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Synthesis of (+)-(2*S*, 3*S*)-Benzodioxane

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(+)-(2*S*, 3*S*)-6-Methoxy-2-methoxymethyl-3-(3,4-methylenedioxyphenyl)-2,3-dihydro-1,4-benzodioxine, a starting material for synthesis of optically active haedoxan, was synthesized from D-glyceraldehyde.

INTRODUCTION

Haedoxan A, a main insecticidal neolignan of haedokusou (*Phyma leptostachya* L.), possesses a 1,2-dioxygenated 3,7-dioxabicyclo[3.3.0]octane and a 2,3-dihydro-1,4-benzodioxine framework in the molecule (Fig. 1). The total synthesis of the racemate of haedoxan has been already reported by Ishibashi *et al.* (Ishibashi and Taniguchi, 1989b), and the optical active haedoxan had only synthesized from (+)- β -vinyl- γ -butyrolactone and (+)-(2*R*, 3*R*)-benzodioxane prepared by the optical resolution of their racemate (Ishibashi, 1987). Recently, synthesis of an enantio active 3,7-dioxabicyclo[3.3.0]octane portion of phrymarolin similar to haedoxan was achieved by use of Evans aldol reaction as a key step (Kitagawa, 1994). In this paper, we tried to synthesize an optically active benzodioxane framework, the remaining portion of haedoxan. Our final destination is to synthesize an optically active haedoxan by combining these processes.

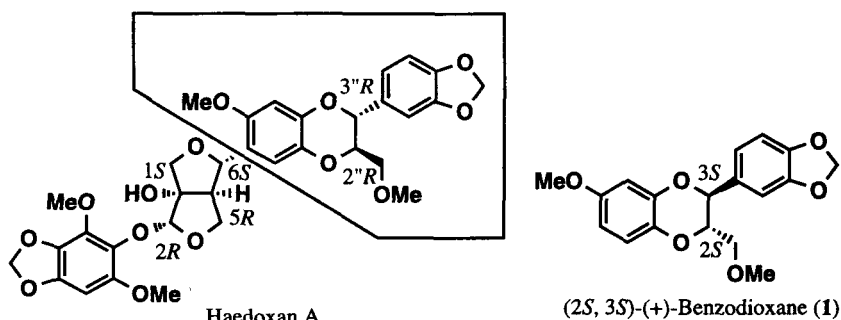


Fig. 1. Structures of Haedoxan A and (+)-Benzodioxane.

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MATERIALS AND METHODS

All melting points (mp.) are uncorrected. ^1H -NMR and ^{13}C -NMR spectra were measured with a JEOL-EX 400 spectrometer (^1H -NMR: 400 MHz, ^{13}C -NMR: 100 MHz), and chemical shifts are reported as values in parts per million relative to tetramethylsilane (δ H/C 0.0) or CDCl_3 (δ C 77.0) as internal standard. Optical rotations were determined on a Union Giken PM-101 polarimeter. Gravity column chromatography was carried out with Merck silica-gel 60 (230–400 mesh ASTM). Preparative TLC was performed on precoated 60F₂₅₄ silica-gel plates supplied by E. Merck.

2-Hydroxy-5-methoxyacetophenone. A mixture of 2,5-dihydroxyacetophenone (9.0 g, 59 mmol), K_2CO_3 (8.3 g, 60 mmol) and MeI (5.54 ml, 89 mmol) was refluxed for 6 hr in acetone (100 ml). After cooling, the solvent was evaporated. The residue was acidified by 2N HCl, and extracted by Et_2O . The extract was washed with brine, dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by silica-gel chromatography (eluent; hexane : EtOAc =4 : 1) to give 2-hydroxy-5-methoxyacetophenone (5.91 g, 60%) as slightly yellow crystals. mp. 44–47°C. ^1H -NMR δ_{H} (CDCl_3): 3.81 (3H, s), 6.92 (1H, d, J =9.27 Hz), 7.11 (1H, dd, J =2.93, 9.27 Hz), 7.17 (1H, d, J =2.93 Hz), 11.85 (1H, s).

2-Benzyloxy-5-methoxyacetophenone. A mixture of 2-hydroxy-5-methoxyacetophenone (5.85 g, 35.2 mmol), benzyl bromide (6.3 ml, 52 mmol), NaOH (4.0 g, 0.1 mol) and adogen 464 (0.2 g) in H_2O : CH_2Cl_2 (50 ml : 80 ml) was vigorously stirred at room temperature for 15 hr. The organic layer was separated, and the aqueous layer was extracted by CH_2Cl_2 . The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by silica-gel chromatography (eluent; hexane : EtOAc =4:1) to give 2-benzyloxy-5-methoxyacetophenone (9.24 g, quant.) as colourless crystals. mp. 43–45°C. ^1H -NMR δ_{H} (CDCl_3): 3.79 (3H, s), 5.12 (2H, s), 6.95–7.02 (2H, m), 7.30 (1H, d, J =2.93 Hz), 7.34–7.44 (5H, m).

2-Benzyloxy-5-methoxyphenol (3). A mixture of 2-benzyloxy-5-methoxyacetophenone (0.50 g, 1.95 mmol), *m*-chloroperbenzoic acid (0.50 g, 2.34 mmol; purity 80%) and NaHCO_3 (0.33 g, 3.9 mmol) in CH_2Cl_2 (10 ml) were stirred at room temperature for 24 hr. The precipitate was filtered, and the filtrate was concentrated to give a crude acetate. To a solution of the crude product in MeOH (15 ml) was added anhydrous K_2CO_3 (1.08 g, 6.24 mmol), and stirred at room temperature for 2 hr. The reaction mixture was neutralized by an addition of 1N HCl and extracted by Et_2O . The extract was washed with brine, dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by silica-gel chromatography (eluent; hexane : EtOAc =4:1) to give 2-benzyloxy-5-methoxyphenol (**3**) (0.35 g, 78%) as colourless crystals. mp. 40–42°C (hexane: EtOAc). ^1H -NMR δ_{H} (CDCl_3): 3.74 (3H, s), 5.05 (2H, s), 5.67 (1H, s), 6.36 (1H, dd, J =2.92, 8.78 Hz), 6.57 (1H, d, J =2.92 Hz), 6.83 (1H, d, J =8.78 Hz), 7.35–7.40 (5H, m). *Anal.* Found: C, 73.07; H, 6.12. Calcd. for $\text{C}_{14}\text{H}_{14}\text{O}_3$: C, 73.63; H, 6.13%.

