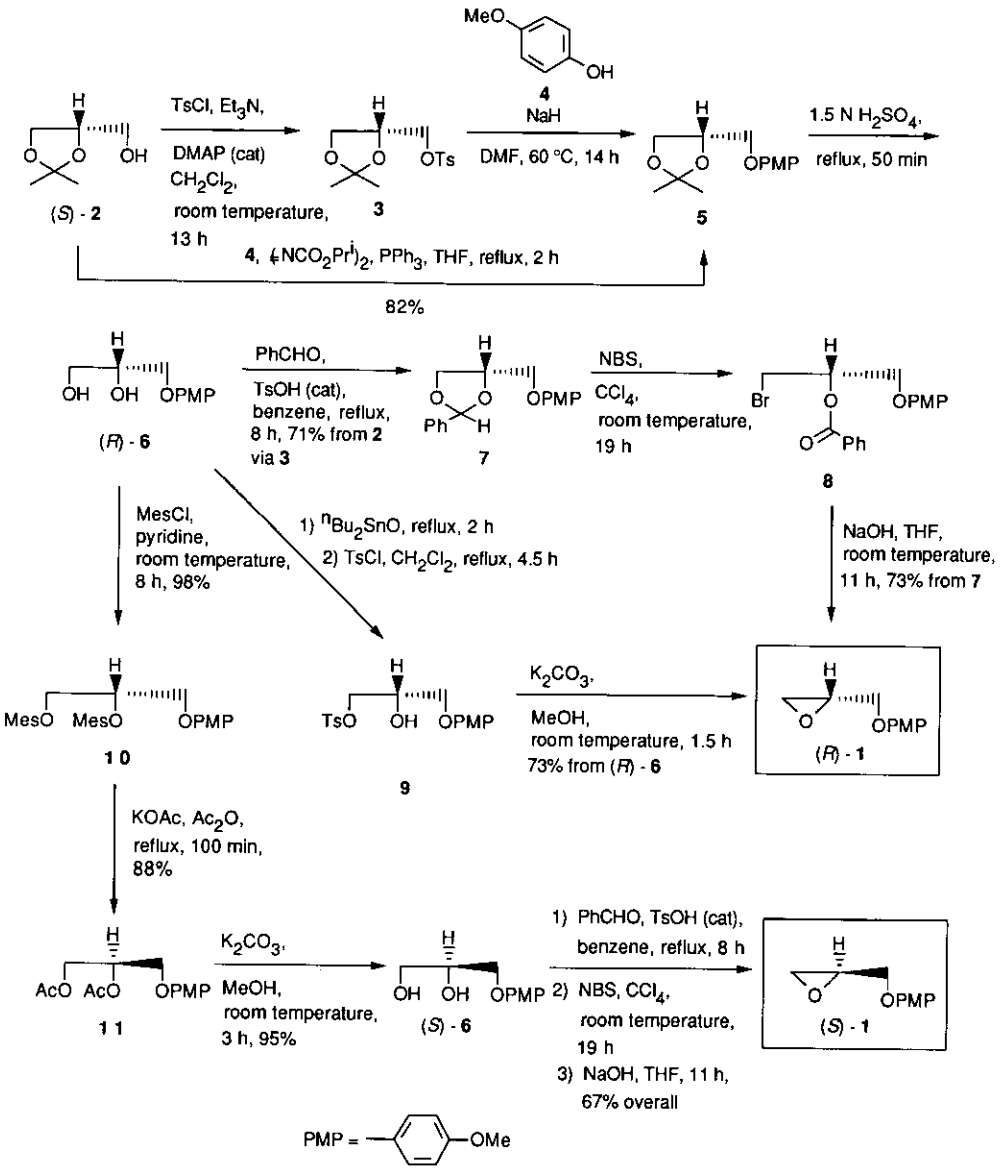
PRACTICAL ROUTE TO BOTH (*S*)- AND (*R*)-ENANTIOMERS OF *O*-(4-METHOXYPHENYL)GLYCIDOL USING (*S*)-1,2-*O*-ISOPROPYLIDENEGLYCEROL AS A COMMON PRECURSOR

Seiichi Takano*, Minoru Moriya, Mahito Suzuki, Yoshiharu Iwabuchi, Takumichi Sugihara, and Kunio Ogasawara
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Abstract —— Practical route to both (*R*)- and (*S*)-enantiomers of *O*-(4-methoxyphenyl)glycidol is devised using (*S*)-1,2-*O*-isopropylideneglycerol as a common chiral starting material.

