Annulation Strategies for Benzo[*b*]fluorene Synthesis: Efficient Routes to the Kinafluorenone and WS-5995 Antibiotics

Ghassan Qabaja and Graham B. Jones*

Bioorganic and Medicinal Chemistry Laboratories, Department of Chemistry, Northeastern University, 360 Huntington Avenue, Boston, Massachussetts 02115-5000

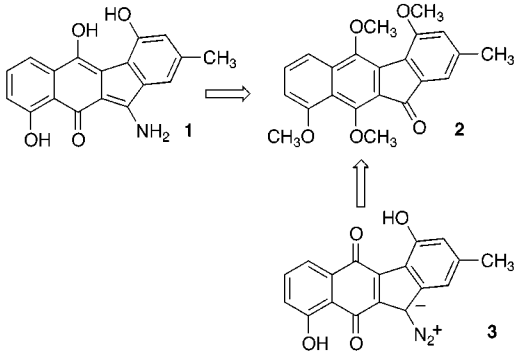
grjones@lynx.neu.edu

Received August 23, 2000

Intramolecular palladium-mediated arylation approaches to benzo[*b*]fluorenes have been investigated. The methodology has been applied in a short synthesis of tri-*O*-methylkinafluorenone, providing an effective alternative to Friedel−Crafts-based approaches. During the course of this work, an acid-promoted quinolactonization of naphthoquinones was also developed, providing direct access to either ortho or para isomers as desired. Application of this methodology in syntheses of the antibiotics WS-5995A, WS-5995C, and functional analogues was demonstrated, and antitumoral activity of this class was determined.

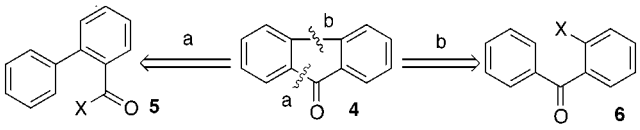
Introduction

The search for new antibiotics continues at a steady pace, and quinonoid-derived systems have been the subject of a number of promising leads.[1] Of the benzo[*b*]fluorenone family, the natural products stealthin C, **1**,[2] and prekinamycin, **3**,[3] have attracted considerable interest, and both are accessible from the benzo[*b*]fluorenone **2**.[4] Additionally, tetracycle **3** is a known intermediate in the biosynthesis of the kinamycin family of antibiotics produced by *Streptomyces murayamaensis*, and a number of these natural products show Gram positive and negative antibacterial properties, and antitumoral activity.[5]



Though a number of different approaches to the basic benzo[*b*]fluorenone skeleton **4** have been reported, most involve variants of Friedel−Crafts type closures of acylbiphenyls **5** (Scheme 1).[6] Due to the versatility of transition metal mediated arylations, we were interested in investigating the potential for a Pd-mediated closure from **6**, which would offer a complimentary strategy for the production of analogues of the natural products.

Scheme 1



Results and Discussion

To demonstrate the feasibility of the approach, appropriate model substrates were assembled, either by coupling arene **7** with 2-iodobenzoic acid, or in the case of **10**, acylation followed by Ti-catalyzed *ortho*-Fries rearrangement (Scheme 2). Palladium-mediated closures on substrates **8** and the methyl ether of **11** were conducted using a variety of methods with limited success, but optimal conditions were eventually found, involving high-temperature closure with $Pd(OAc)_2$ in dimethylacetamide (DMA), as had been previously demonstrated by Ames and Opalko in the cyclization of substituted diphenyl ethers and benzophenones.[7]

With the model study complete, we sought application in the synthesis of key structure **2**.[8] Accordingly, dimethylanisole **13** was converted to iodoaldehyde **14** which was subjected to 1,2 addition with the lithioarene derived from aryl bromide **16**, in turn prepared from methyljuglone **15** (Scheme 3). The resulting benzylic alcohol was oxidized (**17**) and the Pd-mediated closure attempted. Using identical conditions to the model substrates, low

(1) *CRC Handbook of Antibiotic Compounds*; Berdy, J., Ed.; CRC Press: Boca Raton, 1980.

(2) Koyama, H.; Kamikawa, T. *Tetrahedron Lett.* **1997**, *38*, 3973−3976. Gould, S. J.; Melville, C. R.; Cone, M. C.; Chen, J.; Carney, J. R. *J. Org. Chem.* **1997**, *62*, 320−324.

(3) Gould, S. J.; Tamayo, N.; Melville, C. R.; Cone, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 2207−2208. Cone, M. C.; Hassan, A. M.; Gore, M. P.; Gould, S. J.; Borders, D. B.; Alluri, M. R. *J. Org. Chem.* **1994**, *59*, 1923−1924. Gore, M. P.; Gould, S. J.; Weller, D. D. *J. Org. Chem.* **1992**, *57*, 2774−2783.

(4) Gore, M. P.; Gould, S. J.; Weller, D. D. *J. Org. Chem.* **1991**, *56*, 2289−2291. Mohri, S.; Stefinovic, M.; Snieckus, V. *J. Org. Chem.* **1997**, *62*, 7072−7073.

(5) Gould, S. J.; Melville, C. R. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 51−54.

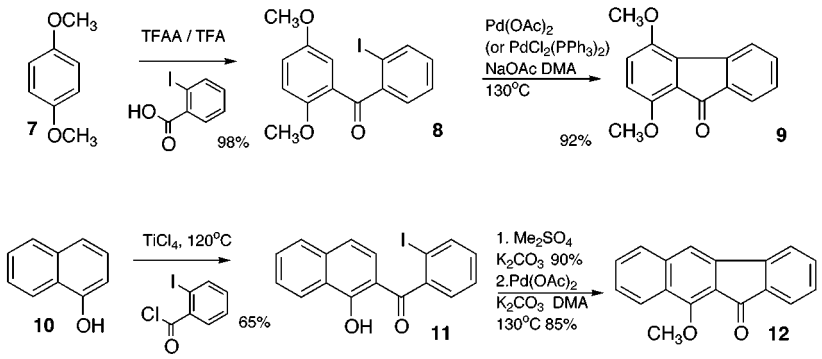
(6) For the phthalide annulation route, see: Hauser, F. M.; Zhou, M. *J. Org. Chem.* **1996**, *61*, 5722−5722.

(7) Ames, D. E.; Opalko, A. *Tetrahedron* **1984**, *40*, 1919−1925. For related Pd-mediated closures, see: Bringmann, G.; Jansen, J. R.; Reuscher, H.; Rubennacker, M.; Peters, K.; von Schnering, H. G. *Tetrahedron Lett.* **1990**, *31*, 643−646; Deshpande, P. P.; Martin, O. R. *Tetrahedron Lett.* **1990**, *31*, 6313−6316; Harayama, T.; Akiyama, T.; Nakano, Y.; Shibaike, K. *Heterocycles* **1998**, *48*, 1989−1992.

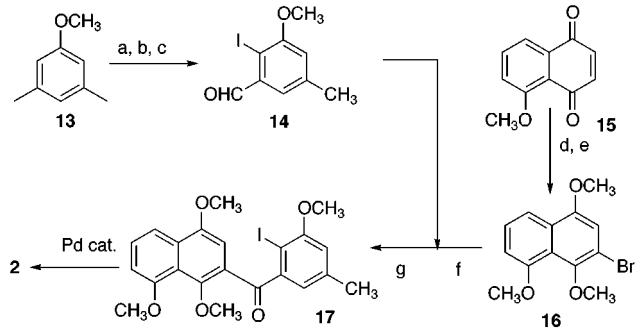
(8) Preliminary communication: Qabaja, G.; Jones, G. B. *Tetrahedron Lett.* **2000**, *41*, 5317−5320.

10.1021/jo0056186 CCC: $19.00
Published on Web 09/26/2000

Scheme 2



Scheme 3



[a] CCl_4, NBS, and then K_2CO_3, dioxane, 40%. [b] *n*BuLi, hexanes, I_2 −78 °C 80%. [c] $COCl_2$, DMSO, 95%. [d] $Na_2S_2O_4$, ether, and then Me_2SO_4, K_2CO_3 85%. [e] CCl_4, Br_2 99%, and then K_2CO_3, Me_2SO_4 60%. [f] *t*BuLi, ether, −78 °C (quant). [g] PCC, CH_2Cl_2, 80%.