(2R,3R/S)-3-(3,4-Methylenedioxyphenyl)-1,2-O-isopropylideneglycerol (4). To a cooled (–75°C) and stirred solution of 4-bromo-(1,2-methylenedioxy)benzene (4.04 ml, 33.43 mmol) in dry tetrahydrofuran (THF) (150 ml) was added dropwise a *sec*-BuLi (30 ml, 33.5 mmol, a 1.13 M in cyclohexane) *via* a syringe under N_2 . After 30 min at –75°C, a solution of 2,3-O-isopropylidene-D-glyceraldehyde (**A**) (4.14 g, 31.8 mmol) prepared from D-mannitol in dry THF (30 ml) was added dropwise to the lithio solution, and stirred for 2 hr before quenching by sat. NH_4Cl . The mixture was extracted by

EtOAc, the extract was washed with brine, dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by silica-gel chromatography (eluent; hexane : EtOAc=3 : 1) to give *syn/anti* mixture **4** (5.49 g, 69%) as a colourless syrup. The ratio of *syn* : *anti* was determined to be 7 : 3 by $^1\text{H-NMR}$ integrated intensity. *syn*-**4**: $^1\text{H-NMR}$ δ_{H} (CDCl_3): 1.36 (3H, s), 1.47 (3H, s), 2.34 (1H, d, $J=1.95$ Hz), 3.81 (1H, dd, $J=6.35, 8.30$ Hz), 3.97 (1H, dd, $J=6.84, 8.30$ Hz), 4.25 (1H, m), 4.81 (1H, dd, $J=1.95, 4.39$ Hz), 5.96 (2H, s), 6.78 (1H, d, $J=7.82$ Hz), 6.83 (1H, dd, $J=1.46, 7.82$ Hz), 6.88 (1H, d, $J=1.46$ Hz). *anti*-**4**: $^1\text{H-NMR}$ δ_{H} (CDCl_3): 1.38 (3H, s), 1.49 (3H, s), 2.85 (1H, d, $J=1.95$ Hz), 3.68 (1H, dd, $J=5.85, 8.79$ Hz), 3.79 (1H, dd, $J=6.34, 8.79$ Hz), 4.14-4.20 (1H, m), 4.46 (1H, dd, $J=1.95, 7.81$ Hz), 5.95 (2H, s), 6.77 (1H, d, $J=7.82$ Hz), 6.81 (1H, d, $J=1.47, 7.82$ Hz), 6.89 (1H, d, $J=1.47$ Hz). *Anal.* Found: C, 61.43; H, 6.48. Calcd. for $\text{C}_{13}\text{H}_{16}\text{O}_3$: C, 61.9; H, 6.39%.

(2*R*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-1-(3,4-methylenedioxyphenyl)-1-propanone (**5**). To a suspension of PCC (0.934 g, 4.34 mmol) and Celite (1.0 g) in CH_2Cl_2 (20 ml) was added a solution of **4** (0.235 g, 0.93 mmol) in CH_2Cl_2 (3 ml) and stirred at room temperature for 12 hr. The precipitate was filtered and the filtrate was concentrated. The residue was chromatographed on silica-gel (eluent; hexane : EtOAc=2 : 1) to give **5** (0.206 g, 0.824 mmol) as white crystals. mp. 70–73°C. $[\alpha]_{\text{D}}^{25}=-6.24^\circ$ (c 2.244, CHCl_3). $^1\text{H-NMR}$ δ_{H} (CDCl_3): 1.43 (3H, s), 1.47 (3H, s), 4.25-4.32 (2H, m), 5.17-5.21 (1H, m), 6.88 (1H, d, $J=8.30$ Hz), 7.50 (1H, d, $J=1.47$ Hz), 7.64 (1H, dd, $J=1.47, 8.30$ Hz).

Reduction of **5** by several reductants.

NaBH_4 : To a cooled (0°C) solution of **5** (30 mg, 0.12 mmol) in EtOH (3 ml) was added NaBH_4 (4.2 mg, 0.224 mmol) and stirred at room temperature for 1.5 hr. The solvent was evaporated, water was added to the residue and extracted by EtOAc. The extract was washed with brine, dried over Na_2SO_4 , filtered and evaporated. The residue was purified by preparative TLC (0.5 mm thickness, developing solvent; hexane : EtOAc=2 : 1) to give **4**. Yield: 28 mg (0.111 mmol), (93%); *syn* : *anti*=35 : 65.

LiAlH_4 : To a cooled (0°C) suspension of LiAlH_4 (5.2 mg, 0.14 mmol) in dry THF (1 ml) was added a solution of **5** (37 mg, 0.148 mmol) in dry THF (3 ml) and stirred for 1 hr. To the reaction mixture was added a diluted HCl soln. and extracted by Et_2O . The extract was treated in the above manner. Yield: 35.1 mg (0.139 mmol), (94%); *syn* : *anti*=14 : 86.

LiBH_4 : To a cooled (0°C) solution of **5** (35 mg, 0.14 mmol) in dry THF (3 ml) was added LiBH_4 (0.08 ml, a 2.0 M in THF, 0.16 mmol) by a syringe under N_2 and stirred for 2 hr. Water was added to the reaction mixture and extracted by EtOAc. The extract was treated in the above manner. Yield: 30.6 mg (0.121 mmol), (86%); *syn* : *anti*=50 : 50.

DIBAH: To a cooled (–78°C) solution of **5** (26 mg, 0.104 mmol) in dry toluene (3 ml) was added DIBAH (0.13 ml, a 1.0 M in toluene, 0.13 mmol) by a syringe under N_2 and stirred for 1 hr. To the reaction mixture was added sat. NH_4Cl and extracted by EtOAc. The extract was treated in the above manner. Yield: 23.7 mg (0.094 mmol), (90%); *syn* : *anti*=71 : 29.

