1,3-dioxole (10b) [(0.21 g, 70%) $[\alpha]^{25}_D$ +17° (*c* 0.73, $CHCl_3$); IR 3060, 3040, 2980, 2940, 1710, 1500, 1460, 1380, 1370, 1050, 1030, 880, 740, 700; ^1H NMR δ 1.34 (3 H, s, CH_3), 1.64 (3 H, s, CH_3), 2.14 (3 H, s, CH_3), 2.93 (1 H, dd, *J* = 16.8 and 7.05 Hz, $COCH_2$), 3.06 (1 H, dd, *J* = 16.8 and 6.6, $COCH_2$), 4.03 (1 H, dd, *J* = 7.1 and 5.1 Hz, H-6), 4.53 (1 H, d, *J* = 12 Hz, CH_2Ph), 4.59 (1 H, dd, *J* = 5.1 and 4.0 Hz, H-6a), 4.67 (1 H, q, *J* = 6.7 Hz, H-5), 4.68 (1 H, d, *J* = 12 Hz, CH_2Ph), 5.68 (1 H, d, *J* = 4 Hz, H-3a), 7.34 (5 H, s, Ar-H); ^{13}C NMR δ 26.1, 26.8, 31.0, 44.5, 72.6, 76.5, 77.1, 78.8, 104.8, 113.5, 127.9, 128.0, 128.5, 137.5, 206.9; MS *m/e* (relative intensity) 291 ($M^+ - CH_3$, 2), 248 (1), 230 (1), 190 (3), 169 (5), 147 (4), 142 (9), 141 (9), 105 (6), 99 (6), 92 (15), 91 (100), 65 (8), 59 (5), 43 (41)] and **[3a*R*(3aα,5β,6α,6aα)]-tetrahydro-2,2-dimethyl-5-(2-oxoprop-1-yl)-6-(phenylmethoxy)furo[2,3-*d*]-1,3-dioxole (9b)** (0.05 g, 90% pure on the basis of GC): IR 3060, 3040, 2980, 1710, 1500, 1460, 1380, 1370, 1050, 1030, 880, 740, 700; ^1H NMR δ 1.35 (3 H, s, CH_3), 1.61 (3 H, s, CH_3), 2.17 (3 H, s, CH_3), 2.50 (1 H, dd, *J* = 15.2 and 8.0 Hz, $COCH_2$), 2.72 (1 H, dd, *J* = 15.2 and 4.0 Hz, $COCH_2$), 3.53 (1 H, dd, *J* = 9.0 and 4.2 Hz, H-6), 4.41 (1 H, ddd, *J* = 9.0, 8.0, and 4.0 Hz, H-5), 4.53 (1 H, d, *J* = 11.8, CH_2Ph), 4.54 (1 H, dd, *J* = 4.2 and 3.7 Hz, H-6a), 4.78 (1 H, d, *J* = 11.8 Hz, CH_2Ph), 5.71 (1 H, d, *J* = 3.7, H-3a), 7.35 (5 H, s, Ar-H); ^{13}C NMR δ 26.6, 26.8, 31.3, 45.9, 72.5, 74.6, 77.2, 81.4, 104.4, 112.8, 128.4, 128.5, 128.9, 137.7, 206.5.

Correlation of Products 7a and 9a to Known Compounds. Acidic hydrolysis of a sample of **7a** containing 10% of **7b** (0.75 g, 2.6 mmol) was carried out in THF (10 mL) with 2 N HCl (10 mL) at 60 °C for 4 h. After cooling to 20 °C, neutralization with 10% $NaHCO_3$ and extraction with ethyl acetate gave 0.63 g of crude product, which was dissolved in EtOH (10 mL), cooled at 0 °C, and treated with 0.1 g (2.76 mmol) of $NaBH_4$. The reaction mixture was stirred at 20 °C for 2 h and then decomposed with brine (2 mL). Ethanol was evaporated under vacuum, and oil obtained was extracted with EtOAc (4 × 15 mL). The organic layer was washed with brine, dried over Na_2SO_4, and chromatographed (cyclohexane–ethyl acetate, 25:75) to give 0.58 g (89%) of **(2*S*,3*S*,4*R*)-3-(phenylmethoxy)-6-heptene-1,2,4-triol (11)** (containing 6% of its 4*S* epimer): IR 3450, 1640, 1090, 1080, 1020, 750, 700; ^1H NMR δ 2.35 (2 H, t, *J* = 7 Hz, H-5), 3.15 (2 H, br s, OH), 3.47 (1 H, dd, *J* = 2 and 4.8 Hz, H-3), 3.6–4.0 (4 H, m, H-1, H-2 and H-4), 4.66 (2 H, s, CH_2Ph), 4.9–5.3 (2 H, m, H-7), 5.4–6.2 (1 H, m, H-6), 7.33 (5 H, s, Ar-H); ^{13}C NMR δ 38.8, 62.5, 70.1, 71.1, 74.6, 80.3, 118.0, 128.2, 128.6, 134.5, 137.7; MS *m/e* (relative intensity) 203 ($M^+ - H_2O$ and $-CH_2OH$, 2.5), 164 (15), 146 (3), 133 (3), 118 (3), 107 (7), 92 (20), 91 (100), 65 (7).

The triol **11** (0.3 g, 1.2 mmol) dissolved in dry acetone (10 mL) was stirred at 20 °C in the presence of pyridinium *p*-toluenesulfonate (10% mol), for 5 h. Water (3 mL) was added, acetone was evaporated, and the aqueous layer was extracted with ethyl acetate. The residue, after solvent evaporation, was dissolved in CH_2Cl_2 (10 mL), treated with pyridine (0.12 mL, 1.6 mmol) and benzoyl chloride (0.14 mL, 1.2 mmol) at room temperature, and stirred overnight. The reaction was decomposed with 10% $NaHCO_3$ and extracted with ether. The ether layer was washed quickly with cold 0.5 N HCl (three times), and then with water, 10% $NaHCO_3$, and brine. Column chromatography (cyclohexane–ethyl acetate, 96:4) gave 0.26 g (80%) of pure **(4*S*)-4-[(1*S*,2*R*)-1-(phenylmethoxy)-2-(benzoyloxy)-4-penten-1-yl]-2,2-dimethyl-1,3-dioxole (13)**, which was identical on the basis of optical rotation and ^1H NMR with the product reported by Williams et al.[13] The same synthetic sequence was repeated starting from pure **9a** to get first **(2*S*,3*R*,4*R*)-3-(phenylmethoxy)-6-heptene-1,2,4-triol (14)** as a solid: mp 54–56 °C; $[\alpha]^{25}_D$ +5.5° (*c* 0.95, $CHCl_3$); IR (Nujol) 3440, 3340, 1640, 1090, 1080, 1025, 755, 705; ^1H NMR (after D_2O exchange) δ 2.15–2.35 (1 H, m, H-5), 2.45–2.65 (1 H, m, H-5), 3.4 (1 H, t, *J* = 6 Hz, H-3), 3.6–4.0 (4 H, m, H-1, H-2, and H-4), 4.6 (1 H, d, *J* = 12 Hz, CH_2Ph), 4.65 (1 H, d, *J* = 12 Hz, CH_2Ph), 5.05–5.25 (2 H, m, H-7), 5.7–6.0 (1 H, m, H-6), 7.35 (5 H, s, Ar-H); ^{13}C NMR δ 38.0, 63.3, 71.5, 72.6, 74.0, 81.7, 118.6, 128.0, 128.4, 128.6, 134.5, 137.8; MS *m/e* (relative intensity) 203 ($M^+ - H_2O$ and $-CH_2OH$, 2.5), 164 (15), 146 (3), 133 (3), 118 (3), 107 (7), 92 (20), 91 (100), 65 (7). The triol **14** was subjected to the previously described acetonation and benzoylation reaction to afford **(4*S*)-4-[(1*R*,2*R*)-1-(phenylmethoxy)-2-(benzoyloxy)-4-penten-1-yl]-2,2-dimethyl-1,3-dioxole (16)** identical with the product described by Williams.[13]

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Registry No. **1**, 23558-05-6; **2**, 63593-02-2; **3**, 39682-04-7; **4**, 120417-90-5; 5α-**5**, 120417-91-6; 5β-**5**, 120520-93-6; **6**, 120520-94-7; **7a**, 89755-56-6; **7b**, 120417-93-8; **7c**, 120417-95-0; **8a**, 120417-92-7; **8b**, 120417-94-9; **9a**, 120417-96-1; **9b**, 120418-00-0; **9c**, 120417-98-3; **10a**, 120417-97-2; **10b**, 120418-01-1; **10c**, 120417-99-4; **11**, 120520-95-8; **13**, 111555-40-9; **14**, 120418-02-2; **16**, 111611-84-8; $H_2C{=}CHCH_2SiMe_3$, 762-72-1; $H_2C{=}C(CH_3)OSiMe_3$, 1833-53-0; $H_2C{=}C(Ph)OSiMe_3$, 13735-81-4; D-glucose, 50-99-7; (*R*,*R*)-tartaric dialdehyde, 66213-22-7; *meso*-tartaric dialdehyde, 58066-70-9.

Isolation, Structure, and Synthesis of Combretastatin C-1[1]

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A new cell growth inhibitory (PS ED_{50} 2.2 μg/mL) phenanthraquinone designated combretastatin C-1 (**2**) has been isolated from the African tree *Combretum caffrum*. The structure (**2**) assigned combretastatin C-1 was based on high-resolution mass and NMR spectral analyses and confirmed by total syntheses. Synthetic routes **5b** → **6b** → **2** and especially **5c** → **6c** → **2** proved to be quite practical.

The Cape bush willow *Combretum caffrum* (Eckl. and Zeyh.) Kuntz (Combretaceae) is a deciduous African tree found principally in the Eastern Cape and Transki (to Natal). In autumn, these trees become quite prominent with displays of reddish-brown fruit and leaves that turn bright red prior to falling.[2] Previously, we summarized[3a] the significance of this plant to the Zulu, application of closely related species in primitive medicine, and isolation of a series of cell growth inhibitory *cis*-stilbenes,[3a,b] bibenzyls,[3c] phenanthrenes,[3d] and dihydrophenanthrenes.[3d]

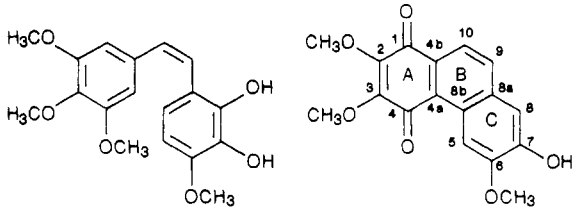
(1) Antineoplastic Agents series contribution 166. For part 165 refer to *Can. J. Chem.*, in press.

(2) Palmer, E.; Pitman, N. In *Trees of Southern Africa*; A. A. Balkema: Cape Town, 1972; Vol. 3.

(3) (a) Pettit, G. R.; Singh, S. B.; Niven, M. L.; Hamel, E.; Schmidt, J. M. *J. Nat. Prod.* **1987**, 50, 119. (b) Pettit, G. R.; Singh, S. B. *Can. J. Chem.* **1987**, 65, 2390. (c) Pettit, G. R.; Singh, S. B.; Niven, M. L.; Hamel, E.; Lin, C. M.; Schmidt, J. M. *J. Nat. Prod.* **1988**, *51*, 517. (d) Pettit, G. R.; Singh, S. B.; Niven, M. L.; Schmidt, J. M. *Can. J. Chem.* **1988**, *66*, 406. (e) Pettit, G. R.; Singh, S. B.; Hamel, E.; Lin, C. M.; Schmidt, J. M.; Alberts, D. S. *Experientia* **1989**, *45*, 209.

