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What Is the Structure of the Antitubercular Natural Product Eucapsitrione?

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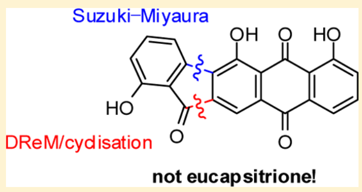
Supporting Information

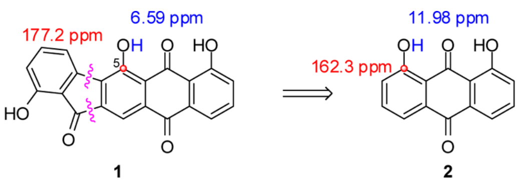
ABSTRACT: 1,5,7-Trihydroxy-6*H*-indeno[1,2-*b*]anthracene-6,11,13-trione (**1**), proposed to be the antitubercular natural product eucapsitrione, has been synthesized in 43% overall yield and six steps, including a key Suzuki–Miyaura biaryl coupling and a directed remote metalation (DReM)-initiated cyclization. The physical and spectroscopic properties of **1** do not match the data reported for the natural product. At this time there is insufficient information available to enable a structure reassignment. During the optimization of the Suzuki–Miyaura coupling, an unprecedented biaryl coupling *ortho* to the borono group was observed. The scope of this unusual reaction has been investigated.



■ INTRODUCTION

In 2010, an investigation of a cyanobacterium of the previously unexplored genus *Eucapsis* was conducted with the aim of isolating and identifying new antitubercular agents.[1] The study led to the isolation of a novel natural product, which was named eucapsitrione and assigned structure **1** (Scheme 1) on the basis of spectroscopic and mass spectrometric data.[1]

Scheme 1. Proposed Structure 1 of Eucapsitrione and Anomalous NMR Data Compared to Chrysazin (2), a Potential Precursor for Total Synthesis



Eucapsitrione exhibits potent activity against rapidly growing *M. tuberculosis* with a minimum inhibitory concentration of 3.1 μM. Importantly, the natural product was also active at a similar concentration in the low-oxygen-recovery assay (LORA),[2] which has been developed to mimic the non-replicating persistent (NRP) state that makes tuberculosis (TB) difficult to treat, and contributes to antimicrobial resistance in *M. tuberculosis*.[3] Conversely, eucapsitrione did not affect the viability of *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans*, or *Mycobacterium smegmatis* at 55 μM, and had an $IC_{50} > 28$ μM against the mammalian Vero cell line, suggesting a mode of action that is selective for *M. tuberculosis*. These properties make eucapsitrione a promising lead for the discovery of novel drugs for the treatment of TB infection, as noted in several reviews.[4−8] In addition, no fluorenones, and only a few anthraquinones,[9] have ever been isolated from a cyanobacterium. Indeed, the fused pentacyclic 6*H*-indeno[1,2-*b*]anthracene-6,11,13-trione skeleton of **1** is unique amongst natural products. Thus, **1** was an attractive candidate for synthesis.

Our interest in eucapsitrione was further piqued because several of the natural product's spectroscopic data did not seem to fit the proposed structure. Most noticeable among these was the assignment of a signal at 6.59 ppm in the ^{1}H NMR spectrum (in d_6-DMSO) to the C5 phenolic proton. Such protons, peri to carbonyl groups, are typically strongly hydrogen-bonded and thus resonate considerably downfield of non-hydrogen bonded phenols. For example, in chrysazin (**2**) (Scheme 1), the analogous protons resonate at 11.98 ppm in d_6-DMSO. Furthermore, a signal in the ^{13}C NMR spectrum of eucapsitrione at 177.2 ppm was assigned to C5. Such carbons generally resonate in the range 150−160 ppm.[10] Indeed, the corresponding carbons of chrysazin (**2**) give rise to a signal at 162.3 ppm (Scheme 1).[11]

The report that **1** produces only one carbonyl absorption band in its IR spectrum (1616 cm^{-1}) also seemed incongruous with the proposed structure. The absorption frequency of a carbonyl group is typically lowered when hydrogen-bonded to a *peri* phenolic proton, as evident in the infrared spectrum of chrysazin (**2**, 1678 and 1621 cm^{-1}),[12] and related α-hydroxyanthraquinones.[12,13] As such, it would be reasonable to expect the structure **1** to give rise to at least two distinct carbonyl absorption bands. It is also worth noting that the exact mass determined for eucapsitrione [M−H]$^-$ (357.04291)[1] is 6.7 ppm out from the calculated mass (357.0405) of the $C_{21}H_9O_6^-$ ion, raising some doubt about the molecular formula.

