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Enantioselective Synthesis of a (+)-(2*R*, 3*R*)-1,4-Benzodioxane-7-carbaldehyde Derivative, a Key Intermediate in the Total Synthesis of Haedoxan Analogs

Yuji NAKAMURA, Makoto HIRATA, Eiichi KUWANO,† and Eiji TANIGUCHI

Department of Agricultural Chemistry, Faculty of Agriculture, Kyushu University, Hakozaki 6-10-1, Higashi-ku, Fukuoka 812-8581, Japan

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(+)-(2*R*, 3*R*)-7-Formyl-6-methoxy-2-methoxymethyl-3-(3,4-methylenedioxyphenyl)-2,3-dihydro-1,4-benzodioxin (2), a key building block for the total synthesis of haedoxan A, was synthesized from (4*R*)-4-(phenylmethyl)-2-oxazolidinone (3) in ten steps with a 12% overall yield.

Key words: benzodioxane; haedoxan A; sesquilignan

Introduction

Haedoxan A, (+)-(1*S*, 2*R*, 5*R*, 6*S*, 2″*R*, 3″*R*)-1-hydroxy-2-[(2′,6′-dimethoxy-3′,4′-methylenedioxyphenyl)-oxy]-6-[2″,3″-dihydro-6″-methoxy-2″-methoxymethyl-3″-(3,4-methylenedioxyphenyl)-1″,4″-benzodioxin-7″-yl]-3,7-dioxabicyclo[3.3.0]octane (**1**, Fig. 1), was isolated from an extract of Haedokusou (*Phryma leptostacha* L.),[1] which exhibits extremely high insecticidal activity against houseflies, the LD_{50} value being estimated to be as low as 0.25 ng per fly in the presence of piperonyl butoxide as a synergist. Studies on the structure-activity relationship of haedoxan A have revealed that the 2,3-dihydro-1,4-benzodioxin moiety in this unique sesquilignan was indispensable for the insecticidal activity.[2] Ishibashi and Taniguchi first synthesized natural (+)-haedoxan A by using optically resolved (+)-(2*R*, 3*R*)-7-formyl-6-methoxy-2-methoxymethyl-3-(3,4-methlenedioxyphenyl)-2,3-dihydro-1,4-benzodioxin (**2**) and (+)-*β*-vinyl-*γ*-butyrolactone as starting materials.[3] Hirata and Taniguchi have recently reported the synthesis of the 1,4-benzodioxane moiety with an opposite (2*S*, 3*S*) configuration by employing 2,3-*O*-isopropylidene-D-glyceraldehyde derived from D-mannitol as a chiral building block.[4] To perform the efficient total synthesis of optically active haedoxan A, we first attempted the enantioselective synthesis of **2**, a key intermediate.

Materials and Methods

Melting point (mp) data are uncorrected. Gravity column chromatography was carried out with Merck silica gel 60 (230–400 mesh ASTM). ^{1}H- and ^{13}C-NMR spectra were recorded with a JEOL-EX 400 spectrometer, and chemical shifts are reported as values in parts per million relative to tetramethylsilane ($\delta_{H/C}$ 0.0) or $CDCl_3$ (δ_C 77.0) as internal standards. Optical rotation values were measured with a Union Giken PM-101 polarimeter. Combustion analyses were performed by Center of Element Analysis in Faculty of Science at Kyushu University for elemental analysis.

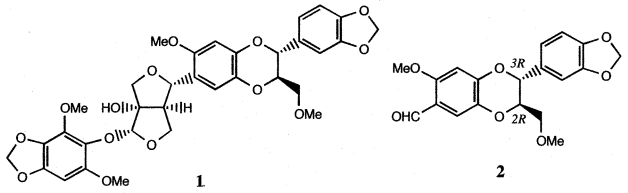


Fig. 1. Structures of Haedoxan A (**1**) and 1,4-Benzodioxane-7-carbaldehyde (**2**).

