RESOLUTION OF RACEMIC *O*-(4-METHOXYPHENYL)-GLYCIDOL

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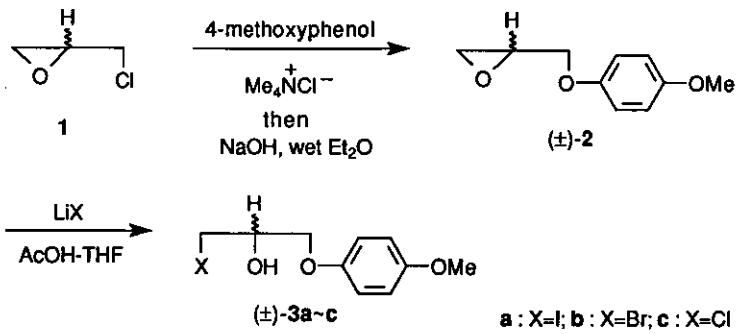
Abstract —— Racemic *O*-(4-methoxyphenyl)glycidol has been resolved in three steps by employing lipase mediated kinetic acylation of the halohydrin intermediates.

Since a facile oxidative cleavage method of 4-methoxyphenyl ether (PMP ether) bond has appeared,[1] optically active *O*-(4-methoxyphenyl)glycidol[2,3] (**2**) has become a potentially useful chiral building block comparable to its *O*-benzyl congener which is known as one of the most powerful and versatile chiral building blocks.[4] We report here a facile method for the resolution of racemic *O*-(4-methoxyphenyl)glycidol[2,3] [(±)-**2**] by employing lipase-mediated kinetic acylation in organic phase[5] as the key step.[6]

Racemic (±)-**2**, prepared from racemic epichlorohydrin [(±)-**1**] and *p*-methoxyphenol, was first transformed into the racemic halohydrins **3a~c** in excellent yields on exposure to the corresponding lithium halides in the presence of acetic acid[7] (**Scheme 1**).

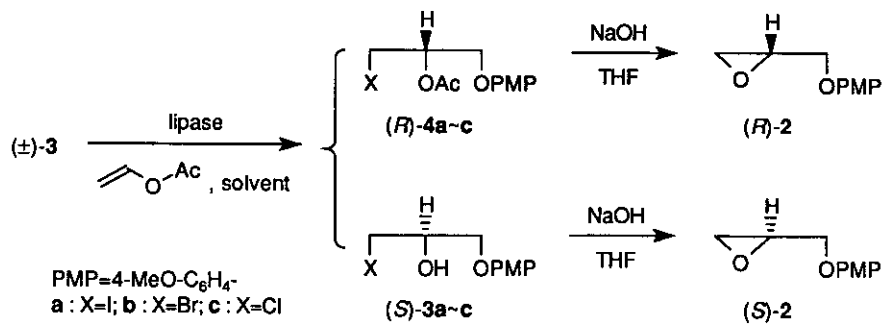
The racemic **3a~c** were then treated with lipases in organic phase containing two molar equivalents of vinyl acetate at room temperature for 100 h. As appeared in Table 1, optical yields of the products were largely depending on the lipases used and ranging from 5 to 100% ee though enantiotopical selectivity was found to be invariable irrespective of the lipases and the halides **3**. Among the halides and the lipases used, the combination of the chloride **3c** and lipase PS seemed to be the most



Scheme 1

appropriate and the rate of the acylation could be controlled by changing the solvent. Thus, when benzene is used, optically pure chlorohydrin (*S*)-**3** remained to be unchanged (Entry 16), while in dichloromethane optically pure acetate (*R*)-**4c** could be obtained (Entry 17), both in acceptable yields. Furthermore, repetition of the same treatment on the optically enriched (75% ee) chlorohydrin [(*S*)-**3c**] improved its optical purity to 96% ee in 82% yield accompanied by 7% yield of the optically active acetate [(*R*)-**4c**] (82% ee) (Entry 18).

Conversion of both optically active chlorohydrin (*S*)-**3c** and the acetate (*R*)-**4c** into the corresponding chiral *O*-(4-methoxyphenyl)glycidol (**2**) could be readily accomplished under the same conditions, respectively. Thus, the secondary alcohol (*S*)-**3c** afforded (*S*)-**2** in an excellent yield on exposure to sodium hydroxide in



Scheme 2

Table 1: Resolution of the halohydrins [(±)-3] with lipase[a)]