0022-3263/89/1954-4105$01.50/0

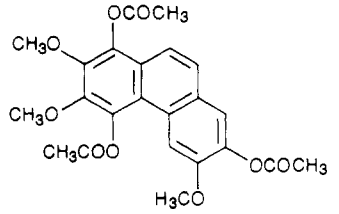
Among the *cis*-stilbenes combretastatin A-1 (**1**)[3a] and its 2-desoxy derivative combretastatin A-4[3e] were found to be powerful inhibitors of tubulin[4] polymerization. Further study of *C. caffrum* constituents active against the P388 lymphocytic leukemia (PS system) has now led to the isolation and characterization of another PS cell growth inhibitory (ED_{50} = 2.2 μg/mL) substance named combretastatin C-1 (**2**).



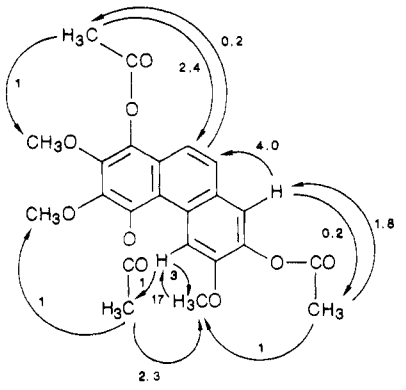
1

2

combretastatin C-1



3



4

C-1 triacetate with % NOE

A methylene chloride–methanol extract of the stem wood (77 kg dry weight) was employed as previously summarized[3] to prepare a PS active methylene chloride fraction that was separated by a series of solvent partitioning, size exclusion (Sephadex LH-20), and partition chromatographic steps to afford combretastatin C-1 (**2**, NSC 381091) as an orange powder. The structure of this interesting quinone was elucidated and confirmed by total syntheses as summarized in the sequel.

Mass spectral (by HREIMS) analysis of combretastatin C-1 (**2**) revealed a molecular formula $C_{17}H_{16}O_5$. The results of UV/vis (432 nm) and infrared (1642 and 1636 cm^{-1}) spectral analysis combined with the orange appearance suggested a quinone. The presence of a phenolic group (IR, ν_{max} 3280 cm^{-1}) ortho to a methoxyl group was suggested by the base-induced bathochromic shift of 432–486 nm in the UV/vis spectrum. The 400-MHz ^1H NMR spectrum (Table I) of C-1 (**2**) exhibited three methoxyl group resonances (δ 4.104, 4.114 and 4.144), two ortho coupled aromatic protons (δ 7.925 and 8.036, J = 8.4 Hz) and two noncoupled aromatic protons at 7.257 and 9.069 ppm. The latter signal appeared to correspond to an unsubstituted C-4 or C-5 position in a phenanthrene nucleus.[3d] Another broad proton singlet was found at δ 6.173 and disappeared on deuterium exchange, again suggesting a phenolic group. The ^{13}C NMR spectrum of combretastatin C-1 revealed two conjugated carbonyls, four oxygenated aromatic carbons, four aromatic methine carbons, four quaternary aromatic carbons, and three methoxyl carbons. Two of the methoxyl groups appeared at δ 61.35 and 61.44, and indicated an ortho relationship.[3d]

Reductive acetylation (zinc–acetic acid) of combretastatin C-1 produced a colorless triacetate (**3**). The 400-MHz ^1H NMR spectrum (Table I) of acetate **3** displayed three acetoxy methyl signals (δ 2.385, 2.504, and 2.541). Aromatic ring induced shielding was observed in most of the spectrum. The ^{13}C NMR spectrum (Table II) of the triacetate was devoid of quinone carbonyl signals and instead showed two additional oxygenated quaternary carbons. The remaining carbon spectrum of triacetate **3** was consistent with the acetylation-induced shifts.

Resolution of the C-1 and C-7 ^{13}C signals was noted when a mixture of C_6D_6 and $CDCl_3$ was used as solvent. The remaining signals did not exhibit any noticeable positional change. On the basis of results, a partial structure for combretastatin C-1 was assigned that still

Table I. 400-MHz ^1H NMR Spectra of Combretastatin C-1 (2) and Leucotriacetate (3), Assignments Relative to Tetramethylsilane[a]

		3	
position no.	2* [b] $CDCl_3$	$CDCl_3$	$CDCl_3$ + C_6D_6 (1:1)
5	9.069	8.672	8.654
8	7.257	7.528	7.382
9	7.925	7.560	7.417
10	8.036[d,8.4]	7.616[d,8.96]	7.604[d,9.3]
2-OCH_3	4.104[c]	3.988	3.826
3-OCH_3	4.114[c]	3.993	3.826
6-OCH_3	4.144[c]	4.022	3.694
1-CH_3COO	–	2.504	2.156
4-CH_3COO	–	2.541	2.167
7-CH_3COO	–	2.385	2.118

[a] Signals are singlets unless otherwise stated. [b] 2* 6.173 (1 H, OH). [c] Assignment may be interchanged.

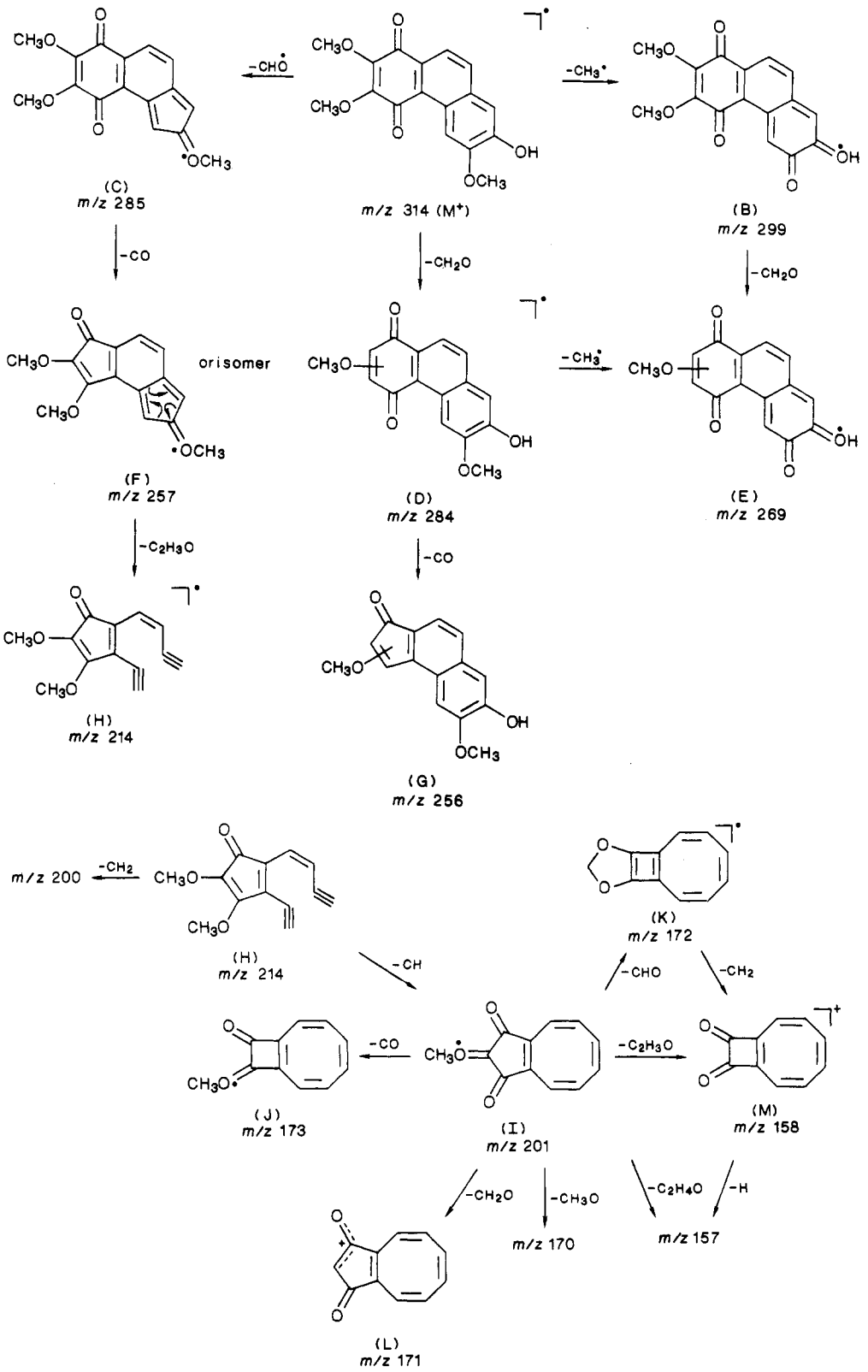
Table II. ^{13}C NMR (100-MHz) Spectra (Assignment Based on ^1H, ^{13}C COSY) of Combretastatin C-1 (2) and Triacetate (3) Relative to Tetramethylsilane[a]

		3	
carbon	2 $CDCl_3$	$CDCl_3$	$CDCl_3$ + C_6D_6
1	185.20[a]	139.90[a]	139.95[a]
2	144.96	144.62[b]	144.68[b]
3	144.96	143.92[b]	143.98[b]
4	182.91[a]	137.52[a]	137.57[a]
5	105.86	108.50	108.50
6	150.92	150.44	150.44
7	147.76	139.90[a]	140.01[a]
8	109.95	117.62	117.62
9	120.83	121.66	121.62
10	132.98	127.05	127.05
4a	124.46	119.83	119.83
4b	129.67[b]	123.55[c]	123.55[c]
8a	134.40[b]	127.62[c]	127.62[c]
8b	126.02[b]	127.73[c]	127.73[c]
2-OCH_3	61.39[c]	60.97[d]	61.13[d]
3-OCH_3	61.44[c]	61.13[d]	61.97[d]
6-OCH_3	56.25	55.99	55.99

[a] Acetate signals in 3-CH_3COO ($CDCl_3$), 168.95, 168.76, 168.22, 21.14, 20.75, 20.62: 3 ($CDCl_3$ + C_6D_6) 168.80, 168.64, 168.10, 20.97, 20.61, 20.44. Chemical shifts with the same superscript letters in the same columns may be reversed.

(4) (a) Manser, E. J.; Bayley, P. M. *Biochem. J.* **1987**, *241*, 105. (b) Rava, R. P.; Hastie, S. B.; Myslik, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 2202. (c) Spann, U.; Renner, W.; Mandelkow, E.-M.; Bordas, J.; Mandelkow, E. *Biochemistry* **1987**, *26*, 1123.

Scheme I. HREI-Mass Spectral Fragmentation of Combretastatin C-1 (See Also Table III)

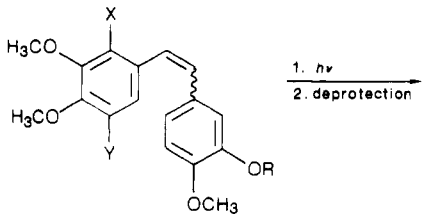


required placement of one methoxyl group either at C-6 or C-7. The exact substitution pattern was established by application of nuclear Overhauser effect difference spectroscopy (NOEDS) techniques to triacetate **3** (in C_6D_6 + $CDCl_3$). Results of the NOE experiments have been entered on structure **4**. The structure (**2**) assigned to combretastatin C-1 received further support by an analysis of the mass spectral fragmentation. The HREIMS interpretations have been summarized in Scheme I and Table III. The structural assignment of combretastatin C-1 (**2**) was unequivocally confirmed by total synthesis.

