Synthesis of (±)-Combretastatin D-1 and Combretastatin D-2

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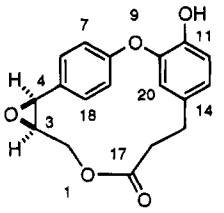
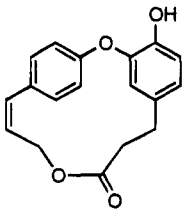
(±)-Combretastatin D-1 was synthesized in 16 steps by way of its congener, combretastatin D-2. In the key step, the strained 15-membered lactone ring was formed using high-dilution Mitsunobu conditions in 89% yield. Saturated seco acid **4** was a much better substrate for the cyclization reaction than the unsaturated seco acid **3**.

Combretastatins D-1 (**1**) and D-2 (**2**) are two 15-membered macrocyclic lactones isolated from the South African tree *Combretum caffrum* that have been found to inhibit PS cell line growth with ED_{50} values of 3.3 and 5.2 μg/mL, respectively.[2] A synthesis of combretastatin D-2 was described by Boger's group,[3] and Deshpande's group subsequently reported a formal total synthesis of the same material.[4,5] We report the first total synthesis of combretastatin D-1 and a new, efficient route to combretastatin D-2.

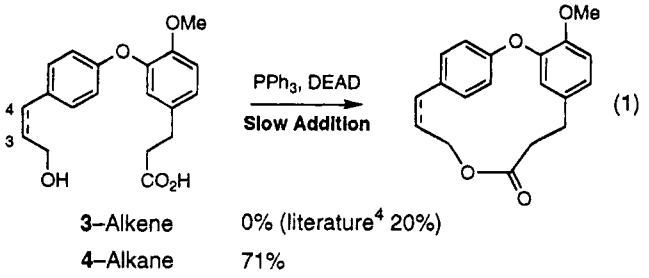


Combretastatin D-1



Combretastatin D-2

Any synthesis of combretastatin D-2 faces two key challenges: formation of the diaryl ether linkage and preparation of the macrocyclic ring. Boger's group attacked both challenges in one step by developing an intramolecular Ullmann cyclization that produced an intermediate containing the strained lactone ring in 37% yield.[3] Our strategy addresses the two problems separately. The $\Delta^{3,4}$ cyclization precursor **3** was prepared by a route similar to one described below and subjected to a gamut of macrocyclization conditions.[6] No monomeric cyclization product was identified under any conditions.[7] About this time Steglich reported the synthesis of a highly strained lactone by a high-dilution, Mitsunobu cyclization.[8] We immediately applied this procedure to seco acid **3**, but without success (eq 1). Deshpande later



reported a 20% yield by going to even higher dilution (6.6×10^{-4} M).[4] The activated allylic alcohol **3** was expected to be particularly prone to S_N1 reactions because of conjugation to a very electron-rich aromatic ring. Assuming that S_N1-initiated side reactions were responsible for the low yield of cyclization, the double bond of **3** was reduced to give the saturated alcohol **4**. Unlike the allylic oxyphosphonium ion intermediate derived from **3**, the primary oxyphosphonium ion derived from **4** is expected to be much more stable and should survive to undergo the desired S_N2 cyclization. We were pleased to find that saturated seco acid **4** cyclized under Steglich–Mitsunobu conditions in 71% yield, eq 1. Our strategy was revised to avoid cyclization of an allylic alcohol,[5] and the resulting successful synthesis of combretastatin D-2 is shown in Scheme 1.

The synthesis began with an Ullmann coupling between 4-bromobenzonitrile (**5**) and guaiacol (**6**) to give diaryl ether **7** in 94% yield.[9] Regioselective iodination of **7** gave aryl iodide **8** in 80% yield. The methoxyl group in **7** is a more powerful *para* director than the aryl ether oxygen and dominates the regioselectivity. Unsaturated ester **9** was prepared in 94% yield by DIBAL-H reduction and a *Z*-selective Wittig reaction.[10] In the synthetic scheme to combretastatin D-2, the alkene was protected by addition of thiophenol, and DIBAL-H reduction gave the alcohol **10** in 94% yield. The cyclization substrates **3** and **4** were also prepared from **9** by omitting the thiophenol addition step. The propionate side chain was introduced using a modified Stille coupling[11] with ethyl (*Z*)-3-(tributylstannyl)acrylate to give **11** in 79% yield.[12] Reduction of the conjugated double bond with Mg metal

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(1) Alfred P. Sloan Research Fellow, 1992–1994. Camille and Henry Dreyfus Teacher-Scholar, 1990–1995.

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(4) Deshpande, V. H.; Gokhale, N. J. *Tetrahedron Lett.* **1992,** *33,* 4213–4216.

(5) After submision of our original manuscript, a new synthesis of combretastatin D-2 based on Mitsunobu cyclization of a saturated alcohol precursor was reported: Couladouros, E. A.; Soufli, I. C. *Tetrahedron Lett.* **1994,** *35,* 4409–4412.

(6) (a) Kurihara, T.; Nakajima, Y.; Mitsunobu, O. *Tetrahedron Lett.* **1976,** 2455–2458. (b) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976,** 49–50. (c) Inanaga, J.; Hirata, K.; Saecki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979,** *52,* 1989–1993. (d) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990,** *55,* 7–9.

(7) Boger's group also attempted to cyclize alkene **3** without success (ref 3).

(8) Justus, K.; Steglich, W. *Tetrahedron Lett.* **1991,** *32,* 5781–5784.

