Synthesis of the Benzodioxane Portion of Haedoxans

Fumito ISHIBASHI and Eiji TANIGUCHI*

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

Received December 12, 1988

(2*R**,3*R**)-6-Formyl-7-methoxy-3-methoxymethyl-2-(3',4'-methylenedioxyphenyl)-2,3-dihydro-1,4-benzodioxine, a starting material for haedoxan synthesis, was synthesized from 2,4-dihydroxybenzaldehyde.

A 2,3-dihydro-1,4-benzodioxine framework is involved in biologically active lignans such as silybin,¹⁾ americanin²⁾ and cleomiscosin A,³⁾ but is still rare in natural products. Haedoxans are novel insecticidal neolignans, which involve a benzodioxane framework in their molecules as illustrated in Fig. 1 (depicted inside the dotted lines). The regiochemistry of the benzodioxane portion of haedoxan A was determined as **1** on the basis of ¹³C-¹H long-range selective proton decoupling (LSPD) experiments, and this assignment was supported by the LSPD spectra of *trans*-6-methoxy-2-methoxymethyl-3-(3',4'-methylenedioxyphenyl)-2,3-dihydro-1,4-benzodioxine (**2a**) and *trans*-6-methoxy-3-methoxymethyl-2-(3',4'-methylenedioxyphenyl)-2,3-dihydro-1,4-benzodioxine (**3**) which were unambiguously

synthesized.⁴⁾ The potent insecticidal activity of haedoxan A prompted our interest in its total synthesis, as well as its derivation and structure-activity relationship. In this paper, details of the preparation of benzodioxanes **2a** and **3**, and benzodioxane aldehyde **4**, which is a starting material for the syntheses of haedoxans, is reported.

A method developed for the unambiguous synthesis of a 2,3-disubstituted benzodioxane portion of silybin^{5,6)} was employed with a little modification for the present synthesis of **2a** (Fig. 2). An alternative synthesis of benzodioxane skeleton has recently been reported in the total synthesis of americanin A.⁷⁾

Regioselective methylation of the *para* hydroxyl group of 2,4-dihydroxybenzaldehyde (**6**), using methyl iodide and potassium car-

Fig. 1.

* To whom correspondence should be addressed.

Fig. 2.

Fig. 3.

bonate⁸⁾ in refluxing acetone, afforded 2-hydroxy-4-methoxybenzaldehyde (**7**) in an appreciable yield. Protection of the *ortho* hydroxyl group as its methoxymethyl (MOM) ether with chloromethyl methyl ether, potassium hydroxide and a catalytic amount of dibenzo-18-crown-6⁵⁾ in acetonitrile gave **8** in 79% yield. The aldehyde was subjected to the Baeyer–Villiger oxidation with *m*-chloroper-

benzoic acid (MCPBA)-potassium fluoride complex⁹⁾ in methylene chloride, and the resulting formate was immediately hydrolyzed in an aqueous alkaline medium to afford phenol **9** in 77% yield.

Etherification of **9** with bromide **10**, obtained by the bromination of methyl 3,4-methylenedioxybenzoate,¹⁰⁾ in the presence of potassium *tert*-butoxide and a catalytic

Table I. DEHYDRATIVE CYCLIZATIONS

Run	Compound	Conditions	Products (% yield)	<i>trans</i> : <i>cis</i> ^a
1	13	PPA, r.t.	16a, b (59)	75 : 25
2	13	P ₂ O ₅ /CH ₂ Cl ₂	16a, b (69)	48 : 52
3	13	KHSO ₄ /CH ₂ Cl ₂	16a, b (56)	54 : 46
4	15	PPA, r.t.	17a, b (60)	88 : 12
5	15	Amberlist-15/PhMe ⁽¹¹⁾	17a, b (58)	77 : 23

^a The ratio was determined by HPLC.

Fig. 4.

ic amount of dibenzo-18-crown-6⁽⁵⁾ in acetonitrile gave **11** in 94% yield. Reduction of the keto-ester using a half molar equivalent of sodium borohydride in a mixture of ethanol and tetrahydrofuran (1 : 1) produced hydroxy ester **12** along with diol **14** in 53% and 27% yields, respectively. When an equimolar equivalent of the reagent was used, triol **15** was obtained as the major product (73% yield) after hydrolysis of methoxymethyl ether **14**.