Optically active *O*-benzylglycidol[1-3] is an important key building block for the synthesis of a variety of optically active materials.[4] Since we encountered with some difficult cases removing the benzyl group from synthetic intermediates originated from *O*-benzylglycidol, we needed replacing the benzyl group to another *O*-protecting group which may be removable under different conditions those from the benzyl group. We report here a practical procedure for the synthesis of an alternative glycidol derivative (**1**) protected by 4-methoxyphenyl group in both enantiomeric forms using (*S*)-*O*-1,2-isopropylideneglycerol (**2**) as a common starting material. Since 4-methoxyphenyl group is removable under mild oxidative conditions[5] remaining the benzyloxy group as well as most of the *O*-protective groups intact, **1** may be used complementarily to the benzyl counterpart.

Thus, (*S*)-1,2-*O*-isopropylideneglycerol[1,6] (**2**) is first transformed into (*R*)-1-*O*-(4-methoxyphenyl)glycerol (**6**). Practically, **2** is tosylated and the tosylate (**3**) obtained is treated with 4-methoxyphenol (**4**) in the presence of sodium hydride to give the ether (**5**) though the Mitsunobu reaction[7] allows the conversion of **2** into **5** in a more straightforward way. Acid hydrolysis of **5** yields the (*R*)-glycerol ether (**6**) as



crystals. At this stage the chirality inversion method,[2,7] which has been established to the optically active 1-*O*-benzylglycerol, is applied to (*R*)-**6** to furnish (*S*)-**6**. Upon reflux with potassium acetate in acetic anhydride, the mesylate (**10**) prepared from (*R*)-**6** affords the inverted diacetate (**11**) which gives the enantiomeric (*S*)-1-*O*-(4-

methoxyphenyl)glycerol (**6**) in a good overall yield after alkaline methanolysis. Although a little racemization (2%) occurs during the conversion, the product may be satisfactorily usable for practical purpose.

Again employing the same methodology[3] converting 1-*O*-benzylglycerol into the corresponding glycidol ether, the benzylidene acetal (**7**) of (*R*)-**6** is treated with *N*-bromosuccinimide, followed by the resulting bromobenzoate (**8**) with sodium hydroxide to give (*R*)-*O*-(4-methoxyphenyl)glycidol[9] (**1**) as crystals in a satisfactory overall yield. The enantiomeric (*S*)-(**6**) can also be transformed into (*S*)-**1** in a comparable overall yield on the same treatment.

Furthermore, an alternative method via the mono-tosylate (**9**) is also established to give the same glycidol ether (**1**) in a satisfactory yield as exemplified by the conversion of (*R*)-**6** into (*R*)-**1**. Thus, sequential treatment of (*R*)-**6** with di-*n*-butyltin oxide[10] followed by *p*-toluenesulfonyl chloride allows regioselective tosylation to give the primary tosylate (**9**) which on exposure to methanolic potassium carbonate affords (*R*)-**1** in a satisfactory overall yield.

EXPERIMENTAL SECTION

Optical rotations were measured with a JASCO-DIP-4 automatic polarimeter. Optical purity of the glycidol products were estimated by hplc using a EYELA PLC-10 instrument equipped with CHIRALCEL OD (DAICEL) column. Mass spectra were recorded with a JEOL-O1SG-2 instrument, ir spectra with a JASCO A102 spectrophotometer, and ^{1}H nmr spectra on JEOL-JNM-FX90A (90 MHz) and JEOL-JNM-GX500 (500 MHz) spectrometers. Reactions were carried out under argon.

