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SYNTHESIS AND ABSOLUTE CONFIGURATION OF THE INSECTICIDAL SESQUILIGNAN (+)-HAEDOXAN A

IN HONOUR OF PROFESSOR G. H. NEIL TOWERS 75TH BIRTHDAY

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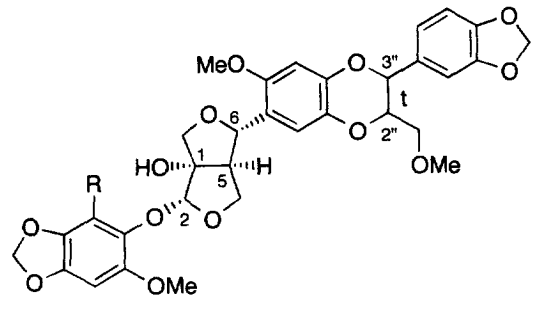
Key Word Index—*Phryma leptostachya* L.; Phrymaceae; insecticidal sesquilignan; synthesis; absolute configuration; (+)-haedoxan A

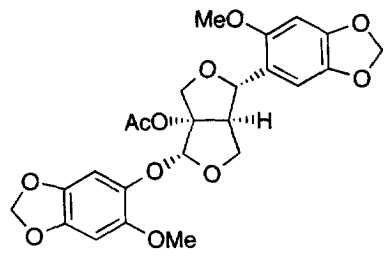
Abstract—The insecticidal neolignan, (+)-haedoxan A, was synthesized from (*S*)-(+)-β-vinyl-γ-butyrolactone and (2*R*,3*R*)-(+)-6-formyl-7-methoxy-3-methoxymethyl-2-(3,4-methylenedioxyphenyl)-1,4-benzodioxane, and its absolute configuration was unequivocally established as 1*S*,2*R*,5*R*,6*S*,2″*R*,3″*R*.

INTRODUCTION

The herbaceous perennial plant *Phryma leptostachya* L. has been traditionally used as a natural insecticide in Japan. From the root extract of this plant, various lignans of the 3,7-dioxabicyclo[3.3.0]octane (furofuran) type have been isolated [1–4]. Haedoxan A (**1a**) is a representative member of the lignans of this plant and is shown to exhibit significant insecticidal activity against various insect species [5]. The basic chemical structure of **1a** involving 1*S**,2*R**,5*R**,6*S**-relative configuration of the 3,7-dioxabicyclo[3.3.0]octane moiety and 2″,3″-*trans* relationship of the benzodioxane moiety had been elucidated on the basis of spectroscopic data and partial synthesis [6]. However, its complete stereochemistry including absolute configuration has not been established. Herein, we describe the unambiguous synthesis of (+)-**1a** from chiral synthons of definite stereochemisty, which enable us to determine the absolute configuration of the natural product.



1a (R = OMe)
2a (R = H)



phrymarolin I

RESULTS AND DISCUSSION

Synthetic strategy

The strategy for the synthesis of (+)-**1a** is basically the same as that for our previous synthesis of racemic **1a** [7] except for using optically active starting materials and the method for introduction of the aryloxy group at C-2. In the synthesis of the racemate, the 6α-aryl-1α-hydroxy-3,7-dioxabicyclo[3.3.0]octane

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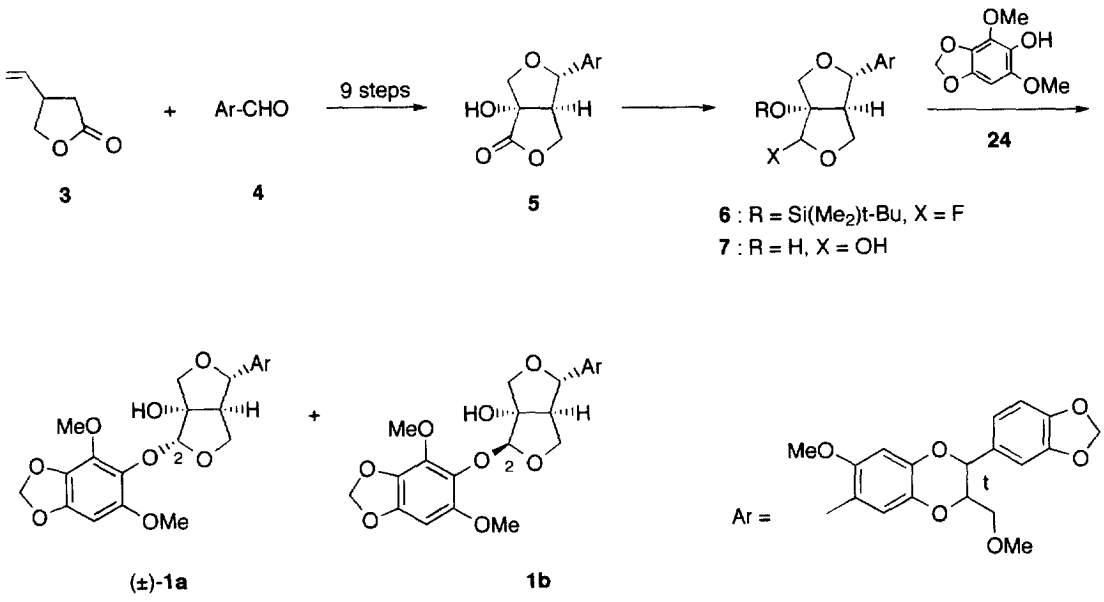
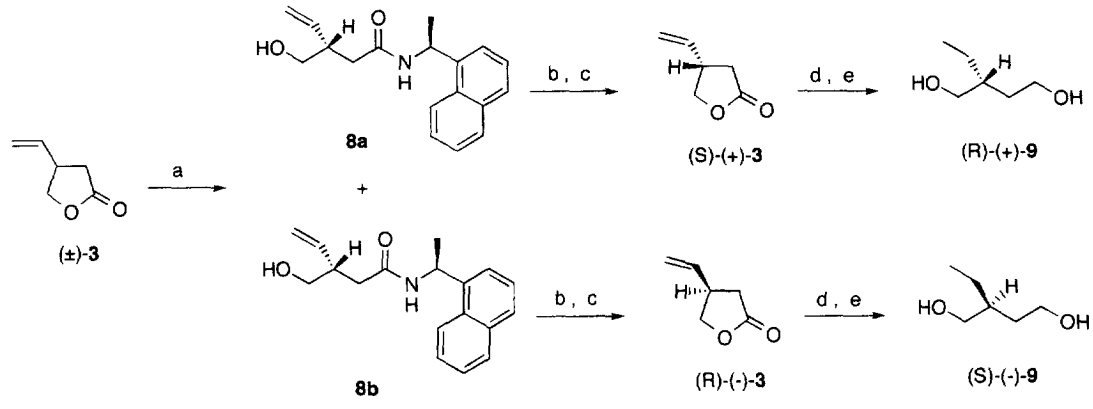


Scheme 1



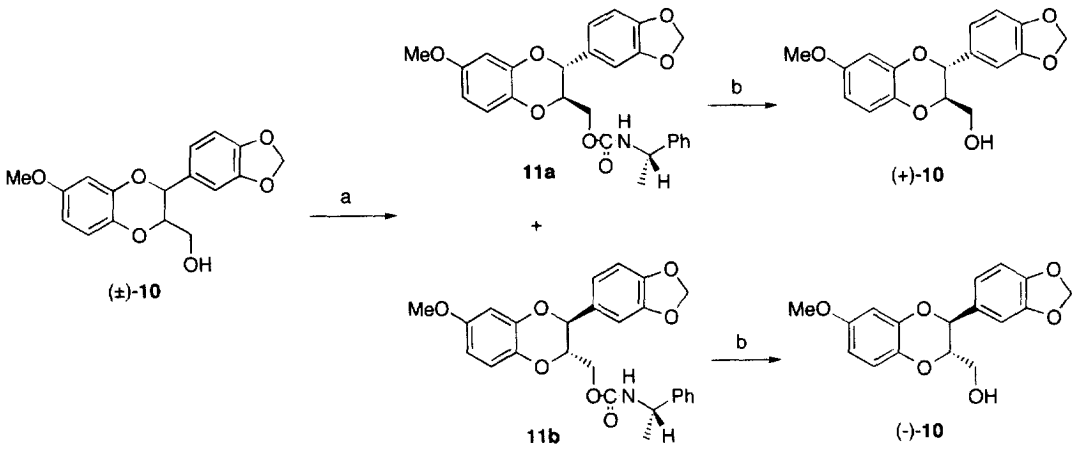
Scheme 2. (a) (*S*)-(-)-naphthylethylamine, 2-hydroxypyridine; (b) KOH, ethylene glycol; (c) p-TsOH, benzene; (d) H_2, Pd/C, EtOH; (e) $LiAlH_4$, ether.

framework (**5**) was stereoselectively constructed from β-vinyl-γ-butyrolactone (**3**) and the aromatic aldehyde **4** (Scheme 1). However, the final tin(II) chloride-silver perchlorate promoted acetalization [8] of the fluoride **6** with the phenol **24** gave an equimolar mixture of 2α-**1a** and its 2β-epimer **1b**, as well as their stereoisomers formed by epimerization at C-6. In the present synthesis, a PPTS catalyzed 2α-selective acetalization, developed for the synthesis of (+)-sesamolin [9], was successfully applied for the final acetalization of the lactol **7**.

