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Organometallic Routes to 2,5-Dihydroxy-3-(indol-3-yl)benzoquinones. Synthesis of Demethylasterriquinone B4

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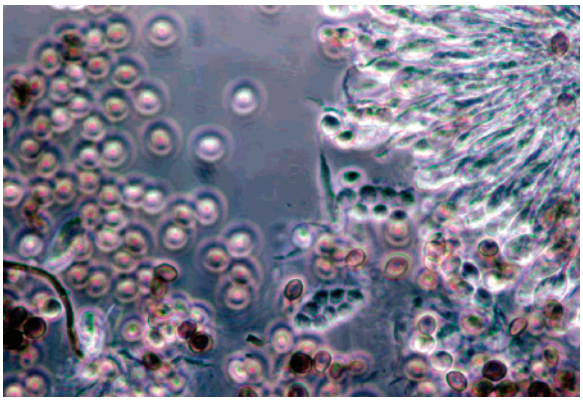

A method has been developed to sequentially add indole-3-mercurials to dichlorinated quinones using palladium catalysis. These reactions can be used in the modular assembly of bis(indol-3-yl)-benzoquinones, a significant natural product family.

Introduction

A large class of fungal natural products derived from *Aspergillus, Chaetomium,* and *Pseudomassaria* species contains the bis-indolylquinone core structure. They are believed to arise biosynthetically by dimerization of indolepyruvic acid, with the resulting dihydroxy-bis-indolylquinone being variously prenylated and sometimes methylated. Most often they are called asterriquinones, after *Aspergillus terreus*, and they have been extensively studied, primarily by the groups of Yamamoto[1] and Kaji.[2] Their extended conjugated systems and indole donor-quinone acceptor structures give the asterriquinones strong visible absorption and deep blue, purple, or red coloring.

The bis-indolylquinones exhibit a range of biological activities against cancer and diabetes.[3] Asterriquinones inhibit the interaction between the SH2 domains of receptor tyrosine kinases, such as the epidermal growth factor receptor, and their adapter proteins, such as Grb2, and thereby inhibit trans-membrane signaling by this oncogene.[4] The bis-indolylquinone family has been the subject of previous synthetic study. The first total synthesis, of cochliodinol, used as a key step the alumina/potassium carbonate-promoted condensation of bromanil

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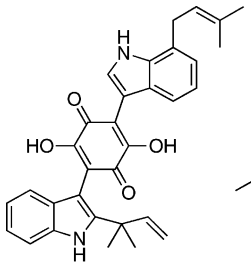
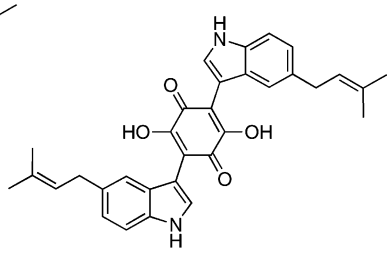
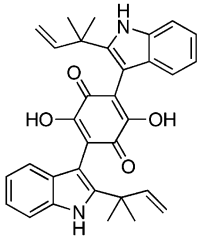
with 2 equiv of 5-bromoindole.[5] A later study used cesium carbonate in acetonitrile in a two-step, one-pot synthesis of demethyltetrahydroasterriquinone E, a non-natural product.[6] Neither of these syntheses controls the rate of the addition of the first indole versus the second indole, making it difficult to use them to prepare unsymmetrical derivatives, nor do they control the position of attachment of the second indole. A late-stage convergent route leading to the directed total synthesis of the insulin mimetic compound demethylasterriquinone B1 has been reported,[7] as have two fully regiocontrolled modular syntheses.[8]



demethylasterriquinone B1



cochliodinol

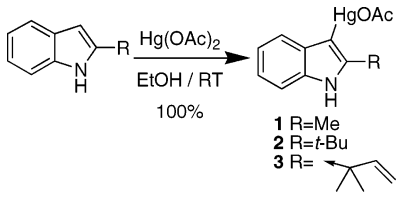


demethylasterriquinone B4

We have investigated approaches to the synthesis of the bis-indolylquinones[9] focused on the controlled, sequential coupling of two indoles to a quinone core using organometallic methods. This paper reports a synthesis of a simple, symmetrical member of the class, demethylasterriquinone B4.