Table 1. Attempted Pd-Catalyzed Arylation of 17

entry	catalyst	solvent	temp, °C	time	% **2**
1	$Pd(OAc)_2$/NaOAc[7]	DMA	130	12 h	0
2	$PdCl_2(PPh_3)_2$/NaOAc	DMA	130	18 h	29
3	$Pd(OAc)_2(PPh_3)_2$/NaOAc	DMA	130	6 h	31
4	$Pd(OAc)_2/Et_3N$	CH_3CN	80	24 h	0
5	$Pd(PPh_3)_4/Et_3N$	THF/CH_3CN	80	36 h	<5
6	$PdCl_2(PPh_3)_2$/NMI	NMI	170	24 h	0
7	$Pd(OAc)_2/Bu_4NCl/NaOAc$[27]	DMA	130	24 h	0
8	$Pd(OAc)_2$/LiCl/NaOAc[28]	DMA	130	24 h	0
9	$PdCl_2(PPh_3)_2$/NaOAc	DMA-mW	140	1 min	53
10	$Pd(OAc)_2(PPh_3)_2$/NaOAc	DMA-mW	160	1 min	49

yields of **2** were isolated, presumably reflecting a combination of the electronic influence of the *o*-methoxy group in the oxidative addition step and developing (repulsive) interactions between the aryloxy groups.

Complicating the process was product decomposition which ensued at the high temperatures and extended reaction times necessary to effect closure (Table 1). Since metal-catalyzed processes are often ideal candidates for acceleration using microwaves,[9,10] a reaction was conducted using microwave irradiation (mW). Additionally, DMA, which has a dielectric constant of 37.8D, would be expected to heat rapidly during the irradiation process. Accordingly, a sample of **17**, $PdCl_2(PPh_3)_2$, and sodium acetate dissolved in DMA, in a round-bottomed flask was placed in the center of a conventional microwave oven and irradiated for 60 s.[11] During this period, the solution temperature reached 140 °C and gave a 53% yield of desired product **2**, along with traces of unreacted **17**. Efforts to improve the product yields by extended thermolysis were unsuccessful, and after 2 min the solution began to reflux, necessitating cessation of the reaction. Similarly, microwave-accelerated closures to model substrates **9** and **12** were successful, in both cases giving comparable yields of product to the thermal process (Scheme 2) within 1 min.

The speed and efficiency of the mW-accelerated coupling suggests additional applications in transition metal mediated processes may be worthy of investigation, particularly in cases where product decomposition is an issue. The described synthesis of **2** is competitive with existing routes and may allow development of additional natural product analogues. Gould has previously demonstrated that the product of per-demethylation (BBr_3) of compound **2** (tri-*O*-methylkinafluorenone) is an intermediate in the biosynthesis of both kinamycin C and D, and it may be a realistic possibility to probe biosynthesis of structural analogues using the requisite microorganism (*S. murayamaensis*).[5]

This synthesis notwithstanding, we were also interested in investigating additional acylation routes to core structure **4**, via appropriately substituted biaryls **5** (Scheme 1). Of particular interest was a route to differentially methylated analogue **23**, which might serve as a useful starting material for QSAR analysis, and we anticipated access via acylation of **22** (Scheme 4). Accordingly, aryl aldehyde **14** was converted to acyl chloride **19** and reacted with dihydroquinone **18**, in turn prepared from quinone **6** (Scheme 4).

The resulting product was first methylated and then subjected to Pd-catalyzed closure using established conditions.[7] Our original plan was to effect hydrolysis of the lactone moiety and attempt some form of acyl capture on **22** to yield benzo[*b*]fluorene **23**. To our initial surprise, the sole product isolated was quinone **24**, presumably formed by in situ oxidation. This serendipitous observation prompted us to search for applications in the synthesis of quinonoid antibiotics. Indeed, one could predict that close geometric isomers of the kinamycin family would retain some vestiges of biological activity. On the basis of the structure of **24** itself, our attention was directed to the naphthoquinone lactone WS-5995, first isolated from *Streptomyces auranticolor* and structurally determined in 1983.[12] Though several pyranon-

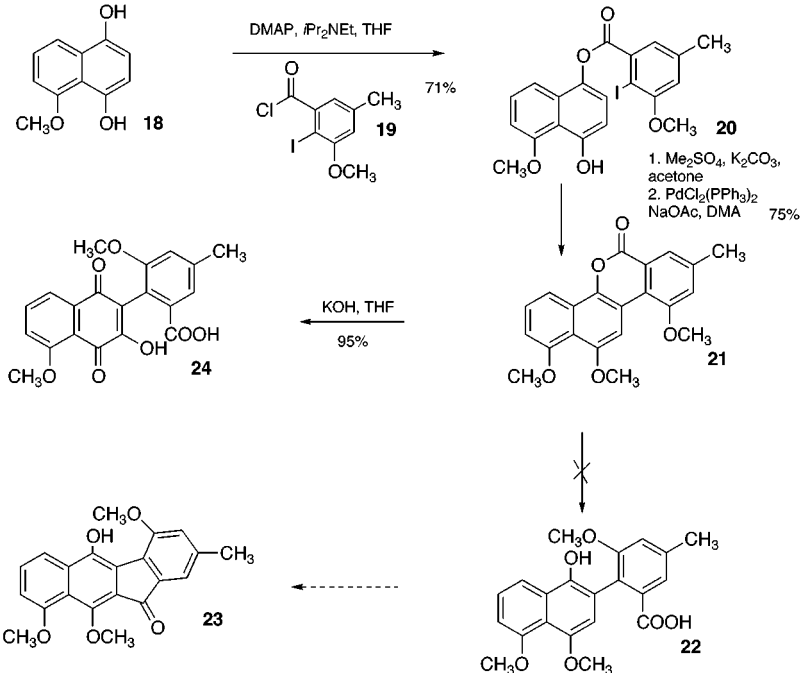
(9) Mingos, D. M. P.; Baghurst, D. R. *Chem. Soc. Rev.* **1991**, *20*, 1−47.

(10) For pioneering examples in organic synthesis, see: Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.* **1986**, *27*, 4945−4948.

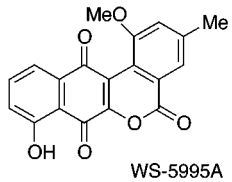
(11) For previous reports from this laboratory, see: Huber, R. S.; Jones, G. B. *J. Org. Chem.* **1992**, *57*, 5778−5780. Jones, G. B.; Huber, R. S.; Chau, S. *Tetrahedron.* **1993**, *49*, 369−380; Jones, G. B.; Chapman, B. J. *J. Org. Chem.* **1993**, *58*, 5558−5559.

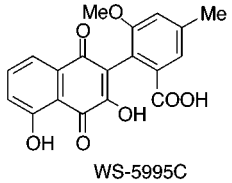
(12) Ikushima, H.; Takase, S.; Kawai, Y.; Itoh, Y.; Okamoto, M.; Tanaka, H.; Imanaka, H. *Agric. Biol. Chem.* **1983**, *47*, 2231−2235.

Scheme 4



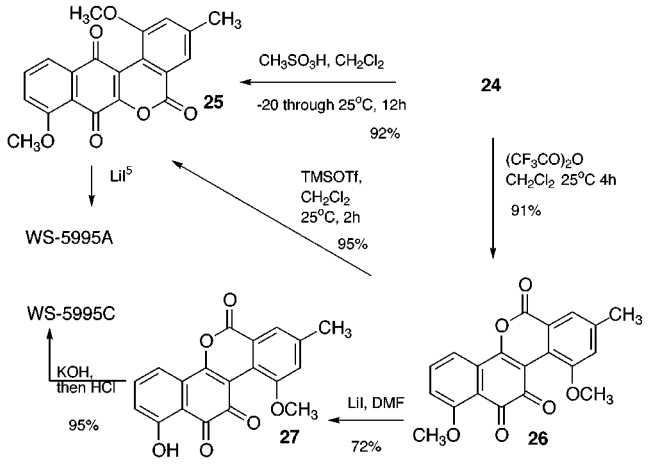
aphthoquinone antibiotics have been identified, including nanaomycin A, kalafungin, and eleutherin, relatively few members of the corresponding naphthoquinone lactones have been found, making WS-5995A an interesting target. Structural analogues including its open form WS-5995C are known,[13] and these agents have demonstrated chemoprotective activity against *Eimeria tenella* infection.[14] Though the origin of their biological activity remains to be clarified, it has been shown that the bacterium *Streptomyces acidizcabies* (present in acidic soils) produces the WS-5995 compounds, and that they likely contribute to the observed pathogenicity of this organism.[15] Furthermore, on the basis of structural similarities between WS5995A and the gilvocarcin antibiotics, it is conceivable that these agents may function as topoisomerase inhibitors, rendering them potential antitumor agents.[16] We opted to develop an expeditious route to the core structure of the WS-5995 family, focusing on novel annulation chemistry.