Hänsel *et al.* reported that ethyl 3-(3',4'-dimethoxyphenyl)-2-[4''-formyl-2''-(methoxymethoxy)phenoxy]-3-hydroxypropionate (**5**) was easily cyclized to the corresponding benzodioxane (*trans/cis*=75/25) in 2% sulfuric acid in acetic acid (Fig. 2).⁽⁶⁾ Under these conditions, however, congener **12** was decomposed to give a mixture of unidentified products. Dehydrative cyclizations of diol **13** and triol **15** were tried under several conditions (Table I). The cyclization by polyphosphoric acid (PPA) was best accomplished with moderate stereoselectivity (runs 1 and 4). After removing the methoxymethyl group of **12** in an acidic medium, crude diol **13** was treated with PPA to afford a *trans/cis* mixture of cyclized products **16a** and **16b** in 59% yield in the ratio of 75/25 by HPLC analysis. The *trans* isomer, **16a**, was purely isolated by recrystallization

from ethanol. Cyclization of triol **15** under similar conditions as those for **13** gave a mixture of *trans* and *cis* isomers (**17a** and **17b**) in the ratio of 88/12. Assuming a half-chair conformation for benzodioxane as shown in Fig. 4, the coupling constants ($J=7$ and 4 Hz) of the vicinal protons (Ha and Hb) are in good accord with the reported values ($J_{trans}=6$ Hz and $J_{cis}=3$ Hz) for 1,4-benzodioxanes,⁽⁶⁾ and strongly suggested the stereochemistries as **16a** and **16b**. Due to the anisotropic effect of either the benzene ring at the 3-position or the ester group at the 2-position, the axial protons (Ha and Hb) of **16a** resonated upfield by 0.32 and 0.31 ppm, respectively, from the chemical shift values of the respective protons of **16b**.

Lithium aluminum hydride reduction of **16a** in tetrahydrofuran quantitatively gave alcohol **17a**, which, on methylation using methyl iodide and sodium hydride in tetrahydrofuran, gave **2a** in 93% yield. Compound **2a** was successfully formylated with hexamethylenetetramine in refluxing acetic acid to furnish 6-formyl-7-methoxy-3-methoxymethyl-2-(3',4'-methylenedioxyphenyl)-2,3-dihydro-1,4-benzodioxine (**4**) in 71% yield. In a conventional Vilsmeier reaction using dimethylformamide and phosphoryl chloride, **2a** gave **4** in 28% yield.

Fig. 5.

In processes similar to those used for **2a**, regioisomer **3** was synthesized from 5-methoxy-2-methoxymethoxybenzaldehyde (**18**)¹² in 17% overall yield (Fig. 5).

With key intermediate **4** at hand, the total syntheses of haedoxan **A** and **D** were challenged, details of the work being described in the subsequent paper.

Experimental

All melting points (mp) and boiling points (bp) are uncorrected. Infrared (IR) spectra were determined on a Shimadzu IR-420 spectrophotometer. ¹H- and ¹³C-nuclear magnetic resonance (NMR) spectra were obtained on a JEOL FX-100 spectrometer. Low-resolution electron impact mass spectra (MS) were measured by an ESCO FMD-05A spectrometer operated at 70 eV.

Gravity column chromatography and flush chromatography were done with Merck silica gel 60 (70~230 mesh ASTM) and Merck Kieselgel 60G, respectively. High-pressure liquid chromatography (HPLC) was performed with a Shimadzu LC-5A instrument.