L-Selectride: To a cooled (–78°C) solution of **5** (50 mg, 0.20 mmol) in dry THF (3 ml) was added L-Selectride (0.28 ml, a 1.0 M in THF, 0.28 mmol) by a syringe under N_2 and stirred for 2 hr. To the reaction mixture was added water and extracted by EtOAc. The extract was treated in the above manner. Yield: 38.9 mg (0.154 mmol), (77%); *syn* : *anti*<1 : >99.

(1*R*/5*R*)-1-Chloro-2,3-dihydroxy-2,3-*O*-isopropylidene-1-(3,4-methylenedioxyphenyl)propane (**6**). To an ice-cooled and stirred solution of **4** (0.12 g, 0.48 mmol) and 4-dimethylaminopyridine (DMAP) (0.15 g, 1.2 mmol) in CH₂Cl₂ (3 ml) was added *p*-toluenesulfonyl chloride (0.18 g, 0.96 mmol), and stirred at room temperature for 24 hr. The solution was diluted by CH₂Cl₂, washed with water, 1*N* HCl, sat. NaHCO₃, brine, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by silica-gel chromatography (eluent; hexane : EtOAc=8 : 1) to give *syn/anti* mixture **6** (0.81 g, 53%) as a colourless oil. ¹H-NMR δ_H (CDCl₃): 1.32 (2.1H, s), 1.40 (0.9H, s), 1.42 (2.1H, s), 1.46 (0.9H, s), 3.62 (0.3H, dd, *J*=5.86, 8.79 Hz), 3.84 (0.3H, dd, *J*=6.35, 8.79 Hz), 4.13 (0.7H, dd, *J*=4.89, 8.79 Hz), 4.22 (0.7H, dd, *J*=5.86, 8.79 Hz), 4.43-4.50 (1H, m), 4.67 (0.7H, d, *J*=9.28 Hz), 4.72 (0.3H, d, *J*=8.30 Hz), 5.97-5.99 (2H, m), 6.75-6.93 (3H, m).

(1*S*, 2*R*)-1-(2-Benzoyloxy-5-methoxyphenoxy)-2,3-dihydroxy-2,3-*O*-isopropylidene-1-(3,4-methylenedioxyphenyl)propane (**7**). To an ice-cooled and stirred mixture of **4** (1.18 g, 4.68 mmol), **3** (1.19 g, 5.15 mmol) and triphenylphosphine (1.35 g, 5.15 mmol) in dry THF (20 ml) was added portionwise diethyl azodicarboxylate (DEAD) (1.72 ml, 5.15 mmol; 40% in toluene solution) under N₂, and stirred at room temperature for 48 hr. To the reaction mixture was added water and extracted by Et₂O. The extract was washed with 1*N* NaOH, brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica-gel chromatography (eluent; hexane : EtOAc=2 : 1) to give *syn/anti* mixture (5.49 g, 69%) as a colourless syrup. Diastereomer was separated by an additional silica-gel chromatography (eluent; hexane : EtOAc=8 : 1). (2*R*, 3*S*)-**7** in a 19% yield as a colourless oil. *R*_f=0.46 (TLC, hexane : EtOAc=2 : 1). [α]_D¹⁵=+17.5° (c 0.63, CHCl₃). ¹H-NMR δ_H (CDCl₃): 1.33 (3H, s), 1.43 (3H, s), 3.63 (3H, s), 4.12 (1H, dd, *J*=6.35, 8.79 Hz), 4.21 (1H, dd, *J*=4.88, 8.79 Hz), 4.35 (1H, m), 4.96 (1H, d, *J*=7.32 Hz), 5.05 (2H, s), 5.93 (2H, s), 6.32-6.36 (2H, m), 6.74 (1H, d, *J*=7.82 Hz), 6.80-6.90 (3H, m), 7.32-7.45 (5H, m). *Anal.* Found: C, 69.58; H, 6.42. Calcd. for C₂₇H₂₈O₇: C, 69.81; H, 6.08%. (2*R*, 3*R*)-**7** in a 10% yield as colourless crystals. *R*_f=0.41 (TLC, hexane : EtOAc=2 : 1). mp. 145-148°C (isoPr₂O). [α]_D¹⁵=-24.9° (c 0.241, CHCl₃). ¹H-NMR δ_H (CDCl₃): 1.36 (3H, s), 1.38 (3H, s), 3.65 (3H, s), 3.68-3.75 (1H, m), 3.79 (1H, dd, *J*=6.35, 8.79 Hz), 4.52 (1H, m), 5.06 (2H, s), 5.13 (1H, d, *J*=6.35 Hz), 5.93 (2H, s), 6.33 (1H, dd, *J*=2.93, 8.79 Hz), 6.42 (1H, d, *J*=2.45 Hz), 6.72 (1H, d, *J*=8.30 Hz), 6.79-6.89 (3H, m), 7.29-7.47 (5H, m). *Anal.* Found: C, 69.73; H, 6.1. Calcd. for C₂₇H₂₈O₇: C, 69.81; H, 6.08%.

(1*S*, 2*R*)-1-(2-Benzoyloxy-5-methoxyphenoxy)-2,3-dihydroxy-1-(3,4-methylenedioxyphenyl)propane (**8**). To a solution of (1*S*, 2*R*)-**7** (0.398 g, 0.858 mmol) in THF (3 ml) was added conc. HCl (0.4 ml), and stirred at room temperature for 30 min. The solution was neutralized by 1*N* NaOH and extracted by Et₂O. The extract was washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica-gel chromatography (eluent; hexane : EtOAc=1 : 1) to give **8** (0.267 g, 73%) as a colourless syrup. [α]_D¹⁷=+33.98° (c 2.59, CHCl₃). ¹H-NMR δ_H (CDCl₃): 2.64 (1H, br.), 2.96 (1H, d, *J*=6.84 Hz), 3.60-3.66 (1H, m), 3.63 (3H, s), 3.81-3.88 (2H, m), 5.08 (2H, s), 5.12 (1H, d, *J*=4.39 Hz), 5.95 (2H, d, *J*=0.97 Hz), 6.31 (1H, d, *J*=2.44 Hz), 6.38 (1H, dd, *J*=2.93, 8.79 Hz), 6.75-6.86 (4H, m), 7.33-7.45 (5H, m). *Anal.* Found: C, 67.91; H, 6.50. Calcd. for C₂₄H₂₄O₇: C, 67.91; H, 5.7%.

