Stereoselective *syn*-Reduction of (*R*)-4-Acyl-2,2-dimethyl-1,3-dioxolanes with Metal Hydride Reagents

Hidenori Chikashita,* Toshiki Nikaya, Hiromitsu Uemura, and Kazuyoshi Itoh
Department of Applied Chemistry, Faculty of Engineering, Kansai University, Suita, Osaka 564

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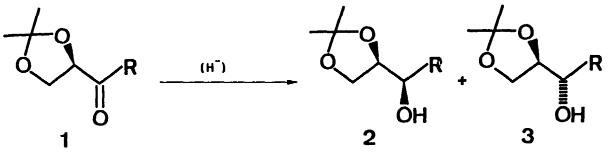
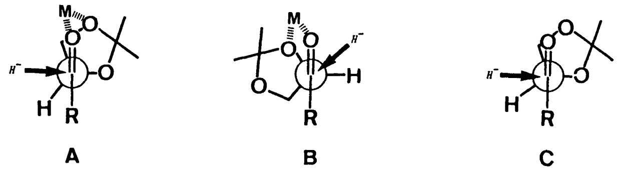
Synopsis. Lithium tri-*s*-butylborohydride and lithium aluminum hydride were found to be efficient reducing agents for the stereoselective preparation of *syn*-glycerol derivatives from (*R*)-4-acyl-2,2-dimethyl-1,3-dioxolanes. The scope and limitation of the stereoselective L-Selectride reduction of (*R*)-4-acyl-2,2-dimethyl-1,3-dioxolanes were also described.

2,3-*O*-Isopropylideneglyceraldehyde is a very useful chiral starting material for the synthesis of a variety of optically active molecules including natural products[1] because of ready availability of both the (*S*)-[2] and (*R*)-forms.[3] Among the methodologies developed in this field, much interest has been concentrated on the diastereoselective addition of C-nucleophiles such as organometallic reagents to the glyceraldehyde. Although the stereochemical course in this reaction has been extensively studied in recent years, the addition of organometallic reagents usually produces *anti*-glycerol derivatives as major products with varying degree of diastereoselectivity depending on the reagents and conditions employed.[4] On the other hand, however, an efficiently controlled method for the preparation of syn-adducts based on this methodology is rare.[5] A different approach to obtain *syn*-glycerol derivatives selectively would be to employ the diastereoselective carbonyl addition of hydride to 4-acyl-2,2-dimethyl-1,3-dioxolanes.[6] We have now examined the diastereofacial selectivity of the reduction of (*R*)-4-acyl-2,2-dimethyl-1,3-dioxolanes (**1**) with a variety of metal hydride reagents and found that lithium tri-*s*-butylborohydride (L-Selectride) and lithium aluminum hydride were excellent candidates as reducing agents for the syn-selective hydride addition to **1** producing *syn*-glycerol derivatives **2**. In this paper, we describe these results including the scope and limitation of the stereoselective L-Selectride reduction of **1**.



Scheme 1.

Reduction of ketone **1a** to the glycerols **2a** and **3a** was initially examined with a variety of metal hydride reagents and the results are presented in Table 1. In all cases of the reducing agents and conditions examined, the reduction proceeded in high yield and provided the syn-diastereomer **2a** as the major product. These results indicate that the β-chelation transition state A which predicts the syn selectivity should be favored over the α-chelation transition state B when chelatable reagents are employed (Entries 1—6). On the other hand, reduction with diisobutylaluminum hydride (DIBAL-H) which is known to have low chelating ability showed very low selectivity (Entry 7). Thus, non-chelation reaction which should predict the syn selectivity according to the Felkin-Ahn transition state model C is regarded to be ineffective for the present type of diastereofacial selection of **1**. Higher diastereoselectivity was obtained in the reaction with a series of lithium metal hydrides (Entries 3—5) with the following order of selectivity: $LiBH(s\text{-}Bu)_3 > LiAlH_4 \gg LiAlH(Ot\text{-}Bu)_3$. This shows the high chelation efficiency of the Li^+ counterion in the transition state A rather than the transition state B leading to the formation of the minor anti-addition product **3a**.



Scheme 2.

