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A VERSATILE APPROACH TO THE SYNTHESIS OF COMBRETASTATINS

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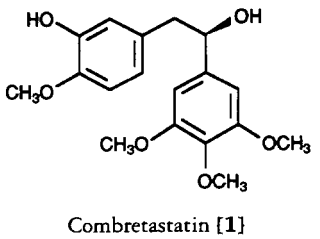
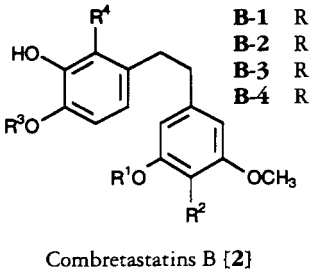
ABSTRACT.—A new and versatile synthesis of combretastatins has been developed. Starting from commercially available materials, 2-phenyl-2-benzyl-1,3-dithianes were easily prepared and used as intermediates in the synthesis of several families of combretastatins. This approach facilitates the preparation of representative intermediates in a few steps, with or without an oxygenated function in the ethylenic residue. Many different analogues suitable for pharmacological evaluation can also be obtained from some of these intermediates.

Combretastatins are natural products that inhibit microtubule assembly, and therefore produce mitosis inhibition, causing accumulation of cells in metaphase (1,2). The activity of this kind of natural antimitotics depends on their ability to interact with tubulin, the predominant protein component of microtubules, which make up the mitotic spindle. Inhibitors of microtubule assembly fall into two broad classes, depending on the site of binding to the protein: those acting by bonding to the colchicine site and those bonded to the vinblastine site (3). Some clinically used anticancer drugs, such as vincristine and related alkaloids, belong to the second type. However, no products of the first type have been introduced into clinical use up to the present. Etoposide and teniposide, two well-established anticancer drugs which are analogues of the antitubulin compound podophyllotoxin, have DNA topoisomerase II as the target (4,5). It would be of interest to find new compounds able to inhibit tubulin polymerization by selective binding to the colchicine site.

Combretastatins [**1**, **2B-1**–**2B-4**] constitute a family of compounds belonging to the latter category, with the initial representative being combretastatin [**1**], which was isolated from *Combretum caffrum* (6). The genus *Combretum*, the largest in the family Combretaceae, includes some 250 species of tropical trees, widespread in Africa and India, that are well known for their medical applications (7). Preliminary biological assays, carried out with a diverse group of combretastatins, showed their ability to produce mitotic arrest of neoplastic cells in culture (8,9), and to display potent cytotoxicity against several human cancer cell lines (6,10). Combretastatins have structural similarities with colchicine and it has been demonstrated that they are competitive inhibitors of the binding of colchicine to tubulin, thus indicating that they bind at the same site on the protein. Unlike colchicine, but similar to the structurally related steganacin and podophyllotoxin (11), the binding is not temperature-dependent (12).



Combretastatin [**1**]



Combretastatins B [**2**]

B-1 $R^1,R^3=CH_3$, $R^2=OCH_3$, $R^4=OH$
B-2 $R^1,R^4=H$, $R^2=OCH_3$, $R^3=CH_3$
B-3 $R^1=CH_3$, $R^2=OCH_3$, $R^3,R^4=H$
B-4 $R^1=CH_3$, $R^2,R^3,R^4=H$

Most combretastatins and analogues have two substituted benzene rings linked by a two-carbon spacer, usually ethylene, which can be functionalized. Some of the naturally occurring combretastatins, as well as a great number of analogues, have been synthesized (13,14). They have usually been obtained by means of Wittig olefination (15) or by the addition of organometallics to aldehydes (16), followed by later manipulations in order to prepare derivatives for bioactivity testing (17,18).

We now report a simple and versatile approach to the synthesis of combretastatins starting from a common 1,3-dithiane intermediate, which is suitable for the preparation of diversely functionalized derivatives in the ethylene residue. This methodology is applied to the synthesis of combretastatin B-3 [**2B-3**] and a series of analogues, which could help in the understanding of the structure-activity relationships for colchicine derivatives. Some of them, which we name combretastatones, carry a keto group in one of the benzylic positions and are described herein for the first time.

RESULTS AND DISCUSSION

Among the large number of methods used in the formation of C-C bonds, those yielding an acyl residue equivalent are very convenient, due to the ease of transforming carbonyl groups into a great number of derivatives. In addition, the alkylation of dithioacetal substrates, as the base reaction for the construction of such type of bonds, is one of the most useful methods (19,20), because the starting materials are easily obtained from the parent aldehydes and the yields attained are very high. Furthermore, the dithio- derivatives are easily and quantitatively transformed into methylene and keto compounds. We therefore decided to synthesize a natural combretastatin and a number of its analogues in order to test the utility of this methodology for the preparation of several representative compounds.