(1*S*, 2*R*)-1-(2-Benzoyloxy-5-methoxyphenoxy)-3-*tert*-butyldimethylsilyloxy-2-hydroxy-1-(3,4-methylenedioxyphenyl)propane (**9**). A mixture of **8** (49 mg,

0.116 mmol), Et₃N (0.02 ml, 0.14 mmol), DMAP (1 mg) and *tert*-butyldimethylsilyl chloride (0.02 g, 0.128 mmol) in dry CH₂Cl₂ (2 ml) was stirred at room temperature for 36 hr. The mixture was washed with 5% citric acid, sat. NaHCO₃, brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by preparative TLC (1.0 mm thickness; developing solvent; hexane : EtOAc=3 : 1) to give **9** (40 mg, 65%) as a colourless oil. ¹H-NMR δ_H (CDCl₃): 0.02 (6H, s), 0.87 (9H, s), 2.64 (1H, d, *J*=4.88 Hz), 3.63 (3H, s), 3.73–3.82 (2H, m), 3.98 (1H, m), 5.03–5.05 (3H, m), 5.92 (2H, s), 6.32 (1H, dd, *J*=2.93, 8.30 Hz), 6.40 (1H, d, *J*=2.93 Hz), 6.75 (1H, d, *J*=8.30 Hz), 6.80 (1H, d, *J*=8.79 Hz), 6.87 (1H, dd, *J*=1.47, 7.82 Hz), 6.93 (1H, d, *J*=1.47 Hz), 7.31–7.45 (5H, m).

(1*S*, 2*R*)-3-*tert*-Butyldimethylsilyloxy-2-hydroxy-1-(2-hydroxy-5-methoxyphenoxy)-1-(3,4-methylenedioxyphenyl)propane (**10**). A mixture of **9** (40 mg, 75.8 μmol), 20% Pd(OH)₂-C (8 mg) and cyclohexene (0.5 ml) in EtOAc (1 ml) was refluxed for 2 hr. The palladium catalyst was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by preparative TLC (0.5 mm thickness; developing solvent; hexane : EtOAc=3 : 1) to give **10** (31.7 mg, 95%) as a colourless resin. ¹H-NMR δ_H (CDCl₃): 0.07 (6H, s), 0.90 (9H, s), 3.63 (3H, s), 3.65 (1H, dd, *J*=4.39, 10.26 Hz), 3.86 (1H, dd, *J*=6.84, 10.26 Hz), 4.00 (1H, m), 5.00 (1H, d, *J*=4.88 Hz), 6.34 (1H, d, *J*=2.93 Hz), 6.42 (1H, dd, *J*=2.45, 8.79 Hz), 6.78–6.92 (5H, m).

3-*tert*-Butyldimethylsilyloxy-1-(2-hydroxy-5-methoxyphenoxy)-1-(3,4-methylene-dioxyphenyl)propene (**11**). To an ice-cooled and stirred solution of **10** (31.7 mg, 70.6 μmol) and triphenylphosphine (18.5 mg, 70.6 μmol) in dry THF (1 ml) was added portionwise DEAD (24 μl, 71 μmol; 40% in toluene solution) in dry THF (0.5 ml) under N₂, and stirred at room temperature for 48 hr. To the reaction mixture was added water and extracted by Et₂O. The extract was washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by preparative TLC (0.5 mm thickness; developing solvent; hexane : EtOAc=4 : 1) to give **11** (12.2 mg, 40%) as a colourless syrup. ¹H-NMR δ_H (CDCl₃): 3.57 (3H, s), 4.31 (1H, d, *J*=6.35 Hz), 5.49 (1H, br.), 5.77 (1H, t, *J*=6.35 Hz), 5.87 (2H, s), 6.28 (1H, d, *J*=2.93 Hz), 6.35 (1H, dd, *J*=2.93, 8.79 Hz), 6.64 (1H, d, *J*=8.30 Hz), 6.81 (1H, d, *J*=8.79 Hz), 6.85–6.91 (2H, m). ¹³C-NMR δ_C (CDCl₃): -5.10 (q×2), 18.31 (s), 25.89 (q×3), 55.60 (q), 58.18 (t), 101.27 (t), 102.09 (d), 105.90 (d), 106.72 (d), 108.33 (d), 115.46 (d), 116.30 (d), 119.68 (d), 128.21 (s), 139.49 (s), 144.26 (s), 147.94 (s), 148.12 (s), 148.84 (s), 153.37 (s). *Anal.* Found: C, 63.9; H, 7.02. *Calcd.* for C₂₃H₃₀O₆Si: C, 64.16; H, 7.02%.

(2*R*, 3*S*)-3-(2-Benzoyloxy-5-methoxyphenoxy)-2-hydroxy-3-(3,4-methylenedioxyphenyl)propyl pivaloate (**12**). To an ice-cooled and stirred solution of **8** (0.158 g, 0.373 mmol) and pyridine (0.06 ml, 0.746 mmol) in dry CH₂Cl₂ (3 ml) was added portionwise a solution of pivaloyl chloride (0.051 ml, 0.41 mmol) in dry CH₂Cl₂ (0.5 ml), and stirred at ice-temp. for 3 hr. The solution was washed with 1N HCl, sat. NaHCO₃, brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica-gel chromatography (eluent; hexane : EtOAc=3 : 1) to give **12** (0.128 g, 68%) as a colourless syrup. ¹H-NMR δ_H (CDCl₃): 1.17 (9H, s), 2.02 (1H, br.), 3.62 (3H, s), 4.11 (1H, m), 4.21–4.23 (2H, m), 5.03 (1H, d, *J*=5.37 Hz), 5.05 (2H, s), 5.90 (2H, s), 6.35–6.39 (2H, m), 6.74 (1H, d, *J*=7.81 Hz), 6.81–6.84 (2H, m), 6.92 (1H, d, *J*=1.47 Hz), 7.31–7.45 (5H, m). *Anal.* Found: C, 68.19; H, 6.41. *Calcd.* for C₂₉H₃₂O₈: C, 68.49; H, 6.34%.