Although a similar stereochemical outcome of the L-Selectride reduction has been obtained by Macdonald et al. for a model compound,[7] the scope and limitations of the reduction have not been clari-

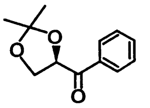
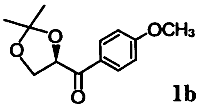
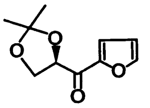
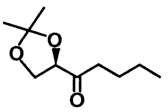
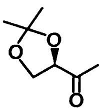
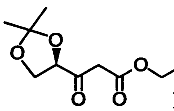
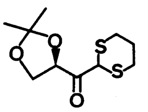
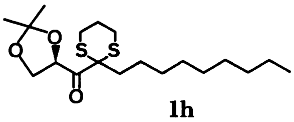
Table 1. Reduction of **1a** (R=Ph) with Various Metal Hydrides

Entry	Metal hydride	Solvent	Temp/°C (Time/h)	Yield/%[a]	Product ratio[b] *syn*-**2a** : *anti*-**3a**
1	$NaBH_4$	Ethanol	−78(1.5)	89	67:33
2	$Zn(BH_4)_2$	Ether	−78(1.5)	57	63:37
3	$LiBH(s\text{-}Bu)_3$	THF	−78(3.0)	83	97: 3
4	$LiAlH_4$	THF	−78(1.5)	87	94: 6
5	$LiAlH(OBu^t)_3$	Ether	−78(3.0)	78	73:27
6	$NaAlH_2(OCH_2CH_2OMe)_2$	Benzene	0(1.2)	98	60:40
7	$AlH(i\text{-}Bu)_2$	Benzene	0(3.0)	90	59:41

a) Isolated yield. b) Determined by HPLC analyses.

fied yet. Thus, to establish the generality, we examined the reduction of a variety of (*R*)-4-acyl-2,2-dimethyl-1,3-dioxolanes (**1b—h**). The results are summarized in Table 2. A variety of aromatic (Entries 1—3) and aliphatic (Entries 4,5) ketones were efficiently reduced to the corresponding *syn*-glycerols **2b—e** in high yields with excellent stereoselectivity. Keto ester **1f** and 1,3-dithian-2-yl ketone **1g** were similarly reduced in high yield with excellent syn-selectivity to give the β-hydroxy ester **2f** and the dithianyl alcohol **2g**, respectively. However, the reduction of the 1,3-dithian-2-yl ketone **1h** with L-Selectride did not proceed at all (Entry 8). This result suggests that L-Selectride can not be used for the reduction of highly hindered ketones due to the strong hindrance of the reaction because of the steric bulks of both the reducing agent and the substrate, and shows the limitation of the present L-Selectride reduction. In contrast to this, the reduction of **1h** with $LiAlH_4$, which is the another excellent candidate as shown previously (Table 1), proceeded in high yield to give the syn-product **2h** in good selectivity (Entry 8).

Table 2. Stereoselective Reduction of (*R*)-4-Acyl-2,2-dimethyl-1,3-dioxolanes (**1**) with L-Selectride[a)]

Entry	Substrate	Isolated yield/%	Product ratio[b)] *syn*-**2**:*anti*-**3**
1	 **1a**	83	97: 3
2	 **1b**	81	97: 3
3	 **1c**	98	>99: 1
4	 **1d**	67	96: 4
5	 **1e**	33	85:15
6	 **1f**	55	96: 4
7	 **1g**	82	>99: 1
8	 **1h**	No reaction (87)[c)]	(80:20)[c)]

a) All the reactions were carried out with 3 equiv of L-Selectride in THF at −78 °C for 3 h. b) Determined by HPLC analyses (Entries 1—3 and 7), GLC analyses (Entries 4 and 5), and 400 MHz ^1H NMR analyses (Entries 6 and 8). c) Reactions with 3 equiv of $LiAlH_4$ in THF at −78 °C for 3 h.

In conclusion, the L-Selectride reduction of (*R*)-4-acyl-2,2-dimethyl-1,3-dioxolanes (**1**) was found to be a fairly general method for the stereoselective preparation of *syn*-glycerol derivatives **2**. On the other hand, $LiAlH_4$ was also found to be useful as another selective reducing agent especially in the case of the reduction of highly hindered substrates.

