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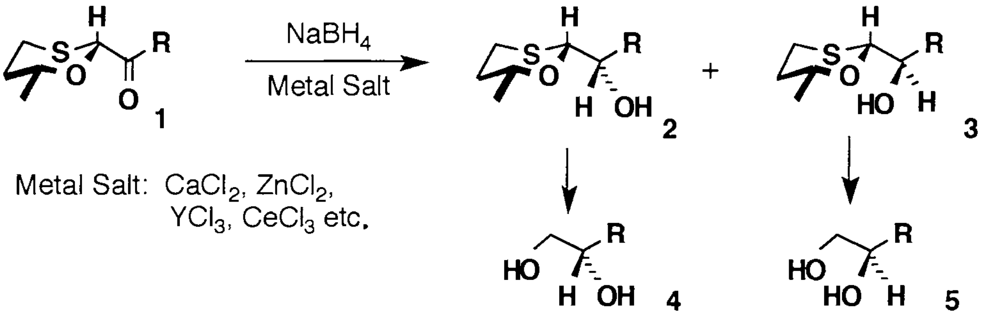
Stereocontrolled Reduction of 2-Acyl-1,3-oxathiane Derivatives by $Zn(BH_4)_2$ and YCl_3-$NaBH_4$

Seijiro MATSUBARA,* Hideya TAKAHASHI, and Kiitiro UTIMOTO*
Department of Industrial Chemistry, Faculty of Engineering, Kyoto University, Yoshida, Kyoto 606-01

Both enantiomers of 1,2-alkanediols were prepared by the diastereocontrolled reduction of ketones containing (*R*)-6-methyl-1,3-oxathiane moiety as a chiral auxiliary; reduction with $Zn(BH_4)_2$ selected one diastereoface to give one diastereomer and that with YCl_3-$NaBH_4$ produced another diastereomer selectively.

The diastereoface selective reduction of ketones containing a chiral auxiliary with various metal hydrides has provided useful methods for the preparation of optical active secondary alcohols.[1] The selectivity of the reduction strongly depends upon the nature of the metals in the reducing agents and improvement of the selectivity has been focused on the selection of the key metals. Since one chiral auxiliary is generally applied to the preparation of one enantiomer, both enantiomers of chiral auxiliary are needed to produce both enantiomers of the products. A reversal of diastereoselectivity has been reported by the mediation of organomagnesium reagents with lanthanoid salts; reaction of a chiral 2-acyl-1,3-oxathiane derivative with an alkynylmagnesium bromide gave one optically pure tertiary alcohol, whereas reaction with lanthanoid-mediated reagent afforded the enantiomer.[2,3] These observations prompted us the preparation of both enantiomers of chiral 1,2-alkanediols **4** and **5** from one substrate **1** by means of diastereoselective reductions giving either **2** or **3**.[4] Here we wish to describe a diastereocontrolled reduction of chiral 2-acyl-1,3-oxathianes **1**[5] with metal borohydride; $Zn(BH_4)_2$ gave one diastereomer **2** and $NaBH_4$-YCl_3 yielded another isomer **3** in high purity.



The reduction of (2*R*, 6*R*)-6-methyl-2-propanoyl-1,3-oxathiane (**1**, R = Et)[5] with $NaBH_4$ in THF (tetrahydrofuran) afforded a mixture of **2** (R = Et) and **3** (R = Et) in a ratio of 74:26. Any significant improvement of selectivity was not observed by the reaction in EtOH. Reduction in the presence of various metal salts such as LiCl, $ZnCl_2$, and lanthanoid salts was examined.[6,7] The reaction was performed according to the following procedure: To a mixture of dried metal salt (1.75 mmol) and $NaBH_4$ (1.5 mmol) was added 5 mL of anhydrous THF and the resulting mixture was sonicated for 30 min, or stirred for 1 h at room temperature. To the mixture was added a THF solution of **1** (1.0 mmol in 1 mL of THF) at –78 °C. The reaction mixture was stirred at the same temperature for 10 min and then the cold bath was removed. The resulting mixture was stirred for 1 h at the room temperature. The product was isolated by an aqueous workup and subjected to GC and NMR analyses to determine the diastereomeric ratio.[8)] The yield was obtained after a purification with a short silica-gel column chromatography. Meerwein–Pondorf–Verley type reduction using lanthanoid trialkoxides gave predominantly **3** (entries 15-17).[9)] The results were summarized in Table 1.