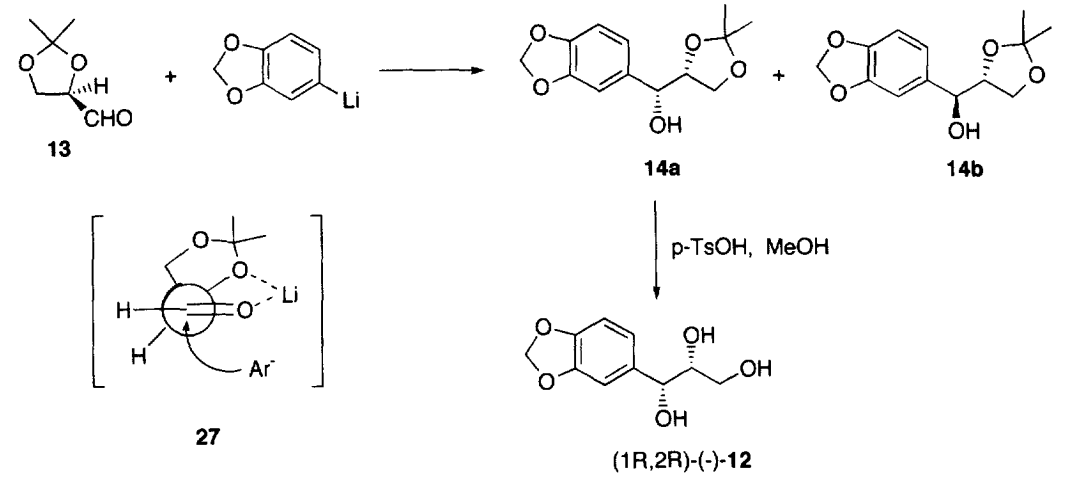
Preparation of the chiral synthons

Each enantiomer of β-vinyl-γ-butyrolactone (**3**), was prepared from its racemate [10] by optical resolution (Scheme 2). The racemate was reacted (150°) with (*S*)-(−)-naphthylethylamine in the presence of a catalytic amount of 2-hydroxypyridine [11] to give an oily mixture of the hydroxy amides (**8a** and **8b**) in 60% combined yield. After separation of the mixture by medium-pressure liquid chromatography (MPLC) on silica gel, each diastereomer was subjected to alkaline hydrolysis (KOH, ethyleneglycol, 170°) followed by lactonization (*p*-TsOH, benzene) to give the respective enantiomer of **3** with an enantiomeric excess (ee) over 95% whose absolute configurations was determined by converting to the known diol **9** [13] by subsequent reductions [12].

Another building block, (2*R*,3*R*)- or (2*S*,3*S*)-7-formyl-6-methoxy-2-methoxymethyl-3-(3,4-methylenedioxyphenyl)-1,4-benzodioxane (**4**) was prepared through optical resolution of (±)-2-hydroxymethyl-6-methoxy-3-(3,4-methylenedioxyphenyl)-1,4-benzodioxane (**10**) (Scheme 3). The racemic alcohol [14] was reacted with (*S*)-(−)-α-methylbenzyl



Scheme 3 (a) (*S*)-(-)-α-methylbenzyl isocyanate, cat. DMAP, toluene, 55°; (b) Cl_3SiH, Et_3N, CH_2Cl_2.



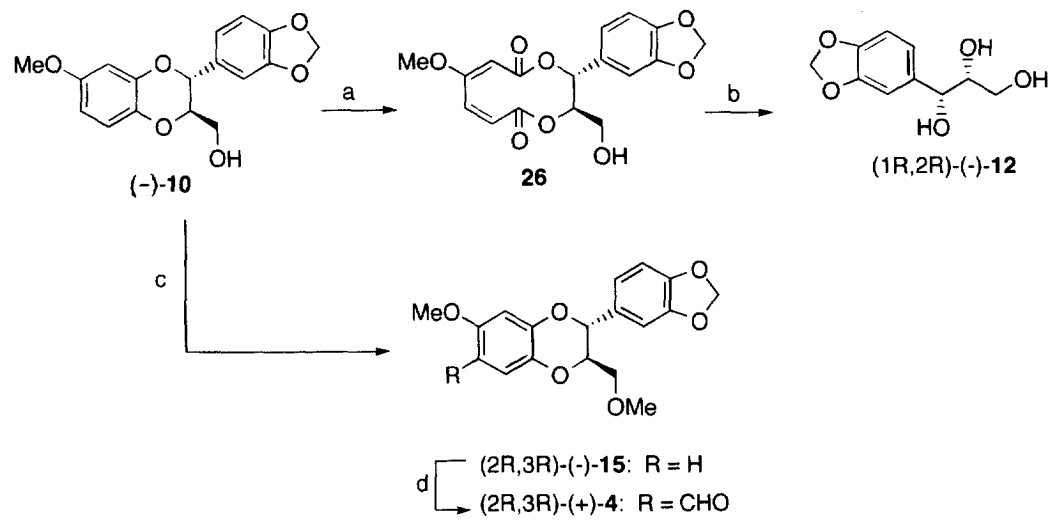
Scheme 4.

isocyanate [15] (DMAP, toluene, 55°) to quantitatively give a mixture of the carbamates (**11a** and **11b**). Each diastereomer was separated by MPLC on silica gel followed by recrystallization. Decarbamoylation (Cl_3SiH, Et_3N, CH_2Cl_2) [16] of **11a** furnished (−)-**10** in 76% yield, whereas another diastereomer **11b** gave (+)-**10** in 87% yield.

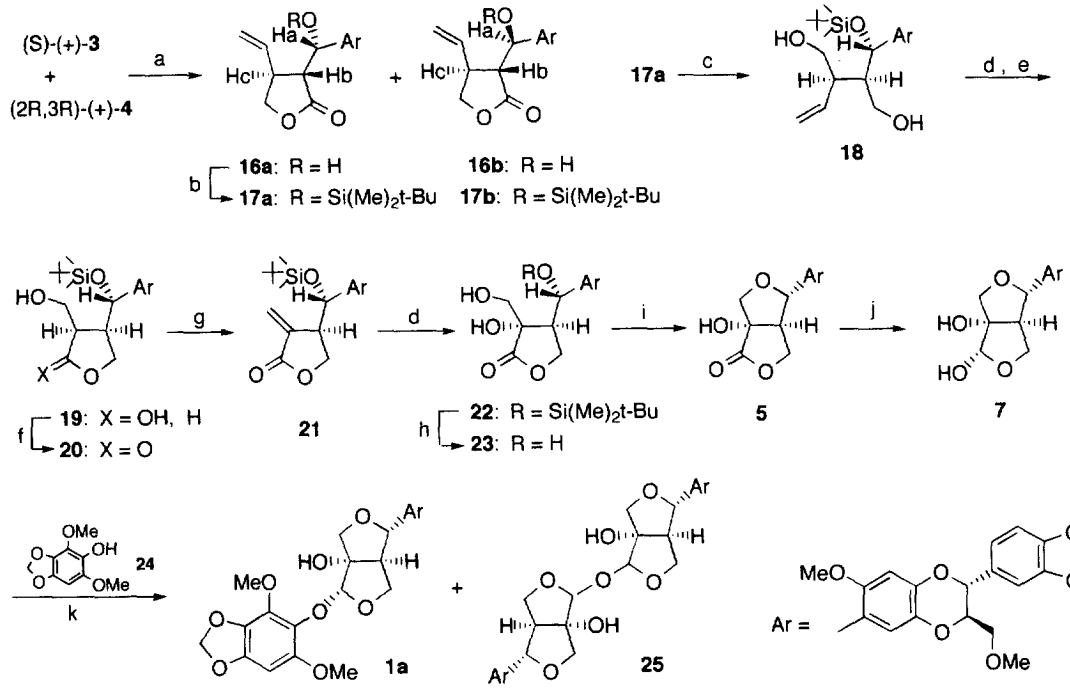
The absolute configurations of (+)- and (−)-**10** were determined by converting them to the optically active triols **12** and comparing their optical rotations with that of (1*R*,2*R*)-(−)-**12** which was unequivocally prepared from D-mannitol. The reference sample of the triol was prepared as shown in Scheme 4. Addition of 1-lithio-3,4-methylenedioxybenzene (1-bromo-3,4-methylenedioxybenzene, *t*-BuLi, −75°, Et_2O) to isopropylidene-D-glyceraldehyde (**13**) prepared from D-mannitol [17] gave a mixture of the *threo* and *erythro* adducts in the ratio of 62/38 (based on HPLC) in 33% combined yield. In accord with the description of Mulzer and Angermann [18], this reaction predominantly proceeded *via* a chelated intermediate (**27**) to afford preferentially the *threo*-isomer **14a** as an *anti*-Cram adduct, whereas in a polar solvent such as Et_2O-THF the reaction favoured the Cram product, *erythro*-**14b**. The *threo*-acetonide **14a** quantitatively gave (1*R*,2*R*)-(−)-**12** by methanolysis.

