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Synthesis of Benzo[*b*]carbazoloquinones by Coupling of Organostannanes with Bromoquinones

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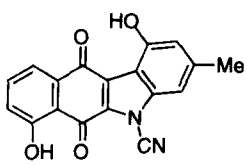
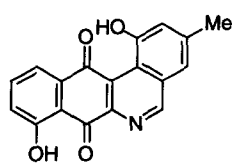
Abstract: The synthesis of 5-carbonitrile-1,7-dihydroxy-3-methyl-5H-benzo[*b*]carbazole-6,11-dione, the quinone originally proposed as prekinamycin, was completed by using a palladium and copper catalyzed Stille reaction as the key step. A subsequent heterocyclization afforded a mixture of para-(benzo[*b*]carbazole-6,11-dione) and ortho (benzo[*a*]carbazole-5,6-dione) quinones. A procedure for the N-cyanation of model indoles is also described. © 1997 Elsevier Science Ltd.

Introduction

Structure **1** was assigned for a metabolite isolated by Gould in 1989 from cultures of *Streptomyces murayamaensi*.[1,2] This structure was assigned on the basis of its spectroscopic data and its proposed biosynthetic relationship with the kinamycin antibiotics [3] whose structures had been apparently secured on the basis of the X-ray structure of one derivative.[4] Intermediate **1**, named "prekinmaycin",[1,2] was also structurally related to a small class of natural occurring quinones represented by phenanthrovirinone (**2**)[2b] and jadomycin A (**3**).[2c] However, synthesized **1**[5,6] was shown to be different from the natural quinone. This led to a reinvestigation of the structures of these antibiotics which concluded, on the basis of a more accurate X-ray structure determination, that the kinamycins are indeed 5-diazobenzo[*b*]fluorenes.[7,8] Prekimamycin was therefore reassigned structure **4**.[7] However, two recent parallel synthetic efforts have demonstrated that the metabolite isolated in 1989 was not **4**,[9,10] although a search on the extracts of *S. murayamaensis* revealed that **4** is indeed a natural product.[9] To date, the structure of the original "prekinamycin", isomeric with **4**, remains undetermined.[11]



1



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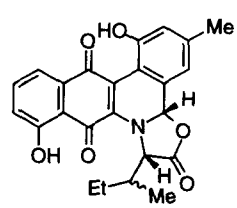

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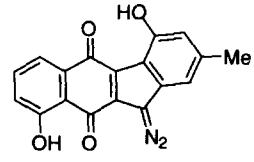


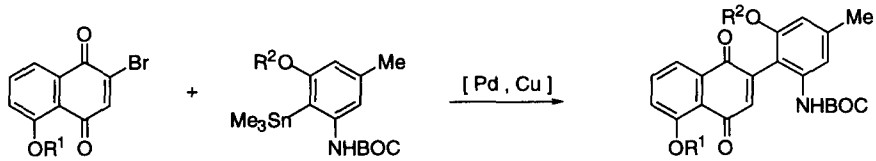
4

Our synthesis of **1** relied upon the coupling of 2-bromonaphthoquinones with stannanes in the presence of palladium and copper as the catalysts,[5,12] a reaction that we have used successfully as a key step for the

concise synthesis of several naturally occurring quinones.[13,14,15] Although the first communicated synthesis of **1** was concise, the heterocyclization step was shown to give a mixture of two benzo[*b*]carbazole-6,11-diones and one benzo[*a*]carbazole-5,6-dione. Herein we report full details of the synthesis and characterization of **1** and two of its regioisomers.

Results and Discussion

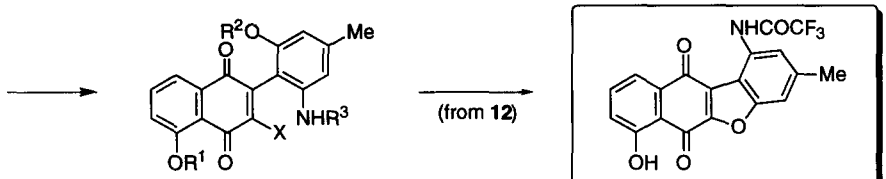
Palladium- and Copper Catalyzed Couplings and Heterocyclization Reactions



5 : R^1 = H
6 : R^1 = Me

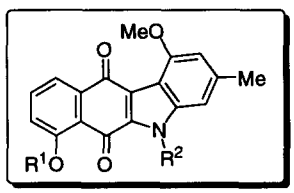
7 : R^2 = MOM
8 : R^2 = Me

9 : R^1 = H, R^2 = MOM
10 : R^1 = R^2 = Me

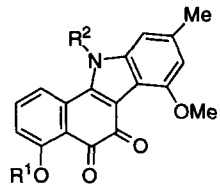


11 : X = H, R^1 = R^2 = H, R^3 = $COCF_3$
12 : X = OH, R^1 = R^2 = H, R^3 = $COCF_3$
13 : X = OH, R^1 = R^2 = Me, R^3 = BOC

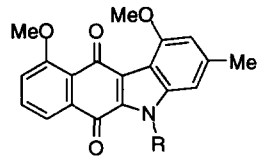
Coupling of naphthoquinones **5**-**6**[16] with arylstannanes **7**-**8**[13] with $Pd(PPh_3)_4$ and CuBr (5 mol% each) as the catalysts proceeded in 1,4-dioxane under reflux to give **9** and **10** in good to excellent yields (Scheme 1).[13] Exchange of the protecting group of the amine of **9** and cleavage of the MOM was achieved in a single step with a 1:1 mixture of trifluoroacetic acid and trifluoroacetic anhydride to give **11** (63%), which reacted with *t*-BuOOH and Triton B (aqueous THF, 23 °C) to give 3-hydroxy quinone **12**. Similar hydroxylation of **10** afforded **13** in quantitative yield. In contrast with **13**, which was a stable compound, quinone **12** underwent cyclization to form benzo[*b*]naphtho[*2,3-d*]furane **14**. This cyclization was more cleanly performed in DMSO at 80 °C with crude **12** to give **14** in 40% overall yield.



