A FACILE SYNTHESIS OF (*S*)-*O*-BENZYLGLYCIDOL

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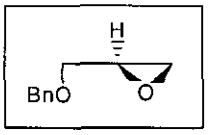
Abstract —— A facile synthesis of (*S*)-*O*-benzylglycidol has been developed starting from (*R*)-1-*O*-benzylglycerol by sequential monohalogenation and cyclization.

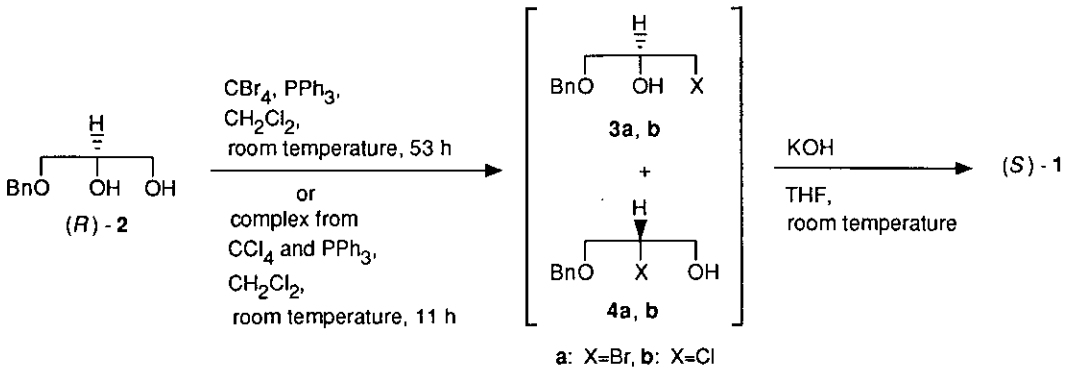
Optically active *O*-benzylglycidol[1] (**1**) is a powerful building block for the construction of a wide variety of optically active compounds.[2] We report here a simple and facile procedure for the synthesis of (*S*)-*O*-benzylglycidol [(*S*)-**1**] from (*R*)-1-*O*-benzylglycerol[3] [(*R*)-**2**] under mild conditions which may be generally applicable to the transformation of a terminal 1,2-glycol functionality into the corresponding 1,2-epoxide functionality with retention of the chirality.



(*S*)-1

Figure 1

Treatment of (*R*)-1-*O*-benzylglycerol [(*R*)-**2**] with each small excess of carbon tetrabromide and triphenylphosphine[4~6] in dichloromethane at room temperature afforded the bromohydrins (**3a**) and (**4a**) as a separable mixture. When the mixture without separation was exposed to potassium hydroxide in tetrahydrofuran at room temperature, the major component (**3a**) reacted faster rate to leave the minor



Scheme 1

component (**4a**) which could be isolated. The mixture, however, was ultimately transformed into a single (*S*)-*O*-benzylglycidol [(*S*)-**1**] in an excellent overall yield in 98.2% ee of optical purity on prolonged stirring (~6 h).

The mixture could be separated by a flash column chromatography to give the primary bromide (**3a**) and the secondary bromide (**4a**) in a ratio of 3.4:1. Both of **3a** and **4a** afforded the same (*S*)-*O*-benzylglycidol [(*S*)-**1**] in yield of 92 and 88% with 98.3 and 98.1% ee, respectively, on the same alkaline treatment. This concludes us that the present procedure did not bring about racemization despite of the formation of the secondary bromide (**4a**).

We next examined the synthesis of the same (*S*)-*O*-benzylglycidol [(*S*)-**1**] by employing the chlorinating method.[4~7] In order to avoid the bis-chlorination, we first prepared a complex by refluxing triphenylphosphine with carbon tetrachloride. Upon treatment with this complex in dichloromethane at room temperature, (*R*)-1-*O*-benzylglycerol [(*R*)-**2**] furnished an inseparable mixture of the primary chloride (**3b**) and the secondary chloride (**4b**) which can be directly transformed into (*S*)-*O*-benzylglycidol [(*S*)-**1**] in 88% yield in >98% ee of optical purity.

In conclusion, neither serious racemization nor bis-halogenation occurred during the formation of the glycidol [(*S*)-**1**] from the glycerol [(*R*)-**2**] under two conditions.

