Journal of Natural Products
Vol. 47, No. 3, pp. 445-452, May-Jun 1984

CONSTITUENTS OF *CANNABIS SATIVA*, XXV. ISOLATION OF TWO NEW DIHYDROSTILBENES FROM A PANAMANIAN VARIANT

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ABSTRACT.—Two new dihydrostilbene compounds (named cannabistilbenes I and II) were isolated from a polar acidic fraction of a Panamanian variant of *Cannabis sativa* grown in Mississippi. The structure of cannabistilbene I was shown to be 3,4′-dihydroxy-5-methoxy-3′-(3-methylbut-2-enyl)-dihydrostilbene (**1**) from spectral data which was confirmed by synthesis. There is spectral evidence to indicate that cannabistilbene II could be represented by either structure **3** or **4**.

A polar acidic fraction of a Panamanian variant of *Cannabis sativa* L. grown in Mississippi yielded the known spiro-indan compounds cannabispiran, iso-cannabispiran, dehydrocannabispiran, β-cannabispiranol, and two dihydrostilbene derivatives, canniprene and 3-[2(3-hydroxy-4-methoxyphenyl)-ethyl]-5-methoxyphenol (1, 2). Two polyhydroxylated cannabinoids, (+)-*trans*-cannabitriol (3) and cannabitetrol (4), were also isolated.

Further fractionation of an equivalent polar acidic fraction afforded two new dihydrostilbene derivatives with M^+ 312 (compound A) and M^+ 304 (compound B).

The mass spectrum of compound A indicated that it was cleaved into two fragments: fragment A with *m/z* 137 (5%) and fragment B which appears at *m/z* 175 (100%). This pattern of fragmentation is very similar to that of canniprene (1, 5), which is a dihydrostilbene derivative. Further proof for a dihydrostilbene nucleus was found in the pmr spectrum. The *bis*-methylene bridge resonated at δ 2.80, and one aromatic methoxy appeared at δ 3.74. The presence of prenyl unit was indicated by a benzylic resonance at δ 3.33 (d, 2H, J=7 Hz), an olefinic proton at δ 5.25 (br, t, 1H) and two olefinic methyls at δ 1.78 (s, 6H).

These data indicated that fragment B, with *m/z* 175, bears a hydroxy group and a prenyl unit. A comparison of the multiplicity of the aromatic protons (ring B) at δ 6.90-6.70 with that of 3-[2(3-hydroxy-4-methoxyphenyl)-enyl]-5-methoxyphenol suggested that the two substituents are *ortho*-disposed. Fragment A appearing at *m/z* 137 indicated that it carries one methoxy group and one hydroxy group. The multiplicity of the signals for the aromatic protons at δ 6.33-6.20 suggested that the hydroxy and methoxy groups are *meta*-disposed. Thus, compound A was proposed to be 3,4′-dihydroxy-5- methoxy-3′(3-methylbut-2-enyl)-dihydrostilbene (**1**), which we named cannabistilbene I. Final proof of the structure of cannabistilbene I was obtained through synthesis (Scheme 1).

p-Hydroxybenzaldehyde (**7**) was converted into the dimethyl prop-2-ynyl ether (**8**). Semihydrogenation and Claisen rearrangement at 134° for 40 min gave the 3-prenylated *p*-hydroxybenzaldehyde (**10**). This was benzylated, and the benzyl derivative (**11**) was used as the aldehyde component in a Wittig reaction with the phosphonium salt (**15**) to give the *mono*-benzylated stilbene derivative (**16**). Reduction with sodium and *n*-BuOH (6) resulted in selective reduction of the stilbene double bond and cleavage of the benzyl group without affecting the double bond of the prenyl unit to give a compound identical (gc, ir, pmr, ms) with the natural material (**1**).

