Antineoplastic Agents. 565. Synthesis of Combretastatin D-2 Phosphate and Dihydro-combretastatin D-2[1]

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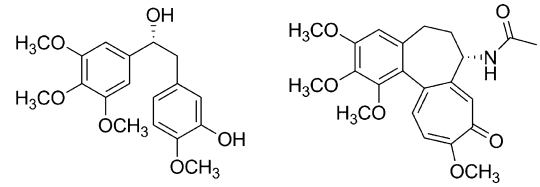
A modified synthetic route to combretastatin D-2 (**5**) was devised in order to further evaluate its biological activity, for its conversion to phosphate prodrugs (**25**−**28**), and as a route to obtaining dihydro-combretastatin D-2 (**42**). A parallel first total synthesis of dihydro-combretastatin D-2 was completed, proceeding from a saturated 3-phenylpropionic ester intermediate via the Ullmann biaryl ether reaction (**39**−**41**). In contrast to the cancer cell growth inhibitory activity exhibited by combretastatin D-2, relatively minor structural modifications (**41**, **42**) caused elimination of those properties.

The naturally occurring series of cancer cell growth inhibitors designated combretastatins was isolated from the South African bush willow tree *Combretum caffrum*.[2] We reported the first of the series, designated combretastatin (**1**), in 1982.[3,4] Bibenzyl **1** inhibited growth of the murine P388 lymphocytic leukemia cell line (ED_{50} 1.1 × 10^{-2} μg/mL), inhibited tubulin polymerization (IC_{50} 5−7 μM), and competitively inhibited the binding of colchicine (**2**) to tubulin.[3,4] Subsequently, we found the *C. caffrum* tree to contain a series of stilbenes designated the combretastatin A series,[5−7] and two of these, combretastatins A-1 (**3a**)[5] and A-4 (**3d**),[7] exhibited substantial promise on the basis of antineoplastic activity and inhibition of tubulin polymerization. Owing to the remarkable cancer vascular targeting activity of combretastatin A-4 (**3d**, P388 ED_{50} 3.4 × 10^{-3} μg/mL),[7] the phosphate prodrug (CA4P)[2,8a] of *cis*-stilbene **3d** has been undergoing extended clinical trials[8b] in the United States and Europe. Those advances toward improving human cancer treatments have recently been augmented by initiation of the phase 1 human cancer clinical trial of combretastatin A-1 (**3a**, aka OXI4503) phosphate prodrug (CA1P).[2,8c]

Two macrocyclic lactones, combretastatin D-1 (**4**)[9] and combretastatin D-2 (**5**),[10] were also isolated from *C. caffrum*. Combretastatin D-1 (**4**, P388 ED_{50} 3.3 μg/mL)[9] possesses an epoxide ring, while the D-2 (**5**) contains the corresponding *cis*-olefin and exhibits a P388 ED_{50} of 5.2 μg/mL.[10] Since the initial cancer cell growth inhibitory activities of the D-series did not seem impressive when compared to the A-series, development of useful syntheses to provide enough for further biological evaluations was placed at a lower priority than that of the A-series. We reassessed the priority in 1999 when it was reported[11] that the D-series exhibits a different mode of action from the A-series during cell division. The A-series combretastatins bind to the colchicine binding site on tubulin and prevent microtubule assembly (destabilize), which ultimately prevents cell division. Combretastatins D-1 (CD1) and D-2 (CD2) were shown to allow assembly of the microtubules (stabilize) but not allow the microtubules to disassemble later in cell division.[11] That led us to reinvestigate the potential of combretastatin D-2 (**5**) by first completing a useful synthesis, followed by conversion to a phosphate prodrug to increase aqueous solubility/transport and reduction to the dihydro derivative for SAR purposes, and to examine the tubulin stabilization effects. At this point in 1999, six syntheses of lactone **5** had already been reported,[12a−h] and it was clear from these studies, and others, that cyclization of biaryl ethers to form relatively small macrocyclic lactones is a challenge and usually results in low yields.



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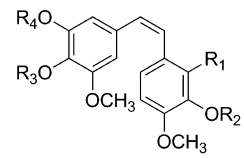
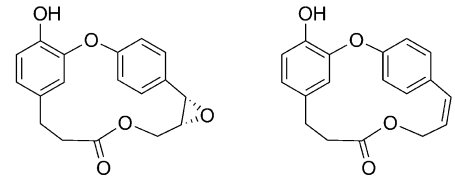


3a, R_1 = OH, R_2 = H, R_3 = R_4 = CH_3, combretastatin A-1
b, R_1 = R_2 = H, R_3 = R_4 = -CH_2-, combretastatin A-2
c, R_1 = R_2 = R_4 = H, R_3 = CH_3, combretastatin A-3
d, R_1 = R_2 = H, R_3 = R_4 = CH_3, combretastatin A-4
e, R_1 = R_4 = H, R_2 = R_3 = CH_3, combretastatin A-5



4 **5**

Results and Discussion

As was previously demonstrated,[12] combretastatin D-2 (**5**) was, surprisingly, a synthetic challenge. One of the initial goals in developing a new synthesis of CD2 was to reduce the number of synthetic steps while optimizing the yield of the ring closure reaction, a macrocyclization using the Ullmann ether synthesis (Figure 1). A benzyl protecting group for the phenol was utilized in hopes of improving the overall yield from that achieved with the methyl protection used in previous syntheses, when regeneration of the phenol group of CD2 proved problematic.[12a]

Commercially available 3,4-dihydroxybenzaldehyde (**6**, Scheme 1) was selectively protected at the 4-position to afford in good yield aldehyde **7**,[13] which was then subjected to a Wittig elongation to afford α,β-unsaturated ester **9**.[12g,h,14] Hydrogenation of the olefin

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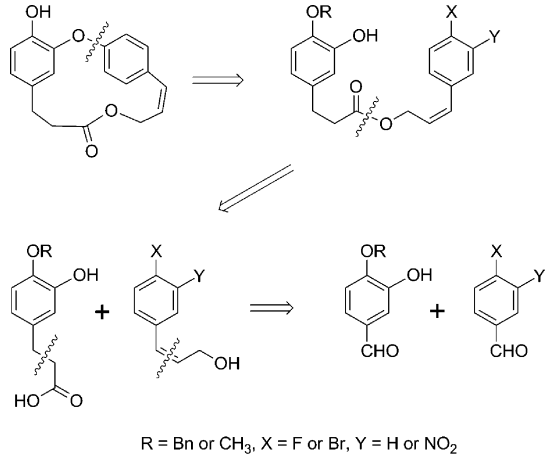
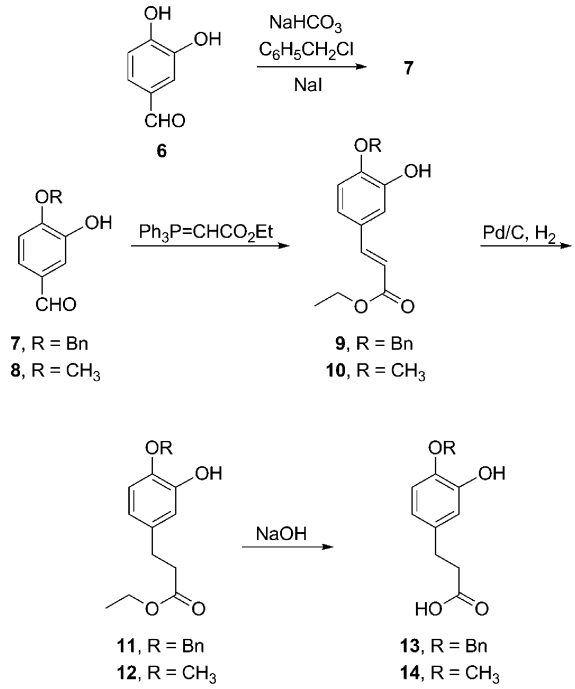


Figure 1. Retrosynthesis of combretastatin D-2.

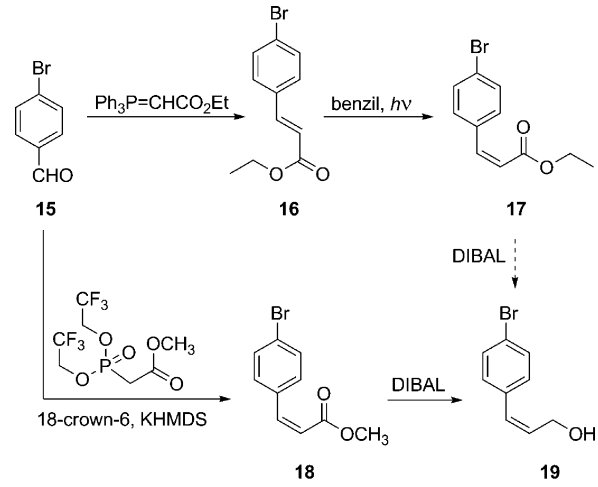
Scheme 1. Synthesis of 3-Phenylpropionic Acid Derivatives



with 5% palladium on carbon in benzene provided saturated ester **11**.[12h] The choice of solvent was vital to selectivity of the reduction. Significant cleavage of the benzyl group resulted when ethanol was the solvent choice, but yields of ester **11** improved by switching to benzene. Magnesium in methanol[12c,d] is specifically used for the reduction of α,β-unsaturated esters in the presence of other reducible functionalities,[15,16] but no reaction occurred on several attempts with this method. Hydrolysis of ester **11** using NaOH in THF−water afforded carboxylic acid **13** in nearly quantitative yield. The Wittig elongation, olefin reduction, and ester hydrolysis were also conducted on 3-hydroxy-4-methoxybenzaldehyde (**8**) to afford carboxylic acid **14** in high overall yield.

