(t, J = 7.6 Hz, 1 H); IR (neat) 3600–3100, 3050–2800, 1750, 1720, 1305, 1170, 1050, 1030, 870, 790, 760 cm^{-1}; high-resolution FAB MS m/z (rel intensity) calcd for $C_{13}H_{24}NO_4$ (MH^+) 258.1705, found 258.1642 (25, MH^+), 202 (100, MH^+ – *tert*-butyl), 158 (18, MH^+ – Boc), 141 (65); GC retention times of CHIRASIL-VAL column 14.1 (minor isomer 40%), 14.75 (major isomer 60%) min.

(*R*)-*N*-Boc-2-Aminononanol (13). Unsaturated amino alcohol **9d** (0.200 g, 0.765 mmol) was hydrogenated overnight in 95% ethanol (10 mL) over 5% palladium on carbon (10 mg) under 1 atm of hydrogen gas. After filtration of the catalyst and removal of the solvent under reduced pressure, pure **13** (0.201 g, 100% yield) was obtained as a low-melting white solid: R_f 0.24 (4:1 hexane/ethyl acetate); mp 39–40 °C; $[\alpha]^{30}_D$ + 8.46° (c = 1.075, MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.6 (b m, 1 H), 3.6 (b m, 2 H), 2.38 (b s, 1 H), 1.46 (s, 9 H), 1.3 (m, 12 H), 0.89 (t, J = 6.6 Hz, 3 H); IR (neat) 3700–3200, 3010–2830, 1700, 1505, 1220, 1175 cm^{-1}; MS (CI) m/z (rel intensity) 260 (16, MH^+), 244 (7, M^+ – CH_3), 232 (13, MH^+ – C_2H_4), 204 (100, MH^+ – *tert*-butyl), 186 (26, MH^+ – *tert*-butyl alcohol), 160 (98, MH^+ – Boc). Anal. Calcd for $C_{14}H_{29}NO_3$: C, 64.83; H, 11.27; N, 5.40. Found: C, 64.63; H, 11.38; N, 5.17.

(*R*)-*N*-Boc-2-aminononanoic Acid, Methyl Ester (14). Amino alcohol **13** (0.077 g, 0.30 mmol) was oxidized following the procedure of method A using 4 × 1.5 mL of Jones' reagent[27] (1.4 M, 8.4 mmol). The oxidation was complete after 2 h as judged by TLC. After conversion of the free acid to its methyl ester using excess diazomethane in ether, pure **14** (0.078 g, 91% yield) was obtained as an oil after flash chromatography (5:1 hexane/ethyl acetate): R_f 0.43 (4:1 hexane/ethyl acetate); $[\alpha]^{30}_D$ +13.2° (c = 1.06, MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.99 (b d, J = 9.1 Hz, 1 H), 4.29 (b q, J = 5.9 Hz, 1 H), 3.74 (s, 3 H), 1.48 (s, 9 H), 1.32 (m, 12 H), 0.88 (t, J = 6.6 Hz, 3 H); IR (neat) 3600–3200, 3100–2800, 1745, 1720, 1510, 1450, 1370, 1250, 1175, 1055, 1030 cm^{-1}; high-resolution MS (FAB) m/z (rel intensity) calcd for $C_{15}H_{30}NO_4$ 288.2175, found 288.2171 (17, MH^+), 232 (97, MH^+ – *tert*-butyl), 216 (40, MH^+ – *tert*-butyl alcohol), 188 (100, MH^+ – Boc), 172 (57), 128 (97); GC retention time on CHIRASIL-VAL column 18.9 min (>95%).

Acknowledgment. We thank Dr. Neil Moss for helpful suggestions and Dr. François Bruderlein for performing the enantiomeric purity determinations. We would also like to acknowledge Dr. Michael Evans of the Université de Montréal mass spectral laboratory and Dr. Gordon Hanson of the analytical chemistry department of Boehringer Ingelheim Pharmaceuticals Inc. We are also grateful to the Natural Sciences and Engineering Research Council of Canada for a scholarship to one of us (C.J.).

