Synthesis of (*S*)-1-Benzylglycerol and (*R*)-Benzyl 2,3-Epoxypropyl Ether from (*R*)-1-Benzylglycerol

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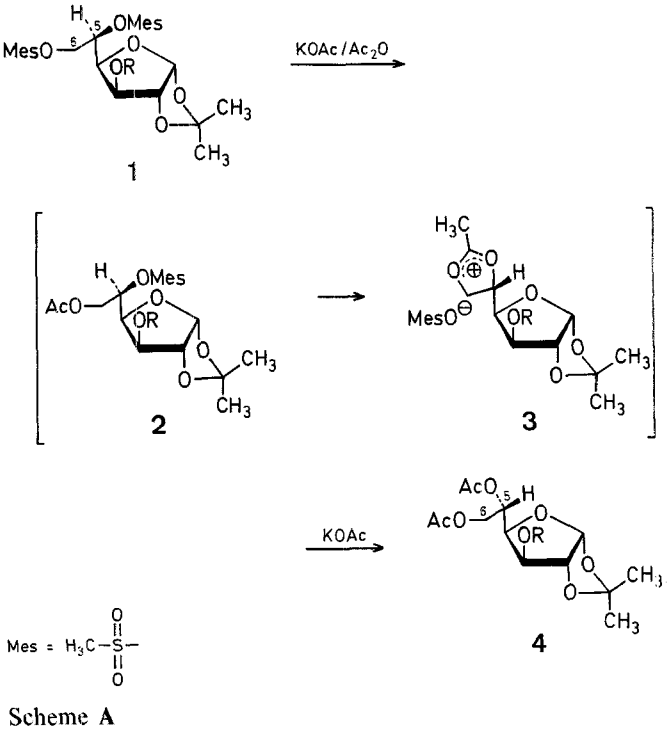
Optically active glycerol derivatives such as 1-benzylglycerol (**5**) and benzyl 2,3-epoxypropyl ether (**10**) are used as key chiral building blocks in enantioselective syntheses of a variety of natural products[1-5]. While (*R*)-1-benzylglycerol [(*R*)-**5**] is readily prepared from (D)-mannitol[6,7,8], the (*S*)-enantiomer is difficult to obtain from chiral progenitors of natural origin.

Although two methods[9,10] for the synthesis of the (*S*)-enantiomer starting from L-ascorbic acid have been developed, both are far from being practical. We report here a simple and efficient preparation of (*S*)-1-benzylglycerol [(*S*)-**5**] starting from its enantiomer (*R*)-1-benzylglycerol [(*R*)-**5**].

It has been reported[11,12] that the reaction of 1,2-*O*-isopropylidene-5,6-bis[methanesulfonyloxy]-D-glucofuranose derivatives **1** with potassium acetate in boiling acetic anhydride proceeds in the following manner: nucleophilic substitution of the mesyl group at the primary carbon atom C-6 by the acetoxy group leads to the formation of the intermediate **2**. This is then followed by an intramolecular displacement of the mesyl group at C-5 by neighbouring group participation of the newly introduced acetoxy group. Finally, the intermediate **3** is converted to the diacetate **4** characterised by an inverted carbon atom C-5 (Scheme **A**).



Scheme **A**

We have now applied the same principle to the bis-methanesulfonate **6** derived from (*R*)-1-benzylglycerol [(*R*)-**5**]. Treatment of **6** with potassium acetate in boiling acetic anhydride for 1.5 h furnished the diacetate **9** in quantitative yield. Methanolysis of the diacetate **9** in the presence of potassium carbonate gave (*S*)-1-benzylglycerol [(*S*)-**5**] with $[\alpha]_D$: $-3.73°$ ($CHCl_3$) in 91% yield (Scheme **B**). Since the starting (*R*)-enantiomer (*R*)-**5** possessed the optical rotation $[\alpha]_D$: $+3.71°$ ($CHCl_3$)[3], it may be concluded that the inversion took place in a highly stereoselective fashion. Compound (*S*)-**5** was further converted into benzyl (*R*)-2,3-epoxypropyl ether [(*R*)-**10**] in 61% yield by treatment with diethyl azodicarboxylate and triphenylphosphine[13] (Scheme **B**). Since the (*R*)-epoxide (*R*)-**10** obtained from (*S*)-**5** gives a similar optical rotation with opposite sign, $[\alpha]_D$: $+13.9°$ (neat), compared to the *S*-epoxide (*S*)-**10**, $[\alpha]_D$: $-12.06°$ (neat)[14], no inversion has occurred at the C-2 center under the reaction conditions.

All the reactions were carried out under argon. I.R. spectra were measured with a Shimadzu IR-400 spectrometer. ^{1}H-N.M.R. spectra were measured in $CDCl_3$ with a JEOL-PMX 60 spectrometer using TMS as an internal reference. Mass spectra were measured with a JEOL-D300 spectrometer. Optical rotations were measured with a JASCO-DIP-SL automatic polarimeter.