(2*R*, 3*S*)-3-(2-Benzoyloxy-5-methoxyphenoxy)-3-(3,4-methylenedioxyphenyl)-2-*p*-

toluenesulfonyloxypropyl pivaloate (**13**). To an ice-cooled and stirred solution of **12** (0.12 g, 0.237 mmol) and DMAP (37 mg, 0.30 mmol) in dry CH_2Cl_2 (2 ml) was added *p*-toluenesulfonyl chloride (53 mg, 0.28 mmol), and stirred at room temperature for 24 hr. The solution was washed with 1N HCl, sat. NaHCO_3 , brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by silica-gel chromatography (eluent; hexane : EtOAc =3 : 1) to give **13** (0.132 g, 79%) as a colourless syrup. $^1\text{H-NMR}$ δ_{H} (CDCl_3): 1.20 (9H, s), 2.44 (3H, s), 3.67 (3H, s), 4.57 (2H, d, J =4.40 Hz), 5.02–5.11 (3H, m), 5.28 (1H, d, J =5.37 Hz), 5.95 (2H, d, J =11.23 Hz), 6.28 (1H, d, J =2.93 Hz), 6.40 (1H, dd, J =2.93, 8.79 Hz), 6.68 (1H, d, J =7.82 Hz), 6.76–6.79 (2H, m), 6.85 (1H, d, J =8.79 Hz), 7.23 (2H, d, J =8.31 Hz), 7.36–7.50 (5H, m), 7.63 (2H, d, J =8.31 Hz). *Anal.* Found: C, 64.74; H, 5.9. Calcd. for $\text{C}_{26}\text{H}_{26}\text{O}_{10}\text{S}$: C, 65.24; H, 5.78%.

(2*R*,3*S*)-3-(2-Hydroxy-5-methoxyphenoxy)-3-(3,4-methylenedioxyphenyl)-2-*p*-toluenesulfonyloxypropyl pivaloate (**14**). A mixture of **13** (0.132 g, 0.199 mmol), 20% $\text{Pd}(\text{OH})_2\cdot\text{C}$ (27 mg) and cyclohexene (1.5 ml) in EtOAc (3 ml) was refluxed for 2 hr. The palladium catalyst was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by silica-gel chromatography (eluent; hexane : EtOAc =3 : 1) to give **14** (0.117 g, quant.) as colourless crystals. mp. 104–107°C (dec.). $^1\text{H-NMR}$ δ_{H} (CDCl_3): 1.16 (9H, s), 2.04 (3H, s), 3.60 (3H, s), 4.08 (1H, dd, J =7.32, 12.21 Hz), 4.25 (1H, dd, J =3.91, 12.21 Hz), 5.16 (1H, d, J =3.90 Hz), 5.26 (1H, m), 5.90 (2H, d, J =8.30 Hz), 6.17 (1H, d, J =2.93 Hz), 6.25 (1H, s), 6.35 (1H, dd, J =2.44, 8.79 Hz), 6.69 (1H, d, J =7.81 Hz), 6.75–6.82 (3H, m), 7.26 (2H, d, J =8.30 Hz), 7.72 (2H, d, J =8.30 Hz).

(2*S*,3*S*)-6-Methoxy-3-(3,4-methylenedioxyphenyl)-2-pivaloyloxymethyl-2,3-dihydro-1,4-benzodioxine (**15**). A mixture of **14** (19.0 mg, 33.2 μmol) and K_2CO_3 (9.2 mg, 64 μmol) in dry acetone (3 ml) was refluxed for 2 hr. The solvent was evaporated, and to the residue was added water and extracted by Et_2O . The extract was washed with brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by preparative TLC (0.25 mm thickness; developing solvent; hexane : EtOAc =3 : 1) to give **15** (8.7 mg, 65%) as a colourless oil. $[\alpha]_{\text{D}}^{25}=-9.72^\circ$ (c 0.72, CHCl_3). $^1\text{H-NMR}$ δ_{H} (CDCl_3): 1.21 (9H, s), 3.74 (3H, s), 3.90 (1H, dd, J =4.39, 12.21 Hz), 4.15 (1H, m), 4.33 (1H, dd, J =2.93, 12.21 Hz), 4.88 (1H, d, J =7.81 Hz), 5.99 (2H, s), 6.48 (1H, dd, J =2.93, 8.79 Hz), 6.54 (1H, d, J =2.93 Hz), 6.82–6.88 (4H, m).

(2*S*,3*S*)-2-Hydroxymethyl-6-methoxy-3-(3,4-methylenedioxyphenyl)-2,3-dihydro-1,4-benzodioxine (**16**). A mixture of **15** (36 mg, 0.09 mmol) and an excess of NaOH in MeOH (2 ml) and H_2O (0.4 ml) was stirred at room temperature for 8 hr. The solution was concentrated *in vacuo*, to the residue was added water and extracted by Et_2O . The extract was washed with brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by preparative TLC (0.25 mm thickness; developing solvent; hexane : EtOAc =3 : 1) to give **16** (23.8 mg, 84%) as colourless crystals. mp. 98–99.5°C. $[\alpha]_{\text{D}}^{15}=+42.0^\circ$ (c 0.476, CHCl_3). $^1\text{H-NMR}$ δ_{H} (CDCl_3): 1.95 (1H, br.), 3.51–3.57 (1H, m), 3.74 (3H, m), 3.78 (1H, m), 3.95 (1H, m), 4.93 (1H, d, J =8.30 Hz), 6.00 (2H, s), 6.47 (1H, d, J =2.93 Hz), 6.55 (1H, d, J =2.93 Hz), 6.83–6.93 (4H, m). *Anal.* Found: C, 64.43; H, 5.07. Calcd. for $\text{C}_{17}\text{H}_{16}\text{O}_6$: C, 64.55; H, 5.10%.