(R)-1,2-*O*-Isopropylidene-3-*O*-(4-methoxyphenyl)glycerol (5): (a) via tosylate (**3**) —— To a solution of (*S*)-1,2-*O*-isopropylideneglycerol (**2**: 50.5 g, 382 mmol) in dichloromethane (300 ml) are added sequentially triethylamine (58.5 ml, 420 mmol), *p*-toluenesulfonyl chloride (80.2 g, 421 mmol) and 4-dimethylaminopyridine (464 mg, 3.8 mmol) at 0 °C with stirring and the stirring is continued for 13 h at room temperature. The mixture is evaporated under reduced

pressure (below 20 °C) and the residue is taken up into ether (300 ml). The ethereal solution is washed successively with water (200 ml) and brine (50 ml), and dried with $MgSO_4$. Evaporation of the solvent under reduced pressure leaves the crude tosylate (**3**: 112 g, 103%) which is used for the next reaction without further purification.

To a stirred suspension containing sodium hydride [obtained by washing oil dispersion (60%); 16.8 g, 421 mmol, with *n*-hexane (100 ml)] in *N*,*N*-dimethylformamide (DMF) (300 ml) is added 4-methoxyphenol (**4**: 42.5 g, 382 mmol) portionwise during 50 min at room temperature, followed by the above crude tosylate (**3**: 112 g) portionwise at the same temperature. After stirring for 20 min at the same temperature, the mixture is warmed to 60 °C and the stirring is continued for 14 h at the same temperature. After cooling, the mixture is diluted with ether (900 ml) and the solution is washed successively with water (300 ml), brine (3 x 80 ml), and dried with $MgSO_4$. Evaporation of the solvent under reduced pressure leaves the crude ether (**5**: 94.0 g) as a pale yellow oil, which is used for the next reaction. For the analytical purpose, a small amount of the product is purified by chromatography on a silica gel column using a mixture of ether-hexane (1:7 v/v) as eluent to give pure (*R*)-1,2-*O*-isopropylidene-3-*O*-(4-methoxyphenyl)glycerol (**5**) as a colorless oil: $[\alpha]_D^{22}$ +10.45° (*c* 1.09, $CHCl_3$). ^1H Nmr ($CDCl_3$) δ: 1.40 (s, 3H), 1.46 (s, 3H), 3.77 (s, 3H), 3.80-4.53 (m, 5H), 6.84 (s, 4H); ms (m/z): 238 (M^+, 100%). *Anal.* Calcd for $C_{13}H_{18}O_4$: C 65.73, H 7.61. Found: C 65.62, H 7.73.

(b) via the Mitsunobu reaction —— To a stirred mixture of (*S*)-1,2-*O*-isopropylideneglycerol (**2**: 511 mg, 3.87 mmol), 4-methoxyphenol (**4**: 1.42 g, 11.5 mmol), triphenylphosphine (1.32 g, 5.03 mmol) in tetrahydrofuran (THF) is added diisopropyl azodicarboxylate (0.98 ml, 4.97 mmol) dropwise at 0 °C and the mixture is refluxed for 2 h. After cooling the mixture is taken up into ether (20 ml) and the ethereal solution is washed successively with 15% aqueous NaOH (2 x 5 ml), brine (2 x 5 ml), and dried with K_2CO_3. After evaporation of the solvent under reduced pressure, the residue is purified by chromatography on a silica gel column (45 g) using a mixture of ether-hexane (1:7 v/v) as eluent to give pure **5** as a colorless oil; yield 740 mg (82%).

(*R*)-1-*O*-(4-Methoxyphenyl)glycerol (6) ----- A suspension of the above crude ether (**5**: 94.0 g) in 1.5 N sulfuric acid (300 ml) is refluxed for 50 min. After cooling

the mixture is neutralized by addition of 15% aqueous NaOH with cooling and the mixture is extracted with dichloromethane (800 ml). The extract is washed with brine (3 x 80 ml), dried with $MgSO_4$, and evaporated under reduced pressure to leave the glycerol ether (**6**: 67.0 g) as a pale brown crystalline solid which is used for the next reaction. For the analytical purpose, a small amount of the product is recrystallized from a mixture of dichloromethane-hexane to give pure (*R*)-1-*O*-(4-methoxyphenyl)-glycerol (*R*-**6**) as colorless needles: mp 78 °C; bp 160 °C/0.2 torr (Kugelrohr); $[\alpha]_D^{32}$ −8.25° (*c* 1.15, MeOH) [100% ee by ^1H Nmr (500 MHz) of the (*R*)- and (*S*)-di-MTPA esters[11]]. Ir (film) ν_{max}: 3350 cm^{-1}; ^1H Nmr ($CDCl_3$) δ: 2.07 (s, 2H, exchangeable with D_2O), 3.77 (s, 3H), 3.71-4.17 (m, 5H), 6.85 (s, 4H), 6.85 (s, 4H); ms (m/z): 198 (M^+), 124 (100%). *Anal.* Calcd for $C_{10}H_{14}O_4$: C 60.59, H 7.12. Found: C 60.58, H 7.40.