Registry No. (*S*)-**5b** (*Z* isomer), 125700-58-5; (*S*)-**5b** (*E* isomer), 120133-46-2; (*S*)-**7a**, 117833-92-8; (*R*)-**7b**, 95715-87-0; (*S*)-**7b**, 102308-32-7; **8a**, 133625-87-3; (*R*)-**8b**, 133625-90-8; (*S*)-**8b** (*Z* isomer), 133625-88-4; (*S*)-**8b** (*E* isomer), 133625-89-5; **8c** (*Z* isomer), 132639-29-3; **8c** (*E* isomer), 132652-65-4; (*R*)-**8d**, 133625-91-9; (*S*)-**8d**, 133625-92-0; **8e**, 133625-93-1; **8f**, 133625-94-2; **8g**, 117833-93-9; **8h**, 117833-94-0; **8i**, 133625-95-3; **8j** (*Z* isomer), 133625-97-5; **8j** (*E* isomer), 133625-96-4; **9a**, 91103-37-6; (*R*)-**9b** (*Z* isomer), 125700-60-9; (*R*)-**9b** (*E* isomer), 133625-98-6; (*S*)-**9b**, 125700-57-4; **9c** (*Z* isomer), 132682-38-3; **9c** (*E* isomer), 133625-99-7; (*R*)-**9d**, 133626-00-3; (*R*)-**9d** (*S*-Mosher ester), 133626-07-0; (*S*)-**9d**, 133626-01-4; (*S*)-**9d** (*S*-Mosher ester), 133626-08-1; **9e**, 133626-02-5; **9f**, 133626-03-6; **9f** (methyl ester), 133626-09-2; **9i**, 133626-04-7; **9j** (*Z* isomer), 133626-05-8; **9j** (*E* isomer), 133626-06-9; **10a**, 133626-15-0; **10a** (acetonide), 117833-95-1; **10b**, 133626-16-1; **10b** (acetonide), 117833-96-2; **11a**, 117833-97-3; **11a** (methyl ester), 133626-17-2; **11b**, 117833-98-4; **11b** (methyl ester), 133626-18-3; (*R*)-**12b** (*Z* isomer), 133696-71-6; (*R*)-**12b** (*E* isomer), 133696-72-7; (*R*)-**12d**, 133696-73-8; (*S*)-**12d**, 133696-74-9; **12e**, 133626-10-5; **12f**, 133626-11-6; **12j** (*Z* isomer), 133626-13-8; **12j** (*E* isomer), 133626-12-7; **13**, 133626-19-4; **14**, 133626-20-7; (*R*)-**15d**, 133626-14-9; (*R*)-MTPA-Cl, 39637-99-5; EtI, 76-03-9; $PhCH_2Br$, 100-39-0; $Me(CH_2)_5I$, 638-45-9; $Br(CH_2)_3Ph$, 637-59-2; $Br(CH_2)_3COOH$, 2623-87-2; $Br(CH_2)_3CN$, 5332-06-9; $Br(CH_2)_4CN$, 5414-21-1; MeCHIEt, 513-48-4; $MePPh_3^+Br^-$, 1779-49-3; $Ph_3P{=}CHCOOMe$, 2605-67-6; $EtPPH_3^+I^-$, 4736-60-1; $PhCH_2PPh_3^+Br^-$, 1449-46-3; $Me(CH_2)_5PPh_3^+I^-$, 60106-53-8; $Ph(CH_2)_3PPh_3^+Br^-$, 7484-37-9; $HOOC(CH_2)_3PPh_3^+Br^-$, 17857-14-6; $NC(CH_2)_3PPh_3^+Br^-$, 7752-62-7; $NC(CH_2)_4PPh_3^+Br^-$, 7743-27-3; $MeEtCHPPh_3^+I^-$, 4762-30-5.

Supplementary Material Available: ^{1}H and/or ^{13}C NMR spectra for compounds **8**, **9**, and **11–14** (35 pages). Ordering information is given on any current masthead page.

Total Synthesis of Combretastatin D-2: Intramolecular Ullmann Macrocyclization Reaction

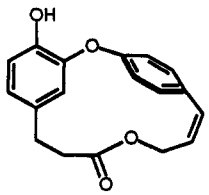
Dale L. Boger,* Subas M. Sakya, and Daniel Yohannes

Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

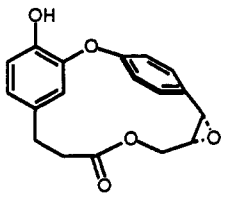
Received January 28, 1991

The total synthesis of combretastatin D-2, a cytotoxic constituent of *Combretum caffrum* (Combretaceae), is detailed and is based on the implementation of a key intramolecular Ullmann macrocyclization reaction for formation of the cyclic 15-membered caffrane biaryl ether.

Combretastatin D-2 (**1**),[1] a trace [(7.5×10^{-6})%] cytotoxic constituent of *Combretum caffrum* (Combretaceae) identified through extensive spectroscopic studies, has been shown to possess an unusual 15-membered meta- and paracyclophane subunit now characteristic of a range of antitumor antibiotics.[2-7]



1 Combretastatin D-2



2 Combretastatin D-1

In conjunction with our interest in the total synthesis and comparative evaluation of agents possessing this cyclic biaryl ether structural subunit[8-16] and as a consequence

(1) Singh, S. B.; Pettit, G. R. *J. Org. Chem.* **1990**, *55*, 2797.

(2) Pettit, G. R.; Singh, S. B.; Niven, M. L. *J. Am. Chem. Soc.* **1988**, *110*, 8539.

(3) Jolad, S. D.; Hoffmann, J. J.; Torrance, S. J.; Wiedhopf, R. M.; Cole, J. R.; Arora, S. K.; Bates, R. B.; Gargiulo, R. L.; Kriek, G. R. *J. Am. Chem. Soc.* **1977**, *99*, 8040.

(4) Itokawa, H.; Takeya, K.; Mori, N.; Sonobe, T.; Mihashi, S.; Hamanaka, T. *Chem. Pharm. Bull.* **1986**, *34*, 3762 and references cited therein.

(5) Sano, S.; Ikai, K.; Katayama, K.; Takesako, K.; Nakamura, T.; Obayashi, A.; Ezure, Y.; Enomoto, H. *J. Antibiot.* **1986**, *39*, 1685.

(6) Kase, H.; Kaneko, M.; Yamada, K. *J. Antibiot.* **1987**, *40*, 450.

(7) Tamai, S.; Kaneda, M.; Nakamura, S. *J. Antibiot.* **1982**, *35*, 1130, 1137.

(8) Boger, D. L.; Yohannes, D. *J. Am. Chem. Soc.* **1991**, *113*, 1427.

(9) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1991**, *56*, 1763.

(10) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1990**, *55*, 6000.