(9) (a) Lindley, J. *Tetrahedron* **1984,** *40,* 1433–1456. (b) Moroz, A. A.; Shvartsberg, M. S. *Russ. Chem. Rev.* **1974,** *43,* 679–689.

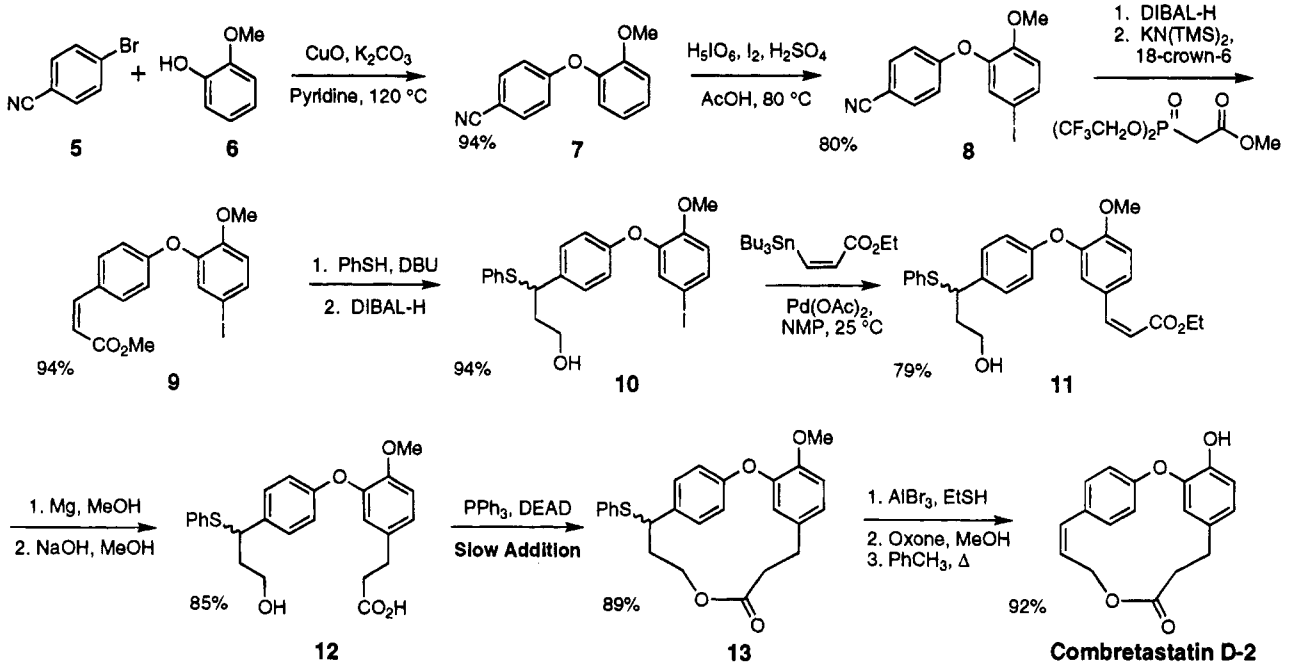
(10) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983,** *24,* 4405–4408.

(11) (a) Roth, G. P.; Sapino, C. *Tetrahedron Lett.* **1991,** *32,* 4073–4076. (b) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986,** *25,* 508–524.

(12) (a) Ma, S.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1990,** 1643–1644. (b) Ma, S.; Lu, X.; Li, Z. *J. Org. Chem.* **1992,** *57,* 709–713. (c) Seitz, D. E.; Lee, S.-H. *Tetrahedron Lett.* **1981,** *22,* 4909–4912.

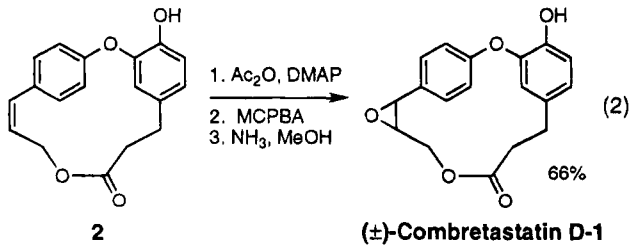
0022-3263/94/1959-5414$04.50/0

Scheme 1



in methanol[13] followed by ester hydrolysis gave the cyclization precursor **12** in 85% yield. The cyclization was carried out by syringe pump addition of a solution of seco acid **12** to 7.5 equiv of PPh_3 and 7.7 equiv of diethyl azodicarboxylate in toluene over 20 h to give lactone **13** in 89% yield. Deprotection of the methyl ether, a problematic step in all previous syntheses of combretastatin D-2,[3-5] was carried out using 8 equiv of $AlBr_3$ and 100 equiv of EtSH.[14] The $\Delta^{3,4}$ double bond was introduced by oxidation of the phenyl sulfide to the phenyl sulfoxide followed by thermal elimination to give combretastatin D-2 in 92% yield from **13**. The physical data (^1H NMR, ^{13}C NMR, IR, MS, mp) for synthetic combretastatin matched those reported for the natural material.[2,15]

Attempted oxidation of combretastatin D-2 to combretastatin D-1 was not clean, so a three-step sequence was developed. Acylation of the free phenol in **2** followed by treatment with MCPBA gave a clean oxidation, eq 2. Deprotection of the acetate by treatment with NH_3-saturated MeOH gave (±)-combretastatin D-1 in 66% yield from **2**. Synthetic combretastatin D-1 showed ^1H NMR, ^{13}C NMR, IR, and MS data identical with those reported for the natural material.[2]



Combretastatin D-2 was prepared in 13 steps and 36% overall yield from commercially available materials, while combretastatin D-1 was prepared in 16 steps and 23% overall yield. The key features of these syntheses are the early formation of the diaryl ether by an Ullmann coupling and a highly effective Mitsunobu cyclization reaction that avoids the use of an allylic alcohol substrate.

