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Total Syntheses of Demethylasterriquinone B1, an Orally Active Insulin Mimetic, and Demethylasterriquinone A1

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Two total syntheses of the unsymmetrical bis-indolylquinone natural product demethylasterriquinone B1 (also known as L-783,281) have been accomplished. The first exploits a known base-promoted condensation of indoles with bromanil, which stops at monoaddition using the sterically hindered 2-isoprenylindole. This permits addition of the second indole, 7-prenylindole, which gives both meta- and para-substituted bis-indolylquinone products. This regiochemical control problem was solved by extension of a method we recently developed for acid-promoted addition of indoles to 2,5-dichlorobenzoquinone. Under our original mineral acid conditions, reaction of 2-isoprenylindole with dichlorobenzoquinone fails, but it succeeds with 3-bromo-2,5-dichlorobenzoquinone using acetic acid as the promoter. The regiochemistry established in such selectively bromine-substituted quinones can be exploited in Stille couplings. As a model system, the synthesis of demethylasterriquinone A1 was accomplished using as the key step a Stille coupling of a 2,5-dibromobenzoquinone with an (*N*-isoprenylindol-3-yl)tin, producing the para-substituted bis-indolylquinone exclusively. Use of a (7-prenylindole)tin in coupling with a bromo-2,5-dichloro-4-indolylbenzoquinone gives the demethylasterriquinone B1 precursor. The dihaloquinone products of these indole/quinone coupling processes can be hydrolyzed to the dihydroxyquinone natural products. Demethylasterriquinone B1 is of high recent interest as a small molecule insulin mimetic with oral anti-diabetic activity in mice.

Introduction

A large class of fungal natural products derived from *Aspergillus*, *Chaetomium*, and *Pseudomassaria* species is based upon a dihydroxy-bis-indolylquinone unit that is variously prenylated and sometimes O-methylated. Most often, they are called asterriquinones (Figure 1), after *Aspergillus terreus*, and they have been extensively studied, primarily by the groups of Yamamoto[1] and Kaji.[2] The bis-indolylquinones exhibit a range of medicinal activities. They have antitumor activity, with asterriquinone A1 forming DNA interstrand cross-links (IC_{50} 1 μM), causing arrest of the cell cycle at G_1 and apoptotic cell death. Members of the family also inhibit the interaction between phosphorylated receptor tyrosine kinases, such as the epidermal growth factor receptor, and their adapter proteins, such as Grb2, an interaction mediated through the SH2 domains of Grb2. These demethylasterriquinones thereby inhibit trans-membrane signaling by the EGF oncogene product.[3] Demethylasterriquinone B1 (DAQ B1 or L-783,281) was recently isolated from a Congo fungus classified as a

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(2) Kaji, A.; Saito, R.; Hata, Y.; Kiriyama, N. *Chem. Pharm. Bull.* **1999**, *47*, 77−82. Kaji, A.; Saito, R.; Nomura, M.; Miyamoto, K.-i.; Kiriyama, N. *Biol. Pharm. Bull.* **1998**, *21*, 945−949. Kaji, A.; Kimura, K.; Teranishi, M.; Kiriyama, N.; Nomura, M.; Miyamoto, K.-i. *Chem. Pharm. Bull.* **1998**, *46*, 1325−1329. Kaji, A.; Iwata, T.; Kiriyama, N.; Nomura, M.; Miyamoto, K.-i. *J. Antibiot.* **1998**, *51*, 235−238. Kaji, A.; Saito, R.; Nomura, M.; Miyamoto, K.-i.; Kiriyama, N. *Anticancer Res.* **1997**, *17*, 3675−3679. Kaji, A.; Saito, R.; Shinbo, Y.; Kiriyama, N. *Chem. Pharm. Bull.* **1996**, *44*, 2340−2341. Kaji, A.; Kimura, K.; Iwata, T.; Kiriyama, N. *Chem. Pharm. Bull.* **1995**, *43*, 1818−20. Kaji, A.; Iwata, T.; Kiriyama, N.; Wakusawa, S.; Miyamoto, K.-i. *Chem. Pharm. Bull.* **1994**, *42*, 1682−4.

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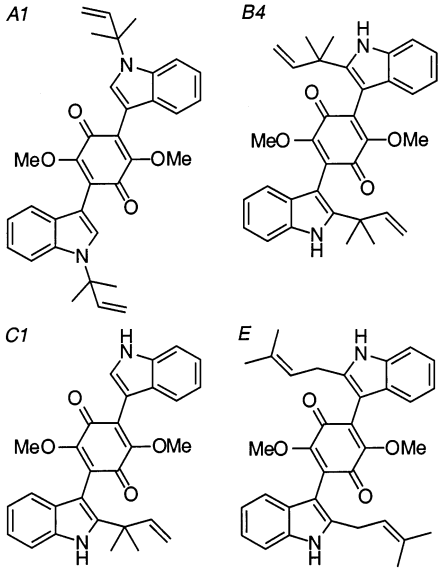
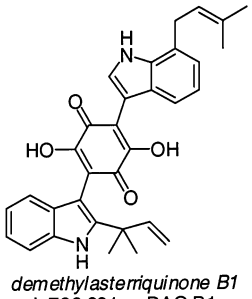


FIGURE 1. Asterriquinones from *Aspergillus terreus*.

Pseudomassaria, but DAQ B1 was already known as a synthetic material from earlier work.[1e] A Merck group



demethylasterriquinone B1
L-783,281 or DAQ B1
1

discovered the compound in nature by screening for insulin receptor tyrosine kinase activators.[4] Small molecule agonists of growth factor receptors are quite rare,[5] with the only other example being a granulocyte-colony-stimulating factor mimic,[6] so its activity as an insulin receptor activator was remarkable. DAQ B1 shows cellular activity in triggering the insulin receptor tyrosine kinase with a 3−6 μM IC_{50}, and its action is specific. It induces phosphorylation of the insulin receptor β (in its tyrosine kinase domain), but not insulin-like growth factor receptor or epidermal growth factor receptor. A related natural product (demethylasterriquinone B4) shows no insulin receptor activation. DAQ B1 stimulates glucose uptake in rat adipocytes and mouse soleus muscle and shows oral anti-diabetic activity in *ob*/*ob* mice (a noninsulin dependent diabetes mellitus (NIDDM) model). DAQ B1 is believed to bind to the intracellular domain of the receptor because it does not compete with insulin and it alters the proteolysis pattern of the insulin receptor near the ATP binding site. Like insulin, activation of insulin receptor in β-cells by DAQ B1 stimulates insulin gene transcription (EC_{50} 50 nM),[7] but unlike insulin, DAQ B1 does not cause undesirable proliferation of vascular smooth muscle cells.[8] Further studies have shown that DAQ B1 alone does not result in hypoglycemia in the streptozotocin-induced diabetic mouse model (similar to type I diabetes) or in lean non-diabetic mice, but causes glucose lowering in diabetic mice in the presence of a sub-effective dose of insulin.[9] The biology of DAQ B1 is thus a bit unclear, as it is a full insulin mimetic in cells expressing insulin receptor but is an insulin receptor activator with utility as an insulin sensitizer in animal models.