0022-3263/91/1956-4204$02.50/0 © 1991 American Chemical Society

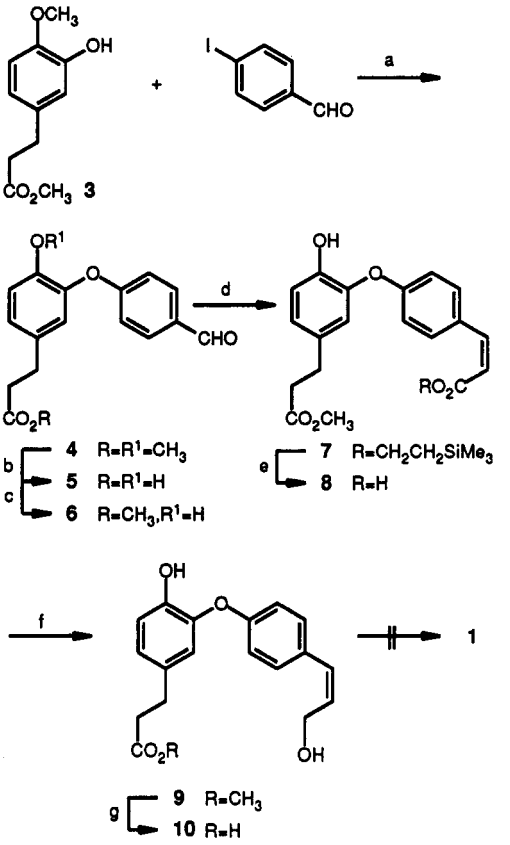
Table I

entry	base (equiv)	copper reagent (equiv)	solvent (bath temp, °C	reaction time, h	yield, %	(% rec SM)
1	K_2CO_3 (6)	CuBr·SMe_2 (10)	pyridine (140)	13	10	nd
2	K_2CO_3 (8)	CuBr·SMe_2 (10)	pyridine (140)	13	18	(2)
3	K_2CO_3 (8)	CuBr·SMe_2 (3)	pyridine (140)	24	26	(39)
4	K_2CO_3 (8)	CuBr·SMe_2 (10)	dioxane (110)	13	trace	nd
5	K_2CO_3 (8)	CuBr·SMe_2 (10)	collidine (160)	13	9	nd
6	K_2CO_3 (8)	CuO (5–15)	pyridine (140)	20–27	trace	nd
7	K_2CO_3 (8)	CuOTf (5)	pyridine (140)	24	0	nd
8	NaH (1.2)	CuBr·SMe_2 (10)	pyridine (140)	13	14	nd
9	NaH (1.2)	CuBr·SMe_2 (3)	pyridine (140)	19	4	nd
10	NaH (1.2)	CuBr·SMe_2 (10)	collidine (160)	13	trace	nd
11		$CuCH_3$ (1.3)	pyridine (140)	19	31	(30)
12		$CuCH_3$ (1.5)	pyridine (140)	20	35	(7)
13		$CuCH_3$ (1.5)	pyridine (140)	24.5	37	trace
14		$CuCH_3$ (1.5)	dioxane (110)	24	trace	(90)

of our continued interest in mitotic inhibitors[17-19] including agents that bear a biosynthetic relationship with combretastatin D-1 (2),[20-26] herein we detail a total synthesis of combretastatin D-2 (1). The key to the synthesis of 1 proved to be the implementation of an intramolecular Ullmann macrocyclization reaction[8,9] for formation of the biaryl ether and successful execution of a problematic macrocyclization reaction.[27] The synthesis provides access to sufficient authentic material for the continued evaluation of the natural product and is expected to be amenable to the preparation of additional members of this new class of antineoplastic agents.

Ullmann condensation of methyl 3-(3-hydroxy-4-methoxyphenyl)propanoate[28] (3) with 4-iodobenzaldehyde provided 4 in excellent yield (78%, 1 equiv of NaH, 1 equiv of CuBr–SMe_2, pyridine, reflux, 8 h). Aryl methyl ether deprotection (2 equiv of BI_3, CH_2Cl_2, 0 °C, 5 min)[29,30] was accompanied by partial ester demethylation and provided an approximately 2:1 mixture of 6:5, which was subjected to the conditions of methyl ester reesterification (catalytic H_2SO_4, MeOH) to afford 6 cleanly in 85% overall yield from 4 (Scheme I). Introduction of the *Z* olefin was accomplished by employing the Still–Gennari modification[31] of the Wadsworth–Horner–Emmons reaction and cleanly provided 7 (90%, >25:1 *Z*:*E*, 2.5 equiv of $(CF_3CH_2O)_2P(O)CH_2CO_2CH_2CH_2SiMe_3$,[32] 2.5 equiv of KHMDS, 12 equiv of 18-crown-6, THF, –60 °C, 30 min). Selective fluoride-induced deprotection of the β-(trimethylsilyl)ethyl ester followed by reduction of the resulting carboxylic acid 8 (1 equiv of $EtN(iPr)_2$, 1 equiv of Cl_3CCH_2OCOCl, THF, 0 °C, 45 min; 3 equiv of $NaBH_4$, 1:1 THF–DMF, 0 °C, 15