Experimental Section

General Experimental Details. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on EM reagent silica gel 60 (230–400 mesh).[16] Commercial CH_2Cl_2 was distilled from CaH_2 under N_2. Air and/or moisture sensitive reactions were carried out under N_2 or Ar using flame-dried glassware and standard syringe/septa techniques. NMR data for ^{13}C DEPT experiments are reported as quaternary (*C*), tertiary (*C*H), secondary (CH_2), and primary (CH_3) carbon atoms. For overlapping signals, the number of carbon atoms are given in parentheses.

4-(2-Methoxyphenoxy)benzonitrile (7). A solution of 4-bromobenzonitrile (15.0 g, 0.082 mol), guaiacol (22.48 g, 0.181 mol), and K_2CO_3 (45.5 g, 0.33 mol) in dry pyridine under N_2 was warmed to 100 °C. After 1.5 h, CuO (32.8 g, 0.41 mol) was added, and then the reaction mixture was warmed at reflux (120 °C; 21 h). The cooled reaction mixture was filtered through Celite. Ethyl acetate was added to the filtrate, and the resulting organic layer was washed with 1 N $NaHSO_4$ (3×) and saturated NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 30% ethyl acetate/hexanes) gave 17.4 g (0.077 mol, 94%) of **7** as a white solid: mp = 91–92 °C; R_f = 0.46 (30% ethyl acetate/hexanes); IR ($CDCl_3$) 3110, 3069, 2944, 2839, 2225, 1607, 1501, 1303, 1024, 837, 757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, J = 8.7 Hz, 2 H), 7.23 (td, J = 7.6, 1.4 Hz, 1 H), 7.08–6.95 (m, 3 H), 6.91 (d, J = 8.7 Hz, 2 H), 3.77 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 161.8, 151.5, 142.3, 118.9, 104.9; *C*H, 133.8 (2), 126.5, 122.4, 121.2, 116.4 (2), 112.9; CH_3, 55.7; HRMS (EI) calcd for $C_{14}H_{11}NO_2$ (M^+) 225.0789, found 225.0789. Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92. Found: C, 74.64; H, 5.08.

4-(5-Iodo-2-methoxyphenoxy)benzonitrile (8). To a mixture of **7** (16.9 g, 75 mmol), H_5IO_6 (3.76 g, 16.5 mmol), and iodine (7.62 g, 30 mmol) was added a solution of concd H_2SO_4

(13) (a) Youn, I. K.; Yon, G. H.; Pak, C. S. *Tetrahedron Lett.* **1986**, *27*, 2409–2410. (b) Hudlicky, T.; Sinai-Zingde, G.; Natchus, M. G.; *Tetrahedron Lett.* **1987**, *28*, 5287–5290.

(14) Node, M.; Nishide, K.; Fuji, K.; Fujita, E. *J. Org. Chem.* **1980**, *45*, 4275–4277.

(15) The ^{13}C chemical shifts match those previously reported for combretastatin D-2, but the DEPT data are inconsistent with the peak assignments in the literature. New peak assignments are listed in the Experimental Section.

(16) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

(7.4 mL) and water (45 mL) in AcOH (237 mL). The resulting purple solution was heated at 90 °C with stirring for approximately 2 h until the color of iodine disappeared. The reaction mixture was diluted with 200 mL of water, and the orange solid was collected on a Büchner funnel and washed with 75 mL of water. The solid was dissolved in a minimum amount of boiling acetone, and the solution was stored overnight in a refrigerator. The product was collected by filtration through a Büchner funnel and washed with 10% ethyl acetate in hexanes, yielding 11.59 g of the product as colorless, fine needles. The filtrate was concentrated under reduced pressure, and the resulting solid was dissolved in a minimum amount of boiling acetone. The solution was stored overnight in a refrigerator, filtered, and washed gave 6.03 g of the product. The filtrates were treated twice more in the same way to give 2.48 g and 0.94 g of the product, respectively. Overall, 21.04 g (60 mmol, 80%) of **8** was obtained as colorless, fine needles: mp = 127.5–128.5 °C; R_f = 0.43 (30% ethyl acetate/hexanes); IR ($CDCl_3$) 2939, 2839, 2225, 1605, 1490, 1293, 1134 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, J = 8.7 Hz, 2 H), 7.52 (dd, J = 8.6, 2.0 Hz, 1 H), 7.36 (d, J = 2.0 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 2 H), 6.77 (d, J = 8.6 Hz, 1 H), 3.74 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 161.4, 151.9, 143.5, 118.9, 105.9, 81.9; *CH*, 135.5, 134.1 (2), 131.3, 116.7 (2), 115.1; CH_3, 56.1; HRMS (EI) calcd for $C_{14}H_{10}INO_2$ (M^+) 350.9758, found 350.9738. Anal. Calcd for $C_{14}H_{10}INO_2$: C, 47.89; H, 2.87. Found: C, 47.89; H, 2.72.