On ozonolysis (CH_2Cl_2, −15°, 1.5 h, Et_3N workup) followed by alkaline hydrolysis (NaOH, aq. EtOH), (−)-**10** produced a levorotatory triol (−)-**12** in 4% yield with 94% recovery of (−)-**10**. A similar ozonolysis (MeOH, −15°, 1.5 h, Me_2S workup, then NaOH, aq. EtOH) of diacetate of (+)-**10** gave a dextrorotatory triol (+)-**12** in 6% yield (Scheme 5). Consequently, the absolute configurations of (+)- and (−)-**10** were determined as 2*S*,3*S* and 2*R*,3*R*, respectively.

The chiral building blocks, (2*R*,3*R*)-**4** or (2*S*,3*S*)-**4** were obtained by sequential methylation (MeI, NaH, THF-DMF) and formylation (Duff reaction) of (2*R*,3*R*)-(−)-**10** and (2*S*,3*S*)-(+)-**10**, respectively.



Scheme 5. (a) O_3, CH_2Cl_2, 15° then Et_3N; (b) NaOH, aq. EtOH; (c) NaH, MeI, DMF; (d) hexamethylenetetramine, AcOH, reflux.



Scheme 6. (a) LDA, THF, −75°; (b) *t*-Bu(Me$_2$)SiOTf, 2,6-lutidine, CH_2Cl_2, −15°; (c) $LiAlH_4$, THF, −10°; (d) OsO_4, NMO, acetone-*t*-BuOH-H_2O; (e) $NaIO_4$, MeOH, 0°; (f) Ag_2CO_3-Celite, benzene, reflux; (g) MsCl, Et_3N, CH_2Cl_2 then DBU; (h) TBAF, THF, 0°; (i) cat.CSA, CH_2Cl_2; (j) i-Bu_2AlH, CH_2Cl_2, −75°; (k) cat. PPTS, benzene, reflux.

Synthesis of (+)-haedoxan A

We have established the (1*S*,2*R*,5*R*,6*S*)-configuration of (+)-phrymarolin I [1], which is a lignan isolated from the same source as **1a**, on the basis of synthesis of the natural (+)-enantiomer from (*S*)-(+)-**3** [12]. This suggested that the dioxabicyclo[3.3.0]octane moiety of (+)-**1a** would have the same absolute configuration as that of phrymarolin I and would be also enantiotopically constructed from (*S*)-(+)-**3**. However, it was not obvious which enantiomer of the aldehydes **4** would afford (+)-**1a** by combination with (*S*)-**3** since the relative stereochemistry between the benzodioxane and dioxabicyclo[3.3.0]octane moieties of **1a** was unknown. Thus, a small quantity of each enantiomer of **4** was preliminary condensed with (*S*)-(+)-**3**. As the result, the silyl ethers of the aldol products of (*S*)-(+)-**3** and

(2*R*,3*R*)-(−)-**4**, **17a** and **17b**, were found to be the enantiomers of two of the four diastereomers derived from (±)-**3** and (±)-**4** which gave rise to racemic **1a**. Consequently, it was suggested that combination of (*S*)-(+)-**3** and (2*R*,3*R*)-(+)-**4** would be suitable for obtaining (+)-**1a**.

Thus, the synthesis of (+)-**1a** was commenced with the condensation between (*S*)-(+)-**3** and (2*R*,3*R*)-(−)-**4** (LDA, THF, −75°), in which α,β-*trans* disubstituted butyrolactones **16a** and **16b** (**16a**/**16b** = 70/30, based on NMR) were selectively produced due to steric hindrance of the β-vinyl group of (*S*)-(+)-**3**. Their stereochemical features were readily assigned from the coupling constants according to the criteria of J_{threo} (6–9 Hz) > $J_{erythro}$ (2–4 Hz) [19]; the *erythro* isomer **16a** displayed two double doublets at δ 5.48 (Ha, J_{ab} = 3, J_{ad} = 5 Hz) and δ 3.05 (Hb, J_{ab} = 3, J_{bc} = 10 Hz), whereas the *threo* isomer **15b** showed a doublet and a double doublet at δ 5.11 (Ha, J_{ab} = 7 Hz) and δ 2.48 (Hb, J_{ab} = 7, J_{bc} = 10 Hz), respectively. The mixture of the aldol adducts was silylated [*t*-Bu(Me)$_2$SiOTf, 2,6-lutidine [20], CH_2Cl_2, −15°, 80%] and the diastereomers were separated by chromatography on silica gel. The separation was not always necessary for the synthesis since both diastereomers furnished the same intermediate (**5**) at a succeeding synthetic step. On reduction ($LiAlH_4$, Et_2O-THF, −10°) followed by aqueous workup, the *erythro* isomer **17a** gave the diol **18** in 91% yield. The vinyl group of **18** was then oxidized to carbonyl functionality by successive treatment with OsO_4 and *N*-methylmorpholine *N*-oxide (NMO) (Me_2CO-*t*-BuOH-H_2O) [21], followed by $NaIO_4$ (aq. MeOH), and finally Ag_2CO_3-Celite (benzene, reflux) [22] to give the hydroxy-lactone **20** in 84% overall yield for the three steps. The alcohol **20** was dehydrated by sequential mesylation (MsCl, Et_3N, benzene) and desulfonation (DBU), giving the methylene lactone **21** in 88% yield. Stereoselective glycolization (OsO_4-NMO, Me_2CO-*t*-BuOH-H_2O) from the less hindered α-face of **21** gave the (3S,4R)-glycol **22** in quantitative yield. Desilylation of **22** (*n*-Bu_4NF [23], THF, 0°, 82%) and subsequent dehydrative cyclization of the resulting triol **23** [cat. 10-camphorsulfonic acid (CSA), CH_2Cl_2] furnished (+)-(1*S*,5*R*,6*S*,2′*R*,3′*R*)-perhydrofurofuranone **5** in 76% yield as a sole product. This key intermediary lactone was also obtained from the *threo*-isomer **17b** by the same procedure as from *erythro*-**17a**. Reduction of **5** (*i*-Bu_2AlH, CH_2Cl_2, −75°) produced the lactol **7** in 89% yield. Finally, the lactol **7** was reacted with the phenol **24** in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) [9] in refluxing benzene under an azeotropic removal of the water to selectively produce 2α-isomer **1a** in 38% yield along with the dimeric compound **25**. In the acetalization reaction, epimerization at the C-6 and C-3′ position was totally exclusive.