The starting dithianes were readily obtained from commercial aldehydes or their benzylic derivatives (**3 a–e**; Scheme 1) by treatment with 1,3-propanedithiol in the presence of acid (21). The lithiated dithianes (**4 a–e**) reacted with bromo- derivatives (**5 x–y**) at −78°, according to the usual methodology (22), to give the alkylated products (**6 ax–ex**) in very high yields. These products showed characteristic nmr signals for a dithiane group (1.8–2.1 and 2.5–2.8 ppm in ^{1}H- and 60, 27.5, and 25.0 ppm in the ^{13}C-nmr spectra) and for a benzylic methylene (3.15 and 51.8 ppm) as the main observations used in their structural identification (Tables 1 and 2).

By treatment with Raney Ni (23), dithianes **6** were desulfurized and, in the case of benzyl ethers, debenzylated, to produce the corresponding combretastatin or an analogue in quantitative yield. Following this sequence, combretastatin B-3 (**2B-3**; **9fx**) was obtained from *O*-dibenzylprotocatechuic aldehyde in three steps, in 75% overall yield. Combretastatin B-3 was previously synthesized by Pettit *et al.* in two steps from **3e** by Wittig olefination followed by hydrogenation, in 55.5% total yield (24). The previously unknown derivatives **9ax**, **9bz**, and **9gx** have been prepared by the same method. Compound **9ax** has been previously obtained by methylation of a mixture of combretastatins B-2 [**2B-2**] and B-3 [**2B-3**], while our methodology allowed us to obtain this compound in 86% overall yield from veratraldehyde [**3a**].

Deprotection of the dithianes by reaction with HgO (25), produced the keto derivatives **7** in high yield. Some of these constitute the keto analogues of *O*-methylated combretastatins; for example, **7ax** is the keto analogue of *O,O'*-dimethyl-combretastatin B-3 (24). To prepare the free phenols the debenzylation reactions were carried out by BF_3-catalyzed displacement of the benzyl group with NaI (21). Compounds of type **7** and **8** are the first examples of keto analogues of combretastatins. The synthetic versatility of the keto group can be used for the preparation of many other analogues, namely hydroxyl,

i
ii
iii
iv
v
vi
3
a, b, c, d, e
4
a, b, c, d, e
5
x, y
6
ax, ay, by, dx, cx, cy, ex
7
ax, ay, by, cx
8
az, bz, gx
9
ax, bz, fx, gx
10 ax
R1 R2 R3 R4
a CH3 OCH3 x OCH3 CH3
b -CH2O- y H Bn
c Bn OCH3 z H H
d Bn H
e Bn OBn
f H OH
g H OCH3
i: Propanedithiol, ClSiMe3, CHCl3;
ii: n-BuLi, THF, −78°, TMEDA;
iii: HgO, BF3-Et2O, THF, H2O;
iv: INa, BF3-Et2O, CH3-C≡N;
v: Raney Ni, Me2CO;
vi: NaBH4/MeOH

SCHEME 1

TABLE 1. ^{1}H-Nmr Data (200 MHz) for Combretastatin Analogues.[a]