The initial synthesis of the allylic alcohol intermediate **19** proceeded through a photochemical isomerization of the *trans*-α,β-unsaturated ester **16** to generate the necessary *cis*-olefin moiety (Scheme 2). Commercially available 4-bromobenzaldehyde (**15**) was subjected to Wittig elongation using the stabilized ylide (carbethoxymethylene)triphenylphosphorane to yield the *trans*-α,β-unsaturated ester **16**,[12h] which was then photochemically isomerized (254 nm, 450 W mercury lamp) to the *cis*-olefin **17** using benzil in benzene.[17] The *cis*-olefin was typically generated in 45−65% yields and allowed for the recovery of the *trans*-isomer. A change in

Scheme 2. Synthesis of Allylic Alcohol **19**

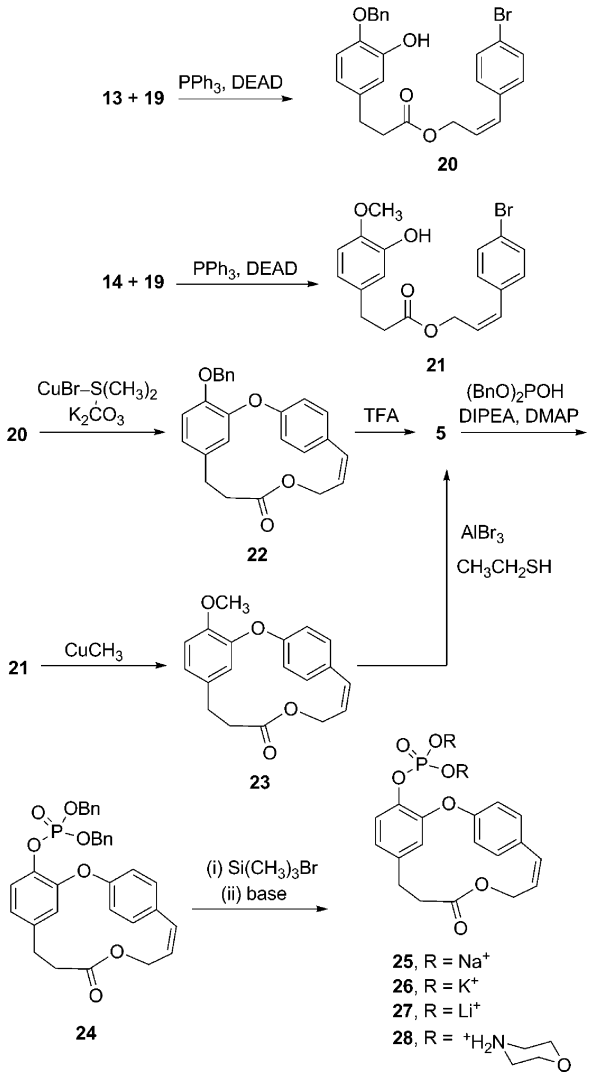


synthetic strategy was implemented owing to the moderate yields and the difficulty in separation of the *cis*-olefin from the *trans*-isomer and large quantities of benzil. Employment of the Still−Gennari modification of the Wadsworth−Horner−Emmons reaction[18] led to synthesis of the *cis*-α,β-unsaturated ester **18** in high yield and high stereoselectivity from 4-bromobenzaldehyde (**15**) (Scheme 2). The Horner−Emmons reaction is the traditional method for the synthesis of unsaturated esters, but it tends to form the more stable *trans*-olefin. The Still−Gennari modification employs electrophilic bistrifluoroethylphosphonoesters and strongly dissociated base systems such as KHMDS and 18-crown-6 to convert aldehydes to *cis*-unsaturated esters in high stereoselectivity.[18] DIBAL reduction[12a,h] of the *cis*-α,β-unsaturated ester **18** provided propenol derivative **19** in high yield.

Upon construction of the two subunits of combretastatin D-2, formation of the ester and biaryl ether was next undertaken. The route of choice was to first use the Mitsunobu-type reaction for ester formation, followed by the biaryl ether synthesis employing Ullmann conditions. Carboxylic acid **13** or **14** and alcohol **19** were coupled using Mitsunobu conditions[19a−e] to afford the new esters **20** and **21** (Scheme 3). Subsequent intramolecular biaryl ether formation to give **22** and **23**, respectively, was accomplished in low yields (0−25%) utilizing conditions (varying equivalents of CuBr-dimethyl sulfide complex and K_2CO_3 or methylcopper in pyridine) outlined by Boger.[12a] The methyl protecting group was removed from **23** using aluminum bromide and ethanethiol to afford CD2 (**5**) in 19% yield.[12d] Removal of the benzyl group from **22** using hydrogenation was not practical in the presence of the olefin, so instead neat trifluoroacetic acid was utilized.[20] These conditions removed the benzyl group but also opened the lactone at the ester group, preventing good yields of CD2 (**5**) from being realized. The structure of combretastatin D-2 was further confirmed by X-ray crystal structure determination (Figure 2).

Once the synthesis of CD2 was achieved, a series of phosphate salts was synthesized to investigate the effects of different cations on both the anticancer activity of the prodrug (Table 1) and its solubility characteristics (Table 2). Synthesis of the sodium phosphate (**25**) and other prodrugs (**26**−**28**) resulted from first treating phenol **5** with dibenzyl phosphite to yield the corresponding bis(benzyl)phosphate. The benzyl protecting groups were cleaved with bromotrimethylsilane, and subsequent treatment of the phosphoric acid with the appropriate cation precursor ($NaOCH_3$, KOH, LiOH, and morpholine, respectively) yielded prodrugs **25**−**28**. As recorded in Table 2, the prodrug salts had substantially increased water solubility, which is very important for transport to metastatic cancer,[2,8a] compared to the very sparingly soluble CD2. However, presumably owing to lack of the phosphatases needed to regenerate the drug in the isolated cancer cells, the prodrug salts did not

Scheme 3. Synthesis of Combretastatin D-2 (**5**) and Prodrug Salts



enhance inhibition of the cancer cell line growth compared to combretastatin D-2 (Table 1). Cancer tissue in vivo has greatly increased concentrations of the necessary phosphatases for cleavage of the prodrug ester bond.

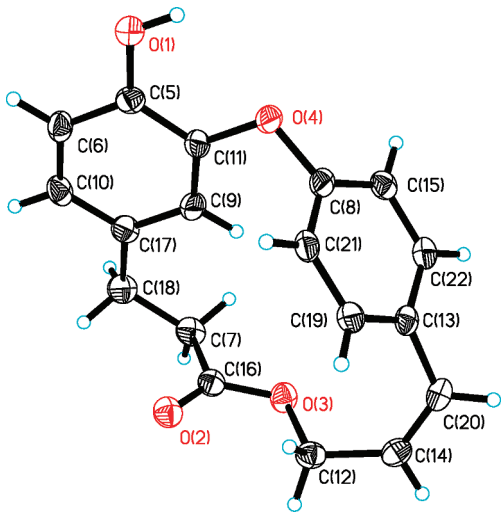


Figure 2. X-ray crystal structure of combretastatin D-2 (**5**) with 50% thermal ellipsoids.

Table 1. Results of Human Cancer Cell Line (GI_{50}, μg/mL) and Murine P388 Lymphocytic Leukemia Cell Line Inhibitory (ED_{50}, μg/mL) Evaluations

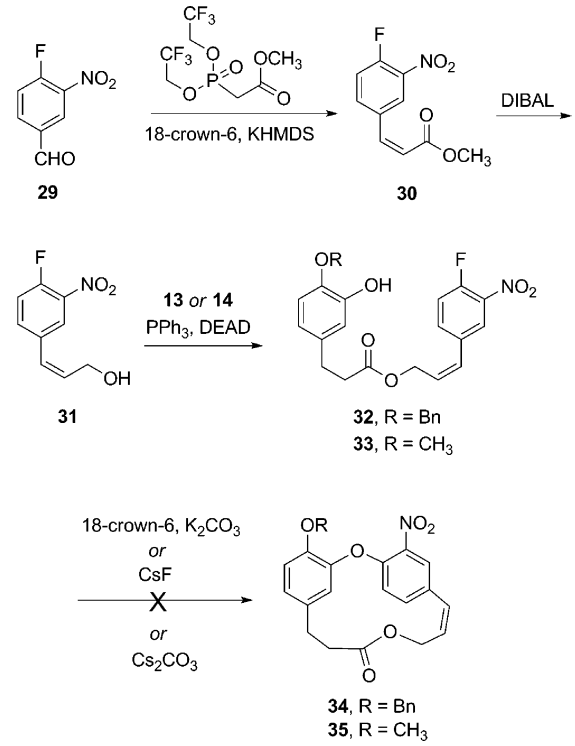
	structure no.						
cell line	**21**	**23**	**5**	**25**	**26**	**27**	**28**
P388[a]	>100	8.1	16.8	23.9	23.9	27.1	86.2
pancreas	16.4	7.3	4.8	22.1	40.1	35.9	>10
breast	16.4	0.83	6.6	30.5	34.5	26.1	>10
brain	18.5	2.2	4.7	36.3	45.2	37.9	>10
lung	16.5	6.6	6.0	13.3	27.8	14.4	>10
colon	17.1	9.4	>10	25.5	40.6	27.5	>10
prostate	8.9	5.6	2.7	18.2	14.4	4.3	>10

[a] Compounds **20**, **22**, **32**, and **40**−**42** led to ED_{50} > 100 and **33** gave ED_{50} 27.0 μg/mL.