(4R)-4-Benzyl-3-(benzyloxyacetyl)-2-oxazolidinone (**4**). To a solution of (4*R*)-4-(phenylmethyl)-2-oxazolidinone (**3**; 10.59 g, 59.8 mmol) in THF (300 ml) was added 1.57 M *n*-BuLi in hexane (38.1 ml, 59.8 mmol) at −78° C. Benzyloxyacetyl chloride (10.4 ml, 65.74 mmol) was then added after completing the addition of *n*-BuLi. The resulting solution was stirred for 1 h at −78°C and then allowed to warm to ambient temperature over a 30-min period. The excess benzyloxyacetyl chloride was quenched by adding sat. aq. NH_4Cl (60 ml). The bulk of THF and hexane was removed under reduced pressure, and the resulting slurry was extracted twice with CH_2Cl_2 (100 ml). The combined organic extracts were sequentially washed with 1 N NaOH (75 ml) and brine (75 ml), dried over Na_2SO_4, and filtered. The solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica gel by eluting with 25% EtOAc in hexane to give a colorless oil. The resulting oil was crystallized from EtOH to give *N*-acyloxazolidinone (**4**; 18.87 g, 97%) as a colorless crystal: mp 69–69.5°C; $[\alpha]_D^{26}$ −65° (*c* 0.2, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 2.80 (1H, dd, J=9.3, 13.7 Hz), 3.30 (1H, dd, J=2.9, 13.7 Hz), 4.18–4.26 (2H, m), 4.64–4.72 (5H, m), 7.18–7.42 (10H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 37.77, 54.81, 67.28, 69.68, 73.52, 127.49, 128.09, 128.53, 129.04, 129.42, 134.93, 137.18, 153.38, 170.15. *Anal.* Found: H, 5.89; C, 69.95; N, 4.27%. Calcd. for $C_{19}H_{19}O_4N$: H, 5.89; C, 70.14; N, 4.30%.

(4R)-4-Benzyl-3-[(2R, 3S)-2-benzyloxy-3-hydroxy-3-(3,4-methylenedioxyphenyl)propionyl]-2-oxazolidinone (**5**). To a solution of acylated oxazolidinone **4** (7.42 g,

† To whom correspondence should be addressed. Fax: +81-92-642-2864; E-mail: ekuwano@agr.kyushu-u.ac.jp

22.8 mmol) in CH_2Cl_2 (70 ml) were added 22.8 ml (22.8 mmol) of $(n\text{-Bu})_2BOTf$ (a 1.0 M solution in CH_2Cl_2) and then 3.5 ml (25.3 mmol) of Et_3N. After completing the addition of Et_3N, the solution was stirred for 2 h at −78°C, and then 1.9 g (12.7 mmol) of 3,4-methylenedioxybenzaldehyde in CH_2Cl_2 (20 ml) was added. The solution was stirred for 1 h at −78°C and then for 1 h at 0°C. The reaction mixture was quenched by adding 22 ml of a pH 7 phosphate buffer, 65 ml of MeOH, and 77 ml of 30% aq. H_2O_2–MeOH (1:2). After stirring for 1 h at 0°C to room temperature, the reaction mixture was poured into a mixture of water (80 ml) and 25% CH_2Cl_2 in hexane (500 ml). The organic layer was washed with brine (60 ml), dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel by eluting with 50% EtOAc in hexane to give aldol adduct **5** (6.0 g, 99%) as a colorless oil: $[\alpha]_D^{29}$ −81.9° (*c* 1.55, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 2.63 (1H, dd, *J*=9.3, 13.7 Hz), 3.05 (1H, d, *J*=6.1 Hz), 3.14 (1H, dd, *J*=2.9, 13.7 Hz), 3.93 (1H, m), 4.08 (1H, dd, *J*=2.0, 9.3 Hz), 4.42–4.50 (1H, m), 4.55 (1H, d, *J*=11.7 Hz), 4.60 (1H, d, *J*=11.7 Hz), 4.90 (1H, dd, *J*=4.6, 6.1 Hz), 5.40 (1H, d, *J*=4.6 Hz), 5.93 (2H, s), 6.75 (1H, d, *J*=8.1 Hz), 6.85 (1H, dd, *J*=1.5, 8.1 Hz), 6.94 (1H, d, *J*=1.5 Hz), 7.17 (2H, m), 7.23–7.34 (8H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 37.59, 55.60, 66.72, 73.43, 74.53, 80.99, 100.99, 107.12, 107.80, 119.81, 127.40, 128.15, 128.37, 128.94, 129.34, 133.02, 134.96, 136.66, 147.19, 147.48, 152.95, 170.45. *Anal.* Found: H, 5.44; C, 67.86; N, 2.88%. Calcd. for $C_{27}H_{25}NO_7$: H, 5.30; C, 68.2; N, 2.95%.