Results

An adaptation of a method reported by Hegedus for Heck reactions on indole-3-mercurials was investigated.[10] Such reagents are readily generated in quantitative yield by treatment of indoles with mercuric acetate (ethanol, 12 h) followed by concentration in vacuo. The known mercurial **1**[11] was generated from 2-methylindole. 2-*tert*-Butylindole and 2-isoprenylindole (prepared by Williams' method[12]) were converted to reagents **2** and **3**. The mercuration of 2-isoprenylindole is notably selective for the more electron-rich indole and is without interference from the adjacent monosubstituted alkene. However, with another indole building block that would be useful for asterriquinone synthesis, 7-prenylindole, the trisubstituted alkene is mercurated competitively with the indole 3-position.



Reactions of these mercurials with 2,5-dichlorobenzoquinone in the presence of catalytic palladium acetate have been conducted in two ways. Acetonitrile was used as solvent with copper chloride as the reoxidant (vide infra), or acetic acid was used as solvent with copper acetate as the reoxidant. The latter process was based on Knolker's report of carbazolquinone synthesis via intramolecular Heck reaction.[13] He proposed for his reaction that acetic acid promotes electrophilic palladation of an aromatic ring by protonating acetate ligands on Pd. Using our first procedure, compound **4** (which we had earlier produced by another route[14]) was obtained in 99% yield. Using the second procedure, compound **5** (also made earlier) was obtained in 96% yield. Treatment of 2,5-dichlorobenzoquinone with 2 equiv of **3** in the presence of catalytic $Pd(OAc)_2$ at room temperature in acetonitrile gave indolylquinone **6**, a valuable intermediate for asterriquinone synthesis, in excellent yield (82%). In these reactions, little variation in efficiency was noted regardless of the bulk of the indole 2-substituent, which is a virtue of this methodology compared to our acid-promoted technology for the addition of indoles to dichlorobenzoquinone.[15]

As a general approach to the asterriquinones, the addition of a second indole mercurial to the mono-indolylquinones **4**−**6** was examined under similar conditions, and a surprising observation was made. We expected compounds **4**−**6** to exhibit reactivity similar to dichlorobenzoquinone despite the presence of the indole. This is because the biaryl bond, with four flanking substituents, should strongly prefer a nonplanar conformation, as suggested by molecular mechanics calculations in our earlier work.[14] With a nonplanar biaryl, the electronic effect of the indole on the quinone is expected to be small, which *should* translate into reactivity similar to dichlorobenzoquinone, but does not. That is, while the addition of the 2-methylindole mercurial to mono-indolylquinone **4** gives **7** in excellent yield, poorer results are

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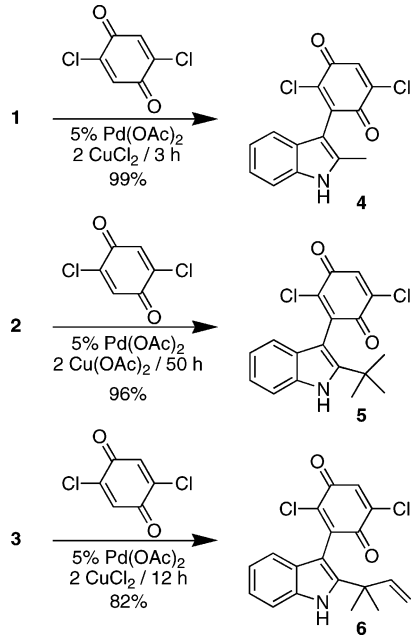
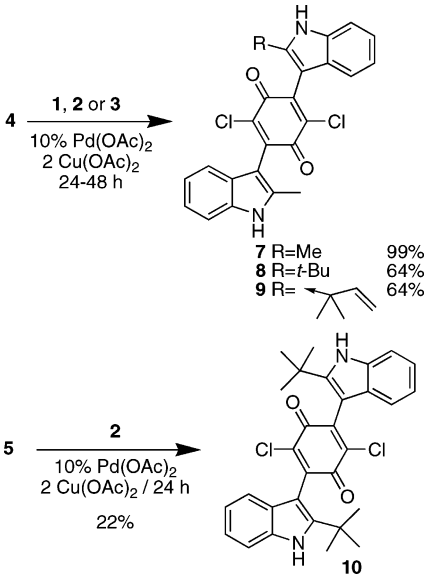


seen using the more hindered mercurials **2** and **3**. When mercurial **2** is used with mono-indolylquinone **5**, compound **10** is obtained in only modest yield. These observations are against intuition.