Table 2. Solubility Comparison of Combretastatin D-2 and Prodrugs in Water (mg/mL) at 25 °C

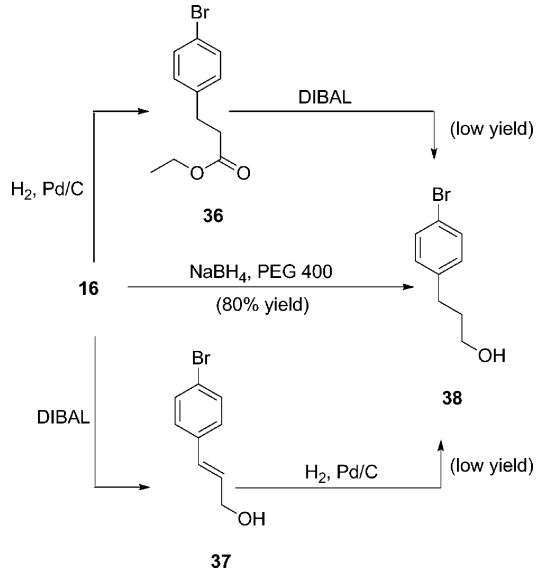
structure no.	mg/mL
5	0.5
25	>70
26	>50
27	20
28	5

Scheme 4. Attempted Synthesis of Nitro-combretastatin D-2 Benzyl and Methyl Ethers



The low yields of the intramolecular Ullmann ether synthesis during cyclization and the inability to cyclize using Mitsunobu conditions prompted a change in conditions for the synthesis of CD2 (**5**). A review of the literature led to a significant volume of work devoted to biaryl ether synthesis using 4-fluoro-3-nitrophenyl derivatives.[21a−k] To explore this approach, commercially available 4-fluoro-3-nitrobenzaldehyde (**29**) was subjected to the Still−Gennari modification of the Wadsworth−Horner−Emmons reaction[18] to afford the *cis*-α,β-unsaturated ester **30** in moderate yield (Scheme 4). DIBAL reduction of the ester provided allylic alcohol **31**, which was then subjected to Mitsunobu conditions in the presence of carboxylic acids **13** and **14** to afford esters **32** and **33**, respectively. However, attempts to cyclize **32** and **33** utilizing different reaction conditions failed (K_2CO_3, 18-crown-6, DMF; Cs_2CO_3, DMF; CsF, DMF, Scheme 4). Although use of the nitroaryl moiety initially

Scheme 5. Synthetic Routes to 3-Phenylpropyl Alcohol **38**

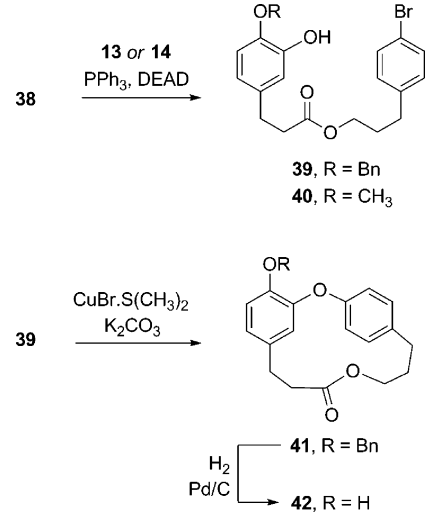


looked promising for effecting ring closure and for obtaining higher yields of CD2 (**5**) than the procedure outlined by Boger,[12a] the cyclization step proved difficult owing to the presence of the *cis*-double bond.

The difficulty of obtaining acceptable yields in the macrocyclization step leading to combretastatin D-2 led to examination of the necessity of the *cis*-olefin group to maintain cancer cell growth inhibition. It was expected that the ring closure would proceed in much higher yields in the absence of the *cis*-olefin, as seen in previous syntheses of combretastatin D-2,[12d,f,h] and that cyclization could proceed with either an Ullmann ether synthesis or a Mitsunobu ester formation. First, the *trans*-α,*β*-unsaturated ester **16** was hydrogenated using 5% palladium on carbon to yield ester **36** (Scheme 5). Hydrogenation of the olefin gave low yields owing to partial cleavage of the bromide group, as ascertained by spectroscopic analyses (mass spectrometry and IR). An alternative pathway via reduction of the ester to allylic alcohol **37** was next utilized. Hydrogenation of olefin **37** to produce saturated alcohol **38** also resulted in low yields, again owing to the removal of the bromide group. However, a one-step reaction was discovered that converted α,*β*-unsaturated ester **16** directly to alcohol **38** in good yield, using sodium borohydride and polyethylene glycol (PEG 400).[22] Next, propanol **38** and carboxylic acids **13** and **14** were subjected to Mitsunobu esterification to afford esters **39** and **40**, respectively. Intramolecular biaryl ether synthesis from **39** using Ullmann conditions afforded dihydro-combretastatin D-2 benzyl ether (**41**, 11% yield, Scheme 6), although ester **40** failed to cyclize under Ullmann conditions. Unfortunately, the yield of the macrolactonization applied to ester **39** was unexpectedly low, comparable to yields obtained in the presence of the double bond. Subsequent cleavage (hydrogenation) of the benzyl protecting group from **41** afforded dihydro-combretastatin D-2 (**42**) in good yield.

Although the absence of the olefin did not lead to an improved yield of the biaryl ether synthesis, dihydro-CD2 (**42**) was important for structure−activity relationship studies. Dihydro-CD2 (**42**) proved to be inactive (>100 *μ*g/mL, P388 cell line, Table 1), indicating that the olefin was necessary for cancer cell growth inhibition by combretastatin D-2 (**2**). The same lack of significant P388 cancer cell line activity held for all the intermediates from the different synthetic pathways utilized in the synthesis of combretastatin D-2. However, very important SAR results were provided by these cancer cell line evaluations and suggested that even some minor changes in the CD1 and CD2 natural product's structure can cause loss of activity.

Scheme 6. Synthesis of Dihydro-combretastatin D-2 (**42**)



Evaluation of combretastatin D-2 (**5**), dihydro-combretastatin D-2 (**42**), and their synthetic intermediates against the following microorganisms did not reveal any significant antibacterial or antifungal activity: *Candida albicans* (ATCC 90028), *Cryptococcus neoformans* (ATCC 90112), *Micrococcus luteus* (Presque Isle 456), *Staphylococcus aureus* (ATCC 29213), *Streptococcus pneumoniae* (ATCC 6303), *Escherichia coli* (ATCC 25922), *Stenotrophomonas maltophilia* (ATCC 13637), *Enterobacter cloacae* (ATCC 13047), *Enterococcus faecalis* (ATCC 29212), and *Neisseria gonorrhoeae* (ATCC 49226). In addition, both combretastatins D-1 (**4**) and D-2 (**5**) were found to be inactive ($IC_{50} > 40$ *μ*M) as inhibitors of tubulin assembly.[5]

Experimental Section

General Experimental Procedures. DCM refers to dichloromethane, DMF to dimethylformamide, THF to tetrahydrofuran, DIBAL to diisobutylaluminum hydride, DEAD to diethyl azodicarboxylate, and KHMDS to potassium hexamethyldisilazane; CC refers to silica gel column chromatography, and room temperature (rt) refers to 22−25 °C. All solvents were anhydrous. Reactions that required dry conditions were carried out under argon in flame-dried glassware equipped with a magnetic stir bar and a rubber septum. Distilled water was used in all aqueous solutions. Reactions were monitored by thin-layer chromatography using Analtech silica gel GHLF uniplates visualized with short-wavelength UV (254 nm) and stained with phosphomolybdic acid solution. Organic extracts were dried with anhydrous magnesium sulfate. Solvents for chromatography were redistilled prior to use, and column chromatography was achieved with either gravity (70−230 mesh ASTM) or flash (230−400 mesh ASTM) silica from EM Science. Melting points are uncorrected and were measured with a digital Electrothermal 9100 apparatus. The ^{1}H and ^{13}C NMR spectra were referenced to TMS or the deuterated solvent ($CDCl_3$). APT, HMQC, and HMBC techniques were utilized to assist in peak assignments.

