An Efficient Synthesis of (*S*)-*O*-Benzylglycidol

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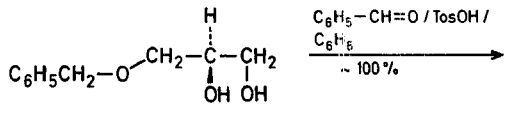
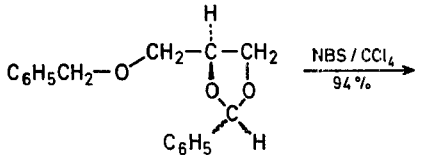
Optically acitve *O*-benzylglycidol **(5)** is widely used as a key chiral building block in enantioselective syntheses of a variety of natural products[1-14]. An efficient synthetic route for this material is, therefore, very important. Synthesis of this material so far has been carried out from optically active 1-*O*-benzylglycerol **(1)** in two steps[15,16] via the monotosylate intermediate or in one step[17] by using the Mitsunobu reaction[18]. Although both the methods are sufficiently practical for a small scale synthesis, formation of the ditosylate by-product and its separation in the former synthesis, and neccessity of expensive reagent and chromatographic separation in the latter synthesis, make these methods less convenient for large scale production. We report here a simple and efficient conversion of optically active 1-*O*-benzylglycerol **(1)** into optically active *O*-benzylglycidol **(5)** via the reaction of the benzylidene derivative **2** with *N*-bromosuccinimide[19] as the key step. The present synthesis requires three steps to convert the glycol **1** into the epoxide **5**, however, the overall yield is high and it does not involve any difficult manipulations.

Treatment of **1** with one equivalent of benzaldehyde in refluxing benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid gave the benzylidene acetal **2**[20] in quantitative yield as an inseparable mixture (~1:1) of epimers at the benzylidene carbon. This mixture, without purification, was treated with one equivalent of *N*-bromosuccinimide in

carbon tetrachloride at room temperature to give 2-benzoyloxy-3-benzyloxypropyl bromide (**3**), exclusively, in 94% yield. The crude bromide **3**, upon treatment with 2.5 equivalents of sodium hydroxide in dimethoxyethane for 24 h[21], afforded the epoxide **5** in 71% yield via spontaneous cyclization of the intermediate **4**. Overall yield of the epoxide **5** from the starting glycol **1** is 71%.



(*R*)-1



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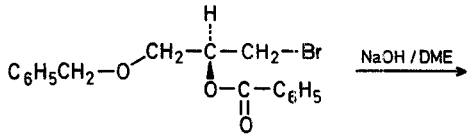

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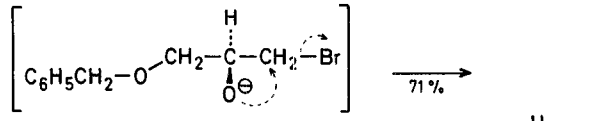

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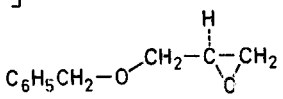

(*S*)-5

Although the present report describes the synthesis of the (*S*)-enantiomer [(*S*)-**5**], the (*R*)-counterpart may be also prepared from the same enantiomeric precursor, as we have already developed[17] an efficient conversion of (*R*)-glycol [(*R*)-**1**] into the less available (*S*)-counterpart [(*S*)]-**1**)].

All reactions were carried out under argon. I.R. spectra were measured with a JASCO A-102 spectrophotometer. ^{1}H-N.M.R. spectra were recorded on a JEOL-PMX 60 spectrometer. Mass spectra were measured with a JEOL-OISG-2 instrument. Optical rotations were measured with a JASCO-DIP-4 automatic polarimeter.

(4*S*,2*R*/*S*)-4-Benzyloxymethyl-2-phenyl-1,3-dioxolane (2):
A mixture of 1-*O*-benzylglycerol (**1**[16]; 18.20 g, 100 mmol) and benzaldehyde (10.62 g, 100 mmol) is refluxed in benzene (200 ml) for 5 h in the presence of *p*-toluenesulfonic acid (400 mg) with removal of water using a Dean-Stark trap. The mixture is washed with 5% sodium hydrogen carbonate (2 × 100 ml), brine (100 ml), and dried with magnesium sulfate. Evaporation of the solvent under reduced pressure gives the benzylidene acetal **2** in a practically pure state; yield: 28.60 g (106%). A small amount of sample is purified by distillation; b.p. 205°C/0.4 torr (Kugelrohr).

$C_{17}H_{18}O_3$	calc.	C 75.53	H 6.71
(270.3)	found	75.48	6.86

M.S. (high resolution): *m/e* = 270.1239 (calc. 270.1254).

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 3.45–4.16 (m, 4H); 4.33 (m, 1H); 4.56 (s, 1H); 4.58 (s, 1H); 5.80 (s, 1/2H); 5.93 (s, 1/2H); 7.22–7.62 (m, 5H); 7.28 ppm (s, 5H).

(*S*)-2-Benzoyloxy-3-benzyloxypropyl Bromide (3):
A mixture of the crude benzylidene acetal **2** (28.60 g, 106 mmol) and *N*-bromosuccinimide (19.80 g, 111 mmol) in carbon tetrachloride (250 ml) is stirred in the dark for 26 h. The mixture is filtered to remove succinimide and the filtrate is washed with 5% sodium hydrogen carbonate (2 × 100 ml), brine (150 ml), and dried with magnesium sulfate. Evaporation of the solvent under reduced pressure gives the bromide **3** as a pale yellow oil in practically pure state; yield: 34.86 g (94%). A small amount of sample is purified through a silica gel column (1% ether/*n*-hexane); $[\alpha]_D^{16}$: + 11.06° (*c* 2.134, chloroform).

$C_{17}H_{17}BrO_3$	calc.	C 58.47	H 4.91
(349.2)	found	58.45	4.85

M.S. (high resolution): *m/e* = 349.0396 (calc. 349.0438).

I.R. (film): ν = 1722 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 3.59 (d, 2H, *J* = 5.4 Hz); 3.68 (d, 2H, *J* = 5.4 Hz); 4.46 (s, 2H); 5.27 (quin, 1H, *J* = 5.4 Hz); 7.14–7.64 (m, 3H); 7.16 (s, 5H); 7.74–8.08 ppm (m, 2H).

(*S*)-*O*-Benzylglycidol (5):
A mixture of the crude bromide **3** (25.46 g, 73 mmol) and sodium hydroxide (7.30 g, 182 mmol) in dimethoxyethane (300 ml) is stirred at room temperature for 24 h. The mixture is poured into brine (100 ml) and is extracted with ether (2 × 100 ml). The combined extracts are washed with 5% sodium hydrogen carbonate (2 × 70 ml), brine (100 ml), and dried with magnesium sulfate. Evaporation of the solvent under reduced pressure gives a pale yellow oil which is distilled using a rotary pump to give pure (*S*)-*O*-benzylglycidol [(*S*)-**5**]; yield: 8.50 g (71%; 71% overall from **1**); b.p. 120°C/0.2 torr (Lit.[15,17], b.p. 135–145°C/0.26 torr); $[\alpha]_D$: − 15.25° (neat) [Lit.[17], $[\alpha]_D^{20}$: − 15.3° (neat); − 12.06° (neat)]. Spectral data (I.R. and ^{1}H-N.M.R.) are identical with those of an authentic material[16].

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21 The formation of epoxide **5** is more facile with potassium carbonate in alcoholic solvent (methanol, ethanol or isopropanol, less than 1 h at room temperature), but chromatographic purification is unavoidable to separate the benzoate ester which could not be achieved by distillation.