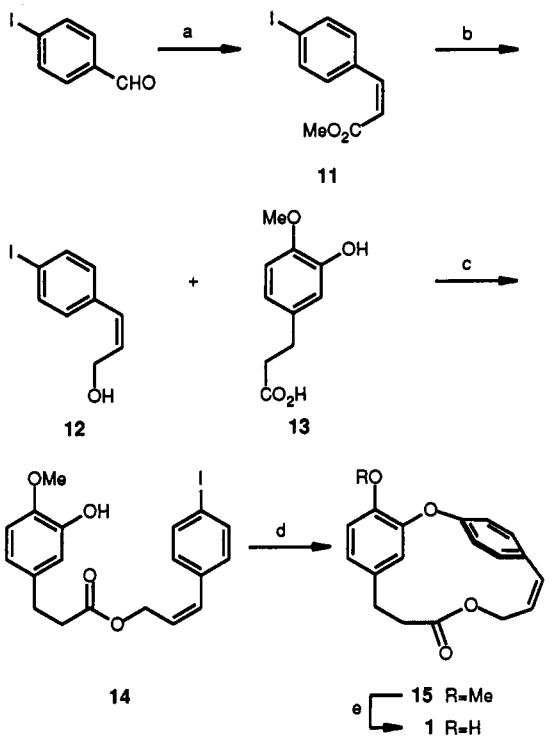
Scheme I[a]



[a] (a) 1 equiv of NaH, 2 equiv of CuBr–SMe_2, pyridine, reflux, 8 h, 78%, (b) 2 equiv of BI_3, CH_2Cl_2, 0 °C, 5 min; (c) cat. H_2SO_4, MeOH, reflux, 3 h, 85% from 4; (d) 2.5 equiv of $(CF_3CH_2O)_2P(O)CH_2CO_2CH_2CH_2TMS$, 2.5 equiv of KHMDS, 12 equiv of 18-crown-6, THF, –60 °C, 30 min, 90%; (e) 2 equiv of *n*-Bu_4NF, THF, 50 °C, 12 h, 91%; (f) 1 equiv of $Et(iPr)_2N$, 1 equiv of Cl_3CCH_2OCOCl, THF, 0 °C, 45 min; 3 equiv of $NaBH_4$, THF–DMF, 0 °C, 15 min, 65%; (g) 6.8 equiv of LiOH, THF–MeOH–H_2O (3:1:1), 25 °C, 5 h, 82%.

(11) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1989**, *54*, 2498.
(12) Boger, D. L.; Yohannes, D. *Tetrahedron Lett.* **1989**, *30*, 5061.
(13) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1988**, *53*, 487.
(14) Boger, D. L.; Yohannes, D. *Synlett.* **1990**, *1*, 33.
(15) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1987**, *52*, 5283.
(16) Boger, D. L.; Yohannes, D. *Tetrahedron Lett.* **1989**, *30*, 2053.
(17) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1986**, *108*, 6713.
(18) Boger, D. L.; Brotherton-Pleiss, C. E. *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: London, 1990; Vol. 2, p 147.
(19) Boger, D. L.; Mitscher, L. A.; Mullican, M. D.; Drake, S. D.; Kitos, P. *J. Med. Chem.* **1985**, *28*, 1543.
(20) Lin, C. M.; Ho, H. H.; Pettit, G. R.; Hamel, E. *Biochemistry* **1989**, *28*, 6984.
(21) Pettit, G. R.; Singh, S. B.; Lin, C. M.; Hamel, E.; Alberts, D. S.; Garcia-Kendall, D. *Experientia* **1989**, *45*, 209.
(22) Lin, C. M.; Singh, S. B.; Chu, P. S.; Dempcy, R. O.; Schmidt, J. M.; Pettit, G. R.; Hamel, E. *Mol. Pharmcol.* **1988**, *34*, 200.
(23) Pettit, G. R.; Singh, S. B.; Schmidt, J. M.; Niven, M. L.; Hamel, E.; Lin, C. M. *J. Nat. Prod.* **1988**, *51*, 517.
(24) Pettit, G. R.; Singh, S. B.; Niven, M. L.; Schmidt, J. M. *Can. J. Chem.* **1988**, *66*, 406.
(25) Pettit, G. R.; Singh, S. B. *Can. J. Chem.* **1987**, *65*, 2390.
(26) Pettit, G. R.; Singh, S. B.; Niven, M. L.; Hamel, E.; Schmidt, J. M. *J. Nat. Prod.* **1987**, *50*, 119.
(27) As detailed herein, efforts to close the 15-membered ring through use of conventional macrolactonization techniques have not yet proven successful.
(28) The compounds 3 and 13 were prepared from isovanillin by the sequence (i) 1.0 equiv of $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, 25 °C, 12 h, 80%; (ii) 1 atm of H_2, 0.1 wt equiv of 10% Pd/C, MeOH, 25 °C, 6 h, 97%; (iii) 5 equiv of LiOH·H_2O, THF–MeOH–H_2O (3:2:1), 25 °C, 15 h, 99%. See ref 10 and McCorkindale, N. J.; McCulloch, A. W.; Magrill, D. S.; Caddy, B.; Martin-Smith, M.; Smith, S. J.; Stenlake, S. *J. Tetrahedron* **1969**, *25*, 5475.
(29) Lansinger, J. M.; Ronald, R. C. *Synth. Commun.* **1979**, *9*, 341.
(30) Efforts to convert 4 to 6 employing a range of alternative demethylation conditions (BBr_3, CH_2Cl_2; LiBr, DMF; 48% HBr–HOAc; EtS-Na, DMF; $AlCl_3$, CH_2Cl_2, ± pyridine; BBr_3–SMe_2, CH_2Cl_2) were not as successful as the procedure employing BI_3. For others, see: Bhatt, M. V.; Kulkarni, S. U. *Synthesis* **1983**, 249.
(31) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
(32) Hatakeyama, S.; Satoh, K.; Sakurai, K.; Takano, S. *Tetrahedron Lett.* **1987**, *28*, 2713, 2717.