Accordingly, lactonization of hydroxy acid **24** was investigated using methanesulfonic acid, which gave the *p*-quinone **25** in good yield (Scheme 5). Subsequent demethylation gave WS-5995A directly, identical in all respects with natural material. Intriguingly, in an attempt to optimize the lactonization step, when **24** was exposed to TFAA, *the alternate o-quinone **26** was produced exclusively*. Interconversion of this, presumably less thermodynamically stable, quinone isomer to **25** was possible either using MSA or TMSOTf, but using TFAA even after refluxing with **26** for 18 h, a 2.5:1 ratio of ortho:para isomers still existed. *o*-Quinone **26** underwent regioselective demethylation using lithium iodide to give phenol **27**, hydrolysis of which resulted in concomitant formation of the natural product WS-5995C. Furthermore, interconversion of WS-5995C into WS-5995A was effected using a published procedure,[13] thus establishing two independent routes to the target compound.

Scheme 5



Prompted by the unexpected quinolactonization to give **26**, a model compound was prepared to investigate the generality of the annulation process. Commercially available **28** was esterified and then subjected to Pd-mediated closure to give **30** (Scheme 6). Following hydrolysis, the substrate **31** was subjected to a variety of acid-catalyzed

(13) Syntheses of WS-5995A−C antibiotics: (a) Watanabe, M.; Date, M.; Furukawa, S. *Chem. Pharm. Bull.* **1989**, *37*, 292−297. de Frutos, O.; Echavarren, A. M. *Tetrahedron Lett.* **1996**, *37*, 8953−8956. (b) Tamayo, N.; Echavarren, A. M.; Paredes, M. C. *J. Org. Chem.* **1991**, *56*, 6488−6491. (c) Echavarren, A. M.; Tamayo, N.; Cardenas, D. J. *J. Org. Chem.* **1994**, *59*, 6075−6083. (d) McKenzie, T. C.; Choi, W.-B. *Synth. Commun.* **1989**, *19*, 1523−1532.

(14) Ikushima, H.; Okamoto, M.; Tanaka, H.; Ohe, O.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1980**, *33*, 1107−1113 and references cited therein.

(15) King, R. R.; Lawrence, C. H. *J. Agric. Food Chem.* **1996**, *44*, 2849−2851.

(16) Matson, J. A.; Rose, W. C.; Bush, J. A.; Myllymaki, R.; Bradner, W. T.; Doyle, T. W. *J. Antibiot.* **1989**, *42*, 1446−1448.

Scheme 6

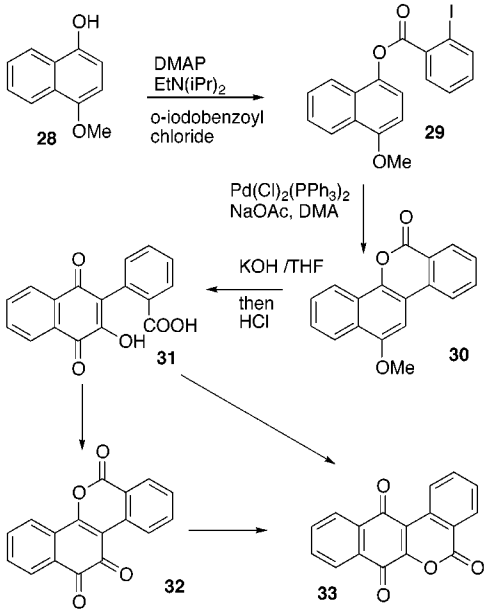


Table 2. Acid-Promoted Quinolactonizations (Scheme 6)[a]

entry	substrate	reagent	solvent	temp (°C)	time	% **32**	% **33**
1	31	MSA	–	25	12 h	19	81
2	31	TFAA	CH_2Cl_2	25	6 h	25	75
3	31	$(COCl)_2$	CH_2Cl_2	40	24 h	75	25
4	31	TFAA	THF	25	36 h	16	84
5	31	TMSOTf	CH_2Cl_2	25	4 h	74	26
6	31	TMSOTf	CH_2Cl_2	−78	4 h	75	25
7	31	TFAA	Et_2O	25	4 h	0	100
8	32	TFAA	CH_2Cl_2	−78	12 h	55	45
9	32	MSA	–	25	4 h	–	100
10	33	TFAA	CH_2Cl_2	25	4 h	–	100

[a] All reactions run to quantitative conversion (HPLC), and then isomer ratios were determined by ^{1}H NMR.

quinolactonization procedures, which would normally be expected to yield para quinone **33** via the corresponding mixed anhydride. Though acetic anhydride was ineffective, TFAA gave product **33** cleanly and in high yield (Table 2). However, under the influence of specific Lewis acids, the alternate *o*-quinone product **32** could again be produced. As in the case of **26**, this is presumably the result of enolization of the *p*-quinone carbonyl, encouraged by chelation of the phenol with the Lewis acid. Attempts were made to optimize the yield of isomer **32**, and TMS triflate was found to be most effective, giving good isolated yields of the desired product, easily separable from the para isomer **33** by precipitation. As expected, extended exposure of **32** to various acids resulted in isomerization to the more thermodynamically stable **33**, methanesulfonic acid proving most efficient. On the basis of these findings, regioselective quinolactonizations may in fact be general in the naphthoquinone family. Such methods could perhaps best be applied in the synthesis of "unnatural isomers" of natural products, a developing theme in chemical genetics.[17]

Since quinones as a class are generally biologically active, we decided to investigate and compare both the reduction potential and antiproliferative ability of the synthetic analogues and also the natural products.

(17) Schreiber, S. L. *Bioorg. Med. Chem.* **1998**, *6*, 1127−1152.

Table 3. Electrochemistry and Cytotoxicity of Ortho/Para Quinones

			growth inhibition[c]		
compound	$E°$ (mV)[a]	IC_{50} (μM)[b]	H-460	MCF-7	SF-268
WS-5995A	−370	1			
WS-5995C	−1415	100			
27	−550	15	−	−	+
26	−585	2	+	+	−
24	−1025	>15[d]	−	−	−
32	−360	10	−	+	+
33	−370	5	+	+	−
31	−1015	125	−	−	−

[a] Values relative to Ag/AgCl reference electrode. [b] Determined using MTS:PMS assay on L1210 mouse lymphoma cells. [c] Denotes ability (+) of candidate to reduce growth of H-460 lung, MCF-7 breast, or SF-S68 CNS cancer cells to 32% or less using sulforhodamine assay. [d] Insolubility precluded studies at higher concentration.

Analysis of their reduction potentials highlighted measurable differences between the ortho/para isomers, a phenomenon which could be expected to have an impact under biological conditions (Table 3). Initial cytotoxicity assays against a murine cell line revealed that in addition to WS-5995, *o*-quinone **26** and model quinone **32** were appreciably cytotoxic, and they were subjected to a broader screen (Table 3).[18] Comparison of the cytotoxicities of **26** and **27** suggests that the hydrogen bonding phenolic group may attenuate the function of the *o*-quinone moiety to some degree, and it also has a noticeable impact on the reduction potential. On the basis of these results, compounds **26**, **32**, and **33** are now the focus of additional studies at NCI.[19] It is well-known that the differing reduction potentials of ortho and para quinones can play a dramatic role in electron transfer chemistry, and we are currently investigating the antiproliferative capacity of the entire family of analogues under a variety of hypoxic and aerobic screens.