The irregularities in the mass spectrometric and spectroscopic data discussed above suggested that the proposed structure **1** required validation.

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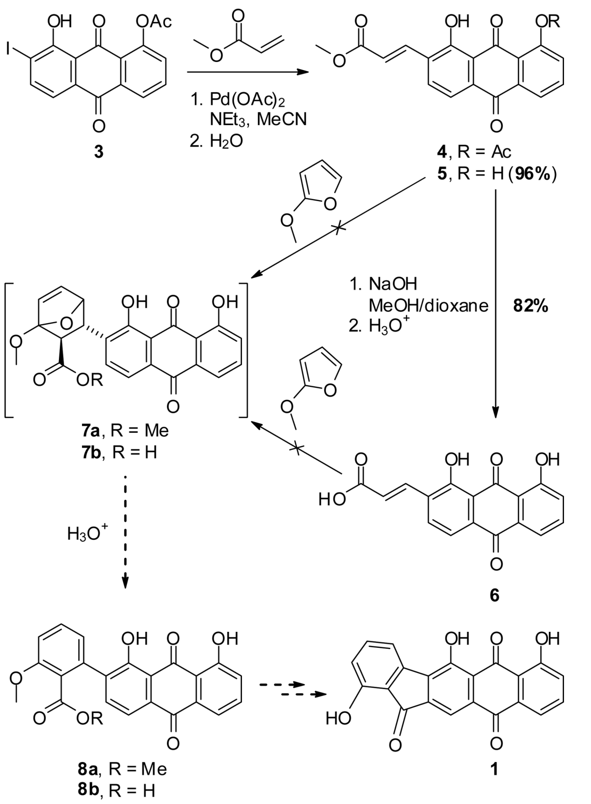
■ RESULTS AND DISCUSSION

Synthesis of the ring system represented by **1** has only been reported a handful of times, often without substitution;[14,15] otherwise, substituted derivatives have been produced in low yield[16] and as reaction byproducts.[17] With no existing practical routes upon which to base the synthesis of structure **1**, two novel pathways were devised beginning from the cheap and readily available chrysazin (**2**) (Scheme 1).

The first approach is outlined in Scheme 2. The known iodide **3**, prepared simply in two steps from chrysazin (**2**),[18,19] was subjected to a Heck reaction with methyl acrylate, under standard conditions,[20] initially providing a mixture of the expected coupling product **4** and the corresponding phenol **5** resulting from deacetylation. Deprotection of the phenol was actually desired, and was forced to completion by the addition of water to the reaction mixture once the Heck coupling was complete, affording **5** exclusively, in excellent yield. Our intention was to effect a regioselective Diels–Alder cycloaddition of **5** with 2-methoxyfuran to provide adduct **7a**, which we assumed would aromatize upon acidic workup to give the biaryl **8a**. Subsequent electrophilic ring closure could then provide access to **1**.

Scheme 2. Unsuccessful Approach to Eucapsitrione Involving Key Heck and Diels–Alder Reactions



Although 2-methoxyfuran reacts readily with very good dienophiles,[21−24] and with some less electron-deficient dienophiles in the presence of Lewis acid catalysts,[25] our attempts to induce a Diels–Alder reaction with **5** were unsuccessful. Heating the pair under reflux in toluene led to partial decomposition of 2-methoxyfuran and no trace of a Diels–Alder adduct by ^{1}H NMR spectroscopy.

It was reasoned that addition of a Lewis acid catalyst may be able to activate the dienophile through coordination to both the ester carbonyl group and chelation with the anthraquinone carbonyl/*peri* hydroxy moiety in **5**, the latter mitigating the electron-donating effects of the phenol. With multiple potential coordination sites in the dienophile **5**, experiments were therefore conducted in the presence of both sub- and super-stoichiometric quantities of Lewis acids and a range of temperatures. The attempted Diels–Alder reaction of **5** in the presence of $Yb(OTf)_3$;[26−29] a silica-supported $TiCl_4$-based catalyst that has been used previously with 2-methoxyfuran;[25] and phenylboronic acid, which was expected to form a chelate borate complex with α-hydroxyquinone moiety;[30] were all unsuccessful, leading only to decomposition of the diene.