Scheme II[a]



[a](a) 1.2 equiv of $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, 1.2 equiv of KHMDS, 5 equiv of 18-crown-6, THF, −78 °C, 30 min, 97%; (b) 2 equiv of Dibal, CH_2Cl_2, −60 °C, 45 min, 80%; (c) 1.1 equiv of Ph_3P, 1.1 equiv of DEAD, THF, 25 °C, 52 h, 97%; (d) 1.5 equiv of CuC-H_3, pyridine (0.004 M), reflux, 24.5 h, 37%; (e) 1 equiv of BI_3, 1.2 equiv of dimethylaniline, benzene, 25 °C, 1 h.

min) afforded the alcohol **9**. Ester hydrolysis provided **10** and, in contrast to initial expectations, preliminary but not exhaustive efforts to close the 15-membered ring through use of a range of macrolactonization procedures[33-38] failed to provide combretastatin D-2 (**1**).[39]

Consequently, we elected to examine an intramolecular Ullmann reaction for macrocyclic ring closure with expectations that the problematic macrocyclization, like that of preceding efforts,[8,9] could be effectively addressed using this approach. Esterification of 3-(3-hydroxy-4-methoxyphenyl)propanoic acid (**13**)[10] with (*Z*)-3-(4-iodophenyl)-2-propenol (**12**) under the Mitsunobu conditions[40] of alcohol activation provided **14** (Scheme II). Subjection of **14** to the protocol introduced for effecting an intramolecular Ullmann reaction with macrocyclization (1.2 equiv of NaH, 10 equiv of CuBr–SMe_2, 0.004 M pyridine, 140 °C, 19 h)[9] provided **15** in acceptable yields, and the conversion could be improved by employing methylcopper[41] to generate the cuprous phenoxide required for cyclization. Using this modified protocol, **15** was obtained in an optimized yield of 37% from **14**, and Table I summarizes the results of a representative range of conditions examined. Aryl methyl ether deprotection[42] of **15** provided combretastatin D-2 (**1**), identical in all compared respects (^1H NMR, ^{13}C NMR, IR, mp, EIHRMS) with that reported for natural material thus confirming the structural assignment.

Thus, the implementation of an intramolecular Ullmann macrocyclization reaction for formation of the 15-membered ring of combretastatin D-2 with introduction of the unusual isodityrosine-derived biaryl ether provided a successful alternative to the more conventional and problematic macrolactonization reaction. The use of this approach in the preparation of structural analogues of the combretastatins [L1210 IC_{50} = 15 μg/mL (**1**), 30 μg/mL (**15**)] and additional applications of the Ullmann macrocyclization reaction are in progress and will be reported in due course.

Experimental Section[43]

Methyl (*Z*)-3-(4-Iodophenyl)-2-propenoate (11). A solution of methyl bis(2,2,2-trifluoroethyl)phosphonoacetate[31] (4.77 g, 15.0 mmol, 1.2 equiv) and 18-crown-6 (13.6 g, 62.5 mmol, 5 equiv) in dry THF (120 mL) at −78 °C was treated sequentially with potassium bis(trimethylsilyl)amide (30 mL of 0.5 M solution, 15.0 mmol, 1.2 equiv) and *p*-iodobenzaldehyde (2.91 g, 12.5 mmol, 1.0 equiv) in 8 mL of THF. The resulting reaction solution was stirred at −78 °C for 30 min. The reaction mixture was treated with saturated aqueous NH_4Cl (10 mL), diluted with H_2O (100 mL), and extracted with EtOAc (2 × 100 mL). The EtOAc layer was washed with saturated NaCl (50 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 3 × 15 cm, 0–30% ether–hexane, gradient elution) provided **11** (3.50 g, 3.60 g theoretical, 97%, >25:1 *Z*:*E*) as a white solid: mp 48–50.5 °C (white needles, ether–hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.67 (d, 2 H, *J* = 8.4 Hz, C3- and C5-H), 7.32 (d, 2 H, *J* = 8.4 Hz, C2- and C6-H), 6.83 (d, 1 H, *J* = 12.6 Hz, ArC*H*=CHCO$_2$CH$_3$), 5.95 (d, 1 H, *J* = 12.6 Hz, ArCH=C*H*CO$_2$Me), 3.69 (s, 3 H, CO$_2$Me); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.05 (C=O), 142.26 (o), 137.02 (o), 133.95 (e), 131.31 (o), 119.85 (o), 95.31 (e), 51.36 (Me); IR (KBr) ν_{max} 3024, 2950, 1721, 1626, 1580, 1482, 1436, 1414, 1392, 1240, 1204, 1156, 1062, 1006, 996, 954, 924, 846, 812, 792, 744, 728 cm^{-1}; EIMS *m*/*e* (relative intensity) 288 (M$^+$, base), 287 (6), 257 (48),