15 : R^1 = Me, R^2 = H
18 : R^1 = R^2 = Me
19 : R^1 = Me, R^2 = CH_2Ph
25 : R^1 = H, R^2 = CH_2Ph



16 : R^1 = Me, R^2 = H
20 : R^1 = R^2 = Me
21 : R^1 = Me, R^2 = CH_2Ph

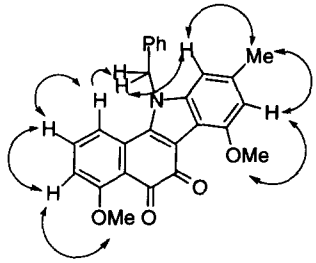


17 : R = H
22 : R = Me
23 : R = CH_2Ph

Removal of the BOC protecting group of **13** could be effected in small scale experiments (*ca.* 5 mg) by thermolysis at 180 °C[17] leading to a mixture of **15** and **16**. However, this reaction was more conveniently

carried out under acidic conditions (MeOH, cat. H_2SO_4, reflux) to yield a 1:1 mixture of **15** and **16** (80% yield). Highly insoluble ortho-quinone **16** could be routinely separated by recrystallization from DMSO. In several occasions we obtained a third quinone **17** as a minor product.[18,19] After much experimentation, we have concluded that formation of this unexpected rearranged quinone can be traced back to the use as the starting material in the cyclization of crude **13** which was prepared by exposing **10** to a large excess of *t*-BuOOH and Triton B for longer reaction times (14-24 h) (see bellow). Although the precise precursor of rearranged **17** could not be isolated, formation of this para-quinone can be avoided by performing the hydroxylation of **10** under controlled conditions and by using carefully purified **13** for the heterocyclization reaction.

Characterization of these quinones was more conveniently carried out after methylation (MeOTs, K_2CO_3, DMF, 100 °C) or benzylation (BnCl, K_2CO_3, DMF, 100 °C) to form more soluble products **18-23**. The structure of **21** was secured by the observation of the nOe shown as well as by HMBC and HMQC experiments. The structure of benzo[*b*]carbazoloquinole **19** was confirmed by a NOESY experiment on its reduced derivative **24**. Additionally, the structure of **19** was confirmed by chemical correlation with known **25**.[15a]



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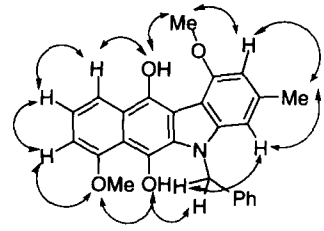
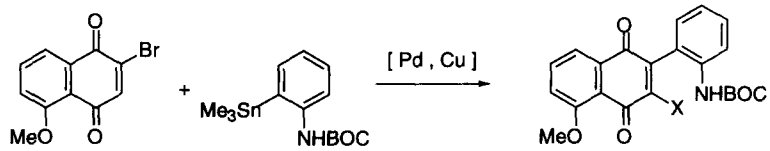


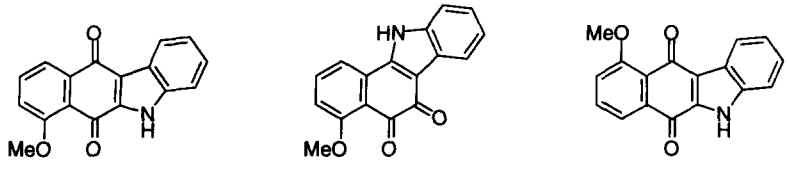
24

The cyclization behavior of a more simple analogue of **12** and **13** was also examined. Thus, the palladium and copper-catalyzed coupling[13] of **6** with stannane **26**[20] afforded **27** (77% yield) which was hydroxylated at C-3 by using excess of *t*-BuOOH and Triton B (aqueous THF, 23 °C) to give crude **28** contaminated with small amounts of the intermediate epoxide.



6 **27** **26** : X = H **28** : X = OH

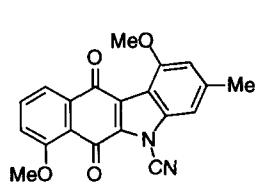
Treatment of crude **28** with aqueous HCl in 1,4-dioxane under reflux lead to a mixture of *p*- and *o*-quinones **29-31**,[21] although the overall yield of this process was rather low (26%).



29 **30** **31**

N-Cyanation and Synthesis of Quinone 1

The desired regioisomer **15** was finally N-cyanated with excess BrCN in the presence of Et_3N and DMAP in CH_2Cl_2 at 23 °C to give N-cyanamide **32** in quantitative yield.[22] Demethylation of **32** with BBr_3 gave **1** (90% yield), whose ^1H NMR was clearly distinct from that published for the quinone proposed to be **1**.[1]



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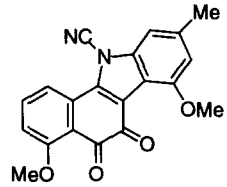

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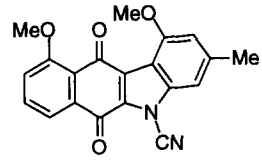

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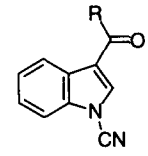

35 : R = H
36 : R = OEt

Similarly, N-cyanation of **16**, **17**, and two indoles by using the above developed conditions afforded **33-36**. The cyanamide functional group of these synthetic intermediates displays a characteristic IR absorption around 2250-2240 cm^{-1}, distinct from that found for diazobenzo[*b*]fluorenes (usual range: 2120-2090 cm^{-1}). Additionally, long range ^1H-^{13}C correlation (HMBC) experiments on N-cyano indoles **35** and **36** allowed to assign the cyanamide carbon resonance at 105-106 ppm.

Conclusions

We have completed a synthesis of **1**, the structure originally proposed for the metabolite prekinamycin, and two of its regioisomers by using a palladium and copper catalyzed coupling between a 2-bromonaphthoquinone and an arylstannane as the key step. Although the formation of the C ring leads to a mixture of para and ortho quinones, their ready separation allows for the concise and effective synthesis of **1**. By performing the heterocyclization reaction with carefully purified hydroxyquinone **13**, the formation of unwanted rearranged *p*-quinone **17** could be eliminated. In this work we have also synthesized heterocyclic ortho quinones **16**, **20**, **21**, and **31** which are congeners of methylamine dehydrogenase and aromatic amine dehydrogenase enzymes TTQ (tryptophan tryptophylquinone)[23] and PQQ (pyrroloquinoline quinone, methoxatin).[24] A study on the reactivity of some of these quinone towards amines is in progress.

Experimental Section

NMR spectra were recorded at 23 °C, unless otherwise stated. Only the most significant IR absortions and MS fragmentations (electron impact, 70 eV) are given. "Usual workup" means cooling to room temperature (if appropiate), partitioning between the stated solvents, washing with water, drying (Na_2SO_4) followed by filtration, and evaporation. Chromatographic purifications were carried out using flash grade silica gel. All reactions were carried out under Ar.