Simple structure−activity relationships based on modifications of the natural product have been reported.[10] Reduction or hydroxylation of the prenyl groups or N-methylation are tolerated, but the only change permitted in the quinone is methylation of one hydroxyl. Further medicinal chemistry has led to related active structures.[11]

DAQ B1 is also an agonist of the neurotrophin receptors *Trk*A, B, and C, which like the insulin receptor are tyrosine kinases.[12] DAQ B1 activates *Trk* phosphorylation in neuronal cells and in Chinese hamster ovary (CHO) cells transfected with *Trk*, and it was suggested that DAQ B1 interacts with the intracellular domain of *Trk* and noncovalently triggers receptor dimerization. Key steps in many signal transduction pathways mediated by growth factor receptors (such as those for insulin and neurotrophin) are receptor dimerization followed by autophosphorylation. The ability of DAQ B1 to promote receptor dimerization would therefore be crucial and unique. It is reasonable to suggest that the extended molecular structure of DAQ B1 may accomplish this through the two structural domains of its indole rings, each of which might interact with one chain of a tyrosine kinase receptor. In other words, DAQ B1 might act as a chemical inducer of dimerization.[13] The asterriquinone family of natural products thus seems to be able to affect, either positively or negatively, members of the receptor tyrosine kinase family. Access to diverse structures based on the bis-indolylquinone scaffold could therefore be valuable in discovery of ligands not only for the insulin receptor, but for other growth factor receptors. A total

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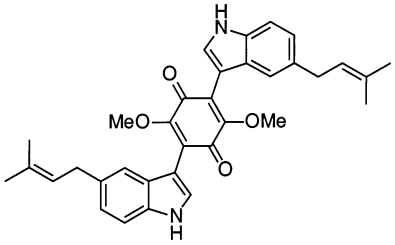
chemical synthesis of the most prominent member of the family, DAQ B1, is a first step toward that goal.

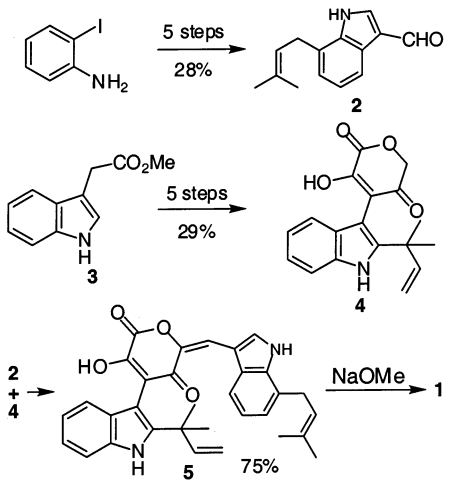


cochliodinol

The bis-indolylquinone family has been the subject of previous synthetic study. The first total synthesis of an asterriquinone was directed toward cochliodinol and used as a key step the alumina/potassium carbonate-promoted condensation of bromanil with 2 equiv of 5-bromoindole.[14] A later study used cesium carbonate in acetonitrile in a two-step, one-pot synthesis of demethyltetrahydroasterriquinone E, a nonnatural product that was obtained in reasonable efficiency after purification by reversed-phase HPLC.[15] Several related symmetric asterriquinones were also obtained from 2-substituted indoles. Neither of these syntheses controls the rate of the addition of the first indole versus the second indole, making it difficult to use either synthesis to prepare unsymmetrical derivatives, nor do they control the position of attachment of the second indole. A recent synthesis of DAQ B1 addressed this issue utilizing a *p*-substituted quinone bearing leaving groups of differential reactivity.[16] The first reported total synthesis of DAQ B1 (Scheme 1) comprised a late-stage convergent route wherein indole carboxaldehyde **2** and pyrandione **4** were united in a Knövenagel condensation to give **5**. A base-catalyzed rearrangement led to the natural product. This synthesis requires about a dozen steps and proceeds in about 20% overall yield.[17]

Convergency,[18] as represented in Scheme 1, has traditionally been accorded high value in natural products synthesis owing to its ability to permit parallel processing in the production of advanced intermediates used in late-stage coupling. While convergency is a virtue in most efficiently providing a *single* target, it impairs efficiency when the goal is gaining a *family* of structurally variant targets. For example, applying the foregoing synthesis toward DAQ B1 derivatives with modified indoles could require a unique synthetic route to be executed from modified starting materials to each target. As has long been appreciated in medicinal chemistry, a more efficient strategy in generating many targets involves synthesis of a common late-stage intermediate and substitution of a readily available set of modules into the synthesis for

SCHEME 1



diversification. With increasing interest in the use of library methods that form carbon−carbon bonds to access natural products and complex natural product-like compounds,[19] this "divergent" or modular approach is likely to become more important in natural products synthesis design. The asterriquinones are inherently modular molecules that should be amenable to a modular synthesis design[20] and, potentially, combinatorial synthetic approaches to molecular libraries. Indeed, two syntheses of the asterriquinones[14,15] are modular. Our modular synthesis design for the asterriquinones focuses on controlled addition of indoles to a central quinone unit, any of which could be varied to create a family of bis-indolylquinone compounds for investigation. One of the modular synthetic approaches to DAQ B1 described in full detail here was communicated earlier.[21]

Results

Initial efforts focused on obtaining the two indoles required for the total synthesis, 2-isoprenylindole (**6**) and 7-prenylindole (**10**), which are known. Williams prepared the former in two steps and 25% overall yield from prenyl bromide via the Fisher indole synthesis.[22] This process proved adequate for obtaining multigram quantities of **6** and was applied to the preparation of several methylated analogues.[23] A reported four-step synthesis of **10**[24] was replicated, with some difficulty in controlling the initial mono-BOC protection of *o*-iodoaniline. While multigram lots of **10** were also obtained, this route was not very versatile or scalable. Subsequently, a method based on the fascinating Bartoli reaction[25] was developed that permitted 7-prenylindole to be obtained in two steps and

