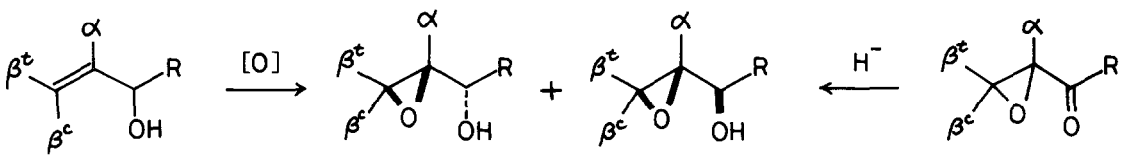
Tetrahedron Letters,Vol.22,No.47,pp 4723-4726,1981 0040-4039/81/474723-04$02.00/0
Printed in Great Britain

HIGHLY STEREOSELECTIVE SYNTHESIS OF ERYTHRO-α, β-EPOXY ALCOHOLS BY THE REDUCTION OF α, β-EPOXY KETONES WITH ZINC BOROHYDRIDE[1]

Tadashi Nakata,* Tadasu Tanaka, and Takeshi Oishi*
The Institute of Physical and Chemical Research (Riken)
Wako-shi, Saitama, 351 Japan

Summary: Erythro-α, β-epoxy alcohols were prepared in high stereoselectivity by zinc borohydride reduction of the corresponding α, β-epoxy ketones regardless of the substituents on the epoxide ring.

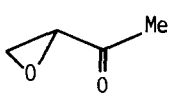
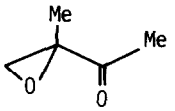
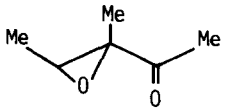
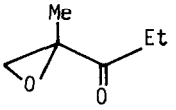
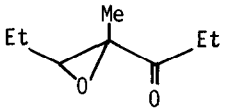
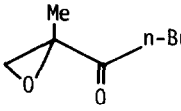
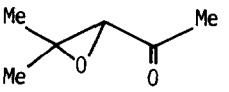
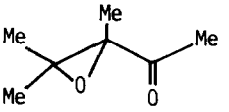
Epoxidation of the allyl alcohols (1) with tert-butyl hydroperoxide catalyzed by $VO(acac)_2$ was reported to give the corresponding erythro-α, β-epoxy alcohols (2), a useful synthon for the syntheses of polyoxo macrolide antibiotics, in high stereoselectivity.[2] The same erythro-α, β-epoxy alcohols (2) can also be obtained by $NaBH_4$ reduction of the corresponding α, β-epoxy ketones (4).[3] However, in both cases, the stereoselectivity is known to be subtly affected by the substituents on the starting materials. Namely, the rather low selectivity was obtained when the α substituent is hydrogen in the epoxidation of 1. On the other hand, the selectivity is almost lost when the substituent at the α position is methyl in the reduction of 4. In the cases where the substituent at the β^c position is methyl in 1, the isomeric threo-epoxy alcohols (3) are produced in high selectivity on epoxidation. We now report that zinc borohydride reduction of α, β-epoxy ketones (4) affords the erythro-epoxy alcohols (2) in high stereoselectivity irrespective of the substitution pattern of the epoxide.[4]



(1) erythro (2) threo (3) (4)

In the previous paper,[5] we reported that zinc borohydride reduction of β-keto esters afforded the erythro-β-hydroxy esters almost exclusively when the ketones were conjugated with the unsaturated systems. These results were reasonably rationallized by taking account of a cyclic transition state in which both of the carbonyl oxygens coordinated to a zinc cation. This type of mechanism was expected to be valid for the reduction of the α, β-epoxy ketones (4), since both oxygens were nicely located to form a zinc mediated transition state. In fact, when α, β-epoxy ketones (4)[6] were treated with zinc borohydride[7] in ether, the erythro-α, β-epoxy alcohols (2) were produced in high stereoselectivity in all cases examined. The results were summerized in Table 1. The reported data for $NaBH_4$ reduction[3] were also presented in Table 1 for comparison.