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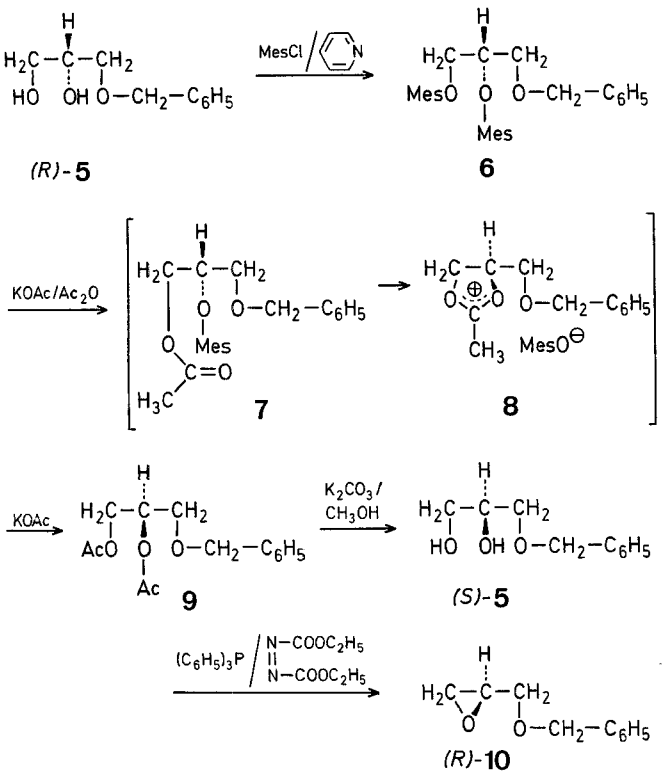

Scheme **B**

(*S*)-2,3-Diacetoxy-1-benzylglycerol (9):

(*R*)-1-Benzylglycerol (**5**; 1.30 g, 7.14 mmol) is treated with methanesulfonyl chloride (2.04 g, 17.85 mmol) in dry dichloromethane (20 ml) in the presence of pyridine (2.88 ml) for 4 h. During the reaction time the temperature is increased from 0 °C at the beginning to room temperature. After addition of ice/water (25 ml), the reaction mixture is extracted with dichloromethane (3 × 30 ml). The extract is washed with brine (1 × 25 ml), 5% hydrochloric acid (2 × 30 ml), brine (1 × 25 ml), 5% sodium hydrogen carbonate (2 × 30 ml), brine (1 × 25 ml), and then dried with sodium sulfate. Evaporation of the solvent under reduced pressure gives the crude dimesylate **6** in quantitative yield. The crude dimesylate (1.66 g, 4.91 mmol) is then refluxed with anhydrous potassium acetate (2.45 g, 25 mmol) in acetic anhydride (25 ml) for 1.5 h. The reaction mixture is evaporated under reduced pressure and the residue is extracted with dichloromethane (3 × 30 ml). The extract is washed with brine (2 × 25 ml), 5% sodium hydrogen carbonate (2 × 30 ml), brine (1 × 25 ml), and dried with sodium sulfate. Evaporation of the solvent gives a brown oil which is distilled using a rotary pump to give pure (*S*)-2,3-diacetoxy-1-benzylglycerol **(9)**; yield: 1.31 g (91%); b.p. 135–145 °C/0.17 torr; $[\alpha]_D$: −16.37° (*c* 4.56, CH_3OH). For comparison (*R*)-**9** from (*R*)-**5** has $[\alpha]_D$: +17.05° (*c* 4.188, CH_3OH).

$C_{14}H_{18}O_5$	calc.	C 63.14	H 6.81
(266.3)	found	62.81	6.97

M.S.: $m/e = 266$ (M^+).

I.R. (neat): $\nu = 1735$ cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.03$ (s, 3H); 2.07 (s, 3H); 3.60 (d, 2H, $J = 5$ Hz); 4.2–4.4 (m, 2H); 4.53 (s, 2H); 5.0–5.4 (m, 1H); 7.30 ppm (s, 5H).

(*S*)-1-Benzylglycerol (5):

The (*S*)-diacetate **9** (2.66 g, 10 mmol) is stirred with potassium carbonate (3.04 g, 22 mmol) in methanol (50 ml) at 25 °C for 0.5 h. After filtration, most of the solvent is evaporated under reduced pressure and the residue is dissolved in water (~15 ml). The mixture is extracted with dichloromethane (3 × 30 ml), the extract is washed with brine (1 × 25 ml), and dried with sodium sulfate. Evaporation of the solvent gives a colorless oil which is distilled using a rotary pump to give pure (*S*)-1-benzylglycerol [(*S*)-**5**]; yield: 1.66 g (91%); b.p. 135–145 °C/0.26 torr; $[\alpha]_D$: −3.73° (*c* 17.64, $CHCl_3$). For comparison (*R*)-**9**[3] has b.p. 110–120 °C/0.15 torr; $[\alpha]_D$: +3.71° (*c* 19.9, $CHCl_3$).