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(21) Pirrung, M. C.; Park, K.; Zhao, Y.; Webster, N. J. G. *ChemBioChem*, in press.
(22) Sanz-Cerveral, J. F.; Glinka, T.; Williams, R. M. *Tetrahedron* **1993**, *49*, 8471.
(23) Pirrung, M. C.; Halstead, D. Unpublished results.
(24) Kondo, Y.; Kojima, S.; Sakamoto, T. *Heterocycles* **1996**, *43*, 2741−2746.
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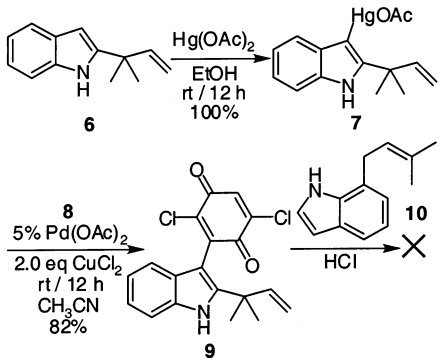
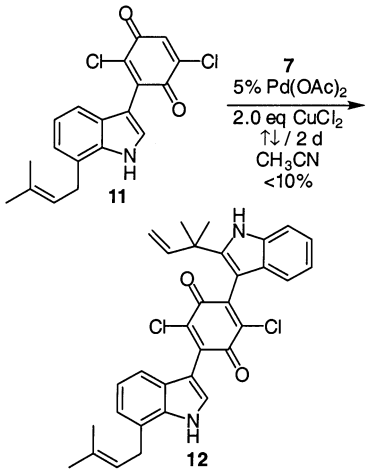
SCHEME 2



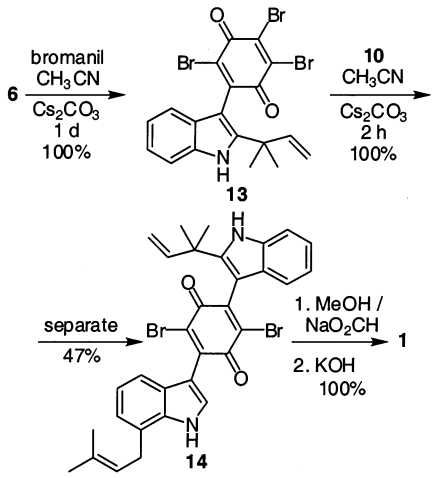
SCHEME 3



~50% yield from *o*-bromonitrobenzene and prenyl bromide.[26] A number of 7-prenylindole relatives can also be prepared by analogous two-step procedures.

The acid-promoted condensation of indoles with 2,5-dichlorobenzoquinone[27] (**8**) was investigated for application to the synthesis of DAQ B1. However, 2-isoprenylindole does not undergo reaction with **8** when promoted by HCl. Though 2-*tert*-butylindole does give an addition product in 54% yield, the steric demand of **6** is evidently too great. An alternative process was investigated (Scheme 2) for adding very sterically hindered indoles to **8** based on Hegedus's report on the conversion of indoles to their 3-mercurio derivatives and their use in Heck reactions with acrylates.[28] These methods have been useful in approaches to other sterically hindered asterriquinones.[29] The conversion of **6** to the mercurial proceeds quantitatively without interference from the terminal alkene, and **7** requires no purification. Upon treatment with 2,5-dichlorobenzoquinone in the presence of catalytic palladium acetate with cuprous chloride as reoxidant, the quinone **9** is obtained in excellent yield. However, it did not prove possible to add **10** to **6** with mineral acid as the promoter. An alternative strategy (Scheme 3) would first add 7-isoprenylindole and then perform the Heck reaction on **11**. While the initial condensation is successful,[27] the product is relatively unstable, so it was submitted without isolation to the Heck conditions with **7**. However, the desired **12** was obtained only in low yield.

SCHEME 4



An expedient, first-generation synthetic route to DAQ B1 was then executed (Scheme 4) on the basis of the known base-catalyzed nucleophilic addition methods. While the addition of **10** to bromanil was difficult to control, 2-isoprenylindole (**6**) undergoes slow (1 d) but clean monoaddition to give the purple **13** in 100% yield (with 56% recovered **6**). Attempts to improve the conversion by longer reaction times, refluxing, and/or using excess *p*-bromanil were not fruitful. Treatment of **13** with **10** under similar conditions rapidly gives a ~1:1 mixture of the meta- and para-substituted indolylquinones that could be rectified by silica gel chromatography. The seemingly straightforward hydrolysis of **14** to DAQ B1 required some investigation. Use of the 4 N KOH conditions reported by Harris[15] completely destroyed the compound. Saturated sodium formate in refluxing MeOH gives a regioisomeric mixture of monohydroxy/monomethoxy bis-indolylquinones that could be hydrolyzed in 2 N KOH in MeOH at reflux (quantitative for two steps), but this method was slow when the scale was increased. A procedure developed in our syntheses of dihydroxyindolylquinones[27] involving addition of 10% aqueous NaOH to a warm, dilute solution of **14** in MeOH and heating at reflux for 30 min provided DAQ B1 that was purified by chromatography on oxalic acid precoated silica gel (65% yield). Spectroscopic data of synthetic **1** were directly compared to data obtained on an authentic sample of DAQ B1; they proved identical. The synthetic compound was also evaluated for its ability to cause phosphorylation of the insulin receptor β-tyrosine kinase domain in a rat fibroblast cell line overexpressing human insulin receptor (hIRcB cells).[18] At 30 μM, synthetic **1** resulted in levels of insulin receptor phosphorylation that were comparable to insulin at 10 ng/mL.