(2*S*,3*S*)-6-Methoxy-2-[(*S*)- α -methoxy- α -(trifluoromethyl)phenylacetyloxymethyl]-3-(3,4-methylenedioxyphenyl)-2,3-dihydro-1,4-benzodioxine (**17**). A solution of **16** (3.8 mg, 12 μmol), (*S*)- α -methoxy- α -(trifluoromethyl)phenylacetyl chloride (MTPACl)

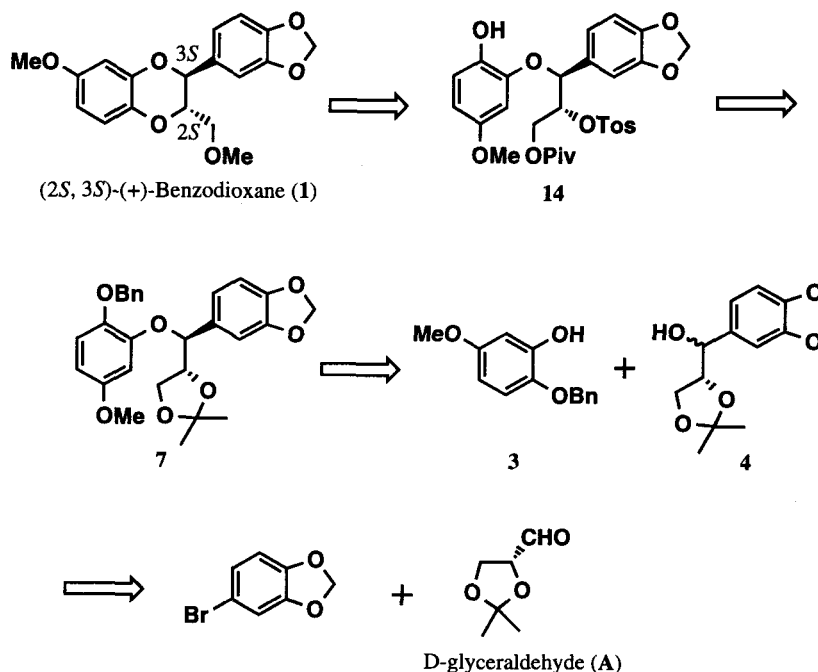
(9.8 mg, 38.8 μ mol) and DMAP (12.2 mg, 0.10 mmol) in dry CH_2Cl_2 (2 ml) was stirred at room temperature for 8 hr. The solution was washed with 1N HCl, sat. NaHCO_3 , brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by preparative TLC (0.25 mm thickness; developing solvent; hexane : EtOAc=3 : 1) to give a mosher ester **17** (6.4 mg, quant.) as a colourless resin. $^1\text{H-NMR}$ δ_{H} (CDCl_3): 3.58 (3H, d, $J=0.97$ Hz), 3.74 (3H, s), 3.90 (1H, dd, $J=3.42, 12.21$ Hz), 4.15 (1H, m), 4.11–4.17 (2H, m), 5.98 (2H, d, $J=0.98$ Hz), 6.48–6.59 (3H, m), 6.69–7.73 (2H, m), 6.86 (1H, d, $J=8.79$ Hz), 7.35–7.42 (3H, m), 7.57 (2H, d, $J=7.32$ Hz). In the same manner, racemic benzodioxane (\pm)-**17** (3.8 mg, 40.5 μ mol) was treated to give mosher esters (19.3 mg, 87%) as a colourless resin with (*S*)-MTPACl (17.9 mg, 71 μ mol). $^1\text{H-NMR}$ δ_{H} (CDCl_3): 3.56 (1.5H, s), 3.59 (1.5H, d, $J=0.97$ Hz), 3.73 (3H, s), 3.90 (0.5H, dd, $J=3.42, 12.21$ Hz), 4.08 (0.5H, dd, $J=4.40, 12.21$ Hz), 4.13–4.19 (1H, m), 4.66 (1H, m), 4.73–4.80 (1H, m), 5.97–6.00 (2H, m), 6.47–6.88 (6H, m), 7.32–7.42 (3H, m), 7.53 (1H, d, $J=7.32$ Hz), 7.57 (1H, d, $J=7.32$ Hz).

(2*S*, 3*S*)-6-Methoxy-2-methoxymethyl-3-(3,4-methylenedioxyphenyl)-2,3-dihydro-1,4-benzodioxine (**1**). To an ice-cooled suspension of NaH (4.4 mg, 0.11 mmol; 60% in mineral oil) in dry THF (1 ml) was added portionwise a solution of **16** (23.0 mg, 72.8 μ mol) in dry THF (1 ml), and stirred for 15 min. To the solution was added MeI (12.3 μ l, 0.20 mmol) *via* a micro syringe, and stirred at room temperature for 3 hr. To the reaction mixture was added water and extracted by EtOAc. The extract was washed with brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by preparative TLC (0.5 mm thickness; developing solvent; hexane : EtOAc=4 : 1) to give **1** (14.2 mg, 59%) as colourless crystals. mp. 152–155 $^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{25} = +22.7^{\circ}$ (c 0.132, CHCl_3). $^1\text{H-NMR}$ δ_{H} (CDCl_3): 3.30 (1H, dd, $J=3.90, 10.74$ Hz), 3.34 (3H, s), 3.57 (1H, dd, $J=2.44, 10.74$ Hz), 3.73 (3H, s), 3.99 (1H, m), 4.97 (1H, d, $J=8.30$ Hz), 6.00 (2H, s), 6.46 (1H, dd, $J=2.93, 8.79$ Hz), 6.53 (1H, d, $J=2.93$ Hz), 6.83–6.93 (4H, m). $^{13}\text{C-NMR}$ δ_{C} (CDCl_3): 55.69 (q), 59.49 (q), 71.23 (t), 76.44 (d), 77.16 (d), 101.28 (t), 102.30 (d), 107.52 (d), 107.59 (d), 108.47 (d), 117.46 (d), 121.30 (d), 130.43 (s), 137.34 (s), 143.93 (s), 148.08 (s \times 2), 154.30 (s). *Anal.* Found: C, 64.92; H, 5.67. Calcd. for $\text{C}_{18}\text{H}_{18}\text{O}_6$: C, 65.45; H, 5.49%.