Compounds **8**−**10** exhibit doubling of NMR signals due to atropisomers. That is, the nonplanar biaryl bond with four different flanking substituents exhibits restricted rotation (Scheme 1), so the two conformational diastereomers are interconverted slowly on the NMR time scale. This situation is contrasted with compound **11**, prepared by hydrolysis of **7** in refluxing 4 N KOH followed by column chromatography on oxalic acid precoated silica gel.[16] This bis-indolyldihydroxybenzoquinone does not exhibit NMR signal doubling. The 2,6-dihydroxybenzoquinone substructure undergoes rapid tautomerism that effectively makes the two different flanking substituents

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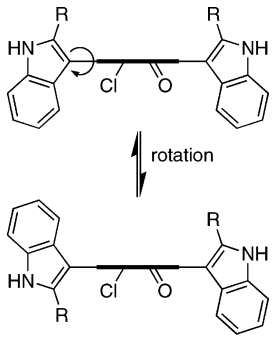
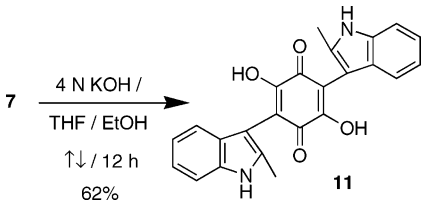
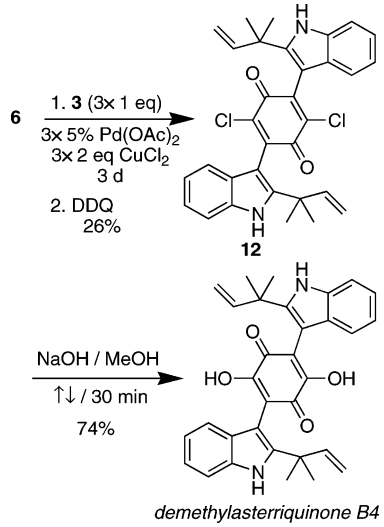
SCHEME 1



identical and creates a higher symmetry compound (on the NMR time scale). It also presumably lowers the barrier to rotation.

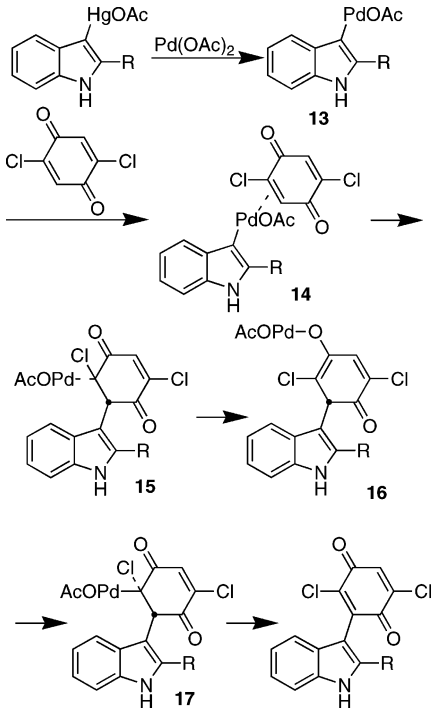


The addition of **3** to indolylquinones is useful for the synthesis of natural asterriquinones. Application of this chemistry to demethylasterriquinone B4 required the preparation of **12** from indolylquinone **6**. This reaction required stringent conditions (3 × 1 equiv of **3**, 3 × 5 mol % $Pd(OAc)_2$, 3 × 2 equiv $CuCl_2$, 3 d, reflux) and gives a mixture of reduced product and starting material. It is unclear how the reduced materials are produced or what is the reducing agent, but we commonly observe these types of products in palladium-based reactions on these quinone substrates. These reduced compounds are easily oxidized by DDQ. Compound **12** is isolated by chromatography (in meager yield). The synthesis of demethylasterriquinone B4 was achieved by the alkaline hydrolysis of **12**. The resulting material, obtained in 20% overall yield from the indole, exhibited NMR, IR, and UV spectra identical to the natural product.



A putative mechanism is given in Scheme 2 for coupling of a mercurated indole to give the indolylquinone

SCHEME 2

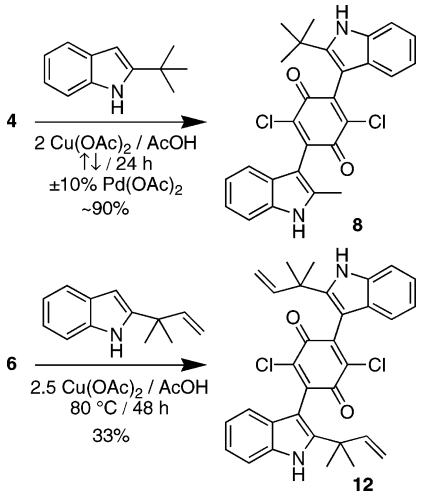


involving simple modification of the conventional Heck mechanism. Transmetalation from mercury to palladium gives **13**. Coordination to the quinone gives π-complex **14**, from which syn oxidative addition gives **15**. Because this intermediate has the incorrect stereochemistry for a syn β-hydrogen elimination, an isomerization via an $\eta1 \rightarrow \eta3 \rightarrow \eta1$ equilibration that produces **16** is proposed. A reversal of this process can occur on the other face of the cyclohexadiene ring, giving **17** that can undergo β-hydrogen elimination. The copper salt presumably serves to oxidize the resulting Pd^0 species to make the reaction catalytic in noble metal.