2-Bromo-5-hydroxy-1,4-naphthoquinone (**5**)[25a] (mp 134-135 C, lit[25b] 136 °C) was prepared according to known procedures. Methylation of of **5** with MeI (excess) and Ag_2O (1.5-2.0 equiv) in $CHCl_3$ under refluxing conditions furnished 2-bromo-5-methoxy-1,4-naphthoquinone (**6**) (70%, mp 135-136 °C, lit[16] 134 °C). The following compounds were prepared according to published procedures: [2-[(*tert*-butoxycarbonyl)amino]-6-(methoxymethoxy)-4-methylphenyl]trimethylstannane (**7**),[13] [2-[(*tert*-butoxycarbonyl)amino)-6-methoxy-4-methylphenyl]trimethylstannane (**8**),[13] 2-[2-[(*tert*-butoxycarbonyl)amino]-4-methyl-6-(methoxymethoxy)phenyl]-5-hydroxy-1,4-naphthoquinone (**9**),[13] and *N*-(*tert*-butoxycarbonylamino)phenyltrimethylstannane (**27**).[20]

2-[2-[(*tert*-Butoxycarbonyl)amino]-6-methoxy-4-methylphenyl]-5-methoxy-1,4-naphthoquinone (10). A mixture of **6** (267 mg, 1.0 mmol), **8** (396 mg, 1.03 mmol), $Pd(PPh_3)_4$ (116 mg, 0.1 mmol), and CuBr (48 mg, 0.33 mmol) in 1,4-dioxane (35 mL) was heated at 100 °C for 1 h. After being cooled to room temperature, the solvent was evaporated and the residue was chromatographed (2:1 hexane-EtOAc) to give **10** as an orange solid (390 mg, 92%): mp 135-137 °C; IR (KBr) 3340, 1730 1650, 1590 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.81 (dd, J = 8.0, 1.7 Hz, 1H), 7.71 (t, J = 8.0 Hz, 1H), 7.44 (s, 1H), 7.34 (dd, J = 8.4, 1.3 Hz, 1H), 6.87 (s, 1H), 6.53 (s, 1H), 6.22 (br s, 1H), 4.03 (s, 3H), 3.70 (s, 3H), 2.38 (s, 3H), 1.42 (s, 9 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 183.9 (s), 183.6 (dd, J = 10.2, 3.8 Hz), 159.3 (m), 157.0 (br s), 152.7 (s), 142.6 (s), 140.7 (d, J = 166.7 Hz), 140.7 (q, J = 6 Hz), 136.3 (s), 134.6 (d, J = 8 Hz), 134.5 (dd, J = 165.5, 2.7 Hz), 119.7 (q, J = 4.8 Hz), 119.5 (dd, J = 168.1, 7.5 Hz), 117.4 (dd, J = 163.2, 8.1 Hz), 114.6 (dq, J = 164.0, 5.0 Hz), 111.9 (m), 107.3 (dquintet, J = 159.7, 5.4 Hz), 80.3 (m), 56.2 (q, J = 145.3 Hz), 55.6 (q, J = 144.4 Hz), 28.0 (septet, J = 126.9, 4.1 Hz, 3C), 21.9 (qt, J = 126.8, 4.9 Hz); EI-MS *m/z* 423 (M^+, 7), 349 (12), 323 (32), 306 (35), 305 (100); HR-EI-MS calcd for $C_{24}H_{25}NO_6$ *m/z* 423.1682, found *m/z* 423.1682.

5-Hydroxy-2-[(2-hydroxy-4-methyl-6-(trifluoroacetylamino)phenyl]-1,4-naphthoquinone (11). A solution of **9** (170 mg, 0.40 mmol) in a 1:1 mixture of trifluoroacetic acid and trifluoroacetic anhydride (5 mL) at 0 °C was stirred for 1.5 h. After the usual workup (EtOAc, 5% KH_2PO_4 aqueous solution) and chromatography (3:1 hexane-EtOAc), **11** was obtained as a purple solid (98 mg, 63%): mp 188-189 °C; IR (KBr) 3295, 1705, 1640, 1630 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.78 (s, 1H), 10.86 (br s, 1H), 9.83 (s, 1H), 7.78 (t, J = 7.9 Hz, 1H), 7.55 (dd, J = 7.5 Hz, 1.0 Hz, 1H), 7.37 (dd, J = 7.5, 0.9 Hz, 1H), 6.81 (s, 1H), 6.77 (br s, 1H), 6.70 (br s, 1H), 2.28 (s, 3H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$; DEPT) δ 189.5 (C), 181.5 (C), 160.1 (C), 155.6 (C), 155.0 [C, q, $^2J(^{13}C\text{-}^{19}F)$ = 36.7 Hz], 146.1 (C), 140.2 (C), 137.0 (CH), 136.9 (CH), 133.4 (C), 132.4 (C), 124.4 (C), 123.6 (CH), 118.9 (CH), 117.6 (CH), 115.6 [C, q, $^1J(^{13}C\text{-}^{19}F)$ = 298.0 Hz], 114.9 (CH), 114.7 (C), 20.9 (CH_3). Anal. Calcd for $C_{19}H_{12}F_3NO_5$: C, 58.32; H, 3.09; N, 3.58. Found: C, 58.15; H, 2.88; N, 3.29.

2-[2-Hydroxy-4-methyl-6-(trifluoroacetylamino)phenyl]-3,5-dihydroxy-1,4-naphthoquinone (12). To a solution of **11** (148 mg, 0.38 mmol) in THF (15 mL) was added Triton B (0.47 mL of a 40 % aqueous solution, 1.14 mmol) and *tert*-butyl hydroperoxide (0.46 mL of a 80% solution in di-*tert*-butyperoxide, 4.56 mmol) at 23 °C. After being stirred at this temperature for 3 h, the usual workup (EtOAc,10% aqueous HCl solution) gave **12** contaminated with variable amounts of cyclized product **14**. Attempted purification by chromatography led to **14**. Acetylation with Ac_2O and conc. H_2SO_4 as the catalyst at 23 °C yielded **2-(6-acetylamino-2-acetyloxy-4-methylphenyl)-3,5-bis(acetyloxy)-1,4-naphthoquinone**: ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J = 7.6 Hz, 1H), 7.79 (t, J = 7.8 Hz, 1H), 7.71 (br s, 1H), 7.43 (d, J = 7.9 Hz, 1H), 7.15 (br s, 1H), 6.86 (br s, 1H), 2.45 (s, 3H), 2.41 (s, 3H), 2.19 (s, 3H), 2.06 (s, 3H), 2.00 (s, 3H).