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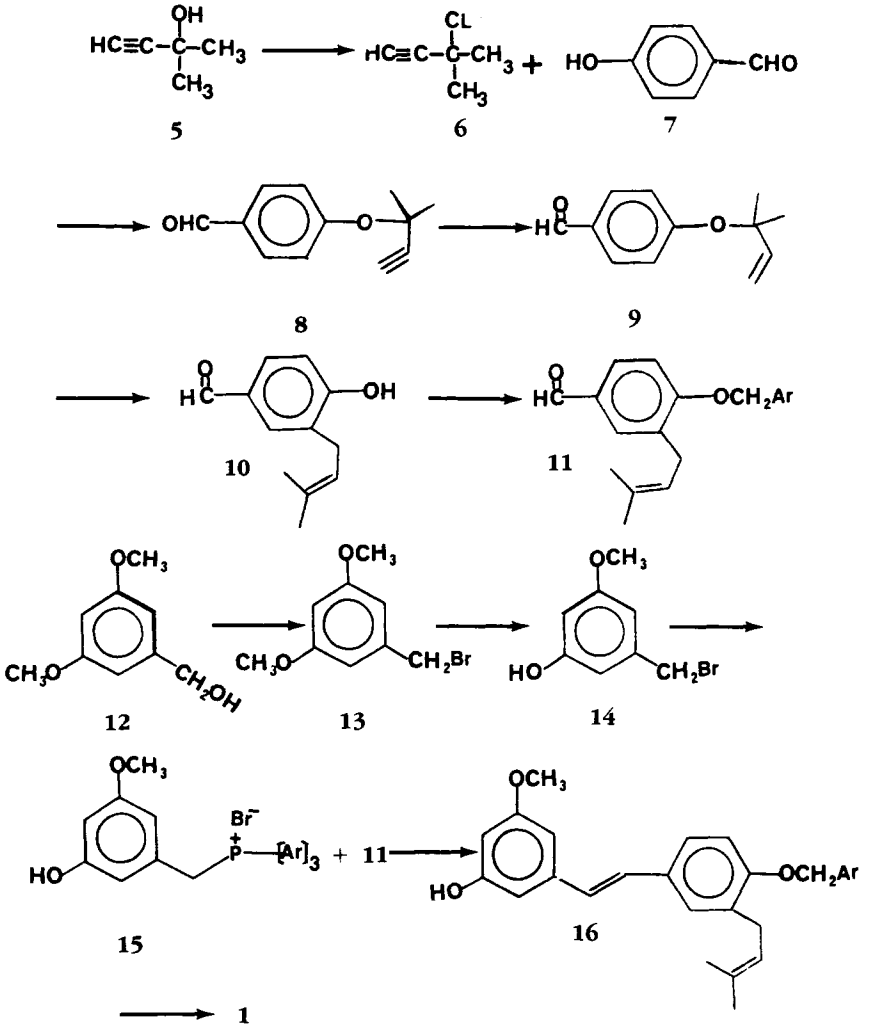
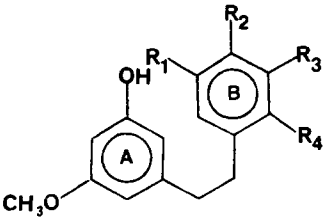


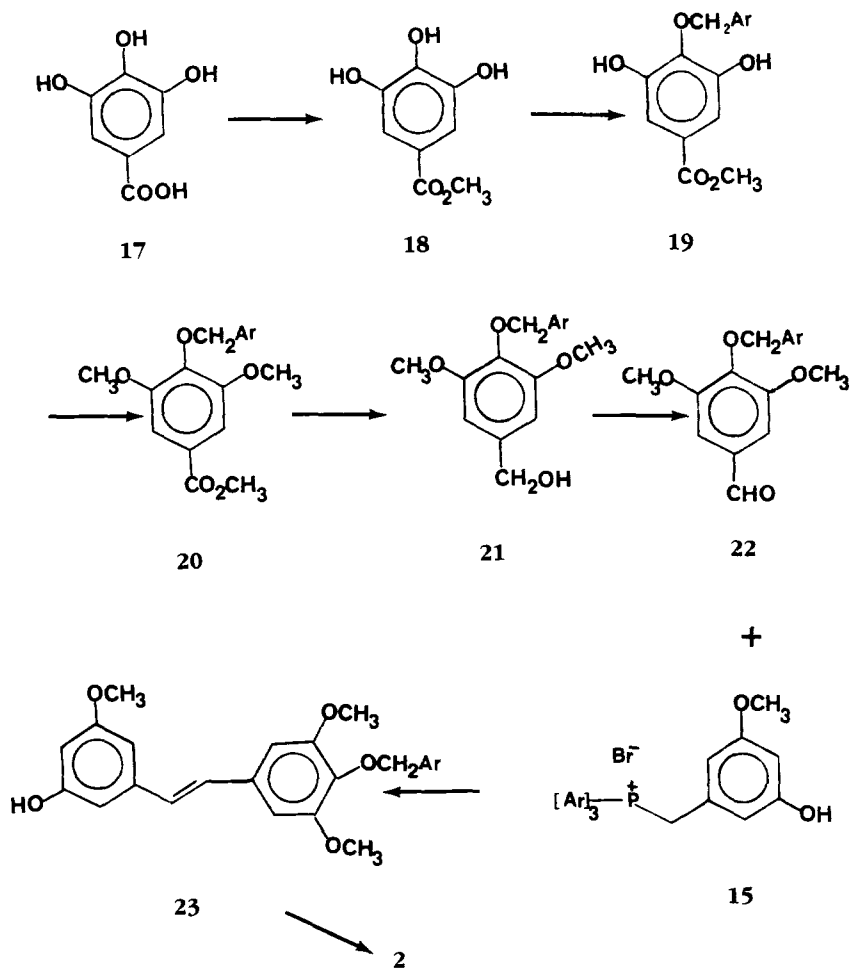
SCHEME 1. Synthesis of 3,4′-dihydroxy-5-methoxy-3′-(3-methylbut-2-enyl)-dihydrostilbene.

The mass and pmr data of compound B indicated a new dihydrostilbene derivative which we named cannabistilbene II. The mass spectrum showed two characteristic fragments at *m/z* 137 (fragment A) and at *m/z* 167 (base peak, fragment B). The pmr indicated that fragment A contains one hydroxy and one methoxy group *meta*-disposed (δ 6.43-6.31, m, 3H), and fragment B contains one hydroxy and two methoxy groups.