H	Compound								
	6ax	**6ay**	**6by**	**6dx**	**6cx**	**6cy**	**6ex**	**7ax**	**7ay**
2	7.24 s	7.17 d (2.0)	7.33 d (1.8)	6.91 d (8.9)	7.31 d (1.9)	7.2–7.5 m	7.2–7.5 m	7.58 d (1.7)	7.56 d (2.0)
3	—	—	—	7.62 d (8.9)	—	—	—	—	—
5	6.62 d (8.5)	6.75 d (8.8)	6.67 d (8.0)	7.62 d (8.9)	6.84 d (8.4)	6.84 d (8.4)	6.94 d (8.2)	6.87 d (8.4)	6.87 d (8.4)
6	7.33 d	7.30 dd (8.8, 2.0)	7.20 dd (8.0, 1.8)	6.91 d (8.9)	7.34 dd (8.4, 1.9)	7.2–7.5 m	7.2–7.5 m	7.67 dd (8.4, 1.7)	7.65 dd (8.4, 2.0)
1a	—	—	—	—	—	—	—	—	—
1′a	3.16 s	3.16 s	3.16 s	3.18 s	3.15 s	3.16 s	3.15 s	4.19 s	4.15 s
2′,6′	5.92 s	6.65 d (8.0)	6.74 d (8.0)	5.90 s	5.90 s	6.65 d (8.0)	5.90 s	6.49 s	6.93 d (8.7)
3′,5′	—	7.32 d (8.0)	7.35 d (8.0)	—	—	7.33 d (8.0)	—	—	7.19 d (8.7)
3-OMe	3.77 s	3.68 s	—	—	3.74 s	3.70 s	—	3.84 s	3.90 s
4-OMe	3.87 s	3.84 s	—	—	—	—	—	3.90 s	3.93 s
O-CH_2-O	—	—	5.96 s	—	—	—	—	—	—
3′,5′-OMe	3.63 s	—	—	3.59 s	3.59 s	—	3.60 s	3.84 s	—
4′-OMe	3.73 s	—	—	3.77 s	3.73 s	—	3.74 s	3.95 s	—
S-CH_2-CH_2-	1.92–2.05 m	1.8–2.1 m	1.8–2.1 m	1.6–1.8 m	1.8–2.1 m	1.8–2.1 m	1.8–2.1 m	—	—
S-CH_2-CH_2-	2.5–2.8 m	2.5–2.8 m	2.5–2.8 m	1.9–2.1 m	2.5–2.8 m	2.5–2.8 m	2.5–2.8 m	—	—
Bn″-CH_2	—	—	—	5.05 s	5.14 s	4.95 s	5.15 s	—	—
Bn″	—	—	—	7.3–7.5 m	7.3–7.5 m	7.3–7.5 m	7.2–7.5 m	—	—
Bn‴-CH_2	—	4.93 s	4.97 s	—	—	5.13 s	5.15 s	—	5.03 s
Bn‴	—	7.2–7.4 m	7.3–7.5 m	—	—	7.2–7.5 m	7.2–7.5 m	—	7.3–7.4 m

TABLE 1. Continued.

H	Compound								
	7by	**7cx**	**8az**	**8bz**	**8gx**	**9ax**	**9bz**	**9gx**	**10ax**
2	7.46 d (1.7)	7.50 d (2.0)	7.58 d (2.0)	7.44 d (1.8)	7.57 d (2.0)	6.80 d (1.8)	6.65 d (1.7)	6.62 d (2.0)	6.6–6.9 m
3	—	—	—	—	—	—	—	—	—
5	6.82 d (8.0)	6.89 d (8.5)	6.87 d (8.4)	6.81 d (8.2)	6.94 d (8.2)	6.80 d (8.1)	6.71 d (8.0)	6.83 d (8.0)	6.6–6.9 m
6	7.64 dd (8.0, 1.7)	7.60 dd (8.5, 2.0)	7.67 dd (8.4, 2.0)	7.60 dd (8.2, 1.8)	7.62 dd (8.2, 2.0)	6.70 dd (8.1, 1.8)	6.58 dd (8.0, 1.7)	6.70 dd (8.0, 2.0)	6.6–6.9 m
1a	—	—	—	—	—	2.85 s	2.78 s	2.83 s	4.83 t (6.7)
1′a	4.13 s	4.15 s	4.19 s	4.10 s	4.16 s	2.85 s	2.78 s	2.83 s	2.92 m
2′,6′	6.92 d (8.6)	6.47 s	6.76 d (8.5)	6.72 d (8.4)	6.48 s	6.37 s	6.72 d (8.3)	6.36 s	6.37 s
3′,5′	7.16 d (8.6)	—	7.11 d (8.5)	7.05 d (8.4)	—	—	6.99 d (8.3)	—	—
3-OMe	—	3.82 s	3.84 s	—	3.82 s	3.84 s	—	3.84 s	3.81 s
4-OMe	—	—	3.90 s	—	—	3.84 s	—	—	3.82 s
O-CH_2-O	6.01 s	—	—	6.00 s	—	—	5.89 s	—	—
3′,5′-OMe	—	3.82 s	—	—	3.83 s	3.82 s	—	3.83 s	3.81 s
4′-OMe	—	3.92 s	—	—	3.93 s	3.86 s	—	3.85 s	3.87 s
S-CH_2-CH_2-	—	—	—	—	—	—	—	—	—
S-CH_2-CH_2-	—	—	—	—	—	—	—	—	—
Bn″-CH_2	—	5.23 s	—	—	—	—	—	—	—
Bn″	—	7.3–7.5 m	—	—	—	—	—	—	—
Bn‴-CH_2	5.04 s	—	—	—	—	—	—	—	—
Bn‴	7.3–7.5 m	—	—	—	—	—	—	—	—

[a]Coupling constants (*J*) in Hz in parentheses.

