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Highly stereoselective Luche reduction of α-enonesulfoxides to 2-sulfinyl allylic alcohols

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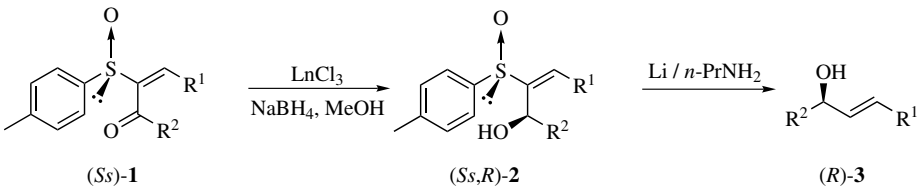
Abstract—Luche reduction of α-enonesulfoxides with $NaBH_4$ in methanol in the presence of $YbCl_3$ afforded 2-sulfinyl allylic alcohols in high yields and with excellent diastereoselectivity.

1. Introduction

The methodologies and strategies for the stereoselective construction of chiral allylic alcohols are very powerful synthetic tools that can be applied to many naturally occurring products, such as steroids,[1] prostaglandins,[2] and ceramides.[3] We have previously reported that *n*-alkane-6,8-diols have strong antitumor effects and that four optically active isomers could be synthesized from the corresponding chiral allylic alcohols.[4] However, this synthetic method gave the products in low yield, which meant that we have searched for a better route for *n*-alkane-6,8-diol synthesis. Our novel approach to the synthesis of the *n*-alkane-6,8-diol unit is based on a strategy we developed for the stereoselective Luche reduction of α-enonesulfoxides. Luche reductions, using lanthanoid chlorides, especially $CeCl_3$, are known to be efficient for the regioselective 1,2-reduction of α-enones by $NaBH_4$ in methanol solution,[5] although the stereoselectivity of the products was not described. Recently, several reports have been published incorporating stereoselective Luche reductions for total synthesis.[6] Herein we report the synthesis of optically active allylic alcohols by a highly stereoselective reduction of α-enonesulfoxide **1**, followed by stereoselective desulfurization with Li/*n*-$PrNH_2$ systems (Scheme 1).[7]

2. Results and discussion

Optically active α-enonesulfoxide **1a** was easily prepared from *l*-menthyl (−)-(*S*)-toluenesulfinate in four steps.[8] We first investigated that the reduction of **1a** under different conditions, such as the general use of DIBAL with or without a Lewis acid[9,10] or with $Yb(OTf)_3$[11] and Luche reduction. However, the DIBAL reduction of **1a** did not occur. The use of Luche reduction did not give good stereoselectivity and a 68:32 mixture of epimers (*Ss*,8*R*)-**2a**, and (*Ss*,8*S*)-**2a** was obtained in high yield (entry 2). Next, we



(*Ss*)-**1** (*Ss*,*R*)-**2** (*R*)-**3**

1a: $R^1 = C_5H_{11}$, $R^2 = C_7H_{15}$

Scheme 1. Stereoselective synthesis of allylic alcohols.

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Table 1. Diastereoselective reduction of **1a** with $NaBH_4$ in MeOH in the presence of lanthanoid chlorides

Entry[a]	Lanthanoid	**2a** Yield[b] (%)	De[c] (%)
1	$LaCl_3{\cdot}7H_2O$	90	44
2	$CeCl_3{\cdot}7H_2O$	96	36
3	$NdCl_3{\cdot}6H_2O$	89	38
4	$SmCl_3{\cdot}6H_2O$	Quant.	64
5	$GdCl_3{\cdot}6H_2O$	84	64
6	$TbCl_3{\cdot}4H_2O$	84	76
7	$HoCl_3{\cdot}6H_2O$	94	84
8	$ErCl_3{\cdot}6H_2O$	96	96
9	$YbCl_3{\cdot}6H_2O$	94	>99

[a] All reactions were carried out on a 0.15 mmol scale at 0 °C for 15 min with 2 equiv of lanthanoid chloride hydrate, 2.5 equiv of $NaBH_4$, and 2 mL of MeOH.
[b] Diastereoisomeric mixture yield.
[c] Diastereomeric excess by HPLC measurements.

attempted the diastereoselective reduction of enonesulfoxide **1a** under the optimal conditions using various lanthanoid chlorides. The reduction of **1a** was carried out by reacting 2.0 equiv of lanthanoid chloride and 2.5 equiv of $NaBH_4$ in methanol at 0 °C for 15 min (Table 1).