(33) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614.
(34) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(35) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394.
(36) Masamune, S.; Kim, C. U.; Wilson, K. E.; Spessard, G. O.; Georghiou, P. E.; Bates, G. S.; Yamamoto, H.; Kamata, S.; Schilling, W.; Fukuzawa, A. *J. Am. Chem. Soc.* **1975**, *97*, 3512, 3513, 3515.
(37) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49.
(38) Kurihara, T.; Nakajima, Y.; Mitsunobu, O. *Tetrahedron Lett.* **1976**, 2455.
(39) Only the cyclic diolide could be isolated from the macrolactonization attempts including those conducted with use of high dilution techniques. For the diolide methyl ether: mp 180–182.5 °C (white plates, Et$_2$O–hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.11 (d, 4 H, *J* = 8.6 Hz), 6.93 (dd, 2 H, *J* = 8.2, 1.9 Hz), 6.92 (d, 2 H, *J* = 8.2 Hz), 6.90 (d, 4 H, *J* = 8.6 Hz), 6.75 (d, 2 H, *J* = 1.9 Hz), 6.58 (dd, 2 H, *J* = 11.6, 0.9 Hz), 5.68 (dt, 2 H, *J* = 11.6, 6.9 Hz), 4.74 (dd, 4 H, *J* = 6.9, 0.9 Hz), 3.83 (s, 6 H), 2.86 (t, 4 H, *J* = 7.4 Hz), 2.60 (t, 4 H, *J* = 7.4 Hz); IR (KBr) ν_{max} 3024, 2956, 2928, 2844, 1740 (C=O), 1654, 1602, 1578, 1512, 1464, 1444, 1424, 1410, 1372, 1336, 1318, 1286, 1224, 1196, 1158, 1126, 1046, 1024, 962, 848, 830, 812 cm^{-1}; EIMS *m*/*e* (relative intensity) 620 (M$^+$, base); CIMS (isobutane) *m*/*e* 621 (M$^+$ + H, base).
(40) Mitsunobu, O. *Synthesis* **1981**, 1.
(41) Whitesides, G. M.; Sadowski, J. S.; Lilburn, J. *J. Am. Chem. Soc.* **1974**, *96*, 2829. For use of phenylcopper, see: Kawaki, T.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1499.
(42) Narayana, C.; Padmanabhan, S.; Kabalka, G. W. *Tetrahedron Lett.* **1990**, *31*, 6977.
(43) Proton and carbon nuclear magnetic resonance spectra (^1H and ^{13}C NMR) were recorded on a General Electric QE-300 or Varian Gemini 200 and chemical shifts are reported in parts per million relative to internal tetramethylsilane (0.00 ppm). For ATP ^{13}C NMR, e = even and o = odd number of attached protons. Infrared spectra (IR) were recorded on a Perkin-Elmer 1710 Fourier transform spectrometer as KBr pellets (solids) or thin films (liquids). Ultraviolet spectra (UV) were recorded on a Perkin-Elmer Lambda 3B spectrophotometer. Melting points (mp) were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Electron impact mass spectra (EIMS) and chemical ionization mass spectra (CIMS) were recorded on a Finnigan 4000 spectrometer. High-resolution mass spectra (HRMS) were recorded on a Kratos MS-50 spectrometer. Flash chromatography[44] was performed on 230–400-mesh silica gel. Tetrahydrofuran (THF) and dioxane were distilled from sodium benzophenone ketyl. Methylene chloride (CH_2Cl_2) was distilled from phosphorus pentoxide. Pyridine, collidine, *N*,*N*-dimethylformamide (DMF) and diisopropylethylamine were distilled from calcium hydride and stored under nitrogen or argon. All extraction and chromatographic solvents [ethyl acetate (EtOAc), hexane, diethyl ether (Et$_2$O), and methylene chloride (CH_2Cl_2)] were distilled prior to use. All commercially available reagents were used without further purification. Reactions requiring anhydrous conditions were run under an atmosphere of argon or nitrogen.
(44) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

130 (56), 102 (40), 77 (2), 76 (16); CIMS (isobutane) *m/e* (relative intensity) 289 ($M^+ + H$); EIHRMS *m/e* 287.9644 ($C_{10}H_9IO_2$ requires 287.9647).

Anal. Calcd for $C_{10}H_9IO_2$: C, 41.69; H, 3.15; I, 44.05. Found: C, 42.08; H, 3.24; I, 43.71.

(*Z*)-3-(4-Iodophenyl)-2-propenol (12). A solution of **11** (4.74 g, 16.5 mmol) in dry CH_2Cl_2 (55 mL) under argon at −60 °C was treated with diisobutylaluminum hydride (33 mL of 1 M solution in hexane, 33 mmol, 2.0 equiv) and was stirred for 45 min (−60 °C). The reaction mixture was quenched with the addition of a solution of 1 M aqueous sodium potassium tartrate (25 mL), and the mixture was extracted with CH_2Cl_2 (1 × 200 mL). After a few minutes, the precipitated aluminum salts were filtered off. The CH_2Cl_2 layer was washed with 1 M aqueous sodium potassium tartrate (50 mL) and saturated NaCl (50 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 3 × 13 cm, 0–30% ether–hexane, gradient elution) provided **12** (3.43 g, 4.29 g theoretical, 80%) as a white crystalline solid: mp 89–91 °C (white flakes, ether–hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.67 (d, 2 H, *J* = 8.4 Hz, C3- and C5-H), 6.95 (d, 2 H, *J* = 8.4 Hz, C2- and C6-H), 6.49 (d, 1 H, *J* = 11.7 Hz, ArC*H*=CH), 5.90 (dt, 1 H, *J* = 11.7, 6.5 Hz, ArCH=C*H*), 4.41 (dd, 2 H, *J* = 6.5, 5.3 Hz, CH_2OH), 1.46 (t, 1 H, *J* = 5.3 Hz, CH_2OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.32 (o), 136.0 (e), 131.92 (o), 130.54 (o), 129.92 (o), 92.85 (e), 59.4 (e); IR (KBr) ν_{max} 3252 (OH), 3014, 2926, 2860, 1632, 1580, 1486, 1460, 1418, 1388, 1322, 1116, 1066, 1040, 1022, 1002, 974, 954, 834 cm^{-1}; EIMS *m/e* (relative intensity) 260 (M^+, base), 218 (23), 217 (62), 204 (18), 133 (61), 131 (14), 116 (25), 115 (35), 105 (25), 91 (31), 77 (43); CIMS (isobutane) *m/e* (relative intensity) 260 (M^+, 4), 243 ($M^+ + H - H_2O$, base), 116 (58); EIHRMS *m/e* 259.9701 (C_9H_9IO requires 259.9698).