Conclusions

In summary, efficient routes to both the kinafluorenone and WS-5995 family of antibiotics have been developed. Key outcomes include the synthesis of an unprecedented and biologically active *o*-quinone analogue of WS-5995A, and the finding that a Pd-catalyzed intramolecular arylation can be accelerated by nonconventional means. The annulation strategies demonstrated in each offer opportunity for application in related natural product syntheses and the design of antiproliferatives.

Experimental Section

General experimental procedures have been published.[20] Unless otherwise stated, all reagents were purchased from the Aldrich Chemical Co. and used as supplied. ^{1}H and ^{13}C NMR spectra were obtained either on a 300 MHz Varian Mercury, 300 MHz Bruker AC 300, or 500 MHz Varian Unity machine. HRMS determinations were conducted at the University of Illinois mass spectrometry laboratories. Chromatographic separations were made using E. Merck 230−400 mesh 60H silica gel or using a Harrison Research Inc. chromatotron unit.

(18) Preliminary communication: Qabaja, G.; Perchellet, E.; Perchellet, J.; Jones, G. B. *Tetrahedron Lett.* **2000**, *41*, 3007−3010.

(19) Compounds **26**, **32,** and **33** were selected for evaluation against the NCI panel of 60 human tumor cell lines. Full details of this and cell cycle assays will be reported elsewhere.

(20) General experimental procedures have been reported: Jones, G. B.; Wright, J. M.; Plourde, G. W., II; Hynd, G.; Huber, R. S.; Mathews, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 1937−1944.

Solvents were condensed in vacuo using a Buchler rotary evaporator, with recirculating refrigerant maintained at −15° C by means of an Isotemp 1013S unit.

(2,5-Dimethoxyphenyl)(2-iodophenyl)methanone (8). A mixture of 2-iodobenzoic acid (1.59 g, 6.41 mmol) and 1,4-dimethoxybenzene (0.88 g, 6.41 mmol) were refluxed in trifluoroacetic acid (10 mL) and trifluoroacetic anhydride (5 mL) for 12 h. On cooling to room temperature, crushed ice (20 g) was added followed by ether (100 mL) and the organic layer washed with $NaHCO_3$. The solution was dried over Na_2SO_4 and condensed in vacuo to give the title compound (2.38 g, 100%) as white solid: mp = 74−75 °C; ^{1}H NMR ($CDCl_3$) δ 7.88 (dd, 1H, *J* 8.1 and 1.32 Hz), 7.36 (dt, 1H, *J* 7.44 and 1.08 Hz), 7.23−7.3 (m, 2H), 7.05−7.13 (m, 2H), 6.87 (d, 1H, *J* 9.0 Hz), 3.79 (s, 3H), 3.55 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 196.16, 153.8, 153.5, 145.9, 139.67, 130.85, 128.64, 127.59, 126.92, 120.88, 115.24, 113.88, 91.71, 56.43, 55.8. Anal. Calcd for $C_{15}H_{13}IO_3$: C, 48.93; H, 3.56. Found: C, 49.25; H, 3.57.

1,4-Dimethoxy-9*H*-fluorenone (9). A mixture of **8** (0.111 g, 0.300 mmol), $PdCl_2(PPh_3)_2$ (0.048 g, 0.070 mmol), and sodium acetate (0.1 g, 1.2 mmol) was dissolved in dry dimethylacetamide (10 mL), and the solution was degassed and then heated to 130 °C for 15 h. On cooling to room temperature, the solution was diluted with ether (50 mL) and washed with HCl, and the ethereal extracts were dried over Na_2SO_4. The solution was filtered, the filtrate condensed in vacuo, and the resulting oil purified by SGC (hexane:ethyl acetate 7:3) to give the title compound (0.1 g, 92%) as a yellow solid: mp = 148−150 °C;^{1}H NMR ($CDCl_3$) δ 7.83 (d, 1H, *J* 8.4 Hz), 7.6 (d, 1H, *J* 7.2 Hz), 7.43 (t, 1H, *J* 7.7 Hz), 7.23 (t, 1H, *J* 7 Hz), 7.03 (d, 1H, *J* 9.3 Hz), 6.78 9 (d, 1H, *J* 9.0 Hz), 3.93 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 192.29, 152.73, 149.85, 142.71, 134.3 134.2, 132.61, 128.47, 124.51, 123.90, 121.36, 120.49, 114.36, 56.46, 56.27. Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 75.25; H, 5.18.

(1-Hydroxy-2-naphthyl)(2-iodophenyl)methanone (11). A solution of 2-iodobenzoyl chloride (2.76 g, 11.40 mmol) in dry THF (10 mL) was added over a 5 min period to a precooled (0 °C) solution of 1-naphthol (1.49 g, 10.36 mmol), DMAP (0.127 g, 1.040 mmol), and ethyldiisopropylamine (3.6 mL, 20.6 mmol) in dry THF (10 mL). The reaction mix was stirred for 2 h and then diluted with ether (150 mL), washed with $NaHCO_3$ and HCl, dried (Na_2SO_4). Condensation in vacuo gave the 1-naphthyl 2-iodobenzoate (3.77 g, 97.5%) as an oil. The crude 1-naphthyl 2-iodobenzoate (0.73 g, 1.95 mmol) and $TiCl_4$ (0.34 mL, 3.12 mmol) were heated at 120 °C for 2 h. The resulting brown solid was cooled to 80 °C and hydrolyzed with 4 N HCl and ether, and the organic layer was washed successively with 4 N HCl, water, and $NaHCO_3$ and dried over Na_2SO_4. The product was isolated and purified by flash chromatography using hexane:ethyl acetate (9:1) to give the title compound (0.45 g, 51%) as a yellow solid: mp = 104−105 °C;^{1}H NMR ($CDCl_3$) δ 14.0 (s, 1H), 8.58 (d,1H, *J* 8.4 Hz), 8.12 (d, 1H, *J* 8.8 Hz), 7.95 (d, 1H, *J* 8.1 Hz), 7.82 (dt, 1H, *J* 6.9 and 1.0 Hz), 7.66−7.78 (m, 2H), 7.58 (dd,1H, *J* 7.7 and 1.6 Hz), 7.36−7.48 (m, 2H), 7.2 (d, 1H, *J* 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 206.94, 165.33, 145.32, 141.14, 139.52, 133.11, 132.6, 130.06, 129.63, 129.5, 128.56, 128.07, 126.64, 125.67, 120.47, 114.2, 93.15. Anal. Calcd for $C_{17}H_{11}IO_2$: C, 54.57; H, 2.96. Found: C, 54.79; H, 3.14.

10-Methoxy-11*H*-benzo[*b*]fluoren-11-one (12). Compound **11** (1.30 g, 3.48 mmol), K_2CO_3 (2.0 g, 14.5 mmol), and dimethyl sulfate (2.00 mL, 21.13 mmol) were dissolved in acetone (50 mL) and refluxed for 24 h. On cooling to room temperature, the solution was filtered through Celite and condensed in vacuo, and the residue was dissolved in ether (100 mL). Triethylamine (4 mL, 29 mmol) was added, the mixture was stirred for 1 h and then washed with water and 10% HCl, and the ethereal extracts were dried over Na_2SO_4. Condensation in vacuo gave (1.21 g, 90%) as an essentially pure yellow oil: ^{1}H NMR ($CDCl_3$) δ 8.2 (d, 1H, *J* 8.0 Hz), 7.98 (d, 1H, *J* 7.6 Hz), 7.88 (d, 1H, *J* 7.8 Hz), 7.5−7.72 (m, 4H), 7.4 (m, 2H), 7.18 (m, 1H), 3.8 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 196.6, 154.94, 144.78, 140.15, 137.07, 131.54, 129.69, 128.58, 128.03, 127.99, 127.71, 126.77, 126.6, 125.76, 123.96, 123.56, 92.38, 63.87. Without further purification, the methyl ether (0.63 g, 1.63 mmol), $Pd(OAc)_2$ (36.60 mg, 0.16 mmol), and Na_2CO_3 (0.26 g, 2.45 mmol) were dissolved in dry dimethylacetamide (30 mL), and the mixture was heated at 130 °C for 10 h. On cooling, the solution was diluted with ether (50 mL), the mixture washed with HCl, and the organic extracts were condensed in vacuo to give a residual oil. Purification by SGC (hexane:ethyl acetate 9:1) gave the title compound (0.36 g, 85%) as a yellow solid: mp = 127−129 °C; ^{1}H NMR ($CDCl_3$) δ 8.26 (d, 1H *J* 8.1 Hz), 7.68 (d, 2H, *J* 7.8 Hz), 7.61 (d, 1H, *J* 7.2 Hz), 7.36−7.55 (m, 4H), 7.28 (t, 1H, *J* 7.2 Hz), 4.35 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 190.74, 157.33, 144.21, 139.51, 138.24, 136.49, 134.54, 129.84, 129.79, 129.28, 128.60, 126.8, 125.45, 124.21, 120.78, 118.63, 114.52, 63.51. Anal. Calcd for $C_{18}H_{12}O_2$: C, 83.06; H, 4.64. Found: C, 83.36; H, 4.85.