Both the ^{1}H NMR spectral data, as well as the sign and magnitude of the optical rotation of synthetic (1*S*,2*R*,5*R*,6*S*,2″*R*,3″*R*)-**1a** ($[\alpha]_D$ + 114.0°) were in good agreement with those of the natural (+)-**1a** ([α]D + 118.4°). In addition, (+)-haedoxan D (**2a**), similarly synthesized by the acetalization of **7** with 2-methoxy-4,5-methylenedioxyphenol, exhibited insecticidal activity as high as natural (+)-haedoxan D, whereas enantiomeric (−)-**2a** synthesized from (*R*)-**3** and (2*S*,3*S*)-**4** was totally inactive (Table 1). The absolute configuration of the natural (+)-haedoxan A was thus established as 1*S*,2*R*,5*R*,6*S*,2″*R*,3″*R* on the basis of the absolute configuration of starting (+)-**3** and (+)-**4**, and the α,β-*trans* stereoselectivity of the condensation between them.

EXPERIMENTAL

Mps are uncorr. Unless stated otherwise ^{1}H NMR spectra were measured in $CDCl_3$ at 100 MHz. *J* values are in Hz. Gravity CC and medium-pressure liquid chromatography (MPLC) used Merck silica gel 60 (70–230 mesh ASTM) and Merck Lichroprep Si 60 (40–63 μm), respectively. Prep. TLC was performed on precoated silica gel plates 60 F_{254}, 0.5 mm thickness supplied by E. Merck.

Optical resolution of β-vinyl-γ-butyrolactone (**3**).

A mixture of (±)-**3** (5.50 g, 44.6 mmol), (*S*)-(−)-naphthylethylamine (7.50 g, 43.8 mmol) and 2-hydroxypyridine (0.62 g, 6.6 mmol) was heated at 150° for 10 hr. The mixture was then cooled to room temp, diluted with EtOAc, washed with water, dried (Na_2SO_4), and concd. MPLC [EtOAc-*n*-hexane-*i*-PrOH (15:5:1)] gave 3.58 g of **8a** (12.5 mmol) and 3.93 g of **8b** (13.9 mmol) in 60% combined yield. **8a**: mp 118–120°; $[\alpha]_D^{20}$ −87.3° ($CHCl_3$; *c* 1.0). **8b**: mp 116–118°; $[\alpha]_D^{20}$ −49.0° ($CHCl_3$; *c* 1.0). An analytically pure sample was obtained by recrystallization from *i*-Pr_2O-benzene. Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.30; H, 7.47; N, 4.94. Found: C, 76.26; H, 7.44; N, 4.86%.

A soln of **8a** (3.58 g, 12.5 mmol) and KOH (1.12 g, 20.0 mmol) in ethylene glycol (20 ml) was heated at 165° for 10 hr. The mixture was then cooled to room temp, acidified with 2 M HCl (20 ml), diluted with brine, extracted 3 times with EtOAc, dried (Na_2SO_4), and concd. The crude product was dissolved in benzene (50 ml) containing a catalytic amount (*ca* 10 mg) of *p*-TsOH. The resulting soln was heated under reflux with azeotropic removal of water for 10 min. The mixture was then cooled to room temp and concd. Silica gel CC [*n*-hexane-ether (1:1)] gave crude (+)-**3**, which upon distillation with micro-Kugelrohr gave 0.81 g of (*S*)-(+)-**3** (7.2 mmol, 58%) as a colorless oil: bp 160° (oven temp)/20 mmHg; $[\alpha]_D^{19}$ + 6.0° (EtOH; *c* 1.68).

In the same manner as above, the amide **8b** gave (*R*)-(−)-**3** in 64% yield: $[\alpha]_D^{19}$ −5.6° (EtOH; *c* 1.60).

Optical resolution of (±)-2-*hydroxymethyl*-6-*methoxy*-3-(3′,4′-*methylenedioxyphenyl*)-2,3-*dihydro*-1,4-*benzodioxine* (**10**)

A soln of alcohol **10** (5.92 g, 16.7 mmol), (*S*)-(−)-α-methylbenzyl isocyanate (3.00 g, 20.4 mmol) and

Table 1. Insecticidal activity of (+)-, (±)-, and (−)-haedoxan D against *Musca domestica* [mortality (%)].*

	dose (ng/fly)				LD_{50}
	10	7.5	5	2.5	(ng/fly)
(+)-**2a**	90	–	50	20	4.6
(±)-**2a**	90	40	20	–	7.2
(−)-**2a**	0	0	0	–	

*Each compound was topically applied to adult female houseflies as a solution of acetone with piperonyl butoxide (5 mg/fly). The insecticidal activity was evaluated as the mortality after 24 hr at 27°.

DMAP (100 mg) in dry toluene (50 ml) was heated at 55°C for 17 hr. After cooling to room temp, the crystalline amides were collected by filtration. The filtrate was concd and the residue was chromatographed [benzene-EtOAc (95:5)] to give a second crop of the carbamates. The two diastereomers, **11a** and **11b**, were separated by MPLC [benzene-EtOAc (95:5)]. **11a**: yield 3.92 g, 8.47 mmol, 51%, mp 165–166°; $[\alpha]_D^{32}$ −48.1° ($CHCl_3$; *c* 1.04). **11b**: yield 3.64 g, 7.86 mmol, 47%, mp 164–165°C; $[\alpha]_D^{32}$ −1.7° (*c* 1.21, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1048, 1155, 1190–1255 (br), 1445, 1550 (br), 1602, 1740, 3450 (br); MS: *m/z* 463 (M+), 316, 178, 160, 150, 147, 135, 132 (base), 122, 105, 77. Anal. Calcd for $C_{26}H_{25}O_7N$: C, 67.38; H, 5.44; N, 3.02. Found: C, 67.02; H, 5.40; N, 2.95.

A soln of **11a** (3.92 g, 8.47 mmol), Cl_3SiH (1.11 ml, 11.01 mmol) and Et_3N (1.77 ml, 12.71 mmol) in dry CH_2Cl_2 (80 ml) was stirred at room temp for 3 hr. The mixture was then poured into 10% aq. NH_4Cl and filtered through a pad of Celite with the aid of CH_2Cl_2. The CH_2Cl_2 layer was separated and the aq. layer was extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and concd. Recrystallization (benzene) gave 1.50 g of (−)-**10**: mp 99–100°; $[\alpha]_D^{30}$ −29.3° ($CHCl_3$; *c* 0.75). Silica gel CC of the concentrate of the mother liquor [benzene-EtOAc (95:5)] gave a second crop of (−)-**10** (0.53 g).

In the same manner as above, **11b** afforded (+)-**10** in 87% yield: mp 100–101°; $[\alpha]_D^{30}$ +36.4° ($CHCl_3$; *c* 0.88).

Degradation of (+)/(−)-6-*methoxy*-2-*methoxy methyl*-3-(3′,4′-*methylenedioxyphenyl*)-2,3-*dihydro*-1,4-*benzodioxine to* (+)/(−)-1,2,3-*trihydroxy*-1-(3′,4′-*methylenedioxyphenyl*)*propane* [(+)/(−)-**10** *to* (+)/(−)-**12**]

A CH_2Cl_2 (20 ml) soln of (−)-**10** (0.62 g, 1.96 mmol) was subjected to ozonolysis by bubbling O_3 (ca. 5.8 mmol)/O_2 for 12 min at −15°. After the remaining O_3 had been removed by air bubbling, Et_3N (0.55 ml, 3.92 mmol) was added and the reaction mixture was gradually warmed up to room temp over 1.5 hr. The mixture was then diluted with EtOAc, washed with 5% aq. $NaHCO_3$, dried (Na_2SO_4), and concd. Silica gel CC [*n*-hexane-EtOAc (1:1)] gave ca 100 mg of crude oxidized products with 94% recovery of (−)-**10**. The products showed one major (R_f 0.17) and three minor spots (R_f 0.22, 0.14 and 0.09) on TLC [*n*-hexane-EtOAc (1:1)], and the former was characterized as diester **26**: ^1H NMR: δ 1.17–1.18 (1H, br, OH), 3.37–3.90 (2H, m, CH_2OH), 3.65 (3H, s, OCH_3), 5.07 (1H, m, –CHOC=O), 5.24 (1H, s, MeO–C=CH–CO_2), 5.96 (2H, s, OCH_2O), 6.06 (1H, d, J=10, Ar–CH), 6.17 (1H, d, J=12, CH=CH–CO_2), 6.36 (1H, d, J=12, –CH=CH–CO_2), 7.69–7.98 (3H, m, Ar–H's).