(1S, 2S)-2-Benzyloxy-1-(3,4-methylenedioxyphenyl)-1,3-propanediol (**6**). To a solution of imide **5** (2.07 g, 4.4 mmol) in THF (30 ml) at 0°C were added MeOH (0.4 ml, 9.6 mmol) and $LiBH_4$ (a 2.0 M solution in THF, 6.5 ml, 13.1 mmol). The resulting solution was gradually allowed to warm to room temperature and stirred for 24 h. The reaction was quenched by adding 0.5 N aq. sodium potassium tartrate and Et_2O. The mixture was stirred for 2 h at room temperature, and the ethereal layer was separated. The aqueous layer was extracted twice with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel by eluting with 50% EtOAc in hexane to give diol **6** (1.33 g, 99%) as a colorless oil. At the same time, chiral auxiliary **3** was recovered in a 98% yield. $[\alpha]_D^{27}$ +60° (*c* 0.45, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 1.87 (1H, dd, *J*=4.9, 6.8 Hz), 2.90 (1H, d, *J*=2.7 Hz), 3.43–3.49 (1H, m), 3.53–3.56 (1H, m), 3.68–3.73 (1H, m), 4.62 (1H, d, *J*=11.2 Hz), 4.68 (1H, d, *J*=11.2 Hz), 4.73 (1H, dd, *J*=2.7, 6.8 Hz), 5.95 (2H, s), 6.77 (1H, d, *J*=8.1 Hz), 6.84 (1H, dd, *J*=1.8, 8.3 Hz), 6.89 (1H, d, *J*=1.8 Hz), 7.30–7.39 (5H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 60.92, 73.15, 73.87, 83.89, 101.06, 107.20, 108.19, 120.37, 128.02, 128.16, 128.67, 134.23, 137.69, 147.33, 147.82. *Anal.* Found: H, 6.13; C, 66.26%. Calcd. for $C_{17}H_{18}O_5 \cdot 1/3H_2O$: H, 6.10; C, 66.22%.

(1S, 2S)-1-(3,4-Methylenedioxyphenyl)-1,2,3-triacetoxypropane (**7**). Diol **6** (330 mg, 1.09 mmol) was dissolved in EtOAc (5 ml), and to this solution was added palladium on carbon (40 mg). The reaction mixture was stirred at room temperature in a hydrogen atmosphere until the starting diol had been consumed. The mixture was filtered through a pad of Celite, and then concentrated. The resulting residue was purified by column chromatography on silica gel by eluting with 50% EtOAc in hexane to give a triol (108 mg, 47%) as a colorless oil. The resulting triol (108 mg, 0.51 mmol) was dissolved in pyridine (3 ml), and to the solution was added acetic anhydride (0.29 ml, 3.06 mmol) at 0°C. The mixture was allowed to warm to room temperature, and then stirred for 24 h. The mixture was neutralized with 0.5 N HCl, and extracted twice with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel by eluting with 33% EtOAc in hexane to give triacetate **7** (117 mg, 90%) as a colorless oil: $[\alpha]_D^{24}$ +37.5° (*c* 0.33, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 2.06 (3H, s), 2.07 (3H, s), 2.07 (3H, s), 3.80 (1H, dd, *J*=5.9, 12.2 Hz), 4.25 (1H, dd, *J*=3.4, 12.2 Hz), 5.35–5.39 (1H, m), 5.86 (1H, d, *J*=5.4 Hz), 5.96 (2H, s), 6.77–6.85 (3H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 20.72, 20.85, 21.00, 62.33, 72.35, 73.74, 101.33, 107.48, 108.48, 121.14, 129.66, 148.02, 148.08, 169.77, 170.10, 170.48. *Anal.* Found: H, 5.45; C, 56.76%. Calcd. for $C_{16}H_{18}O_8$: H, 5.36; C, 56.80%.