2-Iodo-3-methoxy-5-methylbenzyl Alcohol. Prepared from 3-methoxy-5-methylbenzyl alcohol according to the procedure of Jung and Jung,[21] giving the title compound (43%) as a white solid: mp = 110 °C (lit.[21] 112−113 °C); ^{1}H NMR ($CDCl_3$) δ 6.92 (s,1H), 6.61 (s, 1H), 4.7 (s, 2H), 3.9 (s, 3H), 2.35 (s, 3H), 2.12 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 157.8, 143.9, 139.75, 121.9, 111.2, 85.4, 69.6, 56.5, 21.3.

2-Iodo-3-methoxy-5-methylbenzaldehyde (14). Dry DMSO (1.05 mL, 14.74 mmol) in CH_2Cl_2 (5 mL) was added to oxalyl chloride (0.70 mL, 8.04 mmol) in CH_2Cl_2 (20 mL) at −78 °C after 5 min as solution of the alcohol (1.86 g, 6.70 mmol) in CH_2Cl_2 (20 mL) added dropwise, after 15 min triethylamine (4.7 mL, 33.5 mmol) added dropwise, the mix was allowed to warm to RT, diluted with ether (100 mL), and washed with water and HCl, and organic extracts were dried over Na_2SO_4 and concentrated in vacuo to give the title compound (1.78 g, 96%) as a pale yellow solid: mp = 70−72 °C; ^{1}H NMR ($CDCl_3$) δ 10.16 (s, 1H), 7.33 (s, 1H), 6.88 (s, 1H), 3.93 (s, 3H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 196.74, 158.33, 140.19, 136.40, 123.07, 117.44, 90.34, 56.99, 21.37. Anal. Calcd for $C_9H_9IO_2$: C, 39.16; H, 3.29. Found: C, 39.22; H, 3.5.

2-Bromo-1,4,8-trimethoxynaphthalene (16). A mixture of 2-bromo-4,8-dimethoxynaphthol[22] (0.427 g, 1.510 mmol), dimethyl sulfate (1.0 mL, 10.6 mmol), and K_2CO_3 (1.00 g, 7.25 mmol) in acetone (30 mL) was refluxed for 24 h. On cooling, the mixture was filtered through Celite, the filtrate condensed in vacuo, and the resulting residue dissolved in a mixture of ether (100 mL) and triethylamine (3.00 mL, 21.75 mmol). The resulting solution was stirred for 0.5 h and then washed with water and HCl. The organic extracts were dried (Na_2SO_4) and condensed in vacuo, and the residual solid was purified by SGC (hexane:ethyl acetate 97:3) to give the title compound (0.350 g, 78%) as a pale yellow solid, mp = 72−73 °C; ^{1}H NMR ($CDCl_3$) δ 7.83 (dd, 1H, *J* 8.4 and 0.9 Hz), 7.39 (t, 1H, *J* 8.1 Hz), 6.947 (d, 1H, *J* 7.8 Hz), 6.942 (s, 1H), 4.01 (s, 3H), 3.96 (s, 3H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.41, 151.76, 146.99, 128.12, 126.02, 121.2, 115.01, 114.19, 108.95, 107.92, 61.67, 56.37, 55.92. Anal. Calcd for $C_{13}H_{13}BrO_3$: C, 52.55; H, 4.41. Found: C, 52.74; H, 4.51.

(2-Iodo-3-methoxy-5-methylphenyl)(1,4,8-trimethoxy-2-naphthyl)methanone (17). *tert*-Butyllithium (1.68 M in hexane, 1.32 mL, 2.25 mmol) was added dropwise over 5 min to a solution of 2-bromo-1,4,8-trimethoxynaphthalene (0.45 g, 1.50 mmol) in ether (20 mL) at −78 °C. After stirring for 15 min, a solution of aldehyde **14** (0.33 g, 1.20 mmol) in ether (10 mL) was added, the mixture allowed to warm to 25 °C, and then water (10 mL) added cautiously. The solution was extracted with ether, and the ethereal extracts were dried ($MgSO_4$) and then condensed in vacuo, the residual oil was dissolved in CH_2Cl_2 (10 mL) and added quickly to a suspension of PCC (522 mg, 2.42 mmol) in CH_2Cl_2 (10 mL), and the resulting mixture was stirred at 25 °C for 12 h. The mixture was diluted with ether (100 mL), filtered through a pad of silica gel, and then condensed in vacuo. The resulting solid was purified by SGC (hexane:ethyl acetate 4:1) to give the title

(21) Jung, M. E.; Jung, Y. H. *Tetrahedron Lett.* **1988**, *29*, 2517−2520.

(22) Hannan, R. L.; Barber, R. B.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 2153-2158.

compound (0.470 g, 80%) as a white solid: mp = 160−162 °C; ^{1}H NMR ($CDCl_3$) δ 7.9 (dd, 1H, *J* 8.3 and 0.96 Hz), 7.5 (t, 1H, *J* 8.0 Hz), 7.1 (s, 1H), 6.97 (d, 1H, *J* 7.8 Hz), 6.82 (s, 1H), 6.7 (s, 1H), 4.03 (s, 3H), 4.0 (s, 3H), 3.95 (s, 3H), 3.6 (s, 3H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 198.14, 157.82, 157.08, 152.01, 151.39, 147.97, 139.37, 131.36, 128.18, 127.86, 122.13, 120.24, 114.83, 113.02, 107.42, 104.4, 80.64, 64.0, 56.57, 56.17, 55.88, 21.3. Anal. Calcd for $C_{22}H_{21}IO_5$: C, 53.67; H, 4.3. Found: C, 54.08; H, 4.16.

Preparation of 2 [conventional method]. A suspension of ketone**17** (0.1 g, 0.2 mmol), sodium acetate (32 mg, 0.4 mmol), and $PdCl_2(PPh_3)_2$ (28.5 mg, 0.04 mmol) in dimethylacetamide (5 mL) was degassed (triple freeze−thaw cycle) and then heated at 130 °C for 24 h. On cooling to 25 °C, the mixture was diluted with ether (**5** ml) and then washed with HCl (10%, 3 × 30 mL), and the organic extracts were dried (Na_2SO_4). Condensation of the extracts in vacuo followed by SGC of the residual solid (CH_2Cl_2:ethyl acetate 95:5) gave the title compound (0.023 g, 30%) as an orange solid: mp 108−110 °C (Lit.[3] 104−112 °C).