TABLE 2. ^{13}C-Nmr Data (50.3 MHz) for Combretastatin Analogues.[a]

C	Compound																
	6ax	**6ay**	**6by**	**6dx**	**6cx**	**6cy**	**6ex**	**7ax**	**7ay**	**7by**	**7cx**	**8az**	**8bz**	**8gx**	**9ax**	**9bz**	**9gx**	**10ax**
1	132.7	132.6	134.7	135.2	133.4	133.6	133.5	130.6	130.1	131.6	130.6	130.0	131.4	129.7	134.3	133.9	133.5	137.1
2	113.3	112.7	109.8	131.2	113.5	113.6	115.9	110.8	110.3	108.5	111.5	111.1	108.5	110.6	112.2	109.1	111.3	111.3
3	148.5	148.2	148.3	114.5	149.2	149.3	148.5	149.1	149.2	148.3	149.6	149.2	148.3	146.9	148.9	147.6	146.3	149.2
4	147.9	147.6	147.2	157.5	147.2	147.1	147.9	153.4	153.5	151.8	150.7	153.6	151.9	153.5	147.4	145.7	143.9	148.7
5	110.8	110.3	107.6	114.5	114.2	113.8	114.4	110.1	110.2	108.0	112.5	110.3	108.0	113.9	111.5	108.2	114.3	109.5
6	122.1	121.8	123.5	131.2	122.1	122.1	122.8	123.4	123.5	125.0	123.2	123.5	125.2	124.2	120.4	121.4	121.1	116.3
1a	59.5	59.7	59.8	59.5	60.5	60.0	60.7	196.2	196.5	196.0	196.2	196.2	196.6	196.2	37.4	37.3	37.6	75.1
1'a	51.8	50.6	50.9	52.0	51.8	50.9	51.8	45.3	44.4	44.5	45.4	44.4	44.5	45.4	38.4	37.7	38.6	46.5
1'	129.7	136.8	137.1	129.9	129.7	137.2	129.7	129.8	137.3	137.1	130.2	127.1	126.6	130.7	137.4	135.9	137.6	133.7
2'	108.1	131.7	131.9	108.4	108.3	132.1	108.4	106.5	130.4	130.4	106.8	130.6	130.6	106.6	105.8	129.8	106.0	106.6
3'	151.9	113.4	113.8	152.2	151.9	113.6	152.0	153.3	115.3	115.2	153.5	115.7	115.7	153.5	153.0	115.3	153.1	153.3
4'	137.0	157.5	158.5	137.0	137.1	157.9	137.2	137.2	157.9	157.8	137.2	154.8	154.8	137.2	137.4	153.6	137.5	136.7
5'	151.9	113.4	113.8	152.2	151.9	113.6	152.0	153.3	115.3	115.2	153.5	115.7	115.7	153.5	153.0	115.3	153.1	153.3
6'	108.1	131.7	131.9	108.4	108.3	132.1	108.4	106.5	130.6	130.4	106.8	130.6	130.6	106.6	105.8	129.8	106.0	106.6
O-CH_2-O			101.2							101.9			101.9			100.1		
3-OMe	55.8	55.6			56.0	56.1		56.1			56.2	56.1		56.3	56.0		56.0	56.1
4-OMe	55.8	55.6						56.0				56.1			56.0			56.1
3'-OMe	55.6			56.0	55.7		55.8	56.1			56.2			56.3	56.1		56.1	56.2
4'-OMe	60.5			60.6	59.5		59.5	60.7			60.6			60.7	60.7		60.7	60.6
5'-OMe	55.6			56.0	55.7		55.8	56.1			56.2			56.3	56.1		56.1	56.2
S-*CH_2*-CH_2-	25.0	24.9	25.1	26.5	25.0	25.2	25.0											
S-CH_2-*CH_2*-	27.4	27.3	27.5	27.7	27.5	27.7	27.5											
1"Bn		126.6	126.8	125.1	128.4	128.0	128.1		126.8	126.7	126.9							
2"		127.1	127.5	127.4	127.0	127.5	127.2		127.5	127.5	127.2							
3"		128.2	128.5	128.7	128.3	128.6	128.5		128.6	128.9	128.8							
4"		127.6	127.9	127.5	127.7	128.0	127.8		127.9	128.0	128.2							
5"		128.2	128.5	128.7	128.3	128.6	128.5		128.6	128.9	128.8							
6"		127.1	127.5	127.4	127.0	127.5	127.2		127.5	127.5	127.2							
7"		69.5	69.9	70.2	70.9	71.0	70.6		70.2	70.1	70.9							