A soln of the crude products in a mixture of EtOH (5 ml) and 1 M NaOH (1.8 ml, 1.8 mmol) was stirred at room temp for 3 hr. The soln was then concd and the residue was extracted with EtOAc, washed with brine, dried (Na_2SO_4), and concd. Purification by prep. TLC (EtOAc) gave 17 mg of (1*R*,2*R*)-(−)-**12** (0.08 mmol) in 4% overall yield from (−)-**10**: $[\alpha]_D^{25}$ −31.0° (CHCl; *c* 1.0). Triacetate of (−)-**12**: $[\alpha]_D^{25}$ −39.0° ($CHCl_3$; *c* 1.0); ^1H NMR: δ 2.06 (6H, s, Ac's), 2.07 (3H, s, Ac), 3.76 (1H, dd, J=6, 12, H-3), 4.23 (1H, dd, J=4, 2, H-3), 5.34 (1H, m, H-2), 5.83 (1H, d, J=8, H-1), 5.93 (2H, s, OCH_2O), 6.64–6.88 (3H, m, Ar–H's).

In a similar manner as above, (+)-**10**-acetate (0.46 g, 1.28 mmol) afforded 17 mg of (1*S*,2*S*)-**12** (0.08 mmol) in 6% overall yield: $[\alpha]_D^{25}$ +34.0° ($CHCl_3$; *c* 1.0).

(2*R*,3*R*)-1,2,3-*Trihydroxy*-3-(3′,4′-*methyl-enedioxyphenyl*)*butane* 1,2-*O*-*isopropylideneketal* (**14a**)

A 1.48 M *n*-pentane soln of *t*-BuLi (6.86 ml, 10.16 mmol) was dropwise added *via* a syringe to a soln of 4-bromo-1,2-methylenedioxybenzene (1.18 g, 5.85 mmol) in dry ether (20 ml) with keeping the temp between −60 and −70° under Ar. The resulting soln was stirred at −75° for 20 min and treated dropwise with a soln of isopropylidene-D-glyceraldehyde [14]

(**13**, 0.30 g, 2.54 mmol) in dry ether (15 ml). After 30 min at −75°, the reaction was quenched by addition of 10% aq. NH_4Cl (30 ml) and the mixture was allowed to warm up to room temp. The organic layer was separated, washed with 5% aq. $NaHCO_3$, dried (Na_2SO_4), and concd. Silica gel CC [*n*-hexane-EtOAc (3:1)] gave 0.21 g of a diastereomeric mixture of **14a** and **14b** (0.83 mmol, 33%), which were separated by MPLC [*n*-hexane-EtOAc (2:1)]. The ratio of **14a**:**14b** was determined to be 62:38 by HPLC analysis [Zorbax-SIL column (25 cm × 4.6 mm); pressure, 80 kg/cm²; flow rate, 1 ml/min; detection 286 nm; solvent, *n*-hexane-EtOAc (2:1)]. (2*R*,3*R*)-**14a**: $[\alpha]_D^{25}$ −12.5° (EtOH; *c* 1.68); ^{1}H NMR: δ 1.35 (3H, s, CH_3), 1.45 (3H, s, CH_3), 2.08–2.60 (1H, br, OH), 3.79 (1H, dd, *J* = 7, 9, H-1), 3.94 (1H, t, *J* = 9, H-1), 4.07–4.31 (1H, m, H-2), 4.73 (1H, d, *J* = 5, H-3), 5.91 (2H, s, OCH_2O), 6.63–6.88 (3H, m, Ar–H's). (2*R*,3*S*)-**14b**: $[\alpha]_D^{25}$ −5.3° (EtOH; *c* 1.51); ^{1}H NMR: δ 1.38 (3H, s, CH_3), 1.48 (3H, s, CH_3), 2.24–2.80 (1H, br, OH), 3.53–3.89 (2H, m, H-1), 4.00–4.28 (1H, m, H-2), 4.44 (1H, d, *J* = 8, H-3), 5.92 (2H, s, OCH_2O), 6.63–6.93 (3H, m, Ar–H's).

(1*R*,2*R*)-1,2,3-*Trihydroxy*-1-(3′,4′-*methylenedioxyphenyl*)*propane* (**12**)

(2*R*,3*R*)-**14a** was treated with a catalytic amount of *p*-TsOH in MeOH at room temp to give (1*R*,2*R*)-**12** after purification by prep. TLC (EtOAc). (1*R*,2*R*)-**12**: colorless oil; $[\alpha]_D^{25}$ −28.0° ($CHCl_3$; *c* 1.0). Triacetate of (1*R*,2*R*)-**12**: colorless oil; $[\alpha]_D^{25}$ −37.3° ($CHCl_3$; *c* 0.83).

(2*S*,3*S*) *and* (2*R*,3*R*)-6-*Methoxy*-2-*methoxymethyl*-3-(3′,4′-*methylenedioxyphenyl*)-2,3-*dihydro*-1,4-*benzodioxines* (**15**)

To a stirred slurry of NaH (0.24 g, 6.00 mmol 60% in oil), washed free of oil with dry petrol, in dry DMF (10 ml) was added dropwise a soln of (2*S*,3*S*)-(+)-**10** (1.59 g, 5.03 mmol) in dry THF (10 ml) at −10° and the soln was stirred at room temp for 30 min. To this MeI (0.62 ml, 10.0 mmol) was dropwise added and stirred for another 2 hr. The reaction was then quenched by addition of 10% aq. NH_4Cl, extracted with EtOAc, dried (Na_2SO_4), and concd. Silica gel CC [*n*-hexane-EtOAc (3:1)] gave 1.58 g of (2*S*,3*S*)-**15** (4.79 mmol, 95%) as white crystals: mp 151–153°; $[\alpha]_D^{21}$ +28.6° ($CHCl_3$; c 0.63); ^{1}H NMR: δ 3.27 (1H, dd, *J* = 10, 5, H-1), 3.32 (3H, s, OCH_3), 3.55 (1H, dd, *J* = 10, 3, H-1), 3.71 (3H, s, $ArOCH_3$), 3.96 (1H, m, H-2), 4.95 (1H, d, *J* = 8, H-3), 5.96 (2H, s, OCH_2O), 6.30–6.53 (2H, m, Ar–H's), 6.70–7.00 (4H, m, Ar–H's); 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. (2*R*,3*R*)-**15**: $[\alpha]_D^{21}$ −25.6° ($CHCl_3$; *c* 0.43). Anal. Found: C, 65.33; H, 5.51. Calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.45%.

(2*S*,3*S*) *and* (2*R*,3*R*)-6-*Formyl*-7-*methoxy*-3-*methoxymethyl*-2-(3′,4′-*methylenedioxyphenyl*)-2,3-*dihydro*-1,4-*benzodioxines* (**4**)

A soln of (2*R*,3*R*)-(−)-**15** (0.70 g, 2.12 mmol) and hexamethylenetetramine (0.45 g, 3.18 mmol) in AcOH (15 ml) was heated under reflux for 10 hr. The mixture was then cooled to room temp, poured into water, and concd. The residue was taken up in EtOAc, washed successively with water and 5% $NaHCO_3$, dried (Na_2SO_4), and concd. Silica gel CC [*n*-hexane-EtOAc (3:1)] gave 0.45 g of (2*R*,3*R*)-**4** (1.26 mmol, 59%) as a viscous oil: $[\alpha]_D^{20}$ +28.3° ($CHCl_3$; *c* 0.92); ^{1}H NMR: δ 3.28 (1H, dd, *J* = 11, 5, H-1), 3.33 (3H, s, OCH_3), 3.60 (1H, dd, *J* = 11, 3, H-1), 3.81 (3H, s, $ArOCH_3$), 3.96 (1H, m, H-2), 5.06 (1H, d, *J* = 8, H-3), 5.98 (2H, s, OCH_2O), 6.51 (1H, s, H-5), 6.85 (3H, s, Ar–H's), 7.45 (1H, s, H-8), 10.22 (1H, s, CHO); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1020, 1128, 1245, 1308, 1495, 1590, 1620, 1675. (2*S*,3*S*)-**4**: mp 150–151°; $[\alpha]_D^{20}$ −31.9° ($CHCl_3$; *c* 1.13). Anal. Found: C, 63.32; H, 5.11. Calcd for $C_{19}H_{18}O_7$: C, 63.68; H, 5.06%.