Arylboronic acids have successfully catalyzed a number of Diels–Alder cycloadditions of furan, though where the dienophile is an α,β-unsaturated carboxylic acid.[31,32] In these cases, *ortho*-bromo- and -iodobenzeneboronic acids are noted as being among the most effective catalysts,[31−33] and the carboxylic acid group of the dienophile is key to their mode of activation.[31,34,35] Thus, the acrylic acid **6** was prepared, and the cycloaddition with 2-methoxyfuran was attempted in the presence of *ortho*-bromobenzeneboronic acid. The reaction was first tried in 1,2-dichloroethane (DCE); however, **6** is poorly soluble in DCE and other solvents compatible with arylboronic acid catalysis,[32] so solvent-free experiments with a 10-fold excess of diene were attempted. In all cases, only decomposition of 2-methoxyfuran was observed with no evidence for a Diels–Alder reaction.

With further experimentation, and judicious choice of catalyst and/or phenol protecting groups that render the dienophile more electron-deficient, it may have been possible to achieve the desired cycloaddition. However, with no indication of any cycloadduct formation across all attempts, an alternative synthetic pathway was pursued.

In the second and ultimately successful synthetic route to **1**, a Suzuki–Miyaura cross-coupling of iodide **3** was used to construct the key biaryl bond (Scheme 3 and Table 1). Initially, boronic acid **9a**,[36] derived via directed ortho-lithiation/borylation of the corresponding diisopropylamide, was investigated for this purpose.

Suzuki–Miyaura coupling of halophenols can be carried out under very convenient conditions (aqueous K_2CO_3, Pd/C),[37,38] and we thought these should be applicable to the current synthesis. Following workup and chromatography, the reaction of boronic acid **9a** with iodide **3** under these conditions yielded a product that displayed twice the number of ^{1}H NMR resonances expected of biaryl **11a**. Initially, this observation was tentatively attributed to atropisomerism about the biaryl and arylcarboxamide bonds, giving rise to a mixture of diastereomers. A simplification of the ^{1}H NMR spectrum of this material at high temperature would have confirmed our hypothesis; however, there was little change in the spectrum on heating. Similarly, cleavage of the very bulky diisopropylamide should lead to a simplified ^{1}H NMR spectrum in the resulting carboxylic acid if atropisomerism was at play, but the amide was remarkably resistant to hydrolysis under basic conditions, with only starting material recovered after 9 days of heating under reflux in 1 M NaOH/dioxane.

An attempt to effect hydrolysis under strongly acidic conditions instead resulted in a mixture of products arising from N-dealkylation.[39] Analysis of this mixture made it clear that our atropisomerism hypothesis was incorrect and that, rather, the Suzuki–Miyaura coupling had produced two constitutional isomers. Two of the products isolated from this reaction

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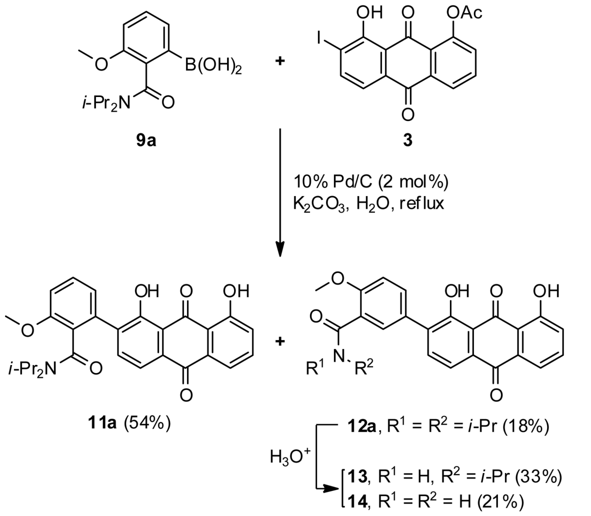
Scheme 3. Suzuki Coupling of Iodide 3 and Boronic Acid 9a Produces Two Regioisomers, 11a and 12a, Discovered after Isolation of the *N*-Dealkylation Products 13 and 14[a]



[a]Yields of **11a** and **12a** are based on NMR spectroscopy.

appeared, by ^{1}H NMR spectroscopy, to possess a 1,2,4-trisubstituted benzene moiety. Ultimately, NOESY and 2D NMR spectroscopic experiments confirmed the unexpected substitution pattern in compounds **13** and **14** (Scheme 3).