$LaCl_3{\cdot}7H_2O$, $CeCl_3{\cdot}7H_2O$, and $NdCl_3{\cdot}6H_2O$ exhibited almost the same low diastereoselectivity in the reduction of **1a**. By using $SmCl_3{\cdot}6H_2O$ and $GdCl_3{\cdot}6H_2O$, **1a** gave **2a** with similar diastereoselectivity, while $TbCl_3{\cdot}4H_2O$ and $HoCl_3{\cdot}6H_2O$ gave somewhat better diastereomeric excess (de). $ErCl_3{\cdot}6H_2O$ and $YbCl_3{\cdot}6H_2O$ were found to be excellent additives with respect to both chemical yields and diastereomeric excess of the product. On the other hand, when **1a** and $NaBH_4$ were allowed to react in methanol without lanthanoid chloride, the sense of diastereomeric reduction was reversed, and (*Ss*,8*S*)-**2a** was obtained with 95% diastereomeric excess in 40% isolated yield.

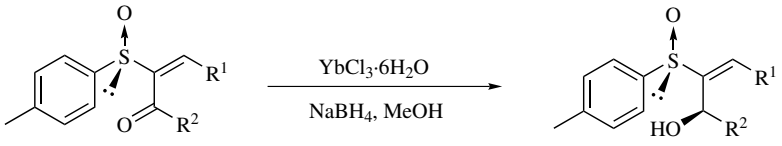
We further investigated this reduction with various substrates and the results are shown in Table 2. Compounds **1b–e**, **1i** and **1j** were synthesized via the same procedure as **1a**.[8] Compound **1f–h** were prepared from *l*-menthyl(−)-(*S*)-toluene sulfinate in three steps using the Wittig reaction.[12] As shown in Table 2, a highly diastereoselective reduction occurred, and 2-sulfinyl allylic alcohols (*Ss*,*R*)-**2b–2j** were obtained in excellent diastereomeric excess (95–99%) and reasonably good yields (82–98%). We tentatively rationalize these results in terms of an approximately six-membered planar ring formation such as the Posner model[13] in which the nucleophilic reduction occurs on the side of the plane which contains the non-bonding electron pair of sulfur and opposite to the side containing the aryl group.

Finally, desulfurization of (*Ss*,*R*)-**2** with Li/*n*-$PrNH_2$ under argon at ambient temperature led to the desired allylic alcohols (*R*) *E*-**3** with somewhat low selectivity (*E*/*Z* = 78/22–90/10) without the concomitant reduction of the double bond (Table 3). Moreover, the allylic alcohols (*R*) *E*-**3** were obtained with excellent enantiomeric excess (>99% ee).

3. Conclusion

In conclusion, we have reported the first highly stereoselective Luche reduction of α-enonesulfoxides using $YbCl_3$–$NaBH_4$. The reaction is considered to proceed via a six-membered ring Yb-chelate formation, similar to Posner's model. In addition, enantiomerically pure allylic alcohol was obtained by the use of Li/*n*-$PrNH_2$ without racemiza-

Table 2. Diastereoselective reduction of (*Ss*)-**1a–j** in the presence of Yb^{3+}