4-(5-Iodo-2-methoxyphenoxy)benzaldehyde. A solution of **8** (6.0 g, 17.1 mmol) in 330 mL of ether under N_2 was cooled to −78 °C. DIBAL-H (1 M solution in cyclohexane, 22 mL, 22 mmol) was added dropwise over 20 min. The reaction mixture was stirred for 7 h at −78 °C, and the reaction flask was transferred to an ice–water bath. After 30 min, the reaction mixture was transferred into a stirred solution of 10% AcOH (300 mL) by cannula. The organic layer was separated, washed (water, 1 N $NaHCO_3$, and brine), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, 20%–30% ethyl acetate/hexanes), affording 6.0 g (16.94 mmol, 99%) of the aldehyde as a white crystalline solid: mp = 63–64 °C; R_f = 0.36 (30% ethyl acetate/hexanes); IR ($CDCl_3$) 3069, 3013, 2966, 2940, 2840, 2738, 1696, 1602, 1492 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.90 (s, 1 H), 7.82 (d, J = 8.7 Hz, 2 H), 7.52 (dd, J = 8.6, 2.1 Hz, 1 H), 7.37 (d, J = 2.1 Hz, 1 H), 6.97 (d, J = 8.7 Hz, 2 H), 6.78 (d, J = 8.6 Hz, 1 H), 3.76 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 162.9, 151.9, 143.9, 131.4, 81.9; *CH*, 190.7, 135.3, 131.9 (2), 131.2, 116.5 (2), 115.0; CH_3, 56.1; HRMS (EI) calcd for $C_{14}H_{11}IO_3$ (M^+) 353.9754, found 353.9731. Anal. Calcd for $C_{14}H_{11}IO_3$: C, 47.48; H, 3.13. Found: C, 47.60; H, 2.96.

Methyl (*Z*)-3-[4-(5-Iodo-2-methoxyphenoxy)phenyl]-acrylate (9). A solution of phosphono ester (5.59 g, 17.6 mmol) and 18-crown-6 (13.54 g, 51.3 mmol) in 350 mL of dry THF was cooled to −78 °C under N_2, and $KN(TMS)_2$ (0.75 M solution in toluene, 23.5 mL, 17.6 mmol) was added dropwise over 15 min. After 10 min, a solution of the aldehyde (5.19 g, 14.6 mmol) in 80 mL of dry THF was added by cannula, and the resulting mixture was stirred for 10 h at −78 °C. Saturated NH_4Cl was added, and the product was extracted into ether (2×). The ether extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude yellow crystalline solid was dissolved in hexanes, and the yellow, insoluble solid was removed by filtration. The filtrate was concentrated to give **9** (5.64 g, 13.75 mmol, 94%) as a white crystalline solid: mp = 98.5–100 °C; R_f = 0.45 (30% ethyl acetate/hexanes); IR ($CDCl_3$) 2946, 2963, 2838, 1720, 1625, 1602, 1504, 1491, 1294, 1024 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 8.7 Hz, 2 H), 7.44 (dd, J = 8.6, 2.0 Hz, 1 H), 7.29 (d, J = 2.0 Hz, 1 H), 6.88 (d, J = 8.7 Hz, 2 H), 6.86 (d, J = 12.7 Hz, 1 H), 6.75 (d, J = 8.6 Hz, 1 H), 5.87 (d, J = 12.7 Hz, 1 H), 3.78 (s, 3 H), 3.71 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) δ *C*, 166.7, 158.4, 151.8, 145.3, 129.4, 81.9; *CH*, 143.0, 134.2, 132.1 (2), 130.3, 117.8, 116.4 (2), 114.9; CH_3, 56.1, 51.4; HRMS (EI) calcd for $C_{17}H_{15}IO_4$ (M^+) 410.0017, found 410.0002. Anal. Calcd for $C_{17}H_{15}IO_4$: C, 49.78; H, 3.69. Found: C, 49.98; H, 3.80.

Methyl 3-[4-(5-Iodo-2-methoxyphenoxy)phenyl]-3-(phenylsulfanyl)propionate. To a solution of DBU (0.93 mL, 6.2 mmol) in 200 mL of dry THF under Ar was added thiophenol (10.6 mL, 104 mmol) at ambient temperature. Unsaturated ester **9** (1.7 g, 4.14 mmol) dissolved in 50 mL of dry THF was added by cannula, and the reaction mixture was heated under reflux for 30 h. The mixture was cooled and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 5% ethyl acetate in 50% dichloromethane/hexanes) afforded the product (2.03 g, 3.9 mmol, 94%) as a white crystalline solid: mp = 92–93 °C; R_f = 0.43 (5% ethyl acetate in 50% CH_2Cl_2/hexanes); IR ($CDCl_3$) 3002, 2949, 2838, 1737, 1581, 1504, 1491, 1294, 1025 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (dd, J = 8.6, 2.0 Hz, 1 H), 7.31–7.23 (m, 5 H), 7.18–7.15 (m, 3 H), 6.83 (d, J = 8.6 Hz, 2 H), 6.73 (d, J = 8.6 Hz, 1 H), 4.63 (t, J = 7.7 Hz, 1 H), 3.79 (s, 3 H), 3.59 (s, 3 H), 2.96 (dd, J = 15.7, 7.2 Hz, 1 H), 2.89 (dd, J = 15.7, 8.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 171.1, 156.2, 151.2, 146.0, 135.1, 133.2, 81.8; *CH*, 133.5(2), 133.3, 128.8 (5), 127.9, 117.5 (2), 114.5, 48.4; CH_2, 40.6; CH_3, 55.9, 51.8; HRMS (CI) calcd for $C_{23}H_{21}O_4IS$ (M^+) 520.0207, found 520.0213. Anal. Calcd for $C_{23}H_{21}O_4IS$: C, 53.09; H, 4.07. Found: C, 53.24; H, 4.17.