Anal. Calcd for C_9H_9IO: C, 41.56; H, 3.49; I, 48.79. Found: C, 41.93; H, 3.63; I, 48.70.

3-(4-Iodophenyl)-(*Z*)-2-propenyl 3-(3-Hydroxy-4-methoxyphenyl)propanoate (14). A solution of **12** (1.58 g, 6.08 mmol), **13** (1.19 g, 6.08 mmol, 1.0 equiv), and triphenylphosphine (1.75 g, 6.69 mmol, 1.1 equiv) in dry THF (8.0 mL, 0.8 M) at 25 °C was treated dropwise with diethyl azodicarboxylate (DEAD, 1.1 mL, 6.69 mmol, 1.1 equiv). The resulting pale orange solution was stirred vigorously (25 °C, 52 h), and the solvent was removed in vacuo. Flash chromatography (SiO_2, 3 × 13 cm, 30–100% CH_2Cl_2–hexane, gradient elution) provided **14** (2.63 g, 2.66 g theoretical, 97%) as a colorless oil that solidified upon standing: mp 75–76.5 °C (fine white needles, EtOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.67 (d, 2 H, *J* = 8.3 Hz, C3′- and C5′-H), 6.94 (d, 2 H, *J* = 8.3 Hz, C2′- and C6′-H), 6.78 (d, 1 H, *J* = 1.9 Hz, C2-H), 6.76 (d, 1 H, *J* = 8.0 Hz, C5-H), 6.68 (dd, 1 H, *J* = 8.0, 1.9 Hz, C6-H), 6.56 (d, 1 H, *J* = 11.7 Hz, Ar*C*H=CHCH$_2$), 5.81 (dt, 1 H, *J* = 11.7, 6.7 Hz, ArCH=*C*HCH$_2$), 5.57 (s, 1 H, ArOH), 4.78 (dd, 2 H, *J* = 6.7, 1.3 Hz, ArCH=CHCH_2), 3.86 (s, 3 H, OCH_3), 2.86 (t, 2 H, *J* = 7.4 Hz, ArCH_2), 2.61 (t, 2 H, *J* = 7.4 Hz, CH_2CO_2); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 172.6 (o), 145.5 (o), 137.4 (e), 135.4 (o), 133.6 (o), 131.9 (e), 130.4 (e), 126.6 (e), 119.6 (e), 114.4 (e), 110.6 (e), 93.1 (o), 61.1 (o), 56.0 (e), 36.0 (o), 30.3 (o); IR (KBr) ν_{max} 3414 (OH), 2964, 1730, 1620, 1588, 1516, 1486, 1460, 1446, 1416, 1390, 1372, 1334, 1308, 1276, 1244, 1222, 1204, 1182, 1158, 1128, 1064, 1028, 1004, 990, 974, 830, 816 cm^{-1}; EIMS *m/e* (relative intensity) 438 (M^+, 4), 195 (base), 153 (65), 137 (53), 116 (56), 115 (20), 91 (8), 77 (6); CIMS (isobutane) *m/e* (relative intensity) 439 ($M^+ + H$, 3), 438 (M^+, 4), 243 (base), 209 (13), 116 (14); EIHRMS *m/e* 438.0319 ($C_{19}H_{19}IO_4$ requires 438.0328).

Anal. Calcd for $C_{19}H_{19}IO_4$: C, 52.07; H, 4.37. Found: C, 52.20; H, 4.47.