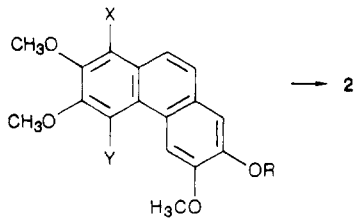
Highly oxygenated phenanthrenes can be conveniently synthesized by employing photochemical cyclization[5] of the corresponding stilbene, and we therefore employed this general approach to combretastatin C-1. However, it be-

(5) Stoessl, A.; Rock, G. L.; Fisch, M. H. *Chem. Ind.* **1974**, 703.

came necessary to devise three different routes of this type (**5** → **6**) to effectively reach quinone **2**. The first procedure involved cyclization of stilbene **5a** → **6a** and mild oxidation to quinone **2**. The second (**5b** → **6b**) and third (**5c** → **6c**) routes were expected to yield quinone **2** following cyclization and selective oxidation. The stilbenes were prepared via Wittig reactions.[3a,5]

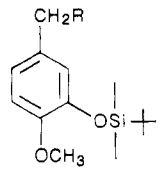


5a: X = Y = OR
b: X = H; Y = OR
c: X = OR; Y = H

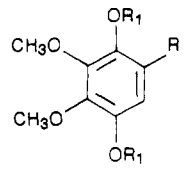


6a: X = Y = OH
b: X = H; Y = OH
c: X = OH; Y = H

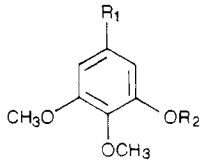
The common C-ring precursor of C-1 phosphonium bromide **7a** was readily prepared from benzyl alcohol **7b**.[6] The aldehyde (**8a**) required for the Wittig coupling reaction was synthesized from 3-hydroxy-4,5-dimethoxybenzoic acid as follows. Disilylation and lithium aluminum hydride reduction led to benzyl alcohol **9a**. Cleavage of the silyl protecting groups with tetrabutylammonium fluoride gave benzyl alcohol **9b** in 75% yield. Oxidation of the alcohol (**9b**) with potassium nitrosodisulfonate (Fremy's salt)[7] afforded *p*-benzoquinone **10a** in 80% yield. Repeated attempts to reduce quinone **10a** to the corresponding hydroquinone followed by selective protection were unsuccessful, and consequently this approach was modified.

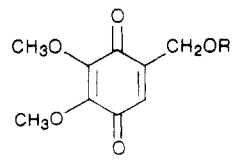


7a: R = $^{+}$PPh3^{-}Br
b: R = OH
c: R = Br



8a: R = CHO; R_1 = $CH_2C_6H_5$
b: R = $CH_2OSi(CH_3)_2C(CH_3)_3$; R_1 = $CH_2C_6H_5$
c: R = CH_2OH; R_1 = $CH_2C_6H_5$

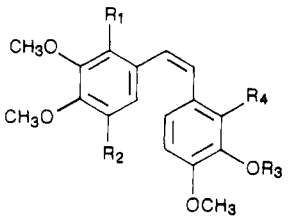




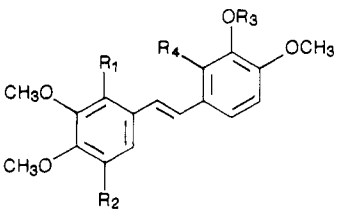
9a: R_1 = CH_2OH; R_2 = $Si(CH_3)_2C(CH_3)_3$
b: R_1 = CH_2OH; R_2 = H
c: R_1 = CHO; R_2 = $Si(CH_3)_2C(CH_3)_3$
d: R_1 = $CH_2{}^{+}PPh_2{}^{-}Br$; R_2 = $Si(CH_3)_2C(CH_3)_3$

10a: R = H
b: R = $Si(CH_3)_2C(CH_3)_3$

Alcohol **10a** was silylated[6] with *tert*-butyldimethylsilyl chloride to afford benzyl silyl ether **10b**. Sodium borohydride reduction of quinone **10b** and addition of benzyl bromide in ethanol afforded benzyl ether **8b** (50% recovery). Desilylation gave alcohol **8c** (99.5% yield), which was oxidized with pyridinium chlorochromate (PCC) to give benzaldehyde **8a** in 93.3% yield. The ylid from phosphonium bromide **7a** (using butyllithium) on reaction with benzaldehyde **8a** yielded (96%) a mixture (*Z*/*E* ratio of 1:2) of stilbenes **11a** and **12a**. Attempts at photochemical cyclization of the stilbene geometrical isomers failed to produce phenanthrene **13a**. Whether the cyclization failure was due to the benzyl protecting group or to the electron density in the highly substituted ring was not ascertained. But it has been reported[8] that a methoxy group at C-2 can be cleaved during photochemical cyclization of stilbenes to phenanthrenes.



11



12

a: R_1 = R_2 = $OCH_2C_6H_5$; R_3 = $Si(CH_3)_2C(CH_3)_3$; R_4 = H
b: R_1 = H; R_2 = $OSi(CH_3)_2C(CH_3)_3$; R_3 = $CH_2C_6H_5$; R_4 = H
c: R_1 = H; R_2 = OH; R_3 = $CH_2C_6H_5$; R_4 = H
d: R_1 = H; R_2 = $OSi(CH_3)_2C(CH_3)_3$; R_3 = $Si(CH_3)_2C(CH_3)_3$; R_4 = H
e: R_1 = $OSi(CH_3)_2C(CH_3)_3$; R_2 = H; R_3 = $Si(CH_3)_2C(CH_3)_3$; R_4 = H
f: R_1 = H; R_2 = R_3 = R_4 = $OSi(CH_3)_2C(CH_3)_3$

Attention was next directed to the **5b** → **6b** and **5c** → **6c** routes. Aldehyde **9c** was prepared by PCC oxidation of benzyl alcohol **9a**. Reaction with the ylid generated from [3-(benzyloxy)-4-methoxybenzyl]phosphonium bromide[4] led to a mixture (3:2 *Z*/*E*) of stilbenes **11b** and **12b** in 71% yield. Desilylation with fluoride ion gave phenols **11c** and **12c**. Attempted oxidation of phenols **11c** and **12c** to the corresponding *p*-quinones with Fremy's salt was unsuccessful primarily due to the sparingly soluble nature of these compounds in aqueous systems. The problem was circumvented by postponing the oxidation step to the phenanthrene stage. The phosphorane prepared from phosphonium bromide **7a** was condensed with aldehyde **9c** to afford a mixture (1:1) of stilbenes **11d** and **12d** in 86% yield. Irradiation of the *Z*/*E* stilbene mixture in the presence of iodine afforded the anticipated structural isomers (2:1:0.16, respectively) phenanthrenes **13c**, **13d**, and **13e** in 62.5% total yield. The lower yield of phenanthrene **13d** was expected due to steric compression around the silyl group at C-4. Both phenanthrenes **13d** and **13c** were desilylated to phenols **13b** and **13f** in excellent yield. Structures were assigned by application of 400-MHz NOEDS methods. Oxidation of phenol **13b** with slightly more than a 2 molar excess of Fremy's radical[9] at pH 7 gave quinone **2** in 62% yield. The quonine was found to be identical with natural combretastatin C-1.

Although the preceding synthesis confirmed the structure of combretastatin C-1, difficulties encountered in the purification of silyl ether **13d** and the relatively low overall

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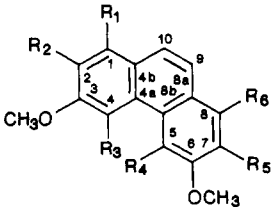
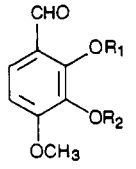
(8) Giles, R. G. F.; Sargent, M. V. *J. Chem. Soc., Chem. Commun.* **1974**, 215; *J. Chem. Soc., Perkin Trans. 1* **1974**, 2447.

(9) Flitsch, W.; Rubkamp, P. *Justus Liebigs Ann. Chem.* **1985**, 1422. Cannon, J. R.; Lojanapiwanta, V.; Raston, C. L.; Sinchai, W.; White, A. H. *Aust. J. Chem.* **1980**, *33*, 1073. Irradiation of the singlet at δ 7.800 (H-5) gave 7.8% enhancement of the singlet at δ 7.7532 (H-4) whereas a 7% enhancement was observed at the former singlet when the latter singlet was irradiated. Interestingly, with a 4- or 5-substituted phenanthrene, the proton chemical shift of the unsubstituted position (4 or 5) appears appreciably downfield (δ 9.0 ppm). When both positions are unsubstituted, the chemical shifts move (relatively) upfield.[8]



13a: $R_1 = R_3 = OCH_2C_6H_5$; $R_2 = OCH_3$; $R_4 = R_6 = H$; $R_5 = OSi(CH_3)_2C(CH_3)_3$
b: $R_1 = R_4 = H$; $R_2 = OCH_3$; $R_3 = R_5 = OH$; $R_6 = H$
c: $R_1 = R_4 = H$; $R_2 = R_5 = OSi(CH_3)_2C(CH_3)_3$; $R_3 = OCH_3$; $R_6 = H$
d: $R_1 = R_4 = H$; $R_2 = OCH_3$; $R_3 = R_5 = OSi(CH_3)_2C(CH_3)_3$; $R_6 = H$
e: $R_1 = R_5 = H$; $R_2 = R_4 = OSi(CH_3)_2C(CH_3)_3$; $R_3 = OCH_3$; $R_6 = H$
f: $R_1 = R_4 = H$; $R_2 = R_6 = OH$; $R_3 = OCH_3$; $R_6 = H$
g: $R_1 = R_5 = OSi(CH_3)_2C(CH_3)_3$; $R_2 = OCH_3$; $R_3 = R_4 = R_6 = H$
h: $R_1 = R_4 = OSi(CH_3)_2C(CH_3)_3$; $R_2 = OCH_3$; $R_3 = R_5 = R_6 = H$
i: $R_1 = R_5 = OH$; $R_2 = OCH_3$; $R_3 = R_4 = R_6 = H$
j: $R_1 = H$; $R_2 = OSi(CH_3)_2C(CH_3)_3$; $R_3 = OCH_3$; $R_4 = H$; $R_5 = R_6 = OSi(CH_3)_2C(CH_3)_3$
k: $R_1 = H$; $R_2 = OCH_3$; $R_3 = R_5 = R_6 = OSi(CH_3)_2C(CH_3)_3$; $R_4 = H$

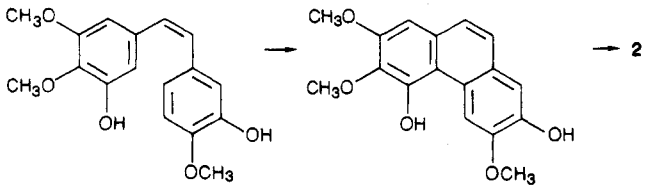


14a: $R_1 = Si(CH_3)_2C(CH_3)_3$; $R_2 = CH_3$
b: $R_1 = R_2 = CH_3$
c: $R_1 = R_2 = H$
d: $R_1 = H$; $R_2 = CH_3$
e: $R_1 = CH_3$; $R_2 = H$
f: $R_1 = R_2 = Si(CH_3)_2C(CH_3)_3$

yield required development of an improved synthesis. As such, the first synthesis was modified so that phenanthrene **13g** would be the major product of photochemical cyclization. The starting aldehyde **14a** was prepared by selective demethylation (90%+ yields) of methyl ether **14b** with 1 equiv of aluminum chloride (in benzene) followed by silylation of phenol **14d** or by selective methylation of phenol **14c** with diazomethane in anhydrous ether–tetrahydrofuran (devoid of protic solvents to prevent intermolecular H-bonding) to yield phenol **14d** followed by silylation. The aluminum chloride method[10] has been known for over 50 years using either ethyl ether or toluene as solvent. Here the yield was greatly increased by substituting benzene.[11] Aldehyde **14a** was allowed to react with the ylide generated from bromide **7a** to give (98%) stilbenes **11e** and **12e** (Z/E ratio of 1:2.5). Photochemical cyclization of the stilbenes (**11e** and **12e**) in benzene–hexane (2:1) containing iodine led to a 2.5:1 mixture of phenanthrenes **13g** and **13h**, respectively, in 68% total yield. The phenanthrenes were separated on silica gel, and isomer **13g** was easily obtained in a 49% overall yield. Desilylation of phenanthrene **13g** with tetrabutylammonium fluoride gave phenol **13i**, which upon Fremy's salt oxidation[9] yielded quinone **2** (54.5% yield) identical with natural combretastatin C-1.