3-[4-(5-Iodo-2-methoxyphenoxy)phenyl]-3-(phenylsulfanyl)propan-1-ol (10). A solution of starting ester (1.82 g, 3.5 mmol) in 250 mL of ether under N_2 was cooled to −78 °C. DIBAL-H (1 M solution in cyclohexane, 10.6 mL, 10.6 mmol) was added dropwise over 20 min. The reaction mixture was stirred for 2 h at −78 °C, and the reaction flask was transferred to an ice–water bath. After 30 min, the reaction mixture was transferred into a stirred solution of 10% AcOH (250 mL) by cannula. The organic layer was separated, washed (water, 1 N $NaHCO_3$, and brine), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, 40% ethyl acetate/hexanes), affording 1.72 g (3.49 mmol, 99%) of **10** as colorless, sticky liquid: R_f = 0.26 (40% ethyl acetate/hexanes); IR (neat) 3600–3200, 3056, 3003, 2938, 2838, 1606, 1581, 1504, 1439, 1294, 1025 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (dd, J = 8.6, 2.0 Hz, 1 H), 7.26–7.13 (m, 8 H), 6.82 (d, J = 8.6 Hz, 2 H), 6.72 (d, J = 8.6 Hz, 1 H), 4.33 (t, J = 7.5 Hz, 1 H), 3.8–3.69 (m, 4 H), 3.62–3.54 (m, 1 H), 2.27–2.03 (m, 2 H), 1.71 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 156.0, 151.2, 146.4, 136.5, 134.2, 81.9; *CH*, 133.3, 132.9 (2), 129.1 (2), 128.8 (2), 128.7, 127.4, 117.7 (2), 114.6, 49.6; CH_2, 60.4, 38.6; CH_3 56.0; HRMS (EI) calcd for $C_{22}H_{21}O_3IS$ (M^+) 492.0258, found 492.0276. Anal. Calcd for $C_{22}H_{21}O_3IS$: C, 53.67; H, 4.30. Found: C, 53.70; H, 4.46.

Ethyl (*Z*)-3-{3-[4-(3-Hydroxy-1-(phenylsulfanyl)propyl)phenoxy]-4-methoxyphenyl}acrylate (11). A solution of $Pd(OAc)_2$ (72 mg, 0.32 mmol) and ethyl (*Z*)-3-(tributylstannyl)acrylate[12] (6.72 g, 17.3 mmol) in 100 mL of *N*-methyl-2-pyrrolidinone (NMP) under N_2 was stirred for 30 min at ambient temperature. To the resulting dark suspension was added a solution of **10** (1.58 g, 3.2 mmol) in 50 mL of NMP by cannula, and the reaction mixture was stirred for 40 h. The mixture was diluted with ethyl acetate and washed with water (3 × 200 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, 40% ethyl acetate/hexanes) to yield **11** (1.185 g, 2.55 mmol, 79%) as colorless oil: R_f = 0.21 (40% ethyl acetate/hexanes); IR (neat) 3600–3200, 3057, 2935, 2838, 1714, 1603, 1505, 1273, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (dd, J = 8.5, 2.0 Hz, 1 H), 7.32 (d, J = 2.0 Hz, 1 H), 7.27–7.13 (m, 7 H), 6.94 (d, J = 8.5 Hz, 1 H), 6.84 (d, J = 8.6 Hz, 2 H), 6.74 (d, J = 12.7 Hz, 1 H), 5.81 (d, J = 12.7 Hz, 1 H), 4.33 (t, J = 7.6 Hz, 1 H), 4.11 (q, J = 7.1 Hz, 2 H), 3.82 (s, 3 H), 3.76–3.67 (m, 1 H), 3.61–3.52 (m, 1 H), 2.26–2.02 (m, 2 H), 1.69 (s, 1 H), 1.21 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 166.3, 156.8, 152.2, 144.4, 135.9, 134.6, 127.9; *CH*, 142.2, 132.7 (2), 129.0 (2), 128.8 (2), 127.5, 127.3, 122.8, 118.3, 117.4 (2), 111.9, 49.6; CH_2, 60.5, 60.3, 38.8; CH_3, 56.0, 14.2; HRMS (EI) calcd for $C_{27}H_{28}O_5S$ (M^+) 464.1657, found 464.1669.

Methyl 3-{3-[4-(3-Hydroxy-1-(phenylsulfanyl)propyl)-phenoxy]-4-methoxyphenyl}propionate. The flask charged

with Mg turnings (13.4 g, 0.55 mmol, predried at 200 °C) under N_2 was cooled in an ice–water bath. Dry MeOH (400 mL) was added, and a solution of **11** (2.54 g, 5.47 mmol) in 60 mL of dry MeOH was added by cannula. The reaction mixture was allowed to warm slowly to rt. After 22 h, the reaction was quenched with 1 N HCl, and the mixture was extracted with ether. The organic layer was washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by chromatography (SiO_2, 30–40% ethyl acetate/hexanes) yielded the methyl ester (2.17 g, 4.8 mmol, 88%) as colorless oil: R_f = 0.31 (50% ethyl acetate/hexanes); IR (neat) 3600–3200, 3000, 2949, 2837, 1735, 1605, 1582, 1505, 1480, 1271, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27–7.13 (m, 7 H), 6.95–6.75 (m, 5 H), 4.33 (t, J = 7.5 Hz, 1 H), 3.8–3.69 (m, 4 H), 3.63–3.53 (m, 4 H), 2.83 (t, J = 7.7 Hz, 2 H), 2.55 (t, J = 7.7 Hz, 2 H), 2.26–2.04 (m, 2 H), 1.69 (bs, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 173.4, 157.1, 149.9, 145.1, 135.9, 134.7, 133,7; *C*H, 132.8 (2), 129.1 (2), 128.9 (2), 127.4, 124.5, 120.9, 117.4 (2), 113.1, 49.7; *C*H_2, 60.6, 38.9, 35.9, 30.3; *C*H_3, 56.2, 51.8; HRMS (EI) calcd for $C_{26}H_{28}O_5S$ (M^+) 452.1657, found 452.1655. Anal. Calcd for $C_{26}H_{28}O_5S$: C, 69.00; H, 6.24. Found: C, 68.88; H, 6.24.