Further experiments were aimed at increasing the environmental friendliness of this reaction sequence by omitting the mercuration step. The addition of 2-methylindole to **4** using catalytic palladium acetate and copper chloride in acetonitrile gives **7**, though in lower yield (50%) than from the mercurial. The direct palladation of the indole is one mechanism that can be used to explain this observation, which is precedented in Hegedus' work.[10] In acetic acid, the addition of 2-*tert*-butylindole to **4** in excellent yield does not require palladium, but does require copper acetate. In its absence, a large fraction of the product mixture is 2,5-dichlorohydroquinone. We suggest the copper acetate plays a dual role in promoting the conjugate addition by Lewis acidity and oxidizing the hydroquinone to the quinone. In some instances, this may prove to be a convenient procedure, as it could be used in the generation of compound **12**, an intermediate in the foregoing natural product synthesis, more efficiently than via the mercurial.

Experimental Section

Caution! Organomercury compounds are often highly toxic. Compounds **1**−**3** have not been evaluated for toxicity and therefore should be treated as if they have been shown to be highly toxic. They should be prepared and handled in a



properly operating fume hood and only while wearing appropriate personal protective equipment. Residues from reactions involving the generation or use of compounds **1**−**3** should be disposed of in accordance with current statutes and prudent chemical hygiene practices.

2-*tert*-Butyl-1*H*-indol-3-ylmercuric acetate (2). 2-*tert*-Butylindole (1.61 g, 9.29 mmol) and $Hg(OAc)_2$ (3.26 g, 10.2 mmol, 1.1 equiv) were dissolved in ethanol (100 mL) under argon and stirred at room temperature for 25 h. The ethanol was evaporated under reduced pressure, giving the product as a gray solid (4.01 g, 100%). ^{1}H NMR (DMSO-d_6): δ 1.43 (s, 9H), 1.93 (s, 3H), 6.89 (td, J = 0, 0 Hz, 1 H), 6.97 (dt, J = 0, 0 Hz, 1H), 7.28 (d, J = 0 Hz, 1H), 7.60 (s, 1H), 7.78 (br s, 1H). Compound **2** was not further characterized because of toxicity concerns.

2-(1,1-Dimethyl-allyl)-1*H*-indol-3-ylmercuric Acetate (3). To a solution of 2-(1,1-dimethylallyl)-1*H*-indole (1.25 g, 6.76 mmol) in ethanol (100 mL) was added $Hg(OAc)_2$ (2.17 g, 6.82 mmol) at room temperature, and the mixture was stirred for 2 d. The solvent was evaporated to give **3** (3.00 g, 100%) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 9.18 (bs, 1H), 7.41 (d, J = 7.9 Hz, 1H), 7.27 (d, J = 7.9 Hz, 1H), 7.03 (m, 2H), 6.05 (dd, J = 17.4, 10.5 Hz, 1H), 5.24 (d, J = 10.5 Hz, 1H), 5.19 (d, J = 17.4 Hz, 1H), 2.06 (s, 3H), 1.42 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 176.7, 147.1, 135.3, 132.3, 128.2, 121.6, 121.2, 119.8, 114.2, 110.8, 38.4, 27.9, 22.9. Compound **3** was not further characterized because of toxicity concerns.

2,5-Dichloro-3-(2-methyl-1*H*-indol-3-yl)[1,4]-benzoquinone (4). A mixture of 2,5-dichlorobenzoquinone (18 mg, 0.102 mmol), 2-methyl-3-indolylmercuric acetate (84 mg, 0.216 mmol), $Pd(OAc)_2$ (1.2 mg, 0.0054 mmol), and $CuCl_2$ (27 mg, 0.201 mmol) in CH_3CN (2 mL) was stirred at room temperature for 3 h. The reaction mixture was filtered through Celite, washed with CH_3CN, and the combined filtrates were evaporated. The residue was purified by silica gel column chromatography using hexanes−ethyl acetate (5:1) as eluent to give **4** (36 mg, 100%) as a blue solid. ^{1}H NMR ($CDCl_3$): δ 8.34 (bs, 1H), 7.35−7.10 (m, 5H), 2.32 (s, 3H). FAB-MS: *m/z* 305 (M^+). This is a known compound prepared earlier in our laboratory.[14]