EXPERIMENTAL SECTION

Optical rotations were measured with a JASCO-DIP-370 digital polarimeter. Ir spectra were measured with a JASCO-IR-700 spectrophotometer. ^{1}H Nmr spectra were recorded on JEOL-JNM-FX90A (90 MHz) and JEOL-JNM-GX500 (500 MHz) spectrometers. Mass spectra were measured with a JEOL JMS-DX303 instrument. Optical purity of both (*R*)-1-*O*-benzylglycerol [(*R*)-**2**] and (*S*)-*O*-benzylglycidol [(*S*)-**1**] was determined by hplc using a EYELA PLC-10 instrument equipped with a CHIRALCEL OD (DAICEL) column using a mixture of *i*-PrOH-Hexane-Et_2NH (20:80:0.1) for (*R*)-**2** and *i*-PrOH-Hexane (1:20) for (*S*)-**1** as eluent. Reactions were carried out under argon.

Preparation of (*S*)-*O*-Benzylglycidol [(*S*)-1] via the Bromohydrins, (3a) and (4a) —— To a stirred solution of (*R*)-1-*O*-benzylglycerol[3] [(*R*)-**2**: 1.00 g, 5.49 mmol, >98% ee by hplc] and carbon tetrabromide (2.01 g, 6.06 mmol) in dichloromethane (6 ml) is added a solution of triphenylphosphine (1.59 g, 6.06 mmol) in dichloromethane (9 ml) dropwise at 0 °C and the mixture is stirred at room temperature for 53 h. The mixture is washed with water, dried over $MgSO_4$, and evaporated under reduced pressure to leave the residue (4.12 g) containing the bromohydrins (**3a**) and (**4a**). To a stirred solution of the residue in tetrahydrofuran (THF) (30 ml) is added ground KOH (2.42 g, 43.1 mmol) at 0 °C and the mixture is stirred at room temperature for 6 h. In this reaction, a less polar major component (**3a**) is consumed completely after 3 h and a more polar minor component (**4a**) can be isolated if the reaction is quenched at this stage.

After having both components had been consumed, the mixture is diluted with ether and washed with H_2O and brine, and the organic layer is separated. The organic layer is dried over $MgSO_4$ and evaporated under reduced pressure to leave the crude epoxide which is purified by chromatography on a silica gel column (60 g) using a mixture of hexane-ether (8:1 v/v) as eluent to give pure (*S*)-*O*-benzylglycidol [(*S*)-**1**] as a colorless oil; yield: 748 mg (83%); $[\alpha]_D^{31}$ –10.61° (*c* 5.36, MeOH) [98.2% ee by hplc]. Spectral data are identical in all respects with those of an authentic material.[1]

Separation of (*S*)-1-Benzyloxy-3-bromo-2-propanol (3a) and (*S*)-1-Benzyloxy-2-bromo-1-propanol (3b) from the Mixture —— A part of the

mixture is separated by a flash column (SiO_2) using a mixture of hexane-ether (8:1 v/v) as eluent to give the primary bromide (**3a**) as a less polar fraction and the secondary bromide (**4a**) as a more polar fraction in a ratio of 3.4:1.

(*S*)-1-Benzyloxy-3-bromo-2-propanol (3a): a colorless oil; $[\alpha]_D^{31}$ –1.81° (c 1.27, $CHCl_3$). Ir (neat) ν_{max} 3438 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 2.51 (d, *J*=6.1 Hz, 1H, exchangeable with D_2O), 3.48 (dd, *J*=6.1, 10.4 Hz, 1H), 3.54 (dd, *J*=5.5, 10.4 Hz, 1H), 3.59 (dd, *J*=4.9, 9.8 Hz, 1H), 3.62 (dd, *J*=5.5, 9.8 Hz, 1H), 4.00 (m, 1H), 4.57 (s, 2H), 7.34 (m, 5H); ms (m/z): 246, 244 (M^+), 91 (100%). Calcd for $C_{10}H_{13}O_2{}^{81}Br$: 246.0078. Found: 246.0070. Calcd for $C_{10}H_{13}O_2{}^{79}Br$: 244.0099. Found: 244.0086.

