PRACTICAL PREPARATION OF OPTICALLY ACTIVE *O*-BENZYLGLYCIDOL FROM OPTICALLY ACTIVE EPICHLOROHYDRIN

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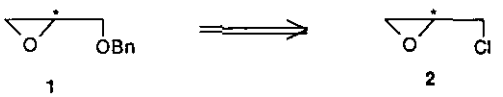
Abstract —— *Practical preparation of optically active O-benzyl-*glycidol has been developed starting from optically active epichlorohydrin by employing either basic or acidic conditions in the key stage.

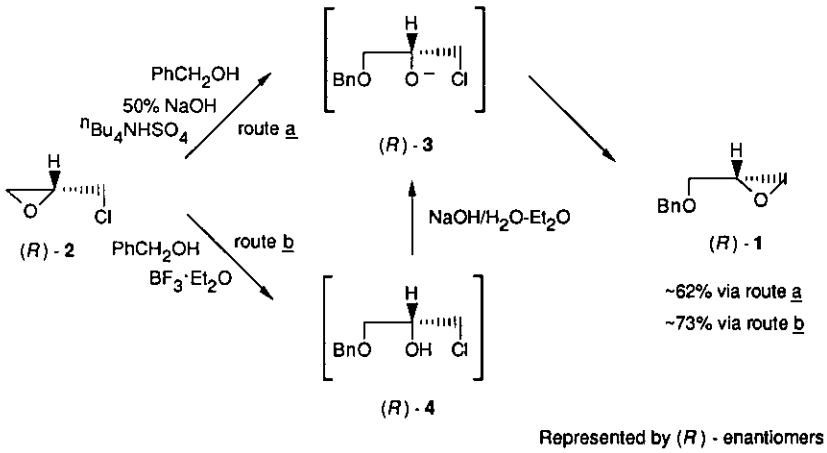
Optically active *O*-benzylglycidol[1~3] (**1**) is an important key building block for the synthesis of a wide variety of optically active compounds such as natural products.[4] Although **1** can be most readily accessible from D-mannitol, it requires a little lengthy sequence of reactions.[1~3] We report here a simple practical procedure for the preparation of optically active *O*-benzylglycidol (**1**) starting from optically active



1 **2**

Scheme 1

epichlorohydrin[5] (**2**) by employing either basic (route a) or acidic (route b) conditions in the key stage. It has been confirmed that **2** is selectively cleft at the epoxy-end[6] under both basic and acidic conditions in high selectivity which is concluded by optical rotation of the product (**1**) and comparison of optical purities between the starting



Scheme 2

material (**2**) (~98% ee) and the product (**1**) (~95% ee). Although both of the basic (route a)[7] and the acidic (route b)[8] procedures are based on the established methods for racemic production of *O*-benzylglycidol where a large excess of racemic epichlorohydrin has been used, the present method is modified in order to avoid wasting of valuable chiral starting material.

Thus treatment of (*R*)-epichlorohydrin[9] [(*R*)-**2**] with 0.9 molar equivalent of benzyl alcohol in 50% aqueous sodium hydroxide solution in the presence of phase transfer catalyst afforded (*R*)-*O*-benzylglycidol [(*R*)-**1**] in one step in an acceptable yield (~65%) with a minor loss (1~2%) of original chiral integrity (route a). On the same treatment the enantiomeric chloride[9] [(*S*)-**2**] gave the enantiomeric ether [(*S*)-**1**] in a comparable yield with a comparable optical purity. These indicate that the reaction proceeds with initial epoxy-end cleavage followed by cyclization of the chlorohydroxide intermediate (**3**) under the conditions.[6]

On the other hand, treatment of a mixture of (*R*)-epichlorohydrin [(*R*)-**2**] and 2.5 molar equivalents of benzyl alcohol with a catalytic amount of boron trifluoride at 50 °C allows smooth reaction at the epoxy-end to give the chlorohydrin intermediate (**4**) which without isolation is directly treated with aqueous sodium hydroxide in the same reaction flask to furnish an acceptable yield (~75%) of (*R*)-*O*-benzylglycidol [(*R*)-**1**] with a minor loss (1~2%) of original chiral integrity (route b). On the similar

treatment the (*S*)-chloride [(*S*)-**2**] gives the enantiomeric ether [(*S*)-**1**] in a comparable yield with a comparable optical purity.

Although a little racemization is found to be unavoidable under both basic and acidic conditions, the present procedure converting optically active epichlorohydrin (**2**) into optically active *O*-benzylglycidol (**1**) has of great practical value for the construction of a wide variety of optically active compounds.

EXPERIMENTAL SECTION

Optical rotations were measured with a JASCO-DIP-370 digital automatic polarimeter. Optical purity of epichlorohydrin was estimated by ^{1}H nmr spectra (500 MHz) using (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol[10] as shift reagent with a JEOL-JNM-GX 500 instrument. Optical purity of *O*-benzylglycidol was estimated by hplc using a EYELA PLC-10 instrument equipped with a CHIRALCEL OD (DAICEL) column using a mixture of *i*-PrOH-hexane (1:20) as eluent. Mass spectra were recorded with a JEOL-JMS-AX500 instrument. Reactions were carried out under argon.