(1R, 2R)-1-(3,4-Methylenedioxyphenyl)-1,2,3-triacetoxypropane (**9**). (2*R*, 3*R*)-3-(3,4-Methylenedioxyphenyl)-1,2-*O*-isopropylideneglycerol (**8**), which had been prepared from 2,3-*O*-isopropylidene-D-glyceraldehyde according to Hirata's procedure,[4] was treated with a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) in MeOH at room temperature to give a triol. The resulting crude triol was acetylated in the same manner as that just described to afford triacetate **9** as a colorless oil: $[\alpha]_D^{25}$ −37.3° (*c* 0.83, $CHCl_3$).

(4S, 5S)-5-Benzyloxy-2,2-dimethyl-4-(3,4-methylenedioxyphenyl)-1,3-dioxane (**10**). To a solution of diol **6** (1.33 g, 4.4 mmol) in CH_2Cl_2 (20 ml) were added 2,2-dimethoxypropane (1.1 ml, 8.8 mmol) and pyridinium *p*-toluenesulfonate (PPTS; 0.11 g, 0.4 mmol). After 24 h at room temperature, Et_3N was added, and the resulting mixture was concentrated. The residue was purified by column chromatography on silica gel by eluting with 25% EtOAc in hexane to give acetonide **10** (1.39 g, 92%) as a colorless crystal: mp 93.5–94°C; $[\alpha]_D^{23}$ +30° (*c* 0.11, $CHCl_3$); ^{1}H-NMR (400 Mz, $CDCl_3$) δ_H: 1.52 (3H, s), 1.56 (3H, s), 3.26–3.28 (1H, m), 3.99 (1H, dd, *J*=2.0, 12.7 Hz), 4.06 (1H, dd, *J*=2.0, 12.7 Hz), 4.26 (2H, s), 4.92 (1H, d, *J*=2.0 Hz), 5.95 (1H, d, *J*=1.2 Hz), 5.96 (1H, d, *J*=1.2 Hz), 6.77-6.81 (2H, m), 6.98–7.02 (3H, m), 7.20–7.23 (3H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 19.04, 29.17, 62.66, 71.60, 72.40, 73.30, 99.14, 100.90, 107.79, 107.95, 119.82, 127.45, 127.82, 128.11, 132.86, 137.97, 146.82, 147.49. *Anal.* Found: H, 6.49; C, 70.28%. Calcd. for $C_{20}H_{22}O_5$: H, 6.48; C, 70.16%.

(4S, 5S)-5-Hydroxy-2,2-dimethyl-4-(3,4-methylenedioxyphenyl)-1,3-dioxane (**11**). To a solution of acetonide **10** (3.94 g, 11.5 mmol) in EtOAc (10 ml) was added palladium hydroxide on carbon (wet, Degussa type, 0.4 g). The reaction mixture was stirrred at room temperature in a hydrogen atmosphere, before being filtered through a pad of Celite and then concentrated. The residue was purified by column chromatography on silica gel by eluting with 50% EtOAc in hexane to give secondary alcohol **11** (2.8 g, 96%) as a colorless oil: $[\alpha]_D^{28}$ +68° (*c* 0.5, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 1.54 (3H, s), 1.56 (3H, s), 2.05 (1H, br), 3.56–3.57 (1H, m), 3.94 (1H, dd, *J*=2.0, 12.2 Hz), 4.21 (1H, dd, *J*=1.5, 12.2 Hz), 4.95 (1H, s), 5.95 (2H, s), 6.80–6.83 (2H, m), 6.92 (1H, d, *J*=1.5 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 18.43, 29.63, 65.65, 66.59, 73.39, 99.45, 101.01, 107.00, 108.16, 119.27, 132.50, 147.00, 147.75. *Anal.* Found: H, 6.47; C, 61.47%. Calcd. for $C_{13}H_{16}O_5$: H, 6.39; C, 61.90%.