Phenanthrenes **13j** and **13k** were also prepared (ratio 2.5:1) as part of this study. Comparison of all the photochemical cyclizations suggests that the failure encountered with attempted cyclization of stilbenes **11a** and **12a** is probably due to substituent effects rather than steric crowding as cleavage of the benzyl group was also observed.

Biogenetically, combretastatin C-1 can be considered a biosynthetic product of combretastatin A-3 (**15**), i.e. cyclization to 4,7-dihydroxy-2,3,6-trimethoxyphenanthrene followed by selective enzymatic oxidation to 1,4-quinone **2**. As we previously reported[3b] combretastatin A-3 (**15**) occurs with quinone **2** in *Combretum caffrum* while 4,7-dihydroxy-2,3,6-trimethoxyphenanthrene has been isolated from *Combretum molle*.[13] The latter substance may also be a precursor of 7-hydroxy-2,3,4,6-tetramethoxyphenanthrene isolated from *C. caffrum*.[3d]



15
combretastatin A-3

A small number of naturally occurring cell growth inhibitory and/or antineoplastic stilbenes (such as the *cis*-combretastatins[3] and the *trans*-piceatannol[14]) as well as related cytotoxic dihydrophenanthrenes[3] include the orchid phytoalexins[15] such as orchinol[16] are now known. However, phenanthraquinones have rarely been encountered as biosynthetic products.[17] Illustrative here is the red dermatogenic quinone cypridedin.[18] Further biological evaluation of quinone **2** is under way.

Experimental Section

Each of the synthetic intermediates were used as received from Sigma, Aldrich, or Lancaster Synthesis. All chromatographic solvents were redistilled. Sephadex LH-20 (particle size 25–100 μm) was obtained from Pharmacia Fine Chemicals AB (Uppsala, Sweden) and silica gel 60 (70–230 mesh) from E. Merck (Darmstadt, Germany). Altech, Inc. (Newark, DE) silica gel GHLF U plates (0.25 mm layer thickness) were employed for thin- and preparative-layer chromatograms (TLC and PLC) and developed with an anisaldehyde–acetic acid or ceric sulfate–sulfuric acid spray reagent (heated at approximately 150 °C for 5–10 min) and/or by use of ultraviolet light. In each of the synthetic procedures, solvent extracts of aqueous solutions were dried over anhydrous sodium sulfate. Ether refers to diethyl ether and THF to tetrahydrofuran. Unless otherwise noted each pure specimen was colorless.

Melting points are uncorrected and were determined with a Kofler-type hot-stage apparatus. Ultraviolet spectra were obtained using a Hewlett-Packard Model 8540A UV/vis spectrophotometer. Infrared spectra were measured with a Nicolet FT-IR Model MX-1 unit, and nuclear magnetic resonance spectra were obtained with a Bruker AM-400 instrument (deuteriochloroform as solvent and tetramethylsilane as internal standard with chemical shifts recorded using the δ scale). The SFORD technique was used for determining multiplicities in ^{13}C NMR spectra. The mass spectral measurements were performed with a MS-50 instrument at the NSF Regional Facility, University of Nebraska, Lincoln, NE.

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(12) The structure of phenanthrene **13g** was confirmed by NOEDS.

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Elemental microanalyses were determined at MicAnal, Tucson, AZ.

Isolation of Combretastatin C-1 (2). The methylene chloride fraction from a methylene chloride–methanol (1:1) extract of *Combretum caffrum* stem wood (77 kg) was partitioned between hexane and methanol–water (9:1).[3] The methanol–water (9:1) was adjusted to 3:2 and extracted with methylene chloride, and the chlorocarbon extract was separated[3,5] by size-exclusion chromatography on Sephadex LH-20, as previously summarized, to provide fractions A and B.[3,5] Fraction A (28.6 g) was further separated by partition chromatography using hexane–toluene–methanol (3:1:1) on a column of Sephadex LH-20 (2.5 kg) to afford an active fraction (1.97 g, PS ED_{50} 1.8×10^{-2} μg/mL). After redissolution in 3:1:1 hexane–toluene–methanol (20 mL), the solution was filtered and the solvent was removed. The residue was collected, washed with the same solvent, and crystallized from acetone–hexane to furnish combretastatin C-1 as an orange powder (11 mg, (1×10^{-7}) % yield): mp 215–7 °C; UV/vis (CH_3OH) λ_{max} 252 (ε 21 349), 291 (8750), 302 (8868), 338 (4658), 432 (3946); UV/vis (CH_3OH + CH_3ONa) λ_{max} 262 (21 810), 331 (6356), 486 (3590); IR ν_{max} (NaCl) 3280, 1642, 1636, 1625, 1487, 1286, 1281, 1212, 1201, 1173, 1061 cm^{-1}; ^1H NMR, ^{13}C NMR, and HREIMS (see Tables I, II, and III, respectively).

Reductive Acetylation of Combretastatin C-1. Combretastatin C-1 (**2**, 71 mg) was heated at reflux for 24 h with a mixture of acetic acid (3 mL), zinc (20 mg), and sodium acetate (20 mg). The reaction mixture was cooled, water (1 mL) was added, the solution filtered, and the solvent was evaporated at reduced pressure. **Combretastatin C-1 leucotriacetate (3)** was purified by PLC (1:1 hexane–ethyl acetate) and obtained as a homogeneous gum: IR ν_{max} (NaCl) 1773, 1474, 1404, 1370, 1264, 1195, 1172, 1117, 1060, 1021 cm^{-1}; ^1H NMR and ^{13}C NMR (see Tables I and II); HREIMS (*m/z*) 442.1262 (M^+, 23, calcd for $C_{23}H_{22}O_9$ 442.1264), 400.1158 ($M^+ - CH_2CO$, 28, calcd for $C_{21}H_{20}O_8$ 400.1158), 358.1058 ($M^+ - 2CH_2CO$, 100, calcd for $C_{19}H_{18}O_7$ 358.1053), 316.0953 ($M^+ - 3CH_2CO$, 96, calcd for $C_{17}H_{16}O_6$ 316.0947), 301.0706 ($M^+ - 3CH_2CO - CH_3$, 39, calcd for $C_{16}H_{13}O_6$ 301.0712), 229.0506 (9, calcd for $C_{13}H_9O_4$ 229.0501), 201.0549 (12, calcd for $C_{12}H_9O_3$ 201.0552), 172.0538 (6, calcd for $C_{11}H_8O_2$ 172.0524).

[3-[(*tert*-Butyldimethylsilyl)oxy]-4-methoxybenzyl]triphenylphosphonium Bromide (7a). To a cooled solution (0 °C) of benzyl alcohol **7b**[8] (5.36 g, 20 mmol) in methylene chloride (75 mL) was added (dropwise) a solution of phosphorous tribromide (1.81 mL, 10 mmol) in the same solvent (25 mL). The mixture was stirred at 0 °C for 10 min, and then the solution was washed with a saturated solution of sodium bicarbonate and water and dried to give benzyl bromide **7c** (6.0 g) as an oil. To a solution of the bromide in anhydrous toluene (70 mL) was added triphenylphosphine (4.74 g, 18.12 mmol) in toluene. The mixture was stirred for 10 min and heated at reflux for 2 h. After 50 mL of toluene was removed, heating was discontinued and the mixture was slowly allowed to return to room temperature. The resulting precipitate was stirred for 24 h, collected by filtration, and dried at 110 °C (overnight), to yield phosphonium salt **7a** as a colorless powder (9.1 g, 77% based on alcohol **7b**): recrystallization from ethanol–ether gave a pure sample: mp 209–14 °C; IR ν_{max} (NaCl) 2956, 2929, 2893, 2888, 2857, 1513, 1438, 1273, 1136, 1111, 985, 841, 744, 721, 690 cm^{-1}; ^1H NMR (90 MHz) δ 0.01 (6 H, s, 2 CH_3), 0.85 (9 H, s, 3 CH_3), 3.73 (3 H, s, OCH_3), 5.20 (2 H, d, *J* = 13.6 Hz, $ArCH_2$), 6.30 (1 H, t, *J* = 2.2 Hz, H-2), 6.62 (1 H, d, *J* = 8.3 Hz, H-5), 6.93 (1 H, dt, *J* = 8.3, 2.2 Hz, H-6), 7.59–7.82 (15 H, ArH).

Anal. Calcd for $C_{32}H_{38}SiBrPO_2$: C, 64.75; H, 6.45; Br, 13.46. Found: C, 65.07; H, 6.42; Br, 12.8.

3-Hydroxy-4,5-dimethoxybenzyl Alcohol (9b). A solution of 3-[(*tert*-butyldimethylsilyl)oxy]-4,5-dimethoxybenzyl alcohol (**9a**)[3b] (9.15 g, 30 mmol) in THF (100 mL) was stirred with tetrabutylammonium fluoride (1 M THF solution, 31 mL, 31 mmol) under argon for 10 min. The reaction mixture was poured into ethyl acetate (300 mL), the solution was washed with cold water (2 × 100 mL) and dried, and the solvent was evaporated to give an oily product, which crystallized from acetone–hexane to give alcohol **9b** as flakes (4.20 g, 75%): mp 94–6 °C; IR ν_{max} (NaCl) 3407, 1595, 1509, 1464, 1432, 1347, 1237, 1202, 1167, 1140, 1103 cm^{-1}; ^1H NMR (90 MHz) δ 1.61 (1 H, br s, OH), 3.87 (3 H, s, OCH_3), 3.89 (3 H, s, OCH_3), 4.59 (2 H, s, CH_2), 5.80 (1 H, br s, OH), 6.52 (1 H, d, *J* = 1.65 Hz, ArH), 6.59 (1 H, d, *J* = 1.65 Hz, ArH).

Anal. Calcd for $C_9H_{12}O_4 \cdot {}^1/_2H_2O$: C, 55.95; H, 6.78. Found: C, 56.26; H, 6.56.

3-[(*tert*-Butyldimethylsilyl)oxy]-4,5-dimethoxybenzaldehyde (9c). To a mixture of pyridinium chlorochromate (2.8 g, 13.02 mmol) and anhydrous sodium acetate (1.10 g, 13.4 mmol) in methylene chloride (100 mL) was added benzyl alcohol[3b] **9a** (3.5 g, 11.74 mmol) in methylene chloride (20 mL). The mixture was stirred for 1 h, and the solution was filtered through a column of silica gel. Evaporation of the eluent (1:1 hexane–ethyl acetate) afforded aldehyde **9c** as a chromatographically homogeneous oil (3.3 g, 95%): bp 135 °C (0.04 mm); IR ν_{max} (NaCl) 2932, 1697, 1582, 1496, 1433, 1386, 1342, 1134, 1117, 837 cm^{-1}; ^1H NMR (90 MHz) δ 0.21 (6 H, s, 2 CH_3), 1.02 (9 H, s, 3 CH_3), 3.87 (3 H, s, OCH_3), 3.92 (3 H, s, OCH_3), 7.02 (1 H, d, *J* = 1.8 Hz, ArH), 7.11 (1 H, d, *J* = 1.8 Hz, ArH), 9.82 (1 H, s, CHO).

Anal. Calcd for $C_{15}H_{24}O_4Si$: C, 60.78; H, 8.16. Found: C, 60.51; H, 8.06.