This revelation prompted a reinvestigation of the Suzuki–Miyaura coupling of **3** and **9a**, and careful preparative TLC allowed the separation of the two isomeric products of this reaction. Thus, in addition to the expected biaryl **11a**, this reaction gave the minor regioisomer **12a**, which must arise from direct arylation of the aromatic methine para to the methoxy group, a process that must be either preceded or followed by a deboronation step in order to furnish **12a**.

Reports of Pd/C-catalyzed C–H activations,[40−49] while still relatively uncommon, have become more prevalent in recent years, as palladium on carbon is being applied to transformations previously reserved for more complicated homogeneous catalytic systems.[50−52] Among these, direct arylations remain limited[53−58] and are rarely reported for non-heteroaromatic systems.[59] The formation of a significant proportion of **12a** from the reaction of **3** and **9a** under simple conditions therefore presented an interesting side-reaction worth investigating further (Table 1).

The Suzuki–Miyaura reaction conditions were applied to 2-iodochrysazin (**10a**), which confirmed that the direct arylation to give **12a** was not an aberration, and that the acetyl group of **3** likely has no role in the reaction (entry 2). These initial experiments revealed that **9a** is readily deboronated under the reaction conditions,[60−62] as a significant quantity of amide **9b** was observed in the crude reaction product in both cases. Therefore, to assess the importance of the borono group, the arylation with **9b** was attempted (entry 3). This reaction gave only a trace of biaryl **12a**. While this result is informative, hinting at a mechanism involving electrophilic attack at the most activated positon para to the methoxy substituent in both **9a** and **9b**, the increased yield of **12a** in entry 1 suggests that the borono group directs the ortho-arylation of **9a**, prior to deboronation. To the best of our knowledge, this transformation is unique among metal-catalyzed arylation reactions. (However, a similar transformation has been achieved with a hypervalent iodine reagent.[63])

The regioselectivity of the reaction, and prevalence of intramolecular direct arylation reactions in the literature,[64−69] suggest that the borono substituent is acting as a directing group, perhaps via an intermediate phenyl boronate such as **15**. Protection of the free hydroxyl of iodide **3** should preclude formation of such an intermediate, and so the methyl ethers **10b** and **10c** were prepared (entries 3 and 4). Unfortunately, neither iodide **10b**[70] nor **10c** underwent any reaction with **9a**, (i.e., the normal Suzuki–Miyaura coupling was also completely suppressed), providing no insight into the mechanism by which the borono substituent activates the ortho position.

Before conducting more intensive investigations regarding the mechanism of this direct arylation, the scope of the reaction was probed. It was apparent from the reaction of the less hindered *N*,*N*-diethylamidoboronic acid **9c** that the extremely bulky substituent ortho to the boronic acid is required for the direct arylation to compete with conventional cross-coupling, as only a trace of the direct arylation product **12c** was observed (entry 5). The hindered boronic acid **9a** was therefore retained in subsequent reactions with selected alternative aryl iodides **10d–f**. The reaction of 2-iodophenol (**10d**) gave only the expected Suzuki–Miyaura coupling product **11d** in modest yield (entry 6). This suggested that the anthraquinone moiety in the iodochrysazins **3** and **10a** played a role in the direct arylation reaction. The carbonyl groups in the anthraquinones enhance the acidity of the phenolic hydroxyl, decrease the electron density of the aryl iodide, and provide some steric encumbrance. We thus chose other iodides that mimicked these properties. 4-Nitro-2-iodophenol (**10e**) gave only a low yield of the normal Suzuki–Miyaura product **11e** (entry 7), indicating that enhanced phenol acidity is not sufficient to promote direct arylation. The Suzuki–Miyaura coupling of dimethyl iodophthalate **10f**, which should quite closely mimic the stereoelectronic properties of the iodochrysazins, was accompanied by saponification to give the phthalic acid **11f**, but again, no direct arylation product **12f** was observed (entry 8). The importance of oxidative properties of the chrysazin anthraquinone moiety[71,72] of **3** were also considered; benzoquinone (BQ) promotes a variety of C–H activations,[73−75] and so was also tested as an additive in the reaction with 2-iodophenol (entry 9), but this only led to a reduction in yield of the expected Suzuki–Miyaura product **11d**. Finally, addition of an equivalent of chrysazin (**2**) to the experiment with 2-iodophenol (**10d**) had no significant effect on the outcome of that reaction.