2-[2-[(*tert*-Butoxycarbonyl)amino]-6-methoxy-4-methylphenyl]-3-hydroxy-5-methoxy-1,4-naphthoquinone (13). To a solution of **10** (390 mg, 0.92 mmol) in THF (25 mL) was added benzyltrimethylammonium hydroxide (Triton B) (1.21 mL of a 40 % aqueous solution, 2.76 mmol) and *tert*-butyl hydroperoxide (1.11 mL of a 80% solution in di-*tert*-butyperoxide, 11.06 mmol) at 23 °C. After being stirred at this temperature for 2 h, the the usual workup (EtOAc, saturated aqueous tartaric acid solution) and chromatography (1:1 hexane-EtOAc) gave **13** as an orange solid (400 mg, quantitative): mp 182-183 °C; IR (KBr) 3360, 1730, 1650, 1590 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (dd, J = 7.6, 1.4 Hz, 1H), 7.73 (t, J = 8.3 Hz, 1H), 7.51 (br s, 1H), 7.27 (dd, J = 8.4, 1.1 Hz, 1H), 6.53 (s, 1H), 6.30 (s, 1H), 4.05 (s, 3H), 3.70 (s, 3H), 2.39 (s, 3H), 1.43 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.6 (d, J = 3.8 Hz), 179.4 (s), 160.3 (sextet, J = 4.2 Hz), 157.2 (br s), 154.1 (s), 152.9 (s), 140.5 (q, J = 5.9 Hz), 137.2 (s), 136.6 (d, J = 163.5 Hz), 135. 6 (s), 120. 3 (dd, J = 168.8, 7.4 Hz), 117. 2 (t, J = 5.5 Hz), 116.7 (dd, J = 161.2, 7.1 Hz), 115.1 (s), 114.5 (br d, J = 164.3 Hz), 107. 4 (br s), 107.4 (dquintet, J = 159.3, 5.1 Hz), 80.3 (m), 56.5 (q, J = 145.7 Hz), 55.9 (q, J = 144.0 Hz), 28.3 (qseptet, J = 126.8, 4.0 Hz), 22.1 (qt, J = 126.6, 4.5 Hz);

EI-MS *m/z* 439 (M^+, 8), 383 (22), 365 (38), 339 (30), 322 (55), 321 (100); HR-EI-MS calcd for $C_{24}H_{25}NO_7$ *m/z* 439.1631, found *m/z* 439.1631.

7-Hydroxy-3-methyl-1-(trifluoroacetylamino)benzo[*b*]naphtho[*2,3-d*]furan-6,11-dione (14). A solution of crude **12** (235 mg, *ca.* 0.58 mmol) in DMSO (15 mL) was heated at 80 °C for 12 h. After the usual workup (EtOAc ,water) and chromatography (2:1 hexane-EtOAc) **14** was obtained as an orange solid (91 mg, 40 %, two steps): mp > 340 °C; IR (KBr) 1720, 1630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 12.11 (br s, 1H), 11.95 (s, 1H), 8.50 (s, 1H), 7.84 (dd, J = 7.5, 1.1 Hz, 1H), 7.69 (t, J = 8.0 Hz, 1H), 7.37 (dd, J = 8.5, 1.1 Hz, 1H), 7.34 (s, 1H), 2.58 (s, 3H); EI-MS *m/z* 389 (M^+, 3), 363 (7), 294 (21), 293 (100). Anal. Calcd for $C_{19}H_{10}F_3NO_5$: C, 58.62; H, 2.59; N, 3.60. Found: C, 58.31; H, 2.55; N, 3.36.

1,7-Dimethoxy-3-methyl-5*H*-benzo[*b*]carbazole-6,11-dione (15) and 4,7-Dimethoxy-9-methyl-11*H*-benzo[*a*]carbazole-5,6-dione (16). To a solution of **13** (680 mg, 1.55 mmol) in MeOH (18 mL) was added conc. H_2SO_4 (1 drop). The mixture was heated under refluxing conditions for 3 h. The mixture was diluted with water (8 mL) and the resulting solid was filtered to give a 1:1 mixture of **15** and **16** (400 mg, 80%). Chromatography (silica gel deactivated with 99:1 MeOH-HOAc; 1:1 hexane-EtOAc) led to **15** (40%) as an orange-red solid: mp 173-175 °C; IR (KBr) 3260, 1650, 1590 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 50 °C) δ 9.22 (br s, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.66 (t, J = 8.2 Hz, 1H), 7.24 (d, J = 7.9 Hz, 1H), 6.90 (br s, 1H), 6.57 (br s, 1H), 4.06 (s, 3H), 4.04 (s, 3H), 2.48 (s, 3H); ^1H NMR (300 MHz, DMSO-d_6, 50 °C) δ 12.55 (br s, 1H), 7.80-7.70 (m, 2H), 7.46 (dd, J = 6.4, 3.3 Hz, 1H), 6.93 (s, 1H), 6.60 (s, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (50 MHz, DMSO-d_6, 55 °C) δ 176.9 (br d, J = 2 Hz), 176.2 (s), 159.5 (m), 154.66 (m), 139.9 (d, J = 3.4 Hz), 137.9 (d, J = 3.5 Hz), 137. 6 (q, J = 6.0 Hz), 137.2 (m), 134.8 (d, J = 162.3 Hz), 119.2 (dd, J = 166.4, 7.7 Hz), 118.0 (m), 117.6 (dt, J = 159.5, 6.1 Hz), 116.3 (s), 112.29 (m), 105.8 (ddd, J = 156.7, 7.0, 5.1 Hz), 105.4 (dt, J = 162.8, 5.5 Hz), 56.2 (q, J = 145.4 Hz), 55.4 (q, J = 144.1 Hz), 21.4 (qt, J = 126.6, 4.8 Hz); EI-MS *m/z* 322 (M^++1, 25), 321 (M^+, 100), 292 (33), 290 (31), 274 (30), 262 (22); UV-vis ($CHCl_3$) λ_{max} (ε) 267 (45 000), 284 (50 000), 292 (50 000), 408 (15 000) nm; HR-EI-MS calcd for $C_{19}H_{15}NO_4$ *m/z* 321.1001, found *m/z* 321.1000. More insoluble regioisomer **16** was obtained by recrystallization from a solution of **15** and **16** in DMSO at 60 °C as a red solid: mp > 315 °C (dec.); IR (KBr) 3240, 1650, 1600 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6, 40 °C) δ 12.60 (br s, 1H), 7.73 (t, J = 8.0 Hz, 1H), 7.61 (dd, J = 7.7, 1.0 Hz, 1H), 7.22 (br d, J = 7.6 Hz, 1H), 6.89 (br s, 1H), 6.56 (br s, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 2.40 (s, 3H); HR-EI-MS calcd for $C_{19}H_{15}NO_4$ *m/z* 321.1001, found *m/z* 321.1000. The above procedure led reproducibly to **15** and **16**. When the hydroxylation of **10** was carried out for longer reaction times, and the cyclization was performed with crude **13**, regioisomer **17** was also obtained as a minor product.