2-(Hydroxymethyl)-5,6-dimethoxy-1,4-benzoquinone (10a). To a solution of alcohol **9b** (3.85 g, 20.92 mmol) in methanol (500 mL) was added sodium acetate (1.80 g, 21.95 mmol). After stirring for 15 min, water (800 mL) and potassium nitrosodisulfonate (Fremy's salt, 12.4 g, 46.26 mmol) were added to the clear colorless solution. The solution became purple and warm. Stirring was continued overnight, and the yellow-orange solution was extracted with chloroform. The combined extract was washed with water and dried, and solvent was evaporated to afford benzoquinone **10a** as an orange powder (3.4 g, 80%): mp 59–63 °C; IR ν_{max} (NaCl) 3480, 3297, 1658, 1605, 1313, 1288, 1264, 1215, 1197, 1148, 1135, 1037 cm^{-1}; ^1H NMR (90 MHz) δ 1.26 (1 H, s, OH), 4.00 (3 H, s, OCH_3), 4.04 (3 H, s, OCH_3), 4.53 (2 H, d, *J* = 1.8 Hz, CH_2), 6.62 (1 H, t, *J* = 1.8 Hz, H-3); HREIMS (*m/z*) 198.0535 (M^+, 72, calcd for $C_9H_{10}O_5$ 198.0528).

2-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-5,6-dimethoxy-1,4-benzoquinone (10b). To a mixture of benzoquinone **10a** (1.2 g, 6.06 mmol) in DMF (10 mL) and diisopropylethylamine (1.5 mL, 9.09 mmol) was added *tert*-butyldimethylsilyl chloride (1.1 g, 7.2 mmol). The reaction mixture was stirred under argon for 30 min, and ice (20 g) was added. After being stirred for 10 min, the mixture was poured into ether (100 mL). The orange ether layer was washed with cold water (2 × 50 mL), dried, and concentrated to afford silyl ether **10b** as a pure (chromatographically) orange oil (1.85 g, 98%): bp 140 °C (0.1 mm); IR ν_{max} (NaCl) 2955, 2932, 2858, 1660, 1605, 1473, 1316, 1262, 1151, 1133, 1052, 839 cm^{-1}; ^1H NMR (90 MHz) δ 0.10 (6 H, s, 2 CH_3), 0.93 (9 H, s, 3 CH_3), 3.99 (3 H, s, OCH_3), 4.03 (3 H, s, OCH_3), 4.53 (2 H, d, *J* = 2.3 Hz, CH_2), 6.65 (1 H, t, *J* = 2.3 Hz, H-3).

Anal. Calcd for $C_{15}H_{24}O_5Si$: C, 57.67; H, 7.74. Found: C, 57.79; H, 7.93.

3,4-Dimethoxy-2,5-bis(benzyloxy)benzyl *tert*-Butyldimethylsilyl Ether (8b). Sodium borohydride (70 mg, 1.84 mmol) was added to an orange ethanolic solution (50 mL) of benzoquinone **10b** (1.70 g, 5.44 mmol). After the solution was stirred under argon for 5 min, potassium carbonate (3.0 g) and benzyl bromide (1.35 mL, 11.42 mmol) were added to the colorless solution. The mixture was heated at reflux for 24 h, solvent was evaporated (in vacuo), and the residue was diluted with ice water and extracted with ether (3 × 75 mL). The ethereal solution was washed with water (2 × 50 mL), dried, and concentrated to an oil, which was chromatographed on a column of silica gel (250 g). Gradient elution with hexane–ethyl acetate (49:1 → 19:1) yielded benzyl ether **8b** as a homogeneous (chromatographically) gum (1.35 g, 50%): IR ν_{max} (NaCl) 2954, 2931, 2910, 2884, 2856, 1488, 1461, 1454, 1126, 1067 cm^{-1}; ^1H NMR (90 MHz) δ 0.03 (6 H, s, 2 CH_3), 0.91 (9 H, s, 3 CH_3), 3.94 (3 H, s, OCH_3), 3.96 (3 H, s, OCH_3), 4.60 (2 H, d, *J* = 0.55 Hz, CH_2), 4.98 (2 H, s, CH_2), 5.11 (2 H, s, CH_2), 6.83 (1 H, br s, H-6), 7.36–7.41 (10 H, m, ArH).

Anal. Calcd for $C_{29}H_{38}O_5Si$: C, 70.41; H, 7.74. Found: C, 70.15; H, 7.75.

3,4-Dimethoxy-2,5-bis(benzyloxy)benzyl Alcohol (8c). To a THF (10 mL) solution of silyl ether **8b** (1.0 g, 2.02 mmol) was added tetrabutylammonium fluoride (2.02 mL, 2.02 mmol). After 10 min the mixture was poured into ether (70 mL), and the organic layer was washed with cold water (2 × 25 mL), dried, and concentrated to provide alcohol **8c** as an oil (0.77 g, 99.5%): IR ν_{max}

(NaCl) 3450, 1489, 1454, 1434, 1416, 1122, 1088, 1050, 1028, 697 cm^{-1}; ^1H NMR (90 MHz) δ 1.63 (1 H, br s, OH), 3.95 (3 H, s, OCH_3), 3.98 (3 H, s, OCH_3), 4.49 (2 H, br s, CH_2), 5.06 (2 H, s, CH_2), 5.09 (2 H, s, CH_2), 6.70 (1 H, s, H-6), 7.39–7.42 (10 H, m, ArH); HREIMS (m/z) 380.1632 (M^+, 2, calcd for $C_{23}H_{24}O_5$ 380.1624).

3,4-Dimethoxy-2,5-bis(benzyloxy)benzaldehyde (8a). Pyridinium chlorochromate (435 mg, 2.02 mmol) was added to a stirred mixture prepared from benzyl alcohol **8c** (0.70 g, 1.84 mmol), sodium acetate (0.17 g, 2.02 mmol), and methylene chloride (20 mL). Stirring at room temperature was continued for 1 h, and the solution was filtered through a column of silica gel. Elution with hexane–ethyl acetate (4:1) afforded aldehyde **8a** (0.65 g, 93%) as a pure (chromatographically) oil: IR ν_{max} (NaCl) 1680, 1589, 1481, 1454, 1432, 1420, 1370, 1339, 1127, 1073 cm^{-1}; ^1H NMR (90 MHz) δ 3.98 (3 H, s, OCH_3), 4.03 (3 H, s, OCH_3), 5.11 (2 H, s, CH_2), 5.15 (2 H, s, CH_2), 7.18 (1 H, s, H-6), 7.38–7.43 (10 H, m, ArH), 10.12 (1 H, s, CHO); HREIMS (m/z) 378.1470 (M^+, 2, calcd for $C_{23}H_{22}O_5$ 378.1468).

3′-[(*tert*-Butyldimethylsilyl)oxy]-3,4,4′-trimethoxy-2,5-bis(benzyloxy)-(*Z*)- and -(*E*)-stilbene (11a and 12a). *n*-Butyllithium (1.12 mL, 1.68 mmol) was added to a cooled (−20 °C) and stirred mixture (under argon) of phosphonium bromide **11a** (995 mg, 1.68 mmol) in THF (110 mL). The orange-red phosphorane solution formed immediately: cooling was discontinued, and the reaction mixture was stirred at room temperature for 10 min. A solution of aldehyde **9c** (0.53 g, 1.4 mmol) in THF (10 mL) was added (syringe) to the Wittig ylide. The color changed to pale yellow, and reaction was complete in 10 min. Ice (20 g) was added, and the mixture was poured into ether (150 mL). The ethereal solution was washed with cold water (3 × 40 mL), dried, concentrated, and passed through a column of silica gel to yield a mixture of oily stilbenes **11a** and **12a** (0.83 g, 97%) with *Z*/*E* ratio 1:2. The *Z* and *E* isomer mixture was separated by TLC (hexane–ethyl acetate, 95:5, 3×). The *Z* isomer (**11a**) was obtained as a gum: IR ν_{max} (NaCl) 2932, 1509, 1486, 1454, 1433, 1416, 1281, 1232, 1074, 840 cm^{-1}; ^1H NMR (400 MHz) δ 0.050 (6 H, s, 2 CH_3), 0.926 (9 H, s, 3 CH_3), 3.773 (3 H, s, OCH_3), 3.912 (3 H, s, OCH_3), 3.944 (3 H, s, OCH_3), 4.733 (2 H, s, $ArCH_2$), 4.977 (2 H, s, $ArCH_2$), 6.474 (1 H, d, J = 12.2 Hz, CH=CH), 6.523 (1 H, d, J = 12.2 Hz, CH=CH), 6.590 (1 H, s, H-6), 6.717 (1 H, d, J = 8.32 Hz, H-5′), 6.762 (1 H, d, J = 2.0 Hz, H-2′), 6.811 (1 H, dd, J = 8.32, 2.0 Hz, H-6′), 7.270–7.484 (10 H, m, ArH); HREIMS (m/z) 612.2889 (M^+, 3, calcd for $C_{37}H_{44}O_6Si$ 612.2907).

The *E* isomer (**12a**) also proved to be a gum: IR ν_{max} (NaCl) 2930, 1511, 1461, 1454, 1416, 1275, 1256, 1134, 1083, 1035, 1029 cm^{-1}; ^1H NMR (400 MHz) 0.169 (6 H, s, 2 CH_3), 1.020 (9 H, s, 3 CH_3), 3.815 (3 H, s, OCH_3), 3.952 (3 H, s, OCH_3), 3.972 (3 H, s, OCH_3), 4.967 (2 H, s, $ArCH_2$), 5.143 (2 H, s, $ArCH_2$), 6.805 (1 H, d, J = 8.2 Hz, H-5′), 6.808 (1 H, d, J = 16.4 Hz, CH=CH), 6.937 (1 H, s, H-5), 6.967 (1 H, dd, J = 8.2, 2.0 Hz, H-6′), 6.990 (1 H, d, J = 2.0 Hz, H-2′), 7.157 (1 H, d, J = 16.4 Hz, CH=CH), 7.328–7.502 (10 H, m, ArH); HREIMS (m/z) 612.2915 (M^+, 5, calcd for $C_{37}H_{44}O_6Si$ 612.2907).

3-[(*tert*-Butyldimethylsilyl)oxy]-3′-(benzyloxy)-4,4′,5-trimethoxy-(*Z*)- and -(*E*)-stilbene (11b and 12b). To a cooled (−20 °C) and stirred mixture of [3-(benzyloxy)-4-methoxybenzyl]phosphonium bromide[4] (1.25 g, 2.2 mmol) in THF (100 mL) under argon was added *n*-butyllithium (1.47 mL, 2.2 mmol). The red solution was stirred at room temperature for 20 min, and aldehyde **9c** (0.59 g, 2.0 mmol) was added. After stirring at room temperature for 1 h ice (20 g) and water (20 mL) were added, and the mixture was extracted with ether (2 × 150 mL). The ethereal extract was washed with water (100 mL), dried, and concentrated to an oil, which was chromatographed on a column of silica gel (50 g). Elution with hexane–ethyl acetate (97:3) afforded *Z* isomer **11b** (0.35 g) as a chromatographically homogeneous gum: IR ν_{max} (NaCl) 2953, 2931, 1574, 1512, 1499, 1428, 1251, 1237, 1116, 837 cm^{-1}; ^1H NMR (400 MHz) δ 0.099 (6 H, s, 2 CH_3), 0.956 (9 H, s, 3 CH_3), 3.677 (3 H, s, OCH_3), 3.758 (3 H, s, OCH_3), 3.855 (3 H, s, OCH_3), 4.931 (2 H, s, CH_2), 6.384 (1 H, d, J = 12.0 Hz, CH=CH), 6.416 (1 H, d, J = 1.9 Hz, H-2 or H-6), 6.438 (1 H, d, J = 12.0 Hz, CH=CH), 6.466 (1 H, d, J = 1.9 Hz, H-6 or H-2), 6.773 (1 H, d, J = 8.8 Hz, H-5′), 6.849 (1 H, dd, J = 8.8, 1.8 Hz, H-6′), 6.857 (1 H, d, J = 1.8 Hz, H-2′), 7.261–7.340 (5 H, m, ArH).