(2*R*/*S*,4*S*)-4-(4-Methoxyphenyl)-2-phenyl-1,3-dioxolane (7) ——— A mixture of the above crude glycerol ether (**6**: 67.0 g) and benzaldehyde (41.1 ml, 389 mmol) in benzene (400 ml) is refluxed for 8 h in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate (3.22 g, 16.9 mmol) with removal of generating water using a Dean-Stark apparatus. After cooling, the mixture is diluted with ether (150 ml) and the solution is washed with 15% aqueous NaOH (100 ml), brine (2 x 50 ml), and dried with $MgSO_4$. Evaporation of the solvent under reduced pressure leaves a crystalline residue which is purified by chromatography on a silica gel column (400 g) using a mixture of ether-hexane (1:10 v/v) as eluent to give the acetal (**7**) as colorless needles; yield: 30.1 g (71% overall from **2**); mp 61-65 °C (ether-hexane). ^1H Nmr ($CDCl_3$) δ: 3.77 (s, 3H), 3.98-4.62 (m, 5H), 5.86 (s, 0.5 H), 6.01 (s, 0.5H), 6.84 (s, 2H), 6.86 (s, 2H), 7.33-7.46 (m, 5H); ms (m/z): 286 (M^+, 100%). *Anal.* Calcd for $C_{17}H_{18}O_4$: C 71.31; H 6.34. Found: C 71.31, H 6.40.

(*R*)-*O*-(4-Methoxyphenyl)glycidol (*R*-1): (a) via the bromobenzoate (**8**) ——— To a stirred solution of the acetal (**7**: 17.5 g, 61.2 mmol) in carbon tetrachloride (300 ml) is added *N*-bromosuccinimide (NBS) (12.0 g, 67.3 mmol) portionwise at 0 °C and the mixture is then warmed to 80 °C for 2 min and the stirring is continued for 19 h at room temperature. The mixture is filtered through Celite and the filtrate diluted with dichloromethane (200 ml) is washed successively with saturated aqueous $NaHCO_3$ (100 ml), 10% aqueous $Na_2S_2O_3$ (2 x 100 ml), brine (100 ml), and dried with $MgSO_4$.

Evaporation of the solvent under reduced pressure leaves the crude bromobenzoate (**8**: 24.6 g, 110%) as a yellow oil which is used for the next reaction immediately.

To a stirred solution of the above crude bromobenzoate (**8**: 24.6 g) in THF (400 ml) is added powdered sodium hydroxide (14.4 g, 35.8 mmol) at room temperature and the stirring is continued for 11 h at the same temperature. After diluting with ether (200 ml), the mixture is washed successively with water (200 ml), brine (3 x 80 ml), and dried with $MgSO_4$. After evaporation of the solvent under reduced pressure, an oily residue is purified by chromatography on a silica gel column (350 g) using a mixture of ether-hexane (1:6 v/v) as eluent to give (*R*)-*O*-(4-methoxyphenyl)glycidol (*R*-**1**) as colorless crystals; yield: 9.38 g (73% from **7**); mp 42-43 °C; $[\alpha]_D^{26}$ –11.72° (*c* 1.06, MeOH) [Optical purity is determined to be 100% ee by hplc using a CHIRACEL OD column (hexane-^{i}PrOH, 10:1)]. ^{1}H Nmr ($CDCl_3$) δ: 2.69-2.95 (m, 2H), 3.77 (s, 3H), 3.81-4.26 (m, 2H); ms (m/z): 180 (M^+, 100%). *Anal.* Calcd for $C_{10}H_{12}O_3$: C 66.65, H 6.71. Found: C 66.45, H 6.92.