1,7-Dimethoxy-3,5-dimethyl-5*H*-benzo[*b*]carbazole-6,11-dione (18). A mixture of **15** (30 mg, 0.10 mmol), K_2CO_3 (28 mg, 0.20 mmol), and methyl *p*-toluenesulfonate (0.024 mL, 0.16 mmol) in DMF (5 mL) was heated at 100 °C for 12 h. After the usual workup (CH_2Cl_2,10% aqueous HCl) and chromatography (1:1 hexane-EtOAc), **18** was obtained as an orange solid (32 mg, 94%): mp 268-269 °C; IR (KBr) 1660, 1585 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.95 (dd, J = 7.7 Hz, 1.1 Hz, 1H), 7.63 (dd, J = 8.4, 7.7 Hz, 1H), 7.22 (dd, J = 8.5, 1.1 Hz, 1H), 6.81 (br s, 1H), 6.55 (br s, 1H), 4.17 (s, 3H), 4.05 (s, 3H), 4.03 (s, 3H), 2.47 (s, 3H); ^1H NOEDIFF (300 MHz, $CDCl_3$): irradiation at δ 4.17 (NMe) gives rise to an enhancement at 6.81 (H-4, 4 %), irradiation at δ 4.05 (MeO-1) gives rise to an enhancement at 6.55 (H-2, 3 %), irradiation at δ 4.03 (MeO-10) gives rise to an enhancement at 7.22 (H-9, 4 %); ^{13}C NMR (50 MHz, $CDCl_3$)[26] δ 179.2 (s), 178.7 (d, J = 4.0 Hz), 159.0 (m), 155.5 (m), 142.2 (q, J = 3.0 Hz), 138.8 (q, J = 3.6 Hz), 137.2 (d, J = 8.0 Hz), 136.1 (m), 134.7 (d, J = 162.1 Hz), 120.5 (m), 120.0 (dd, J = 165.0, 7.6 Hz), 118.3 (m), 116.7 (dd, J = 159.3, 8.2 Hz), 111.9 (s), 106.0 (dquintet, J = 143.5, 6.0 Hz), 103.1 (dq, J = 155.0, 5.7 Hz), 56.4 (q, J = 144.8 Hz), 56.0 (q, J = 144.2 Hz), 32.5 (q, J = 141.1 Hz), 22.4 (qt, J = 126.8, 4.8 Hz); UV-vis ($CHCl_3$) λ_{max} (ε) 242 (24 000), 263 (20 000) 273 (21 000), 295 (23 000), 397 (9000). Anal. Calcd for $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.18. Found: C, 71.48; H, 4.99; N, 4.31.

1,7-Dimethoxy-3-dimethyl-5-methylphenyl-5*H*-benzo[*b*]carbazole-6,11-dione (19). A mixture of **15** (5 mg, 0.017 mmol), K_2CO_3 (10 mg, 0.07 mmol), and benzyl chloride (0.010 mL, 0.09 mmol) in DMF (0.3 mL) was heated at 100 °C for 14 h. After the usual workup (CH_2Cl_2, water) and chromatography (3:1 hexane-EtOAc) **19** was obtained as a dark orange solid (5 mg, quantitative): mp 244-245 °C; IR (KBr) 1650, 1590, 1510 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.97 (dd, J = 7.6, 1.0 Hz, 1H), 7.64 (dd, J = 8.4, 7.7 Hz, 1H), 7.27-7.21 (m, 4H), 7.11-7.09 (m, 2H), 6.77 (br s, 1H), 6.57 (br s, 1H), 6.00 (s, 2H), 4.07 (s, 3H), 3.99 (s, 3H), 2.42 (s, 3H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$)[26] δ 178.9, 178.8, 160.1, 155.6, 142.1, 139.2, 137.2, 136.8, 135.8, 134.8, 128.7 (2 C), 127.3, 126.3 (2 C), 120.6, 120.0, 119.0, 116.9, 112.2, 106.3, 103.9, 56.4, 56.0, 48.5, 22.5; EI-MS *m/z* 413 (M^++2, 4), 411 (M^+, 42), 382 (13), 320 (15), 91 (100). Anal. Calcd. for $C_{26}H_{21}NO_4$: C, 75.90; H, 5.14; N, 3.40. Found: C, 75.91; H, 5.36; N, 3.57. Quinone **19** was also obtained quantitatively by methylation (MeI, 20% aqueous NaOH-CH_2Cl_2, $BnMe_3NCl$, 48 h at 23°C) of a sample of **1,7-dihydroxy-3-methyl-5-phenylmethyl-5*H*-benz[*b*]carbazole-6,11-dione (25)** provided by Prof. Murphy.[15a]

4,7-Dimethoxy-9,11-dimethyl-11*H*-benzo[*a*]carbazole-5,6-dione (20). A 10:1 mixture of **15** and **16** (40 mg, 0.12 mmol), methyl *p*-toluene sulfonate (0.060 mL, 0.38 mmol), K_2CO_3 (64 mg, 0.48 mmol) in DMF (10 mL) was heated at 100 °C for 24 h. After the usual workup (CH_2Cl_2, 10% aqueous HCl), chromatography (1:1 hexane-EtOAc) gave **18** as an orange solid (4 mg, quantitative) and **20** as a brown solid (14 mg, 38%). **20**: mp 256-257 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.58 (t, J = 8.2 Hz, 1H), 7.41 (d, J = 7.9 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 6.79 (s, 1H), 6.54 (s, 1H), 4.05 (s, 3H), 3.98 (s, 6H), 2.48 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 175.4, 161.6, 154.4, 142.5, 139.1, 137.0, 136.3, 136.2, 131.8, 131.8, 118,3, 115.0, 112.7, 110.0, 107.4, 104.3, 56.5, 56.2, 34.8, 21.8 (the signal of a carbonyl carbon was not observed).

4,7-Dimethoxy-9-methyl-11-phenylmethyl-11*H*-benzo[*a*]carbazole-5,6-dione (21). A mixture of **16** (3 mg, 0.01 mmol), K_2CO_3 (10 mg, 0.07 mmol), and benzyl chloride (0.01 mL, 0.09 mmol) in DMF (0.2 mL) was heated at 100 °C for 14 h. After the usual workup (CH_2Cl_2, water) and chromatography (EtOAc) **21** was obtained as a red solid (2 mg, 67%): mp 236-237 °C; IR (KBr) 1730, 1655, 1665, 1580 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.38 (m, 3H), 7.35 (t, J = 8.1 Hz, 1H), 7.22 (br d, J = 7.3 Hz, 2H), 7.03 (br d, J = 8.1 Hz, 1H), 6.95 (br d, J = 8.3 Hz, 1H), 6.60 (s, 1H), 6.55 (s, 1H), 5.61 (s, 2H), 4.00 (s, 3H), 3.98 (s, 3H), 2.4 (s, 3H); ^1H NOEDIFF ($CDCl_3$, 300 MHz):[27] irradiation at δ 5.63 (CH_2) gives rise to enhancements at δ 7.11-7.09 (m, 2H) (4%), 7.03 (H-1, 16 %), and 6.60 (H-10, 15%); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$)[26] δ 183.7, 176.2, 161.9, 154.7, 143.7, 142.5, 137.3, 135.7, 135.3, 131.9, 129.4 (2 C), 127.9, 125. 7 (2 C), 118.7, 117.0, 114.1, 113.6, 113.0, 106.7, 103.5, 60.3, 56.2, 56.0, 22.1; EI-MS *m/z* 413 (M^++2, 5), 411 (M^+, 17), 383 (5), 382 (4), 320 (38), 91 (100); UV-vis ($CHCl_3$) λ_{max} (ε) 269 (12 400), 288 (13 500), 299 (13 500), 307 (13 500), 388 (3600); HR-EI-MS calcd. for $C_{26}H_{21}NO_4$ *m/z* 411.1471, found *m/z* 411.1469.