1 R_1=H, R_2=OH, R_3=isoprenyl, R_4=H
2 R_1, R_3=OCH_3, R_2=OH, R_4=H
3 R_1=H, R_2, R_3=OCH_3, R_4=OH
4 R_1=H, R_2, R_4=OCH_3, R_3=OH

The presence of a two protons singlet at δ 6.80 in the pmr spectrum suggested that fragment B is symmetric, and thus cannabistilbene II could be accommodated by structure **2**. Synthesis of **2** was carried out following the procedure outlined in Scheme 2. Although the aromatic protons of fragment B of compound **2** appeared as a singlet in the pmr spectrum, their chemical shift was at a higher field (δ 6.36) than those of cannabistilbene II. Study of the pmr spectra of related dihydrostilbenes, for example, canniprene (6), showed that the two *ortho*-aromatic protons on the tetrasubstituted ring appear as a singlet around δ 6.80 as is the case with cannabistilbene II. Thus, the relative distribution of substituents on ring B is proposed to be as shown in either structure **3** or **4**. The synthesis of both compounds is currently underway to prove the structure of cannabistilbene II unequivocally.



SCHEME 2. Synthesis of 3,4′-dihydroxy-3′5,5′-trimethoxy dihydrostilbene.

Several dihydrostilbene derivatives were previously isolated from *Cannabis* (5, 7) and synthesized (6, 8). Batatasins III-V, which are dihydrostilbenes isolated from *Dioscorea batatas*, are known to have plant growth inhibitory properties (9, 10).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were carried on a Thomas Hoover melting point apparatus and are uncorrected. The *ir* spectra were obtained on a Perkin-Elmer 281B recording spectrophotometer. Pmr spectra were recorded in the stated solvent on a Varian EM-390 90 MHz nmr

spectrometer using TMS as internal standard. Cmr spectra were taken on a JEOL FX 60 spectrometer operating at 15.03 MHz. Mass spectra were measured on a Finnigan 3200, MS/DS system. Gc analyses were performed using a 2% OV-17 column according to a previously published procedure (11).

PLANT MATERIAL.—A Panamanian variant of *C. sativa* grown in Mississippi was used in this study. Herbarium specimens are deposited in the Herbarium, Research Institute of Pharmaceutical Sciences, University of Mississippi.

EXTRACTION AND FRACTIONATION.—Powdered leaves (7 kg) were extracted by percolation with 95% EtOH (see Figure 1).

FRACTIONATION OF FRACTION F (EQUIVALENT).—This material (4.4 g) was chromatographed on a silica gel 60 (E. Merck) column for flash chromatography (230-400 mesh) using 5% EtOAc in CH_2Cl_2 (1.0 liter) followed by 10% EtOAc in CH_2Cl_2 (500 ml), 15% EtOAc in CH_2Cl_2 (500 ml) and 20% EtOAc in CH_2Cl_2 (2.5 liters). 207 fractions, each of 20 ml, were collected.

ISOLATION OF CANNABISTILBENE I.—Fractions 56-59 (29 mg), eluted with 5% EtOAc in CH_2Cl_2, showed two spots on precoated silica gel G plates with Rf values of 0.76 and 0.66 in 10% EtOAc in CH_2Cl_2 (system A). Further purification was achieved on precoated silica gel 60 F_{254} plates (E. Merck) (20