(b) via the tosylate (**9**) —— A mixture of the pure glycerol ether (*R*-**6**: 1.46 g, 7.37 mmol) and dibutyltin oxide (1.92 g, 7.71 mmol) in benzene (30 ml) is refluxed for 2 h. After evaporation of the solvent under reduced pressure, the residue is dissolved in dichloromethane (20 ml) and the solution is refluxed with *p*-toluenesulfonyl chloride (1.48 g, 7.77 mmol) for 3.5 h, then the mixture after the addition of aqueous dioxane (15% v/v) (15 ml) is further refluxed for 1 h. After cooling the mixture is diluted with dichloromethane (50 ml) and the solution is washed successively with saturated aqueous $NaHCO_3$ (2 x 25 ml), brine (25 ml), and dried with $MgSO_4$. The evaporation of the solvent under reduced pressure leaves the crude tosylate (**9**: 2.75 g, 106%) as a colorless oil which is used for the next reaction. For the analytical purpose a small amount of the product is purified by chromatography on a silica gel column using a mixture of ether-hexane (3:2) as eluent to give the pure tosylate (**9**) as a colorless oil: $[\alpha]_D^{32}$ +12.3° (*c* 1.04, $CHCl_3$). Ir (film) ν_{max}: 3300 cm^{-1}; ^{1}H Nmr ($CDCl_3$) δ: 1.80-2.33 (m, 1H, exchangeable with D_2O), 2.43 (s, 3H), 3.77 (s, 3H), 3.86-4.06 (m, 2H), 4.06-4.37 (m, 3H), 6.78 (s, 4H), 7.31 (d, 2H, *J*=8.4 Hz), 7.80 (d, 2H, *J*=8.4 Hz); ms (m/z): 352 (M^+), 160 (100%). *Anal.* Calcd for $C_{17}H_{20}O_6S$: C 57.94, H 5.72, S 9.08. Found: C 57.92, H 5.79, S 9.15.

A solution of the above crude tosylate (**9**: 2.75 g, 7.81 mmol) and potassium carbonate (1.09 g, 7.89 mmol) in methanol (20 ml) is stirred at room temperature for 1.5 h. The mixture is diluted with ether (40 ml) and water (20 ml) and the organic layer is separated. The aqueous layer is extracted with ether (2 x 30 ml) and the combined organic layers are washed with brine (2 x 30 ml), and dried with $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue is purified by chromatography on a silica gel column (30 g) using a mixture of ether-hexane (1:9 v/v) as eluent to give (*R*-**1**) as colorless needles; yield: 970 mg (73% overall from (*R*)-**6**); mp 43-44 °C. Optical purity is determined to be 100% ee by hplc using a CHIRACEL OD column (hexane-^{i}PrOH, 10:1).

Inversion of (*R*)-1-*O*-(4-Methoxyphenyl)glycerol (*R*-6) into (*S*)-1-*O*-(4-methoxyphenyl)glycerol (*S*-6) —— To a stirred solution of the (*R*)-glycerol ether (*R*-**6**: 1.98 g, 10 mmol) and pyridine (4.04 ml, 50 mmol) in dichloromethane (20 ml) is added methanesulfonyl chloride (1.86 ml, 24 mmol) dropwise at 0 °C and the stirring is continued for 8 h at room temperature. The mixture is diluted with dichloromethane (20 ml) and the solution is washed successively with 5% aqueous HCl (30 ml), brine (20 ml), saturated aqueous $NaHCO_3$ (20 ml), brine (20 ml), and dried with $MgSO_4$. Evaporation of the solvent under reduced pressure leaves the dimesylate (**10**) as colorless solid as virtually pure state; yield: 348 g (98%); mp 82-83 °C. ^{1}H Nmr ($CDCl_3$) δ: 3.10 (s, 3H), 3.15 (s, 3H), 3.77 (s, 3H), 4.18 (d, 2H, *J*=5.4 Hz), 4.45-4.60 (m, 2H), 5.00-5.80 (m, 1H), 6.84 (s, 4H); ms (m/z): 354 (M^+), 135 (100%).