Combretastatin D-2 Methyl Ether (15). A solution of CuI–$(SBu_2)_2$[41] (801 mg, 1.89 mmol, 1.5 equiv) in dry Et_2O (5 mL) under argon in a flame-dried centrifuge tube at −78 °C was treated with methyllithium (1.40 mL of 1.4 M solution in ether, 1.89 mmol, 1.5 equiv). The resulting bright yellow precipitate of methylcopper was collected by centrifugation and washed with dry Et_2O (2 × 5 mL). The methylcopper (1.5 equiv) was taken up in pyridine (10 mL) at 0 °C and transferred through a cannula under nitrogen into a solution of **14** (553 mg, 1.26 mmol) in pyridine (5 mL) at 25 °C. The resulting amber solution was stirred at 25 °C for 45 min. The solution was diluted further with pyridine (300 mL) and warmed at reflux under nitrogen for 24.5 h. Removal of the solvent in vacuo followed by flash chromatography (SiO_2, 3 × 15 cm, 60–100% CH_2Cl_2–hexane, gradient elution) afforded **15** (147 mg, 392 mg theoretical, 37%) as a white crystalline solid: mp 130–132 °C (white needles, acetone–hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.31 (d, 2 H, *J* = 8.3 Hz, C18- and C6-H), 7.10 (d, 2 H, *J* = 8.3 Hz, C19- and C7-H), 7.09 (d, 1 H, *J* = 11.0 Hz, C4-H), 6.82 (d, 1 H, *J* = 8.2 Hz, C12-H), 6.67 (d, 1 H, *J* = 8.2 Hz, C13-H), 6.04 (dt, 1 H, *J* = 11.0, 6.8 Hz, C3-H), 5.11 (s, 1 H, C20-H), 4.65 (d, 2 H, *J* = 6.8 Hz, C2-H_2), 3.94 (s, 3 H, OCH_3), 2.88 (t, 2 H, *J* = 5.4 Hz, C15-H_2), 2.88 (t, 2 H, *J* = 5.4 Hz, C16-H_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.1 (C17), 155.7 (C8), 151.17 (C10 or C11), 145.9 (C11 or C10), 137.7 (C3), 134.9 (C4), 132.2 (C5), 128.8 (C14), 125.3 (C6, C18), 123.9 (C19, C7), 121.1 (C13), 113.0 (C20), 111.9 (C12), 58.9 (C2), 56.1 (OCH_3), 31.0 (C15), 26.5 (C16); UV ($CHCl_3$) λ_{max} (nm) 244 (ε = 14000), 287 (3200), 306 (1100); IR (KBr) ν_{max} 3018, 2950, 2902, 2830, 1740 (C=O), 1586, 1526, 1504, 1424, 1376, 1346, 1268, 1206, 1154, 1132, 1102, 1034, 992 cm^{-1}; EIMS *m/e* (relative intensity) 310 (M^+, 30), 223 (13), 135 (17), 132 (10), 131 (base), 121 (27), 120 (13), 115 (20), 111 (20), 107 (17), 103 (63), 102, 97 (37), 85 (43), 77 (53); CIMS (isobutane) *m/e* (relative intensity) 311 ($M^+ + H$, base); EIHRMS *m/e* 310.1209 ($C_{19}H_{18}O_4$ requires 310.1205).

Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.33; H, 5.85. Found: C, 73.36; H, 5.85.

Combretastatin D-2 (1). A solution of *N,N*-dimethylaniline (12.6 mg, 0.10 mmol, 1.2 equiv) in dry benzene (0.2 mL) under nitrogen at 25 °C was treated with BI_3 (70 μL of 1.24 M solution, 0.087 mmol, 1.0 equiv). The resulting solution was cooled to 0 °C, and a solution of **15** (27 mg, 0.087 mmol) in dry benzene (0.4 mL) was added. The resulting solution was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was recooled to 0 °C, and solid sodium bicarbonate (200 mg) was added followed by the addition of ice water (10 mL). After extraction with EtOAc (2 × 10 mL), the organic layer was washed with saturated NaCl (5 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 1 × 11 cm, 80–100% CH_2Cl_2–hexane, gradient elution) provided combretastatin D-2 (**1**) as a white solid: mp 152–154.5 °C (white needles, Et_2O–hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.33 (d, 2 H, *J* = 8.5 Hz, C18-H and C6-H), 7.11 (d, 1 H, *J* = 10.5 Hz, C4-H), 7.09 (d, 2 H, *J* = 8.5 Hz, C19-H and C7-H), 6.85 (d, 1 H, *J* = 8.2 Hz, C12-H), 6.63 (dd, 1 H, *J* = 8.2, 1.8 Hz, C13-H), 6.07 (dt, 1 H, *J* = 10.5, 6.8 Hz, C3-H), 5.47 (s, 1 H, OH), 5.06 (d, 1 H, *J* = 1.8 Hz, C20-H), 4.64 (d, 2 H, *J* = 6.8 Hz, C2-H), 2.87 (t, 2 H, *J* = 5.3 Hz, C15-H_2), 2.29 (t, 2 H, *J* = 5.3 Hz, C16-H_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.3 (C17), 155.4 (C8), 149.2 (C10 or C11), 142.31 (C11 or C10), 137.7 (C3), 135.4 (C4), 131.9 (C5), 120.02 (C14), 128.96 (C6), 125.6 (C18), 123.9 (C19 and C7), 121.8 (C13), 115.3 (C12), 112.4 (C20), 59.0 (C2), 31.3 (C16), 26.8 (C15); UV ($CHCl_3$) λ_{max} (nm) 242 (ε = 11300), 284 (3100), 303 (800); IR (thin film) ν_{max} 3426, 3028, 2958, 2924, 2854, 1730 (C=O), 1594, 1520, 1502, 1466, 1440, 1378, 1342, 1282, 1216, 1154, 978, 870 cm^{-1}; EIMS *m/e* (relative intensity) 296 (M^+, 77), 237 ($M^+ - CH_3CO_2$, 13); 138 (48), 135 (49), 131 (15), 116 (base), 103 (16), 91 (25), 77 (39), 65 (23); CIMS (isobutane) *m/e* (relative intensity) 297 ($M^+ + H$, base); EIHRMS *m/e* 296.1052 ($C_{18}H_{16}O_4$ requires 296.1049).

Synthetic and authentic **1** exhibited identical TLC and HPLC chromatographic behavior.

Acknowledgment. We gratefully acknowledge the financial support of the National Institutes of Health (CA 41101, 42056). We thank Dr. Jim Myers for the preparation of **10** and for preliminary studies on the macrolactonization reaction of **10** and wish to thank Professor G. R. Pettit for an authentic sample of **1**.

Supplementary Material Available: Full experimental details for the preparation of **5–10**, Table II containing yield data for **5** and **6**, and ^1H NMR spectra (300 MHz) of **1**, **7**, **9–10** (10 pages). Ordering information is given on any current masthead page.