Table 1. Reduction of α, β-Epoxy Ketones (4) with $Zn(BH_4)_2$

α, β-Epoxy Ketone (4)		Product erythro (2) : threo (3)	Yield[a]	$NaBH_4$[b] erythro (2) : threo (3)
4a:		98 : 2[c]	80 %	100 : 0
4b:		90 : 10[d]	76 %	55 : 45
4c:		84 : 16[d]	79 %	65 : 35
4d:		99 : 1[d]	76 %	-----
4e:		99 : 1[d]	83 %	-----
4f:		97 : 3[d]	87 %	-----
4g:		>99 : <1[d]	83 %	86 : 14
4h:		>99 : <1[d]	86 %	46 : 54

[a]Combined isolated yield. [b]Cited from ref. 3. [c]Ratio determined by ^{13}C NMR data. [d]Ratio determined by GLC on 2 m column packed with 10 % Carbowax 20M/Celite-545.

A typical procedure is as follows: To an ice cold solution of 165 mg (1.45 m mol) of 3, 4-epoxy-4-methyl-2-pentanone (4g) in 2 ml of anhyd. ether was added 3 ml (ca. 0.44 m mol) of zinc borohydride in ether under argon with stirring. After 45 min at 0 °C, 1 ml of water was added and stirring was continued for an additional 30 min, and then the solvent was dried over $MgSO_4$. The ether solution was directly subjected to GLC to determine the ratio of erythro - and threo-alcohols (2 and 3).[8] The solvent was then evaporated to give 140 mg of erythro-3, 4-epoxy-4-methyl-2-pentanol (2g).

Recently, excellent methods for the synthesis of optically active α, β-epoxy ketones or α, β-epoxy alcohols are reported.[9] Therefore, when the present reduction is combined with these methods, optically active erythro-α, β-epoxy alcohols are expected to be prepared.

Chautemps and Pierre[3] have proposed the chelated model (A) for the transition state of the $NaBH_4$ reduction of the epoxy ketones (4) as shown in Fig. 1, in which the hydride attacked a carbonyl group from the less hindered side. The fact that the stereoselectivity is almost lost when the α-substituent is methyl in their cases (2b : 3b = 55 : 45, 2c : 3c = 65 : 35; see Table 1) can be explained by this model. However, Bartlett[10] has considered that a contribution of the chelated transition state involving sodium cation is unlikely particularly in alcohol solvents and he suggested that the transition state of the reduction would be resembling for the conformation (B) when the α-substituent was hydrogen. The diminished stereoselectivity observed for the compounds having a methyl group at the α-position can be ascribed for the destabilization of the conformation (B) due to an interaction of R with the α-methyl group.

On the other hand, the high erythro-selectivity was obtained in our $Zn(BH_4)_2$ reduction regardless of the substituents on the epoxide ring (Table 1). Therefore, further elaboration should be necessary to account for these observations. Since $Zn(BH_4)_2$ is used in our case, the chelated model (C) or (D) should now be considered for the transition state.[11] It is apparent that the model (C) is much favoured over the model (D) because a severe interaction is present between the reagent and the methylene group at the β-position of the model (D). Internal hydride transfer subsequently takes place from the model (C). Here, it is highly expected that the hydride transfer proceeds from the direction shown by the arrow even if a sterically demanding methyl group is present at the α-position, affording the expected erythro-isomers.

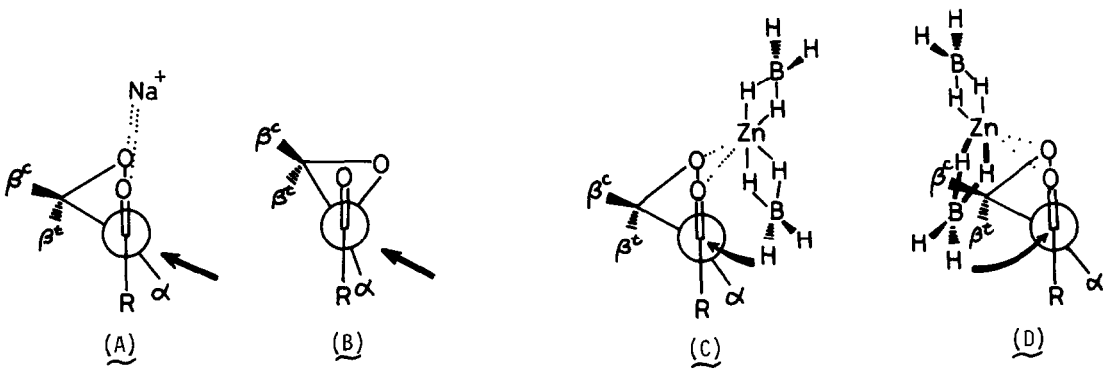


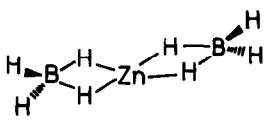
Fig. 1

Further studies are continuing in our laboratory for the stereoselective $Zn(BH_4)_2$ reduction of various ketones in other systems and an application of the present method to natural products synthesis is in progress.