Continued elution led to the *E* isomer **12b** (0.21 g, 71% total yield based on 31 mg of recovered aldehyde). Crystallization from ethanol afforded flakes: mp 95–96 °C; IR ν_{max} (NaCl) 2930, 2860, 1576, 1512, 1463, 1427, 1356, 1261, 1251, 1231, 1116, 838 cm^{-1}; ^1H NMR (400 MHz) 0.207 (6 H, s, 2 CH_3), 1.028 (9 H, s, 3 CH_3), 3.793 (3 H, s, OCH_3), 3.900 (3 H, s, OCH_3), 3.906 (3 H, s, OCH_3), 5.201 (2 H, s, CH_2), 6.608 (1 H, d, J = 1.88 Hz, H-2 or H-6), 6.683 (1 H, d, J = 1.88 Hz, H-6 or H-2), 6.763 (1 H, d, J = 16.2 Hz, CH=CH), 6.859 (1 H, d, J = 16.2 Hz, CH=CH), 6.882 (1 H, d, J = 8.28 Hz, H-5′), 7.058 (1 H, dd, J = 8.28, 1.88 Hz, H-6′), 7.094 (1 H, d, J = 1.88 Hz, H-2′), 7.303–7.499 (5 H, m, ArH).

Anal. Calcd for $C_{30}H_{38}O_5Si$: C, 71.11; H, 7.56. Found: C, 71.22; H, 7.74.

3-Hydroxy-3′-(benzyloxy)-4,4′,5-trimethoxy-(*Z*)- and -(*E*)-stilbene (11c and 12c). Solutions of silyl ethers **11b** (0.35 g, 0.69 mmol) and **12b** (0.31 g, 0.6 mmol) in THF (10 mL) were stirred separately with a 1 M THF solution of tetrabutylammonium fluoride (0.79 mL, 0.79 mmol and 0.65 mL, 0.65 mmol respectively) for 10 min. Ice (10 mg) was added followed by water (10 mL). In each case the product was extracted with ether (2 × 15 mL), washed with cold water (2 × 10 mL), and dried. Solvent was concentrated, and the solution was filtered through a pipette filled with silica gel to give *Z* isomer **11c** (0.26 g, 96%) as a homogeneous gum and *E* isomer **12c** (0.24 g quantitative). *Z* isomer **11c**: IR ν_{max} (NaCl) 3432, 3428, 2934, 1583, 1510, 1429, 1263, 1236, 1138, 1105 cm^{-1}; ^1H NMR (90 MHz) δ 3.67 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 3.87 (3 H, s, OCH_3), 4.93 (2 H, s, CH_2), 5.50 (1 H, br s, OH), 6.38 (1 H, d, J = 1.7 Hz), 6.39 (1 H, d, J = 12.0 Hz), 6.41 (1 H, d, J = 12.0 Hz), 6.55 (1 H, d, J = 1.7 Hz), 6.70–6.90 (3 H, m), 7.31 (5 H, br s). The *trans*-stilbene **12c** was recrystallized from acetone–hexane to give plates: mp 127–28 °C; IR ν_{max} (NaCl) 3422, 1585, 1511, 1462, 1456, 1429, 1357, 1263, 1253, 1137, 1105 cm^{-1}; ^1H NMR (90 MHz) δ 3.91 (9 H, s, 3 OCH_3), 5.20 (2 H, s, CH_2), 5.74 (1 H, s, OH), 6.58 (1 H, d, J = 1.8 Hz, H-2 or H-6), 6.74 (1 H, d, J = 1.8 Hz, H-6 or H-2), 6.80 (1 H, d, J = 16 Hz, CH=CH), 6.82 (1 H, d, J = 16 Hz, CH=CH), 6.88 (1 H, d, J = 7.0 Hz, H-5′), 7.05 (1 H, dd, J = 7.0, 1.8 Hz, H-6′), 7.08 (1 H, d, J = 1.8 Hz, H-2′), 7.26–7.46 (5 H, m, ArH).

Anal. Calcd for $C_{24}H_{24}O_5$: C, 73.46; H, 6.16. Found: C, 72.99; H, 6.20.

3,3′-Bis[(*tert*-butyldimethylsilyl)oxy]-4,4′,5-trimethoxy-(*Z*)- and -(*E*)-stilbene (11d and 12d). *n*-Butyllithium (15 mL, 20.1 mmol) was added to a cooled (−20 °C), stirred suspension of phosphonium bromide **7a** (11.45 g, 19.31 mmol) in THF (200 mL). The deep red solution was stirred at room temperature for 10 min. Aldehyde **9c** (4.4 g, 14.86 mmol) was added, and the red color was discharged at once. Ice was added, and the mixture was poured into ether (600 mL). The ethereal solution was washed with cold water (3 × 100 mL) and dried. Following removal of solvent the product was chromatographed on a column of silica gel (100 g). Elution with hexane–ethyl acetate (9:1) afforded a 1:1 mixture of *Z* and *E* isomers[3b] **11d** and **12d** (6.8 g, 86.3%).

4,7-Bis[(*tert*-butyldimethylsilyl)oxy]-2,3,6-trimethoxyphenanthrene (13d) and Isomeric Phenanthrenes 13c and 13e. Argon was passed through a solution of silylated stilbenes **11d** and **12d** (6.6 g) in benzene–hexane (1:1, 6.0 L), and iodine (0.45 g) was added. The mixture was irradiated (through a Pyrex filter water jacket) for 3 h using a medium-pressure mercury lamp (450 W). After removing iodine by washing with a 10% solution of sodium thiosulfate, the organic solution was dried, solvent was evaporated, and the residue in hexane–ethyl acetate (19:1) was chromatographed on a column of silica gel (250 g). Elution with the same solvent afforded a mixture of regioisomers **13c**, **13d**, and **13e** (4.11 g, 62.5%) in a ratio of 2:1:0.16. The isomers exhibited very similar chromatographic properties and were finally purified by repeated flash chromatography on a silica gel (13–24 μm) column (50 mm × 20 cm). Elution with hexane–ethyl acetate (99:1) at 8 psi yielded pure **13c** (1.33 g), **13d** (0.62 g), and a fraction enriched with **13e**, which was purified by PLC (hexane–ethyl acetate, 19:1) to yield **13e** (0.10 g).

Phenanthrene 13c was recrystallized from ethanol to afford colorless fine needles: mp 103–4 °C; IR ν_{max} (NaCl) 2955, 2930, 1499, 1468, 1295, 1264, 1126, 1046, 836, 782 cm^{-1}; ^1H NMR (400 MHz) δ 0.219 (6 H, s, 2 CH_3), 0.254 (6 H, s, 2 CH_3), 1.052 (9 H, s, 3 CH_3), 1.064 (9 H, s, 3 CH_3), 3.979 (3 H, s, OCH_3), 4.011 (3 H, s, OCH_3), 4.018 (3 H, s, OCH_3), 7.087 (1 H, s, H-1), 7.239 (1

H, s, H-8), 7.397 (1 H, d, J = 8.7 Hz, CH=CH), 7.464 (1 H, d, J = 8.7 Hz, CH=CH), 9.036 (1 H, s, H-5).

Anal. Calcd for $C_{29}H_{44}O_5Si_2$: C, 65.87; H, 8.39. Found: C, 65.68; H, 8.47.

Recrystallization of **phenanthrene 13d** from ethanol also furnished needles: mp 130–31 °C; IR ν_{max} (NaCl) 2955, 2930, 2858, 1471, 1423, 1296, 1262, 1130, 1087, 829 cm^{-1}; ^1H NMR (400 MHz) δ 0.049 (6 H, s, 2 CH_3), 0.207 (6 H, s, 2 CH_3), 1.026 (9 H, s, 3 CH_3), 1.052 (9 H, s, 3 CH_3), 3.888 (3 H, s, OCH_3), 3.993 (6 H, s, 2 OCH_3), 6.938 (1 H, s, H-1), 7.223 (1 H, s, H-8), 7.418 (1 H, d, J = 8.6 Hz, CH=CH), 7.458 (1 H, d, J = 8.6 Hz, CH=CH), 8.878 (1 H, s, H-5).

Anal. Calcd for $C_{29}H_{44}O_5Si_2$: C, 65.87; H, 8.39. Found: C, 65.96; H, 8.35.

Similarly, recrystallization of **phenanthrene 13e** from ethanol yielded fine fibrous needles: mp 114–7 °C; IR ν_{max} (NaCl) 2953, 2930, 2857, 1460, 1447, 1430, 1425, 1333, 1115, 835 cm^{-1}; ^1H NMR (400 MHz) δ 0.362 (6 H, s, 2 CH_3), 0.596 (6 H, s, 2 CH_3), 1.221 (9 H, s, 3 CH_3), 1.420 (9 H, s, 3 CH_3), 3.918 (3 H, s, OCH_3), 4.290 (3 H, s, OCH_3), 4.314 (3 H, s, OCH_3), 7.323 (1 H, s, H-1), 7.543 (1 H, d, J = 8.5 Hz, H-7), 7.585 (1 H, d, J = 8.7 Hz, CH=CH), 7.697 (1 H, d, J = 8.5 Hz, H-8), 7.708 (1 H, d, J = 8.7 Hz, CH=CH).

Anal. Calcd for $C_{29}H_{44}O_5Si_2$: C, 65.87; H, 8.39. Found: C, 65.76; H, 8.33.

4,7-Dihydroxy-2,3,6-trimethoxyphenanthrene (13b). A solution of silyl ether **13d** (0.49 g, 0.93 mmol) in THF (10 mL) was stirred under argon with tetrabutylammonium fluoride (1 M THF solution, 2.04 mL, 2.04 mmol) for 10 min. The reaction mixture became yellow, and a yellow solid separated. Ice (5 g) was added followed by ether (125 mL). The ethereal solution was washed with cold water (2 × 50 mL), dried, and evaporated to give phenol **13b** as a colorless powder (0.27 g, 97%). Recrystallization from ethyl acetate–hexane gave colorless prisms: mp 189–94 °C (lit.[12] mp 195–6 °C); IR ν_{max} (NaCl) 3466, 3460, 3453, 1513, 1482, 1462, 1277, 1232, 1211, 1123 cm^{-1}; ^1H NMR (400 MHz) δ 4.009 (3 H, s, OCH_3), 4.030 (3 H, s, OCH_3), 4.093 (3 H, s, OCH_3), 5.858 (1 H, s, OH), 6.884 (1 H, s, H-1), 7.026 (1 H, s, OH), 7.307 (1 H, s, H-8), 7.459 (1 H, d, J = 8.7 Hz, CH=CH), 7.529 (1 H, d, J = 8.7 Hz, CH=CH), 9.110 (1 H, s, H-5).

Anal. Calcd for $C_{17}H_{16}O_5$: C, 68.00; H, 5.37. Found: C, 67.75; H, 5.21.