1,10-Dimethoxy-3,5-dimethyl-5*H*-benzo[*b*]carbazole-6,11-dione (22). Methylation of a crude cyclization mixture derived from **13** with methyl *p*-toluenesulfonate (aprox. 1 mol equiv) and K_2CO_3 (aprox. 1 mol equiv) in DMF led to a mixture of **18**, **20**, and **22** which was separated by chromatography (3:2 hexane-EtOAc) to give **22** as an orange-red solid (usual yields from crude **13**: 0-10%): mp 215-216 °C; IR (KBr) 1650, 1580 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)[27] δ 7.81 (dd, J = 7.6, 1.2 Hz, 1H), 7.58 (t, J = 8.0 Hz, 1H), 7.28 (dd, J = 8.5, 1.1 Hz, 1H), 6.80 (br s, 1H), 6.54 (br s, 1H), 4.17 (s, 3H), 4.40 (s, 3H), 4.01 (s, 3H), 2.49 (s, 3H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$)[26] δ 178.8 (2 C), 160.0, 155.9, 142.6, 139.4, 135.6, 135.2, 133.1, 122.7, 118.7, 118.6, 114.8, 113.2, 105. 8, 102. 8, 56.7, 56.0, 32.1, 22.5; UV-vis ($CHCl_3$) λ_{max} 248, 272, 295, 388, 457 nm. Anal. Calcd for $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.18. Found: C, 71.50; H, 4.80; N, 3.92.

1,10-Dimethoxy-3-methyl-5-phenylmethyl-5*H*-benzo[*b*]carbazol-6,11-dione (23). Benzylation of a crude cyclization mixture derived from **1** with benzyl chloride (aprox. 1 mol equiv) and

K_2CO_3 (aprox. 1 mol equiv) led to a mixture of **19**, **21**, and **23** which was separated by chromatography (3:1 hexane-EtOAc) to give **23** as an orange solid (usual yields from crude **13**: 0-10%): mp 234-235 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (dd, J = 7.6, 1.1 Hz, 1H), 7.56 (dd, J = 8.4, 7.6 Hz, 1H), 7.28 (dd, J = 6.3, 0.8 Hz, 1H), 7.27-7.22 (m, 3H), 7.12 (dd, J = 8.2 ,1.8 Hz, 2H), 6.78 (s, 1H), 6.54 (s, 1H), 5.94 (s, 2H), 4.05 (s, 3H), 4.02 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$)[26] δ 180.0, 178.4, 159.9, 155. 9, 142.4, 139.7, 136.8, 135.5, 133.1, 128.7, 127.4, 126.3, 122.3, 118.7, 118.5, 112.9, 105.9, 103.2, 56.6, 56.0, 48.2, 22.5 (the signals of two quaternary carbons were not observed).

6,11-Dihydroxy-1,7-dimethoxy-3-methyl-5-phenylmethyl-5*H*-benzo[*b*]carbazole (24). A mixture of **19** (10 mg, 0.024 mmol) and Zn (100 mg, 1.5 mmol) in HOAc (1.5 mL) was stirred at 23 °C for 15 min. The resulting mixture was partitioned between CH_2Cl_2 and a saturated $NaHCO_3$ aqueous solution. The organic extract was dried ($MgSO_4$) and evaporated at 0 °C under an Ar stream to give **24** (10 mg, quantitative) as a yellow compound that was oxidized immediately in the presence of oxygen to give the parent quinone: ^{1}H NMR (300 MHz, $CDCl_3$)[27] δ 9.68 (s, 1H), 9.23 (s, 1H), 8.01 (dd, J = 8.7, 1.0 Hz, 1H); 7.25-7.14 (m, 6H), 6.76 (s, 1H), 6.74 (br d, J = 7.6 Hz, 1H), 6.54 (s, 1H), 5.94 (s, 2H), 4.17 (s, 3H), 4.04 (s, 3H), 2.47 (s, 3H).

1,7-Dihydroxy-3-methyl-5-phenylmethyl-5*H*-benzo[*b*]carbazole-6,11-dione (25). A solution of **19** (5 mg, 0.013 mmol) at -78 °C was treated with BBr_3 (1 M solution in CH_2Cl_2, 0.25 mL, 0.25 mmol). The mixture was warmed up to 23 °C and stirred at this temperature for 18 h. After the usual workup (CH_2Cl_2, water) and chromatography (1:1 hexane-EtOAc), **25** was obtained as a dark red solid (3 mg, 60%) which was identical with a sample provided by Prof. Murphy: ^{1}H NMR (200 MHz, $CDCl_3$) δ 12.29 (s, 1H), 10.78 (s, 1H), 7.77 (br d, J = 7.8 Hz, 1H), 7.57 (t, J = 8.1 Hz, 1H), 7.22-7.17 (m, 6H), 6.70 (s, 1H), 6.63 (s, 1H), 5.88 (s, 2H), 2.41 (s, 3H).

2-[2-[(*tert*-Butoxycarbonyl)aminophenyl]-5-methoxy-1,4-naphthoquinone (27). A mixture of **6** (464 mg, 1.74 mmol), stannane **26** (743 mg, 2.09 mmol), $Pd(PPh_3)_4$ (179 mg, 0.15 mmol), and CuBr (83 mg, 0.58 mmol) in 1,4-dioxane (62 mL) was heated at 100 °C for 6 h. After being cooled to room temperature, the solvent was evaporated and the residue was chromatographed (2:1 hexane-EtOAc) to give **27** as a dark orange solid (640 mg, 77%): mp 178-179 °C; IR (KBr) 3340, 2990, 1710, 1660, 1575, 1525, 1490, 1260, 1160 cm^{-1} ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (dd, J = 7.5, 1.1 Hz, 1 H), 7.73 (t, J = 7.9 Hz, 1 H), 7.47-7.40 (m, 1 H), 7.36 (dd, J = 8.7, 1.2 Hz, 1 H), 7.21-7.17 (m, 3 H), 6.90 (s, 1 H), 6.56 (br s, 1 H), 4.04 (s, 3 H), 1.41 (s, 9 H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ 184.73, 184.06, 171.20, 159.42, 153.23, 145.87, 139.85, 135.76, 134.99, 134.35, 130.29, 130.18, 124.46, 123.93, 119.56, 117.97, 80.53, 56.55, 28.14 (3 C); MS *m/z* 379 (M^+, 4), 305 (29), 279 (55), 277 (51), 264 (36), 261 (100); HRMS calcd for $C_{22}H_{21}NO_5$ *m/z* 379.1420, found *m/z* 379.1419.