3-Hydroxy-4-benzyloxybenzaldehyde (7). To a stirred solution of 3,4-dihydroxybenzaldehyde (**6**) (2.32 g, 16.8 mmol) in anhydrous DMF (84 mL) was added $NaHCO_3$ (2.13 g, 25.4 mmol), benzyl chloride (3.8 mL, 33 mmol), and NaI (0.80 g, 5.3 mmol). The mixture was stirred at 40 °C for 24 h. After cooling to rt, 1 N HCl (100 mL) was added and the solution extracted with EtOAc (4 × 75 mL). The combined organic extracts were washed with brine (2 × 75 mL), and the solvent was removed in vacuo to yield a brown oil. Separation by gravity CC (elution with 9:1−4:1 hexane−acetone) provided aldehyde **7** as a colorless solid, which crystallized from EtOH as colorless needles (2.46 g, 64%): mp 120.9−122.9 °C (lit.[13] mp 120−121 °C); spectroscopic data identical to literature data.[13]

Ethyl 3-(3′-Hydroxy-4′-benzyloxyphenyl)-2*E*-propenoate (9). Aldehyde **7** (2.29 g, 10.0 mmol) was treated with (carbethoxymethylene)triphenylphosphorane (4.51 g, 12.9 mmol) as described in the literature,[12h] with toluene (80 mL) replacing benzene, to afford α,*β*-

unsaturated ester **9** as a clear oil that solidified upon further drying under high vacuum. Recrystallization from EtOH provided a colorless, fluffy solid (2.95 g, 99%): mp 83.0−84.7 °C (lit.[12h] mp 80−85 °C); spectroscopic data identical to literature data.[12h]

Ethyl 3-(3′-Hydroxy-4′-methoxyphenyl)-2*E*-propenoate (10). A solution of 3-hydroxy-4-methoxybenzaldehyde (**8**, 8.01 g, 52.6 mmol) and (carbethoxymethylene)triphenylphosphorane (24.33 g, 69.84 mmol) in toluene (200 mL) at rt was stirred for 8 h. The solution was concentrated in vacuo to afford a yellow oil, which was subjected to gravity CC (4:1 hexane−acetone) to yield **10** as a clear oil that solidified upon further drying under high vacuum. Recrystallization from EtOAc−hexane provided colorless needles (11.67 g, 99%): mp 57.4−58.7 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.33 (3H, t, J = 7.2 Hz, OCH_2CH_3), 3.91 (3H, s, OCH_3), 4.25 (2H, q, J = 7.2 Hz, OCH_2CH_3), 5.75 (1H, s, OH), 6.28 (1H, d, J = 15.9 Hz, 2), 6.83 (1H, d, J = 8.1 Hz, 5′), 7.02 (1H, dd, J = 8.1, 2.1 Hz, 6′), 7.13 (1H, d, J = 2.1 Hz, 2′), 7.59 (1H, d, J = 15.9 Hz, 3); HRMS (EI$^+$) *m*/*z*, [M]$^+$ 222.0890 (calcd for $C_{12}H_{14}O_4$, 222.0892).

Ethyl 3-(3′-Hydroxy-4′-benzyloxyphenyl)propanoate (11). Ester **11** was prepared[12h] from olefin **9** (40.6 g, 136 mmol) as a colorless, crystalline solid (29.5 g, 72%): mp 60.4− 62.0 °C (lit.[12h] oil).

Ethyl 3-(3′-Hydroxy-4′-methoxyphenyl)propanoate (12). Palladium on carbon (5%, 704 mg) was added to a stirred solution of olefin **10** (9.48 g, 42.7 mmol) in CH_3OH (75 mL) at rt. Hydrogen gas was bubbled through the suspension until TLC analysis showed complete consumption of starting material. The catalyst was removed by filtration of the solution through a plug of Celite, and the solution was concentrated to a colorless solid that crystallized from EtOAc−hexane as colorless cubic crystals (9.45 g, 99%): mp 71.3−72.8 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.24 (3H, t, J = 7.2 Hz, OCH_2CH_3), 2.57 (2H, t, J = 8.1 Hz, 2), 2.86 (2H, t, J = 8.1 Hz, 3), 3.86 (3H, s, OCH_3), 4.12 (2H, q, J = 7.2 Hz, OCH_2CH_3), 5.60 (1H, s, OH), 6.67 (1H, dd, J = 8.1, 2.1 Hz, 6′), 6.76 (1H, d, J = 8.1 Hz, 5′), 6.77 (1H, d, J = 1.5 Hz, 2′); HRMS (FAB$^+$) *m*/*z* 225.1124 [M + H]$^+$ (calcd for $C_{12}H_{17}O_4$, 225.1127).

3-(3′-Hydroxy-4′-benzyloxyphenyl)propionic Acid (13). To a solution of ester **11** (29.38 g, 97.8 mmol) in THF−H_2O (1:1, 150 mL) was added NaOH (7.95 g, 199 mmol), and the resulting yellow solution was stirred at rt for 5 h. The reaction mixture was acidified to pH 1 with 1.0 N HCl and extracted with DCM (3 × 200 mL). The combined organic extracts were washed with brine (100 mL), dried, filtered, and concentrated in vacuo to afford a tan powder. Crystallization from EtOH provided colorless needles (26.2 g, 98%): mp 128.8−130.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.64 (2H, t, J = 7.8 Hz, 2), 2.87 (2H, t, J = 7.8 Hz, 3), 5.08 (2H, s, $ArCH_2$), 6.67 (1H, dd, J = 8.1, 2.1 Hz, 6′), 6.81 (1H, d, J = 2.1 Hz, 2′), 6.84 (1H, d, J = 8.1 Hz, 5′), 7.40 (5H, bs, 2″− 6″); HRMS (APCI$^+$) *m*/*z* 273.1112 [M + H]$^+$ (calcd for $C_{16}H_{17}O_4$, 273.1127).

3-(3′-Hydroxy-4′-methoxyphenyl)propionic Acid (14). To a stirred solution of ester **12** (63.2 g, 282 mmol) in THF−H_2O (1:1, 300 mL) was added NaOH (22.76 g, 569.0 mmol), and the resulting red-brown solution was heated to reflux for 1.5 h. The dark brown solution was then cooled to rt while stirring continued, and the THF was removed in vacuo. The resulting aqueous solution was acidified and extracted (see **13**), and the extract was washed and dried to afford an off-white solid. Recrystallization from EtOH provided colorless needles (43.9 g, 79%): mp 149.9−151.8 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.64 (2H, t, J = 8.1 Hz, 2), 2.87 (2H, t, J = 8.1 Hz, 3), 3.87 (3H, s, -OCH_3), 6.68 (1H, dd, J = 8.1, 2.1 Hz, 6′), 6.77 (1H, d, J = 8.1 Hz, 5′), 6.78 (1H, d, J = 1.5 Hz, 2′); HRMS (FAB$^+$) *m*/*z* 197.0876 [M + H]$^+$ (calcd for $C_{10}H_{13}O_4$, 197.0814).

Ethyl 3-(4′-Bromophenyl)-2*E*-propenoate (16). Ester **16** (7.63 g, 100%, trace of *Z*-isomer) was prepared from 4-bromobenzaldehyde (**15**, 5.55 g, 30.0 mmol) and (carbethoxymethylene)triphenylphosphorane (15.68 g, 45.0 mmol) as described in the literature,[12h] toluene (100 mL) replacing benzene as solvent.

Ethyl 3-(4′-Bromophenyl)-2*Z*-propenoate (17). A solution of **16** (9.99 g, 39.2 mmol) and benzil (41.26 g, 196.3 mmol) in benzene (2 L) was stirred under argon at rt for 25.5 h. The resulting yellow solution was irradiated with a UV lamp (254 nm) for 4 h. The orange solution was concentrated in vacuo to afford a yellow solid, which was purified by flash CC (19:1 hexane−EtOAc) to yield the *Z*-isomer as a clear oil (5.92 g, 59%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26 (3H, t, J = 7.2 Hz, OCH_2CH_3), 4.18 (2H, q, J = 7.2 Hz, OCH_2CH_3), 5.97 (1H, d, J = 12.6 Hz, 2), 6.86 (1H, d, J = 12.6 Hz, 3), 7.47 (4H, s, 2′, 3′, 5′, 6′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (OCH_2CH_3), 60.3 (OCH_2CH_3), 120.4 (2), 123.1 (4′), 131.0 (2′, 6′), 131.2 (3′, 5′), 133.5 (1′), 141.7 (3), 165.7 (1); HRMS (FAB$^+$) *m*/*z* 257.0008, 255.0019 [M + H]$^+$ (calcd for $C_{11}H_{12}O_2Br$, 257.0000, 255.0021); *anal*. C 52.16%, H 4.36%, calcd for $C_{11}H_{11}O_2Br$, C 51.79%, H 4.35%.

Methyl 3-(4′-Bromophenyl)-2*Z*-propenoate (18). Treatment of **15** (2.31 g, 12.5 mmol) with bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate (3.2 mL, 15 mmol), 18-crown-6 ether (13.63 g, 51.6 mmol), and KHMDS (0.5 M solution in toluene, 31 mL, 16 mmol) as described in the literature[23] yielded ester **18** as a colorless solid (2.84 g, 94%): mp 43.3−44.8 °C (lit.[23] mp 40−42 °C).