Thus, while an interesting diversion, the scope of this direct arylation appears to be limited. Moreover, the side-reaction detracted from the efficiency of the desired synthesis of **1**. Fortunately, the Suzuki–Miyaura coupling of iodide **3** with the less hindered *N*,*N*-diethylamide **9c** produced biaryl **11c** in good yield, with only traces of the undesired direct arylation product. The yield of **11c** was improved simply by increasing the loading of Pd/C to 3 mol %, which furnished the biaryl in 82% isolated yield.

With a good yield of the biaryl intermediate **11c** in hand, our attention turned to the end game (Scheme 4). Cyclization of **11c** via an electrophilic mechanism (e.g., Friedel–Crafts acylation) was considered but predicted to be troublesome for several reasons. The amide is not reactive enough, and hydrolysis was likely to be very difficult. In addition, acylation would be required at the deactivated 3-position on the pendant anthraquinone moiety.

Therefore, we set out to employ the powerful directing ability of the diethylamido group of **11c** in a directed remote metalation

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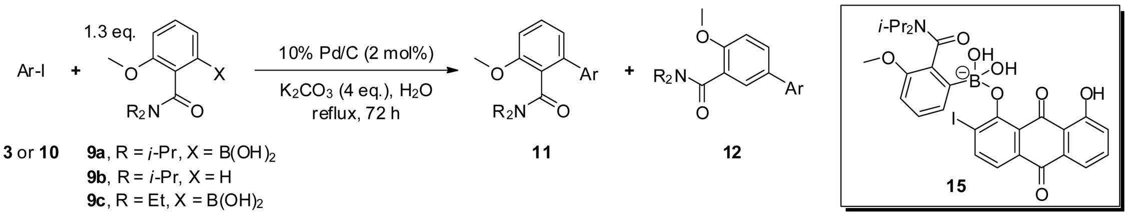
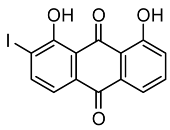
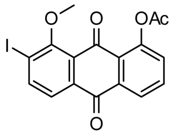
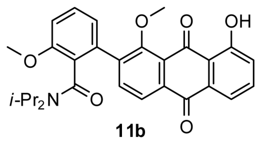
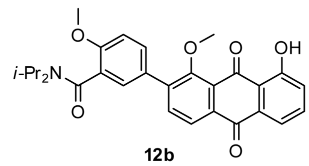
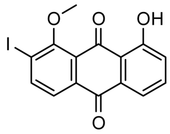
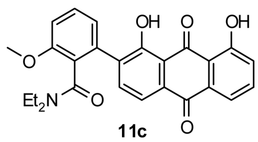
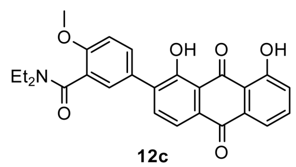
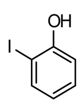
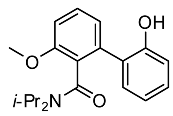
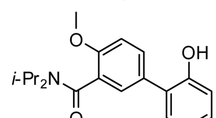
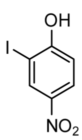
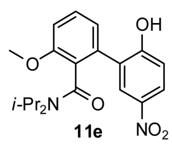
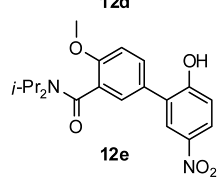
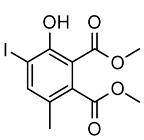
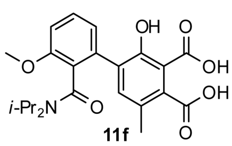
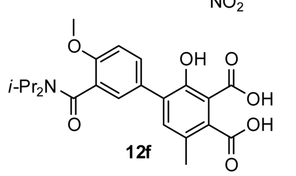
Table 1. Scope and Mechanism Investigation of the Direct Arylation of Arylboronic Acid 9a and Related Compounds



Entry	Iodide	9	11	Yield %[a]	12	Yield %[a]
1	3[b]	9a	11a	54	12a	18
2	 10a	9a	11a	54	12a	13
	3	9b	11a	–	12a	2
3	 10b	9a	 11b	–	 12b	–
4	 10c	9a	11b	–	12b	–
5	3	9c	 11c	79 86 (82)[c]	 12c	2 1[c]
6	 10d	9a	 11d	56 (51)	 12d	–
7	 10e	9a	 11e	7	 12e	–
8	 10f	9a	 11f	60	 12f	–
9	10d[d]	9a	11d	21	12d	–
10	10d[e]	9a	11d	51	12d	–

[a]Yields determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [b]Reaction time 7 d instead of 72 h. [c]3 mol % of Pd/C used; reaction time 36 h instead of 72 h. [d]BQ (1 equiv) added to the reaction mixture. [e]Chrysazin (1 equiv) added to the reaction mixture.