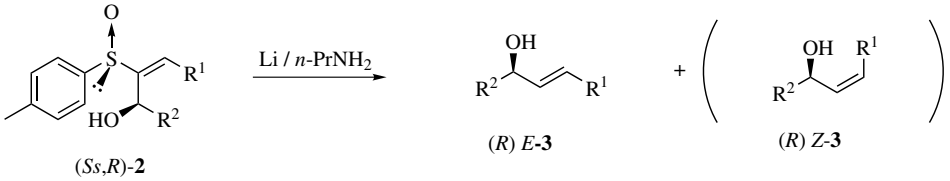


(*Ss*)-**1a-j** (*Ss*,*R*)-**2a-j**

Entry[a]	Substrate			Product			
		R^1	R^2		Yield[b] (%)	De[c] (%)	$[\alpha]_D$
1	**1a**	*n*-Pentyl	*n*-Heptyl	**2a**	94	>99	+65[d]
2	**1b**	*n*-Pentyl	Me	**2b**	85	>99	+60[d]
3	**1c**	*n*-Pentyl	Ph	**2c**	85	>99	+102[d]
4	**1d**	*n*-Pentyl	*n*-C_9H_{19}	**2d**	82	>99	+63[d]
5	**1e**	*n*-Pentyl	*n*-$C_{19}H_{39}$	**2e**	82	>99	+29[e]
6	**1f**	Ph	Me	**2f**	84	95	+140[d]
7	**1g**	Ph	Ph	**2g**	95	>99	+150[d]
8	**1h**	Ph	*n*-Pentyl	**2h**	93	99	+108[d]
9	**1i**	*i*-Pr	*i*-Pr	**2i**	95	96	+27[d]
10	**1j**	*i*-Pr	*n*-Pentyl	**2j**	98	>99	+70[d]

[a] Reaction conditions are described in the general procedure.[14]
[b] Isolated yield.
[c] Diastereomeric excess by HPLC measurement.
[d] Measured in acetone at room temperature.
[e] Measured in $CHCl_3$ at room temperature.

Table 3. Desulfurization of (*Ss*,*R*)-**2** with Li/*n*-$PrNH_2$



(*Ss*,*R*)-**2** (*R*) *E*-**3** (*R*) *Z*-**3**

Entry[a]	Substrate			Product			
		R^1	R^2		Yield[b] (%)	ee (*R*) *E*-**3**[c] (%)	*E*/*Z*[d]
1	**2a**	*n*-Pentyl	*n*-Heptyl	**3a**	75	>99	78/22
2	**2b**	*n*-Pentyl	Me	**3b**	77	>99	72/28
3	**2d**	*n*-Pentyl	*n*-C_9H_{19}	**3d**	81	>99	78/22
4	**2e**	*n*-Pentyl	*n*-$C_{19}H_{39}$	**3e**	60	>99	74/26
5	**2i**	*i*-Pr	*i*-Pr	**3i**	76	>99	79/21
6	**2j**	*i*-Pr	*n*-Pentyl	**3j**	68	>99	90/10

[a] All reactions carried out on 0.3 mmol scale at room temperature for 18 h with 10 equiv of Li and 3 mL of *n*-$PrNH_2$.
[b] *E* and *Z* mixture yield.
[c] (*R*)-**3** were derivated to 2-nitrobenzoates and calculated using HPLC systems.
[d] Calculated from ^1H NMR.

tion. These results provide a very useful method that can be applied to the synthesis of various natural products.

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14. *General procedure for stereoselective reduction.* $YdCl_3{\cdot}6H_2O$ (2 equiv) was added to a solution of α-enonesulfoxide **1** (1 equiv) in methanol (9 mL/mmol) at 0 °C and stirred for 10 min. $NaBH_4$ (2.5 equiv) was added to the solution at 0 °C and the reaction mixture was stirred for 15 min. The reaction was then quenched with saturated aqueous NH_4Cl solution and extracted with ethyl acetate. The organic layer was washed with saturated aqueous NH_4Cl solution, followed by brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude 2-sulfinyl allylic alcohol **2**. Determination of the diastereomeric excess of crude product **2** was calculated from HPLC data (column, INERTSIL100A 4.6 × 250 mm; eluent, hexane/2-propanol = 100/3 or 95/5; detection, 254 nm). Crude product **2** was purified by flash column chromatography (silica gel, hexane/ethyl acetate = 5/1) to give pure (*R*)-**2** in high yield.