3-(4′-Bromophenyl)-2*Z*-propenol (19). To a cooled (−78 °C) solution of **18** (7.46 g, 30.9 mmol) in DCM (56 mL) under argon was added DIBAL (1 M solution in DCM, 80 mL, 80 mmol). After stirring for 2 h the reaction was terminated with H_2O (80 mL) and acidified to pH 1 with H_2SO_4 (18 M). The solution was extracted with DCM (5 × 75 mL), and the combined organic extracts were concentrated in vacuo to afford a solid. Gravity CC (9:1 hexane−acetone) provided **19** as a colorless solid (6.18 g, 94%): mp 69.3−70.6 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.60 (1H, s, OH), 4.39 (2H, dd, J = 6.6, 1.5 Hz, 1), 5.90 (1H, dt, J = 12.0, 6.6 Hz, 2), 6.49 (1H, d, J = 12.0 Hz, 3), 7.08 (2H, d, J = 8.4 Hz, 2′, 6′), 7.46 (2H, d, J = 8.1 Hz, 3′, 5′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 59.5 (1), 121.2 (4′), 129.9 (2), 130.3 (2′, 6′), 131.3 (3′, 5′), 131.7 (3), 135.2 (1′); HRMS (EI$^+$) *m*/*z* 213.9813, 211.9832 [M]$^+$ (calcd for C_9H_9OBr, 213.9816, 211.9837); *anal*. C 50.57%, H 4.55%, calcd for C_9H_9OBr, C 50.73%, H, 4.26%.

3′-(4‴-Bromophenyl)-2′*Z*-propenyl 3-(3″-Hydroxy-4″-benzyloxyphenyl)propanoate (20). A solution of allylic alcohol **19** (6.12 g, 28.7 mmol), carboxylic acid **13** (7.86 g, 28.9 mmol), and Ph_3P (8.39 g, 32.0 mmol) in THF (43 mL) at rt was treated dropwise with DEAD (5.0 mL, 32 mmol). The orange solution was stirred rapidly for 66 h and then concentrated to an orange tar. Gravity CC (9:1 hexane−acetone) provided ester **20** as a colorless solid that crystallized from EtOH (9.75 g, 73%): mp 80.1−81.7 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.61 (2H, t, J = 8.5 Hz, 2), 2.86 (2H, t, J = 8.0 Hz, 3), 4.78 (2H, dd, J = 6.5, 2.0 Hz, 1′), 5.06 (2H, s, $ArCH_2$), 5.64 (1H, s, OH), 5.80 (1H, dt, J = 12.0, 6.5 Hz, 2′), 6.56 (1H, d, J = 12.0 Hz, 3′), 6.65 (1H, dd, J = 8.5, 2.0 Hz, 6″), 6.79 (1H, d, J = 2.0 Hz, 2″), 6.82 (1H, d, J = 8.5 Hz, 5″), 7.07 (2H, d, J = 8.5 Hz, 2‴, 6‴), 7.34−7.39 (5H, m, 2⁗−6⁗), 7.46 (2H, d, J = 8.5 Hz, 3‴, 5‴); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.3 (3), 35.9 (2), 61.1 (1′), 71.2 ($ArCH_2$), 112.2 (5″), 114.7 (2″), 119.6 (6″), 121.6 (4‴), 126.6 (2′), 127.8 (2⁗, 6⁗), 128.3 (4⁗), 128.7 (3⁗, 5⁗), 130.3 (2‴, 6‴), 131.5 (3‴, 5‴), 131.8 (3′), 134.1 (1″), 134.9 (1‴), 136.4 (1⁗), 144.3 (4″), 145.8 (3″), 172.6 (1); HRMS (APCI$^+$) *m*/*z* 469.0817, 467.0810 [M + H]$^+$ (calcd for $C_{25}H_{24}O_4Br$, 469.0838, 467.0858); *anal*. C 64.09%, H 4.93%, calcd for $C_{25}H_{23}O_4Br$, C 64.25%, H 4.96%.

3′-(4‴-Bromophenyl)-2′*Z*-propenyl 3-(3″-Hydroxy-4″-methoxyphenyl)propanoate (21). DEAD (0.90 mL, 5.2 mmol) was added dropwise to a stirring solution of acid **14** (1.03 g, 5.25 mmol), alcohol **19** (1.00 g, 4.69 mmol), and triphenylphosphine (1.39 g, 5.30 mmol) in THF (10 mL) in a flask covered in aluminum foil. After stirring for 25 h, the reaction was terminated by the addition of brine (10 mL) and extracted with EtOAc (3 × 15 mL), and the combined organic extract was concentrated in vacuo. Purification of the residue by gravity CC (9:1 hexane−EtOAc) provided ester **21** as an off-white solid (1.43 g, 78%): mp 61.5−61.9 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.61 (2H, t, J = 8.1 Hz), 2.86 (2H, t, J = 8.1 Hz), 3.83 (3H, s), 4.78 (2H, dd, J = 1.5 Hz), 5.64 (1H, s), 5.81 (1H, dt, J = 12.0 Hz), 6.56 (1H, d, J = 11.4 Hz), 6.66 (1H, dd, J = 1.8 Hz), 6.73 (1H, s), 6.77 (1H, t, J = 2.1 Hz), 7.06 (2H, d, J = 8.4 Hz), 7.45 (2H, d, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.8, 35.5, 55.5, 60.7, 110.2, 114.0, 119.1, 121.1, 126.1, 129.8, 131.0, 131.4, 133.2, 134.4, 144.6, 145.1, 172.2; HRMS (APCI$^+$) *m*/*z* 391.0356 [M + H]$^+$ (calcd for $C_{19}H_{20}O_4Br$, 391.0545); *anal*. C 58.07%, H 5.10%, calcd for $C_{19}H_{19}O_4Br$, C 58.33%, H 4.89%.

Combretastatin D-2 Benzyl Ether (22). Phenol **20** (2.39 g, 5.11 mmol), CuBr−$S(CH_3)_2$ (3.85 g, 18.7 mmol), and K_2CO_3 (5.71 g, 41.3 mmol) were dissolved in pyridine (1 L). The resulting orange solution was heated to reflux under argon for 24 h. The solvent was removed in vacuo to afford a black tar, which was taken up in EtOAc (200 mL) and washed with 1.0 N HCl (3 × 100 mL) to remove copper salts and excess K_2CO_3. The combined organic extracts were concentrated in vacuo to a brown oil, which was separated by gravity CC (9:1 hexane−acetone) to afford ether **22** as a yellow oil that solidified on

standing and crystallized from acetone−hexane as fine colorless needles (0.19 g, 10%): mp 107.2−108.8 °C (lit.[12h] oil); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.29 (2H, t, J = 5.5 Hz, 2), 2.87 (2H, t, J = 5.5 Hz, 3), 4.66 (2H, d, J = 6.5 Hz, 1′), 5.13 (1H, d, J = 2.5 Hz, 2″), 5.24 (2H, s, ArCH_2), 6.05 (1H, dt, J = 11.0, 6.5 Hz, 2′), 6.61 (1H, dd, J = 8.5, 2.0 Hz, 6″), 6.84 (1H, d, J = 8.5 Hz, 5″), 7.10 (1H, d, 3′), 7.10 (2H, d, J = 8.5 Hz, 3‴, 5‴), 7.32 (2H, d, J = 7.0 Hz, 2‴, 6‴), 7.32 (1H, d, J = 8.0 Hz, 4⁗), 7.39 (2H, t, J = 7.5 Hz, 3⁗, 5⁗), 7.51 (2H, d, J = 7.5 Hz, 2⁗, 6⁗); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.7 (3), 31.1 (2), 59.1 (1′), 71.8 (ArCH_2), 113.6 (2″), 115.4 (5″), 121.1 (6″), 124.1 (3‴, 5‴), 125.4 (2′), 127.4 (2⁗, 6⁗), 127.9 (4⁗), 128.6 (3⁗, 5⁗), 128.9 (2‴, 6‴), 133.1 (1″), 135.0 (1‴), 137.3 (1⁗), 137.8 (3′), 145.1 (4″), 152.2 (3″), 156.1 (4‴), 173.2 (1).

Combretastatin D-2 Methyl Ether (23). Compound **23** was synthesized as described in the literature.[12a] Treatment of ester **21** (4.08 g, 10.4 mmol) with $CuCH_3$, prepared from reaction of $CuI-(SBu_2)_2$ (12.57 g, 26.02 mmol) and CH_3Li (1.6 M, 16.0 mL, 25.6 mmol), afforded ether **23** as a pale yellow solid (0.80 g, 25%): mp 132.4−132.8 °C (lit.[12a] mp 130−132 °C); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.2, 30.7, 55.7, 58.5, 111.7, 112.7, 120.7, 123.5, 124.9, 128.4, 131.9, 134.5, 137.3, 145.6, 150.9, 155.4, 172.7.

Combretastatin D-2 (5). To a cooled (−15 °C) solution of $AlBr_3$ (1.0 M in CH_2Br_2, 19.5 mL, 19.5 mmol) and ethanethiol (5.75 mL, 77.6 mmol) was added a cooled (−15 °C for 30 min) solution of lactone **23** (1.20 g, 3.87 mmol) in DCM (120 mL), and the mixture was stirred for 40 min at −13 °C. The reaction was terminated by the addition of H_2O (100 mL), and the mixture was acidified with 1.0 N HCl and extracted with DCM (3 × 50 mL). The organic layer was washed with brine (150 mL) and concentrated in vacuo. Separation by gravity CC (4:1 hexane−EtOAc) followed by crystallization from acetone−hexane afforded lactone **5** as a colorless crystalline solid (0.22 g, 19%): mp 160.4−160.7 °C (lit.[10] mp 148−151 °C, lit.[12a] mp 152−154.5 °C, lit.[12d] mp 154.5−155 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.28 (2H, t, J = 5.5 Hz), 2.86 (2H, t, J = 5.5 Hz), 4.63 (2H, d, J = 6.5 Hz), 5.06 (1H, d, J = 1.5 Hz), 5.48 (1H, s), 6.03−6.08 (1H, m), 6.61−6.63 (1H, m), 6.84 (1H, d, J = 7.5 Hz), 7.07−7.11 (3H, m), 7.32 (2H, d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.8, 31.3, 60.0, 112.5, 115.3, 121.8, 123.9, 125.6, 129.0, 131.9, 135.4, 137.7, 142.4, 149.5, 155.5, 173.3; HRMS (APCI$^+$) m/z 297.1107 $[M + H]^+$ (calcd for $C_{18}H_{17}O_4$, 297.1127); *anal*. C 72.82%, H 5.58%, calcd for $C_{18}H_{16}O_4$, C 72.96%, H 5.44%.