2,7-Dihydroxy-3,4,6-trimethoxyphenanthrene (13f). The preceding method (cf. **13b**) was employed to convert silyl ether **13c** (0.55 g, 1.04 mmol) to give phenanthrene **13f** as a colorless powder (0.31 g, 99.5%) that recrystallized from ethyl acetate–hexane as granules: mp 140–42 °C (lit.[19] mp 143–4 °C); IR ν_{max} (NaCl) 3500, 3420, 1513, 1479, 1464, 1440, 1425, 1414, 1272, 1214, 1176, 1115 cm^{-1}; ^1H NMR (400 MHz) δ 3.994 (3 H, s, OCH_3), 4.103 (3 H, s, OCH_3), 4.117 (3 H, s, OCH_3), 5.873 (1 H, s, OH), 5.946 (1 H, s, OH), 7.171 (1 H, s, H-1), 7.302 (1 H, s, H-1), 7.449 (1 H, d, J = 8.8 Hz, CH=CH), 7.509 (1 H, d, J = 8.8 Hz, CH=CH), 9.021 (1 H, s, H-5).

Anal. Calcd for $C_{17}H_{16}O_5$: C, 68.00; H, 5.37. Found: C, 67.78; H, 5.30.

2-Hydroxy-3,4-dimethoxybenzaldehyde (14d). Method A. To a solution of 2,3,4-trimethoxybenzaldehyde (**14b**, 1.0 g, 5.1 mmol) in anhydrous benzene (15 mL) was added anhydrous aluminum chloride (0.70 g, 5.3 mmol). The solution was stirred under argon at room temperature for 5 min followed by heating at 70–80 °C for 6 h. To the dark-colored solution was added ice–water followed by concentrated HCl (5 mL). After the solution was stirred at room temperature for 10 min the benzene layer was separated and the aqueous phase was extracted with ether (2 × 50 mL). The combined extract was washed with water (2 × 25 mL), dried, and concentrated to give aldehyde **14d** as needles (0.91 g) that recrystallized from acetone–hexane in the same form (0.84 g, 90.5%).

Method B. A solution of 2,3-dihydroxy-4-methoxybenzaldehyde[3a] (**14c**, 5.0 g, 29.76 mmol) in tetrahydrofuran (20 mL) was treated with diazomethane (112 mL of an ether solution, 30 mmol) at 0 °C for 60 min. The ether was evaporated, and the product chromatographed in hexane–ethyl acetate (4:1) on a column of silica gel. Elution with the same solvent afforded aldehyde **14d** (1.4 g, 40% based on recovered starting material). A pure specimen recrystallized from acetone–hexane: mp 69–70 °C (lit.[9] mp 70–72 °C); IR ν_{max} (NaCl) 3500–3200 (broad) 1643, 1624, 1504, 1451, 1429, 1390, 1291, 1264, 1108 cm^{-1}; ^1H NMR (90 MHz) 3.92 (3 H, s, OCH_3), 3.96 (3 H, s, OCH_3), 6.61 (1 H, d, J = 9.0 Hz, H-5), 7.30 (1 H, d, J = 9 Hz, H-6), 9.76 (1 H, s, CHO), 11.20 (1 H, s, OH).

Further elution of the column yielded the isomeric phenol **14e** (0.4 g): mp 104–5 °C (lit.[20] mp 105 °C); IR ν_{max} (NaCl) 3238, 3233, 1664, 1601, 1576, 1500, 1284, 1243, 1223, 1085 cm^{-1}; ^1H NMR (90 MHz) δ 3.97 (3 H, s, OCH_3), 4.04 (3 H, s, OCH_3), 5.77 (1 H, s, OH), 6.74 (1 H, d, J = 8.6 Hz, H-5), 7.43 (1 H, d, J = 8.6 Hz, H-6), 10.24 (1 H, d, J = 0.8 Hz, CHO).

2-[(*tert*-Butyldimethylsilyl)oxy]-3,4-dimethoxybenzaldehyde (14a). Before adding *tert*-butyldimethylsilyl chloride (0.99 g, 6.58 mmol) a solution of aldehyde **14d** (1.09 g, 5.98 mmol) in dimethylformamide (6 mL) was stirred with diisopropylethylamine (1.6 mL, 8.97 mmol) for 10 min under argon. The mixture was stirred for 1 h, ice (10 g) was added followed by ether (100 mL), and the ethereal solution was washed with cold water (2 × 50 mL), saturated sodium bicarbonate solution (2 × 50 mL), and water (50 mL) and dried. Removal of solvent led to aldehyde **14a** as a homogeneous oil (1.75 g, 98% yield), which crystallized from methanol as rods: mp 57–58 °C; IR ν_{max} (NaCl) 2933, 1689, 1589, 1492, 1464, 1309, 1258, 1074, 841, 786 cm^{-1}; ^1H NMR (90 MHz) δ 0.24 (6 H, s, 2 CH_3), 1.02 (9 H, s, 3 CH_3), 3.84 (3 H, s, OCH_3), 4.02 (3 H, s, OCH_3), 6.68 (1 H, d, J = 8.6 Hz, H-5), 7.50 (1 H, d, J = 8.6 Hz, H-6), 10.25 (1 H, s, CHO).

Anal. Calcd for $C_{15}H_{24}O_4Si$: C, 60.78; H, 8.16. Found: C, 60.88; H, 8.22.

2,3′-Bis[(*tert*-butyldimethylsilyl)oxy]-3,4,4′-trimethoxy-(*Z*)- and -(*E*)-stilbenes (11e and 12e). To a cooled (−20 °C) suspension of phosphonium bromide **7a** (3.0 g, 5.06 mmol in THF (150 mL) was added *n*-butyllithium (3.37 mL, 5.06 mmol). The reaction was conducted, and the product was isolated as noted for stilbenes **11b** and **12b** and concentrated to give an approximate ratio of 1:2.5, *Z*/*E* isomer (**11e** and **12e**, 1.75 g, 98% yield). Crystallization from ethanol afforded pure *E* isomer **12e** (1.3 g, 73% yield): mp 135–7 °C; IR ν_{max} (NaCl) 2955, 2930, 1510, 1454, 1427, 1300, 1272, 1103, 838, 783 cm^{-1}; ^1H NMR (400 MHz) δ 0.175 (6 H, s, 2 CH_3), 0.197 (6 H, s, 2 CH_3), 1.019 (9 H, s, 3 CH_3), 1.052 (9 H, s, 3 CH_3), 3.764 (3 H, s, OCH_3), 3.816 (3 H, s, OCH_3), 3.875 (3 H, s, OCH_3), 6.581 (1 H, d, J = 8.7 Hz, H-5), 6.788 (1 H, d, J = 16.4 Hz, CH=CH), 6.814 (1 H, d, J = 8.3 Hz, H-5′), 6.992 (1 H, dd, J = 8.3, 2.0 Hz, H-6′), 7.062 (1 H, d, J = 2.0 Hz, H-2′), 7.224 (1 H, d, J = 16.4 Hz, CH=CH), 7.287 (1 H, d, J = 8.7 Hz, H-6).

Anal. Calcd for $C_{29}H_{46}O_5Si_2$: C, 65.62; H, 8.73. Found: C, 65.61; H, 8.88.

1,7-Bis[(*tert*-butyldimethylsilyl)oxy]-2,3,6-trimethoxyphenanthrene (13g). A mixture of the *Z*/*E* stilbenes **11e** and **12e** (2.4 g) in benzene–hexane (2:1, 1.8 L) was swept with nitrogen for 10 min. Iodine (100 mg) was added, and the nitrogen flow continued while stirring and irradiating (medium-pressure 450-W mercury lamp through a Pyrex filter/water jacket) for 3 h. Iodine was removed by washing with 10% aqueous sodium thiosulfate. The solvent was dried and concentrated, and the product was chromatographed on a column of silica gel (150 g). Elution with hexane–ethyl acetate (49:1) yielded **phenanthrene 13h** (0.40 g). Crystallization from ethanol gave flakes: mp 120 °C; IR ν_{max} (NaCl) 2955, 2931, 2895, 2857, 1471, 1428, 1283, 1257, 1128, 836 cm^{-1}; ^1H NMR (400 MHz) δ 0.021, 0.023 (3 H each, s, CH_3), 0.245 (6 H, s, 2 CH_3), 1.023 (9 H, s, 3 CH_3), 1.100 (9 H, s, 3 CH_3), 3.864 (3 H, s, OCH_3), 3.910 (3 H, s, OCH_3), 4.028 (3 H, s, OCH_3), 7.197 (1 H, d, J = 8.5 Hz, H-7), 7.447 (2 H, d, J = 9.0 Hz, H-8 and CH=CH), 7.872 (1 H, d, J = 9.0 Hz, CH=CH), 8.736 (1 H, s, H-4).

Anal. Calcd for $C_{29}H_{44}O_5Si_2$: C, 65.87; H, 8.39. Found: C, 65.88; H, 8.65.

Continued elution of the column with the same solvent afforded a mixture of unreacted stilbenes (0.35 g) followed by the required **phenanthrene 13g** (1.0 g, 50%, total yield 68% based on the recovered stilbenes). Isomer **13g** recrystallized from ethanol as fine needles: mp 130–2 °C; IR ν_{max} (NaCl) 2955, 2930, 2858, 1517, 1477, 1430, 1275, 1133, 836, 782 cm^{-1}; ^1H NMR (400 MHz) δ 0.217

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Table III. HREI Mass Spectral Fragmentation of Combretastatin C-1 (2)

elemental composition	mass obsd	mass calcd	% rel int	interpretation (see Scheme I)
$C_{17}H_{14}O_6$	314.0792	314.0790	100	M^+
$C_{16}H_{11}O_6$	299.0558	299.0556	80	$M^+ - CH_3 = B$
$C_{16}H_{13}O_5$	285.0758	285.0763	13	$M^+ - CHO = C$
$C_{16}H_{12}O_5$	284.0678	284.0685	5	$M^+ - CH_2O = D$
$C_{15}H_9O_5$	269.0450	269.0449	17	$B - CH_2O = E$
$C_{15}H_{13}O_4$	257.0800	257.0814	3	$C - CO = F$
$C_{15}H_{12}O_4$	256.0730	256.0736	2	$D - CO = G$
$C_{13}H_{11}O_3$	215.0704	215.0708	2	$F - CH_2O_2$
$C_{13}H_{10}O_3$	214.0634	214.0630	1	$F - C_2H_3O = H$
$C_{12}H_9O_3$	201.0547	201.0552	59	$H - CH = I$
$C_{12}H_8O_3$	200.0473	200.0473	26	$H - CH_2$
$C_{11}H_9O_2$	173.0591	173.0603	11	$I - CO = J$
$C_{11}H_8O_2$	172.0529	172.0524	32	$I - CHO = K$
$C_{11}H_7O_2$	171.0445	171.0446	3	$I - CH_2O = L$
$C_{11}H_6O_2$	170.0370	170.0368	3	$I - CH_3O$
$C_{10}H_6O_2$	158.0350	158.0368	2	$K - CH_2 = M$
C_9H_5O	129.0344	129.0340	17	$M - CHO$

(6 H, s, $Si(CH_3)_2$ at C-7), 0.248 (6 H, s, $Si(CH_3)_2$ at C-1), 1.050 (9 H, s, $SiC(CH_3)_3$ at C-7), 1.104 (9 H, s, $SiC(CH_3)_3$ at C-1), 3.856 (3 H, s, OCH_3 at C-2), 4.035 (3 H, s, OCH_3 at C-6), 4.090 (3 H, s, OCH_3 at C-3), 7.262 (1 H, s, H-8), 7.464 (1 H, d, J = 9.0 Hz, H-9), 7.532 (1 H, s, H-4), 7.800 (1 H, s, H-5), 7.920 (1 H, d, J = 9.0 Hz, H-10). The NMR assignments were made on the basis of NOEDS experiments.

Anal. Calcd for $C_{29}H_{44}O_5Si_2$: C, 65.87; H, 8.39. Found: C, 65.75; H, 8.50.