(3*R*,4*S*,1′*R*/*S*,2″*R*,3′*R*)-4-*Ethenyl*-3-[1′-*hydroxy*-1′-[7″-*methoxy*-3″-*methoxymethyl*-2″-(3‴,4‴-*methylenedioxyphenyl*)-2″,3″-*dihydro*-1″,4″-*benzodioxin*-6″-*yl*]*methyl*]*dihydro*-2(3*H*)-*furanones* (**16a** *and* **16b**)

To a cooled (−78°) soln of LDA [prepared from *n*-BuLi (15 wt% in *n*-hexane, 1.35 ml, 2.18 mmol) and diisopropylamine (0.31 ml, 2.18 mmol) at −10° for 15 min in dry THF (12 ml)] was added dropwise a soln of (*S*)-(+)-**3** (0.24 g, 2.18 mmol) in dry THF (3 ml) under Ar. The resulting orange soln was stirred at −75° for 30 min, at which time a soln of (2*R*,3*R*)-(+)-**4** (0.52 g, 1.45 mmol) in dry THF (5 ml) was dropwise added. The soln was stirred at −75° for 3 hr before being quenched with 10% aq. NH_4Cl (20 ml). After being warmed to room temp, the mixture was extracted twice with a 1:1 mixture of ether and EtOAc (30 ml). The combined organic layers were washed with 5% aq. $NaHCO_3$, dried (Na_2SO_4), and concd. Silica gel CC [benzene-EtOAc (9:1)] gave 0.25 g of a diastereomeric mixture of aldols, **16a** and **16b**, (1.11 mmol, 77%) as a pale yellow powder: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350, 1760, 1601, 1500, 1445, 1160, 1065, 1020; MS: *m/z* 470 (M^+), 359, 358, 327, 326, 192, 161, 160 (base), 131, 103, 54. Anal. Calcd for $C_{25}H_{26}O_7$: C, 63.83; H, 5.53. Found: C, 63.77; H, 5.56%.

(3*R*,4*S*,1′*S*/*R*,2″*R*,3″*R*)-3-[1′-[(*t*-*Butyldimethylsilyl*)*oxy*]-1′-[7″-*methoxy*-3″-*methoxymethyl*-2″-(3‴,4‴-*methylenedioxyphenyl*)-2″,3″-*dihydro*-1″,4″-*benzodioxin*-6″-*yl*]*methyl*]-4-*ethenyldihydro*-2(3*H*)-*furanones* (**17a** *and* **17b**)

To a cooled (−15°) soln of the mixture of **16a** and **16b** (0.66 g, 1.40 mmol) and 2,6-lutidine (0.36 ml,

3.08 mmol) in dry CH_2Cl_2 (15 ml) was added dropwise *t*-$BuMe_2SiOTf$ (0.50 ml, 2.18 mmol) in CH_2Cl_2 (3 ml) under Ar. The resulting soln was stirred at −15° for 1 hr, at which time the reaction was quenched by addition of 5% aq. $NaHCO_3$. The mixture was then extracted with ether (50 ml), subsequently washed with 20% aq. $Cu(NO_3)_2$ (15 ml × 2) and 5% aq. $NaHCO_3$ (20 ml), dried (Na_2SO_4), and concd. MPLC [benzene-EtOAc (95:5)] first afforded 0.45 g of **17a** (0.77 mmol, 55%), followed by 0.34 g of **17b** (0.34 mmol, 24%) in order of elution. *Erythro*-**17a**: mp 149–150°; ^{1}H NMR: δ −0.08 (3H, s, Si–CH_3), 0.07 (3H, s, Si–CH_3), 0.90 (9H, s, $SiC(CH_3)_3$), 2.84 (1H, dd, J=7, 3, H-3), 3.07–3.37 (2H, m, H-4 and CHOMe), 3.30 (3H, s, OCH_3), 3.61 (1H, dd, J=11, 3, CHOMe), 3.69 (3H, s, $ArOCH_3$), 3.82–4.03 (2H, m, H-5 and H-3″), 4.37 (1H, t, J=8, H-5), 4.52–4.81 (2H, m, CH=CH_2), 4.96 (1H, d, J=8, H-2″), 5.15–5.47 (1H, m, –CH=CH_2), 5.53 (1H, d, J=2, H-1′), 5.96 (2H, s, OCH_2O), 6.41 (1H, s, H-8″), 6.79–6.89 (3H, m, Ar–H's), 7.07 (1H, s, H-5″); IR$\nu_{max}^{CHCl_3}$cm^{-1}: 3350, 1760, 1601, 1500, 1445, 1160, 1065, 1021. Anal. Calcd for $C_{31}H_{40}O_9Si$: C, 63.68; H, 6.92. Found: C, 63.71; H, 6.92%. *Threo*-**17b**: a white powder; ^{1}H NMR: δ −0.06 (3H, s, Si–CH_3), 0.12 (3H, s, Si–CH_3), 0.93 (9H, s, $SiC(CH_3)_3$), 2.70 (1H, dd, J=4, 8, H-3), 3.00 (1H, deformed t, J=7, H-4), 3.26 (1H, dd, J=4, 11, CHOMe), 3.32 (3H, s, OCH_3), 3.63 (1H, dd, J=3, 11, CHOMe), 3.67 (3H, s, $ArOCH_3$), 3.68–4.14 (3H, m, H-5 and H-3″), 4.97 (1H, d, J=8, H-2″), 4.84–5.24 (2H, m, CH=CH_2), 5.29 (1H, d, J=3, H-1′), 5.50–5.92 (1H, m, –CH=CH_2), 5.96 (2H, s, OCH_2O), 6.41 (1H, s, H-8″), 6.72–6.96 (3H, m, Ar–H's), 7.19 (1H, s, H-5″).

(2R,3R,1′S,2″R,3″R)-2-[1′-[(*t-Butyldimethylsilyl*)*oxy*]-1′-[7″-*methoxy*-3″-*methoxymethyl*-2″-(3‴,4‴-*methylenedioxyphenyl*)-2″,3″-*dihydro*-1″,4″-*benzodioxin*-6″-*yl*]*methyl*]-3-*ethenyl*-1,4-*butanediol* (**18**)

To a stirred slurry of $LiAlH_4$ (0.05 g, 1.32 mmol) in dry ether (15 ml) was added dropwise a soln of **17a** (0.62 g, 1.06 mmol) in dry THF (5 ml) at −10° under Ar. The resulting soln was stirred at −10° for 45 min and the excess reagent was decomposed by careful addition of EtOAc (10 ml) followed by 10% aq. citric acid (50 ml). The organic layer was separated and the aq. layer was extracted with ether (50 ml). The combined organic extracts were washed with 5% aq. $NaHCO_3$ (20 ml), dried (Na_2SO_4), and concd. Silica gel CC [*n*-hexane-EtOAc (1:1)] gave 0.57 g of **18** (0.97 mmol, 91%) as a viscous oil: IR$\nu_{max}^{CHCl_3}$cm^{-1}: 3900, 2950, 1602, 1502, 1445, 1255, 1197, 1155, 1068, 1043; ^{1}H NMR (acetone-d_6): δ −0.18 (3H, s, Si–CH_3), 0.11 (3H, s, Si–CH_3), 0.92 (9H, s, Si–$C(CH_3)_3$), 2.48–2.75 (2H, m, OH's), 3.25 (3H, s, OCH_3), 3.26 (1H, dd, J=12, 4, CHOMe), 3.40–3.98 (7H, m, CH_2OH × 2, H-2, H-3, CHOMe), 3.98–4.17 (1H, m, H-3″), 4.82–5.10 (3H, m, CH=CH_2, H-1′), 5.35 (1H, d, J=6, H-2″), 5.72–6.13 (1H, m, CH=CH_2), 6.01 (2H, s, OCH_2O), 6.50 (1H, s, H-8″), 6.84–6.97 (3H, m, Ar–H's), 7.00 (1H, s, H-5″). Anal. Calcd for $C_{31}H_{44}O_9Si$: C, 63.24; H, 7.53. Found: C, 62.81; H, 7.57%.