(2*S*, 3*S*)-7-Formyl-6-methoxy-2-methoxymethyl-3-(3,4-methylenedioxyphenyl)-2,3-dihydro-1,4-benzodioxine (**18**). To a solution of **1** (11.5 mg, 34.8 μ mol) in dry DMF (1.5 ml) was added POCl_3 (60 μ l, 0.69 mmol), and stirred at 80 $^{\circ}\text{C}$ for 3 hr before quenching by aq. NaOAc soln. (1 g NaOAc in 4 ml water). The mixture was extracted by EtOAc. The extract was washed with water, brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by preparative TLC (0.25 mm thickness; developing solvent; hexane : EtOAc=3 : 1) to give **18** (2.9 mg, 24%) as a colourless resin. $[\alpha]_{\text{D}}^{25} = -27.6^{\circ}$ (c 0.145, CHCl_3). $^1\text{H-NMR}$ δ_{H} (CDCl_3): 3.31 (1H, dd, $J=3.42, 10.74$ Hz), 3.36 (3H, s), 3.61 (1H, dd, $J=2.44, 11.43$ Hz), 3.84 (3H, s), 3.98–4.01 (1H, m), 5.08 (1H, d, $J=8.30$ Hz), 6.01 (2H, s), 6.55 (1H, s), 6.85–6.92 (3H, m), 7.49 (1H, s), 10.29 (1H, s).

RESULTS AND DISCUSSION

Scheme 1 shows the retrosynthetic route of (+)-benzodioxane. In this synthetic plan, two asymmetric centers of 2/3-positions must be possible to induce by the inter- and intramolecular $\text{S}_{\text{N}}2$ reactions. And as a chiral starting block, D-glyceraldehyde (**A**)



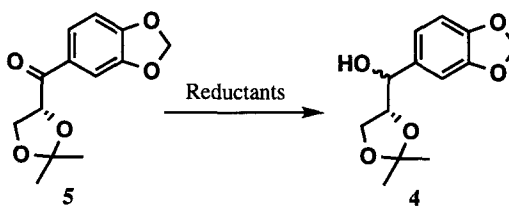
Scheme 1. Retrosynthetic route of (+)-Benzodioxane (**1**).

prepared from D-mannitol (Baer and Fisher, 1939) was selected, though the use of D-glyceraldehyde would give the enantiomer of (2*R*, 3*R*)-benzodioxane portion of the natural haedoxan A. The preparation of **A** from D-mannitol in terms of the easiness of synthesis and yield is superior to that from L-ascorbic acid which give the L-glyceraldehyde (Jung and Shaw, 1980).

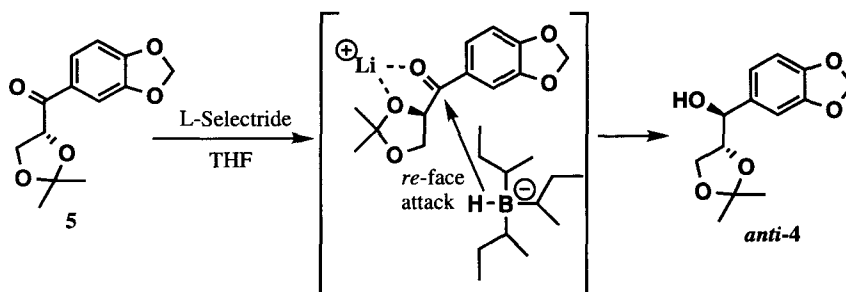
The building block **3** was converted from 2,5-dihydroxyacetophenone in 47% yield through 4 steps. A chiral starting material **A** prepared from D-mannitol reacted with 4-bromo-(1,2-methylenedioxy)benzene to give the *syn-anti* coupling products (**4**) (*syn:anti*=3:7 from ¹H-NMR). The PCC oxidation of the diastereomeric mixture **4** gave one ketone **5**, and the reduction of **5** with several reductants was tried to obtain a diastereomer. Table 1 shows the results. The L-Selectride reduction of **5** exclusively gave an *anti*-**4**. It is presumed that the reduction proceed with *re*-face attack *via* a lithium chelated five-membered transition state (Fig. 2). Treatment of **4** with *p*-toluenesulfonyl chloride and 4-dimethylaminopyridine gave benzyl chloride **6** (Scheme 2), which unreacted with the sodium phenoxide of **3** to furnish **7**.

The Mitsunobu reaction (Mitsunobu, 1981) of **4** and **3** gave the coupling products **7** in poor yield, and unfortunately, this reaction did not proceed in satisfactory yield but also epimerized. This result is probably due to the steric hindrance of 2-benzyloxy function of **3** and acetonide of **4**, and a benzylic hydroxyl function that eliminate easily (Hughes, 1992).

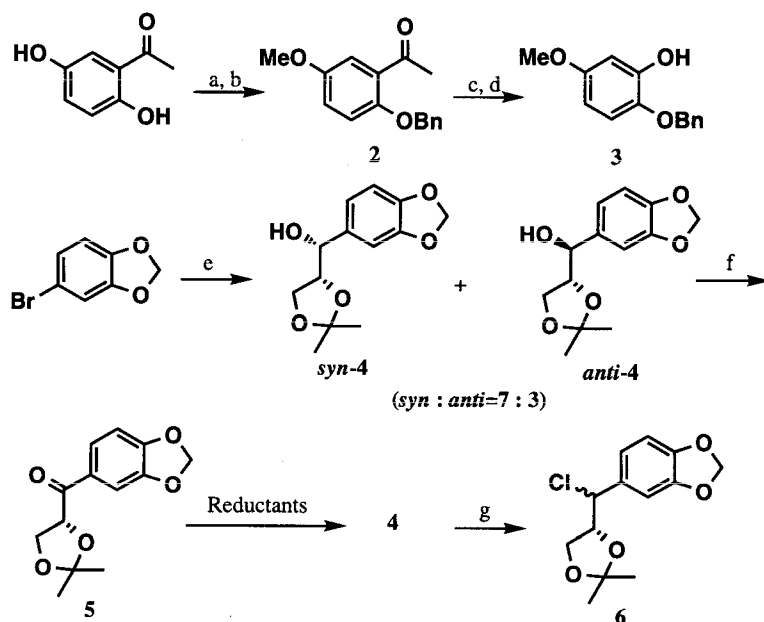
The coupling compounds **7** was chromatographed on silica-gel to separate *syn/anti*

Table 1. Results of the reduction of **5** by several reductants.