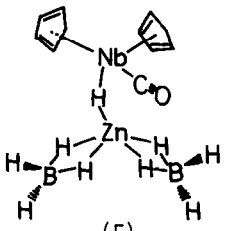
Acknowledgement: This work was supported in part by a Grant-in-Aid for scientific research from the Ministry of Education, Science, and Culture (557495). The authors are grateful to Dr. Hiroshi Yamazaki of this Institute for valuable discussions.

References and Notes

1. This work was presented at the 101st Annual Meeting of the Pharmaceutical Society of Japan at Kumamoto, April, 1981 (Abstracts of Papers, p. 452).
2. a) B. E. Rossiter, T. R. Verhoeven, and K. B. Sharpless, Tetrahedron Lett., 1979, 4733, and references cited therein; cf. E. D. Mihelich, ibid., 1979, 4728; K. Takai, K. Oshima, and H. Nozaki, ibid., 21, 1657 (1980). b) Epoxidation of the allyl alcohol (1h) was carried out in this laboratory according to the Sharpless procedure [erythro (2h) : threo (3h) = 23 : 77].
3. P. Chautemps and J.-L. Pierre, Tetrahedron, 32, 549 (1976).
4. The same type of reduction has also been successfully carried out by Prof. M. Yamaguchi, Kyushu University; private communication.
5. T. Nakata and T. Oishi, Tetrahedron Lett., 21, 1641 (1980).
6. Starting materials (4) were prepared by two methods; i) Epoxidation of enones with 30% H_2O_2 -aq. NaOH[12] (for 4a, b, c, g, and h). ii) Epoxidation of allyl alcohols (1) with MCPBA followed by Jones oxidation (for 4d, e, and f).
7. W. J. Gensler, F. Johnson, and A. D. B. Sloan, J. Am. Chem. Soc., 82, 6074 (1960).
8. Authentic samples of erythro- and threo-epoxy alcohols (2 and 3) were prepared by the method of Sharpless.[2a]
9. S. Julia, J. Masana, and J. C. Vega, Angew. Chem. Intern. Ed., 19, 929 (1980); T. Katsuki and K. B. Sharpless, J. Am. Chem. Soc., 102, 5974 (1980); B. E. Rossiter, T. Katsuki, and K. B. Sharpless, ibid., 103, 464 (1981).
10. P. A. Bartlett, Tetrahedron, 36, 2 (1980).
11. The reagent $Zn(BH_4)_2$ is expected to exist as a contact ion pair in ether[13] and its structure may be shown as E, since the structure of $Cp_2Nb(CO)H{\cdot}Zn(BH_4)_2$ is determined by X-ray crystallography as F.[14] It is known that Zn^{2+} can form a six-coordinated complex (cf. $[Zn(NH_3)_6]^{2+}$).[15] Therefore, in the model (C), a six-coordinated structure is tentatively adopted for a simple understanding of a gross structure for the transition state, although there is no direct evidences for that. The more stable four-coordinated structure produced by Zn-H bond cleavage may also be considered.



(E)



(F)

12. P. S. Wilder and A. A. Polnick, U. S. Patent 2431718 (1947)[C. A., 42, 3430^i (1948)]; P. Baret, J.-L. Pierre, and R. Heilmann, Bull. Soc. Chim. Fr., 4735 (1967); H. O. House and R. S. Ro, J. Am. Chem. Soc., 80, 2428 (1958).
13. cf. E. C. Ashby, F. R. Dobbs, and H. P. Hopkins, Jr., ibid., 95, 2823 (1973); idem , ibid., 97, 3158 (1975).
14. M. A. Porai-Koshits, A. S. Antsyshikina, A. A. Pasynskii, G. G. Sadikov, Yu. V. Skripkin, and V. N. Ostrikova, Inorg. Chem. Acta., 34, L 285 (1979).
15. D. P. Graddon, "An Introduction to Co-Ordination Chemistry", Pergamon Press, 1961, p. 15.

(Received in Japan 4 August 1981)