2-Hydroxy-4-methoxybenzaldehyde (7). A mixture of 2,4-dihydroxybenzaldehyde (100 g, 0.820 mol), anhydrous K₂CO₃ (100 g, 0.725 mol) and methyl iodide (60 ml, 0.965 mol) in acetone (1 l) was heated under reflux for 2 hr. The mixture was concentrated under reduced pressure, diluted with water, and extracted with ether (250 ml × 2). The ethereal layers were combined and extracted twice with 4% NaOH (500 ml each). The aqueous layers were combined, acidified with conc. HCl, and re-extracted with CH₂Cl₂. The CH₂Cl₂ extract was dried over Na₂SO₄, passed through a short silica gel column, and evaporated. The solid residue was recrystallized from 50% EtOH (350 ml) to afford **7** (63.1 g), mp 41~42°C. The mother liquid was

diluted with an equal volume of water and cooled to afford another crop of **7** (13.1 g); total yield 69%. NMR δ_H (CDCl₃): 3.84 (3H, s), 6.24~6.64 (2H, m), 7.40 (1H, d, *J* = 8 Hz), 9.67 (1H, s), 11.44 (1H, s).

4-Methoxy-2-(methoxymethoxy)benzaldehyde (8). A mixture of **7** (13.5 g, 0.089 mol), pulverized KOH (10.0 g, 0.178 mol) and dibenzo-18-crown-6 (1.0 g) in CH₃CN (75 ml) was stirred at room temperature for 2 hr before adding chloromethyl methyl ether (9.0 ml, 0.116 mol). After 6 hr at room temperature, the mixture was diluted with water (150 ml) and extracted twice with ether (100 ml and 50 ml). The ethereal extracts were combined, washed with 5% KOH, dried over Na₂SO₄, and evaporated to give a dark brown oil. The crude product was distilled under reduced pressure to afford **8** (13.7 g, 0.070 mol) as a colorless oil, bp 126~127°C/0.05 mmHg, in 79% yield. NMR δ_H (CDCl₃): 3.50 (3H, s), 3.82 (3H, s), 5.26 (2H, s), 6.40~6.72 (2H, m), 7.76 (1H, d, *J* = 8 Hz), 10.26 (1H, s).

4-Methoxy-2-(methoxymethoxy)phenol (9). To a solution of MCPBA (20.0 g, 0.116 mol) in CH₂Cl₂ (500 ml), anhydrous KF (10.1 g, 0.174 mol, activated at 100°C × 0.5 mmHg) was added. The mixture was stirred at room temperature for 30 min before carefully adding **8** (13.6 g, 0.069 mol) under cooling in an ice-water bath. After 42 hr at room temperature, the mixture was filtered through a pad of celite with the aid of CH₂Cl₂, and the filtrate was concentrated under reduced pressure. To the residue, an aqueous solution of NaOH (10.4 g, 0.260 mol/300 ml) was added, and the resulting mixture was stirred at room temperature for 30 min. The mixture was extracted with ether to remove the unreacted **8**, before the aqueous layer was acidified with conc. HCl and extracted with ether (100 ml × 3). The ethereal extracts were combined, washed with a mixture of 5% NaHCO₃ and 10% Na₂SO₃, dried over Na₂SO₄, and concentrated. The oily residue was distilled under reduced pressure to give **9** (9.8 g, 0.053 mol) as a colorless oil, bp 102~107°C/0.04 mmHg, in 77%

yield. NMR δ_{H} (CDCl_3): 3.33 (3H, s), 3.57 (3H, s), 5.00 (2H, s), 5.51 (1H, br.), 6.31 (1H, dd, $J=9$, 3 Hz), 6.55 (1H, d, $J=3$ Hz), 6.68 (1H, d, $J=9$ Hz). IR ν_{max} (neat) cm^{-1} : 990, 1077, 1152, 1225, 1505, 1612, 3450.

Methyl 2-bromo-2-(3',4'-methylenedioxybenzoyl)-acetate (10). To a solution of methyl 3,4-methylenedioxybenzoylacetate¹⁰⁾ (17.0 g, 0.077 mol) in CHCl_3 (75 ml), bromine (4.0 ml, 0.078 mol) dissolved in CHCl_3 (40 ml) was added dropwise while keeping the temperature below 20°C. After the addition has been completed, the mixture was washed successively with water, 5% NaHCO_3 , 10% Na_2SO_3 and again water. The organic layer was dried over Na_2SO_4 and evaporated to give **10** (22.9 g, 0.076 mol) as a viscous yellow oil in 97% yield. This was used for the next step without further purification.