Experimental

Optical rotations were determined with a Union Digital PM-101 polarimeter. IR spectra were obtained on a JASCO A-202 spectrometer. ^1H NMR spectra were measured with a JEOL JNM-GX400 spectrometer at 400 MHz with tetramethylsilane as an internal reference. GLC analyses were carried out on a Yanagimoto Gas chromatograph G2800T using glass columns (3 m) packed with 10% EG-20W on Shimalite-NAW (60/80 mesh). HPLC analyses were carried out on a Yanagimoto high-pressure liquid chromatograph L-5000. Silica gel (Merck silica gel 60, 230—400 mesh ASTM) was used for medium-pressure liquid chromatography (MPLC). TLC were carried out on Merck precoated silica gel plates (Merck silica gel 60 F_{254}).

Materials. Tetrahydrofuran (THF) was freshly distilled over $LiAlH_4$ before use. The other solvents were purified by the usual methods and were freshly distilled before use. Metal hydride reagents were supplied as high grade commercial products and used without further purification. (*R*)-4-Acyl-2,2-dimethyl-1,3-dioxolanes **1a—e** were prepared by the reaction of 1,2-*O*-isopropylidene-D-glyceraldehyde with organolithium or Grignard reagents followed by oxidation of the resulting diastereomeric mixture of glycerol derivatives. The keto ester **1f** and 1,3-dithian-2-yl ketones **1g,h** were similarly prepared by the reaction with the lithium enolate of ethyl acetate[8)] and 2-lithio-1,3-dithiane derivatives and the subsequent PCC and PDC oxidations, respectively.

General Procedure for the Reduction of (*R*)-4-Acyl-2,2-dimethyl-1,3-dioxolanes with L-Selectride. To a 1 M THF solution of L-Selectride (2 ml, 2 mmol) was added dropwise a solution of the (*R*)-4-acyl-2,2-dimethyl-1,3-dioxolanes **1** (1 mmol) in THF (2 ml) under nitrogen with stirring. The mixture was stirred for 3 h at −78 °C and the solution was allowed to warm to room temperature and then quenched by the addition of water (8 ml). The mixture was extracted with ether (30 ml×5) and the extract was washed with water (30 ml×2). The aqueous washings were again extracted with ether and the combined organic layers were dried with $MgSO_4$. The solution was filtered through silica gel (Wakogel C-300) and the filtrate was concentrated under reduced pressure to give a fairly pure (monitored by TLC and ^1H NMR) diastereomeric mixture of **2** and **3** as a colorless oil. The β-keto ester **1f** was similarly reduced to a mixture of **2f** and **3f** by the general procedure, except that the reaction time was 5 h and a buffer solution (pH=6.86) was used for quenching in place of water.

Identification of products was performed by spectroscopic (NMR and IR) methods. These spectral data were in satisfactory agreement with those of the corresponding authentic samples.

The relative stereochemistry of major and minor diastereoisomers **2a—f** and **3a—f** was assigned by HPLC, GLC, or ^1H NMR comparison with stereochemically defined authentic samples.

The syn and anti diastereoisomers **2g** and **3g** were easily distinguished by ^{1}H NMR on the basis of chemical shift values for the OH protons (δ_{syn}OH>δ_{anti}OH).[9] Full spectroscopic data of the major *syn*-**2g** and the minor *anti*-**3g** which could be separated by MPLC (benzene–ethyl acetate, 20:1 v/v) after conversion into the corresponding benzyl ethers are as follows.

***syn*-2g**: $[\alpha]_D^{24}$+5.00° (*c* 0.95, $CHCl_3$) as a benzyl ether; IR of the benzyl ether (neat) 3030, 2984, 2933, 2896, 1497, 1454, 1422, 1380, 1370, 1248, 1213, 1157, 1069, 1028, 855, 796, 737, and 699 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.39 (s, 3H), 1.46 (s, 3H), 1.94 (m, 1H), 2.11 (m, 1H), 2.68 (d, 1H, *J*=6.0 Hz), 2.81 (m, 2H), 2.92 (m, 2H), 3.75 (ddd, 1H, *J*=6.6, 6.0, 3.9 Hz), 3.93 (dd, 1H, *J*=8.3, 6.6 Hz), 4.10 (d, 1H, *J*=6.6 Hz), 4.12 (dd, 1H, *J*=8.3, 6.6 Hz), and 4.50 (dt, 1H, 3.9, 6.6 Hz).

