isomer can not be ignored, since a Zn cation possesses much greater affinity for divalent sulfide than for the Li cation, which causes decrease of the *syn*-selectivity. In the case where R is a phenyl group, it is highly expected from previous work[1] that the role of ii would be dominant in agreement with the excellent *syn*-selectivity in this reduction.

The present findings that *syn*-**4a**—**c** were synthesized with high selectivity by using L-Selectride or Super-hydride reduction of ketones **3** means that a route to (*Z*)-**5**[2] or *cis*-**6**[3] whose syntheses are rather difficult by other means, has been newly opened.

Experimental

Nuclear magnetic resonance (NMR) spectra were measured on either a JEOL FX-60 (60 MHz) or a GX-400 (400 MHz) instrument in $CDCl_3$. High-resolution mass spectra (high-MS) were taken with a Hitachi JMS-01SG spectrometer.

3-Methoxy-1-phenyl-2-phenylthiopropan-1-one (3a)——1-Phenyl-1-trimethylsilyloxyethene[6] (0.96 g, 5.00 mmol) in dry CH_2Cl_2 (5 ml) was added to a mixture of chloromethyl methyl ether (1.14 ml, 15 mmol) and $ZnBr_2$ (4 mg) in CH_2Cl_2 (4 ml) at 0 °C under an argon atmosphere and the mixture was stirred at room temperature for 1 h. After addition of brine under ice cooling, the mixture was diluted with ether, washed with brine, and dried over Na_2SO_4. The solvent was evaporated and the residue was chromatographed on silica gel (23 g) with *n*-hexane–AcOEt (10 : 1) as an eluent to give 3-methoxy-1-phenylpropan-1-one (0.36 g, 45%). High-MS m/z Calcd for $C_{10}H_{12}O_2$: 164.0836. Found: 164.0827. NMR (400 MHz) δ: 3.24 (1H, t, J=6.4 Hz, one of $C\underline{H}_2CH_2O$), 3.25 (1H, t, J=6.4 Hz, one of $C\underline{H}_2CH_2O$), 3.38 (3H, s, Me), 3.83 (1H, t, J=6.4 Hz, one of $CH_2C\underline{H}_2O$), 3.93 (1H, t, J=6.4 Hz, one of $CH_2C\underline{H}_2O$). 5-Methoxy-1-phenylpent-1-en-3-one (40% yield. High-MS m/z Calcd for $C_{12}H_{14}O_2$: 190.0993. Found: 190.1013. NMR δ: 2.93 (2H, t, J=5.9 Hz, $C\underline{H}_2CH_2O$), 3.37 (3H, s, Me), 3.75 (2H, t, J=5.9 Hz, $CH_2C\underline{H}_2O$), 6.74 (1H, d, J=16.2 Hz, $PhCH{=}C\underline{H}$), 7.59 (1H, d, J=16.2 Hz, $PhC\underline{H}{=}CH$)) and 5-methoxy-1-phenylpentan-3-one (40% yield. High-MS m/z Calcd for $C_{12}H_{16}O_2$: 192.1150. Found: 192.1194. NMR δ: 2.67 (2H, t, J=6.2 Hz, $C\underline{H}_2CH_2OMe$), 2.89 (4H, br, $PhCH_2CH_2$), 3.37 (3H, s, Me), 3.69 (2H, t, J=6.2 Hz, $CH_2C\underline{H}_2OMe$)) were prepared in the same manner as described above.

Freshly prepared phenylsulfenyl chloride (13 mmol) in tetrahydrofuran (THF) (4 ml) was added slowly to an enol silyl ether[6] [prepared from 3-methoxy-1-phenylpropan-1-one (10 mmol) as described above] in THF (4 ml) at −65 °C under an argon atmosphere. The reaction temperature was gradually raised to 13 °C over 7.5 h with stirring. After addition of brine under ice cooling, the mixture was diluted with ether, washed with sat. $NaHCO_3$ and brine, and dried over Na_2SO_4. The solvent was evaporated and the residue was chromatographed on silica gel (120 g) with n-hexane–AcOEt (15 : 1) as an eluent to give **3a** (2.34 g, 87%). High-MS m/z Calcd for $C_{16}H_{16}O_2S$: 272.0870. Found: 272.0872. NMR (400 MHz) δ: 3.37 (3H, s, Me), 3.76 (1H, dd, J=9.5, 5.6 Hz, one of CH_2), 3.95 (1H, dd, J=9.5, 8.3 Hz, one of CH_2), 4.67 (1H, dd, J=8.3, 5.6 Hz, $C\underline{H}CH_2$). Compounds **3b** and **3c** were prepared in the same manner as described above. **3b**: 73% yield. High-MS m/z Calcd for $C_{18}H_{18}O_2S$: 298.1025. Found: 298.1017. NMR δ: 3.38 (3H, s, Me), 3.64—4.20 (3H, m, $CHCH_2$), 6.99 (1H, d, J=15.9 Hz, $PhCH{=}C\underline{H}$), 7.65 (1H, d, J=15.9 Hz, $PhC\underline{H}{=}CH$). **3c**: 64% yield. High-MS m/z Calcd for $C_{18}H_{20}O_2S$: 300.1182. Found: 300.1171. NMR δ: 2.94 (4H, br, $PhCH_2CH_2$), 3.31 (3H, s, Me), 3.56—3.96 (3H, m, $CHCH_2$).