7-Methoxy-5*H*-benzo[*b*]carbazole-6,11-dione (29), 4-Methoxy-11*H*-benzo[*a*]carbazole-5,6-dione (30), and 10-Methoxy-5*H*-benzo[*b*]carbazole-6,11-dione (31), i. To a solution of **27** (110 mg, 0.29 mmol) in THF (10 mL) was added Triton B (0.38 mL of a 40% aqueous solution, 0.87 mmol) and *tert*-butyl hydroperoxide (0.35 mL of a 80% solution in di-*tert*-butyl peroxide, 3.48 mmol) at 23 °C. After being stirred at this temperature for 2 h, the mixture was partitioned between EtOAc and a saturated aqueous tartaric acid solution, dried (Na_2SO_4), and evaporated. The residue was chromatographed (1:1 hexane-EtOAc) to give the 3-hydroxy derivative **28** as an orange solid contaminated with a small amount of intermediate epoxide (68 mg, 60%, crude yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (br d, J = 7.5 Hz, 1 H), 7.68 (d, J = 7.4 Hz, 1 H), 7.56 (t, J = 8.0 Hz, 1 H), 7.29 (br t, J = 6.7 Hz, 1 H), 7.18-7.01 (m, 3 H), 6.72 (br s, 1 H), 3.82 (s, 3 H), 1.36 (s, 9 H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ 183.24, 179.17, 160.00, 157.70, 153.46, 136.63, 136.44, 134.83, 131.16, 129.17, 123.26, 122.60, 121.68, 119.69, 117.71, 116.71, 116.48, 80.49, 56.27, 28.14 (3 C). **ii.** A solution of crude 3-hydroxyderivative (100 mg, 0.25 mmol) in 1,4-dioxane (6 mL) and 35% aqueous HCl (0.15 mL) was heated under reflux conditions for 5 h. After being cooled to room temperature, the mixture was diluted with water and the solid was filtered to give a

1:1.2:2.1 mixture of **29**, **30**, and **31** as a brown solid (17 mg, 26%). A 1:3.7:1.2 ratio of the same quinones was obtained by heating crude **28** in a 5:1 mixture of 1,4-dioxane-35% aqueous HCl (29%). The most soluble isomer, presumably **29**, showed: mp 280-282 °C; IR (KBr) 3240, 1650, 1590 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 50 °C) δ 12.32 (br s, 1 H), 8.10 (d, J = 7.8 Hz, 1 H), 7.74-7.71 (m, 2 H), 7.55 (d, J = 8.1 Hz, 1 H), 7.50-7.24 (m, 3 H), 3.92 (s, 3 H); $^{13}C\{^1H\}$ NMR (50 MHz, DMSO-d_6) δ 179.97, 176.78, 160.10, 138.66, 137.83, 136.47, 135.42, 126.39. 125.60, 123.66, 122.19, 119.46, 118.74, 118.30, 115.47, 113.74, 56.34; HRMS calcd for $C_{24}H_{25}NO_6$ *m/z* 423.1682, found *m/z* 423.1681. The less soluble *p*-quinone **31** showed: ^1H NMR (300 MHz, DMSO-d_6) δ 12.79 (br s, 1 H), 7.91 (d, J = 7.3 Hz, 1 H), 7.73 (d, J = 7.9 Hz, 1 H), 7.67 (t, J = 6.7 Hz, 1 H), 7.56 (d, J = 7.9 Hz, 1 H), 7.50 (d, J = 7.6 Hz, 1 H), 7.22 (t, J = 9 Hz, 2 H), 3.90 (s, 3 H). The *o*-quinone **30** showed:[28] ^1H NMR (300 MHz, DMSO-d_6) δ 10.84 (br s, 1 H), 9.03 (d, J = 7.8 Hz, 1 H), 7.94 (t, J = 8.1 Hz, 1 H), 7.87 (d, J = 7.6 Hz, 1 H), 7.45 (d, J = 8.4 Hz, 1 H), 7.27 (td, J = 7.6, 0.9 Hz, 1 H), 7.05 (t, J = 7.6 Hz, 1 H), 6.88 (d, J = 7.7 Hz, 1 H), 3.99 (s, 3 H).

5-Carbonitrile-1,7-dimethoxy-3-methyl-5*H*-benzo[*b*]carbazole-6,11-dione (32). To a suspension of **15** (20 mg, 0.06 mmol) in CH_2Cl_2 (5 mL) at 23 °C was added 4-*N*,*N*-dimethylaminopyridine (DMAP) (2 mg, 0.02 mmol), Et_3N (0.017 mL, 0.12 mmol) and cyanogen bromide (32 mg, 0.30 mmol). The mixture was stirred at this temperature for 3 h. After the usual workup (CH_2Cl_2,water) and chromatography (1:1 hexane-EtOAc) **32** was obtained as a yellow solid (21 mg, quantitative): mp 191-192 °C; IR (KBr) 2250, 1680, 1650, 1590 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.92 (dd, J = 7.7, 1.1 Hz, 1H), 7.72 (dd, J = 8.5, 7.7 Hz, 1H), 7.32 (dd, J = 8.5, 1.1 Hz, 1H), 7.13 (br s, 1H), 6.73 (br s, 1H), 4.06 (s, 6H), 2.54 (s, 3H); ^1H NOEDIFF (300 MHz, $CDCl_3$): irradiation at δ 4.06 (MeO-1 and MeO-7) gives rise to enhancements of the signals at 7.32 (H-7, 1.5%) and 7.13 (H-2); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$, 48 °C)[26] δ 177.9, 175.0, 160.6, 156.1, 142.6, 141.1, 136.5, 135.6, 122.3, 120.5, 119.2, 117.9, 111.8, 109.1, 104.8, 104.3, 56.6, 56.2, 22.4; EI-MS *m/z* 347 (M^++1, 29), 346 (M^+, 100), 319 (25), 290 (28), 262 (47); HR-EI-MS calcd for $C_{20}H_{14}N_2O_4$ *m/z* 346.0954, found *m/z* 346.0954.