2,5-Dichloro-3-(2-*tert*-butyl-1*H*-indol-3-yl)[1,4]-benzoquinone (5). A mixture of 2,5-dichlorobenzoquinone (20 mg, 0.112 mmol), 2-*tert*-butyl-3-indolylmercuric acetate (100 mg, 0.232 mmol), $Pd(OAc)_2$ (2.6 mg, 0.012 mmol), $Cu(OAc)_2$ (42 mg, 0.230 mmol) in AcOH (2 mL) was stirred at room temperature for 50 h. The reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography using hexanes−ethyl acetate (10:1) as eluent to give **5** (38 mg, 96%) as a blue solid. ^{1}H NMR ($CDCl_3$): δ 8.30 (bs, 1H), 7.34 (dt, J = 8.1, 0.9 Hz, 1H), 7.24 (s, 1H), 7.18−7.12 (m, 1H), 7.08−7.02 (m, 2H), 1.33 (s, 9H). ESI-MS: *m/z* 348 $(M + H)^+$. This is a known compound prepared earlier in our laboratory.[14]

2,5-Dichloro-3-[2-(1,1-dimethylallyl)-1*H*-indol-3-yl][1,4]-benzoquinone (6). To a solution of 2-(1,1-dimethylallyl)-3-indolylmercuric acetate **3** (100 mg, 0.225 mmol) in CH_3CN (5 mL) were added 2,5-dichloro-1,4-benzoquinone (16 mg, 0.090 mmol), $CuCl_2$ (61 mg, 1.3 mmol), and $Pd(OAc)_2$ (2.0 mg, 9.0 μmol) at room temperature. After stirring for 48 h at room temperature, the reaction mixture was filtered through Celite. The filtrate was concentrated and the residue was purified by flash column chromatography using 15% EtOAc in hexane as eluent to afford pure **6** (26 mg, 82%) as a blue solid. $R_f = 0.33$ (1:4, EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 8.28 (bs, NH), 7.34 (dt, $J = 8.1$, 0.9 Hz, 1H), 7.21 (s, 1H), 7.20−7.07 (m, 3H), 5.98 (dd, $J = 17.4$, 10.5 Hz, 1H), 5.11 (dd, $J = 17.4$, 0.9 Hz, 1H), 5.07 (dd, $J = 10.5$, 0.9 Hz, 1H), 1.43 (s, 3H), 1.42 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 177.6, 177.3, 144.9, 144.8, 142.6, 142.0, 141.8, 134.7, 132.8, 126.5, 122.3, 120.3, 118.4, 113.1, 110.9, 102.8, 39.3, 27.9, 26.7. This is a known compound prepared earlier in our laboratory.[14]

2,5-Dichloro-3,6-bis-(2-methyl-1*H*-indol-3-yl)[1,4]-benzoquinone (7). A mixture of **4** (20 mg, 0.066 mmol), 2-methyl-3-indolylmercuric acetate (80 mg, 0.205 mmol), $Pd(OAc)_2$ (2.0 mg, 0.009 mmol), and $Cu(OAc)_2$ (36 mg, 0.198 mmol) in AcOH (2 mL) was stirred at room temperature for 28 h. The reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography using hexanes−ethyl acetate (5:1) as eluent to give **7** (28 mg, 99%) as a blue solid. ^{1}H NMR (acetone-d_6): δ 10.58 (bs, 2H), 7.40−7.27 (m, 4H), 7.13−6.99 (m, 4H), 2.41 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (acetone-d_6): δ 178.2, 140.9, 140.4, 138.0, 136.8, 128.4, 122.0, 120.7, 120.4, 111.7, 106.0, 13.6. ESI-MS: *m/z* 435 $[M + H]^+$. HRMS (FAB): calcd for $C_{24}H_{18}Cl_2N_2O_2$ - $[M + 2H]^+$ 436.0745, found 436.0760.