This synthesis was short and modular but suffered from a lack of regiocontrol, so improvements were sought in a second-generation route. It was thought that predetermination of the para regiochemistry of DAQ B1 could be accomplished by initial addition of **6** to 3-bromo-2,5-dichlorobenzoquinone and use of a bromide-selective Stille coupling reaction for installation of the second indole. This general approach was validated through the preparation of a simple symmetrical asterriquinone, DAQ

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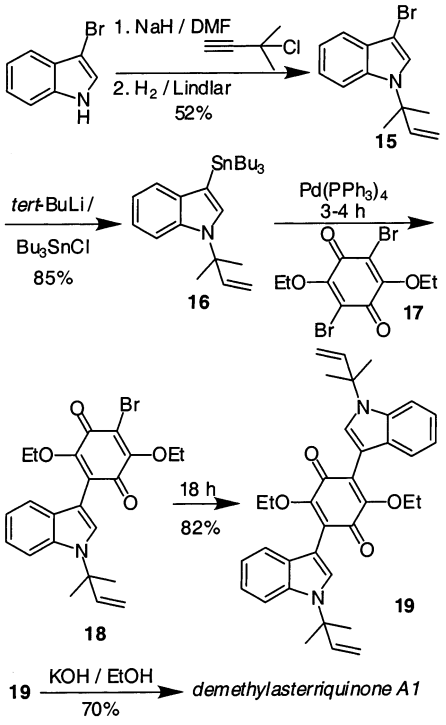
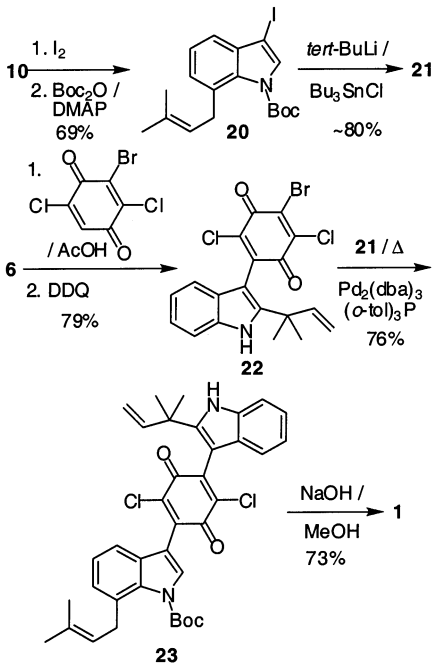
(29) Pirrung, M. C.; Park, K. Unpublished results.

SCHEME 5



SCHEME 6



A1 (Scheme 5), which required indole-tin reagent **16**. The challenging introduction of the *N*-isoprenyl group was addressed using a method from Wipf's muscoride synthesis[30] that was developed originally by Hansen.[31] While the mechanism of alkylations with dimethylpropargyl chloride is unknown, limiting possibilities include direct S_N2 substitution, more permissible at a tertiary center than is ordinarily expected due to the reduced steric demands of an ethyne group or an elimination/addition mechanism via the vinylidene. The efficiency of the dimethylpropargylation of 3-bromoindole is adequate, and the two remaining steps in the route to **16** are efficient. It was generally used in crude (though quite clean) form as obtained following KF treatment of the stannylation reaction mixture to remove tin residues. The bromoquinone reactant **17** for the Stille coupling was obtained from bromanil by ethanolysis in the presence of potassium fluoride.[32] The Stille coupling was performed under standard conditions, with the notable feature that at shorter reaction times the monoindolylquinone **18** dominates the reaction mixture, implying that it should be possible to substitute a different 3-indolyltin at this intermediate stage to produce an unsymmetrical bis-indolylquinone. In this instance, coupling was simply allowed to proceed with excess **16** to generate **19** in excellent yield for two steps (90% yield per coupling). Hydrolysis to give demethylasterriquinone A1 followed literature precedent,[33] giving material that was spectroscopically identical[34] to the natural compound. This synthesis proceeds in an overall yield of 25% for five steps. One shortcoming of this synthetic approach is that it cannot be applied to asterriquinones bearing 2-isoprenylindoles because steric factors prevent stannylation of the lithium reagents derived from them (Zhu, J., unpublished results).

A total synthesis of DAQ B1 was performed exploiting the precedents from the DAQ A1 synthesis (Scheme 6). A tin reagent was prepared from **10** by selective iodination at the 3-position, protection of the nitrogen with a Boc group (→ **20**) and metal−halogen exchange followed by trapping of the 3-indolyllithium with tri-*n*-butyltin chloride (~55% overall). To form a reactant suitable for Stille coupling with **21**, a method was needed to add **6** to a brominated quinone. The mercurial chemistry used to prepare **9** could have been used, but limiting the stoichiometric use of heavy metals was desirable. It was discovered that while **6** does not undergo addition to **8** under the influence of mineral acid, it does add to bromo-2,5-dichlorobenzoquinone in acetic acid, giving **22** in 79% yield. The substitution pattern of this compound is built into the starting quinone and directs selective production of the *para*-bis-indolylquinone regiochemistry based on the reactivity of vinyl bromides vs vinyl chlorides in the Stille coupling.[35] The Stille coupling was adequate under conventional conditions ($Pd(Ph_3P)_4$), but could be improved using bulky phosphines,[36] producing **23** in 76% yield. The hydrolysis of the carbamate and vinyl halides

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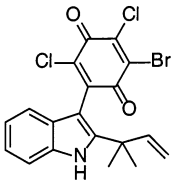
(35) Both **22** and its isomer **i** were examined in base-catalyzed condensations with **10**, and both gave mixtures.



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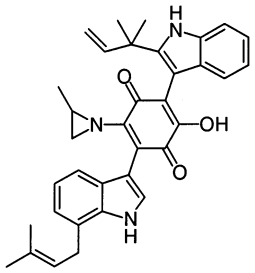
(36) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046−2067.

under basic conditions using our earlier procedure[27] gives the natural product in 73% yield.

Intermediates from these syntheses provide access to chemical reagents useful for studying the biochemical properties of DAQ. For example, the monohydroxy/monomethoxy quinones derived from **14** react with methylaziridine to give the monoaziridinylquinone **24**, which may prove useful as an affinity label to identify proteins with which DAQ interacts.



24

Discussion and Conclusion

The two total syntheses of DAQ B1 described here have longest linear sequences from commercially available materials of five and seven steps, respectively. The former proceeds in 12% yield, the latter in 13% yield (average of the two linear routes); the latter requires no isomer separations. Using these syntheses, gram quantities of DAQ B1 have been prepared, and its biological activity has been verified. The first-generation route should be generally applicable to asterriquinone synthesis on the basis of the work of Harris.[13] However, these routes do not represent ideal syntheses for families of asterriquinones, due to the lack of regiocontrol or the necessity to convert one indole to its tin derivative to gain regiocontrol. Coupling reactions that proceed with indoles (or other heterocycles) without pre-functionalization would permit the wide variety of commercially available heterocycles to be used directly in the creation of molecular libraries. An ideal asterriquinone synthesis would involve only two steps: selective condensation of a quinone core with first one and then a second indole. Completion of a third generation synthesis of the asterriquinones reflecting this ideal is thus a high priority.

Experimental Section

General Methods. Oxalic-acid precoated silica gel was prepared by a literature procedure:[37] suspension of silica gel 60 (230−400 mesh) in 0.1 N oxalic acid overnight, filtration, washing with H_2O, and drying in an oven at 100 °C overnight.