[a]Additional benzylic signals (ppm): **6cy** (126.9, 127.5, 128.6, 128.0, 128.6, 127.5, 69.9) and **6ex** (128.1, 127.2, 128.5, 127.8, 128.5, 127.2, 70.6).

amino, hydroxylamino, or thio derivatives. As an example, $NaBH_4$ reduction of **7ax** produced the alcohol **10ax**.

In conclusion, keto [**7** and **8**], hydroxy [**10**], and reduced [**9**] derivatives and analogues of combretastatins can be obtained in high yields from common precursors of type **6**. Furthermore, the developed methodology facilitates the preparation of many different types of analogues in a short, versatile, and high-yielding fashion.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEUDRES.—Mps were determined on a Büchi 510 apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter in a 1-dm cell, in $CHCl_3$ solution (λ are given in nm). Uv spectral data were obtained on a Hitachi 100-60 spectrophotometer, in 1-cm cells, using EtOH as solvent (λ max are given in nm and ϵ in M^{-1} cm^{-1}). Ir spectra were performed on a Beckman (Acculab 8) spectrophotometer, in $CHCl_3$ solution (ν max are given in cm^{-1}). Nmr spectra were recorded on a Bruker WP 200 SY instrument (200 MHz for ^1H and 50.3 MHz for ^{13}C) in $CDCl_3$ solution, unless otherwise stated. Chemical shifts (δ) are given in ppm, referred to internal TMS, and coupling constants (J) in Hz. Mass spectra (ei) were recorded on a VG-TS-250 instrument; ionization energy was 70 eV. Column chromatography was performed over Si gel Merck 60 (0.063–0.2 mm). For flash chromatography, an Eyela EF-10 apparatus was used, with a 3-85 ml/min flow rate, over Si gel Merck 60 (0.040–0.063 mm). Tlc was performed on precoated Si gel polyester plates (0.25 mm thickness) with fluorescent indicator UV254 (Polychrom SI F_{254}). A solution of 10% phosphomolybdic acid in EtOH or 10% H_2SO_4 in EtOH were used for visualization, after heating at 110°. Prep. tlc was developed on Merck 60 SiF_{254} plates.

BENZYLATIONS.—Hydroxybenzaldehyde derivatives in dry Me_2CO, K_2CO_3, KI, and benzyl chloride were heated at reflux for 12 h, then cooled to room temperature and K_2CO_3 was removed by filtering. The solution was successively washed with saturated aqueous $Na_2S_2O_3$ and 2 N HCl, dried over Na_2SO_4, and the solvent eliminated at reduced pressure.

METHOD 1: ALDEHYDE PROTECTION.—To a 1M solution of **3** (**a**, **b**, **c**, **d**, and **e**) in dry $CHCl_3$ at room temperature under N_2, first 2 equivalents of propanedithiol and then $ClSiMe_3$ were added. The reaction mixture was maintained at room temperature for 20 h and then washed with 4% aqueous NaOH. After neutralization and evaporation, products **4** (**a**, **b**, **c**, **d**, and **e**) were collected by crystallization in Me_2CO.

METHOD 2: ALKYLATION REACTIONS.—*2-(4-Benzyloxy-3-methoxyphenyl)-2-(3,4,5-trimethoxybenzyl)-1,3-dithiane* [**6cx**].—To a 0.1 M solution of benzylvanillyne dithiane **4c** (425 mg; 1.28 mmol) in dry THF (13 ml) at −78° under Ar, 0.85 ml of *n*-BuLi (1.6 M) in hexane (1.05 equivalents) were added. The reaction mixture was maintained at −78° for 30 min and then 1 equivalent of trimethoxybenzyl bromide **5x** (339 mg; 1.28 mmol) in dry THF (3.0 ml) and 1 equivalent of TMEDA (0.2 ml) was introduced in the reaction flask at −78° and the mixture allowed to react overnight at −20°. After addition of an aqueous NH_4Cl saturated solution and extraction with EtOAc, the solution was dried over Na_2SO_4 and evaporated. The crude product was purified by flash chromatography on Si gel with *n*-hexane/EtOAc mixtures of increasing polarity, yielding 599 mg (92.0%) of **6cx** as a colorless oil; ir ν max 2840, 1600, 1510, 1465, 1430, 1140, 1040, 1010, 990 cm^{-1}; ^1H nmr, see Table 1; ^{13}C nmr, see Table 2; ms *m/z* M^+ 513 (512).