3-{3-[4-(3-Hydroxy-1-(phenylsulfanyl)propyl)phenoxy]-4-methoxyphenyl}propionic acid (12). To a mixture of 80 mL of 2 N NaOH and 200 mL of MeOH was added a solution of the methyl ester (2.07 g, 4.57 mmol) in 20 mL of MeOH at ambient temperature. The reaction mixture was stirred for 3 h. The reaction was quenched with 1 N $NaHSO_4$, and the mixture was extracted with ether. The organic layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, 50% ethyl acetate/hexanes–3% AcOH in 50% ethyl acetate/hexanes) to furnish **12** (1.95 g, 4.44 mmol, 97%) as a colorless oil: R_f = 0.29 (3% AcOH in 50% ethyl acetate/hexanes); IR (neat) 3600–2400, 2934, 2837, 1714, 1605, 1514, 1480, 1269, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26–7.12 (m, 7 H), 6.95–6.75 (m, 5 H), 6.56 (bs, 2 H), 4.32 (t, J= 7.7 Hz, 1 H), 3.77 (s, 3 H), 3.78–3.67 (m, 1 H), 3.62–3.53 (m, 1 H), 2.83 (t, J = 7.6 Hz, 2 H), 2.58 (t, J = 7.6 Hz, 2 H), 2.26–2.03 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 178.1, 156.7, 149.6, 144.9, 135.5, 134.3, 133.1; *C*H, 132.6 (2), 128.9 (2), 128.6 (2), 127.2, 124.1, 120.5, 117.3 (2), 112.8, 49.4; *C*H_2, 60.3, 38.5, 35.6, 29.7; *C*H_3, 55.9; HRMS (CI) calcd for $C_{25}H_{30}NO_5S$ (M^+ + NH_4) 456.1844, found 456.1869. Anal. Calcd for $C_{25}H_{30}NO_5S$: C, 68.47; H, 5.98. Found: C, 68.66; H, 6.08.

4-Methoxy-14-(phenylsulfanyl)-2,11-dioxatricyclo-[13.2.2.1^{3,7}]eicosa-1(18),3,5,7(20),1(19),16-hexaen-10-one (13). To a solution of PPh_3 (2.77 g, 10.56 mmol) in 1.3 L of dry toluene under Ar was added diethyl azodicarboxylate (DEAD) (1.7 mL, 11.0 mmol) at ambient temperature. After 20 min, a solution of **12** (926 mg, 2.11 mmol) in 5 mL of THF and 15 mL of toluene was added dropwise using a syringe pump. The reaction mixture was stirred vigorously at ambient temperature during the addition. Half of the solution of **12** was added over 6.6 h, and then the mixture was stirred for 6.5 h. Second portions of PPh_3 (1.38 g, 5.26 mmol) and DEAD (0.8 mL, 5.18 mmol) were added, and the remaining solution of **12** was added over 7 h. The reaction mixture was stirred for another 10 h and then concentrated under reduced pressure to give a red oil. The crude product was purified by chromatography on silica gel, eluting with 20–30% ethyl acetate/hexanes, to give **13** (790 mg, 1.88 mmol, 89%) as a white crystalline solid: mp = 127–128 °C; R_f = 0.31 (30% ethyl acetate/hexanes); IR ($CDCl_3$) 3057, 2956, 2835, 1730, 1518, 1265, 1219 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (dd, J = 8.5, 2.0 Hz, 1 H), 7.38 (d, J = 7.5 Hz, 2 H), 7.28–7.18 (m, 4 H), 7.12 (dd, J = 8.5, 2.3 Hz, 1 H), 6.96 (dd, J = 8.1, 2.3 Hz, 1 H), 6.79 (d, J = 8.2 Hz, 1 H), 6.64 (d, J = 8.2 Hz, 1 H), 5.33 (s, 1 H), 4.28 (dd, J = 11.1, 5.0 Hz, 1 H), 4.14 (dd, J = 12.0, 7.6 Hz, 1 H), 3.96–3.89 (m, 4 H), 3.04 (dd, J = 16.8, 10.9 Hz, 1 H), 2.63 (dd, J = 16.8, 7.8 Hz, 1 H), 2.50–2.31 (m, 2 H), 2.24–2.11 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 173.9, 155.9, 151.2, 146.4, 137.3, 134.7, 133.4; *C*H, 131.9 (2), 131.2, 129.4, 129.1 (2), 127.4, 124.8, 123.1, 121.1, 113.6, 112.1, 52.1; *C*H_2, 63.1, 35.5, 32.9, 27.1; *C*H_3, 56.4; HRMS (EI) calcd for $C_{25}H_{24}O_4S$ (M^+) 420.1395, found 420.1411. Anal. Calcd For $C_{25}H_{24}O_4S$: C, 71.41; H, 5.75. Found: C, 71.66; H, 5.70.