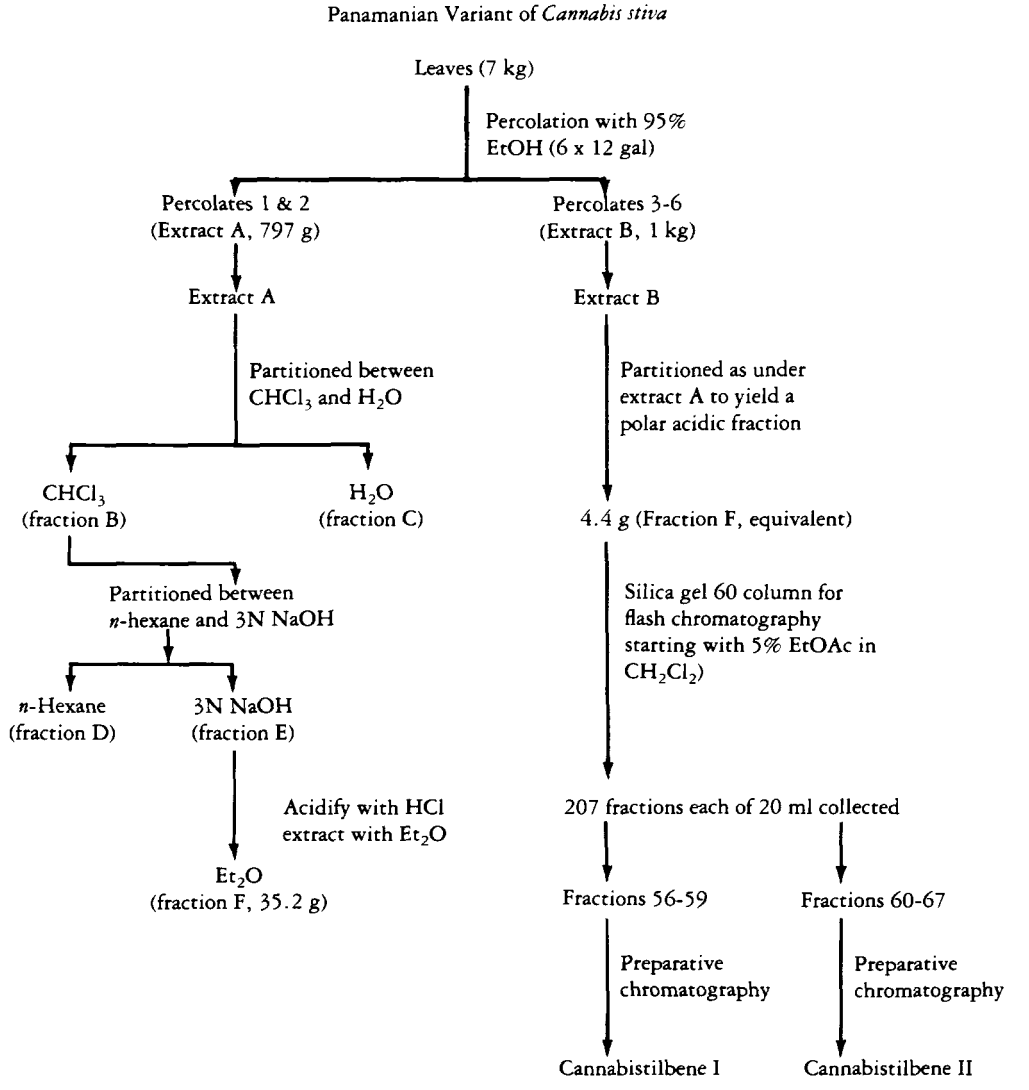


FIGURE 1. Flow chart for the fractionation of the ethanol extract of the leaves of a Panamanian variant of *Cannabis sativa* grown in Mississippi.

× 20, 0.25 mm) using system A. The band with Rf 0.76 was scraped and eluted with 5% MeOH in $CHCl_3$. The residue obtained upon evaporation of the solvent (3 mg) was identical with canniprene (ir, ms, pmr).

The band with Rf 0.66 was scraped and eluted with a MeOH-$CHCl_3$ mixture. Evaporation to dryness yielded a residue (5.7 mg) that was further purified on Whatman reversed phase plate KC18F using MeOH-H_2O (8:2, system B). The major band (Rf 0.39) was scraped, eluted with MeOH, and the solvent evaporated to yield 3 mg of a pure but oily residue (cannabistilbene I). Because of the scarcity of material, no attempts were carried out to crystallize it.

IDENTIFICATION OF CANNABISTILBENE I.—This compound was obtained as a light oil; gc RR_t (1.6) relative to 4-androstene-3,17-dione; ir ν max (film) 3340 (OH), 2845, 1610, 1590, 1510, 1150 and 1060 cm^{-1} ms *m/z* (rel. int., %) 312 (M^+, 4) obs. 312.1719, calc. 312.1725 for $C_{20}H_{24}O_3$, 175 (100), 157 (9), 145 (2.4), 137 (5), 119 (13.5), 105 (4), 91 (20.5); pmr ($CDCl_3$) δ 6.90-6.70 (m, 3H), 6.33-6.20 (m, 3H), 5.25 (t, br, 1H), 3.74 (s, 3H), 3.33 (d, 2H, J=7 Hz), 2.80 (s, 4H), and 1.78 (s, 6H).

ISOLATION OF CANNABISTILBENE II.—Fractions 60-67 (53 mg) eluted with 10% EtOAc in CH_2Cl_2 showed three spots with Rf values 0.76 (trace), 0.66, and 0.56 using system A. Gc/ms analysis revealed three compounds with molecular weight of 342, 312, and 304. Separation of the three components was achieved on silica gel 60 F_{254} using system A, followed by reversed-phase chromatography on Whatman KC18F plates using system B. The band with Rf 0.59 in system B was scraped, eluted with MeOH, and the solvent was evaporated to yield 4 mg of a pure residue (tlc), which was labeled as cannabistilbene II.

IDENTIFICATION OF CANNABISTILBENE II.—This compound was obtained as a colorless oil; gc RR_t (1.2) relative to 4-androstene-3,17-dione; ms *m/z* (rel. int., %) 304 (M^+ 3.5) obs. 304.1249, calcd 304.1310 for $C_{17}H_{20}O_5$, 167 (100) and 137 (84); pmr ($CDCl_3$) showed signals at δ 7.73 (s, 1H, OH), 6.80 (s, 2H), 6.43-6.31 (m, 3H), 5.53 (br, s, 1H, OH), 3.88 (s, 3H), 3.76 (s, 6H), and 2.68 (s, 4H).