1,7-Dihydroxy-2,3,6-trimethoxyphenanthrene (13i). To a stirred solution of 1,7-bis(silyloxy)phenanthrene **13g** (0.50 g, 0.95 mmol) in THF (25 mL) was added a 1 M THF solution of tetrabutylammonium fluoride (2.0 mL, 2 mmol) under argon. Reaction was complete at once, and the mixture became gelatinous. Water (10 mL) was added and the product extracted with ether (3 × 25 mL). The ethereal solution was washed with water (2 × 20 mL) and dried, and solvent was evaporated to a powder, which on crystallization from chloroform–hexane afforded needles (**13i**, 0.245 g, 86% yield): mp 194–6 °C; IR ν_{max} (NaCl) 3435, 3240, 1653, 1628, 1614, 1540, 1480, 1469, 1451, 1413, 1240, 1125 cm^{-1}; ^1H NMR (90 MHz) δ 4.00 (3 H, s, OCH_3), 4.10 (3 H, s, OCH_3), 4.12 (3 H, s, OCH_3), 7.33 (1 H, s, H-8), 7.40 (1 H, s, H-4), 7.50 (1 H, d, J = 8.9 Hz, H-9), 7.77 (1 H, s, H-5), 7.95 (1 H, d, J = 8.9 Hz, H-10).

Anal. Calcd for $C_{17}H_{16}O_5 \cdot {}^1/_4H_2O$: C, 66.99; H, 5.37. Found: C, 67.10; H, 5.20.

Combretastatin C-1 (2). Method A. A solution of 4,7-dihydroxy-2,3,6-trimethoxyphenanthrene (**13b**) (47 mg, 0.16 mmol) in methanol (35 mL)–water (20 mL) was swept with N_2, and a solution of Fremy's salt (0.10 g, 0.39 mmol) in water (5 mL) was added. The mixture was stirred for 2 min, a few drops of 0.17 M potassium monohydrogen phosphate solution was added (to raise the pH to 6.5–7.0), and it was cooled to 0 °C. After the mixture was stirred, for 1 h, a diquinone side product appeared as a more polar (TLC) product. The reaction was terminated with concentrated HCl (pH 1.0), water (50 mL) was added, and the mixture was extracted with chloroform (3 × 75 mL). The dark yellow chloroform phase was washed with cold water (50 mL) and dried, and the solvent was evaporated. The residue was chromatographed on a column of silica gel (20 g). Elution with hexane–ethyl acetate led to unreacted phenol **13b** (10 mg) and combretastatin C-1 (24 mg, 62% yield based on recovered starting material).

Method B. The experiment summarized in method A was repeated employing Fremy's salt (0.30 g, 1.12 mmol) and 1,7-dihydroxy-2,3,6-trimethoxyphenanthrene (**13i**, 0.14 g, 0.47 mmol) in methanol–acetone–water (8:5:9, 220 ml). Elution of the yellow band with hexane–ethyl acetate (7:3) yielded combretastatin C-1 as an orange powder (80 mg, 54.5% yield). Recrystallization from ethyl acetate yielded combretastatin C-1 as fine fibers: mp 215 °C, identical (TLC, IR, ^1H NMR) with the natural product.

Anal. Calcd for $C_{17}H_{14}O_6$: C, 64.97; H, 4.49. Found: C, 64.86; H, 4.39.

3,2′,3′-Tris[(*tert*-butyldimethylsilyl)oxy]-4,4′,5-trimethoxy-(*Z*)- and -(*E*)-stilbene (11f, 12f). The Wittig reaction described for the synthesis of the *Z*/*E* stilbenes **11a** and **12a** was repeated using phosphonium bromide[3b] **9d** (93.12 g, 5 mmol) in THF (200 mL), *n*-butyllithium (93.12 g, 5 mmol), and 2,3-bis-[(*tert*-butyldimethylsilyl)oxy]-4-methoxybenzaldehyde[3a] (**14f**) (1.98 g, 5.0 mmol). The product was chromatographed on a column of silica gel (75 g) and eluted with hexane–ethyl acetate (24:1) to yield a 1:1 mixture of (*Z*)- and (*E*)-stilbene (**11f** and **12f**) (3.35 g, 85% yield). A sample of the *E* isomer (**12f**) was purified by PLC (hexane–ethyl acetate, 24:1) and found to crystallize from benzene–methanol as flakes: mp 141–44 °C; IR ν_{max} (NaCl) 2956, 2930, 2858, 1576, 1498, 1473, 1463, 1453, 1314, 1255, 1118, 1102, 838 cm^{-1}; ^1H NMR (400 MHz) δ 0.112 (6 H, s, 2 CH_3), 0.132 (6 H, s, 2 CH_3), 0.197 (6 H, s, 2 CH_3), 0.997 (9 H, s, 3 CH_3), 1.020 (9 H, s, 3 CH_3), 1.084 (9 H, s, 3 CH_3), 3.788 (3 H, s, OCH_3), 3.791 (3 H, s, OCH_3), 3.866 (3 H, s, OCH_3), 6.545 (1 H, d, J = 8.8 Hz, H-5′), 6.607 (1 H, d, J = 1.9 Hz), 6.718 (1 H, d, J = 1.9 Hz), 6.748 (1 H, d, J = 16.4 Hz, CH=CH), 7.198 (1 H, d, J = 16.4 Hz, CH=CH), 7.210 (1 H, d, J = 8.8 Hz, H-6′).

Anal. Calcd for $C_{35}H_{60}O_6Si_3$: C, 63.59; H, 9.15. Found: C, 63.53; H, 9.27.

2,7,8-Tris[(*tert*-butyldimethylsilyl)oxy]-3,4,6-trimethoxyphenanthrenes (13j, 13k). The method used for obtaining phenanthrenes **13d** and **13e** was repeated with stilbenes **11f** and **12f** (1.41 g) in benzene–hexane (1:3, 800 mL). Separation of the crude product was achieved by chromatography on a silica gel (40 g) column and elution with hexane–ethyl acetate (98.5:1.5). By this means a 2.5:1 mixture of phenanthrenes **13j** and **13k** (1.1 g, 78.5%) was obtained. The mixture was resolved by PLC (hexane–ethyl acetate, 47:3). Both bands were eluted to give the structural isomers **13j** (0.58 g) and **13k** (0.25 g). Crystallization of phenanthrene **13j** from ethanol afforded needles: mp 130–31 °C; IR ν_{max} (NaCl) 2957, 2930, 2859, 1471, 1260, 1134, 1044, 843, 828, 783 cm^{-1}; ^1H NMR (90 MHz) δ 0.10 (6 H, s, 2 CH_3), 0.16 (6 H, s, 2 CH_3), 0.25 (6 H, s, 2 CH_3), 1.06 (9 H, s, $C(CH_3)_3$), 1.10 (9 H, s, $C(CH_3)_3$), 1.14 (9 H, s, $C(CH_3)_3$), 3.97 (6 H, s, 2 CH_3), 4.01 (3 H, s, OCH_3), 7.08 (1 H, s, H-1), 7.37 (1 H, d, J = 9.5 Hz, H-9 or H-10), 7.92 (1 H, d, J = 9.5 Hz, H-10 or H-9), 8.78 (1 H, s, H-5).

Anal. Calcd for $C_{35}H_{58}O_6Si_3$: C, 63.78; H, 8.87. Found: C, 63.74; H, 9.14.

Analogous recrystallization from ethanol also gave phenanthrene **13k** as needles: mp 148–50 °C; IR ν_{max} (NaCl) 2957, 2931, 2859, 1473, 1259, 1135, 1123, 836, 816, 785 cm^{-1}; ^1H NMR (90 MHz) δ 0.02 (6 H, s, 2 CH_3), 0.10 (6 H, s, 2 CH_3), 0.15 (6 H, s, 2 CH_3), 0.98 (9 H, s, 3 CH_3), 1.02 (9 H, s, 3 CH_3), 1.12 (9 H, s, 3 CH_3), 3.89 (3 H, s, OCH_3), 3.97 (3 H, s, OCH_3), 3.99 (3 H, s, OCH_3), 6.93 (1 H, s, H-1), 7.39 (1 H, d, J = 9.2 Hz, CH=CH), 7.91 (1 H, d, J = 9.2 Hz, CH=CH), 8.55 (1 H, s, H-5).

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Synthesis of the Chiral (8*S*)-7-Aza-1,3(*E*),9-decatriene System from Natural α-Amino Acids and Its Intramolecular Diels–Alder Reaction Directed toward Chiral *trans*-Hydroisoquinolones

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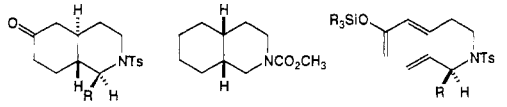
L-Alanine and L-valine were converted into optically active 7-aza-1,3(*E*),9-decatrienes containing a (*tert*-butyldimethylsilyl)oxy group at C(2) and a methyl or isopropyl group at C(8). Intramolecular thermal [4 + 2] cycloaddition reactions of these trienes gave optically active *trans*-nonahydro-6(2*H*)-isoquinolones. The relatively bulky isopropyl group at C(8) increased the trans selectivity in the ring closure. These results are in contrast with literature reports on ring closure of analogous aza trienes that lack the (*tert*-butyldimethylsilyl)oxy group at C(2), which give predominantly cis-fused rings.

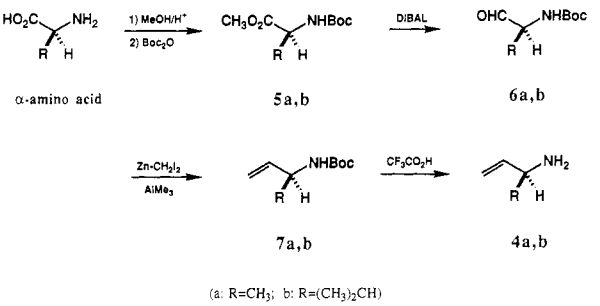
Trans-fused hydroisoquinoline frameworks are frequently encountered in bioactive alkaloids such as yohimbine, levonantradol, and modified dopamine agonists.[1] We have been interested in the synthesis of the trans-fused hydroisoquinolone skeleton **1** by intramolecular [4 + 2] cycloaddition of substituted azatrienes.[2] Oppolzer,[3] Martin,[4] and others[5] have used the intramolecular Diels–Alder reaction of amino or amido trienes to gain access to cis-fused hydroisoquinoline derivatives such as **2**, which are also building blocks for the total synthesis of alkaloids with such a structural array.[4]



1 **2** **3**

Although most reports on the intramolecular thermal [4 + 2] cycloaddition reaction of aza trienes indicate a cis addition, both cis and trans ring junctions can result depending on the choice of diene geometry and stereoelectronic effects.[2-5] A practical trans-selective cycloaddition has not previously been achieved. We wished to examine whether modification of the diene structure and introduction of a chiral center at C(8) in **3** could affect the stereochemical outcome of its intramolecular [4 + 2] cycloaddition reaction. In particular, we hoped to establish whether the alkyl substituent at C(8) of **3** can cause the preferential formation of a *trans*-isoquinolone rather than the cis isomer.

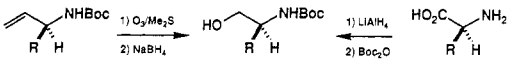
Scheme I



α-amino acid **5a,b** **6a,b** **7a,b** **4a,b**

(a: R=CH_3; b: R=$(CH_3)_2CH$)

Scheme II



7 **8** L-α-amino acid

Results and Discussion

Synthesis of Substrates. We have reported on the synthesis of the chiral allylamines **4** without any detectable reacemization (Scheme I).[6] The N-protected amino ester **5** is reduced to aldehyde **6** followed by olefination of the carbonyl group. It was necessary to olefinate **6** without racemization of the chiral center. However, owing to the basicity of traditional olefinating reagents, such as the Wittig reagent, amino aldehyde **6** enolizes with such reagents and racemizes in such an olefination.[7] Luly et

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