(4S, 5R)-2,2-Dimethyl-5-[[4-methoxy-2-(methoxymethoxy)phenyl]oxy]-4-(3,4-methylenedioxyphenyl)-1,3-dioxane (**12**). To a stirred mixture of secondary alcohol **11** (2.8 g, 11.1 mmol), triphenylphosphine (3.49 g, 13.3 mmol) and 4-methoxy-2-(methoxymethoxy)phenol (2.45 g, 13.3 mmol) in benzene (40 ml) at 0°C was added diethyl azodicarboxylate (40% in toluene, 4.9 ml, 13.3 mmol). The mixture was gradually allowed to warm to room temperature, and then refluxed for 24 h. The reaction mixture was cooled to room temperature, to the mixture was added sat. aq. $NaHCO_3$, and the product was extracted twice with Et_2O. The combined organic extracts were successively washed with 1 N NaOH and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel by eluting with 25% EtOAc in hexane to give **12** (2.33 g, 54%) as a colorless oil: $[\alpha]_D^{18}$ +8.4° (*c* 2.25, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 1.48 (3H, s), 1.62 (3H, s), 3.43 (3H, s), 3.70 (3H, s), 3.95–4.11 (3H, m), 4.82 (1H, d, *J*=8.8 Hz), 4.99 (1H, d, *J*=6.6 Hz), 5.04 (1H, d, *J*=6.6 Hz), 5.91 (1H, d, *J*=1.5 Hz), 5.93 (1H, d, *J*=1.5 Hz), 6.31 (1H, dd, *J*=2.9, 8.8 Hz), 6.46 (1H, d, *J*=8.8 Hz), 6.65 (1H, d, *J*=2.9 Hz), 6.76 (1H, d, *J*=7.8 Hz), 6.98 (1H, dd, *J*=1.5, 7.8 Hz), 7.02 (1H, d, *J*=1.5 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 28.34, 55.38, 55.95, 62.77, 74.71, 77.82, 95.01, 99.28, 100.79, 103.81, 105.93, 107.74, 119.56, 121.20, 133.24, 141.32, 147.19, 147.41, 148.93, 155.46. *Anal.* Found H, 6.20; C, 63.21%. Calcd. for $C_{22}H_{26}O_8$: H, 6.26; C, 63.15%.

(1S, 2R)-2-[(2-Hydroxy-4-methoxyphenyl)oxy]-1-(3,4-methylenedioxypheyl)-1,3-propanediol (**13**). To a MeOH solution (10 ml) of **12** (1.0 g, 2.6 mmol) was added a catalytic amount of *p*-TsOH. After stirring at room temperature for 2 h, the mixture was quenched by a few drops of Et_3N and then concentrated. The residue was purified by column chromatography on silica gel by eluting with 50% EtOAc in hexane to give triol **13** (770 mg, 90%) as a colorless oil: $[\alpha]_D^{28}$ −14.7° (*c* 0.95, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ_H: 2.70 (1H, br), 3.63–3.67 (1H, m), 3.68 (3H, s), 3.83–3.91 (2H, m), 4.21 (1H, br), 4.95 (1H, d, *J*=4.4 Hz), 5.90 (2H, s), 6.27 (1H, dd, *J*=2.9, 8.8 Hz), 6.69–6.74 (3H, m), 6.75 (1H, s), 8.16 (1H, br); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 55.31, 60.29, 73.18, 85.83, 100.92, 102.40, 105.09, 106.57, 108.00, 119.47, 120.11, 133.33, 138.89, 146.95, 147.56, 149.15, 156.24. *Anal.* Found: H, 5.55; C, 59.26%. Calcd. for $C_{17}H_{18}O_7 \cdot 1/3H_2O$: H, 5.50; C, 58.96%.