(DReM).[76−79] Literature precedents suggested that both the phenolic hydroxyls and quinone carbonyl groups of **11c** required protection for a successful DReM-initiated cyclization.[76,78] Indeed, when **11c** was converted to the dimethyl ether **16** and treated with excess LDA, a drastic color change resulted but returned only starting material on workup. A subsequent D_2O quench experiment revealed that no lithiation of **16** had occurred. It was reasoned that LDA was reducing the quinone through α-hydride transfer,[80] and the hydroquinone dianion was responsible for the intense color. Lithium hexamethyldisilazide

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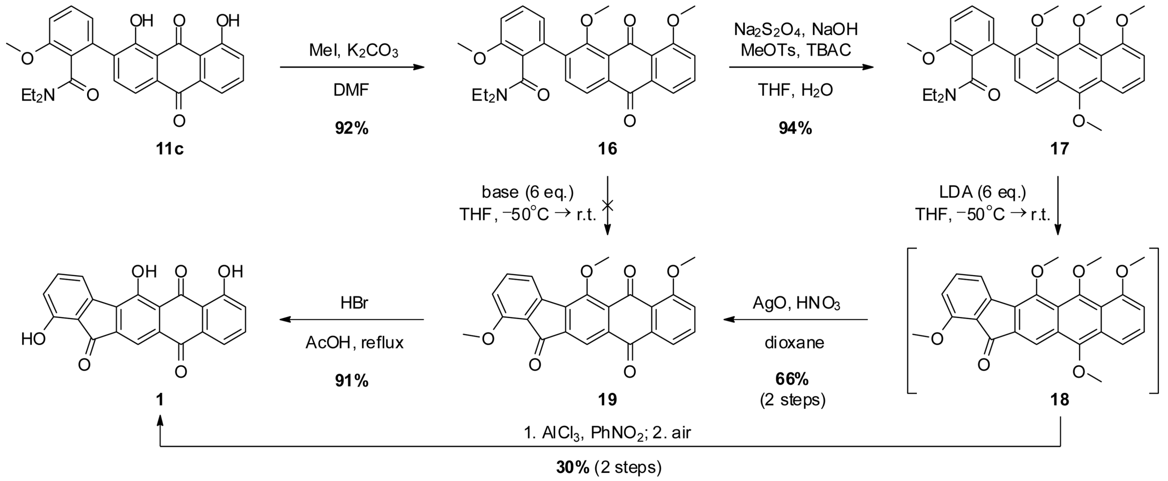
Scheme 4. Completion of the Total Synthesis of the Proposed Structure 1 of Eucapsitrione, by DReM/Cyclization and Deprotection



(LHMDS) or lithium 2,2,6,6-tetramethylpiperidide (LTMP) cannot effect reduction through this mechanism; however, treatment of **16** with these bases delivered the same results as treatment with LDA. We surmise that the lithium amide bases form an electron-transfer complex with **16** in a manner similar to that of alkyllithiums with quinones,[81] resulting in a color change but no apparent reaction post-workup.

Relenting, we prepared the anthracene **17** in excellent yield by reductive methylation of **16** (Scheme 4). Methyl tosylate[82] proved to be as effective as dimethyl sulfate for this reaction, which was fortunate given the scheduling of the latter. DReM–cylization of **17** proceeded smoothly, though attempts to purify fluorenone **18** resulted in significant degradation, likely via photooxidation to its corresponding endoperoxide,[83,84] and as a result, it was not isolated. Instead, freshly prepared crude **18** was subjected to global demethylation,[85] and aerial oxidation[86] furnished the target structure **1** in modest yield across two steps from **17**. The remarkably poor solubility of **1** complicated purification, contributing to the low yield. Therefore, oxidative demethylation of crude **18**, followed by demethylation of **19** proved a more convenient and higher yielding route to **1**.

The first empirical evidence indicating that **1** does not represent the structure of the natural product eucapsitrione relates to solubility. The spectroscopic data for the natural product were obtained in d_6-DMSO, a solvent in which the synthetic material was practically insoluble. Even at elevated temperature, a ^{1}H NMR spectrum of **1** in DMSO could not be obtained; thus, a direct comparison of synthetic **1** with the natural product could not be achieved. The recalcitrant insolubility of **1** forced us to acquire NMR spectra in d_5-pyridine.