Methyl 2-{4'-methoxy-2'-(methoxymethyl)phenoxy}-3-(3'',4''-methylenedioxyphenyl)-3-oxopropionate (11). A mixture of phenol **9** (9.2 g, 0.050 mol), *tert*-BuOK (6.0 g, 0.053 mol) and dibenzo-18-crown-6 (1.8 g, 5 mmol) in dry CH_3CN (130 ml) was stirred at room temperature for 2 hr. A solution of bromide **10** (19.0 g, 0.063 mol) in CH_3CN (15 ml) was then added to the mixture, and stirring was continued for another 14 hr at room temperature. The mixture was poured into water (600 ml) and extracted with EtOAc (120 ml $\times$ 3). The organic layers were combined, washed successively with 0.5 N NaOH, 5% NaHCO_3 and brine, dried over Na_2SO_4 , and evaporated. The oily residue was chromatographed on silica gel with iso-Pr₂O–benzene (1 : 3) as the eluant to give **11** (18.9 g, 0.047 mol) as a viscous oil in 94% yield. NMR δ_{H} (CDCl_3): 3.43 (3H, s), 3.71 (3H, s), 3.77 (3H, s), 5.11 (2H, s), 5.59 (1H, s), 6.01 (2H, s), 6.37 (1H, dd, $J=9$, 3 Hz), 6.69 (1H, d, $J=3$ Hz), 6.82 (1H, d, $J=9$ Hz), 6.94 (1H, d, $J=9$ Hz), 7.59 (1H, d, $J=2$ Hz), 7.79 (1H, dd, $J=9$, 2 Hz). IR ν_{max} (CHCl_3) cm^{-1} : 800, 1030, 1075, 1160, 1205, 1250, 1445, 1560, 1745. MS m/z : 404 (M^+), 150, 149 (base), 121, 65.

Methyl 3-hydroxy-2-{4'-methoxy-2'-(methoxymethoxy)phenoxy}-3-(3'',4''-methylenedioxyphenyl)propionate (12). To a solution of **11** (6.7 g, 16.6 mmol) in a mixture of EtOH (20 ml) and THF (20 ml), NaBH_4 (0.3 g, 7.9 mmol) dissolved in EtOH (20 ml) was added dropwise at -10°C . The solution was stirred at -10°C for 45 min and gradually warmed up to room temperature over a period of 45 min. The mixture was then acidified (pH 6) with 2 N HCl, concentrated under reduced pressure, and extracted with EtOAc. The organic layer was washed with 5% NaHCO_3 , dried over Na_2SO_4 , and evaporated. The oily residue was chromatographed on silica gel with benzene–EtOAc (4 : 1) as the eluant to give **12** (3.6 g, 8.9 mmol) as a viscous oil in 53% yield. NMR δ_{H} (CDCl_3): 3.48 (3H, s), 3.67 (3H, s), 3.72 (3H, s), 3.64–3.95 (1H, br.), 4.61 (1H, d, $J=6$ Hz), 4.87–5.10 (1H, br.), 5.15 (2H, s), 5.91 (2H, s), 6.38 (1H, dd, $J=9$, 4 Hz), 6.60–7.00 (5H, m). Compound **12** was followed by the elution of another

compound (**14**; 1.75 g, 4.5 mmol) in 27% yield.

2-[(2'-Hydroxy-4'-methoxy)phenoxy]-1-(3'',4''-methylenedioxyphenyl)-1,3-propanediol (15). A solution of **11** (22.3 g, 0.055 mol) and NaBH_4 (2.1 g, 0.055 mol) in a mixture of THF (100 ml) and EtOH (100 ml) was stirred at room temperature for 20 hr. The mixture was acidified (pH 2) with 2 N HCl and allowed to stand at room temperature for 2 days before being concentrated under reduced pressure. The residue was taken up in EtOAc, washed with brine, and dried over Na_2SO_4 . After removing the solvent, the residue was purified by flush chromatography on silica gel. Elution with *n*-hexane–EtOAc (2 : 1–1 : 1) afforded **15** (13.4 g, 0.040 mol) as a viscous oil in 73% yield. NMR δ_{H} (CDCl_3): 2.00–3.20 (3H, br.), 3.50–4.00 (3H, m), 3.72 (3H, s), 4.99 (1H, d, $J=4$ Hz), 5.92 (2H, s), 6.29 (1H, dd, $J=3$, 9 Hz), 6.47 (1H, d, $J=3$ Hz), 6.63–6.92 (4H, m). IR ν_{max} (CHCl_3) cm^{-1} : 1040, 1160, 1240, 1445, 1490, 1505, 1595, 3350. MS m/z : 334 (M^+), 166, 151, 149, 140 (base), 125, 111, 93, 65.

