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HIGHLY STEREOSELECTIVE REDUCTION OF α-METHYLTHIO AND α-PHENYLTHIO KETONES ---SYNTHESIS OF syn- AND anti-β-METHYLTHIO- AND β-PHENYLTHIOALCOHOLS---

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Summary: Reduction of α-methylthio and α-phenylthio ketones 1 with L-Selectride gave syn-alcohols 2 in high stereoselectivity except when R^1 was cyclohexyl group, while reduction with $Zn(BH_4)_2$ gave the isomeric anti-alcohols 3 provided R^3 was methyl group.

In view of the importance of syn- and anti-β-alkylthioalcohols 2 and 3 as potential intermediates for stereochemically pure olefins[1] and epoxides 4 and 5,[2] aldol-type condensation of alkylthioallyl derivatives with aldehydes, has been widely investigated.[3] In order to develop a still more versatile and effective method for the synthesis of syn-2 and anti-3, we investigated the stereoselective reduction of the corresponding α-methylthio and α-phenylthio ketones 1 by using the properly selected reducing agents. The present method is based on the previous finding that the $Zn(BH_4)_2$ reduction of α-hydroxy ketones afforded the corresponding anti-compounds and the Vitride reduction of α-silyloxy ketones produced the syn-isomers.[4]

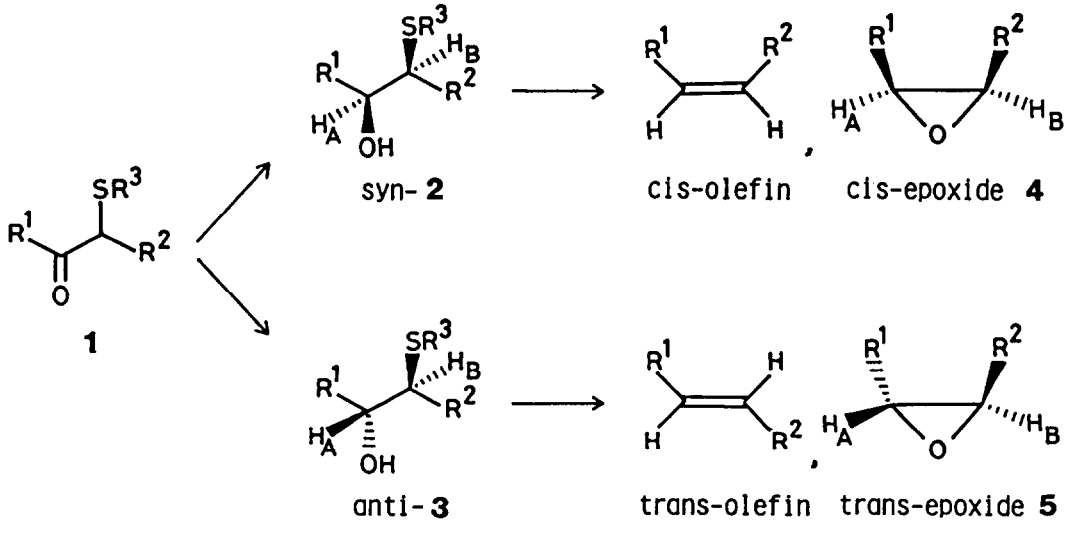


Table 1. Reduction of Methylthio and Phenylthio ketones 1

Ketone	R^1	R^2	R^3	Entry	L-Selectride-THF[a] 2 : 3[b] (Yield%)	Entry	$Zn(BH_4)_2$-Ether 2 : 3[b] (Yield%)
1a	Ph	Et	Me	1	>99 : <1 (49)	14	6 : 94 (84)
1b	Ph	i-Pr	Me	2	96 : 4 (58)	15	<1 : >99 (90)
1c	Ph	Et	Ph	3	>99 : <1 (83)	16	41 : 59 (59)
1d	Ph	i-Pr	Ph	4	>99 : <1 (79)	17	18 : 82 (85)
1e	Ph	CH_2OH	Me		——	18	93 : 7 (65)
1f	Ph	CH_2OAc	Me	5	96 : 4 (78)[c]	19	27 : 73 (53)[c]
1g	PhCH=CH	n-Pr	Me	6	92 : 8 (71)[d]	20	27 : 73 (70)[e]
1h	PhCH=CH	i-Pr	Me	7	95 : 5 (74)[e]	21	1 : 99 (68)[e]
1i	Me	n-Bu	Ph	8	98 : 2 (70)	22	82 : 18 (95)
1j	Me	i-Pr	Ph	9	99 : 1 (74)	23	61 : 39 (98)
1k	$PhCH_2CH_2$	n-Bu	Ph	10	98 : 2 (100)	24	76 : 24 (90)
1l	$PhCH_2CH_2$	i-Pr	Ph	11	>99 : <1 (88)	25	33 : 67 (100)
1m	c-hexyl	n-pent	Me	12	81 : 19 (61)		——
1n	c-hexyl	n-pent	Ph	13	67 : 33 (74)	26	88 : 12 (59)

a) After reduction, the mixture was treated with 10% NaOH solution instead of usual oxidative treatment.[7] b) The ratio was determined by 400 MHz NMR. c) Characterized as the corresponding diol. d) The ratio of the purified products. e) Yields of the corresponding acetates.