^{13}C resonances are typically less solvent dependent than those for protons, and occur over a wide spectral range;[87,88] thus, comparison of the ^{13}C NMR spectrum of **1** with that of the natural product (Figure 1) is more useful than comparing ^{1}H NMR resonances, though the latter is included for completeness (Table 2). To estimate the effect of the solvent on the NMR chemical shifts of **1**, chrysazin (**2**) was used as a comparator. Indeed the ^{13}C resonances of chrysazin in d_5-pyridine and in d_6-DMSO[11] were very similar, having a mean absolute difference of 0.3 ppm, and a maximum difference of 0.7 ppm (Table S1).

The ^{13}C NMR spectroscopic data obtained for **1** vary significantly from those reported for eucapsitrione, with the majority of the resonances differing by >0.7 ppm (the maximum

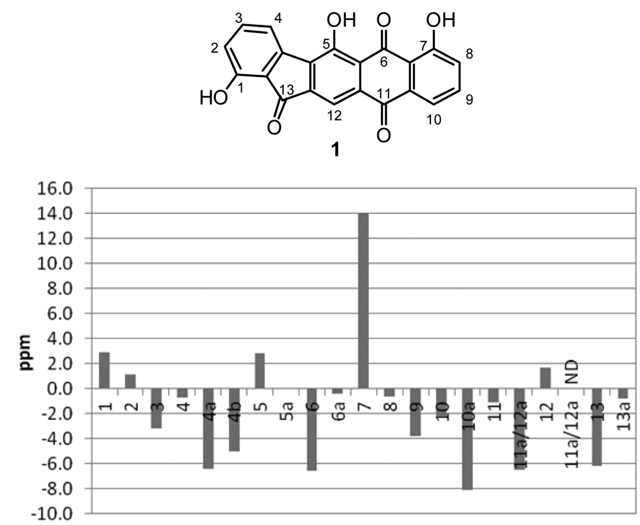


Figure 1. ^{13}C NMR chemical shift differences between eucapsitrione (d_6-DMSO)[1] and synthetic **1** (d_5-pyridine). The mean $|\Delta\delta|$ is 3.7 ppm, and the maximum is 14.0 ppm. A ^{13}C NMR resonance of C11a or C12a in **1** could not be experimentally observed (ND = no data); it is likely obscured by the solvent peak at 136.5–135.5 ppm based upon ^{13}C NMR chemical shift predictions (see Table S2 and Experimental Section for **1**) and so was excluded from these shift difference calculations.

solvent-dependent difference observed with chrysazin) (Table S1), and a number even deviating by >5 ppm (Figure 1). As predicted, **1** does not give rise to a resonance close to 177.2 ppm, the signal in the ^{13}C NMR spectrum of eucapsitrione that raised our suspicions about the assigned structure of the natural product.

Although less meaningful, comparison of the ^{1}H NMR data (Table 2) did reveal a particularly significant discrepancy. The distinctive singlet at 8.34 ppm, arising from H12, peri to two carbonyl groups in **1**, is reported to appear much further upfield at 7.15 ppm in eucapsitrione.[1]

In contrast to the NMR spectroscopic data, the infrared spectra are directly comparable, and the spectrum of synthetic **1** shows considerable disparity with that of eucapsitrione (Table 2). As predicted, **1** gives rise to three distinct carbonyl absorption bands. The absorptions at 1669 and 1628 cm^{-1} are, respectively, characteristic of the free and hydrogen-bonded carbonyl groups

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Table 2. ^{1}H NMR and IR Spectroscopic Data for 1 versus Those Reported for Eucapsitrione[1]

^{1}H NMR (ppm)			IR (ν_{max} cm^{-1})[a]	
1 (d_5-pyr)[b,c]	**1** ($CDCl_3$)[b]	eucapsitrione[1] (d_6-DMSO)[d]	**1**	eucapsitrione[1]
	12.48 (s, OH)[e]	13.99 (s, OH)	3380	
	11.95 (s, OH)[e]	13.28 (s, OH)	1696	
	8.39 (s, OH)[e]		1669	
8.34 (s)	8.16 (s)	7.60 (t)	1628	1616
7.91 (dd)	7.89 (dd)	7.56 (m)		1559
7.78 (d)	7.75 (dd)	7.56 (m)		1457
7.67 (app. t)	7.60 (dd)	7.52 (dd)		1372
7.51 (dd)	7.49 (dd)	7.15 (s)		1331
7.39 (d)	7.35 (dd)	7.14 (dd)		1273
7.13 (d)	6.88 (dd)	7.12 (dd)		1210
		6.59 (s, OH)		1152

[a]Neat, ATR. [b]500 MHz. [c]Exchangeable protons were not observed due to the exchange with residual D_2O.[89] [d]600 MHz. [e]Confirmed by a deuterium exchange experiment.

of an α-hydroxyanthraquinone.[12,13] The remaining peak at 1696 cm^{-1} is therefore attributed to the fluorenone carbonyl group. The lack of an absorption band at this frequency in the IR spectrum of eucapsitrione suggests that it is not a fluorenone.