(2R, 3R)-2-Hydroxymethyl-6-methoxy-3-(3,4-methylenedioxyphenyl)-2,3-dihydro-1,4-benzodioxin (**14**). Triol **13** (715 mg, 2.1 mmol) was well mixed with polyphosphoric acid at room temperature for a few minutes. Cold water was added, and the product was extracted twice with EtOAc. The combined organic layers were successively washed with 5% $NaHCO_3$ and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel by eluting with 25% EtOAc in hexane to give **14** (372 mg, 55%) as a colorless crystal: mp 100–100.5°C; $[\alpha]_D^{28}$ −37.9° (*c* 0.95, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 1.96 (1H, br), 3.53 (1H, dd, *J*=3.9, 12.5 Hz), 3.74 (3H, s), 3.78 (1H, dd, *J*=2.7, 12.5 Hz), 3.94 (1H, ddd, *J*=2.7, 3.9, 8.3 Hz), 4.93 (1H, d, *J*=8.3 Hz), 5.99 (2H, s), 6.47 (1H, dd, *J*=2.9, 8.8 Hz), 6.54 (1H, d, *J*=2.9 Hz), 6.83–6.93 (4H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 55.71, 61.69, 76.46, 77.82, 101.32, 102.43, 107.57, 107.63, 108.56, 117.15, 121.38, 129.96, 137.11, 143.96, 148.15, 148.22, 154.41. *Anal.* Found: H, 5.33; C, 64.45%. Calcd. for $C_{17}H_{16}O_6$: H, 5.10; C, 64.55%. The (3*S*)-epimer of **14**, *i.e.*, **15**, was also obtained in an 11% yield as a colorless oil: $[\alpha]_D^{26}$ +94.1° (*c* 0.85, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 1.70 (1H, br), 3.49 (1H, dd, *J*=3.9, 11.7 Hz), 3.68 (1H, dd, *J*=8.8, 11.7 Hz), 3.76 (3H, s), 4.42–4.46 (1H, m), 5.20 (1H, d, *J*=2.9 Hz), 5.98 (2H, s), 6.49 (1H, dd, *J*=2.9, 8.8 Hz), 6.54 (1H, d, *J*=2.9 Hz), 6.83–6.91 (4H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 55.72, 59.29, 75.53, 76.94, 101.28, 102.63, 106.66, 107.95, 108.45, 117.70, 119.77, 129.79, 135.30, 143.41, 147.64, 148.10, 154.70.

(2R, 3R)-6-Methoxy-2-methoxymethyl-3-(3,4-methylenedioxyphenyl)-2,3-dihydro-1,4-benzodioxin (**16**). A solution of alcohol **14** (79 mg, 0.3 mmol) in THF (3 ml) was added to a stirred slurry of NaH (60% in an oil suspension, 5 mg, 0.4 mmol) in THF (2 ml) at 0°C. After 45 min at room temperature, methyl iodide (36 μl, 0.6 mmol) was added to the reaction mixture and stirring was continued for another 12 h at the same temperature. The reaction was quenched by adding a few drops of MeOH, before Et_2O and a 0.5 N HCl solution were added to the mixture. The organic layer was separared, washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel by eluting with 25% EtOAc in hexane to give **16** (80 mg, 97%) as a colorless crystal: mp 154–155°C; $[\alpha]_D^{27}$ −22.1° (*c* 3.9, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 3.29 (1H, dd, *J*=3.9, 10.7 Hz), 3.33 (3H, s), 3.56 (1H, dd, *J*=2.4, 10.7 Hz), 3.72 (3H, s), 3.99 (1H, ddd, *J*=2.4, 3.9, 8.1 Hz), 4.97 (1H, d, *J*=8.1 Hz), 5.98 (2H, s), 6.45 (1H, dd, *J*=2.7, 8.8 Hz), 6.51

(1H, d, J=2.7 Hz), 6.83–6.92 (4H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 55.88, 59.70, 71.46, 77.38, 77.64, 101.52, 102.53, 107.72, 107.80, 108.69, 117.67, 121.51, 130.64, 137.57, 144.17, 148.32, 154.52. *Anal.* Found: H, 5.76; C, 65.54%. Calcd. for $C_{18}H_{18}O_6$: H, 5.49; C, 65.45%.