PREPARATION OF CANNABISTILBENE I (**1**).—*Conversion of 3-hydroxy-3-methyl-but-1-yne (Aldrich)* (**5**) *to 3-chloro-3-methyl-but-1-yne* (**6**): In a 100 ml three-neck round-bottom flask, 2.8 g anhydrous $CaCl_2$, 2 g CuCl, and 0.1 g copper powder were added, and the mixture was dissolved in 22 ml of cold HCl. The reaction mixture was stirred for 1 h in an ice bath; then 4.2 g (0.05 mole) of **5** was added and stirred at 0° for 1 h. The organic layer was separated, washed twice with 10 ml cold HCl, followed by 15 ml H_2O three times, and then dried over anhydrous K_2CO_3 to yield as an oil (5 g, 97%); ms *m/z* 102 (M^+ 100), 104 (38); pmr ($CDCl_3$) δ 2.6 (s, 1H, C≡C*H*) and 1.88 (s, 6H, gem-dimethyls).

PREPARATION OF DIMETHYL PROP-2-YNYL ETHER OF *p*-HYDROXYBENZALDEHYDE (**8**).—Potassium carbonate (0.85 g) and KI (0.15 g) were added to a solution of *p*-hydroxybenzaldehyde (Eastman) (**7**) (1.2 g) in aqueous Me_2CO (2% v/v, 100 ml), and the mixture was stirred at room temperature for 1 h. To the mixture, 1.2 g of **6** was then added, and the reaction refluxed gently for 6 h after which time, additional amounts of K_2CO_3 (0.85 g) and **6** (1.2 g) were added; refluxing continued for 72 h. Evaporation of the solvent and extraction of the residue with EtOAc gave 1.8 g of an oily product. Chromatography on a dry silica gel 60 (E. Merck) column using hexane-EtOAc (7:3) gave 0.8 g (43%) of the ether **8**; ir ν max (film) cm^{-1} 3290, 2730, 2100, 1685, 1590, 1500, and 830 cm^{-1}; ms *m/z* (rel. int., %) 188 (M^+, 6), 173 (8), 159 (8), 145 (3), 121 (100); pmr ($CDCl_3$) signals at δ 9.9 (s, 1H, C(=O)-*H*), 7.82 (d, 2H, *J* 9 Hz), 7.32 (d, 2H, *H*=9 Hz), 2.63 (s, 1H, C≡C*H*), 1.66 (s, 6H, gem-methyls).

PREPARATION OF DIMETHYL ALLYL ETHER OF *p*-HYDROXYBENZALDEHYDE (**9**).—The acetylenic ether **8** (350 mg) was dissolved in absolute EtOH (20 ml) and hydrogenated using Lindlar catalyst (13) (100 mg) at 24° and atmospheric pressure. The reaction was stopped when one equivalent of hydrogen (36 ml) was consumed. The product was filtered through a bed of celite and the filtrate evaporated to dryness. The residue was purified on a dry silica gel 60 column using hexane-EtOAc (7:3) to yield 221 mg (62%) of **9**; ir ν max (film) 3080, 2985, 2922, 2712, 1680, 1590, 1570, 1500, 1450, 1410, 1375, 1360, 832, and 782 cm^{-1}; ms *m/z* (rel. int., %) M^+ 190; pmr ($CDCl_3$) signals at δ 9.83 (s, 1H, C(=O)-*H*), 7.7 (d, 2H, *J*=9 Hz), 6.97 (d, 2H, *J*= Hz), 6.13 (dd, 1H, *J*=18 Hz and *J*=10 Hz, C*H*=CH_2), 5.1 (d, 1H, *J*=18 Hz, CH=CH_2), 5.06 (d, 1H, *J*=10 Hz, CH=CH_2), 1.36 (s, 6H, gem-methyls).

CONVERSION OF **9** TO **10**.—Compound **9** was heated in an oil bath at 134° for 40 min to yield a dark-green residue (compound **10**) with Rf 0.13, using silica gel 60 F_{254} and hexane-Et_2O (7:3) as a solvent system; ir ν max (film) 3250, 2740, 1660, 1535, 1500, 1435, 1375, 1280, 1250, 1150, 1110, 1090, 968, 942, 890, 822 cm^{-1}; pmr: δ 9.82 (s, 1H, C(=O)-*H*), 7.68 (m, 2H, aromatic), 6.96 (d, 1H, *J*=9 Hz, aromatic), 5.33 (br t, 1H, olefinic proton), 3.4 (d, 2H, benzylic protons), 1.76 (s, 6H, gem-methyls).

CONVERSION OF **9** TO **10**.—Compound **9** was heated in an oil bath at 134° for 40 min to yield a dark-green residue (compound **10**) with Rf 0.13, using silica gel 60 F_{254} and hexane-Et_2O (7:3) as a solvent system; ir ν max (film) 3250, 2740, 1660, 1535, 1500, 1435, 1375, 1280, 1250, 1150, 1110, 1090, 968, 942, 890, 822 cm^{-1}; pmr: δ 9.82 (s, 1H, C-*H*), 7.68 (m, 2H, aromatic), 6.96 (d, 1H, J=9 Hz, aromatic), 5.33 (br t, 1H, olefinic proton), 3.4 (d, 2H, benzylic protons), 1.76 (s, 6H, gem-methyls).