Reductants	Solvent	Yield(%)	<i>syn</i> -4 : <i>anti</i> -4 ^{a)}
NaBH ₄	EtOH	93	35 : 65
LiAlH ₄	THF	94	14 : 86
LiBH ₄	THF	86	50 : 50
DIBALH	Toluene	90	71 : 29
L-Selectride	THF	77	<1 : >99

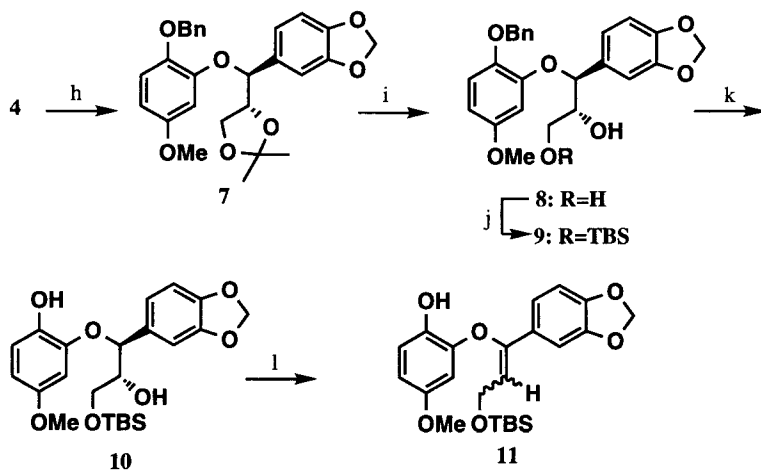
a) The ratio was determined by the integral value of ¹H-NMR.**Fig. 2.** Hypothesis of the reduction of **5** by L-Selectride.

mixture. The separated *anti*-**7** was submitted to HCl treatment in THF to give diol **8**. *Syn*-**7** gave no identical mixture in low yield. After the mono silylation of **8** with *tert*-butyldimethylsilyl chloride, debenzoylation was achieved by H₂/20% Pd(OH)₂-C (Pearlman, 1967). The resulting product **10** was followed by intramolecular Mitsunobu reaction, however, the dehydrated alkene compound **11** formed solely (Scheme 3). Therefore, the primary hydroxyl group of **8** was protected as the less bulky pivaloyl ester than *tert*-butyldimethylsilyl ether to give **12**, and the tosylation of which furnished **13**. After debenzoylation by Pearlman reagent, the resulting product **14** was refluxed with K₂CO₃ in acetone to afford an intramolecular cyclized compound **15** in an acceptable yield. This reaction proceeded completely in stereo inversion. The stereochemistry was assigned from the chemical shift value and the coupling constant of 3-*H* based on ¹H-NMR (δ_{H} 4.88



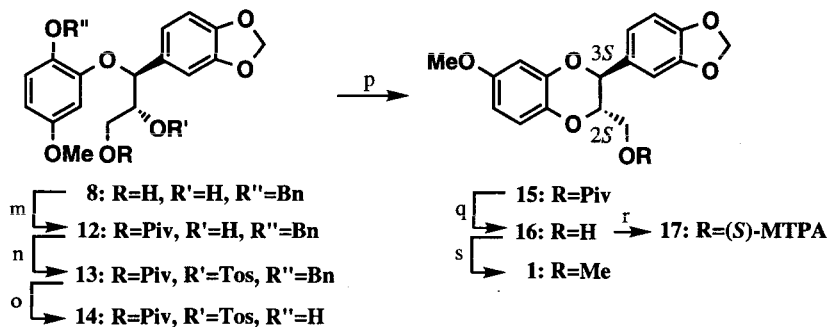
a) MeI, K_2CO_3 , acetone; b) BnBr, NaOH, CH_2Cl_2 - H_2O ; c) *m*CPBA, $NaHCO_3$, CH_2Cl_2 ; d) K_2CO_3 , MeOH; e) *sec*-BuLi, then A; f) PCC, CH_2Cl_2 ; g) TsCl, DMAP, CH_2Cl_2 .

Scheme 2. Synthesis of (+)-Benzodioxane (1).



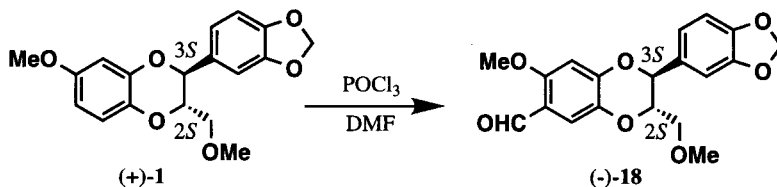
h) 3, DEAD, Ph_3P , THF, then chromatographic separation; i) conc. HCl, THF; j) TBDMSCl, Et_3N , DMAP, CH_2Cl_2 ; k) 20% $Pd(OH)_2$ -C, cyclohexene, EtOAc; l) DEAD, Ph_3P , THF.

Scheme 3. Synthesis of (+)-Benzodioxane (1) (cont).



m) pivaloyl chloride, pyridine, CH_2Cl_2 ; n) tosyl chloride, DMAP, CH_2Cl_2 ;
 o) 20% $\text{Pd}(\text{OH})_2\text{-C}$, cyclohexene, EtOAc ; p) K_2CO_3 , acetone; q) NaOH, MeOH;
 r) (S)-MTPACl, DMAP, CH_2Cl_2 ; s) NaH, THF, then MeI.

Scheme 4. Synthesis of (+)-Benzodioxane (**1**) (cont).



Scheme 5. Synthesis of (-)-Benzodioxane-7-carbaldehyde (**18**).

ppm, $J=7.81$) (Ishibashi and Taniguchi, 1989a). Hydrolysis of pivaloyl ester with NaOH in MeOH and subsequent methyl etheralization yielded (+)-(2*S*, 3*S*)-benzodioxane **1** (Scheme 4). $[\alpha]_D^{15} = +22.7^\circ$ (c 0.132, CHCl_3). The overall yield of **1** was 2.4% based on D-glyceraldehyde after nine steps. The enantio purity of **1** was estimated as 94% ee. by $^1\text{H-NMR}$ integral value of mosher ester **17**. The Vilsmeier reaction of **1** gave a (-)-(2*S*, 3*S*)-benzodioxane-7-carbaldehyde **18** (Scheme 5).

This synthetic manner can be employed as a part of the optically active haedoxan synthesis.

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