2,3,5-Tribromo-6-[2-(1,1-dimethylallyl)-1*H*-indol-3-yl]-[1,4]benzoquinone (13). To a solution of 2-(1,1-dimethylallyl)-1*H*-indole (1.0 g, 5.40 mmol) in CH_3CN (10 mL) were added Cs_2CO_3 (3.52 g, 10.8 mmol) and tetrabromo-1,4-benzoquinone (2.41 g, 5.40 mmol) at room temperature. After the reaction mixture was stirred for 12 h at room temperature, Cs_2CO_3 (1.76 g, 5.40 mmol) and tetrabromo-1,4-benzoquinone (1.21 g, 2.70 mmol) were added to the reaction mixture. After further stirring for 12 h at room temperature, the mixture was diluted with EtOAc (100 mL). The organic solution was washed with 0.5 N HCl (2 × 100 mL) and brine (2 × 100 mL) and dried over Na_2SO_4. The residue was concentrated and purified by flash column chromatography using 10% EtOAc in hexane as eluent to afford pure 2,3,5-tribromo-6-[2-(1,1-dimethylallyl)-1*H*-indol-3-yl][1,4]benzoquinone as a purple solid (1.26 g, 100% based on recovered **6** (56%)). R_f = 0.31 (1:4 EtOAc/hexane). IR (thin film): 3423, 2971, 1677, 1562, cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.28 (bs, NH), 7.33 (dt, J = 8.1, 0.9 Hz, 1H), 7.20−7.05 (m, 3H), 5.98 (dd, J = 17.4, 10.5 Hz, 1H), 5.12 (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 175.0, 171.3, 145.9, 144.8, 142.4, 140.2, 137.6, 135.4, 134.7, 122.4, 120.3, 118.6, 113.4, 110.9, 105.3, 39.3, 28.0, 26.7. Mp: 90 °C dec. Anal. Calcd for $C_{19}H_{14}NO_2Br_3$: C, 43.21; H, 2.65; N, 2.65. Found: C, 43.48; H, 2.81; N, 2.65.

2,5-Dibromo-3-[2-(1,1-dimethylallyl)-1*H*-indol-3-yl]-6-[7-(3-methylbut-2-enyl)-1*H*-indol-3-yl][1,4]benzoquinone (14). To a solution of 2,3,5-tribromo-6-[2-(1,1-dimethylallyl)-1*H*-indol-3-yl][1,4]benzoquinone (**13**, 150 mg, 0.284 mmol) in CH_3CN (1 mL) were added Cs_2CO_3 (185 mg, 0.568 mmol) and 7-(3-methylbut-2-enyl)-1*H*-indole (63 mg, 0.341 mmol) at room temperature. After being stirred for 2 h, the reaction mixture was diluted with EtOAc (20 mL). The organic solution was washed with 0.5 N HCl (2 × 20 mL) and brine (2 × 20 mL) and dried over Na_2SO_4. The residue was concentrated and purified by careful flash column chromatography using 15% EtOAc in hexane as eluent to afford pure 3,6-bisindolyl-2,5-dibromobenzoquinone **14** (85 mg, 47%) and its regioisomer, 3,5-bisindolyl-2,6-dibromobenzoquinone (79 mg, 44%), as purple solids. Data for **14**. R_f = 0.38 (3:7 EtOAc/hexane). IR (thin film): 3410, 2971, 1667, 1570, 1431, 1244 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.77 (bs, NH), 8.27 (bs, NH), 7.53 (d, J = 2.7 Hz, 1H), 7.34 (dd, J = 8.1, 0.9 Hz, 2H), 7.25−7.06 (m, 5H), 6.06 (dd, J = 17.4, 10.8 Hz, 1H), 5.44 (m, 1H), 5.18 (dd, J = 17.4, 1.2 Hz, 1H), 5.14 (dd, J = 10.8, 0.9 Hz, 1H), 3.60 (d, J = 7.2 Hz, 2H), 1.83 (s, 3H), 1.81 (s, 3H), 1.47 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 177.5, 145.5, 145.0, 141.9, 141.7, 137.1, 134.8, 134.7, 133.8, 133.0, 128.7, 126.4, 124.9, 124.7, 122.3, 122.2, 121.8, 120.8, 120.1, 119.7, 118.7, 113.1, 110.9, 109.2, 105.9, 39.4, 30.7, 27.8, 26.8, 25.8, 18.1. HRMS (FAB): calcd for $C_{32}H_{30}Br_2N_2O_2$ $[M + 2H]^+$ 632.0674, found 632.0673. Mp: 134 °C dec.

2-[2-(1,1-Dimethyl-allyl)-1*H*-indol-3-yl]-3-hydroxy-6-methoxy-5-[7-(3-methylbut-2-enyl)-1*H*-indol-3-yl][1,4]-benzoquinone and 2-[2-(1,1-Dimethylallyl)-1*H*-indol-3-yl]-6-hydroxy-3-methoxy-5-[7-(3-methylbut-2-enyl)-1*H*-indol-3-yl][1,4]benzoquinone. To a solution of 3,6-bisindolyl-2,5-dibromobenzoquinone **14** (30 mg, 47.4 μmol) in MeOH (10 mL) was added saturated $NaCO_2H$ or NaOAc solution (5 mL), and the mixture was refluxed for 3 d (monitored by TLC). The reaction mixture was concentrated in vacuo to remove MeOH, and the resulting crude mixture was extracted with EtOAc (3 × 10 mL). The organic solution was washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography using 20% EtOAc in hexane as eluent to afford pure 2,5-bisindolyl-3-hydroxy-6-methoxy-1,4-benzoquinone and 2,5-bisindolyl-6-hydroxy-3-methoxy-1,4-benzoquinone (regioisomers, 23 mg, 94%) as red-purple solids. R_f = 0.28 (3:7 EtOAc/hexane). IR (thin film): 3396, 2970, 2919, 1642, 1605, 1301, 1270 cm^{-1}. ^1H NMR ($CDCl_3$, regioisomers (~1:1)): δ 8.61 (bs, NH), 8.59 (bs, NH), 8.26 (bs, NH), 8.22 (bs, NH), 7.71 (bs, OH), 7.55 (d, J = 2.4 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.46 (bs, OH), 7.43 (d, J = 2.7 Hz, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.31−7.25 (m, 4H), 7.17−7.01 (m, 8H), 6.11 (dd, J = 17.1, 10.2 Hz, 1H), 6.05 (dd, J = 17.4, 10.5 Hz, 1H), 5.42 (m, 2H), 5.20−5.08 (m, 4H), 3.85 (s, 3H), 3.71 (s, 3H), 3.56 (d, J = 6.6 Hz, 4H), 1.81 (s, 3H), 1.791 (s, 3H), 1.788 (s, 3H), 1.78 (s, 3H), 1.47 (s, 6H), 1.46 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 188.7, 183.3, 183.1, 182.3, 157.7, 156.0, 151.4, 149.1, 145.4, 144.9, 142.3, 142.2, 134.8, 134.7, 134.6, 134.3, 133.4, 133.3, 129.7, 128.4, 127.1, 126.9, 126.5, 125.9, 124.2, 124.0, 122.0, 121.91, 121.87, 121.8, 120.6, 120.2, 120.1, 119.73, 119.66, 118.79, 118.77, 118.5, 118.4, 116.7, 114.1, 113.1, 112.3, 111.9, 110.7, 105.1, 104.9, 100.7, 100.1, 61.2, 60.2,