I.R. (neat): $\nu = 3380$ cm^{-1} (broad).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.36$ (br. s, 2H, exchanges with D_2O); 3.5 (t, 4H, $J = 6$ Hz); 3.65–3.95 (m, 1H); 4.48 (s, 2H); 7.27 ppm (s, 5H).

(*R*)-Benzyl-2,3-epoxypropyl ether [(*R*)-10]:

A mixture of the diol [(*S*)-**5**; 4.14 g, 22.7 mmol], triphenylphosphine (8.9 g, 34.2 mmol), and diethyl azodicarboxylate (5.4 ml, 34.2 mmol) in benzene (50 ml) is refluxed for 20 h. After evaporation of the solvent, ether (50 ml) is added to precipitate the phosphine oxide which is removed by filtration. The filtrate is concentrated under reduced pressure and the residue is filtered through a silica gel column (150 g, ether/hexane 1:3) to give a colorless oil which on distillation gives the pure (*R*)-epoxide [(*R*)-**10**]; yield: 2.27 g (61%); b.p. 100–110 °C/0.9 torr; $[\alpha]_D$: +13.9° (neat) [the starting (*R*)-benzylglycerol gives the (*S*)-epoxide (*S*)-**10**, $[\alpha]_D$: −12.06° (neat), in 76% yield on the same treatment].

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.4$–3.0 (m, 2H); 3.0–3.4 (m, 1H); 3.5–4.0 (m, 2H); 4.63 (s, 2H); 7.40 ppm (s, 5H).

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2 S. Takano, K. Ogasawara, *J. Synth. Org. Chem. Soc. Jpn.* **40**, 1037 (1982).
3 S. Takano, Y. Imamura, K. Ogasawara, *Tetrahedron Lett.* **1981**, 4479.
4 S. Takano, E. Goto, M. Hirama, K. Ogasawara, *Chem. Pharm. Bull.* **30**, 2641 (1982).
5 See also literature cited in Ref.[9,10].
6 E. Baer, D. Buchnea, *J. Biol. Chem.* **230**, 447 (1958).
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8 S. Takano, E. Goto, M. Hirama, K. Ogasawara, *Heterocycles* **16**, 381 (1981).
9 M. E. Jung, T. J. Shaw, *J. Am. Chem. Soc.* **102**, 6304 (1980).
10 S. Takano, H. Numata, K. Ogasawara, *Heterocycles* **19**, 327 (1982).
11 K. Kakinuma, *Tetrahedron Lett.* **1978**, 768.
12 R. C. Chalk, D. H. Ball, M. A. Lintner, L. Long, Jr., *J. Chem. Soc. Chem. Commun.* **1970**, 245.
13 O. Mitsunobu, T. Kubo, M. Nishida, N. Tsuda, *Chem. Lett.* **1980**, 1613.
See also, O. Mitsunobu, *Synthesis* **1981**, 1.
14 A. K. M. Aisuzzaman, L. N. Owen, *J. Chem. Soc.* [C] **1967**, 1021.

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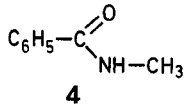
Errata and Addenda 1983

E. Haug, W. Kantlehner, P. Speh, H.-J. Bräuner, *Synthesis* **1983** (1), 35–37:

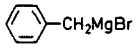
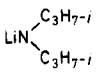
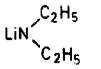
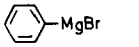
Compound **4** should be *N*-methylbenzamide:



4

A. I. Meyers, K. A. Lutomski, *Synthesis* **1983** (2), 105–107:
The first seven entries in the Table (p. 106) should be as follows:

Table. Addition of Organometallic Reagents to 2-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-1-methoxynaphthalene **(1)** leading to 1-Substituted 2-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-naphthalenes **2**