				Product [yield (%) : opt. yield (% ee)[c)]]					
Entry	(±)-3	lipase[b)]	solvent	(*S*)-3	(%)	(%ee)	(*R*)-4	(%)	(%ee)
1	**3 a**	OF	*tert*-BuOMe	**3 a**	84	14	**4 a**	15	73
2	**3 a**	MY	*tert*-BuOMe	**3 a**	0	–	**4 a**	~100	–
3	**3 a**	AK	*tert*-BuOMe	**3 a**	32	64	**4 a**	64	47
4	**3 a**	AY	*tert*-BuOMe	**3 a**	0	–	**4 a**	~100	–
5	**3 a**	PS	*tert*-BuOMe	**3 a**	29	96	**4 a**	63	41
6	**3 a**	PS	benzene	**3 a**	29	81	**4 a**	53	65
7	**3 a**	PS	CH_2Cl_2	**3 a**	72	37	**4 a**	23	96
8	**3 a**	WAKO	*tert*-BuOMe	**3 a**	66	5	**4 a**	22	83
9	**3 b**	OF	*tert*-BuOMe	**3 b**	83	8	**4 b**	16	59
10	**3 b**	AK	*tert*-BuOMe	**3 b**	84	10	**4 b**	5	24
11	**3 b**	PS	*tert*-BuOMe	**3 b**	20	96	**4 b**	80	46
12	**3 b**	PS	benzene	**3 b**	83	12	**4 b**	10	50
13	**3 b**	PS	CH_2Cl_2	**3 b**	77	20	**4 b**	16	88
14	**3 b**	WAKO	*tert*-BuOMe	**3 b**	89	7	**4 b**	4	91
15	**3 c**	PS	*tert*-BuOMe	**3 c**	12	100	**4 c**	88	21
16	**3 c**	PS	benzene	**3 c**	36	97	**4 c**	45	54
17	**3 c**	PS	CH_2Cl_2	**3 c**	54	75	**4 c**	40	97
18	(*S*)-**3c**[d)]	PS	CH_2Cl_2	**3 c**	7	82	**4 c**	82	96

a) All reactions were carried out 0.5 mmol of **3** with 2 equiv. of vinyl acetate and 50 mg of lipase in 5 ml of solvent at 27 °C for 100 h.

b) Lipase: OF (*Candida cylindracea*, Meito Sangyo Co. Ltd.), MY (*Candida cylindracea*, Meito Sangyo Co. Ltd.), AK (*Pseudomonas* sp., Amano Pharmaceutical Co. Ltd.), AY (*Candida rugosa*, Amano Pharmaceutical Co. Ltd.), PS (*Pseudomonas* sp., Amano Pharmaceutical Co. Ltd.), WAKO (porcine pancreas, WAKO Chemical Co. Ltd.).

c) Optical purities were determined by hplc analysis using a column packed with CHIRALCEL OD (DAICEL Co. Ltd.).

d) Optically enriched substrate (75% ee) was used.

tetrahydrofuran[8] (THF). On the same treatment the acetate (*R*)-**4c** furnished (*R*)-**2** in one step in an excellent yield (**Scheme 2**).

In conclusion although the present procedure does not allow clear-cut resolution of the halohydrins **3** into both enantiomers in a single operation, it can produce a particular enantiomer of the glycidol **2** in satisfactory chemical and optical yields by choosing the organic solvents. Additional advantage is ready crystallization of the glycidol **2** which allows efficient optical purification of the partly resolved **2** by recrystallization. Due to its simplicity and facileness, the present procedure is useful for the production of the optically pure *O*-(4-methoxyphenyl)glycidol **2** which is promising to be a chiral building block for versatile use.

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 purities of the products were determined by hplc using a chiral column (CHIRALCEL OD:DAICEL) using a mixture of *i*-PrOH-hexane as eluents. Chemical reactions were carried out under argon.

Preparation of Racemic *O*-(4-Methoxyphenyl)glycidol [(±)-2] —— A mixture of racemic epichlorohydrin (1.0 g, 10.8 mmol), 4-methoxyphenol (0.45 g, 3.6 mmol), and $(Me)_4NCl\cdot H_2O$ (0.13 g, 0.72 mmol) was stirred at room temperature for 7 days.[9] Then, NaOH (0.22 g, 5.4 mmol) in H_2O (2 ml) and ether (4 ml) were added to the mixture and the mixture was stirred at room temperature for 7 h. The mixture was extracted with ether and the extract was washed with brine, dried over $MgSO_4$, evaporated under reduced pressure, and purified on a silica gel column chromatography (50 g) using hexane-AcOEt (3:1 v/v) as eluent to give pure racemic

O-(4-methoxyphenyl)-glycidol [(±)-**2**] as colorless crystals; yield: 568 mg (88%); mp 44-45 °C.