(37) Yamamoto, Y.; Nishimura, K.; Kiriyama, N. *Chem. Pharm. Bull.* **1976**, *24*, 1853−9.

39.2, 30.61, 30.56, 27.2, 27.0, 26.8, 26.7, 25.78, 25.76, 18.0. HRMS (FAB): calcd for $C_{33}H_{32}N_2O_4$ $[M]^+$ 520.2362, found 520.2365.

Demethylasterriquinone B1 (1). To a solution of 2,5-bisindolyl-3-hydroxy-6-methoxy-1,4-benzoquinone and 2,5-bis-indolyl-6-hydroxy-3-methoxy-1,4-benzoquinone (65 mg, 0.125 mmol) in MeOH (20 mL) was added 2 N NaOH (10 mL), and the mixture was refluxed for 2 h (monitored carefully by TLC). The reaction mixture was concentrated in vacuo to remove MeOH, and the resulting solution was acidified with 2 N HCl. The crude mixture was extracted with EtOAc (3 × 20 mL). The organic solution was washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography using oxalic acid precoated silica gel and 10% EtOAc in hexane as eluent to afford pure demethylasterriquinone B1 (DAQ B1) **1** (61 mg, 96%) as a dark red-purple solid. $R_f = 0.43$ (1:4, EtOAc/hexane, reversed phase RP-18). IR (thin film): 3416, 3345, 2970, 2928, 1637, 1343 cm^{-1}. ^1H NMR (acetone-d_6): δ 10.41 (bs, NH), 10.05 (bs, NH), 9.36 (bs, 2OH), 7.62 (d, $J = 2.7$ Hz, 1H), 7.44 (dd, $J = 6.9$, 2.1 Hz, 1H), 7.33 (dt, $J = 8.1$, 0.9 Hz, 1H), 7.28 (dt, $J = 8.1$, 0.9 Hz, 1H), 7.07−6.91 (m, 4H), 6.17 (dd, $J = 17.4$, 10.5 Hz, 1H), 5.48 (m, 1H), 5.10 (dd, $J = 17.4$, 1.2 Hz, 1H), 5.01 (dd, $J = 10.5$, 1.2 Hz, 1H), 3.64 (d, $J = 6.9$ Hz, 2H), 1.78 (s, 3H), 1.76 (s, 3H), 1.52 (s, 6H). ^{13}C NMR (acetone-d_6): δ 146.4, 143.1, 136.3, 135.7, 133.2, 129.7, 127.8, 127.5, 125.0, 122.9, 121.7, 121.4, 120.4, 120.0, 119.5, 119.4, 113.0, 112.1, 111.4, 111.3, 105.8, 101.3, 39.9, 30.6−29.0 (2C, overlapping with solvent peaks), 27.5, 25.9, 17.9. HRMS (FAB): calcd for $C_{32}H_{31}N_2O_4$ $[M + H]^+$ 507.2284, found 507.2283.

3-Bromo-1-(1,1-dimethylprop-2-ynyl)-1*H*-indole. To a mixture of 3-bromoindole (196 mg, 1 mmol, prepared by the literature procedure[38] in 97% yield) and 3-chloro-3-methylbut-1-yne (204 mg, 2 mmol) in 2 mL of DMF, at 0 °C, was added 60% NaH (100 mg, 2.5 mmol) suspended in 1 mL of DMF. The mixture was stirred at room temperature for 12 h. After workup, the crude compound was purified by silica gel chromatography (1:6 ethyl acetate/hexane) to give a yellow oil (157 mg, 60%). ^1H NMR ($CDCl_3$): δ 7.86 (d, $J = 8.1$ Hz, 1H), 7.57 (d, $J = 8.1$ Hz, 1H), 7.35 (s, 1H), 7.18−7.24 (m, 2H), 2.60 (s, 1H), 1.95 (s, 6H). ^{13}CNMR ($CDCl_3$): δ 134.6, 128.9, 123.8, 122.5, 120.6, 119.8, 90.3, 85.7, 73.2, 53.0, 30.3.

3-Bromo-1-(1,1-dimethylallyl)-1*H*-indole (15). A mixture of 3-bromo-1-(1,1-dimethylprop-2-ynyl)-1*H*-indole (96 mg, 0.37 mmol), quinoline (0.04 mL), and 5% $Pd/BaSO_4$ (10 mg) in benzene (10 mL) was stirred under an H_2 atmosphere at room temperature for 29 h. The reaction mixture was filtered through Celite and purified by flash chromatography (hexane). The product was obtained as a yellow oil (84 mg 87% yield). ^1H NMR ($CDCl_3$): δ 7.56 (1H, m), 7.49 (1H, m), 7.31 (1H, s), 7.16 (2H, m), 6.12 (1H, dd, $J = 10.5$, 17.4 Hz), 5.24 (1H, d, $J = 10.5$ Hz), 5.17 (1H, d, $J = 17.4$ Hz), 1.74 (6H, s). ^{13}C NMR ($CDCl_3$): δ 143.8, 135.0, 128.8, 124.5, 122.0, 120.1, 119.5, 114.1, 89.0, 60.0, 28.3. IR: 3086, 2982, 1568, 1451. Anal. Calcd for $C_{13}H_{14}BrN$: C, 59.11; H, 5.34; N, 5.30. Found: C, 59.07; H,5.47; N, 5.13.