***anti*-3g**: $[\alpha]_D^{23}$+24.4° (*c* 0.45, $CHCl_3$) as a benzyl ether; IR of the benzyl ether (neat) 3031, 2985, 2933, 2896, 1496, 1454, 1422, 1380, 1370, 1341, 1248, 1213, 1157, 1074, 908, 854, 786, 738, 699, and 681 cm^{-1}: ^{1}H NMR ($CDCl_3$) δ=1.37 (s, 3H), 1.44 (s, 3H), 1.94 (m, 1H), 2.11 (m, 1H) 2.35 (d, 1H, *J*=4.2 Hz), 2.93 (m, 4H), 3.88 (dt, 1H, *J*=6.6, 4.2 Hz), 4.02 (dd, 1H, *J*=8.5, 5.4 Hz), 4.09 (dd, 1H, *J*=8.5, 6.6 Hz), 4.32 (td, 1H, 6.6, 5.4 Hz), and 4.35 (d, 1H, *J*=4.2 Hz).

Reduction of 1,3-Dithian-2-yl Ketone 1h with $LiAlH_4$. To a stirred suspension of lithium aluminum hydride (39 mg, 2 mmol) in dry THF (12 ml) was slowly added the ketone **1h** (375 mg, 1 mmol) in dry THF (2 ml) at −78 °C. After stirring for 3 h at −78 °C, the mixture was quenched by the addition of water (10 ml). The aqueous mixture was extracted with ether and the ether extract was washed with water and then dried with $MgSO_4$. Concentration of the solution under reduced pressure gave the fairly pure (monitored by TLC and ^{1}H NMR) diastereomeric mixture of **2h** and **3h** as a colorless oil (323 mg, 86%).

The relative stereochemistry of the syn and anti diastereoisomers was easily distinguished by ^{1}H NMR on the basis of chemical shift values for the OH protons (δ_{syn}OH >δ_{anti}OH).[9] Full spectroscopic data of the major *syn*-**2h** and the minor *anti*-**3h** separated by MPLC (benzene–ethyl acetate, 4:1 v/v) are as follows.

***syn*-2h**: $[\alpha]_D^{25}$−7.28° (*c* 1.24, $CHCl_3$); IR (neat) 3489, 2925, 2854, 1458, 1423, 1370, 1255, 1218, 1158, 1122, 1065, 965, 909, 869, 797, and 722 cm^{-1}: ^{1}H NMR ($CDCl_3$) δ=0.88 (t, 3H, *J*=6.8 Hz), 1.26 (br, 12H), 1.42 (s, 3H), 1.46 (s, 3H), 1.56 (m, 2H), 1.76 (m, 1H), 1.84—2.06 (m, 3H), 2.71 (m, 2H), 2.89 (ddd, 1H, *J*=14.0, 10.4, 3.6 Hz), 2.95 (ddd, 1H, *J*=14.0, 10.4, 3.6 Hz), 3.02 (d, 1H, *J*=5.3 Hz), 3.83 (dd, 1H, *J*=5.3, 3.9 Hz), 3.87 (t, 1H, *J*=8.0 Hz), 4.17 (dd, 1H, *J*=8.0, 6.3 Hz), and 4.53 (ddd, 1H, *J*=8.0, 6.3, 3.9 Hz). Found: C, 60.53; H, 9.44%. Calcd for $C_{19}H_{36}O_3S_2$: C, 60.60; H, 9.63%.

***anti*-3h**: $[\alpha]_D^{25}$+11.7° (*c* 1.05, $CHCl_3$); IR (neat) 3465, 2922, 2853, 1456, 1423, 1370, 1248, 1213, 1159, 1123, 1058, 908, 856, 799, 758, 722, and 655 cm^{-1}: ^{1}H NMR ($CDCl_3$) δ=0.88 (t, 3H, *J*=7 Hz), 1.26 (br, 12H), 1.38 (s, 3H), 1.46 (s, 3H), 1.55 (m, 2H), 1.87 (m, 3H), 2.02 (m, 1H), 2.71 (m, 2H), 2.75 (d, 1H, *J*=2.2 Hz), 3.00 (ddd, 1H, *J*=3.2, 10.6, 14.1 Hz), 3.08 (ddd, 1H, *J*=3.2, 10.6, 14.1 Hz), 4.02 (dd, 1H, *J*=8.1, 6.8 Hz), 4.12 (dd, 1H, *J*=8.1, 6.8 Hz), 4.25 (dd, 1H, *J*=2.9, 2.2 Hz), and 4.59 (td, 1H, *J*=6.8, 2.9 Hz). Found: C, 60.52; H, 9.57%. Calcd for $C_{19}H_{36}O_3S_2$: C, 60.60; H, 9.63%.

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