2,5-Dichloro-3-(2-methyl-1*H*-indol-3-yl)-6-(2-*tert*-butyl-1*H*-indol-3-yl)[1,4]benzoquinone (8). A mixture of **4** (15 mg, 0.049 mmol), 2-*tert*-butyl-3-indolylmercuric acetate (64 mg, 0.148 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), and $Cu(OAc)_2$ (27 mg, 0.148 mmol) in AcOH (1 mL) was stirred at reflux for 24 h. The reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography using hexanes−ethyl acetate (5:1) as eluent to give **8** (15 mg, 64%) as a blue solid. ^{1}H NMR (acetone-d_6, rotational isomers (∼1:1)): δ 10.62 (bs, 1H), 10.42 (bs, 1H), 7.40−7.25 (m, 4H), 7.15−6.95 (m, 4H), 2.43 (s, 3H), 2.39 (s, 3H), 1.44 (s, 9H), 1.43 (s, 9H). ^{13}C NMR (acetone-d_6, rotational isomers (∼1:1)): δ 179.2, 177.9, 146.0, 143.7, 143.2, 140.9, 140.8, 140.7, 138.3, 138.1, 136.8, 136.7, 136.4, 128.3, 128.2, 122.2, 122.1, 120.9, 120.5, 120.1, 120.0, 111.8, 111.7, 105.8, 105.7, 103.0, 34.2, 30.6, 13.7. ESI-MS: *m/z* 477 $[M + H]^+$. HRMS (FAB): calcd for $C_{27}H_{24}Cl_2N_2O_2$ $[M + 2H]^+$ 478.1215, found 478.1213.

2,5-Dichloro-3-[2-(1,1-dimethylallyl)-1*H*-indol-3-yl]-6-(2-methyl-1*H*-indol-3-yl)[1,4]benzoquinone (9). To a solution of **4** (188 mg, 0.614 mmol) in CH_3CN (5 mL) were added 2-(1,1-dimethylallyl)-3-indolylmercuric acetate **3** (390 mg, 0.614 mmol), $CuCl_2$ (165 mg, 1.23 mmol), and $Pd(OAc)_2$ (7.0 mg, 0.0307 mmol) at room temperature. After the reaction mixture was heated at reflux for 24 h, more reagents, **3** (390 mg, 0.614 mmol), $CuCl_2$ (165 mg, 1.23 mmol), $Pd(OAc)_2$ (7.0 mg, 0.0307 mmol), and CH_3CN (2 mL), were added to the mixture, and then the mixture was refluxed for 24 h again. This step was repeated one more time. The reaction mixture was cooled to room temperature and filtered through Celite. The filtrate was concentrated and the residue was purified by flash column chromatography using 20% EtOAc in hexane as eluent to afford the title compound as a purple solid (152 mg, 64% based on 21% recovered starting material **4**). $R_f = 0.31$ (3:7, EtOAc/hexane). IR (thin film): 3398, 2971, 1670, 1574, 1459, 1259 cm^{-1}. ^{1}H NMR (300 MHz, acetone-d_6, rotational isomers (∼1:1)): δ 10.62 (bs, 2NH), 10.45 (bs, 2NH), 7.41−7.43 (m, 8H), 7.14−6.98 (m, 8H), 6.17 (dd, $J = 17.4$, 10.5 Hz, 1H), 6.15 (dd, $J = 17.4$, 10.5 Hz, 1H), 5.19−5.08 (m, 4H), 1.55 (s, 3H), 1.54 (s, 3H), 1.533 (s, 3H), 1.527 (s, 3H). ^{13}C NMR (75 MHz, acetone-d_6, rotational isomers (∼1:1)): δ 178.9, 178.8, 177.7, 177.6, 146.2 (2C), 143.6, 143.6, 142.8, 142.8, 142.3, 142.3, 140.8, 140.8, 140.3, 140.2, 137.9, 137.5, 136.6, 136.5, 136.4, 136.3, 128.1, 128.0, 127.7, 127.7, 122.2, 122.2, 121.9, 121.8, 120.6, 120.4, 120.3, 120.1, 120.1, 120.0, 119.5, 119.4, 112.8, 112.7, 111.8, 111.7, 111.6, 111.5, 105.7, 105.4, 103.9 (2C), 40.0 (2C), 28.5 (2C), 26.83 (2C), 13.66 (2C). HRMS (FAB): calcd for $C_{28}H_{22}N_2O_2Cl_2$ $[M]^+$ 488.1058, found 488.1063.