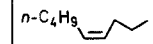
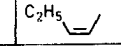
Product	RM	Yield [%]	m.p. [°C]	I.R. (film) $\nu_{C=N}$ [cm^{-1}]	^{1}H-N.M.R. (solvent) δ [ppm]
2a	H_3CLi	84	oil	1645	(CCl_4): 1.36 (s, 6 H); 2.92 (s, 6 H); 3.97 (s, 2 H); 7.3–8.2 (m, 6 H)
2b	*n*-C_4H_9Li	80	oil	1640	(CCl_4): 0.8–1.85 (m, 13 H); 3.45 (br, t, 2 H); 3.95 (s. 2 H); 7.3–8.2 (m, 6 H)
	n-C_4H_9MgBr	89			
2c		59	oil	1635	(CCl_4): 1.30 (s, 6 H); 3.92 (s, 2 H); 4.97 (s, 2 H); 7.0–8.2 (m, 12 H)
2d		68	oil[a]	1645	($CDCl_3$): 1.00 (d, 6 H); 1.12 (d, 6 H); 1.35 (s, 6 H); 3.45–4.19 (hept, 2 H); 4.0 (s, 2 H); 7.3–7.9 (m, 5 H); 8.65 (m, 1 H)
2e		78	oil[b]	1650	($CDCl_3$): 1.05 (t, 6 H); 1.35 (s, 6 H); 3.30 (d, 4 H); 3.95 (s, 2 H); 7.2–7.8 (m, 5 H); 8.3–8.5 (m, 1 H)
2f		84	oil	1660	(CCl_4): 1.12 (s, 6 H); 3.59 (s, 2 H); 7.2–7.9 (m, 11 H)

S. Takano, K. Seya, E. Goto, M. Hirama, K. Ogasawara, *Synthesis* **1983** (2), 116–117:

The title should read "Synthesis of (*S*)-1-*O*-Benzylglycerol and (*R*)-Benzyl 2,3-Epoxypropyl Ether from (*R*)-1-*O*-Benzylglycerol"; the names of compounds (*R*)-**5**, (*S*)-**5**, and **9** should be (*R*)-1-*O*-benzylglycerol, (*S*)-1-*O*-benzylglycerol, and (*S*)-2,3-Di-*O*-acetyl-1-*O*-benzylglycerol, respectively.

D. Michelot, *Synthesis* **1983** (2), 130–134:

The table under the formula scheme (page 131) should be as follows:

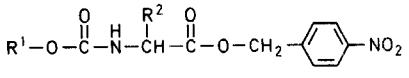
5	m	n	6,7,8,(9)	R
a	4	8	a	*n*-C_4H_9
a	4	8	b	C_2H_5
c		6	c	*n*-C_4H_9 
a	4	8	d	H_2C=CH–
b	6	10	e	C_2H_5 

Compounds **6e**, **7e**, **8c**, and **9e** (p. 133) should be named (*Z*, *Z*)-1-(2-tetrahydropyranyloxy)-11,13-hexadecadiene, (*Z*,*Z*)-11,13-hexadecadienol, (*Z*,*Z*)-7,11-hexadecadien-1-yl acetate, and (*Z*,*Z*)-11,13-hexadecadienal, respectively. Compound **8b** is prepared from **5a** and ethylmagnesium bromide.

M. Künstlinger, E. Breitmaier, *Synthesis* **1983** (2), 161–162:

Compounds **5** and **6** should be named pyrimido[1,2-*a*]benzimidazoles.

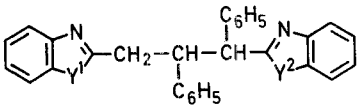
Abstract **6555**, *Synthesis* **1983** (2), 165:

Compound **1** should be: 

1

V. Dryanska, C. Ivanov, *Synthesis* **1983** (2), 143–145:

The formula for compounds **4g, h, 5g, h** (page 144) should be:



4g Y^1 = O, Y^2 = O
4h Y^1 = O, Y^2 = S
5g Y^1 = S, Y^2 = O
5h Y^1 = S, Y^2 = S

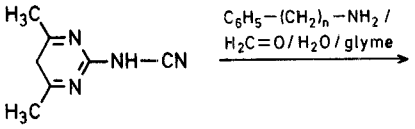
M. A. Brook, T. H. Chan, *Synthesis* **1983** (3), 201–203:

The following addendum should be added:
After publication of our work, our attention was drawn to the fact that the priority for the use of chlorotrimethylsilane for esterification lies with Nakao et al.[24].

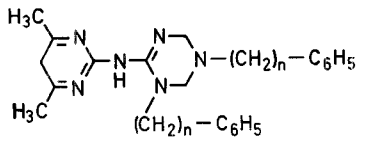
[24] R. Nakao, K. Oka, T. Fukumoto, *Bull. Soc. Chem. Jpn.* **54**, 1267 (1981).

C. W. Thornber, J. M. Farrell, D. S. Clarke, *Synthesis* **1983** (3), 222–223:

The formula scheme **1** ⟶ **10,11** (p. 222) should be:



1



10 n = 1
11 n = 2

H. Takahata, N. Nakajima, Y. Yamazaki, *Synthesis* **1983** (3) 226–228:

Compounds **7** and **8** should be named 3-anilino-6-methyl-1,4,5,6 tetrahydropyrrolo[2,3-*c*]pyrazoles and 3-anilino-7-methyl-4,5,6,7 tetrahydro-1*H*-pyrazolo[3,4-*b*]pyridines, respectively.