1-(1,1-Dimethyl-allyl)-3-(tributylstannyl)-1*H*-indole (16). To a solution of **15** (254 mg, 0.96 mmol) in diethyl ether at −78 °C was added *tert*-butyllithium (1.18 mL of a 1.7 M solution, 2.01 mmol). The solution was stirred for 20 min, and tributyltin chloride (0.27 mL, 0.99 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 10 h. A saturated aqueous solution of KF was poured into the reaction and stirred for 30 min. The aqueous phase was extracted with ethyl acetate (30 mL × 3). The combined organic phase was dried with sodium sulfate, and the solvent was removed in vacuo. Compound **16** was obtained as a yellow oil in 85% yield. ^1H NMR ($CDCl_3$): δ 7.55 (2H, m), 7.18 (1H, s), 7.05 (2H, m), 6.15 (1H, dd, $J = 11.0$, 17.7 Hz), 5.25 (1H, d, $J = 11.0$), 5.16 (1H, d, $J = 17.7$ Hz), 1.78 (6H, s), 1.40 (18H, m), 0.82 (9H, m). The crude material was azeotroped with benzene before being used in the Stille coupling.

2,5-Bis[1-(1,1-dimethylallyl)-1*H*-indol-3-yl]-3,6-diethoxy-[1,4]benzoquinone (19). A solution of quinone **17** (52 mg, 0.15 mmol) and tetrakis(triphenylphosphine)palladium (20 mg, 0.017 mmol) in toluene was bubbled with nitrogen for 10 min. Crude compound **16** was added in portions (255 mg, 0.54 mmol), and the solution was brought to 110 °C. The reaction mixture was stirred for 18 h and filtered through Celite. The solvent was removed in vacuo, and the residue was purified by silica gel chromatography (hexane, then benzene). Compound **19** (68 mg, 82%) was obtained as a purple solid. Mp: 179−181 °C. ^1H NMR ($CDCl_3$): δ 7.77 (2H, s), 7.60 (2H, m), 7.54 (2H, m), 7.15 (4H, m), 6.20 (2H, dd, $J = 10.8$, 17.7 Hz), 5.27 (2H, d, $J = 10.8$ Hz), 5.22 (2H, d, $J = 17.7$ Hz), 3.95 (4H, q, $J = 7.2$ Hz), 1.83 (12H, s), 1.13 (6H, t, $J = 7.2$ Hz). ^{13}C NMR ($CDCl_3$): δ 184.5, 152.7, 143.9, 135.5, 129.5, 128.7, 124.3, 122.4, 121.2, 119.9, 114.1, 103.9, 69.2, 59.9, 28.4, 16.1. IR (thin film): 2959, 2929, 1727, 1651, 1458 cm^{-1}. HRMS: calcd for $C_{36}H_{38}N_2O_4$ 562.2832, found 562.2831 (M^+).

Demethylasterriquinone A1. Compound **19** (8 mg, 0.014 mmol) was dissolved in 1 N potassium hydroxide (1 mL) and ethanol (2 mL). The solution was heated at 70 °C for 1 h. The mixture was acidified with 1 N HCl to pH 2. The precipitate was extracted with ethyl acetate (10 mL × 2). The organic phases were combined and dried over sodium sulfate. After removal of the solvent, the residue was purified with column chromatography on oxalic acid precoated silica gel (benzene). The title compound (5.1 mg, 70%) was obtained as a dark purple solid. ^1H NMR ($CDCl_3$): δ 8.11 (2H, s), 7.74 (2H, s), 7.60 (4H, m), 7.16 (4H, m), 6.21 (2H, dd, $J = 10.8$, 17.7 Hz), 5.28 (2H, d, $J = 10.8$ Hz), 5.25 (2H, d, $J = 17.7$ Hz),1.83 (12H, s). ^{13}C NMR ($CDCl_3$): δ 144.0, 135.6, 128.5, 128.2, 122.2, 121.4, 119.9, 114.2, 114.1, 111.1, 102.6, 59.9, 28.2. These data are consistent with data reported in the literature.

3-Bromo-2,5-dichloro[1,4]benzoquinone. To 7.03 g (40 mmol) of 2,5-dicholoro[1,4]benzoquinone in 120 mL of acetic acid was added 2.68 mL (1.1 equiv) of bromine. The mixture was stirred at room temperature for 4 h and poured into 300 mL of water. The precipitate formed was collected and recrystallized from ethanol to give the product (9.03 g, 92%) as yellow crystals. Mp: 164−165 °C (lit.[39] mp 168 °C).

3-Iodo-7-(3-methylbut-2-enyl)indole-1-carboxylic Acid *tert*-Butyl Ester (20). To a solution of 7-prenylindole (7 mmol) in 26 mL of DMF was added potassium hydroxide pellets (1 g, 18 mmol). A solution of iodine (7 mmol) in 26 mL of DMF was added to the reaction mixture in 20 min under stirring. The reaction mixture was stirred for 1 h at room temperature and poured into 400 mL of ice−water containing 0.5% ammonia and 0.1% sodium metabisulfite. The mixture was extracted with a 1:1 solution of ethyl acetate/hexanes until no product was left in the aqueous phase. The organic phases were combined, washed with cold water, and dried with anhydrous sodium sulfate. The solvent was removed in vacuo, and the crude product was dissolved in 100 mL of dichloromethane. Boc_2O (1.57 g, 7 mmol), K_2CO_3 (1.2 g, 9 mmol), and DMAP (100 mg, 0.8 mmol) were added. The mixture was stirred at room temperature for 12 h and filtered. The crude product was purified by chromatography (0.5% ethyl acetate in hexane) to yield 2.00 g (69%) of the title compound as a colorless oil. IR (thin film): 2977, 2927, 1754, 1746, 1370, 1309, 1150 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.67 (s, 1H), 7.30−7.23 (m, 3H), 5.25 (m, 1H), 3.81 (d, $J = 6.6$ Hz, 2H), 1.73 (s, 3H), 1.72 (s, 3H), 1.64 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 148.6, 133.7, 133.0, 132.5, 129.5, 127.6, 126.4, 124.1, 123.4, 123.1, 119.8, 84.2, 33.7, 28.4, 26.1, 18.4. HRMS (FAB): calcd for $C_{18}H_{22}INO_2$ $[M]^+$ 411.0695, found 411.0696.

7-(3-Methylbut-2-enyl)-3-tributylstannanylindole-1-carboxylic Acid *tert*-Butyl Ester (21). Compound **20** (1.3 g, 3.2 mmol) was dissolved in 65 mL of anhydrous ethyl ether.

(38) Bocchi, B.; Palla, G. *Synthesis* **1982**, 1096−1097.