Combretastatin D-2 (5) X-ray Crystal Structure Determination. A small, block-shaped crystal (~0.10 × 0.11 × 0.19 mm), grown from an acetone−hexane solution, was mounted on the tip of a glass fiber. Cell parameter measurements and data collection were performed at 123 ± 1 K with a Bruker SMART 6000 diffractometer system using Cu Kα radiation. A sphere of reciprocal space was covered using the Multirun technique.[24] Thus, six sets of frames of data were collected with 0.396° steps in ω and a last set of frames with 0.396° steps in φ so that 98.2% coverage of all unique reflections to a resolution of 0.84 Å was accomplished.

Crystal Data: $C_{18}H_{16}O_4$, fw = 296.31, monoclinic, $P2_1$, a = 8.3872(1) Å, b = 10.9512(1) Å, c = 8.9106(1) Å, β = 117.2690(10)°, V = 727.481(14) Å^3, Z = 2, ρ_c = 1.353 mg/m^3, μ(Cu Kα) = 0.782 mm^{-1}, λ = 1.54178.

A total of 5690 reflections was collected, of which 2309 reflections were independent (R(int) = 0.0521). Subsequent statistical analysis of the data set with the XPREP[25] program indicated the space group was $P2_1$. Final cell constants were determined from the set of the 2309 observed (>2$\sigma(I)$) reflections that were used in structure solution and refinement. An absorption correction was applied to the data with SADBS.[26] Structure determination and refinement was readily accomplished with the direct-methods program SHELXTL.[27] All non-hydrogen atom coordinates were located in a routine run using default values for that program. The remaining H atom coordinates were calculated at optimum positions. All non-hydrogen atoms were refined anisotropically in a full-matrix least-squares refinement procedure. The H atoms were included, their U_{iso} thermal parameters fixed at either 1.2 or 1.5 (depending on atom type) of the value of the U_{iso} of the atom to which they were attached and forced to ride that atom. The final standard residual R_1 value for **5** was 0.0338 for observed data and 0.0351 for all data. The goodness-of-fit on F^2 was 1.003. The corresponding Sheldrick R values were wR_2 = 0.0864 and 0.0870, respectively. A final difference Fourier map showed minimal residual electron density, the largest difference peak and hole being +0.164 and −0.174 e/ Å^3, respectively. Final bond distances and angles were all within expected and acceptable limits. The Flack absolute structure parameter for the model shown in Figure 2 is 0.0018(9).[28]

8-Bis(benzyl)phosphorylcombretastatin D-2 (24). A solution of combretastatin D-2 (**5**, 0.10 g, 0.34 mmol) in CH_3CN (5 mL) was cooled to −10 °C, and CCl_4 (0.38 mL, 3.9 mmol) was added dropwise with stirring. After 10 min, diisopropylethylamine (0.12 mL, 0.69 mmol) and dimethylaminopyridine (6.0 mg, 0.049 mmol) were added, and the solution was stirred for another 5 min. Dibenzyl phosphite (0.15 mL, 0.67 mmol) was then added dropwise, and the reaction mixture was stirred for 2 h. The phosphorylation was terminated by the addition of KH_2PO_4 (0.5 M, 2 mL), and the mixture was stirred for an additional 30 min. DCM (5 mL) was added and the phases were separated. The aqueous layer was extracted with DCM (3 × 5 mL), and the extract was concentrated in vacuo. The residue was separated by gravity CC (7:3 hexane−EtOAc) to yield phosphate **24** as a colorless oil (0.16 g, 83%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.28 (2H, t, J = 5.4 Hz), 2.89 (2H, t, J = 5.1 Hz,), 4.63 (2H, d, J = 6.6 Hz), 5.15 (1H, d, J = 1.2 Hz), 5.23 (4H, d, J = 8.4 Hz), 5.99−6.08 (1H, m), 6.64 (1H, dd, J = 1.5, 8.1 Hz), 6.96 (2H, d, J = 9.0 Hz), 7.07 (1H, d, J = 10.8 Hz), 7.12 (1H, dd, J = 1.2, 8.1 Hz), 7.26 (2H, dd, J = 8.1 Hz), 7.31−7.36 (10H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.5, 30.5, 58.5, 69.5, 69.5, 113.8, 121.0, 123.3, 125.0, 127.5, 128.0, 128.1, 128.5, 134.7, 135.2, 135.3, 136.2, 137.2, 152.3, 155.2, 172.4; HRMS (APCI$^+$) m/z 557.1712 $[M + H]^+$ (calcd for $C_{32}H_{30}O_7P$, 557.1729); *anal*. C 69.02%, H 5.61%, calcd for $C_{32}H_{29}O_7P$, C 69.06%, H 5.25%.

Sodium Combretastatin D-2 8-*O*-Phosphate (25). A solution of **24** (0.040 g, 0.07 mmol) and bromotrimethylsilane (0.020 mL, 0.15 mmol) in DCM (1 mL) was stirred at rt for 40 min. The reaction was terminated by the addition of CH_3OH (1 mL), and the solvent was removed in vacuo to yield an oil, which was then dissolved in CH_3OH (1 mL). After the addition of CH_3ONa (7.6 mg, 0.14 mmol), the solution was stirred for 30 min. Removal of solvent and trituration of the residue with hexane (3 × 1 mL) afforded sodium salt **25** as a colorless solid (28 mg, 93%): mp 145.3−146.0 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 2.15−2.18 (2H, m), 2.72 (2H, d, J = 4.8 Hz), 4.52 (2H, d, J = 6.0 Hz), 5.03−5.08 (1H, m), 5.92−5.99 (1H, m), 6.51 (1H, d, J = 8.1 Hz), 6.98 (2H, d, J = 7.8 Hz), 7.22 (3H, d, J = 8.4 Hz).

Potassium Combretastatin D-2 8-*O*-Phosphate (26). Treatment of **24** (0.040 g, 0.07 mmol) with bromotrimethylsilane (0.020 mL, 0.15 mmol) in DCM (1 mL) was carried out as above (see **25**) to yield an oil, which was dissolved in CH_3OH (1 mL). Addition of KOH (9.0 mg, 0.16 mmol), followed by stirring for 30 min and concentration to a residue that was triturated with hexane (3 × 1 mL), afforded potassium salt **26** as a colorless solid (31 mg, 95%): mp (dec) 160 °C.

Lithium Combretastatin D-2 8-*O*-Phosphate (27). Reaction of bromotrimethylsilane (0.020 mL, 0.15 mmol) and **24** (0.040 g, 0.07 mmol) in DCM (1 mL) was conducted as summarized above (see **25**). The resultant oil was dissolved in CH_3OH (1 mL), and LiOH (6.8 mg, 0.16 mmol) was added. The solution was stirred for 30 min and then concentrated to a residue that was triturated with hexane (3 × 1 mL) to afford lithium salt **27** as a colorless solid (27 mg, 96%): mp (dec) 230 °C.

Morpholine Combretastatin D-2 8-*O*-Phosphate (28). Reaction of bromotrimethylsilane (0.020 mL, 0.15 mmol) and **24** (0.040 g, 0.07 mmol) in DCM (1 mL) was carried out as described above (see **25**), and the product was dissolved in CH_3OH (1 mL). Morpholine (0.016 mL, 0.18 mmol) was added, and removal of solvent after 30 min provided an oil that was triturated with acetone−Et_2O to yield morpholine salt **28** as a tan solid (9 mg, 24%): mp (dec) 195 °C; HRMS (APCI$^+$) m/z 547.3941 $[M + H]^+$ (calcd for $C_{26}H_{31}N_2O_9P$, 547.1845).

