

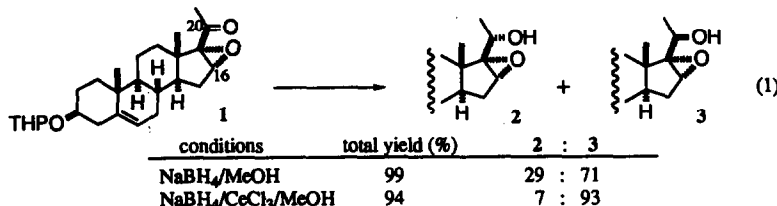
A Convenient, Highly Stereoselective Synthesis of *anti*- α,β -Epoxy Alcohols by the Luche Reduction of α,β -Epoxy Ketones

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Summary: Reduction of α,β -epoxy ketones under the Luche conditions with $\text{NaBH}_4/\text{CeCl}_3$ in MeOH provides *anti*- (or *erythro*-) α,β -epoxy alcohols in high yields and with extremely high stereoselectivity.

α,β -Epoxy alcohols serve as highly versatile synthetic intermediates which can be efficiently elaborated into poly-hydroxyl compounds with multiple chiral centers.¹ While the reduction of epoxy ketones with NaBH_4 to the corresponding epoxy alcohols proceeds with modest stereoselectivity,² the use of $\text{Zn}(\text{BH}_4)_2$ results in the highly *anti*-stereoselective formation of epoxy-alcohols.³ In the following, we report that the use of the Luche conditions⁴ for the reduction of acyclic epoxy ketones constitutes a convenient, highly stereoselective method for the synthesis of *anti*- (or *erythro*-) α,β -epoxy alcohols.

During our study on the synthesis of 16α -hydroxylated 17 -ethylidene steroids, access to the pure stereoisomer of both epoxy alcohols **2** and **3** was required.⁵ To this end, stereoselectivity in the reduction of epoxy ketone **1** was examined with the use of a variety of hydride reducing agents. It was found that the treatment of ketone **1** with NaBH_4 in MeOH produces $20R$ -alcohol **3**⁶ in a highly stereoselective manner when CeCl_3 was used in conjunction with the ketone (see Scheme 1). In an effort to explore the generality of this



anti-selectivity of the reduction, several acyclic α,β -epoxy ketones^{3a} were reduced under the Luche conditions.⁴ Interestingly, in spite of its wide-spread use in reduction of ketones, particularly conjugated ketones, it appears that only a single case of the use of the Luche conditions in the reduction of an α,β -epoxy ketone has been described in the literature. It was noted that two 2,3-epoxycyclohexan-1-ones were reduced exclusively under the Luche conditions to their corresponding *trans*-epoxy alcohols.⁷ As is evident from the results summarized in Table 1, the reduction of epoxy ketones with $\text{NaBH}_4/\text{CeCl}_3$ in MeOH proceeds with high stereoselectivity. The stereoselectivity of the reduction was found to be comparable to or better than that observed for the reduction with $\text{Zn}(\text{BH}_4)_2$, with the exception of the case of 3,4-epoxy-2-butanone (**4a**). The stereochemistry of the products was assigned through comparison of their ¹H NMR spectra with those epoxy alcohols obtained by epoxidation of the corresponding allylic alcohols with *t*-BuOOH/ $\text{VO}(\text{acac})_2$ in CH_2Cl_2 .⁸ In light of the similar, excellent stereoselectivity observed for the reduction with both $\text{Zn}(\text{BH}_4)_2$ and $\text{NaBH}_4/\text{CeCl}_3$, the chelation-based mechanism proposed to account for the observed stereoselectivity for the reduction of α,β -epoxy ketones with $\text{Zn}(\text{BH}_4)_2$ in THF^{3a} may also be postulated as a plausible mechanism of

Table 1. Results of the NaBH₄/CeCl₃-reduction of α,β -Epoxy Ketones

α,β -epoxy ketone	products	NaBH ₄ /CeCl ₃ reduction		Zn(BH ₄) ₂ reduction (ref 3a)	
		<i>syn/anti</i> ratio ^a	yield (%) ^b	<i>syn/anti</i> ratio	yield (%)
4a	5a/6a	19 : 81	75	2 : 98	80
4b	5b/6b	9 : 91	82	10 : 90	76
4c	5c/6c	1 : >99	85	1 : >99	83
4d	5d/6d	7 : 93	90	16 : 84	79
4e	5e/6e	1 : 99	87	1 : 99	76
4f	5f/6f	1 : >99	91	1 : >99	86

a. Ratio determined by proton NMR spectroscopic analysis (300 MHz, CDCl₃) of the crude product mixture.

b. Yield of the purified mixture of *syn*- and *anti*-epoxy alcohols.

the present reduction with NaBH₄/CeCl₃ in MeOH.

The highly stereoselective method described herein for the synthesis of acyclic anti- α,β -epoxy alcohols under the Luche conditions should find use as a convenient alternative to a similar method with Zn(BH₄)₂.

General Procedure: To an ice-cold 0.05 M solution of an α,β -epoxy ketone in MeOH were added first CeCl₃·7H₂O (1.0 mol equiv) and then carefully NaBH₄ (1.05 mol equiv), under nitrogen with stirring. After stirring for 1 h at 0 °C, the reaction mixture was diluted with water. The bulk of the MeOH was removed by distillation and the resulting solution was extracted with ether (x 3). The combined ether layers were washed with aqueous saturated NaCl and were dried (Na₂SO₄). After removal of the solvent by distillation, the product was purified by distillation under reduced pressure.

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References and Notes

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6. In ref. 5, the numbering 7a/7b should be interchanged with 8a/8b throughout the text and the experimental section except those found in the last paragraph in the text. The structures shown with the numbers 7a/7b and 8a/8b are designated correctly. Regarding the R/S-designation, the experimental descriptions including spectroscopic properties correspond to the IUPAC names given for the compounds and not with the assigned compound numbers, 7a/7b and 8a/8b.
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