(*S*)-1-Benzyloxy-2-bromo-1-propanol (4a): a colorless oil; $[\alpha]_D^{31}$ –3.48° (*c* 1.06, $CHCl_3$). IR (neat) ν_{max} 3438 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 2.20 (dd, *J*=6.7, 6.7 Hz, 1H, exchangeable with D_2O), 3.79 (dd, *J*=7.3, 10.5 Hz, 1H), 3.83 (dd, *J*=5.5, 10.5 Hz, 1H), 3.91 (ddd, *J*=5.5, 6.7, 12.2 Hz, 1H), 3.95 (ddd, *J*=5.5, 6.7, 12.2 Hz, 1H), 4.22 (m, 1H), 4.59 (s, 2H), 7.35 (m, 5H); ms (m/z): 246, 244 (M^+), 91 (100%). Calcd for $C_{10}H_{13}O_2{}^{81}Br$: 246.0078. Found: 246.0072. Calcd for $C_{10}H_{13}O_2{}^{79}Br$: 244.0099. Found: 244.0075.

(*S*)-*O*-Benzylglycidol [(*S*)-1] from the Primary Bromide (3a) —— A mixture of the primary bromide (**3a**, 353 mg, 1.44 mmol) and ground KOH (198 mg, 3.53 mmol) in THF (5 ml) is stirred at room temperature for 4 h. After dilution with ether, the mixture is washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to leave the crude epoxide which is purified by chromatography on a silica gel column (4.7 g) using a mixture of hexane-ether (8:1 v/v) as eluent to give pure (*S*)-*O*-benzylglycidol [(*S*)-1] as a colorless oil; yield: 216 mg (92%); $[\alpha]_D^{32}$ –10.26° (*c* 1.83, MeOH) [98.3% ee by hplc]. Spectral data are identical in all respects with those of an authentic material.

(*S*)-*O*-Benzylglycidol [(*S*)-1] from the Secondary Bromide (4a) —— A mixture of the secondary bromide (**4a**, 61 mg, 0.25 mmol) and ground KOH (79 mg, 1.41 mmol) in THF (1 ml) is stirred at room temperature for 6.5 h. After dilution with ether, the mixture is washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to leave the crude epoxide which is purified by chromatography on a silica gel column (4.0 g) using a mixture of hexane-ether (8:1 v/v) as eluent to give pure (*S*)-*O*-benzylglycidol [(*S*)-1] as a colorless oil; yield: 36 mg (88%); $[\alpha]_D^{30}$ –10.95°

(*c* 1.10, MeOH) [98.1% ee by hplc]. Spectral data are identical in all respects with those of an authentic material.[1]

Preparation of (*S*)-*O*-Benzylglycidol [(*S*)-1] via the Chlorohydrins, (3b) and (4b) —— A solution of triphenylphosphine (2.89 g, 11.0 mmol) in carbon tetrachloride (25 ml) is refluxed for 37 h. After cooling the mixture is evaporated under reduced pressure to leave the complex. A solution of this complex in dichloromethane (25 ml) is added dropwise to a stirred solution of (*R*)-1-*O*-benzylglycerol[3] [(*R*)-**2**: 1.00 g, 5.49 mmol, >98% ee by hplc] in dichloromethane (5 ml) at 0 °C and the mixture is stirred at room temperature for 11 h. The mixture is washed with saturated aqueous sodium hydrogen carbonate, brine, dried over $MgSO_4$, and evaporated under reduced pressure to leave the residue (4.45 g) containing the chlorohydrins (**3b**) and (**4b**).

To a stirred solution of the residue in THF (20 ml) is added ground KOH (2.50 g, 44.5 mmol) and the mixture is stirred at room temperature for 2 h. After dilution with ether, the mixture is washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to leave the crude epoxide which is purified by a silica gel column (80 g) using a mixture of hexane-ether (8:1 v/v) as eluent to give pure (*S*)-*O*-benzylglycidol [(*S*)-**1**] as a colorless oil; yield: 794 mg (88%); $[\alpha]_D^{30}$ –10.28° (*c* 5.23, MeOH) [>98% ee by hplc]. Spectral data are identical in all respects with those of an authentic material.[1]

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Received, 18th June, 1991