Table 1. Reduction of (2*R*, 6*R*)-2-Propanoyl-1,3-oxathiane (**1**, R = Et) [a)]

Entry	Reducing agent	Solvent	Temp / °C	Yield / % [b)]	**2** / **3**[c)]
1	$LiBH_4$	THF	-78	> 98	71 / 29
2	$NaBH_4$	THF	0	> 98	74 / 26
3	$NaBH_4$–LiCl	THF	-78 → 25	> 98	74 / 26
4	$NaBH_4$–$CaCl_2$	THF	-78 → 25	> 98	76 / 24
5	$NaBH_4$–$ScCl_3$	THF	-78 → 25	84	52 / 48
6	$NaBH_4$–$ZnCl_2$	THF	-78 → 25	> 98	90 / 10
7	$NaBH_4$–YCl_3	THF	-78 → 25	> 98	4 / 96
8	$NaBH_4$–$CeCl_3$	THF	-78 → 25	84	18 / 82
9	$NaBH_4$–$YbCl_3$	THF	-78 → 25	> 98	13 / 87
10	$NaBH_4$	EtOH	0	> 98	75 / 25
11	$NaBH_4$–YCl_3	EtOH	0	> 98	35 / 65
12	$Zn(BH_4)_2$	THF	-78	> 98	99 / 1
13	$YCl_2(BH_4)$	THF	-78	> 98	4 / 96
14	$YCl(BH_4)_2$	THF	-78	> 98	14 / 86
15	$Y(Oi\text{-}Pr)_3$	i-PrOH	25	89	19 / 81
16	$La(Oi\text{-}Pr)_3$	i-PrOH	25	89	21 / 79
17	$Sm(Oi\text{-}Pr)_3$	i-PrOH	25	99	23 / 77
18	$Al(Oi\text{-}Pr)_3$	i-PrOH	60	99	19 / 81

a) 2-Acyl-1,3-oxathiane **1** (R = Et, 2.0 mmol), $NaBH_4$ (or $LiBH_4$, 3.0 mmol), and metal chloride (3.5 mmol) were used. b) Isolated yield. c) The ratio of diastereomers was determined by ^1H NMR and GC.

Reduction with $ZnCl_2$–$NaBH_4$ afforded predominantly one diastereomer **2** in good yield (entry 6) and selectivity was improved by the use of $Zn(BH_4)_2$ (entry 12).[10)] In contrast to Zn, another diastereomer **3** was produced by the reduction with lanthanoid chloride–$NaBH_4$ and an excellent result was recorded by YCl_3-$NaBH_4$ (1:1), the active species of which seemed $YCl_2(BH_4)$ (entry 7). The same selectivity was observed by the reduction with $YCl_2(BH_4)$ (entry 13).[11,12)] Reduction with $YCl(BH_4)_2$ resulted in a inferior selectivity (entry 14). In summary, a high diastereoselective preparation of **2** can be performed by the reduction with $Zn(BH_4)_2$ and selective preparation of the diastereomer **3** can be achieved by the reduction with YCl_3-$NaBH_4$ (1:1) or $YCl_2(BH_4)$.

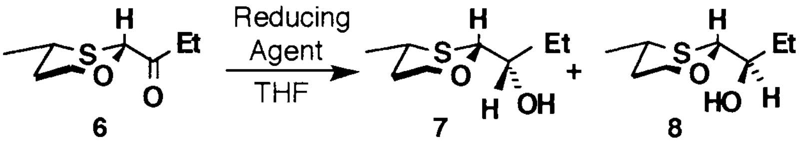
Other 2-acyl-1,3-oxathianes containing the same chiral auxiliary were subjected to the diastereoselective reduction with the above reagents. Results, the combinations of R, reducing agent, yield and diastereomer ratio, are summarized in Table 2. Each diastereomer, **2** and **3**, was easily transformed into the corresponding 1,2-alkanediol in stereospecific manner by successive treatment with $AgNO_3$/NCS and $NaBH_4$.[4,13)]

Table 2. Reduction of (2*R*, 6*R*)-2-Acyl-1,3-oxathiane (**1**)

Entry	R	Reducing agent	Yield / %[a)]	**2** / **3**[b)]
1	Me	$Zn(BH_4)_2$[c)]	>98	99 / 1
2	Me	$NaBH_4$ - YCl_3[d)]	>98	3 / 97
3	i-Bu	$Zn(BH_4)_2$	>98	86 / 14
4	i-Bu	$NaBH_4$ - YCl_3	>98	15 / 85
5	Ph	$Zn(BH_4)_2$	96	92 / 8
6	Ph	$NaBH_4$ - YCl_3	97	9 / 91
7	i-Pr	$Zn(BH_4)_2$	78	88 / 12
8	i-Pr	$NaBH_4$ - YCl_3	98	17 / 83

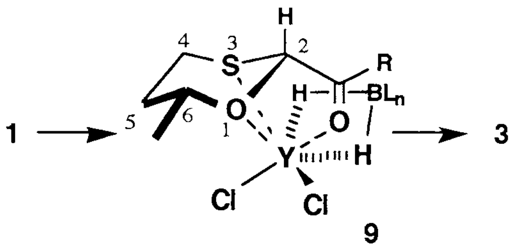
a) Isolated yields. b)The ratio of diastereomers was determined by ^1H NMR and GC. c) Treatment of **1** (1.0 mmol) with $Zn(BH_4)_2$ (2.0 mmol) in THF at -78 °C for 1 h. d) Substrate **1** (2.0 mmol) was added to a mixture of $NaBH_4$ (3.0 mmol) and YCl_3(3.5 mmol) in THF.