Upon checking the literature, Shibuya and co-workers have already reported that when **1**(R^1=Ph, p-MeOPh, R^2=Me, Et, R^3=Me) were treated successively with $NaBH_4$, MeI and KO^tBu, the corresponding cis-epoxides **4** were obtained exclusively.[2b,5] A complication arose through their assumption that the intermediary alcohols were in the anti(erythro)-form while cis-epoxides should be derived in S_N2 fashion from syn(threo)-alcohols. We carried out the reduction of a variety of **1** with the complex metal hydrides having different characteristics and the stereostructures of the resulting alcohols were determined unambiguously. The results were shown in **Table 1.**

Initially, the reduction of **1** with complex metal hydrides having low coordinating ability to ketones was examined. With these reagents, the reduction is highly expected to proceed through an open chain Felkin-Anh model i producing syn-**2** in preference to anti-**3**.[6] L-Selectride was found to be a reagent of choice among others and the major reduction products were assigned as syn-**2**. The $NaBH_4$ reduction of **1** was also found to give syn-**2**,[8] but the selectivity was appreciably lower than that obtained by L-Selectride reduction.

Direct evidence for the above assignment was obtained from the NMR data (see **Table 2**), since it was generally accepted that J_{AB} of the syn-isomer **2** was larger than that of anti-isomer **3** provided two functional groups were possible to form a hydrogen bonding.[9]

Then, $Zn(BH_4)_2$ with high coordinating ability was used for the reduction. Stereostructures of reduction products can now be assigned as shown in **Table 1** by simply comparing the NMR data with those of the known **2** and **3**. The reduction of **1e** and **1f** was carried out to provide additional support for the

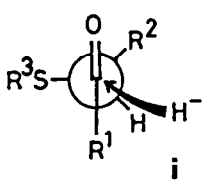
above assignments. The structures of **2e** and **3e** obtained by the $Zn(BH_4)_2$ reduction of **1** were confirmed by NMR technique after converting them into the corresponding acetonides. The coupling constant(J_{AB}=2.69 Hz) of acetonide from **2e** was much smaller than that(J_{AB}=10.25 Hz) of acetonide from **3e**, which clearly showed that **2e** and **3e** were syn- and anti-compounds, respectively.

Table 2. Coupling Constants between H_A and H_B(J_{AB}) of syn-2 and anti-3

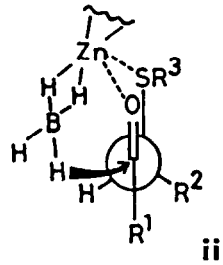
Compound	J_{AB}(Hz) syn-2	anti-3
a	8.30	3.41
b	8.30	6.84
c	8.79	3.20
d	8.79	6.35
e	7.33	6.59
g	7.20	5.98
h	7.20	4.39
i	6.71	3.42
j	7.57	6.13
k	5.62	3.17
l	6.60	4.64
m	6.60	2.08
n	8.06	2.69

It is remarkable that the reduction of **1** with L-Selectride-THF produced syn-isomer **2** with high stereoselectivity except R^1 was branched alkyl group (entry 12,13). These results suggest that the contribution of α-methylthio or α-phenylthio group to the stability of the open chain transition state **i** is significant. On the other hand, in the $Zn(BH_4)_2$ reduction where the attack of hydride is presumed to take place through the zinc mediated cyclic transition state **ii**, the selectivity leading to the expected anti-3 was found to be heavily affected by the nature of R^1 and R^3. Only in the limited cases where R^1 is phenyl or alkenyl group and R^3 is methyl group, anti-selectivity was excellent(entry 14,15,21). Even syn-selectivity was observed(entry 22,23,24,26), which showed that the coordinating ability of phenylthio group to $Zn(BH_4)_2$ decreased appreciably and the rigid transition state **ii** could not be formed in these cases. It should be added that the preferential formation of syn-isomer **2e** from β-hydroxy-α-methylthio ketone **1e**(entry 18) showed that β-hydroxyl group rather than α-methylthio group contributed to the formation of chelated cyclic transition state(see **iii**) as expected, while the reduction of **1f**(entry 19) having masked β-hydroxyl group proceeded through the same transition state as in entry 14, 15 and 21.