Methyl 3-(3′-Nitro-4′-fluorophenyl)-2*Z*-propenoate (30). A solution of 18-crown-6 (38.62 g, 146.1 mmol) and bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphonate (9.2 mL, 44 mmol) in THF (340 mL) at −78 °C was treated dropwise with KHMDS (0.5 M solution in toluene, 85 mL, 43 mmol), followed by 3-nitro-4-fluorobenzaldehyde (**29**, 6.01 g, 35.5 mmol). After stirring for 4 h the dark purple solution was treated with saturated NH_4Cl (30 mL), diluted with H_2O (100 mL), and extracted with EtOAc (5 × 100 mL). The combined organic extracts were concentrated in vacuo to an orange viscous oil. Separation by gravity CC (9:1 hexane−EtOAc) provided olefin **30** as an off-white solid (6.00 g, 75%): mp 67.5−68.9 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.74 (3H, s, OCH_3), 6.10 (1H, d, J = 12.6 Hz, 2), 6.91 (1H, d, J = 12.6 Hz, 3), 7.27 (1H, dd, J = 10.5, 8.7 Hz, 5′), 7.90 (1H, qd, J = 8.1, 3.9, 2.1 Hz, 6′), 8.36 (1H, dd, J = 7.2, 2.1 Hz, 2′); ^{13}C NMR ($CDCl_3$,

75 MHz) δ 51.2 (OCH_3), 117.3 and 117.6 (5′), 121.5 (2), 127.0 (2′), 131.2 (1′ or 3′), 136.3 and 136.5 (6′), 139.4 (3), 153.1 (3′ or 1′), 156.6 (4′), 165.2 (1); HRMS (APCI$^+$) *m/z* 226.0715 $[M + H]^+$ (calcd for $C_{10}H_9FNO_4$, 226.0516); *anal*. C 53.40%, H 3.53%, N 6.18%, calcd for $C_{10}H_8FNO_4$, C 53.34%, H 3.58%, N 6.22%.

3-(3′-Nitro-4′-fluorophenyl)-2*Z*-propenol (31). To a cooled (−78 °C) solution of *Z*-α,β-unsaturated ester **30** (5.97 g, 26.5 mmol) in DCM (47 mL) under argon was added DIBAL (1 M solution in DCM, 68 mL, 68 mmol). After the mixture was stirred for 4 h, the reaction was terminated with cold H_2O (60 mL), and the mixture was acidified to pH 1 with H_2SO_4 (18 M) before extraction with DCM (5 × 80 mL). The extract was concentrated in vacuo to an orange oil, and fractionation by gravity CC (4:1 hexane−EtOAc) provided propenol **31** as a tan oil (4.05 g, 77%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.88 (1H, s, OH), 4.39 (2H, dd, *J* = 6.6, 1.8 Hz, 1), 6.03 (1H, dt, *J* = 11.4, 6.6 Hz, 2), 6.53 (1H, d, *J* = 11.4 Hz, 3), 7.26 (1H, dd, *J* = 10.2, 9.0 Hz, 5′), 7.49 (1H, qd, *J* = 8.4, 3.9, 2.1 Hz, 6′), 7.90 (1H, dd, *J* = 7.2, 2.1 Hz, 2′).

3′-(3‴-Nitro-4‴-fluorophenyl)-2′*Z*-propenyl 3-(3″-Hydroxy-4″-benzyloxyphenyl)propanoate (32). A solution of allylic alcohol **31** (3.98 g, 20.2 mmol), carboxylic acid **13** (5.50 g, 20.2 mmol), and Ph_3P (5.86 g, 22.3 mmol) in THF (41 mL) at rt was treated dropwise with DEAD (3.6 mL, 23 mmol). After rapid stirring for 76.5 h, the solution was concentrated in vacuo to an orange solid. Separation using gravity CC (4:1 hexane−EtOAc) yielded ester **32** as a yellow crystalline solid, which recrystallized from EtOH (5.16 g, 57%): mp 81.6−83.0 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.63 (2H, t, *J* = 8.0 Hz, 2), 2.87 (2H, t, *J* = 8.0 Hz, 3), 4.75 (2H, dd, *J* = 7.5, 1.5 Hz, 1′), 5.07 (2H, s, ArC*H*$_2$), 5.61 (1H, s, OH), 5.94 (1H, dt, *J* = 12.0, 7.0 Hz, 2′), 6.61 (1H, d, *J* = 12.0 Hz, 3′), 6.65 (1H, dd, *J* = 8.5, 2.0 Hz, 6″), 6.79 (1H, d, *J* = 2.5 Hz, 2″), 6.83 (1H, d, *J* = 8.5 Hz, 5″), 7.27 (1H, dd, *J* = 11.0, 9.0 Hz, 5‴), 7.34−7.40 (5H, m, 2⁗−6⁗), 7.47 (1H, qd, *J* = 8.5, 4.0, 2.5 Hz, 6‴), 7.92 (1H, dd, *J* = 7.0, 2.5 Hz, 2‴); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.3 (3), 35.8 (2), 60.5 (1′), 71.2 (Ar*C*H$_2$), 112.2 (5″), 114.7 (2″), 118.4 and 118.6 (5‴), 119.7 (6″), 126.00 and 126.03 (2‴), 127.8 (2⁗, 6⁗), 128.4 (4⁗), 128.66 (2′), 128.70 (3⁗, 5⁗), 129.9 (3′), 132.98 and 133.01 (1‴ or 3‴), 134.0 (1″), 135.35 and 135.42 (6‴), 136.4 (1⁗), 144.3 (4″), 145.8 (3″), 153.5 (3‴ or 1‴), 155.7 (4‴), 172.5 (1); HRMS (EI$^+$) *m/z* 433.1358 $[M - H_2O]^+$ (calcd for $C_{25}H_{20}FNO_5$, 433.1325); *anal*. C 66.49%, H 5.11%, N 3.02%, calcd for $C_{25}H_{22}FNO_6$, C 66.51%, H 4.91%, N 3.10%.

3′-(3‴-Nitro-4‴-fluorophenyl)-2′*Z*-propenyl 3-(3″-Hydroxy-4″-methoxyphenyl)propanoate (33). To a solution of **31** (5.78 g, 29.3 mmol), **14** (5.75 g, 29.3 mmol), and Ph_3P (8.52 g, 32.5 mmol) in THF (60 mL at rt) was added DEAD (5.2 mL, 33 mmol, dropwise), and the mixture was stirred rapidly for 71 h. Removal of solvent afforded a viscous orange oil, which was separated by gravity CC (3:1 hexane−EtOAc) to provide ester **33** as a yellow oil (7.10 g, 65%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.63 (2H, t, *J* = 7.0 Hz, 2), 2.87 (2H, t, *J* = 7.5 Hz, 3), 3.85 (3H, s, OCH_3), 4.75 (2H, dd, *J* = 7.0, 1.5 Hz, 1′), 5.56 (1H, s, OH), 5.94 (1H, dt, *J* = 12.0, 7.0 Hz, 2′), 6.61 (1H, d, *J* = 12.0 Hz, 3′), 6.67 (1H, dd, *J* = 8.0, 2.5 Hz, 6″), 6.76 (1H, d, *J* = 2.5 Hz, 2″), 6.76 (1H, d, *J* = 8.0 Hz, 5″), 7.27 (1H, dd, *J* = 10.5, 8.5 Hz, 5‴), 7.47 (1H, qd, *J* = 8.5, 4.0, 2.5 Hz, 6‴), 7.93 (1H, dd, *J* = 7.0, 2.5 Hz, 2‴); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.3 (3), 35.9 (2), 56.0 (OCH_3), 60.4 (1′), 110.7 (5″), 114.5 (2″), 118.4 and 118.6 (5‴), 119.6 (6″), 126.00 and 126.03 (2‴), 128.7 (2′), 129.9 (3′), 132.98 and 133.02 (1‴ or 3‴), 133.5 (1″), 135.35 and 135.42 (6‴), 145.1 (4″), 145.5 (3″), 153.5 (3‴ or 1‴), 155.7 (4‴), 172.6 (1); HRMS (EI$^+$) *m/z* 447.1506 $[M - H + Si(CH_3)_3]^+$ (calcd. for $C_{22}H_{26}FNO_6Si$, 447.1513); *anal*. C 60.67%, H 4.96%, N 3.83%, calcd for $C_{19}H_{18}FNO_6$, C 60.80%, H 4.83%, N 3.73%.

3-(4′-Bromophenyl)propanol (38). To a stirred solution of ester **16** (3.88 g, 15.2 mmol) in PEG 400 (90 mL) was added slowly $NaBH_4$ (1.72 g, 45.5 mmol). The reaction mixture was heated to 80 °C (oil bath temperature) and stirred for 16.5 h, following an initial evolution of H_2 gas. The reaction was terminated with 1 N HCl (90 mL), followed by extraction with EtOAc (3 × 100 mL). The extract was washed with H_2O (100 mL) and concentrated in vacuo to an oil. Separation by gravity CC (4:1 hexane−acetone) yielded alcohol **38** as a clear oil (2.61 g, 80%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.85 (2H, tt, *J* = 7.8, 6.6 Hz, 2), 2.65 (2H, t, *J* = 7.8 Hz, 3), 2.84 (1H, bs, OH), 3.65 (2H, t, *J* = 6.6 Hz, 1), 7.06 (2H, d, *J* = 8.1 Hz, 2′, 6′), 7.39 (2H, d, *J* = 8.4 Hz, 3′, 5′); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.9 (3), 33.4 (2), 61.4 (1), 119.1 (4′), 129.7 (2′, 6′), 130.9 (3′, 5′), 140.2 (1′); HRMS (EI$^+$) *m/z* 215.9967, 213.9991 $[M]^+$ (calcd for $C_9H_{11}OBr$, 215.9973, 213.9993).