PREPARATION OF 4-BENZYLOXY-3-(3-METHYLBUT-2-ENYL) BENZALDEHYDE (**11**).—Compound **10** (160 mg) was dissolved in dry Me_2CO (5 ml) and stirred with K_2CO_3 (150 mg) and KI (43 mg). Benzyl chloride (157.3 mg) was then added dropwise and the reaction mixture refluxed for 7 h. After work-up the reaction product yielded an oily residue (171 mg, 73%, compound **11**), Rf 0.63 using silica gel 60 F_{254} and hexane-Et_2O (6:4); ms *m/z* (rel. int., %) 280 (M^+, 0.3) 189 (4), and 91 (100); ir ν max (film) 3020, 2720, 1680 cm^{-1}; pmr ($CDCl_3$) signals at 9.84 (s, 1H, $\overset{\overset{O}{\|}}{C}$-*H*), 7.66 (m, 2H, aromatic), 7.4 (s, 5H, aromatic), 6.96 (d, 1H, J=9 Hz, aromatic), 5.33 (br, t, 1H, olefinic), 5.13 (s, 2H, O-CH_2-Ar), 3.14 (d, 2H, Ar-CH_2-$\overset{H}{\underset{|}{C}}$=C<$\begin{matrix}CH_3\\CH_3\end{matrix}$) 1.76 (s, 3H, methyl), 1.66 (s, 3H, methyl).

PREPARATION OF 3,5-DIMETHOXYBENZYL BROMIDE (**13**).—3,5-Dimethoxybenzyl alcohol (Aldrich) (**12**) (17.87 g) was dissolved in CH_2Cl_2 (500 ml) and cooled to 0°. Phosphorous tribromide (7.0 ml) was then added in two equal portions 1 h apart. The reaction was complete 30 min after the addition of the second portion of phosphorous tribromide. Work-up was carried out by the addition of 20 ml H_2O, followed by $NaHCO_3$. The organic layer was then washed three times with 100 ml H_2O, dried over anhydrous Na_2SO_4, and evaporated to yield 17.8 g (72%) of **13** as a yellow oil; ms *m/z* (rel. int., %) 232 (M^+ 18), 230 (18) with a base peak at 151; pmr ($CDCl_3$) signals at δ 6.55 (d, 2H, J=2 Hz), 6.40 (d, 1H, J=2 Hz), 4.40 (s, 2H, Ar-CH_2Br), 3.85 (s, 6H, OCH_3).

PREPARATION OF 3-HYDROXY-5-METHOXYBENZYL BROMIDE (**14**).—Compound **13** (17.8 g) was dissolved in CH_2Cl_2 (500 ml) by stirring at room temperature. Boron tribromide (3 ml) was added in portions over a period of 3 h. The reaction product was examined by tlc and showed a major spot with Rf of 0.50. The organic layer, after work-up, afforded a brown residue (17.0 g) which was purified on a silica gel 60 column using 3% MeOH in $CHCl_3$ to yield a light brown residue (10 g, 60% of compound **14**); ms *m/z* (rel. int., %) 278 (M^+ 11), 216 (10) and a base peak at 137; cmr signals at δ 160.9 (s, C-3), 156.7 (s, C-5), 140.2 (s, C-1), 108.9, 107.5 (both d, for C-2 and/or C-6), 101.9 (d, C-4), 55.5 (q, OCH_3), and 33.3 (t, CH_2-Br).

PREPARATION OF 3-HYDROXY-5-METHOXYBENZYLTRIPHENYL PHOSPHONIUM BROMIDE (**15**).—Compound **14** (10 g, 46.1 mmole) was dissolved in C_6H_6 (150 ml) and the reaction warmed to 50°. Triphenylphosphine (Aldrich, 12.1 g, 46.1 mmole) was added slowly, followed by 50 ml dry Me_2CO and the solution refluxed for 3 h. Examination of the reaction mixture by tlc (silica gel 60 and 1% MeOH in $CHCl_3$) showed no starting material. The reaction product was then cooled, filtered, and the precipitate washed with C_6H_6 to yield a colorless solid (11.6 g, 53%) of compound **15**; pmr (CD_3OD) signals at δ 7.80-7.50 (3 br, s, 15H, Ar_3-P), 6.35-6.00 (m, 3H, Ar), 4.85 (d, 2H, J=15 Hz, Ar-CH_2), 4.80 (br, s, 1H, exchangeable with D_2O), and 3.40 (s, 3H, OCH_3).