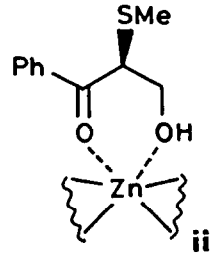
Then **2** and **3** were converted into the corresponding epoxides.[2)] The isomers **2b** and **3b**, **2c** and **3c**, and **2j** and **3j** from **1b,c,j** could be separated cleanly by using Lobar column. These were separately alkylated with trimethyloxonium tetrafluoroborate and then treated with 5% aq. NaOH solution to afford exclusively cis-epoxides **4b,c,j** from **2b,c,j** and trans-isomers **5b,c,j**



i



ii



iii

Table 3. Chemical Shifts and Coupling Constants of H_A and H_B of cis- and trans-Epoxides 4 and 5

Compound	cis-Epoxide 4 Chemical Shift(δ) H_A	H_B	J_{AB}(Hz)	trans-Epoxide 5 Chemical Shift(δ) H_A	H_B	J_{AB}(Hz)
b	4.10	2.86	4.15	3.66	2.76	2.20
c	4.09	3.17	4.39	3.61	2.94	1.95
j	3.06	2.57	4.40	2.80	2.42	2.20

from 3b,c,j, respectively, with complete inversion of the configuration at the carbon next to the sulfonium group. Structures of the epoxides were unequivocally determined by NMR technique[10] (Table 3), which again confirmed the stereostructures of 2 and 3.

Thus, it became possible to synthesize the syn-β-methylthio- and β-phenylthioalcohols 2 by the reduction of α-methylthio and α-phenylthio ketones 1 with L-selectride in extremely high selectivity, which means that cis-olefins[1] and cis-epoxides 4[2] can be synthesized stereospecifically starting from the readily obtainable 1. However, stereoselective synthesis of anti-compounds 3 leading to trans-olefins or trans-epoxides 5 can be achieved only in the limited cases. Experiments aimed to overcome this difficulty will be reported in the forthcoming paper.

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References and Notes

1) T. Mukaiyama and M. Imaoka, Chem. Lett., **1978**, 413. See also R. N. Young, W. Coombs, Y. Guindon, J. Rokach, D. Ethier, and R. Hall, Tetrahedron Lett. **22**, 4933(1981); D. L. J. Clive and V. N. Kale, J. Org. Chem., **46**, 231 (1981).
2) a) J. R. Shanklin, C. R. Johnson, J. Ollinger, and R. M. Coates, J. Am. Chem. Soc., **95**, 3429(1973); b) S. Kano, T. Yokomatsu, and S. Shibuya, Chem. Comm., **1978**, 785; c) W. H. Pirkle and P. L. Rinaldi, J. Org. Chem., **43**, 3803(1978).
3) R. W. Hoffmann and B. Kemper, Tetrahedron Lett., **21**, 4883(1980); Y. Yamamoto, Y. Saito, and K. Maruyama, ibid., **23**, 4959(1982); Y. Ikeda, K. Furuta, N. Meguriya, N. Ikeda, and H. Yamamoto, J. Am. Chem. Soc., **104**, 7663(1982).
4) T. Nakata, T. Tanaka, and T. Oishi, Tetrahedron Lett., **24**, 2653(1983).
5) $NaBH_4$ reduction of acyclic 1 is also reported. P. Brownbridge, S. Warren, J. Chem. Soc., Perkin 1,**1977**, 1131.
6) M. Cherest, H. Felkin, and N. Prudent, Tetrahedron Lett., **1968**, 2199; N. T. Anh and O. Eisenstein, Nouv. J. Chim., **1**, 61(1977).
7) H. C. Brown and S. K. Krishnamurthy, J. Am. Chem. Soc., **94**, 7159(1972).
8) The reported data[2b] that cis-epoxides 4 were obtained from $NaBH_4$ reduction products of 1 could be reasonably explained by the present syn-assignment for the intermediates 2.
9) D. J. Pasto, C. C. Cumbo, and J. Fraser, J. Am. Chem. Soc., **88**, 2194(1966). See also ref. 2c.
10) The chemical shifts of H_A and H_B in cis-4 always appear in the lower field than those of trans-5 and J_{AB} of cis-4 are larger than those of trans-5. G. G. Lyle and L. K. Keefer, J. Org. Chem., **31**, 3921(1966); J.-L. Paladini and J. Chuche, Bull. Soc. Chim. Fr., **1974**, 187 and references therein.

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