Microwave Accelerated Route to 2. A heavy-walled (5 mm) boiling tube (100 mL) equipped with a virgin septum and magnetic stir bar was flame-dried under a stream of nitrogen gas. Ketone **17** (92 mg, 0.18 mmol), sodium acetate (46 mg, 0.54 mmol), and dichlorobis(triphenylphosphine)palladium(II) (20 mg, 0.027 mmol) in dimethylacetamide (50 mL) were introduced, and the mixture was degassed (N_2) for 2 h. The tube was placed in a 100 mL beaker within the cavity of a domestic microwave oven (450 W) and irradiated at full power for 60 s. On cooling, the mixture was poured into ether (100 mL) and washed with HCl (1 M, 3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and condensed in vacuo, and the resulting residue was purified by flash chromatography (5% EtOAc: 95% CH_2Cl_2) to give **2** (36 mg, 53%) isolated as an orange solid spectroscopically identical with authentic material.[3]

5-Methoxy-1,4-naphthalenediol (18). A solution of $Na_2S_2O_4$ (1.0 g, 5.2 mmol) in water (5 mL) was added to a solution of 5-methoxy-1,4-naphthoquinone (0.20 g, 1.06 mmol) in ether (15 mL) and CH_2Cl_2 (3.0 mL). The mixture was shaken vigorously in a 50 mL separatory funnel for 15 min, the aqueous layer separated, and the organic layer then washed with brine, dried (Na_2SO_4), and condensed in vacuo to give the title compound (0.2 g, 99%) as a gray solid: mp 184−188 °C (lit.[23] 183−185 °C); ^{1}H NMR (acetone-d_6) δ 8.9 (s, 1H), 8.8 (s, 1H), 7.88 (dd, 1H, *J* 8.8 and 0.96 Hz), 7.41 (t, 1H, *J* 7.8 Hz), 7.05 (d, 1H, *J* 7.71 Hz), 6.89 (d, 1H, *J* 8.2 Hz), 6.68 (d, 1H, *J* 8.2 Hz), 4.4 (s, 3H).

2-Iodo-3-methoxy-5-methylbenzoic Acid. Prepared by oxidation of 2-iodo-3-methoxy-5-methylbenzyl alcohol according to the method of Suzuki,[24] giving the title compound (94%) as a pale yellow solid: mp = 207 °C (lit.[24] 209 °C); ^{1}H NMR (acetone-d_6) δ 7.16 (d, 1H, *J* 1.0 Hz), 7.05 (d, 1H, *J* 1.0 Hz), 4.0 (s, 3H), 2.4 (s, 3H); ^{13}C NMR (acetone-d_6) δ 169.78, 160.4, 141.7, 141.36, 124.16, 115.67, 83.15, 57.92, 21.9.

2-Iodo-3-methoxy-5-methylbenzoyl Chloride (19). Thionyl chloride (0.51 mL, 6.99 mmol) was added to 2-iodo-3-methoxy-5-methylbenzoic acid (1.71 g, 5.85 mmol) in CH_2Cl_2 (3 mL) and DMF (0.1 mL), and the mix was refluxed under nitrogen atmosphere for 1 h. After cooling to RT, it was concentrated in vacuo to give the title compound (1.81 g, 100%) as a pale yellow solid which was used directly in the next step.

4-Hydroxy-5-methoxy-1-naphthyl 2-Iodo-3-methoxy-5-methylbenzoate (20). A solution of $Na_2S_2O_4$ (5.0 g, 28.7 mmol) in water (10 mL) was added to a solution of 5-methoxy-1,4-naphthoquinone (1.10 g, 5.85 mmol) in ether (20 mL) and CH_2Cl_2 (5 mL). The mixture was shaken vigorously in a 250 mL separatory funnel for 15 min, the aqueous layer separated, and the organic layer then washed with brine (30 mL) and dried (Na_2SO_4). Following condensation in vacuo, the residual solid was dissolved in THF (5 mL), then DMAP (5 mg) and ethyldiisopropylamine (1.05 mL, 6.00 mmol) were added, and the mixture was cooled to 0 °C for 10 min. Freshly prepared **19** (1.81 g, 5.86 mmol) in dry THF (10 mL) was added to the mixture via cannula, and the resulting mixture was stirred at 25 °C for 2 h, diluted with ether (150 mL), and quenched by the addition of water (15 mL). The organic layer was washed with HCl and $NaHCO_3$ and then dried (Na_2SO_4) and concentrated in vacuo: ^{1}H NMR (acetone-d_6) δ 9.4 (s, 1H), 7.65 (dd, 1H, *J* 8.4 and 0.96 Hz), 7.54 (t, 1H, *J* 7.74 Hz), 7.51 (s, 1H), 7.47 (d, 1H, *J* 8.4 Hz), 7.19 (s,1H), 7.145 (d, 1H, *J* 7.5 Hz), 6.93 (d, 1H, *J* 8.4 Hz), 4.10 (s, 3H), 4.03 (s, 3H), 2.4 (s, 3H); ^{13}C NMR (acetone-d_6) δ 168.08, 160.643, 158.33, 154.8, 142.3, 140.41, 140.32, 131.21, 128.78, 124.49, 121.84, 117.11, 116.49, 116.43, 110.49, 106.79, 83.43, 58.07, 57.81, 22.04. Due to decomposition on standing, the crude material was used directly in the next step without further purification.

4,5-Dimethyl-1-naphthyl 2-Iodo-3-methoxy-5-methylbenzoate. The resulting residue (**20**) was dissolved in acetone (50 mL), then dimethyl sulfate (3.0 mL, 31.7 mmol) and K_2CO_3 (3.0 g, 21.7 mmol) were added, and the mixture was refluxed for 24 h. On cooling, the solution was condensed in vacuo, and the residue was resuspended in ether (100 mL) and triethylamine (5 mL, 36.25 mmol). The resulting mixture was stirred at 25 °C for 1 h, washed with water and then HCl, and the organic extracts were dried (Na_2SO_4) and condensed in vacuo. The crude residue was purified by SGC (hexane: EtOAc 6:4) to give the title compound (1.88 g, 67%) as a white solid: mp 130−132 °C; ^{1}H NMR (acetone-d_6) δ 7.63 (dd, 1H, *J* 7.32 and 1.05 Hz), 7.46−7.55 (m, 3H), 7.2 (s, 1H), 7.0−7.1 (m, 2H), 4.05 (s, 6H), 3.95 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (acetone-d_6) δ 168.01, 160.67, 159.54, 157.56, 142.32, 141.74, 140.3, 131.99, 129.18, 124.51, 120.54, 120.4, 116.47, 115.17, 108.65, 107.0, 83.48, 58.09, 57.71, 57.45, 22.05. Anal. Calcd for $C_{21}H_{19}IO_5$: C, 52.74; H, 4.00. Found: C, 52.71; H, 3.89.

1,10,12-Trimethoxy-8-methyl-6*H*-dibenzo[*c*,*h*]chromen-6-one (21). A solution of 4,5-dimethyl-1-naphthyl 2-iodo-3-methoxy-5-methylbenzoate (1.60 g, 3.35 mmol), $PdCl_2(PPh_3)_2$ (0.60 g, 0.77 mmol), and sodium acetate (0.9 g, 11 mmol) in dimethylacetamide (300 mL) was degassed (triple freeze−thaw cycles) and heated at 130 °C for 24 h. On cooling, water (200 mL) and CH_2Cl_2 (300 mL) were added, the aqueous layer was removed, and the organic layer was washed with HCl (2 N, 3 × 30 mL) and then dried (Na_2SO_4). Following condensation in vacuo, the resulting residue was purified by SGC (hexane: ethyl acetate:CH_2Cl_2 4:5:1) to give the title compound (0.88 g, 75%) as a pale yellow solid: mp 240−242 °C; ^{1}H NMR ($CDCl_3$) δ 8.39 (s, 1H), 8.21 (d, 1H, *J* 8.6), 7.93 (s, 1H), 7.5 (t, *J* 8.1 Hz), 7.12 (s, 1H), 6.98 (d, 1H *J* 7.8 Hz), 4.05 (s, 3H), 4.03 (s, 3H), 4.0 (s, 3H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.47, 157.16, 156.63, 152.7, 140.48, 139.75, 127.14, 126.66, 123.15, 122.76, 12.93, 118.08, 117.43, 114.82, 113.7, 107.91, 104.31, 56.7, 56.51, 56.2, 21.62. Anal. Calcd for $C_{21}H_{18}O_5$: C, 71.99; H, 5.18. Found: C, 72.35; H, 5.16.