5-Carbonitrile-1,7-dihydroxy-3-methyl-5*H*-benzo[*b*]carbazole-6,11-dione (1). To a solution of **32** (32 mg, 0.09 mmol) in CH_2Cl_2 (2 mL) at -78 °C was added BBr_3 (0.40 mL, 1 M in CH_2Cl_2, 0.40 mmol). After being stirred at this temperature for 5 min, the mixture was warmed up to 23 °C and stirred for 1 h. After the usual workup (CH_2Cl_2 , water) **1** was obtained as a purple solid (26 mg, 90%): mp 241 °C; ^1H NMR (300 MHz, CD_2Cl_2) δ 11.78 (s, 1H), 10.14 (s, 1H), 7.81 (dd, J = 7.5, 1.2 Hz, 1H), 7.69 (t, J = 7.9 Hz, 1H), 7.35 (dd, J = 8.5, 1.2 Hz, 1H), 7.01 (br s; after irradiation at δ 2.49: d, J = 1.1 Hz, 1H), 6.78 (br s; after irradiation at δ 2.49: d, J = 1.1 Hz, 1H), 2.49 (s, 3H); EI-MS *m/z* 319 (M^++1, 9), 318 (M^+, 35), 293 (45), 292 (11). Acetylation in Ac_2O with conc. H_2SO_4 as the catalyst gives **1,7-diacetyloxy-5-carbonitrile-3-methyl-5*H*-benzo[*b*]carbazole-6,11-dione** in quantitative yield as an orange solid: IR (KBr) 2250, 1770, 1670 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.19 (dd, J = 7.8, 1.2 Hz, 1H), 7.80 (t, J = 8.0 Hz, 1H), 7.46 (br s, 1H), 7.41 (dd, J = 8.2, 1.3 Hz, 1H), 7.06 (br s, 1H), 2.59 (s, 3H), 2.57 (s, 3H), 2.50 (s, 3H); EI-MS *m/z* 360 (M^+-42, 32), 318 (100).

11-Carbonitrile-4,7-dimethoxy-9-methyl-11*H*-benzo[*a*]carbazole-5,6-dione (33).

To a suspension of **16** (15 mg, 0.05 mmol) in DMSO (5 mL) at 23 °C was added DMAP (2 mg, 0.02 mmol), Et_3N (0.011 mL, 0.08 mmol) and cyanogen bromide (21 mg, 0.20 mmol). After being stirred at this temperature for 2 h, the mixture was diluted with water. The solid was filtered and washed with Et_2O and water to give **33** as an orange solid (13 mg, 81%): mp 253 °C; IR (KBr) 2240, 1670, 1660, 1540 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.11 (dd, J = 8.7, 7.8 Hz, 1H), 7.65 (dd, J = 8.7, 7.8 Hz, 1H), 7.14 (dd, J = 8.8, 0.8 Hz, 1H), 7.06 (br s, 1H), 6.70 (br s, 1H), 4.01 (s, 3H), 3.99 (s, 3H), 2.51 (s, 3H)[26] EI-MS *m/z* 348 (M^++2, 37), 347 (M^++1, 24), 346 (M^+, 100), 333 (24), 331 (28), 318 (32); UV-vis ($CHCl_3$) λ_{max} (ε) 268 (17 000), 280 (18 500), 301 (20 000), 444 (4500), 457 (3000); HR-EI-MS Calcd. for $C_{20}H_{14}N_2O_4$ *m/z* 346.0954, found *m/z* 346.0951.

5-Carbonitrile-1,10-dimethoxy-3-methyl-5*H*-benzo[*b*]carbazole-6,11-dione (34). Cyanation of a crude cyclization mixture derived from **13** with DMAP, Et_3N, and cyanogen bromide at 23 °C in an ultrasound bath (*ca.* 30 °C, 4 h) followed by chromatography (4:3 hexane-EtOAc) gave **34** as a yellow solid: mp > 250 °C; IR (KBr) 2240, 1660, 1580 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 40 °C) δ 7.88 (dd, J = 7.6, 1.2 Hz, 1H), 7.66 (dd, J = 8.4, 7.6 Hz, 1H), 7.36 (dd, J = 8.5, 1.2 Hz, 1H), 7.12 (t, J = 0.9 Hz, 1H), 6.72 (br s, 1H), 4.06 (s, 3H), 4.03 (s, 3H), 2.54 (s, 3H); EI-MS *m/z* 348 (M^++2, 6), 346 (M^+, 100), 331 (45); HR-EI-MS calcd for $C_{20}H_{14}N_2O_4$ *m/z* 346.0954, found *m/z* 346.0960.

***N*-Carbonitrileindole-3-carbaldehyde (35).** To a suspension of indole-3-carbaldehyde (55 mg, 0.38 mmol) in CH_2Cl_2 (5 mL) at 23 °C was added DMAP (10 mg, 0.08 mmol), Et_3N (0.064 mL, 0.46 mmol) and cyanogen bromide (52 mg, 0.49 mmol). After being stirred for 2 h, the mixture was partitioned between CH_2Cl_2 and 10% aqueous HCl. After the usual work up and chromatography (5:1 hexane-EtOAc) **35** was obtained as a white solid (49 mg, 75%): mp 132 °C; IR (KBr) 2250, 1670, 1550, 1480, 1450, 1190 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 10.10 (s, 1 H), 8.29 (dd, J = 6.9, 2.3 Hz, 1 H), 7.92 (s, 1 H), 7.67-7.63 (m, 1 H), 7.58-7.53 (m, 1 H), 7.52-7.47 (m, 1 H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$)[26] δ 184.41, 137.34, 135.55, 127.24, 126.07, 123.81, 123.62, 123.18, 111.37, 105.90.Anal. Calcd for $C_{10}H_6N_2O$: C, 70.58; H, 3.56; N, 16.47. Found: C, 70.38; H, 3.83; N, 16.43.

***N*-Carbonitrileindole-3-carboxylic acid ethyl ester (36).** To a suspension of ethyl indole-3-carboxylate (88 mg, 0.46 mmol) in CH_2Cl_2 (5 mL) at 23 °C was added DMAP (11 mg, 0.09 mmol), Et_3N (0.077 mL, 0.55 mmol) and cyanogen bromide (64 mg, 0.60 mmol). After being stirred for 2 h, the mixture was partitioned between CH_2Cl_2 and 10% aqueous HCl. After the usual work up and chromatography (5:1 hexane-EtOAc) **36** was obtained as a white solid (69 mg, 70%): mp 95-96 °C; IR (KBr) 2250, 1750, 1610, 1450, 1270, 1200 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.20 (dd, J = 6.7, 3.6 Hz, 1 H), 7.90 (s, 1 H), 7.65-7.60 (m, 1 H), 7.53-7.50 (m, 1 H), 7.50-7.43 (m, 1 H), 4.42 (q, J = 7.1 Hz, 2 H), 1.43 (t, J = 7.1 Hz, 3 H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$)[26] δ 162.69, 138.97, 136.98, 126.21, 125.30 (2 C), 122.77, 115.37, 111.37, 106.19, 60.88, 14.30; Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.70; N, 13.08. Found: C, 67. 39; H, 4.82; N, 13.15.

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27. The assignment was further supported by a NOESY experiment.

28. The structure of **32** was confirmed by a NOESY experiment of its N-methyl derivative prepared by N-methylation with methyl *p*-toluenesulfonate and K_2CO_3 in DMF (100 °C).

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