2-(3,4,5-Trimethoxybenzyl)-2-(3,4-dimethoxyphenyl)-1,3-dithiane [**6ax**].—By method 2, from 325 mg (1.27 mmol) of veratraldehyde dithiane **4a** and 332 mg (1.27 mmol) of trimethoxybenzyl bromide **5x**, 550 mg (99.3%) of **6ax** were obtained as a pure crude product; colorless oil; ir ν max 2840, 1600, 1510, 1480, 1430, 1290, 1185, 1150, 1040, 1010, 980 cm^{-1}; ^1H nmr, see Table 1; ^{13}C nmr, see Table 2; ms *m/z* M^+ 436.

2-(4-Benzyloxybenzyl)-2-(3,4-dimethoxyphenyl)-1,3-dithiane [**6ay**].—By method 2, from 581 mg (2.27 mmol) of veratraldehyde dithiane **4a** and 630 mg (2.27 mmol) of benzyloxybenzyl bromide **5y**, 995 mg (96.9%) of **6ay** were obtained after chromatography; colorless oil; ir ν max 1610, 1505, 1490, 1470, 1260, 1180, 1140, 1035, 910 cm^{-1}; ^1H nmr, see Table 1; ^{13}C nmr, see Table 2; ms *m/z* M^+ 452.

5-[2-(4-Benzyloxybenzyl)-1,3-dithian-2-yl]-1,3-benzodioxol [**6by**].—By method 2, from 562 mg (2.34 mmol) of piperonal dithiane **4b** and 648 mg (2.34 mmol) of benzyloxybenzyl bromide **5y**, 974 mg (95.5%) of **6by** were obtained after chromatography. White crystals from CH_2Cl_2/hexane, mp 148–150°; ir ν max 1620, 1600, 1520, 1490, 1440, 1240, 1190, 1050, 950 cm^{-1}; ^1H nmr, see Table 1; ^{13}C nmr, see Table 2; ms *m/z* M^+ 436; *anal.* calcd for $C_{25}H_{24}O_3S_2$, C 68.78, H 5.54; found C 68.67, H 5.49.

2-(4-Benzyloxybenzyl)-2-(4-benzyloxy-3-methoxyphenyl)-1,3-dithiane [**6cy**].—By method 2, from 786 mg (2.37 mmol) of benzylvanillyne dithiane **4c** and 656 mg (2.37 mmol) of benzyloxybenzyl bromide **5y**,

1190 mg (95.0%) of **6cy** were obtained after chromatography; colorless oil; ir ν max 1610, 1590, 1500, 1470, 1260, 1180, 1130, 1020, 910 cm^{-1}; ^1H nmr, see Table 1; ^{13}C nmr, see Table 2; ms *m/z* M^+ 528.

2-(4-Benzyloxyphenyl)-2-(3,4,5-trimethoxybenzyl)-1,3-dithiane [**6dx**].—By method 2, from 389 mg (1.27 mmol) of *p*-benzyloxyphenyl dithiane **4d** and 331 mg (1.27 mmol) of trimethoxybenzyl bromide **5x**, 499 mg (81.5%) of **6dx** were obtained after chromatography; colorless oil; ir ν max 1600, 1510, 1470, 1430, 1390, 1340, 1240, 1130, 1010, 980 cm^{-1}; ^1H nmr, see Table 1; ^{13}C nmr, see Table 2; ms *m/z* M^+ 481 (482).

2-(3,4-Dibenzyloxyphenyl)-2-(3,4,5-trimethoxybenzyl)-1,3-dithiane [**6ex**].—By method 2, from 490 mg (1.2 mmol) of 3,4-dibenzyloxyphenyl dithiane **4e** and 313 mg (1.2 mmol) of trimethoxybenzyl bromide **5x**, 617 mg (87.5%) of **6ex** were obtained after chromatography; colorless oil; ir ν max 1610, 1520, 1490, 1440, 1390, 1345, 1150, 1010, 980 cm^{-1}; ^1H nmr, see Table 1; ^{13}C nmr, see Table 2; ms *m/z* M^+ 588.