Preparation[11] of Optically Active *O*-Benzylglycidol (1) from Optically Active Epichlorohydrin (2):

(*R*)-*O*-Benzylglycidol [(*R*)-1]:

(a) Basic conditions (route a) —— To a stirred mixture of (*R*)-epichlorohydrin [(*R*)-**2**: 2.0 g, 21.6 mmol], benzyl alcohol (2.12 g, 19.6 mmol), and tetrabutylammonium hydrogen sulfate (290 mg, 0.86 mmol) is added 50% (w/v) aqueous sodium hydroxide (10 ml) dropwise at 0 °C and the stirring is continued for 30 min at the same temperature and for 4 h at room temperature. The mixture is extracted with ether (4 x 25 ml) and the extract is washed with brine (2 x 10 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The residue is purified by chromatography on a silica gel column using a mixture of hexane-ether (6:1 v/v) as eluent to give pure (*R*)-*O*-benzylglycidol [(*R*)-**1**] as a colorless oil; yield: 2.00 g (62%); bp 120-130 °C/0.6 Torr (Kugelrohr); $[\alpha]_D^{32}$ +9.8±0.2° (*c* 5.13, MeOH) [95±0.5% ee by hplc]. Spectral data (ir, ^{1}H nmr, and mass) are identical with those of an authentic material.

(b) Acidic conditions (route b) —— To a stirred mixture of (*R*)-epichlorohydrin [(*R*)-**2**: 10.0 g, 108.0 mmol] and benzyl alcohol (29.2 g, 270.0 mmol) is added boron trifluoride etherate (0.4 ml, 3.3 mmol) at room temperature and the mixture is further stirred at 50 °C for 18 h. After cooling to room temperature, to a stirred mixture is added sodium hydroxide (6.50 g, 162.0 mmol) in water (160 ml) and ether (80 ml) and the stirring is continued for 18 h at the same temperature. After separating the organic layer, the aqueous layer is extracted with ether (3 x 100 ml). The combined organic layers are washed with brine (2 x 30 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The residue is purified by chromatography on a silica gel column using a mixture of hexane-ether (6:1 v/v) as eluent to give pure (*R*)-*O*-benzylglycidol [(*R*)-**1**] as a colorless oil; yield: 13.2 g (75%); bp 120-130 °C/0.6 Torr (Kugelrohr); $[\alpha]_D^{28}$ +9.8±0.2° (*c* 4.90, MeOH) [95±0.5% ee by hplc]. Spectral data (ir, ^1H nmr, and mass) are identical with those of an authentic material.

(*S*)-*O*-Benzylglycidol [(*S*)-1]:

(a) Basic conditions (route a) —— To a stirred mixture of (*S*)-epichlorohydrin [(*S*)-**2**: 2.0 g, 21.6 mmol], benzyl alcohol (2.12 g, 19.6 mmol), and tetrabutylammonium hydrogen sulfate (290 mg, 0.86 mmol) is added 50% (w/v) aqueous sodium hydroxide (10 ml) dropwise at 0 °C. After stirring for 30 min at 0 °C and for 4 h at room temperature, the mixture is treated quite similarly as for the enantiomer [(*R*)-**1**] to give pure (*S*)-*O*-benzylglycidol [(*S*)-**1**] as a colorless oil; yield: 1.56 g (61%); $[\alpha]_D^{33}$ –9.9±0.2° (*c* 5.00, MeOH) [95±0.5% ee by hplc].

(b) Acidic conditions (route b) —— To a stirred mixture of (*S*)-epichlorohydrin [(*S*)-**2**: 2.00 g, 21.6 mmol] and benzyl alcohol (5.84 g, 54.0 mmol) is added boron trifluoride etherate (0.08 ml, 0.66 mmol) at room temperature and the mixture is further stirred at 50 °C for 18 h. The mixture is treated quite similarly as for the enantiomer [(*R*)-**1**] to give pure (*S*)-*O*-benzylglycidol [(*S*)-**1**] as a colorless oil; yield: 2.60 g (73%); bp 120-130 °C/0.6 Torr (Kugelrohr); $[\alpha]_D^{28}$ –9.9±0.2° (*c* 5.04, MeOH) [96±0.5% ee by hplc]. Spectral date (ir, ^1H nmr, and mass) are identical with those of an authentic material.

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4. A review on the utilization of chiral *O*-benzylglycidol in natural product synthesis, see: S. Takano and K. Ogasawara, *J. Syn. Org. Chem. Jpn.*, 1989, **47**, 813.
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6. Cf. D. E. McClure, B. H. Arison, and J. J. Baldwin, *J. Am. Chem. Soc.*, 1979, **101**, 3666.
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9. Optical purity of both (*R*)- and (*S*)-epichlorohydrins is estimated to be ~98% ee, respectively, by ^{1}H nmr (500 MHz) using (*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol[10] as shift reagent.
10. Cf. G. R. Weisman, "*Asymmetric Synthesis*," Vol. 1, Academic, New York, 1983, p. 153.
11. Each reaction is repeated four times.

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