6-Methoxy-2-methoxycarbonyl-3-(3',4'-methylenedioxyphenyl)-2,3-dihydro-1,4-benzodioxines (16a/16b). A solution of **12** (13.1 g, 0.032 mol) in MeOH (200 ml) containing a few drops of conc. HCl was heated under reflux for 30 min. After cooling to room temperature, the mixture was concentrated under reduced pressure to give crude **13**. The crude product was mixed with PPA (86.7 g) for a few minutes and the mixture was partitioned between cold water and EtOAc. The organic layer was washed with 5% NaHCO_3 , dried over Na_2SO_4 , and evaporated. The residue was chromatographed on silica gel with iso-Pr₂O–benzene (1 : 5) as the eluant to give a mixture of **16a** and **16b** (6.4 g, 0.019 mol) in 59% yield. The ratio of **16a/16b** was determined at 75/25 by HPLC analysis [Zorbax-SIL column, 25 cm $\times$ 4.6 mm; *n*-hexane–ether (3 : 1), 1 ml/min]. Compound **16a** (*trans* isomer) was obtained by recrystallization from EtOH, mp 110–112°C. NMR δ_{H} (CDCl_3): 3.62 (3H, s), 3.71 (3H, s), 4.55 (1H, d, $J=7$ Hz), 5.07 (1H, d, $J=7$ Hz), 5.95 (2H, s), 6.32–6.52 (2H, m), 6.88–6.98 (4H, m). IR ν_{max} (KBr) cm^{-1} : 1745, 1500, 1445, 1250, 1205, 1160, 1075, 1030, 800. MS m/z : 345 (M^+), 208, 206 (base), 176, 145, 89. Anal. Found: C, 62.76; H, 4.72. Calcd. for $\text{C}_{18}\text{H}_{16}\text{O}_7$: C, 62.79; H, 4.65%.

16b (*cis* isomer). Viscous oil. NMR δ_{H} (CDCl_3): 3.60 (3H, s), 3.72 (3H, s), 4.86 (1H, d, $J=4$ Hz), 5.35 (1H, d, $J=4$ Hz), 5.90 (2H, s), 6.32–6.54 (2H, m), 6.68–6.95 (4H, m).

2-Hydroxymethyl-6-methoxy-3-(3',4'-methylenedioxyphenyl)-2,3-dihydro-1,4-benzodioxines (17a/17b). Triol **15** (13.0 g, 0.039 mol) was mixed well with PPA (93 g) at room temperature for a few minutes. Cold water was then added and the mixture was extracted twice with EtOAc (200 ml each). The combined organic layers were washed successively with brine and 5% NaHCO_3 , dried over Na_2SO_4 , and concentrated. The residue was purified by

flush chromatography on silica gel with *n*-hexane–EtOAc (3:1) as the eluant to give an 88/12 mixture (determined by HPLC) of **17a** and **17b** (7.36 g, 0.023 mol) in 60% yield. The *trans* isomer (**17a**; 6.29 g, 51%) was obtained by trituration with ether, mp 73–75°C. NMR δ_{H} (CDCl₃): 2.92 (1H, br.), 3.50 (1H, dd, *J* = 12, 4 Hz), 3.72 (3H, s), 3.71–4.02 (3H, m), 4.90 (1H, d, *J* = 8 Hz), 5.96 (2H, s), 6.32–6.54 (2H, m), 6.68–6.95 (4H, m). IR ν_{max} (KBr) cm⁻¹: 797, 817, 1030, 1042, 1160, 1232, 1500, 3500. MS *m/z*: 316 (M⁺), 178, 150, 135 (base), 148, 91, 89, 69, 52. Anal. Found: C, 64.44; H, 5.16. Calcd. for C₁₇H₁₆O₆: C, 64.56; H, 5.06%.