METHOD 3: DEPROTECTION WITH HgO.—*1-(3,4,5-Trimethoxyphenyl)-4'-benzyloxy-3'-methoxyacetophenone* [**7cx**].—To a suspension of 174 mg of HgO in 15 ml of THF-H_2O (85:15), 200 mg of 1,3-dithiane **6cx** in 2 ml of THF and 1.2 equivalents of $BF_3{\cdot}Et_2O$ (0.1 ml) were successively added. The mixture was maintained 20 h at room temperature and after addition of CH_2Cl_2, solids were eliminated by filtration through a SiO_2 column and the reaction product was directly obtained by solvent elimination. By crystallization from CH_2Cl_2/hexane, 132 mg of **7cx** (80.2%) were obtained; mp 141–142°; ir ν max 1715, 1600, 1510, 1470, 1430, 1265, 1130 cm^{-1}; ^1H nmr, see Table 1; ^{13}C nmr, see Table 2; ms *m/z* M^+ 422; *anal.* calcd for $C_{25}H_{26}O_6$, C 71.07, H 6.20; found C 71.00, H 6.08.

1-(3,4,5-Trimethoxyphenyl)-3',4'-dimethoxyacetophenone [**7ax**].—By method 3, from 129 mg (0.30 mmol) of **6ax**, 53 mg of **7ax** (51.5%) were obtained by crystallization of the crude reaction product. White crystals (CH_2Cl_2/hexane), mp 161–162°; ir ν max 2840, 1670, 1600, 1510, 1470, 1420, 1260, 1140, 1030, 1010, 980 cm^{-1}; ^1H nmr, see Table 1; ^{13}C nmr, see Table 2; ms *m/z* M^+ 346; *anal.* calcd for $C_{19}H_{22}O_6$, C 65.88, H 6.40; found C 65.78, H 6.27.

1-(4-Benzyloxyphenyl)-3',4'-dimethoxyacetophenone [**7ay**].—By method 3, from 200 mg (0.44 mmol) of **6ay**, 145 mg of **7ay** (91.0%) were obtained by crystallization of the crude reaction product. White crystals (CH_2Cl_2/hexane); mp 132–134°; ir ν max 1680, 1605, 1590, 1510, 1470, 1420, 1270, 1140, 1030 cm^{-1}; ^1H nmr, see Table 1; ^{13}C nmr, see Table 2; ms *m/z* M^+ 362; *anal.* calcd for $C_{23}H_{22}O_4$, C 76.22, H 6.12; found C 76.30, H 6.00.

5-(4-Benzyloxyphenylacetyl)-1,3-benzodioxol [**7by**].—By method 3, from 366 mg (0.84 mmol) of **6by**, 280 mg of **7by** (96.0%) were obtained by crystallization of the crude reaction product. White crystals (CH_2Cl_2/hexane), mp 153–155°; ir ν max 1680, 1610, 1590, 1450, 1250, 1110, 1050, 940 cm^{-1}; ^1H nmr, see Table 1; ^{13}C nmr, see Table 2; ms *m/z* M^+ 346; *anal.* calcd for $C_{22}H_{18}O_4$, C 76.29, H 5.24; found C 76.08, H 5.18.

METHOD 4: DEBENZYLATION.—*1-(3,4,5-Trimethoxyphenyl)-4'-hydroxy-3'-methoxyacetophenone* [**8gx**].—To a solution of 88 mg of **7cx** in 10 ml of MeCN, 30 mg of NaI (1 equivalent) and 0.05 ml of $BF_3{\cdot}Et_2O$ (1 equivalent) were successively added. The mixture was maintained 20 h at room temperature; after addition of CH_2Cl_2, the solids were eliminated by filtration through a SiO_2 column and the reaction product was directly obtained by solvent elimination. By crystallization from CH_2Cl_2/hexane, 61 mg (87.5%) of **8gx** were obtained. Mp 118–120°; ir ν max 3540, 2820, 1675, 1600, 1510, 1470, 1430, 1130, 1030, 1010 cm^{-1}; ^1H nmr, see Table 1; ^{13}C nmr, see Table 2; ms *m/z* M^+ 332; *anal.* calcd for $C_{18}H_{20}O_6$, C 65.05, H 6.07; found C 65.15, H 6.02.

