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Syn-epoxidation of Chiral (Z)-2-Methyl-3-alkenal Acetal via Stereo-selective Bromohydrin Formation

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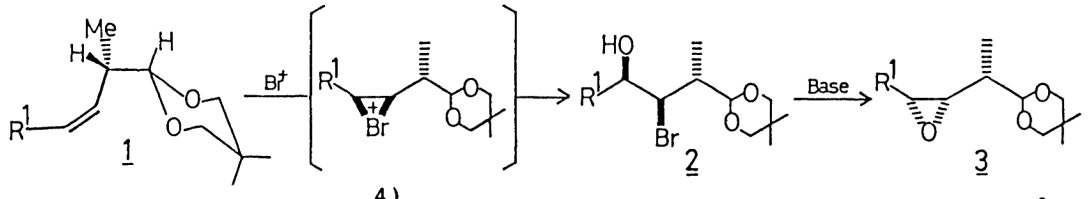
Synthesis of syn-epoxide from chiral (Z)-2-methyl-3-alkenal acetal via stereoselective bromohydrin formation by using a reagent prepared from N-bromosuccinimide (NBS) and dimethyl sulfoxide (DMSO) under irradiation, and regioselective C-C bond formation were described.

Recently we have reported the highly anti-selective epoxidation of (Z)-alkenal acetal (1)[1] via a metal catalyzed epoxidation using *tert*-butyl hydroperoxide (TBHP).[2] Hence it is very important to develop a synthetic procedure of the corresponding syn-epoxide. We interested in the control of stereo- and regio-selectivities by the practical use of the acetal group in acyclic systems.

Two-step conversion of an olefin to an epoxide via bromohydrin formation had been widely used. Dalton had reported a general procedure by using NBS in moist DMSO, and then proposed the mechanism where DMSO attacked to a bromonium ion and followed by hydrolysis.[3] We considered that 2,3-anti-bromonium ion would be generated stereoselectively by the hindrance of the methyl group, since the most stable conformation of 1 would be represented in Eq. 1. Then DMSO would attack at γ-position regioselectively by the hindrance of the methyl and the acetal groups to give 2,3-anti-bromohydrin (2), which would be easily converted into syn-epoxide (3).



(1)

The treatment of (Z)-1[4] with NBS (2 equiv.) in moist DMSO at 15 °C showed a little anti-selectivity (anti/syn=1.5, Table 1, entry 1). As the results of examinations, the selectivity was enhanced by the solvents in the following order diethyl ether > dichloromethane > acetonitrile (Table 1, entries 2,3,4). Moreover it was proven that bromohydrin formation did not proceed at low temperature without light, when bromine was generated to give dibromide as a by-product in the presence of water (entry 5). Typical procedure was as follows: Into NBS (4 mmol) in Pyrex vessel under an argon atmosphere, anhydrous diethyl ether (4 ml) and DMSO (10 mmol) were added at -18 °C. The mixture was irradiated by using a usual fluo-

rescent lamp, and the temperature was raised up until a precipitate (NBS) colored pale yellow. After irradiation for 15 min at -18 °C, water (5 mmol) in THF (6 ml) was added. Into the obtained clear yellow solution, (Z)-1[4] (1 mmol) in diethyl ether (2 ml) was added in dark. After 2 h, an aqueous $Na_2S_2O_3$ (4 equiv.) was added. The mixture was extracted with diethyl ether and evaporated at 0 °C. The residue was purified by silica-gel column chromatography to give 2 (Table 1, entries 7,8).

Table 1. Bromohydrin formation of (Z)-1

Entry	R^1	NBS/equiv.	Solvent	Temp/°C	Yield/%	anti/syn
1	$Ph(CH_2)_3$	2.0	DMSO	15[a]	90	60/40
2	"	"	MeCN	-42→-20[a]	52	59/41
3	"	"	CH_2Cl_2	-78→-42[a]	52	70/30
4	"	"	Et_2O	-78→-12[a]	66	74/26
5	"	"	"	-12,[b,c]-78	56	91/9
6	"	4.0	"	-18,[c]-42	55	89/11
7	"	"	"	-18,[c]-18	83	89/11
8	Me	"	"	"	86	84/16

a) In the natural light. b) with water. c) Irradiated.

We assumed that a bromo radical generated by irradiation of NBS reacted with DMSO to give an unknown yellow compound,[5] which added to olefin to give an adduct or to water to give hypobromous acid. Bromohydrin (2) was treated with sodium hydride in DMF[6] to give syn-epoxide (3) in 85% yields (Fig. 1).

(2S, 3R, 4R)-Syn-epoxide (3) and (2S, 3S, 4S)-anti-epoxide (4)[1] reacted at γ-position regioselectively with some nucleophiles. The treatment of 3 and 4 with MeLi (10 equiv.) - CuI (1 equiv.) gave (2S, 3R, 4S)-5 and (2S, 3S, 4R)-6 in 50% (recovered 46% of 3) and 85% yields, respectively. Thus all diastereomers can be prepared by the selection of R^1, R^2 and the chirality of 1. Moreover the treatment of 5 and 6 with difluoro-(3-tetrahydropyranyloxy-1-propynyl)borane at -78 °C[7] gave 6-alkyloxy-5-alkynes (7 and 8) in 96% yield in both cases (Fig. 1). They are useful chiral synthons for the synthesis of three and more-serial asymmetric centers in acyclic systems. The application of these methodologies to the synthesis of natural product is under current investigation.

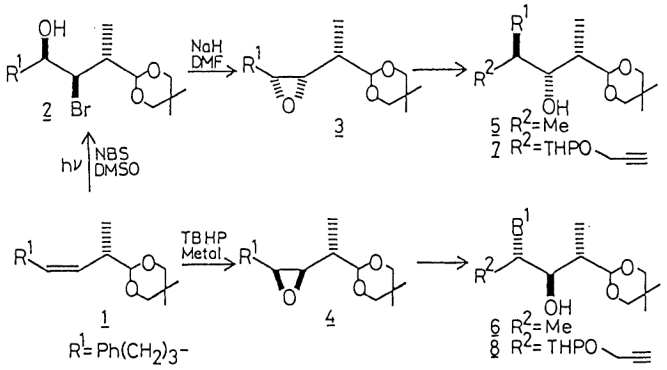


Fig. 1.

References

1) Y. Honda, M. Sakai, and G. Tsuchihashi, *Chem. Lett.*, 1985, 1153.
2) Y. Honda, A. Ori, and G. Tsuchihashi, *Chem. Lett.*, 1986, 1417.
3) D. R. Dalton and D. G. Jones, *Tetrahedron Lett.*, 1967, 2875; D. R. Dalton, V. P. Dutta, and D. C. Jones, *J. Am. Chem. Soc.*, 90, 5498 (1968).
4) (E)-Aldehyde acetal was also converted to a bromohydrin under the same conditions, but it was easily oxidized by NBS to give a corresponding ester.
5) This electrophile might be Br-O-SMe_2^+.
6) The treatment of 2 with *t*-BuOK in *t*-BuOH gave 4-ketone (28%, Fig. 2) as a by-product besides 3 (72%) through hydride rearrangement.
7) M. Yamaguchi and I. Hirao, *Tetrahedron Lett.*, 24, 391 (1983).

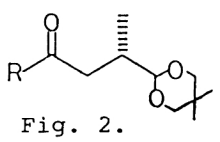


Fig. 2.

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