A mixture of the above dimesylate (**10**: 2.5 g, 7.06 mmol) and potassium acetate (3.46 g, 35.3 mmol) in acetic anhydride (20 ml) is refluxed for 100 min. After evaporation of the solvent under reduced pressure, the residue is taken up into ether (50 ml) and the ethereal layer is washed successively with saturated aqueous $NaHCO_3$ (3 x 20 ml), brine (25 ml), and dried with $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue is purified by chromatography on a silica gel column (80 g) using a mixture of ether-hexane (1:4 v/v) as eluent to give the pure diacetate (**11**) as a colorless oil; yield: 1.75 g (88%); $[\alpha]_D^{30}$ –28.2° (*c* 4.82, MeOH). Ir (film) ν_{max}: 1740 cm^{-1}; ^{1}H Nmr ($CDCl_3$) δ: 2.08 (s, 3H), 2.10 (s, 3H), 3.77 (s, 3H), 4.13 (d, 2H, *J*=5.5 Hz), 4.15-4.55 (m, 2H, 7 lines), 5.20-5.50 (m, 1H), 6.84 (s, 4H); ms (m/z):

282 (M^+), 159 (100%). *Anal.* Calcd for $C_{14}H_{18}O_6$: C 59.57, H 6.43. Found: C 59.79, H 6.52.

A solution of the above acetate (**11**: 900 mg, 3.19 mmol) and potassium carbonate (880 mg, 6.38 mmol) in methanol (10 ml) is stirred for 3 h at room temperature. After removal the solvent under reduced pressure, the residue is taken up into dichloromethane (3 x 30 ml) and the combined organic layers are washed with brine (20 ml), and dried with $MgSO_4$. Evaporation of the solvent under reduced pressure leaves the crude (*S*)-**6** as colorless crystals which is recrystallized from a mixture of dichloromethane-hexane to give pure (*S*)-1-*O*-(4-methoxyphenyl)glycerol (*S*-**6**) as colorless needles; yield: 600 mg (95%); mp 78 °C; $[\alpha]_D^{26}$ +7.79° (*c* 1.03, MeOH) [>95% ee by ^{1}H nmr (500 MHz) of the (*R*)- and (*S*)-MTPA esters[11]].

(*S*)-*O*-(4-Methoxyphenyl)glycidol (*S*-1) from (*S*)-1-*O*-(4-Methoxyphenyl)glycerol (*S*-6) —— Following to the established route above, (*S*)-1-*O*-(4-Methoxyphenyl)glycerol (*S*-**6**: 550 mg, 2.77 mmol) is converted into the (*R*)-*O*-(4-methoxyphenyl)glycidol (*R*-**1**) via the benzylidene acetal and the bromobenzoate; yield: 334 mg (67% overall); mp 42-43 °C; $[\alpha]_D^{28}$ +11.04° (*c* 1.08, MeOH) [Optical purity is determined to be 96% ee by hplc using a CHIRACEL OD column (hexane-^{i}PrOH, 10:1)].

REFERENCES

1. B. T. Golding and P. V. Ioannou, *Synthesis*, **1977**, 423.
2. S. Takano, K. Seya, E. Goto, M. Hirama, and K. Ogasawara, *Synthesis*, **1983**, 116.
3. S. Takano, M. Akiyama, and K. Ogasawara, *Synthesis*, **1985**, 503.
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.
5. T. Fukuyama, M. Laird, and L. M. Hotchkiss, *Tetrahedron Lett.*, 1985, **26**, 6291.
6. S. Takano, E. Goto, M. Hirama, and K. Ogasawara, *Heterocycles*, 1981, **16**, 951.
7. O. Mitsunobu, Synthesis, **1981**, 1.
8. S. Takano, M. Hirama, K. Seya, and K. Ogasawara, *Tetrahedron Lett.*, 1983, **24**, 4233.

9. D. E. McClure, B. H. Arison, and J. J. Baldwin, *J. Am. Chem. Soc.*, 1979, **101**, 3666.

10. K. Yamauchi, F. Une, S. Tabata, and M. Kinoshita, *J. Chem. Soc., Perkin Trans. 1*, **1986**, 765.

11. S. Takano, M. Takahashi, M. Yanase, Y. Sekiguchi, Y. Iwabuchi, and K. Ogasawara, *Chemistry Lett.*, **1988**, 1827.

Received, 15th June, 1990