3′-(4‴-Bromophenyl)propanyl 3-(3″-Hydroxy-4″-benzyloxyphenyl)propanoate (39). A solution of propanol **38** (3.45 g, 16.0 mmol), carboxylic acid **13** (4.40 g, 16.2 mmol), and Ph_3P (4.70 g, 17.9 mmol) in THF (25 mL) at rt was treated dropwise with DEAD (2.9 mL, 18 mmol), and the mixture was stirred rapidly for 63 h. The solution was concentrated to a viscous yellow oil, and fractionation by gravity CC (17:3 hexane−acetone) provided ester **39** as a clear oil (4.04 g, 54%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.88 (2H, tt, *J* = 8.0, 6.5 Hz, 2′), 2.57 (2H, t, *J* = 8.0 Hz, 3′), 2.59 (2H, t, *J* = 7.5 Hz, 2), 2.85 (2H, t, *J* = 7.5 Hz, 3), 4.06 (2H, t, *J* = 6.5 Hz, 1′), 5.04 (2H, s, ArC*H*$_2$), 5.63 (1H, s, OH), 6.65 (1H, dd, *J* = 8.5, 2.0 Hz, 6″), 6.80 (1H, d, *J* = 2.0 Hz, 2″), 6.82 (1H, d, *J* = 8.5 Hz, 5″), 7.01 (2H, d, *J* = 8.0 Hz, 2‴, 6‴), 7.38 (5H, s, 2⁗, 6⁗), 7.38 (2H, d, *J* = 8.0 Hz, 3‴, 5‴); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.0 (2′), 30.4 (3), 31.5 (3′), 35.9 (2), 63.5 (1′), 71.2 (Ar*C*H$_2$), 112.2 (5″), 114.7 (2″), 119.6 (6″), 119.7 (4‴), 127.8 (2⁗, 6⁗), 128.3 (4⁗), 128.7 (3⁗, 5⁗), 130.1 (2‴, 6‴), 131.4 (3‴, 5‴), 134.1 (1″), 136.4 (1⁗), 140.1 (1‴), 144.3 (4″), 145.8 (3″), 172.9 (1); HRMS (APCI$^+$) *m/z* 471.0997, 469.1055, $[M + H]^+$ (calcd for $C_{25}H_{26}O_4Br$, 471.0994, 469.1014); *anal*. C 63.84%, H 5.46%, calcd for $C_{25}H_{25}O_4Br$, C 63.97%, H 5.37%.

3′-(4‴-Bromophenyl)propanyl 3-(3″-Hydroxy-4″-methoxyphenyl)propanoate (40). A solution of propanol **38** (2.09 g, 9.72 mmol), carboxylic acid **14** (1.93 g, 9.84 mmol), and Ph_3P (2.86 g, 10.9 mmol) in THF (20 mL) at rt was treated dropwise with DEAD (1.7 mL, 11 mmol), and the mixture was stirred rapidly for 64 h. The solution was concentrated, and separation by gravity CC (17:3 hexane−acetone) provided ester **40** as a yellow oil that crystallized upon standing and recrystallized from EtOAc−hexane as colorless crystals (2.15 g, 56%): mp 66.8−68.7 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.89 (2H, tt, *J* = 8.4, 6.8 Hz, 2′), 2.57 (2H, t, *J* = 6.8 Hz, 3′), 2.59 (2H, t, *J* = 7.6 Hz, 2), 2.85 (2H, t, *J* = 7.6 Hz, 3), 3.83 (3H, s, OCH_3), 4.07 (2H, t, *J* = 6.8 Hz, 1′), 5.60 (1H, s, OH), 6.67 (1H, dd, *J* = 8.0, 2.0 Hz, 6″), 6.75 (1H, d, *J* = 8.0 Hz, 5″), 6.78 (1H, d, *J* = 2.0 Hz, 2″), 7.01 (2H, d, *J* = 8.4 Hz, 2‴, 6‴), 7.38 (2H, d, *J* = 8.4 Hz, 3‴, 5‴); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.0 (2′), 30.3 (3), 31.5 (3′), 35.9 (2), 55.9 (OCH_3), 63.5 (1′), 110.6 (5″), 114.5 (2″), 119.6 (6″), 119.7 (4‴), 130.1 (2‴, 6‴), 131.4 (3‴, 5‴), 133.7 (1″), 140.1 (1‴), 145.0 (4″), 145.5 (3″), 172.9 (1); HRMS (APCI$^+$) *m/z* 395.0657, 393.0751 $[M + H]^+$ (calcd for $C_{19}H_{22}O_4Br$, 395.0681, 393.0701); *anal*. C 57.92%, H 5.52%, calcd for $C_{19}H_{21}O_4Br$, C 58.03%, H 5.38%.

Dihydro-combretastatin D-2 Benzyl Ether (41). Phenol **39** (3.83 g, 8.16 mmol), K_2CO_3 (9.19 g, 66.5 mmol), and CuBr−$S(CH_3)_2$ (5.23 g, 25.4 mmol) were dissolved in pyridine (1.1 L), and the solution was heated to reflux for 24 h. Removal of solvent afforded a viscous black oil, which was dissolved in EtOAc (150 mL). The solution was washed with 1 N HCl (3 × 150 mL) and concentrated to a brown oil, which was separated using gravity CC (9:1 hexane−acetone) to yield biaryl ether **41** as a colorless solid. Crystallization from acetone−hexane provided fine colorless needles (0.36 g, 11%): mp 136.5−137.6 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.09 (2H, tt, *J* = 6.5, 2.5 Hz, 2′), 2.25 (2H, t, *J* = 5.5 Hz, 2), 2.80 (2H, t, *J* = 6.5 Hz, 3′), 2.83 (2H, t, *J* = 5.0 Hz, 3), 4.07 (2H, t, *J* = 4.5 Hz, 1′), 5.23 (2H, s, ArC*H*$_2$), 5.36 (1H, d, *J* = 1.5 Hz, 2″), 6.57 (1H, dd, *J* = 8.5, 2.0 Hz, 6″), 6.81 (1H, d, *J* = 8.0 Hz, 5″), 7.03 (2H, d, *J* = 8.5 Hz, 3‴, 5‴), 7.29 (2H, d, *J* = 8.5 Hz, 2‴, 6‴), 7.31 (1H, d, *J* = 7.5 Hz, 4⁗), 7.38 (2H, t, *J* = 7.5 Hz, 3⁗, 5⁗), 7.50 (2H, d, *J* = 7.5 Hz, 2⁗, 6⁗); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.9 (3), 28.6 (2′), 32.6 (2), 34.0 (3′), 63.9 (1′), 71.8 (Ar*C*H$_2$), 113.7 (2″), 115.2 (5″), 120.8 (6″), 123.7 (3‴, 5‴), 127.4 (2⁗, 6⁗), 127.8 (4⁗), 128.5 (3⁗, 5⁗), 131.0 (2‴, 6‴), 133.9 (1″), 137.3 (1‴, 1⁗), 145.2 (4″), 152.1 (3″), 154.7 (4‴), 173.8 (1); HRMS (APCI$^+$) *m/z* 389.1779 $[M + H]^+$ (calcd for $C_{25}H_{25}O_4$, 389.1753); *anal*. C 76.80%, H 6.27%, calcd for $C_{25}H_{24}O_4$, C 77.30%, H 6.23%.

Dihydro-combretastatin D-2 (42). Palladium on carbon (5%, 41 mg) was added to a stirred solution of benzyl ether **41** (125 mg, 0.322 mmol) in EtOH−EtOAc (1:1, 10 mL). Hydrogen gas was bubbled through until reaction was complete (by TLC). The catalyst was removed, and concentration of the solution provided a colorless crystalline solid that recrystallized from acetone−hexane as colorless needles (79 mg, 82%): mp 175.4−177.7 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.07−2.12 (2H, m, 2′), 2.25 (2H, t, *J* = 5.6 Hz, 2), 2.81 (2H, t, *J* = 6.8 Hz, 3′), 2.83 (2H, t, *J* = 5.4 Hz, 3), 4.06 (2H, t, *J* = 4.4 Hz, 1′), 5.30 (1H, d, *J* = 2.0 Hz, 2″), 5.52 (1H, s, OH), 6.60 (1H, dd, *J* =

8.4, 2.0 Hz, 6″), 6.82 (1H, d, $J = 8.4$ Hz, 5″), 7.01 (2H, d, $J = 8.4$ Hz, 3‴, 5‴), 7.30 (2H, d, $J = 8.4$ Hz, 2‴, 6‴); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.0 (3), 28.7 (2′), 32.8 (2), 34.0 (3′), 63.9 (1′), 112.6 (2″), 115.0 (5″), 121.5 (6″), 123.5 (3‴, 5‴), 131.1 (2‴, 6‴), 132.7 (1″), 137.9 (1‴), 142.5 (4″), 149.1 (3″), 154.2 (4‴), 173.9 (1); HRMS (APCI$^+$) *m/z* 299.1299 $[M + H]^+$ (calcd for $C_{18}H_{19}O_4$, 299.1283); *anal*. C 72.50%, H 6.17%, calcd for $C_{18}H_{18}O_4$, C 72.47%, H 6.08%.

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References and Notes

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(27) *SHELXTL-Version 5.1*; Bruker AXS Inc.: Madison, WI, 1997. An integrated suite of programs for the determination of crystal structures from diffraction data. This package includes, among others, XPREP (an automatic space group determination program), SHELXS (a structure solution program via Patterson or direct methods), and SHELXL (structure refinement software).

(28) CCDC 714059 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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