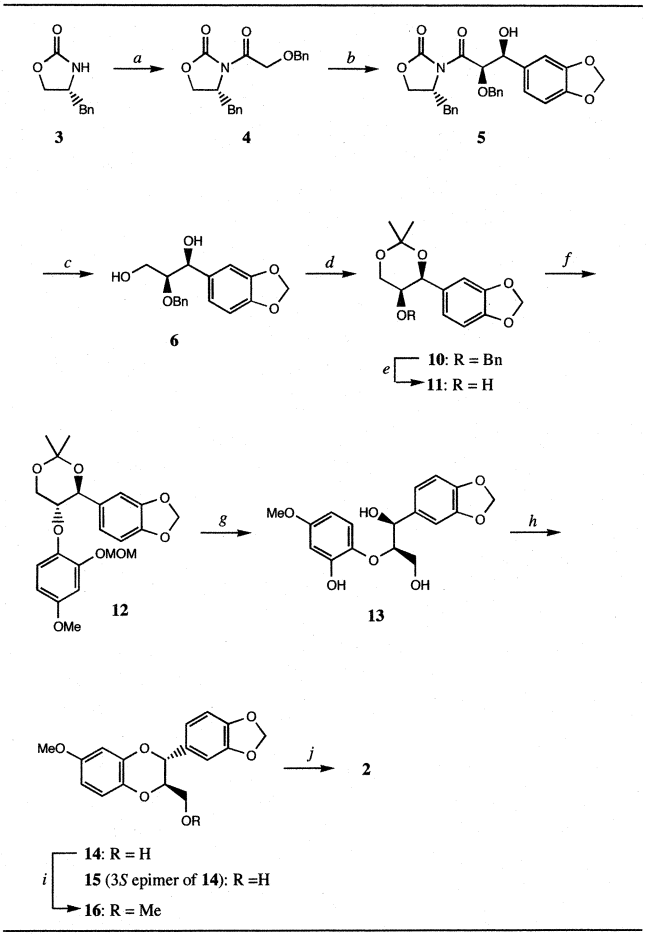
(2R, 3R)-7-Formyl-6-methoxy-2-methoxymethyl-3-(3,4-methylenedioxyphenyl)-2,3-dihydro-1,4-benzodioxin (**2**). Phosphoryl chloride (0.12 ml, 1.31 mmol) was added to a stirred solution of **16** (0.25 g, 0.77 mmol) in DMF (3 ml) at 0°C. After stirring at room temperature for 30 min and then at 100°C for 4 h, the mixture was cooled to room temperature and treated with sat. aq. NaOAc. The product was extracted twice with EtOAc. The combined organic extracts were successively washed with 5% $NaHCO_3$, water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel by eluting with 25% EtOAc in hexane to give aldehyde **2** (0.16 g, 56%) as a colorless oil together with 35% recovery of **16**: $[\alpha]_D^{28}$ +27.9° (*c* 0.95, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 3.29 (1H, dd, J=3.4, 11.2 Hz), 3.34 (3H, s), 3.60 (1H, dd, J=2.4, 11.2 Hz), 3.83 (3H, s), 3.98 (1H, ddd, J=2.4, 3.4, 8.1 Hz), 5.07 (1H, d, J=8.1 Hz), 5.99 (2H, dd, J=1.5, 2.4 Hz), 6.53 (1H, s), 6.84–6.91 (3H, m), 7.84 (1H, s), 10.27 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 55.95, 59.52, 70.84, 77.09, 77.15, 100.39, 101.36, 107.43, 108.51, 116.63, 116.99, 121.29, 129.45, 131.48, 148.11, 148.29, 150.19, 157.63, 188.08. *Anal.* Found: H, 5.05; C, 63.11%. Calcd. for $C_{19}H_{18}O_7$: H, 5.06; C, 63.68%.

Results and Discussion

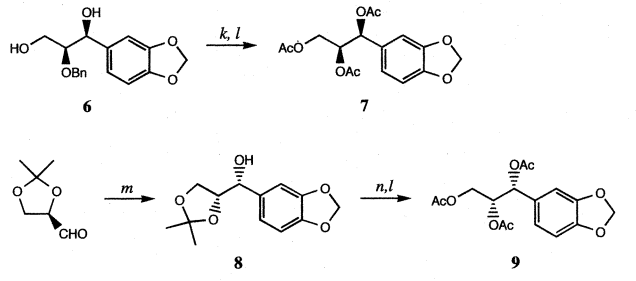
Chiral auxiliary **3**, which had been prepared from D-phenylalanine,[5] was acylated to afford oxazolidinone **4** as a colorless crystal. The aldol reaction[6] of the boron enolate derived from imide **4** with 3,4-methylenedioxybenzaldehyde in CH_2Cl_2 afforded syn aldol adduct **5** in a 99% yield. The diastereomeric excess of **5** was estimated to be more than 98% according to the results of the ^{1}H-NMR analysis. The aldol (**5**) was quantitatively reduced with $LiBH_4$–MeOH to diol **6**, and chiral auxiliary **3** was simultaneously recovered without the loss of its optical purity (Scheme 1).