6-Methoxy-2-methoxymethyl-3-(3',4'-methylenedioxyphenyl)-2,3-dihydro-1,4-benzodioxine (2a/2b). A solution of **16a** (490 mg, 1.4 mmol) dissolved in dry THF (10 ml) was added dropwise to a stirred slurry of LiAlH₄ (60 mg, 1.6 mmol) in THF (10 ml) at –10°C. After 15 min, the excess hydrides were decomposed by carefully adding EtOAc and then 0.5N HCl. The mixture was extracted with ether, washed with brine, dried over Na₂SO₄, and evaporated to give crude **17a** as white crystals.

A solution of crude alcohol **17a** in dry THF (10 ml) was added dropwise to a stirred slurry of NaH (60% in oil, 84 mg, 2.1 mmol) in THF (10 ml) at –10°C. After 45 min, methyl iodide (0.2 ml, 3.2 mmol) was added to the mixture, and stirring was continued for another 2 hr at room temperature. The reaction was then quenched by a few drops of MeOH, before the mixture was partitioned between ether and 0.5N HCl. The ethereal layer was separated, washed with brine, dried over Na₂SO₄, and evaporated. The oily residue was chromatographed on silica gel eluted with iso-Pr₂O to afford **2a** (429 mg, 1.3 mmol), mp 128–129°C, in 93% yield. NMR δ_{H} (CDCl₃): 3.27 (1H, dd, *J* = 10, 5 Hz), 3.32 (3H, s), 3.55 (1H, dd, *J* = 10, 3 Hz), 3.71 (3H, s), 3.96 (1H, m), 4.95 (1H, d, *J* = 8 Hz), 5.96 (2H, s), 6.30–6.53 (2H, m), 6.70–7.00 (4H, m). IR ν_{max} (KBr) cm⁻¹: 1505, 1490, 1275, 1250, 1245, 1125, 1030. MS *m/z*: 330 (M⁺, base), 299, 258, 193, 161, 132, 103. NMR δ_{C} (CDCl₃): 55.6 (q), 59.4 (q), 71.2 (t), 76.4 (d), 77.1 (d), 101.3 (t), 102.4 (d), 107.4 (d), 107.6 (d), 108.4 (d), 117.4 (d), 121.2 (d), 130.4 (s), 137.3 (s), 143.9 (s), 148.0 (s × 2), 154.2 (s). UV λ_{max} (CHCl₃) nm (ϵ): 246 (5,530), 291 (8,840). Anal. Found: C, 65.33; H, 5.51. Calcd. for C₁₈H₁₈O₆: C, 65.45; H, 5.45%.

By the same procedure, oily **2b** was obtained from **16b**. NMR δ_{H} (CDCl₃): 3.23 (1H, dd, *J* = 4, 11 Hz), 3.28 (3H, s), 3.45 (1H, dd, *J* = 8, 11 Hz), 3.74 (3H, s), 4.50 (1H, m), 5.17 (1H, d, *J* = 3 Hz), 5.94 (2H, s), 6.39–6.57 (2H, m), 6.75–6.98 (4H, m).

7-Formyl-6-methoxy-2-methoxymethyl-3-(3',4'-methylenedioxyphenyl)-2,3-dihydro-1,4-benzodioxine (4).

Duff reaction. A solution of **2a** (0.31 g, 0.94 mmol) and hexamethylenetetramine (0.15 g, 1.07 mmol) in AcOH (20 ml) was heated under reflux for 16 hr. After cooling to room temperature, water was added to the reaction mix-

ture. After 1 hr at room temperature, the mixture was concentrated under reduced pressure. The residue was taken up in EtOAc, washed successively with water and 5% NaHCO₃, dried over Na₂SO₄, and evaporated. The oily residue was chromatographed on silica gel with *n*-hexane–EtOAc (3:1) as the eluant to afford **4** (0.24 g, 0.67 mmol) as pale yellow powder in 71% yield.