(2*R*,3*R*,1′*S*,2″*R*,3″*R*)-4-1′-[(*t-Butyldimethylsilyl*)*oxy*]-1′-[7″-*methoxy*-3″-*methoxymethyl*-2″-(3‴,4‴-*methylenedioxyphenyl*)-2″,3″-*dihydro*-1″,4″-*benzodioxin*-6″-*yl*]*methyl*]-3-*hydroxymethyldihydro*-2(3*H*)-*furanone* (**20**)

A soln of **18** (0.55 g, 0.94 mmol), *N*-methylmorpholine *N*-oxide monohydrate (NMO) (0.15 g, 0.94 mmol) and 2% aq. OsO_4 (0.5 ml) in a mixture of acetone (8 ml), *t*-BuOH (2 ml) and water (2 ml) was stirred at room temp for 15 hr under Ar, at which time the reaction was quenched by additions of Celite (0.5 g) followed by 10% aq. $NaHSO_3$ (1 ml). The resulting mixture was filtered with the aid of acetone and the filtrate was concd under reduced pressure. The oily residue was taken up in EtOAc (30 ml), washed with brine (20 ml), dried (Na_2SO_4), and evaporated to give 0.63 g of crude tetraol as an oil.

The crude tetraol was dissolved in MeOH (8 ml) and cooled to 0°. To this was added dropwise a soln of $NaIO_4$ (0.20 g, 0.94 mmol) in water (2 ml) and the resulting soln was stirred at 0° for 20 min, at which time the reaction was quenched with 5% aq. Na_2SO_3 (10 ml). After almost of the MeOH had been removed under reduced pressure, the residue was extracted twice with EtOAc (20 ml), washed with brine (15 ml), dried (Na_2SO_4), and concd. Silica gel CC (EtOAc) gave 0.55 g of crude lactol **19** as an oil.

A mixture of the crude lactol **19** and Ag_2CO_3 on Celite (1.50 g, containing *ca* 1.50 mmol of Ag_2CO_3) in benzene (20 ml) was heated under reflux for 30 min. The mixture was then cooled to room temp and filtered. The residue was washed well with benzene and the filtrate was concd. Silica gel CC [*n*-hexane-EtOAc (2:1)] gave 0.46 g of **20** (0.78 mmol, 84%) as a white powder: IR$\nu_{max}^{CHCl_3}$cm^{-1}: 835, 1067, 1250, 1310, 1500, 1602, 1702, 3100–3600; ^{1}H NMR: δ −0.26 (3H, s, Si–CH_3), 0.08 (3H, s, Si–CH_3), 0.89 (9H, s, Si–$C(CH_3)_3$), 2.60–3.12 (3H, m, H-3, H-4, OH), 3.23 (1H, dd, J=11, 4, CHOMe), 3.33 (3H, s, OCH_3), 3.62 (1H, dd, J=11, 3, CHOMe), 3.72 (3H, s, $ArOCH_3$), 3.78–4.26 (5H, m, H-5's, CH_2OH, H-3″), 4.98 (1H, d, J=8, H-1′), 5.21 (1H, d, J=7, H-2″), 5.98 (2H, s, OCH_2O), 6.45 (1H, s, H-8″), 6.74–6.90 (3H, m, Ar–H's), 6.99 (1H, s, H-5″). Anal. Calcd for $C_{30}H_{40}O_{10}Si$: C, 61.21; H, 6.85. Found: C, 61.04; H, 6.78%.

(4*R*,1′*S*,2″*R*,3″*R*)-4-1′-[(*t-Butyldimethylsilyl*)*oxy*]-1′-[7″-*methoxy*-3″-*methoxymethyl*-2″-(3‴,4‴-*methylenedioxyphenyl*)-2″,3″-*dihydro*-1″,4″-*benzodioxin*-6″-*yl*]*methyl*]-3-*methylenedihydro*-2(3*H*)-*furanone* (**21**)

Methanesulfonyl chloride (0.085 ml, 1.10 mmol) was added to a cooled (0°) soln of **20** (0.43 g,

0.73 mmol) and Et_3N (0.20 ml, 1.43 mmol) in dry benzene (6 ml). The resulting soln was stirred at room temp for 2.5 hr, at which time DBU (0.19 g, 1.25 mmol) was added. The mixture was stirred at room temp for 30 min, diluted with ether (30 ml), washed successively with 10% aq. NH_4Cl and 5% aq. $NaHCO_3$, dried (Na_2SO_4), and concd. Silica gel CC [benzene-EtOAc (9:1)] gave 0.362 g of **21** (0.64 mmol, 88%) as white crystals: mp 154–157°; ^1H NMR: δ −0.18 (3H, s, Si–CH_3), 0.03 (3H, s, Si–CH_3), 0.88 (9H, s, Si–$C(CH_3)_3$), 3.08–3.36 (2H, m, CHOMe, H-4), 3.33 (3H, s, OCH_3), 3.62 (1H, dd, J=3, 12, CHOMe), 3.73 (3H, s, $ArOCH_3$), 3.87–4.32 (3H, m, H-5 and H-3″), 5.00 (1H, d, J=7, H-2″), 5.06 (1H, d, J=6, H-1′), 5.35 (1H, br s, C=CH_2 endo), 5.98 (2H, s, OCH_2O), 6.23 (1H, br s, C=CH_2 exo), 6.45 (1H, s, H-8″), 6.76–6.92 (3H, m, Ar–H), 6.97 (1H, s, H-5″); IR$\nu_{max}^{CHCl_3}$cm^{-1}: 2950, 1755, 1600, 1504, 1493, 1465, 1448, 1309, 1253, 1195, 1163, 1121, 1095, 1067, 1039, 857, 837. Anal. Calcd for $C_{30}H_{38}O_9Si$: C, 63.14; H, 6.71. Found: C, 62.82; H, 6.70%.

(3S,4R,1′S,2″R,3″R)-4-1′-[*(t-Butyldimethylsilyl)oxy*]-1′-[7″-*methoxy*-3″-*methoxymethyl*-2″-(3‴,4‴-*methylenedioxyphenyl*)-2″,3″-*dihydro*-1″,4″-*benzodioxin*-6″-*yl*]*methyl*]-3-*hydroxy*-3-*(hydroxymethyl)dihydro*-2(3*H*)-*furanone* (**22**)

A soln of **21** (0.98 g, 1.72 mmol), NMO (0.25 g, 1.85 mmol) and 2% aq. OsO_4 (0.8 ml) in a mixture of acetone (30 ml), *t*-BuOH (5 ml) and water (5 ml) was stirred at room temp in the dark for 20 hr under Ar. The reaction was then quenched by addition of Celite (1 g) followed by 10% aq. $NaHSO_3$ (2 ml). The resulting mixture was filtered and the residue was washed well with acetone. The filtrate was concd, taken up in EtOAc (50 ml), washed with brine (10 ml), dried (Na_2SO_4), and concd. Silica gel CC [*n*-hexane-EtOAc (1:1)] gave 1.03 g of **22** (1.71 mmol, 99%) as a viscous oil: ^1H NMR: δ −0.26 (3H, s, Si–CH_3), 0.10 (3H, s, Si–CH_3), 0.91 (9H, s, Si–$C(CH_3)_3$), 2.52–2.76 (1H, br, OH), 2.92–3.16 (2H, m, OH, H-4), 3.27 (1H, dd, J=3, 11, CHOMe), 3.33 (3H, s, OCH_3), 3.63 (1H, dd, J=3, 11, CHOMe), 3.73 (3H, s, $ArOCH_3$), 3.84–4.24 (5H, m, H-5, CH_2OH and H-3″), 5.00 (1H, d, J=8, H-2″), 5.28 (1H, d, J=8, H-1′), 5.98 (2H, s, OCH_2O), 6.47 (1H, s, H-8″), 6.80–6.96 (3H, m, Ar–H's), 7.00 (1H, s, H-5″); IR$\nu_{max}^{CHCl_3}$cm^{-1}: 838, 1018, 1040, 1250, 1315, 1495, 1602, 1777, 3200–3650. Anal. Calcd for $C_{30}H_{40}O_{11}Si$: C, 59.59; H, 6.67. Found: C, 59.42; H, 6.71%.

(1*S*,5*R*,6*S*,2′*R*,3′*R*)-1-*Hydroxy*-6-[7′-*methoxy*-3′-*methoxymethyl*-2′-(3″,4″-*methylenedioxyphenyl*)-2′,3′-*dihydro*-1′,4′-*benzodioxin*-6′-*yl*]-3,7-*dioxabicyclo*[3.3.0]*octan*-2-*one* (**5**)

To a cooled (0°) soln of **22** (1.02 g, 1.69 mmol) in dry THF (10 ml) was added a 1 M soln of *n*-Bu_4NF (2.00 ml, 2.00 mmol) in THF. The resulting soln was stirred at 0° for 2 hr, at which time the reaction was quenched by addition of 10% aq. NH_4Cl (20 ml). The mixture was extracted twice with EtOAc (30 ml), dried (Na_2SO_4), and concd. Silica gel CC [EtOAc-THF (2:1)] gave 0.68 g of triol **23** (1.39 mmol, 82%) as a white powder.