4-Hydroxy-14-(phenylsulfanyl)-2,11-dioxatricyclo-[13.2.2.1^{3,7}]eicosa-1(18),3,5,7(20),1(19),16-hexaen-10-one. To a mixture of $AlBr_3$ (1.0 M solution in CH_2Br_2, 2.95 mL, 2.95 mmol) and ethanethiol (2.75 mL, 36.8 mmol) at 0 °C under N_2 was transferred a solution of **13** (155 mg, 0.368 mmol) in 15 mL of CH_2Cl_2 by cannula. After being stirred for 1 h, the reaction mixture was poured into water (60 mL), acidified with 0.5 N HCl, and then extracted with CH_2Cl_2. The aqueous layer was extracted again with CH_2Cl_2. The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and then evaporated to give a crude material. Purification by flash chromatography (SiO_2, 30% ethyl acetate/hexanes) afforded the demethylated product (140 mg, 0.344 mmol, 94%) as a white crystalline solid: mp = 177.5–178.5 °C; R_f = 0.28 (30% ethyl acetate/hexanes); IR ($CDCl_3$) 3600–3200, 3058, 2956, 1727, 1596, 1519, 1503, 1439 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (dd, J = 8.5, 2.2 Hz, 1 H), 7.38 (dd, J = 7.5, 1.1 Hz, 2 H), 7.29–7.17 (m, 4 H), 7.10 (dd, J = 8.5, 2.4 Hz, 1 H), 6.91 (dd, J = 8.5, 2.4 Hz, 1 H), 6.82 (d, J = 8.1 Hz, 1 H), 6.59 (dd, J = 8.1, 1.6 Hz, 1 H), 5.52 (s, 1 H), 5.29 (d, J = 1.6 Hz, 1 H), 4.29 (dd, J = 11.2, 5.0 Hz, 1 H), 4.11 (dd, J = 12, 7.5 Hz, 1 H), 3.94 (dd, J = 12, 7.5 Hz, 1 H), 3.02 (dd, J = 16.6, 11.0 Hz, 1 H), 2.62 (dd, J = 16.6, 7.6 Hz, 1 H), 2.52–2.31 (m, 2 H), 2.22–2.11 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 173.9, 155.4, 148.9, 142.6, 137.7, 134.5, 132.7; *C*H, 131.9 (2), 131.2, 129.4, 129.0 (2), 127.3, 124.6, 122.9, 121.7, 115.2, 112.8, 51.9; *C*H_2, 62.9, 35.3, 32.9, 27.1; HRMS (EI) calcd for $C_{24}H_{22}O_4S$ (M^+) 406.1239, found 406.1262. Anal. Calcd for $C_{24}H_{22}O_4S$: C, 70.91; H, 5.46. Found: C, 70.85; H, 5.64.

Combretastatin D-2 (2). To a solution of the phenol (52 mg, 0.127 mmol) in 50 mL of MeOH was added slowly Oxone (0.25 M aqueous solution, 0.26 mL, 0.065 mmol). The reaction mixture was stirred at ambient condition. After 15 min, another portion of the Oxone solution (0.16 mL, 0.04 mmol) was added. The reaction was monitored by TLC. The mixture was partitioned into ether and brine. The organic layer was washed with water, dried over $MgSO_4$, filtered, and evaporated to give the crude sulfoxides. The sulfoxides were dissolved in toluene (15 mL) and heated under reflux overnight. The mixture was cooled to rt and purified by flash chromatography (SiO_2, 10–20% ethyl acetate/hexanes) to afford combretastatin D-2 (36.8 mg, 0.124 mmol, 98%) as a white crystalline solid: mp = 154.5–155 °C (lit.[2b] mp = 148–151 °C, lit.[3] mp = 152–154.5 °C); R_f = 0.28 (20% ethyl acetate/hexanes); IR ($CDCl_3$) 3387, 3036, 2970, 2915, 1728, 1593, 1438, 1378, 1232 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, J = 8.3 Hz, 2 H), 7.12–7.06 (m, 3 H), 6,83 (d, J = 8.2 Hz, 1 H), 6.62 (dd, J = 8.2, 1.7 Hz, 1 H), 6.05 (dt, J = 10.9, 6.8 Hz, 1 H), 5.51 (s, 1 H), 5.06 (d, J = 1.7 Hz, 1 H), 4.63 (d, J = 6.8 Hz, 2 H), 2.86 (m, 2 H), 2.28 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 173.1 (C17), 155.3 (C8), 149.0 (C10 or C11), 142.2 (C10 or C11), 135.1 (C5 or C14), 131.7 (C5 or C14); *C*H, 137.5 (C4), 128.8 (C6 and C18), 125.4 (C3), 123.7 (C7 and C19), 121.6 (C13), 115.2 (C12), 112.3 (C20); *C*H_2, 58.8 (C2), 31.1 (C16), 26.6 (C15); HRMS (EI) calcd for $C_{18}H_{16}O_4$ (M^+) 296.1048, found 296.1066. Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.74; H, 5.44.