(±)-1-Iodo-3-(4-methoxyphenyloxy)-2-propanol [(±)-3a] —— To a stirred solution of (±)-**2** (1.0 g, 5.6 mmol) and LiI (1.2 g, 9.0 mmol) in THF (20 ml) was added acetic acid (0.96 ml, 16.8 mmol) at room temperature and the mixture was stirred for 15 min at the same temperature. After addition of water, the mixture was extracted with ether. The extract was washed successively with saturated aqueous $NaHCO_3$, 10% $Na_2S_2O_3$, water and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to give virtually pure racemic iodohydrin [(±)-**3a**] as colorless needles; yield: 1.7 g (99%); mp 78 °C. Ir (film) ν_{max}: 3438 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 2.65 (br s, 1H, exchangeable with D_2O), 3.41 (m, 2H), 3.77 (s, 3H), 3.99 (m, 3H), 6.84 (s, 4H); ms (m/z): 308 (M^+), 124 (100%). Exact mass: Calcd for $C_{10}H_{13}O_3I$: 307.9910. Found: 307.9912.

(±)-1-Bromo-3-(4-methoxyphenyloxy)-2-propanol [(±)-3b] —— To a stirred solution of (±)-**2** (1.5 g, 8.3 mmol) and LiBr (1.3 g, 13.5 mmol) in THF (20 ml) was added acetic acid (1.4 ml, 25 mmol) at room temperature and the mixture was stirred for 36 h at the same temperature. The mixture was treated similarly as for **3a** to give virtually pure racemic bromohydrin (**3b**) as colorless needles; yield: 2.13 g (98%); mp 59-60 °C. Ir (film) ν_{max}: 3440 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 3.13 (br s, 1H, exchangeable with D_2O), 3.58 (dd, *J*=5.5, 4.9 Hz, 2H), 3.75 (s, 3H), 4.06 (dd, *J*=5.6, 4.2 Hz, 2H), 3.9-4.3 (m, 1H), 6.83 (s, 4H); ms (m/z): 262, 260 (M^+), 124 (100%). Exact mass: Calcd for $C_{10}H_{13}O_3$*Br: 260.0048 (^{79}Br), 260.0045 (^{81}Br). Found: 262.0029, 262.0013.

(±)-1-Chloro-3-(4-methoxyphenyloxy)-2-propanol [(±)-3c] —— To a stirred solution of (±)-**2** (2.0 g, 11.1 mmol) and LiCl (1.18 g, 27.8 mmol) in THF (40 ml) was added acetic acid (2.5 ml, 44.4 mmol) at room temperature and the stirring was continued for 18 h at the same temperature. The mixture was treated as for **3a** to give virtually pure racemic chlorohydrin (**3c**) as a pale yellow oil; yield: 2.4 g (100%). Ir (film) ν_{max}: 3438 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 2.70 (br s, 1H, exchangeable with D_2O),

3.74 (dd, *J*=5.8, 4.6 Hz, 2H), 4.03 (dd, *J*=5.4, 4.2 Hz, 2H), 4.0-4.3 (m, 1H), 6.84 (s, 4H); ms (m/z): 218, 216 (M^+), 124 (100%). Exact mass: Calcd for $C_{10}H_{13}O_3$*Cl: 216.0553 (^{35}Cl), 218.0527 (^{37}Cl). Found: 216.0541, 218.0487.

Typical Experimental Procedure for the Lipase-mediated Resolution:

(a) Preparation of Optically Active (*S*)-3c and (*R*)-4c (Entry 17) ——— A suspension of (±)-**3c** (1.05 g, 4.86 mmol), lipase PS (500 mg), and vinyl acetate (1 ml, 10.8 mmol) in dichloromethane (50 ml) was stirred at room temperature for 100 h. After separation of the lipase using a Celite pad, the mixture was evaporated under reduced pressure and the residue was purified on a silica gel column (70 g) using hexane-AcOEt (5:1 v/v) as eluent to give optically active acetate (*R*)-**4c** (500 mg, 39.9%) and optically active chlorohydrin **3c** (570 mg, 54.3%).

(*R*)-**4c**: $[\alpha]_D^{30}$ +26.0° (*c* 1.03, MeOH); Optical purity: 96.7% ee [CHIRALCEL OD, *i*-PrOH-hexane (1:49 v/v)]; ir (film) ν_{max}: 1745 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 2.12 (s, 3H), 3.79 (m, 5H), 4.12 (dd, *J*=5.0, 4.4 Hz, 2H), 5.30 (quint, *J*=4.8 Hz, 1H), 6.84 (s, 4H); ms (m/z): 260, 258 (M^+), 43 (100%). Exact mass: Calcd for $C_{12}H_{15}O_4$*Cl: 258.0659 (^{35}Cl), 260.0634 (^{37}Cl). Found: 258.0637, 260.0629.

(*S*)-**3c**: Optical purity: 75% ee [CHIRALCEL OD, *i*-PrOH-hexane (3:17 v/v)]; Spectral data (ir, ^1H nmr, and ms) were identical of those of (±)-**3c**.