(39) Ling, A. R. *J. Chem. Soc.* **1892**, *61*, 558−567.

tert-Butyllithium (3.7 mL of a 1.7 M solution) was added at −78 °C under argon. The solution was stirred for 20 min, and tributyltin chloride (1.1 mL) was added. The solution was allowed to warm to room temperature and stirred for 10 h. Saturated KF solution (50 mL) was poured into the reaction mixture, which was stirred for 30 min. The solution was extracted three times with ethyl acetate (30 mL). The combined organic phase was washed with brine and dried with sodium sulfate, and the solvent was removed in vacuo. The crude compound **21** was obtained as a yellow oil that was used in the next step without further purification (chromatography caused protiodestannylation). The yield was estimated to be 80% on the basis of NMR.

2-Bromo-3,6-dichloro-5[2-(1,1-dimethylallyl)-1*H*-indol-3yl][1,4]benzoquinone (22). A mixture of 2-isoprenylindole (0.93 g, 5 mmol) and 2.55 g (10 mmol) of bromo-2,5-dichlorobenzoquinone in 20 mL of acetic acid was stirred at 50 °C for 2 h and then at room temperature for another 10 h. DDQ (1.15 g, 5 mmol) was added, and the mixture was stirred at room temperature for 2 h. The solvent was removed in vacuo, and the residue was dissolved in 50 mL of ethyl acetate. The solution was washed twice with 50 mL of saturated sodium bicarbonate, followed by 50 mL of water and 50 mL of brine. The resulting solution was dried with anhydrous sodium sulfate, and the solvent was removed in vacuo. The crude product was purified by chromatography (ethyl acetate/hexane, 15/85) to yield 1.72 g (79%) of the title compound and 1.27 g of the starting quinone. IR (KBr): 3426, 2969, 1673, 1565, 1459, 1432, 1055 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.26 (s, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.20 (m, 1H), 7.10 (m, 2H), 5.99 (dd, J = 10.8, 17.7 Hz, 1H), 5.12 (d, J = 17.7 Hz, 1H), 5.09 (d, J = 10.8 Hz, 1H), 1.44 (s, 6H).^{13}C NMR ($CDCl_3$): δ 175.5, 172.0, 145.4, 145.1, 143.3, 142.4, 140.9, 135.0, 134.7, 126.7, 122.8, 120.8, 118.8, 113.7, 111.3, 102.9, 39.6, 28.3, 27.1. HRMS (FAB): calcd for $C_{19}H_{14}BrCl_2NO_2$ $[M]^+$ 436.9585, found 436.9587. Mp: 189−190 °C (benzene).

3-[2,5-Dichloro-4-[2-(1,1-dimethylallyl)-1*H*-indol-3-yl]-3,6-dioxocyclohexa-1,4-dienyl]-7-(3-methylbut-2-enyl)indole-1-carboxylic Acid *tert*-Butyl Ester (23). A mixture of tri(*o*-tolyl)phosphine (22 mg) and $Pd_2(dba)_3$ (39 mg) in 10 mL of anhydrous toluene was stirred under nitrogen for 15 min. To this solution were added compound **22** (160 mg) and crude compound **21** (400 mg) in 10 mL of anhydrous toluene. The mixture was degassed by nitrogen bubbling for 10 min and heated to 90 °C for 30 min, when reaction was complete. The reaction mixture was filtered through Celite, and the solvent was removed in vacuo. The crude product was purified by chromatography (20% ethyl acetate/hexane) to yield 180 mg (76%) of the title compound. IR (KBr): 3417, 2973, 2930, 1754, 1675, 1594, 1145 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.32 (s, 1H), 7.84 (s, 1H), 7.37 (d, J = 7.5 Hz, 1H), 7.28−7.12 (m, 6H), 6.08 (dd, J = 10.8, 17.4 Hz, 1H), 5.31 (m, 1H), 5.19 (d, J = 17.4 Hz, 1H), 5.17 (d, J = 10.8 Hz, 1H), 3.84 (d, J = 7.2 Hz, 2H), 1,77 (s, 3H), 1.75 (s, 3H), 1.68 (s, 9H), 1.50 (s, 3H), 1.49 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 177.9, 177.4, 149.0, 145.3, 142.9, 142.4, 142.1, 141.0, 137.4, 135.0, 134.2, 133.2, 131.7, 129.9, 129.4, 127.1, 127.0, 123.7, 123.1, 122.6, 120.6, 119.2, 118.9, 113.4, 111.3, 110.9, 103.4, 84.7, 39.7, 33.8, 28.4, 28.2, 27.1, 26.2, 18.4. HRMS (FAB): calcd for $C_{37}H_{38}Cl_2N_2O_4$ $[M + 2H]^+$ 644.2209, found 644.2208. Mp: 126−127 °C.

2-[2-(1,1-Dimethylallyl)-1*H*-indol-3-yl]-3,6-dihydroxy-5-[7-(3-methylbut-2-enyl)-1*H*-indol-3-yl][1,4]benzoquinone, DAQ B1 (1). To a refluxing solution of compound **23** (380 mg) in methanol (36 mL) was added 18 mL of 10% NaOH. The solution was refluxed for 30 min and poured into 20 mL of water. The mixture was acidified to pH 1 with 10% H_2SO_4 and extracted three times with ethyl acetate (25 mL). The combined organic phase was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the crude product was purified on oxalic acid precoated silica gel (15% ethyl acetate/hexane) to yield 218 mg (73%) of the natural product. ^1H NMR (acetone-d_6): δ 10.46 (s, 1H), 10.10 (s, 1H), 9.8−9.0 (br, 2H), 7.63 (d, J = 2.7 Hz, 1H), 7.45 (d, J = 7.2 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.29 (d, J = 8.1 Hz, 1H), 7.08−6.93 (m, 4H), 6.18 (dd, J = 10.8, 17.4 Hz, 1H), 5.49 (m, 1H), 5.11(d, J = 17.4 Hz, 1H), 5.02 (d, J = 10.8 Hz, 1H), 3.65 (d, J = 6.9 Hz, 2H), 1.79 (s, 3H), 1.77 (s, 3H), 1.53 (s, 6H).^{13}C NMR ($CDCl_3$): δ 146.0, 142.7, 135.8, 135.2, 132.7, 129.2, 127.4, 127.0, 124.5, 122.4, 121.2, 120.9, 119.9, 119.5, 119.0, 118.9, 112.5, 111.7, 110.9, 110.9, 105.4, 100.8, 39.4, 27.0, 25.4, 17.5.

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Supporting Information Available: NMR spectra of **14**, **19**, **20**, **22**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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