To determine the absolute configuration of **6**, it was led to triacetate **7** by catalytic hydrogenolysis over palladium-carbon, followed by acetylation (Scheme 2). The enantiomer of **7**, *i.e.*, (1*R*, 2*R*)-1-(3,4-methylenedioxyphenyl)-1,2,3-triacetoxypropane (**9**),[4] was easily prepared by starting with the 2,3-*O*-isopropylidene-D-glyceraldehyde. The ^{1}H-NMR spectrum of **7** was identical with that of **9** and they exhibited the opposite specific rotation. Thus, the stereostructure at the 1- and 2-position of **7** was respectively determined to be as *S* and *S*.

After converting **6** to acetonide **10**, deprotection of the benzyl group with the Pearlman reagent furnished secondary alcohol **11** in a 94% yield for the two steps. Next, **11** was condensed with 4-methoxy-2-(methoxymethoxy)phenol in refluxing benzene by the Mitsunobu reaction, using diethyl azodicarboxylate (DEAD) and triphenylphsphine (PPh_3)[7] to afford coupling product **12** as the sole isomer in a 54% yield. In this case, the



Scheme 1. Synthesis of (+)-1,4-Benzodioxane-7-carbaldehyde (**2**).
Reagents and conditions: (a) *n*-BuLi, benzyloxyacetyl chloride, −78°C; (b) $(n\text{-Bu})_2$BOTf, Et_3N, CH_2Cl_2, −78°C, then added 3,4-methylenedioxybenzaldehyde, −78→0°C; (c) $LiBH_4$, MeOH, THF, room temperature; (d) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, room temperature; (e) $Pd(OH)_2$, H_2, EtOAc, room temperature; (f) DEAD, PPh_3, 4-methoxy-2-(methoxymethoxy)phenol, benzene, reflux; (g) *p*-TsOH cat., MeOH, room temperature; (h) PPA, room temperature; (i) MeI, NaH, THF, room temperature; (j) $POCl_3$, DMF, 100°C.



Scheme 2. Determination of the Absolute Configulation of **6**.
Reagents and conditions: (k) Pd-C, H_2, EtOAc, room temperature; (l) Ac_2O, pyridine, room temperature; (m) *sec*-BuLi, 4-bromo-1,2-methylenedioxybenzene, THF, −78°C; (n) *p*-TsOH cat., MeOH, room temperature.

reaction proceeded completely with a Walden inversion. The coupling constant between 4-*H* and 5-*H* of **12** was observed to be 8.8 Hz, indicating that the two hydrogens of the 1,3-dioxane ring were located in *trans* form. Both the acetonide and methoxymethyl groups of **12** were simultaneously liberated to afford triol **13** by exposing to *p*-toluenesulfonic acid (*p*-TsOH). Cyclization of 13 with polyphosphoric acid (PPA)[8] gave *trans*-substituted cyclization product **14** and its *cis*-isomer **15** (*S* epimer) in 55% and 11% yields, respectively, after silica gel chromatographic separation. Confirmation of the relative stereochemistry of **14** and **15** was provided from their ^{1}H-NMR spectra (δ 4.93 ppm, doublet, $J_{2,3}=8.3$ Hz for 3-*H* of **14**; and δ 5.2 ppm, doublet, $J_{2,3}=2.9$ Hz for 3-*H* of **15**). To determine the enantiomeric purity of (−)-**14** prepared in the present study, it was converted into the corresponding (*S*)-(−)-α-methoxy-α-trifluoromethyl(phenyl)acetate (Mosher ester), and a comparison of its ^{1}H-NMR spectrum with that of the Mosher ester of (+)-**14**[4] showed (−)-**14** to have more than 99% *e.e.* Methylation of **14** gave 1,4-benzodioxane **16** as a colorless crystal in a 97% yield. Finally, regioselective formylation by the Vilsmeier reaction afforded desired (+)-(2*R*, 3*R*)-1,4-benzodioxane-7-carbaldehyde **2** in a 56% yield.

Thus, an important intermediate for the synthesis of natural (+)-haedoxan A, (+)-(2*R*, 3*R*)-7-formyl-6-methoxy-2-methoxymethyl-3-(3,4-methylenedioxyphenyl)-2,3-dihydro-1,4-benzodioxin (**2**), was synthesized from (*R*)-4-(phenylmethyl)-2-oxazolidinone (**3**) in ten steps with a 12% overall yield. This synthetic method could be employed for preparing other natural products possessing a 2,3-dihydro-1,4-benzodioxin framework.

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