2-(3-Hydroxymethoxy-1,4-dioxo-1,4-dihydro-2-naphthyl)-3-methyl-5-methoxybenzoic Acid (24). A mixture of pyran **21** (0.13 g, 0.37 mmol) and KOH (10%, 10 mL) in THF (20 mL) was stirred at 25 °C for 5 h, resulting in formation of a deep red solution. Ether (25 mL) was added, and the organic layer was separated and acidified with HCl (concentrated, 2.0 mL), resulting in formation of a yellow solution, which was diluted with CH_2Cl_2 (30 mL) and then dried (Na_2SO_4). Condensation in vacuo gave the title compound (130 mg, 95%) as a residual yellow solid: mp = 228−230 °C; ^{1}H NMR ($CDCl_3$) δ 7.8 (dd, 1H, *J* 7.8 and 1.0 Hz), 7.74 (s, 1H), 7.69 (t, 1H, *J* 7.74 Hz), 7.16 (d, 1H, *J* 8.0 Hz), 7.15 (s, 1H), 4.05 (s, 3H), 3.95 (s, 3H), 2.4 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 183.26, 179.85, 171.04, 160.1, 157.17, 152.35, 139.96, 136.30, 135.4, 130.14, 123.88, 120.00, 118.46, 118.12, 117.2, 116.6, 116.41, 56.43, 56.11, 21.56. Anal. Calcd for $C_{20}H_{16}O_7$: C, 65.22; H, 4.38 Found: C, 65.57; H, 4.38.

1,8-Dimethoxy-3-methyl-7,12-dihydro-5*H*-dibenzo[*c*,*g*]chromene-5,7,12-trione (25). Methanesulfonic acid (0.2 mL) was added to precooled (−20 °C) solution of **24** (30 mg, 0.081 mmol) in CH_2Cl_2 (50 mL), and the resulting yellow solution

(23) Pearson, M. S.; Jensky, B. J.; Greer, F. X.; Hagstrom, J. P.; Wells, N. M. *J. Org. Chem*. **1978**, *43*, 4617−4621.

(24) Hosoya, T.; Takashiro, E.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc*. **1994**, *116*, 1004−1015.

was stirred at −20 °C for 1 h and then warmed through 25 °C for 12 h. Crushed ice (15 g) was added, the mixture was extracted with $CHCl_3$ (2 × 10 mL), and the organic layer washed with water and then $NaHCO_3$ and then dried (Na_2SO_4). Condensation in vacuo gave the title compound (26 mg, 92%) as an orange solid: mp 236−239 °C (lit.[13a] 237 °C); ^{1}H NMR ($CDCl_3$) δ 7.8 (s, 1H), 7.64−7.74 (m, 2H), 7.28 (dd, 1H, *J* 8.0 and 1.19 Hz), 7.10 (s, 1H), 4.05 (s, 3H), 3.95 (s, 3H), 2.5 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 181.62, 174.52, 159.93, 159.36, 156.95, 148.8, 143.76, 136.61, 135.58, 124.41, 122.28, 120.76, 119.36, 119.29, 118.98, 118.26, 117.16, 56.56 (2C), 29.7.

1,10-Dimethoxy-8-methyl-11,12-dihydro-6*H*-dibenzo[*c,h*]-chromene-6,11,12-trione (26)

Trifluoroacetic anhydride (0.20 mL, 1.41 mmol) was added dropwise at −78 °C to a solution of **24** (0.13 g, 0.35 mmol) in CH_2Cl_2 (30 mL), and the resulting deep red solution was warmed through room temperature and stirred for 4 h. The solution was diluted with $CHCl_3$ (30 mL) and then washed with $NaHCO_3$ and the organic layer dried (Na_2SO_4). Condensation in vacuo gave the title compound (112 mg, 91%) as a residual deep red solid: mp = 240−243 °C; ^{1}H NMR ($CDCl_3$) δ 7.8 (dd, 1H *J* 7.8 and 1.0 Hz), 7.74 (s, 1H), 7.69 (t, 1H, *J* 7.74 Hz), 7.16 (d, 1H, *J* 8 Hz), 7.15 (s, 1H), 4.05 (s, 1H), 3.95 (s, 3H), 2.4 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 181.57, 181.19, 161.67, 159.48, 156.12, 155.64, 141.87, 136.86, 132.58, 122.35, 121.77, 119.68, 119.35, 117.7, 117.49, 115.81, 114.92, 56.52, 56.34, 21.8. Anal. Calcd for $C_{20}H_{14}O_6$: C, 68.57; H, 4.03. Found: C, 68.93; H, 4.28.

1-Hydroxy-10-methoxy-8-methyl-11,12-dihydro-6*H*-dibenzo[*c,h*]chromene-6,11,12-trione (27). Lithium iodide (0.011 g, 0.082 mmol) was added to a solution of compound **26** (0.024 g, 0.069 mmol) in 2,6-lutidine (3.0 mL), and the mixture was heated at 170 °C for 7 h. On cooling, ethyl acetate (10 mL) was added followed by HCl (10%, 20 mL), and then the organic layer was separated and washed with HCl (10%, 2 × 10 mL). The organic extracts were dried (Na_2SO_4) and condensed in vacuo, and the resulting residue was purified by SGC (hexane:ethyl acetate 1:1 with 1% v/v HOAc added) to give the title compound (17 mg, 72%) as an orange solid: mp = 140 °C; ^{1}H NMR (acetone-d_6) δ 11.4 (bs, 1H), 7.79 (t, 1H, *J* 8.4 Hz), 7.61 (dd, 1H, *J* 7.32 and 1.0 Hz), 7.54 (s, 1H), 7.31 (dd, 1H, *J* 8.4 and 1.0 Hz), 7.19 (s, 1H), 3.9 (s, 3H), 2.4 (s, 3H); ^{13}C NMR (acetone-d_6) δ 188.0, 183.81, 169.73, 162.44, 158.74, 154.03, 140.91, 138.48, 134.58, 132.58, 124.48, 124.00, 123.92, 120.57, 120.22, 117.28, 115.11, 57.10, 22.36. Anal. Calcd for $C_{19}H_{12}O_6$: C, 67.86; H, 3.6. Found 68.24; H, 3.79.

Preparation of WS-5995C (from 27). A solution of KOH (10%, 2 mL) was added to compound **27** (0.02 g, 0.06 mmol) dissolved in THF (10 mL), and the mixture was stirred at 25 °C for 3 h. The resulting deep red solution was acidified with HCl (concd, 1.0 mL), the resulting yellow solution was extracted with CH_2Cl_2 (2 × 15 mL) and the organic extracts were dried (Na_2SO_4). Condensation in vacuo gave the title compound (20 mg, 95%) as a residual orange solid: mp 210−213 °C (lit.[13d] mp 212−213 °C); ^{1}H NMR (DMSO-d_6) δ 11.4 (s, 1H), 10.5 (s,-1H), 7.73 (t, 1H, *J* 8.6 Hz), 7.47 (dd, 1 H, *J* 7.35 and 1.02 Hz), 7.35 (dd, 1H, *J* 8.34 and 1.02 Hz), 7.12 (s, 1H), 3.7 (s, 3H), 2.4 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 185.98, 183.71, 168.64, 161.35, 158.14, 154.69, 140.28, 138.48, 133.71, 133.11, 126.00, 124.25, 123.59, 120.00, 119.70, 116.83, 114.88, 57.20, 22.30.

4-Methoxy-1-naphthyl-2-iodobenzoate (29). A solution of 2-iodobenzoyl chloride (15.78 mmol, 1.1 equiv) in THF (20 mL) was cannulated dropwise into a mixture of 4-methoxy-1-naphthol (2.50 g, 14.35 mmol), DMAP (0.175 g, 1.430 mmol, 0.1 equiv), and ethyldiisopropylamine (7.5 mL, 28.7 mmol, 2.0 equiv) in THF (150 mL). The solution was stirred at 0 °C for 15 min, warmed to 25 °C, and stirred for a further 3 h. Ether (150 mL) was added, and the mixture was washed with water (100 mL), $NaHCO_3$ (sat. 100 mL), and then HCl (1 N, 30 mL). The combined organic extracts were dried ($MgSO_4$) and then condensed in vacuo to give the title compound (5.1 g, 88%) as a white solid: mp = 95−97 °C; ^{1}H NMR ($CDCl_3$) δ 7.3 (m, 1H), 8.24 (dd, 1H, *J* 7.5 and 1.8 Hz), 8.13 (dd, 1H *J* 8.1 and 1.5 Hz), 7.88 (m, 1H), 7.55 (m, 3H), 7.33 (d, 1H, *J* 8.4 Hz), 7.27 (m, 1H), 6.8 (d, 1H, *J* 8.4 Hz), 4.0 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.55, 153.99, 142.14, 140.28, 134.30, 133.69, 131.89, 128.53, 127.77, 127.47, 126.61, 126.17, 122.87, 121.39, 118.26, 103.26, 95.26, 56.09. Anal. Calcd for $C_{18}H_{13}IO_3$: C, 53.49; H, 3.24. Found: C, 53.01; H, 3.16