(b) Optical Purification of Optically Enriched Chlorohydrin [(*S*)-3c] (Entry 18) ——— A mixture of optically enriched chlorohydrin [(*S*)-**3c**] (75% ee, 570 mg, 2.6 mmol), lipase PS (260 mg), and vinyl acetate (0.5 ml, 5.4 mmol) in dichloromethane (25 ml) was treated as for (±)-**3c**. The mixture after purification on a silica gel column (30 g) using hexane-AcOEt (5:1) as eluent afforded (*R*)-**4c** (46 mg, 6.9%; 82.3% ee by hplc) and (*S*)-**3c**, $[\alpha]_D^{28}$ –4.90° (c 1.00, MeOH) (462 mg, 82%; 95.6% ee by hplc).

(c) Resolution of the Iodohydrin (3a) and the Bromohydrin (3b) ——— Since the procedure was virtually the same as for the chlorohydrin **3c**, only spectral data of the corresponding acetates, **4a** and **4b**, were given below.

(*R*)-**4a** (Entry 5): $[\alpha]_D^{29}$ +14.9° (*c* 1.01, MeOH); Optical purity: 96% ee [CHIRALCEL OD, *i*-PrOH-hexane (1:49 v/v)]; ir (film) ν_{max}: 1743 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 2.12 (s, 3H), 3.47 (dd, *J*=5.5, 5.3 Hz, 2H), 3.77 (s, 3H), 4.10 (dd, *J*=5.1, 5.0 Hz, 3H), 5.06 (quint, *J*=5.1 Hz, 1H), 6.84 (s, 4H); ms (m/z): 350 (M^+), 93 (100%). Exact mass: Calcd for $C_{12}H_{15}O_4I$: 350.0015. Found: 349.9984.

(*R*)-**4b** (Entry 11): Optical purity: 96% ee [CHIRALCEL OD, *i*-PrOH-hexane (1:49 v/v)]; ir (film) ν_{max}: 1744 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 2.12 (s, 3H), 3.64 (m, 2H), 3.76 (s, 3H), 4.22 (dd, *J*=5.4, 4.4 Hz, 2H), 5.29 (quint, *J*=5.1 Hz, 1H), 6.84 (s, 4H); ms (m/z): 304, 302 (M^+), 124 (100%). Exact mass: Calcd for $C_{12}H_{15}O_4$*Br: 302.0154 (^{79}Br), 304.0135 (^{81}Br). Found: 302.0135, 304.0131.

Preparation of Optically Active *O*-(4-Methoxyphenyl)glycidol (2):

(a) (*S*)-2 from the Optically Active Chlorohydrin [(*S*)-3c] —— To a solution of (*S*)-**3c** (95.6% ee, 462 mg, 2.13 mmol) in THF (5 ml) was added ground NaOH (337 mg, 8.42 mmol) at room temperature and the stirring was continued for 22 h at the same temperature. The mixture was diluted with water and extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to give virtually pure (*S*)-**2** as colorless crystals; yield: 349 mg (91%); mp 43-44 °C; $[\alpha]_D^{31}$ +11.3° (*c* 1.01, MeOH) [lit.,[3] $[\alpha]_D^{28}$ +11.04° (*c* 1.08, MeOH)]; Optical purity: 95.3% ee [CHIRALCEL OD, hexane-*i*-PrOH (10:1 v/v)]. Spectral data (ir, ^1H nmr, ms) were identical with those of an authentic material. Recrystallization of this material from EtOH-hexane furnished optically pure (*S*)-**2**: mp 44 °C; $[\alpha]_D^{30}$ +11.3° (*c* 0.98, MeOH); Optical purity: ≥99% ee [CHIRALCEL OD, *i*-PrOH-hexane (9:1 v/v)].

(b) (*R*)-2 from the Optically Active Acetate [(*R*)-4c] —— To a solution of (*R*)-**4c** (96.7% ee, 352 mg, 1.36 mmol) in THF (5 ml) was added ground NaOH (218 mg, 5.46 mmol) at room temperature and the stirring was continued for 22 h at the same temperature. The mixture was diluted with water and extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to give virtually pure (*R*)-**2** as colorless crystals; yield: 240 mg

(98%); mp 43-44 °C (lit.,[3] 42-43 °C); $[\alpha]_D^{29}$ –12.6° (*c* 1.01, MeOH) [lit.,[3] $[\alpha]_D^{26}$ –11.72° (*c* 1.06, MeOH)]; Optical purity: 93.6% ee [CHIRALCEL OD, hexane-*i*-PrOH (10:1 v/v)]. Spectral data (ir, ^{1}H nmr, ms) were identical with those of an authentic material. Recrystallization of this material from EtOH-hexane furnished optically pure (*R*)-**2**: mp 44 °C; $[\alpha]_D^{30}$ –11.4° (*c* 1.06, MeOH); Optical purity: ≥99% ee [CHIRALCEL OD, *i*-PrOH-hexane (9:1 v/v)].

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