Reduction of 3a with $Zn(BH_4)_2$ in Ether——An ethereal solution of $Zn(BH_4)_2$ (0.147 M, 10 ml) was added to **3a** (400 mg, 1.47 mmol) in dry ether (8 ml) at 0 °C and the mixture was stirred at 0 °C for 7 h. After addition of brine, the mixture was stirred at room temperature for 0.5 h and dried over Na_2SO_4. The solvent was evaporated and the residue was subjected to preparative thin layer chromatography (pTLC) on silica gel with n-hexane–AcOEt (7 :1) to give **4a** (351 mg, 87%, *syn* : *anti*=97 : 3). High-MS m/z Calcd for $C_{16}H_{18}O_2S$: 274.1026. Found: 274.1025. *syn*-**4a**: NMR (400 MHz) δ: 3.34 (3H, s, Me), 4.98 (1H, br d, J=4.4 Hz, $C\underline{H}OH$). *anti*-**4a**: NMR (400 MHz) δ: 3.37 (3H, s, Me), 4.98 (1H, d, $C\underline{H}OH$). Reduction of **3b** and **3c** was carried out in the same manner as noted above to give *syn*- and *anti*-**4b** (high-MS m/z Calcd for $C_{18}H_{20}O_2S$: 300.1183. Found: 300.1204) and **4c** (high-MS m/z Calcd for $C_{18}H_{22}O_2S$: 302.1339. Found: 302.1346). *syn*-**4b**: NMR (400 MHz) δ: 3.37 (3H, s, Me), 4.60 (1H, br, $C\underline{H}OH$), 6.36 (1H, dd, J=15.9, 6.1 Hz, $PhCH{=}C\underline{H}$), 6.70 (1H, d, J=15.9 Hz, $PhC\underline{H}{=}CH$). *anti*-**4b**: NMR (400 MHz) δ: 3.37 (3H, s, Me), 4.70 (1H, br, $C\underline{H}OH$), 6.26 (1H, dd, J=15.9, 6.1 Hz, $PhCH{=}C\underline{H}$), 6.69 (1H, d, J=15.9 Hz, $PhC\underline{H}{=}CH$). *syn*-**4c**: NMR (400 MHz) δ: 3.36 (3H, s, Me), 3.94 (1H, br, $C\underline{H}OH$). *anti*-**4c**: NMR δ: 3.35 (3H, s, Me), 3.84 (1H, br, $C\underline{H}OH$).

Reduction of 3a with $Ca(BH_4)_2$ in MeOH——A THF solution of $Ca(BH_4)_2$ (0.5 M, 0.27 ml) was added to **3a** (22 mg, 0.067 mmol) in MeOH (2.2 ml) at −30 °C and the mixture was stirred at −30 °C for 1 h. After addition of brine, the mixture was stirred at room temperature for 0.5 h and dried over Na_2SO_4. The solvent was evaporated and the residue was subjected to pTLC on silica gel with n-hexane–AcOEt (7 : 1) to give **4a** (27 mg, 49%, *syn* : *anti*=92 : 8). Reduction of **3b** and **3c** was carried out in the same manner as described above to give *syn*- and *anti*-**4b**, **c**.

Reduction of 3a with $Ca(BH_4)_2$ in CH_2Cl_2——A THF solution of $Ca(BH_4)_2$ (0.5 M, 0.80 ml) was added to **3a** (54 mg, 0.20 mmol) in CH_2Cl_2 (4 ml) at −30 °C and the mixture was stirred at −30 °C for 1 h. After addition of brine, the mixture was stirred at room temperature for 0.5 h and dried over Na_2SO_4. The solvent was evaporated and the residue was subjected to pTLC on silica gel with n-hexane–AcOEt (7 : 1) to give **4a** (43 mg, 78%, *syn* : *anti*=89 : 11). Reduction of **3b** and **3c** was carried out in the same manner as described above to give *syn*- and *anti*-**4b**, **c**.

Reduction of 3a with L-Selectride in THF——A THF solution of L-Selectride (1.0 M, 0.55 ml) was added to **3a** (50 mg, 0.18 mmol) in THF (2.5 ml) at −72 °C and the reaction temperature was gradually raised to 0 °C. After addition of brine, the mixture was diluted with ether, washed with 10% NaOH and brine, and dried over Na_2SO_4. The solvent was evaporated and the residue was subjected to pTLC on silica gel with n-hexane–AcOEt (7 : 1) to give **4a** (21 mg, 41%, *syn* : *anti*=81 : 19). Reduction of **3b** and **3c** was carried out in the same manner as described above to give *syn*- and *anti*-**4b**, **c**.

Reduction of 3a with Super-hydride in THF——A THF solution of Super-hydride (1.0 M, 0.90 ml) was added to **3a** (49 mg, 0.18 mmol) in THF (1.5 ml) at −65 °C and the reaction temperature was gradually raised to −25 °C. After addition of brine, the mixture was diluted with ether, washed with 10% NaOH and brine, and dried over Na_2SO_4. The solvent was evaporated and the residue was subjected to pTLC on silica gel with n-hexane–AcOEt (7 : 1) to give **4a** (40 mg, 80%, *syn* : *anti*= >99 : 1). Reduction of **3b** and **3c** was carried out in the same manner as described above to give *syn*- and *anti*-**4b**, **c**.

References and Notes

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5) Quite unexpectedly, selectivity was poor when **4a** was reduced with L-Selectride. The reason for this is not known at present.
6) I. Fleming and I. Patterson, *Synthesis*, **1979**, 736.