Combretastatin D-2 Acetate. To a solution of combretastatin D-2 (116 mg, 0.39 mmol) in 30 mL of CH_2Cl_2 under N_2 at ambient temperature were added Et_3N (109 μL, 0.78 mmol), DMAP (4.8 mg, 0.039 mmol), and Ac_2O (74 μL, 0.78 mmol). The reaction mixture was stirred at ambient temperature for 7 h. The reaction was quenched with saturated $NaHCO_3$, and the solution was extracted with ether, washed with 1 N $NaHSO_4$ and water, dried over $MgSO_4$, filtered, and purified by chromatography (SiO_2, 30% ethyl acetate/hexanes) to afford the acetylated product (128 mg, 0.38 mmol, 97%) as a white crystalline solid: mp = 122–123 °C; R_f = 0.33 (30% ethyl acetate/hexanes); IR ($CDCl_3$) 2957, 1764, 1731, 1592, 1502, 1256, 1193, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.3 (d, J = 8.4 Hz, 2 H), 7.10–7.06 (m, 3 H), 6.93 (d, J = 8.2 Hz, 1 H), 6.71 (d, J = 8.2 Hz, 1 H), 6.04 (dt, J = 11.0, 6.8 Hz, 1 H), 5.18 (s, 1 H), 4.64 (d, J = 6.8 Hz, 2 H), 2.90 (m, 2 H), 2.38 (s, 3 H), 2.29 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 173.1, 169.3, 155.8, 153.4, 138.6, 136.7, 135.3; *C*H, 137.8, 129.0 (2),

125.5, 123.9 (2), 122.7, 121.7, 114.2; CH_2, 59.2, 31.1, 27.2; CH_3, 20.9; HRMS (EI) calcd for $C_{20}H_{18}O_5$ (M^+) 338.1154, found 338.1156.

(±)-**Combretastatin D-1 Acetate.** To a solution of the acylated phenol (43 mg, 0.127 mmol) in 5 mL of CH_2Cl_2 under N_2 was added a solution of MCPBA (80–85%, 151 mg, 0.72 mmol) at rt. The reaction mixture was stirred for 4 d. The reaction was quenched with Me_2S (47 μL, 0.64 mmol), and the solution was washed with saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 20% ethyl acetate/hexanes) yielded the expected oxirane (32.4 mg, 0.091 mmol, 72%) as a white crystalline solid: mp = 140.5–141.5 °C; R_f = 0.24 (30% ethyl acetate/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (dd, J = 8.4, 2.2 Hz, 1 H), 7.33 (dd, J = 8.4, 2.2 Hz, 1 H), 7.15–7.04 (m, 2 H), 6.92 (d, J = 8.1 Hz, 1 H), 6.69 (d, J = 8.1 Hz, 1 H), 5.08 (s, 1 H), 4.33 (d, J = 4.1 Hz, 1 H), 4.25 (dd, J = 12, 4.9 Hz, 1 H), 3.90 (dd, J = 12, 9.2 Hz, 1 H), 3.46 (ddd, J = 9.2, 4.9, 4.1 Hz, 1 H), 3.16 (dd, J = 17.0, 12.3 Hz, 1 H), 2.61 (dd, J = 17.0, 7.2 Hz, 1 H), 2.45–2.37 (m, 4 H), 2.14 (dd, J = 17.4, 12.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 169.1, 156.1, 153.0, 138.4, 136.7, 132.1, 128.7, 126.1, 123.7, 123.0, 122.5, 121.6, 113.8, 62.5, 55.7, 52.8, 30.9, 27.1, 20.7; HRMS (EI) calcd for $C_{20}H_{18}O_6$ (M^+) 354.1103, found 354.1105.

(±)-**Combretastatin D-1.** Starting material (46 mg, 0.13 mmol) was dissolved in 10 mL of NH_3-saturated MeOH, and the reaction mixture was stirred overnight at ambient temperature. After removal of solvent, the residue was purified by flash chromatography (SiO_2, 20% ethyl acetate/hexanes) to afford (±)-combretastatin D-1 (38 mg, 0.12 mmol, 94%) as a white crystalline solid: R_f = 0.28 (30% ethyl acetate/hexanes); IR ($CDCl_3$) 3500–3200, 2955, 2917, 2848, 1736, 1597, 1538, 1519, 1506 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, J = 8.5, 2.1 Hz, 1 H), 7.37 (dd, J = 8.5, 2.1 Hz, 1 H), 7.11–7.04 (m, 2 H), 6.83 (d, J = 8.1 Hz, 1 H), 6.61 (d, J = 8.1 Hz, 1 H), 5.53 (s, 1 H), 4.93 (s, 1 H), 4.35 (d, J = 4.0 Hz, 1 H), 4.26 (dd, J = 12.0, 4.9 Hz, 1 H), 3.87 (dd, J = 12.0, 9.2 Hz, 1 H), 3.48 (ddd, J = 9.2, 4.6, 4.0 Hz, 1 H), 3.10 (dd, J = 16.9, 12.4 Hz, 1 H), 2.58 (dd, J = 16.9, 6.2 Hz, 1 H), 2.39 (dd, J = 17.4, 6.2 Hz, 1 H), 2.12 (dd, J = 17.4, 12.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ C, 172.8, 156.1, 149.2, 142,7, 132.6, 132.0; CH, 129.0, 126.5, 124.1, 123.3, 122.2, 115.6, 112.3, 56.0, 53.2; CH_2, 62.7, 31.4, 27.1; HRMS (EI) calcd for $C_{18}H_{16}O_5$ (M^+) 312.0997, found 312.0984.

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Supplementary Material Available: Proton NMR spectra for compound **11** and combretastatins D-2, D-2 acetate, D-1 acetate, and D-1 (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.