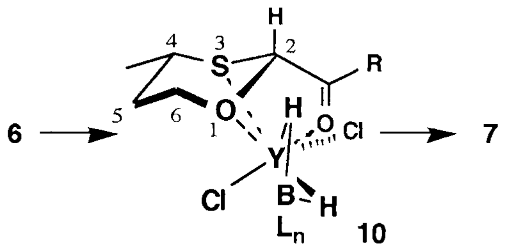
The reduction of 2-propanoyl-4-methyl-1,3-oxathiane **6** with $Zn(BH_4)_2$ gave selectively one isomer **7** (ratio **7** : **8** = 99 / 1), analogous to the above results. Reduction with YCl_3-$NaBH_4$ also gave mainly **7** (**7** : **8** = 85 / 15), in contrast to the reversal of diastereoselectivity observed by the reduction of **1**.



$Zn(BH_4)_2$: 98% (99 / 1)
$NaBH_4$ - YCl_3 : 98% (85 / 15)

The stereoselective reduction of **1** or **6** with $Zn(BH_4)_2$ can be explained by chelation mechanism.[10)] Reduction with YCl_3-$NaBH_4$ can be rationalized by multi-coordination mechanism where direction of hydride attack was controlled by hydride-bridged structure **9**.[12)] The methyl group on either C-6 or C-4 acts as a barrier for the introducing H; **1** gave **3** whereas **6** afforded **7**. Since C-O bond is shorter than C-S, the methyl on C-6 showed stronger effect than the one on C-4.





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4) Eliel reported a preparation of both enentiomers of a 2-hydroxy alkanoic acid by diastrereoselective reduction of a chiral 2-acyl-1,3-oxathiane derived from pulegone; K.-Y. Ko, W. J. Frazee, and E. L. Eliel, Tetrahedron, **40**, 1333 (1984). Lanthanoid-mediated reaction (Ref. 3) suggested the improvement of diastereoselectivity.
5) (*R*)-6-Methyl-1,3-oxathiane was prepared from (*R*)-1,3-butanediol; cf. Ref. 2.
6) Stereoselective reduction using $CeCl_3$-$NaBH_4$ in alcohol; a) A. L. Gemal and J. L. Luche, J. Org. Chem., **44**, 4187 (1979); b) G. A. Molandar, Chem. Rev., **92**, 29 (1992).
7) Application of the reported procedure (Ref. 6a) to the reduction of **1** (R = Et) afforded a mixture of **2** and **3** (40 / 60) in > 98% yield.
8) **2** (R = Et): ^1H NMR ($CDCl_3$): δ 4.86 (d, J = 3.5 Hz, 1H), 3.85-3.53 (m, 2H), 3.03 (dt, J = 13.0, 2.5 Hz, 1H), 2.85 (dt, J = 13.0, 2.5 Hz, 1H), 1.85-1.30 (m, 5H), 1.20 (d. J = 6.0 Hz, 3H), 0.98 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 86.9, 76.4, 74.9, 32.8, 27.5, 25.4, 22.2, 10.1. Found: C, 54.28; H,9.29%. Calcd for $C_8H_{16}O_2S$: C, 54.50; H, 9.15%.
   3 (R = Et): ^1H NMR ($CDCl_3$): δ 4.69 (d, J = 6.6 Hz, 1H), 3.70-3.50 (m, 2H), 3.05 (dt, J = 13.0, 2.5 Hz, 1H),2.83 (dt, J = 13.0, 2.5 Hz, 1H), 2.45 (bs, 1H), 1.85-1.38 (m, 4H), 1.22 (d. J = 6.0 Hz, 3H), 0.98 (t, J = 7.5 Hz, 3H).; ^{13}C NMR ($CDCl_3$): δ 85.9, 76.1, 74.5, 32.6, 27.7, 25.5, 22.2, 9.6. Found: C, 54.28; H,9.37%. Calcd for $C_8H_{16}O_2S$: C, 54.50; H, 9.15%.
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13) See Ref. 4. According to the procedure described for the transformation of 1,3-oxathiane moiety into hydroxymethyl, **2** (R=Me, >98%de) was transformed into (*S*)-1,2-propanediol in 96% yield via two step procedures (1. $AgNO_3$/NCS, 2. $NaBH_4$). $[\alpha]_D^{20}$ +12.7±2.4 (c 0.714, EtOH) ($[\alpha]_D^{20}$ +15.5 (neat), C. Melchionre, Chem. Ind. (London) **1976**, 218). Purity of the diol was obtained by ^1H NMR analysis after the treatment with Mosher's reagent (>98% ee).

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