2,5-Dichloro-3-[2-(1,1-dimethylallyl)-1*H*-indol-3-yl]-6-(2-methyl-1*H*-indol-3-yl)[1,4]benzoquinone (9). A mixture of **4** (20 mg, 0.066 mmol), **3** (70 mg, 0.158 mmol), $Pd(OAc)_2$ (1.5 mg, 0.007 mmol), and $Cu(OAc)_2$ (24 mg, 0.132 mmol) in AcOH (1 mL) was stirred at 80 °C for 24 h. The reaction mixture was dissolved in ethyl acetate, passed through Celite, washed with ethyl acetate, and the combined filtrates were evaporated. The residue was treated again in the same way. The crude product was purified by silica gel column chromatography using hexanes−ethyl acetate (5:1) as eluent to give **9** (17 mg, 54%) as a blue solid. ^{1}H NMR (acetone-d_6, rotational isomers (∼1:1)): δ 10.62 (bs, 1H), 10.43 (bs, 1H), 7.40−7.22 (m, 4H), 7.23−6.96 (m, 4H), 2.42 (s, 3H), 2.40 (s, 3H), 1.54 (s, 3H), 1.53 (s, 3H), 1.522 (s, 3H), 1.520 (s, 3H). ^{13}C NMR (acetone-d_6, rotational isomers (∼1:1)): δ 179.1, 177.9, 146.5, 143.9, 143.0, 142.6, 141.0, 140.6, 140.5, 138.1, 137.8, 136.8, 136.7, 136.6, 128.4, 128.3, 127.9, 122.4, 122.1, 120.8, 120.6, 120.5, 120.2, 119.7, 119.6, 113.0, 112.9, 111.9, 111.8, 111.7, 105.9, 105.6, 104.1, 40.0, 28.5, 26.8, 13.6. ESI-MS: *m/z* 489 $[M + H]^+$. HRMS (FAB): calcd for $C_{28}H_{24}Cl_2N_2O_2$ $[M + 2H]^+$ 490.1215, found 490.1203.

2,5-Dichloro-3,6-bis-(2-*tert*-butyl-1*H*-indol-3-yl)[1,4]-benzoquinone (10). This compound was synthesized from **5** (22% yield) in the same way as **8**. ^{1}H NMR (acetone-d_6, rotational isomers (∼3:2)): δ 10.45 (bs, 2H), 7.40−7.33 (m, 3H), 7.18−7.06 (m, 3H), 7.02−6.96 (m, 2H), 1.46 (s, 9H), 1.41 (s, 9H). ^{13}C NMR (acetone-d_6, rotational isomers (∼3:2)): δ 179.1, 178.9, 146.3, 145.8, 143.9, 143.7, 143.6, 136.5, 128.2, 128.0, 122.3, 120.3, 120.2, 119.5, 118.8, 111.8, 111.7, 102.9, 102.7, 34.3, 30.6. ESIMS: *m/z* 519 $[M + H]^+$. HRMS (FAB): calcd for $C_{30}H_{30}Cl_2N_2O_2$ $[M + 2H]^+$ 520.1684, found 520.1679.

2,5-Dihydroxy-3,6-bis-(2-methyl-1*H*-indol-3-yl)[1,4]-benzoquinone (11). To a solution of 2,5-dichloro-3,6-bis-(2-methyl-1*H*-indol-3-yl)[1,4]benzoquinone (**7**, 0.50 g, 1.15 mmol) in THF/EtOH (15/30 mL) was added 4 N KOH (15 mL, 60 mmol). The reaction mixture was refluxed for 10 h. The organic solvents were removed in vacuo, and the crude mixture was acidified with 1 N HCl. The resulting solution was extracted with EtOAc (3 × 50 mL). The extracts were washed with brine and dried over Na_2SO_4. The residue was concentrated and purified by flash column chromatography using oxalic acid-precoated silica gel [prepared by the literature procedure:[16] suspension of silica gel in 0.1 N oxalic acid overnight, filtration, washing with H_2O, and drying in an oven at 100 °C overnight] and 30% EtOAc in hexane as eluent to afford pure **11** (282 mg, 62%) as a dark red-purple solid. Mp: 277−278 °C. IR (thin film): 3395, 2926, 1617, 1460 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD): δ 10.40 (bs, 2NH), 7.27 (d, $J = 7.8$ Hz, 4H), 7.06−6.94 (m, 4H), 5.00 (bs, 2OH), 2.32 (s, 6H). ^{13}C NMR (75 MHz, CD_3OD): δ 137.0, 136.5, 129.3, 121.4, 120.3, 119.8, 112.6, 111.3, 102.7, 13.4. HRMS (FAB): calcd for $C_{24}H_{19}N_2O_4$ $[M + H]^+$ 399.1345, found 399.1340.