PREPARATION OF 4'-BENZYLOXY-3-HYDROXY-5-METHOXY-3'-(3-METHYLBUT-2-ENYL) STILBENE (**16**).—*n*-Butyl lithium (Aldrich, 0.63 ml, 1.6 M solution in hexane) was added to a suspension of **15** (297 mg, 0.6 mmole) in dry tetrahydrofuran (10 ml), under N_2, and the mixture stirred at room temperature for 20 min. A solution of the aldehyde **11** (135 mg, 0.5 mmole) in dry tetrahydrofuran (3 ml) was added dropwise; stirring continued for 2 h. The reaction mixture was added to NH_4Cl solution and extracted with 25 ml $CHCl_3$ twice. The aqueous phase was rendered just acidic with 10% HCl and again extracted with 25 ml $CHCl_3$ twice. The residue from the combined $CHCl_3$ extracts was purified by column chromatography on a dry silica gel 60 column using hexane-Et_2O (7:3) as eluant. Compound **16** was obtained as an oil (*cis-trans* mixture) (90 mg, 47%) [Rf 0.68 and 0.58; silica gel and hexane-EtOAc (6:4) as a solvent system]; ms *m/z* (rel. int., %) 400 (M^+, 12) 309 (9), 293 (5), 267 (14), 137 (13), 107 (3), and 91 (100); pmr ($CDCl_3$) δ 7.4-7.23 (m, 5H), 7.1-6.26 (m, 7H), 5.14 (br, t, 1H, olefinic), 5.05 (s, 2H, O-CH_2-Ar), 3.63 (s, 3H, OMe), 3.26 (d, 2H, Ar-CH_2-$\overset{H}{\underset{|}{C}}$=C<), 1.66 (s, 3H), and 1.57 (s, 3H, gem-methyls).

REDUCTION OF **16** WITH SODIUM AND *n*-BuOH.—Compound **16** (62 mg, 0.15 mmole) was dissolved in *n*-BuOH (10 ml), stirred under N_2, and heated in an oil bath at 105°. Sodium (0.6 g) was added in small pieces to maintain reflux. When all the sodium had dissolved, the solution was cooled and H_2O (15

ml) was added. The mixture was extracted with 10 ml Et_2O twice, the aqueous layer acidified with dilute HCl and extracted with an additional amount of Et_2O, dried, and evaporated to give an oily residue (48 mg). Purification was carried out on a dry silica gel 60 column using hexane-EtOAc (9:1) as eluting system to yield an oil (15 mg, 31%) identical (gc, ir, ms, pmr) to the natural material **1**.

SYNTHESIS OF 3,4'-DIHYDROXY-3',5,5'-TRIMETHOXY DIHYDROSTILBENE (**2**).—*Preparation of methyl 3,4,5-trihydroxy benzoate* (**18**): 3,4,5-Trihydroxybenzoic acid (**17**) (1 g) was dissolved in MeOH (100 ml) and HCl (2 ml) was added; then the mixture was refluxed for 10 h. The reaction product was evaporated to dryness to yield a residue (1.05 g) of **18** as needle crystals; mp 95-97°, Rf 0.31 using silica gel 60 F_{254} and hexane-EtOAc-MeOH (49:5:1) as a solvent system; ms *m/z* (rel. int., %) 184 (M^+, 100); pmr (Me_2CO-d_6) signals at δ 7.86 (br, s, 3H, exchangeable with D_2O), 7.2 (s, 2H, aromatic), and 3.84 (s, 3H, $-\overset{O}{\overset{\|}{C}}-OCH_3$).

PREPARATION OF METHYL 4-BENZYLOXY-3,5-DIHYDROXY BENZOATE (**19**).—Compound **18** (1.0 g) was dissolved in dry Me_2CO (100 ml) and stirred for 30 min with K_2CO_3 (0.9 g) and KI (0.15 g). Benzyl chloride was then added and the mixture refluxed for 8 h. The reaction product, after work-up, was chromatographed on a dry silica gel 60 column using hexane-EtOAc (7:3) as an eluant to yield **19** (0.8 g, 50%) as needle crystals; mp 126-128° (Me_2CO); Rf 0.62 using silica gel 60 F_{254} and hexane-Et_2O (1:1) as a solvent systemn; ir ν max (KBr) 3480, 3300, 1675, 1590, 1520, 1490 cm^{-1}; ms *m/z* (rel. int., %) 274 (M^1, 1), 243 (0.7), 184 (0.8), 153 (2.1), 107 (3.5) and 91 (100); pmr (Me_2CO-d_6) signals at δ 7.55-7.25 (m, 5H), 7.13 (s, 2H, aromatic), 5.17 (s, 2H, O-CH_2-Ar), 3.88 (s, 3H, $-\overset{H}{\overset{\|}{C}}-OCH_3$).

PREPARATION OF METHYL 4-BENZYLOXY-3,5-DIMETHOXY BENZOATE (**20**).—Compound **19** (0.53 g, 0.002 mole) was dissolved in dry Me_2CO (100 ml) and stirred for 12 h at room temperature with K_2CO_3 (1.4 g) and dimethyl sulfate (0.59 g). The reaction product was centrifuged, the supernatant solution withdrawn, and the solid material washed twice 25 ml Me_2CO. The combined Me_2CO extracts were evaporated and the residue chromatographed on a dry silica gel 60 column using hexane-EtOAc (1:1) as an eluant to give compound **20** (0.53 g, 91%) as yellowish needles; mp 68-71' (Me_2CO); ir ν max (KBr) 1705, 1585, 1495 cm^{-1}; ms *m/z* (rel. int., %) 302 (M^+, 6), 210 (13), 183 (2.5), 165 (2.1), 135 (3), 125 (9), 123 (3), 122 (3), 92 (20) and 91 (100); pmr (Me_2CO-d_6) signals at δ 7.55-7.30 (m, 7H, aromatic), 5.07 (s, 2H, O-CH_2-Ar), 3.89 (s, 9H, C-OCH_3 and OCH_3).