The triol was dissolved in dry CH_2Cl_2 (30 ml) containing CSA (30 mg) and allowed to stand at room temp for 18 hr. The reaction was quenched by addition of one drop of Et_3N and the mixture was concd. Silica gel CC [*n*-hexane-EtOAc (1:2)] gave 0.50 g of lactone **5** (1.06 mmol, 76%) as white crystals: mp 179–180°; $[\alpha]_D^{16}$ +29.6° ($CHCl_3$; *c* 0.81); ^1H NMR: δ 2.98 (1H, s, OH), 3.12 (1H, m, H-5), 3.27 (1H, dd, J=5, 11, CHOMe), 3.33 (3H, s, OCH_3), 3.58 (1H, dd, J=3, 11, CHOMe), 3.73 (3H, s, $ArOCH_3$), 3.97 (1H, m, H-3′), 4.18 (2H, s, H-8's), 4.34 (1H, dd, J=6, 11, H-4β), 4.65 (1H, dd, J=9, 10, H-4α), 4.97 (1H, d, J=8, H-2′), 5.10 (1H, d, J=5, H-6), 5.97 (2H, s, OCH_2O), 6.49 (1H, s, H-8′), 6.72–6.92 (3H, m, Ar–H's), 7.14 (1H, s, H-5′); IR$\nu_{max}^{CHCl_3}$cm^{-1}: 3400, 1777, 1601, 1502, 1495, 1469, 1450, 1335, 1255, 1200, 1170, 1125, 1073, 1042, 1205; MS: *m/z* 472 (M^+), 192 (base), 162, 161, 160, 135, 131, 103. Anal. Calcd for $C_{24}H_{24}O_{10}$: C, 61.02; H, 5.08. Found: C, 60.99; H, 5.17%.

(1*S*,2*S*,5*R*,6*S*,2′*R*,3′*R*)-1,2-*Dihydroxy*-6-[7′-*methoxy*-3′-*methoxymethyl*-2′-(3″,4″-*methylenedioxyphenyl*)-2′,3′-*dihydro*-1′,4′-*benzodioxin*-6′-*yl*]-3,7-*dioxabicyclo*[3.3.0]*octane* (**7**)

To a cooled (−75°) and stirred soln of lactone **5** (38 mg, 0.081 mmol) in dry CH_2Cl_2 (3 ml) was dropwise added a 1 M soln of *i*-Bu_2AlH in *n*-hexane (200 μL, 0.20 mmol) *via* a syringe. The resulting soln was stirred at −75° for 1 hr, at which time the reaction was quenched by addition of 0.5 M aq. HCl (3 ml). The mixture was extracted with EtOAc (5 ml × 2), washed with brine (5 ml), dried (Na_2SO_4), and concd. Silica gel CC (EtOAc) gave 34 mg of lactol **7** (0.072 mmol, 89%) as a white powder: ^1H NMR: δ 2.40–2.64 (1H, m, H-5), 3.29 (1H, dd, J=11, 4, CHOMe), 3.34 (3H, s, OCH_3), 3.39–3.49 (1H, br, OH), 3.59 (1H, dd, J=11, 3, CHOMe), 3.72 (3H, s, $ArOCH_3$), 3.73 (1H, d, J=10, H-8β), 3.84–4.09 (3H, m, H-4β, H-3′, OH), 4.25 (1H, d, J=10, H-8α), 4.32 (1H, dd, J=10, 7, H-4α), 4.86 (1H, d, J=7, H-6), 4.96 (1H, d, J=7, H-2′), 5.19 (1H, br s, H-2), 5.99 (2H, s, OCH_2O), 6.49 (1H, s, H-8′), 6.82–6.92 (3H, m, Ar–H's), 7.24 (1H, s, H-5′); IR$\nu_{max}^{CHCl_3}$cm^{-1}: 1020, 1065, 1195, 1245, 1492, 1503, 3120–3650. Anal. Calcd for $C_{24}H_{26}O_{10}$: C, 60.76; H, 5.52. Found: C, 60.58; H, 5.51%.

(1*R*,2*S*,5*S*,6*R*,2*R*″,3*R*″)-(+)-*Haedoxan A* (**1a**)

A soln of lactol **7** (94.9 mg, 0.200 mmol), 2,6-dimethoxy-3,4-methylenedioxyphenol (79.0 mg, 0.400 mmol) and PPTS (14.0 mg) in dry benzene (8 ml) was reflux for 7 hr with concomitant removal of water (MS

4A). The mixture was then diluted with EtOAc (5 ml), washed with 0.5 M NaOH (5 ml × 2), and the aq. layer was re-extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated, leaving an oily residue. The crude product was purified by prep. TLC [EtOAc-benzene (3:7)], giving **1a** (R_f 0.48, 27.2 mg, 0.0416 mmol, 21%), along with two diastereomeric dimers **25** (R_f 0.32, 26.4 mg and R_f 0.30, 26.8 mg). **1a**: white crystals, mp 156–157° (lit. [3] 158–159°), $[\alpha]_D^{17}+117°$ (EtOH–CH_2Cl_2; *c* 0.24) [lit. [3] $[\alpha]_D^{18}+125°$ (EtOH–CH_2Cl_2; *c* 0.32)]; ^{1}H NMR: δ 2.63 (1H, m, H-5), 3.27 (1H, dd, J=4, 11, CHOMe), 3.34 (3H, s, OMe), 3.58 (1H, dd, J=3, 11, CHOMe), 3.71 (1H, d, J=10, H-8β), 3.72 (3H, s, ArOMe), 3.77 (3H, s, ArOMe), 3.88–4.13 (3H, m, OH, H-3″, H-4β), 4.00 (3H, s, ArOMe), 4.28 (1H, d, J=10, H-8α), 4.55 (1H, dd, J=7, 9, H-4α), 4.91 (1H, d, J=5, H-6), 4.98 (1H, d, J=8, H-2″), 5.22 (1H, s, H-2), 5.85 (2H, s, OCH_2O), 5.97 (2H, s, OCH_2O), 6.27 (1H, s, Ar–H), 6.46 (1H, s, Ar–H), 6.79–6.96 (3H, m, Ar–H), 7.28 (1H, s, Ar–H).

(1*S*,2*R*,5*R*,6*S*,2″*R*,3″*R*)-(+)-*Haedoxan D* (**2a**)

The title compound was synthesized in 34% yield from **7** and 2-methoxy-4,5-methylenedioxyphenol by the same procedure as for (+)-**1a**: a white powder, $[\alpha]_D^{19}+114.0°$ (CH_2Cl_2; *c* 0.67); ^{1}H NMR (400 MHz) δ 1.50–1.75 (1H, br, OH), 2.62–2.68 (1H, m, H-5), 3.30 (1H, dd, J=3.9, 11.0, CHOMe), 3.35 (3H, s, OCH_3), 3.59 (1H, dd, J=2.4, 11.0, CHOMe), 3.73 (3H, s, $ArOCH_3$), 3.76 (1H, d, J=9.8, H-8β), 3.78 (3H, s, $ArOCH_3$), 3.96–4.03 (1H, m, H-3′), 4.08 (1H, dd, J=2.4, 9.3, H-4β), 4.32 (1H, d, J=9.8, H-8α), 4.45 (1H, dd, J=7.5, 9.3, H-4α), 4.95 (1H, d, J=5.9, H-6), 4.99 (1H, d, J=7.8, H-2′), 5.19 (1H, s, H-2), 5.91 (2H, dd, J=1.3, 3.8, OCH_2O), 6.00 (2H, s, OCH_2O), 6.50 (1H, s, H-8′), 6.56 (1H, s, Ar–H), 6.80 (1H, s, Ar–H), 6.80–6.93 (3H, m, Ar–H's), 7.26 (1H, s, H-5′); MS (30 eV): *m/z* 624 (M^+), 456, 192 (base), 168, 161, 160, 153. Anal. Calcd for $C_{30}H_{32}O_{13}$:C, 61.54; H, 5.16. Found: C, 61.49; H, 5.25%.

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