(4-Hydroxyphenyl)-3',4'-dimethoxyacetophenone [**8az**].—By method 4, from 27 mg (0.075 mmol) of **7ay**, 14 mg (70.0%) of **8az** were obtained by crystallization. White crystals (CH_2Cl_2/hexane), mp 156–158°; ir ν max 3600, 3350, 1670, 1600, 1510, 1470, 1420, 1260, 1150, 1020 cm^{-1}; ^1H nmr, see Table 1; ^{13}C nmr, see Table 2; ms *m/z* M^+ 272; *anal.* calcd for $C_{16}H_{16}O_4$, C 70.58, H 5.92; found C 70.29, H 5.78.

5-(4-Hydroxyphenylacetyl)-1,3-benzodioxol [**8bz**].—By method 4, from 58 mg (0.17 mmol) of **7by**, 39 mg (89.7%) of **8bz** were obtained by crystallization. White crystals (CH_2Cl_2/hexane), mp 171–172°; ir ν max 3510, 3350, 1680, 1620, 1510, 1490, 1450, 1240, 1190, 1040, 940 cm^{-1}; ^1H nmr, see Table 1; ^{13}C nmr, see Table 2; ms *m/z* M^+ 256; *anal.* calcd for $C_{15}H_{12}O_4$, C 70.31, H 4.72; found C 70.40, H 4.97.

METHOD 5: DESULFURIZATION.—*1-(4-Hydroxy-3-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethane* [**9gx**].—A mixture of 68 mg of 1,3-dithiane derivative **6cx** and an excess of Raney Ni (10 times weight) in Me_2CO (10 ml) was maintained at reflux for 35 min. The reagent was eliminated by filtration with EtOAc through a SiO_2 column. After solvent elimination, 34 mg of **9gx** (81.0%) were obtained by flash chromatography with *n*-hexane/EtOAc mixtures. Colorless oil; ir ν max 3560, 1600, 1510, 1475, 1420, 1220, 1140, 1050, 940 cm^{-1}; ^1H nmr, see Table 1; ^{13}C nmr, see Table 2; ms *m/z* M^+ 318.

1-(3,4-Dimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethane [**9ax**].—By method 5, 52 mg of **9ax** (82.0%) were obtained from 83 mg (0.19 mmol) of **6ax** by crystallization of the reaction product. White crystals (CH_2Cl_2/hexane), mp 78–80°; ir ν max 2840, 1600, 1515, 1470, 1425, 1240, 1130, 1040, 1010 cm^{-1}; ^1H nmr, see Table 1; ^{13}C nmr, see Table 2; ms *m/z* M^+ 332; *anal.* calcd for $C_{19}H_{24}O_5$, C 68.66, H 7.28, found C 68.50, H 7.10.

5-[2-(4-Hydroxyphenyl)ethyl]-1,3-benzodioxol [**9bz**].—By method 5, 90 mg of **9bz** (85.0%) were obtained from 190 mg (0.43 mmol) of **6by** by crystallization of the reaction product. White crystals (CH_2Cl_2/hexane), mp 92–95°; ir ν max 3600, 3350, 1620, 1600, 1510, 1490, 1450, 1250, 1100, 1050, 940 cm^{-1}; ^1H nmr, see Table 1; ^{13}C nmr, see Table 2; ms *m/z* M^+ 242; *anal.* calcd for $C_{15}H_{14}O_3$, C 74.36, H 5.82, found C 74.22, H 5.64.

1-(3,4-Dihydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethane [**9fx**, *Combretastatin B-3*].—By method 5, 134 mg of **9fx** (88.5%) were obtained from 294 mg (0.50 mmol) of **6ex** by crystallization of the reaction product. White crystals (CH_2Cl_2/hexane), mp 115–117°; spectroscopic properties identical to those described (24).

1-(3,4-Dimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethanol [**10ax**].—To 29 mg (0.08 mmol) of **7ax** in 2 ml of MeOH, $NaBH_4$ in excess was added. The mixture was stirred for 60 min at room temperature under N_2; after neutralization and CH_2Cl_2 extraction, 24 mg (86.0%) of **10ax** were directly obtained as a white crystalline product. Mp 92–96° (from CH_2Cl_2/hexane). Ir ν max 3600, 1600, 1510, 1470, 1420, 1340, 1260, 1030, 1010, 980 cm^{-1}; ^1H nmr, see Table 1; ^{13}C nmr, see Table 2; ms *m/z* M^+ 348; *anal.* calcd for $C_{19}H_{24}O_6$, C 65.5, H 6.94, found C 65.72, H 7.01.

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