2,5-Dichloro-3,6-bis-[2-(1,1-dimethylallyl)-1*H*-indol-3-yl][1,4]benzoquinone (12). To a solution of **6** (81 mg, 0.225 mmol) in CH_3CN (5 mL) were added 2-(1,1-dimethylallyl)-3-indolylmercuric acetate **3** (100 mg, 0.225 mmol), $CuCl_2$ (60.5 mg, 0.45 mmol), and $Pd(OAc)_2$ (2.5 mg, 0.0113 mmol) at room temperature. After the reaction mixture was heated at reflux for 24 h, more reagents, **3** (100 mg, 0.225 mmol), $CuCl_2$ (60.5 mg, 0.45 mmol), $Pd(OAc)_2$ (2.5 mg, 0.0113 mmol) and CH_3CN (2 mL), were added to the mixture, and then the mixture was refluxed for 24 h again. This step was repeated one more time. The reaction mixture was cooled to room temperature, and DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone, 102 mg, 0.45 mmol) was added. The mixture was

stirred for 10 h at room temperature and filtered through Celite. The filtrate was concentrated and the residue was purified by flash column chromatography using 20% EtOAc in hexane as eluent to afford the title compound (32 mg, 26%) as a purple solid. $R_f = 0.31$ (3:7, EtOAc/hexane).

A mixture of **6** (60 mg, 0.167 mmol), 2-(1,1-dimethylallyl)-*1H*-indole (70 mg, 0.378 mmol), and $Cu(OAc)_2$ (78 mg, 0.429 mmol) in AcOH (6 mL) was stirred at 80 °C for 48 h. The reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography using hexanes−ethyl acetate (15:1) as eluent to give 26 mg of **12** (as a purple solid), 33% based on 13% recovered starting material **6**. ^{1}H NMR (acetone-d_6, rotational isomers (∼1:1)): δ 10.46 (bs, 1H), 10.42 (bs, 1H), 7.42−7.36 (m, 2H), 7.30 (d, $J = 8.1$ Hz, 1H), 7.20 (d, $J = 8.1$ Hz, 1H), 7.15−6.96 (m, 4H), 6.21−6.09 (m, 2H), 5.19−5.05 (m, 4H), 1.54 (s, 6H), 1.53 (s, 6H). ^{13}C NMR (acetone-d_6, rotational isomers (∼1:1)): δ 179.1, 178.7, 146.5, 146.4, 144.0, 143.0, 142.7, 136.6, 127.8, 122.5, 120.5, 120.3, 119.8, 119.0, 113.1, 113.0, 112.1, 111.9, 103.9, 103.8, 40.1, 40.0, 28.7, 28.5, 26.9. ESI-MS: *m/z* 543 $[M + H]^+$. HR-MS (FAB): calcd for $C_{32}H_{30}Cl_2N_2O_2$ $[M + 2H]^+$ 544.1684, found 544.1688.

Demethylasterriquinone B4. A solution of **12** (34 mg, 0.063 mmol) in methanol (4 mL) was heated at reflux for 10 min, and aq 10% NaOH (2 mL) was added. After an additional 30 min of reflux, methanol was removed under reduced pressure and the residue was acidified with 2M HCl. The solution was extracted with ethyl acetate, washed with brine, dried over Na_2SO_4 and evaporated. The crude material was purified by oxalic acid-coated silica gel column chromatography using hexanes−ethyl acetate (7:1) as eluent to give demethylasterriquinone B4 (23 mg, 74%) as a purple amorphous solid. The NMR, UV, and IR data were consistent with those reported.[17] FT-IR (KBr):3408, 3332, 2969, 1640, 1346 cm^{-1}. ^{1}H NMR (acetone-d_6, rotational isomers (∼1:1)): δ 10.11 (bs, 1H), 10.07 (bs, 1H), 9.37 (bs, 2H), 7.35 (d, $J = 8.1$ Hz, 1H), 7.33 (d, $J = 8.1$ Hz, 2H), 7.20 (d, $J = 8.1$ Hz, 1H), 7.09−7.02 (m, 2H), 6.99−6.92 (m, 2H), 6.20 (dd, $J = 17.4$, 10.5 Hz, 1H), 6.18 (dd, $J = 17.4$, 10.5 Hz, 1H), 5.17−4.97 (m, 4H), 1.54 (s, 6H), 1.53 (s, 6H). ^{13}C NMR (acetone-d_6, rotational isomers (∼1:1)): δ 146.7, 143.4, 143.2, 136.5, 136.5, 129.9, 129.8, 121.9, 119.7, 119.7, 119.2, 113.5, 111.7, 111.6, 111.4, 101.5, 40.0, 27.5. ESI-MS: *m/z* 505 $[M - H]^-$.

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Supporting Information Available: ^{1}H NMR spectra for **7**−**12** and demethylasterriquinone B4. This material is available free of charge via the Internet at http://pubs.acs.org.

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