PREPARATION OF COMPOUND **21**.—Compound **20** (0.5 g) in Et_2O (20 ml) was added dropwise with stirring to a suspension of lithium aluminum hydride (0.3 g) in Et_2O (60 ml). After 30 min, the reaction was carefully stopped by the addition of ice-cold H_2O. The reaction mixture was then acidified with 10% H_2SO_4 and extracted with 25 ml Et_2O four times. The combined ethereal solutions were dried over anhydrous Na_2SO_4 and evaporated to dryness to yield **21** as an oil (0.44 g, 97%); Rf 0.40 using silica gel 60 F_{254} and hexane-EtOAc (1:1) as a solvent system, ir ν max (film) 3400, 1585, 1495 cm^{-1}; ms *m/z* (rel. int., %) 274 (M^+, 9), 183 (52), 155 (7), 127 (47), 91 (100); pmr ($CDCl_3$) signals at δ 7.55-7.20 (m, 5H), 6.57 (s, 2H), 4.96 (s, 2H, O-CH_2-Ar), 4.57 (s, 2H, Ar-CH_2-OH), 3.77 (s, 6H, 2xOCH_3), 2.20 (br, s, 1H, OH).

PREPARATION OF COMPOUND **22**.—To a stirred soution of compound **21** (136 mg) in CH_2Cl_2 (25 ml), pyridinium chlorochromate (Aldrich, 0.4 g) in CH_2Cl_2 (50 ml) was added dropwise. After 30 min, the reaction was stopped (checked by tlc), filtered, and the residue washed twice 25 ml CH_2Cl_2. The combined organic layers were dried and evaporated to yield 0.1 g of **22** as a brown oil (80%); Rf 0.68 using silica gel 60 F_{254} and hexane-EtOAc (1:1) as a solvent system; ir ν max (film) 2740, 1685, 1580, 1492 cm^{-1}; ms *m/z* (rel. int., %) 272 (M^+, 3), 227 (2), 136 (6), 107 (1), 95 (10), 91 (100); pmr ($CDCl_3$) signals at δ 9.87 (s, 1H, $-\overset{O}{\overset{\|}{C}}-H$), 7.60-7.25 (m, 5H), 7.11 (s, 2H), 3.89 (s, 6H, 2xOCH_3).

PREPARATION OF 4'-BENZYLOXY-3-HYDROXY-3',5,5'-TRIMETHOXY STILBENE (**23**).—*n*-Butyl lithium (0.55 ml, 1.6 M solution in hexane) was added to a suspension of **15** (0.21 g, 0.4 mmole) in dry tetrahydrofuran (10 ml), under N_2, and the mixture stirred at room temperature for 15 min. A solution of the aldehyde **22** (105 mg, 0.4 mmole) in dry tetrahydrofuran (30 ml) was added dropwise and stirring continued for 40 min. The reaction mixture, after work-up, was evaporated to yield a residue (297 mg), which was purified on a dry silica gel 60 column using hexane -EtOAc (7:3) as an eluant to yield compound **23** as an oil (140 mg, 92%) (mixture of *cis* and *trans*) [Rf 0.65 and 0.52; silica gel and hexane-EtOAc (1:1) as a solvent system]; ir ν max (film) 3390, 1580, 1495, 1450 cm^{-1}; ms *m/z* (rel. int., %) 392 (M^+, 6), 301

(20), 286 (10), 277 (16), 241 (20), 213 (6), 183 (12), 152 (9), 128 (7), 127 (7), 115 (12), and 91 (100). This material was used without further purification for the next synthetic step.

CONVERSION OF **23** TO COMPOUND **2**.—Compound **23** (120 mg) was dissolved in 95% EtOH (25 ml) and the resulting solution hydrogenated for 1 h at room temperature using 5% Pd-C (20 mg) and a pressure of 30 lb/sq in. The reaction product was filtered over a bed of celite and the filtrate evaporated to dryness. The residue was purified on a silica gel 60 column using hexane-EtOAc (7:3) as eluant to give compound **2** as an oily material (37 mg, 40%); Rf 0.28 using silica gel and hexane-EtOAc (1:1) as a solvent; ms *m/z* (rel. int., %) 304 (M^+ 2), 167 (100), and 137 (9); pmr ($CDCl_3$) signals at δ 6.36 (s, 2H, aromatic protons on ring B), 6.26 (s, 3H, aromatic protons on ring A) 5.38, 5.10 (br, s, 1H each, exchanges with D_2O), 3.85 (s, 6H, 2 x OCH_3) 3.66 (s, 3H, OCH_3), 2.82 (s, 4H, Ar-CH_2-CH_2-Ar).

ACKNOWLEDGMENTS

This research was supported in part by the National Institute on Drug Abuse, Contract #271-81-3803 and by the Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi.

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Received 9 May 1983