Vilsmeier method. To a cold (c. 5°C) solution of **2a** (548 mg, 1.66 mmol) in dry DMF (5 ml) was added POCl₃ (0.23 ml, 2.5 mmol) in one portion, before the mixture was heated at 60–65°C for 1 hr. After cooling, saturated aqueous AcONa (5 ml) was added, and the mixture was heated on a steam bath for 30 min. After cooling, the mixture was diluted with water and the precipitated solids were collected. The solids were dissolved in EtOAc, washed with brine, dried over Na₂SO₄, and concentrated. The residue was chromatographed on silica gel eluted with benzene–EtOAc (95:5) to give **4** (166 mg, 0.46 mmol) in 28% yield along with 69% recovery of **2a**. NMR δ_{H} (CDCl₃): 3.28 (1H, dd, *J* = 11, 5 Hz), 3.33 (3H, s), 3.60 (1H, dd, *J* = 11, 3 Hz), 3.81 (3H, s), 3.96 (1H, m), 5.06 (1H, d, *J* = 8 Hz), 5.98 (2H, s), 6.51 (1H, s), 6.85 (3H, s), 7.45 (1H, s), 10.22 (1H, s). IR ν_{max} (CHCl₃) cm⁻¹: 1020, 1128, 1245, 1308, 1495, 1590, 1620, 1675. UV λ_{max} (CHCl₃) nm (ϵ): 245 (15,230), 279 (14,840), 342 (8,200). Anal. Found: C, 63.32; H, 5.11. Calcd. for C₁₉H₁₈O₇: C, 63.68; H, 5.03%.

5-Methoxy-2-(methoxymethoxy)phenol (19). A colorless oil, 70% yield, bp 130°C (bath)/0.03 mmHg. NMR δ_{H} (CDCl₃): 3.50 (3H, s), 3.72 (3H, s), 5.07 (2H, s), 6.18 (1H, s), 6.31 (1H, dd, *J* = 3, 10 Hz), 6.51 (1H, d, *J* = 3 Hz), 6.94 (1H, d, *J* = 10 Hz). MS *m/z*: 184 (M⁺), 139, 46, 33, 29 (base).

Ethyl 2-{5'-methoxy-2'-(methoxymethoxy)phenoxy}-3-(3'',4''-methylenedioxyphenyl)-3-oxopropionate (20). A pale yellow oil, 90% yield. NMR δ_{H} (CDCl₃): 1.22 (3H, t, *J* = 7 Hz), 3.44 (3H, s), 3.69 (3H, s), 4.23 (2H, q, *J* = 7 Hz), 5.04 (2H, s), 5.69 (1H, s), 6.60 (2H, s), 6.28–6.60 (2H, m), 6.81 (1H, d, *J* = 8 Hz), 7.00 (1H, d, *J* = 2 Hz), 7.54 (1H, d, *J* = 2 Hz), 7.76 (1H, dd, *J* = 8, 2 Hz).

Ethyl 3-hydroxy-2-{5'-methoxy-2'-(methoxymethoxy)phenoxy}-3-(3'',4''-methylenedioxyphenyl)propionate (21). A pale yellow oil, 63% yield. NMR δ_{H} (CDCl₃): 1.15 (3H, t, *J* = 7 Hz), 3.49 (3H, s), 3.54–3.82 (1H, br.), 3.69 (3H, s), 4.12 (2H, q, *J* = 7 Hz), 4.70 (1H, d, *J* = 7 Hz), 4.88–5.16 (3H, m), 5.90 (2H, s), 6.30–6.58 (2H, m), 6.62–6.86 (2H, m), 6.88–7.06 (2H, m).

3-Ethoxycarbonyl-6-methoxy-2-(3',4'-methylenedioxyphenyl)-2,3-dihydro-1,4-benzodioxines (22a/22b). 64% yield, **22a/22b** = 72/28 (determined by HPLC). **2,3-trans-22a**. White crystals, mp 131–133°C. NMR δ_{H} (CDCl₃): 1.08 (3H, t, *J* = 7 Hz), 3.72 (3H, s), 4.08 (2H, q, *J* = 7 Hz), 4.17 (1H, d, *J* = 7 Hz), 4.98 (1H, d, *J* = 7 Hz), 5.94 (2H, s), 6.32–6.64 (2H, m), 6.64–6.96 (4H, m). MS *m/z*: 358