12-Methoxy-6*H*-dibenzo[*c,h*]chromene-6-one (30). Ester **29** (3.82 g, 9.46 mmol), $PdCl_2(PPh_3)_2$ (1.33 g, 1.90 mmol), and sodium acetate (2.36 g, 28.40 mmol) were dissolved in dimethylacetamide (200 mL), and the solution was degassed and then heated at 130 °C for 24 h. The mixture was diluted with ether (300 mL) and washed with HCl (2 N, 3 × 40 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo, and the residue was purified by SGC (hexane:ethyl acetate 3:1), to give the title compound (1.51 g, 58%) as a white solid: mp = 230−231 °C; ^{1}H NMR ($CDCl_3$) δ 8.55 (dd, 1H, *J* 7.2 and 0.9 Hz), 8.48 (dd, 1H, *J* 7.5 and 1.5 Hz), 8.28 (dd, 1H, *J* 7.5 and 1.5 Hz), 8.15 (d, 1H, *J* 8.1 H), 7,88 (dt, 1H, *J* 7.5 and 1.2 Hz), 7.65 (m, 3H), 7.19 (s, 1H), 4.05 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.4, 153.92, 142.11, 140.18, 134.26, 133.56, 131.84, 128.4, 127.66, 127.34, 126.54, 126.06, 122.72, 121.26, 118.07, 103.12, 95.18, 56.06. Anal. Calcd for $C_{18}H_{12}O_3$: C, 78.25; H, 4.38. Found: C, 78.52; H, 4.17.

2-(3-Hydroxy-1,4-dioxo-1,4-dihydro-2-naphthalenyl)-benzoic Acid (31). KOH (10%, 10 mL) was added to a solution of compound **30** (0.70 g, 2.53 mmol) in THF (30 mL), and the mixture was stirred at 25 °C for 15 h, producing a deep red solution. Ether (25 mL) was added, the mixture was acidified with HCl (concentrated, 2.0 mL), and the resulting yellow solution was diluted with CH_2Cl_2 (30 mL). The organic layer was dried (Na_2SO_4) and then concentrated in vacuo to give the title compound (0.43 g, 65%) isolated as a residual yellow solid: mp = 235 °C; ^{1}H NMR (acetone-d_6) δ 9.5 (br s, 1H), 8.05−8.2 (m, 3H), 7.8−7.95 (m, 2H), 7.65 (dt, 1H, *J* 7.8 and 1.5 Hz), 7.48−7.58 (m, 2H); ^{13}C NMR (acetone-d_6) δ 183.56, 181.82, 167.23, 152.67, 134.94, 133.38, 133.12, 131.94, 131.87 (2C), 131.34, 130.45, 130.4, 128.38, 126.55, 125.93, 124.95. Anal. Calcd for $C_{17}H_{10}O_5$: C, 70.13; H, 3.92. Found: C, 70.47; H, 3.45.

11,12-Dihydro-6H-dibenzo[*c,h*]chromene-6,11,12-trione (32). Trimethylsilyl triflate (1.0 M, CH_2Cl_2, 1.5 mL, 1.5 mmol) was added dropwise to a precooled (−78 °C) solution of **31** (0.039 g, 0.133 mmol) in CH_2Cl_2 (20 mL), and the mixture stirred at −78 °C for 3 h. The solution was diluted with CH_2Cl_2 (30 mL) and washed with $NaHCO_3$, and the organic extracts were dried (Na_2SO_4). Careful condensation in vacuo precipitated the title compound (26 mg, 74%) as an orange solid: mp = 270−272 °C; ^{1}H NMR ($CDCl_3$) δ 9.15 (d, 1H, *J* 8.1 Hz), 8.4 (dd, 1H, *J* 8.1 and 0.9 Hz), 8.27 (d, 1H, *J* 8.4 Hz), 8.19 (dd, 1H, *J* 7.8 and 1.5 Hz), 7.8 (dt, 1H, *J* 8.7 and 1.5 Hz), 7.83 (dt, 1H, *J* 7.5 and 1.2 Hz), 7.7−7.6 (m, 2H); ^{13}C NMR (DMF-d_6) δ 185.65, 179.28, 164.5, 137.85, 137.85, 137.57, 136.89, 136.23, 134.32, 131.5, 130.71, 130.2, 128.60, 128.15, 127.87, 127.12, 122.25. Anal. Calcd for $C_{17}H_8O_4$: C, 73.91; H, 2.92. Found: C, 74.32; H, 3.22.

7,12-Dihydro-5*H*-dibenzo[*c,g*]chromene-5,7,12-trione (33). A solution of **31** (0.030 g, 0.102 mmol) in methanesulfonic acid (5 mL) was stirred at 25 °C for 5 h. Crushed ice (15 g) was added, the mixture was extracted with $CHCl_3$, and the organic extracts were washed with water and $NaHCO_3$ and then dried (Na_2SO_4). Condensation in vacuo gave the title compound (27.5 mg, 99%) as a residual yellow solid: mp = 248 °C; ^{1}H NMR ($CDCl_3$) δ 9.32 (d, 1H, *J* 8.4 Hz), 8.44 (dd, 1 H, *J* 7.8 and 0.9 Hz), 8.22 (m, 2H), 7.92 (t, 1H, *J* 7.2 Hz), 7.7−7.9 (m 3 H); ^{13}C NMR ($CDCl_3$) δ 183.78, 176.89, 159.04, 151.15, 136.22, 135.19, 134.47, 132.68, 132.31, 131.6, 130.6, 130.49, 128.99, 127.39, 126.92, 123.08, 116.99. Anal. Calcd for $C_{17}H_8O_4$: C, 73.91; H, 2.92. Found: C, 74.10; H, 3.08.

Conversion of 32 into 33. Compound **32** (10.0 mg) was dissolved in methanesulfonic acid (5 mL), and the mixture was stirred at RT for 5 h. The reaction mixture was poured onto ice (10 g) and water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL), and the organic extracts were washed with $NaHCO_3$ (sat. 4 × 10 mL), dried (Na_2SO_4), and condensed in vacuo to give compound **33** (9.0 mg, 90%).

General Procedure for Determination of Quinone Reduction Potentials. Published laboratory procedures were

followed.[25] Solutions of quinone (2.0−4.0 mg) in DMF (2 mL, HPLC grade) containing tetraethylammonium fluoroborate (**33** mg) were swept between +0.4 and −1.5 V at a rate of 100 mV/s. $E°$ values were determined against Ag/Ag^+, with a system precalibrated against ferrocene, swept under identical conditions.

Bioassay Methods. Preliminary growth inhibition assays against murine L1210 cells were determined using the MTS method,[26] and H-460, MCF-7, and SF-268 cells using the standard NCI screening protocol.[19]

Acknowledgment. This work was supported by grants from the National Institute of General Medical Sciences (RO1GM57123), The Petroleum Research Fund (33920-AC1), and The American Cancer Society. We thank Professors E. M. Perchellet and J.-P. Perchellet (Anti-Cancer Drug Laboratory, Kansas State University) for performing initial bioassays.

JO0056186

(25) Sivakolundu, S. G.; Mabrouk, P. A. *J. Am. Chem. Soc.* **2000**, *122*, 1513−1521.

(26) Cory, A. H.; Owen, T. C.; Barltrop, J. A.; Cory, J. G. *Cancer Commun.* **1991**, *3*, 207−212; Perchellet, E. M.. Ladesich, J. B.; Magill, M. J.; Chen, Y.; Hua, D. H.; Perchellet, J. P. *Anti-Cancer Drugs* **1999**, *10*, 489−504.

(27) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113−10130.

(28) Jeffery, T.; David, M. *Tetrahedron Lett.* **1998**, *39*, 5751−5754.