(M^+), 312, 286, 220 (base), 175, 148, 89. *Anal.* Found: C, 63.69; H, 5.09. Calcd. for $C_{19}H_{18}O_7$: C, 63.69; H, 5.03%. 2,3-*cis*-**22b**. A viscous oil. NMR δ_H ($CDCl_3$): 1.07 (3H, t, $J=7$ Hz), 3.72 (3H, s), 4.05 (2H, q, $J=7$ Hz), 4.88 (1H, d, $J=3$ Hz), 5.28 (1H, d, $J=3$ Hz), 5.91 (2H, s), 6.32 ~ 6.64 (2H, m), 6.64 ~ 6.96 (4H, m).

3-Hydroxymethyl-6-methoxy-2-(3',4'-methylenedioxy-phenyl)-2,3-dihydro-1,4-benzodioxine (**23**). White crystals, 99% yield, mp 128 ~ 129°C. NMR δ_H ($CDCl_3$): 1.94 ~ 2.15 (1H, br.), 3.39 ~ 3.91 (2H, m), 3.76 (3H, s), 3.91 ~ 4.09 (1H, m), 4.87 (1H, d, $J=9$ Hz), 5.98 (2H, s), 6.45 (1H, dd, $J=9, 3$ Hz), 6.55 (1H, d, $J=2$ Hz), 6.73 ~ 7.04 (4H, m).

6-Methoxy-3-methoxymethyl-2-(3',4'-methylenedioxy-phenyl)-2,3-dihydro-1,4-benzodioxine (**3**). White crystals, 93% yield, mp 96°C. NMR δ_H ($CDCl_3$): 3.26 (1H, dd, $J=5, 11$ Hz), 3.34 (3H, s), 3.54 (1H, dd, $J=3, 11$ Hz), 3.73 (3H, s), 4.04 (1H, m), 4.87 (1H, d, $J=9$ Hz), 5.96 (2H, s), 6.40 (1H, dd, $J=3, 9$ Hz), 6.56 (1H, d, $J=3$ Hz), 6.72 ~ 6.94 (3H, m). NMR δ_C ($CDCl_3$): 55.5 (q), 59.3 (q), 71.2 (t), 75.9 (d), 77.6 (d), 101.2 (t), 102.3 (d), 107.3 (d), 107.6 (d), 108.3 (d), 117.1 (d), 121.2 (d), 130.5 (s), 137.7 (s), 143.5 (s), 148.0 (s $\times 2$), 154.3 (s).

References

- 1) I. Mittel, A. Pelter and R. Hänsel, *Chem. Ber.*, **108**, 790 (1975).
- 2) W. S. Woo, S. S. Kang, H. Wagner and V. M. Chari, *Tetrahedron Lett.*, **1978**, 3239.
- 3) A. B. Ray, S. K. Charttopadhyay, C. Kondo and H. Hikino, *Tetrahedron Lett.*, **21**, 4477 (1980).
- 4) E. Taniguchi, K. Imamura, F. Ishibashi, T. Matsui and A. Nishio, *Agric. Biol. Chem.*, **53**, 631 (1989).
- 5) T.-L. Su, T. Schulz and R. Hänsel, *Chem. Ber.*, **110**, 3867 (1977).
- 6) R. Hänsel, T.-L. Su and T. Schultz, *Chem. Ber.*, **110**, 3664 (1977).
- 7) H. Tanaka, I. Kato and K. Kato, *Chem. Pharm. Bull.*, **35**, 3603 (1987).
- 8) G. N. Vyas and N. M. Shah, *Org. Synth., Coll. Vol.*, **IV**, 836 (1963).
- 9) F. Champs, J. Coll, A. Messeguer and M. A. Pericas, *Tetrahedron Lett.*, **22**, 3895 (1981).
- 10) F. v. Bruchhausen and H. Gerhard, *Chem. Ber.*, **72**, 830 (1939).
- 11) A. Arnoldi, L. Camarda and L. Merlini, *J. Agric. Food. Chem.*, **34**, 339 (1986).
- 12) N. S. Narasimhan, R. S. Mali and M. V. Brave, *Synthesis*, **1979**, 906.