Though the discrepancies between their physical and spectroscopic properties are already strong evidence that eucapsitrione does not possess structure **1**, the inability to directly compare the NMR spectroscopic data is rather unsatisfying. Accordingly, the ^{13}C NMR frequencies for **1** in DMSO solution were calculated.

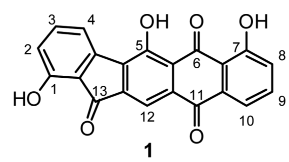
To determine a suitable computational methodology to apply to **1**, chrysazin (**2**) reprized its role as a standard, as the experimental ^{13}C NMR spectrum could be compared with calculated frequencies (Table 3). Several methodology and basis set combinations were employed for these calculations, of which HF 6-31G* proved to be the most accurate for chrysazin (**2**), giving a mean absolute difference between calculated and experimental ^{13}C shifts of 2.9 ppm, and a maximum difference of 7.0 ppm.

Table 3. Comparison of Experimental and Calculated ^{13}C NMR Chemical Shifts for Chrysazin (2)[a]

δ_{exp} **2**[11] (d_6-DMSO)	δ_{calc} **2** HF/6-31G* (DMSO)	δ_{calc} **2** B3LYP/6-31G*//HF/6-311+G(2d,p) (DMSO)	δ_{calc} **2** B3LYP/6-31G* (DMSO)
192.9	192.7	196.2	186.4
182.2	178.8	194.0	177.4
162.3	160.2	166.8	157.1
162.3	160.2	166.8	157.1
138.3	137.0	144.9	131.9
138.3	137.0	144.9	131.9
134.1	133.3	142.0	128.3
134.1	133.3	142.0	128.3
125.3	120.3	128.9	119.5
125.3	120.3	128.9	119.5
120.2	118.1	126.1	116.3
120.2	118.1	126.1	116.3
116.8	109.8	124.5	112.3
116.8	109.8	124.5	112.3
mean |Δδ|	2.9	6.2	5.3
maximum |Δδ|	7.0	11.8	6.5

[a]All values are in ppm.

Using this basis set, the mean and maximum differences between the ^{13}C NMR chemical shifts calculated for **1** and those reported for eucapsitrione were 5.3 and 18.9 ppm, respectively (Figure 2; see also Table S2 for calculations carried out using alternative methodology and basis set combinations). Notably, HF 6-31G* most poorly predicted the shift of the most upfield ^{13}C-resonances in chrysazin, while for eucapsitrione, the significantly larger maximum shift difference again arose from the carbon resonating at 177.2 ppm.



1

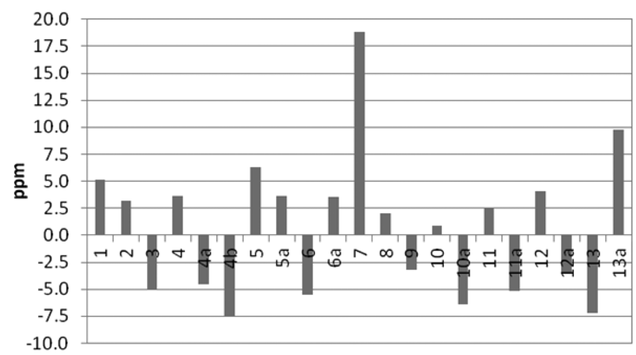


Figure 2. ^{13}C NMR chemical shift differences between eucapsitrione (d_6-DMSO)[1] and the calculated shifts for **1** in DMSO (HF 6-31G*). The mean |Δδ| is 5.3 ppm, and the maximum is 18.9 ppm.

CONCLUSION

In conclusion, 1,5,7-trihydroxy-6*H*-indeno[1,2-*b*]anthracene-6,11,13-trione (**1**) has been synthesized in 43% overall yield, and six steps, from the known boronic acid **9c** and iodide **3** (eight steps from commercially available starting materials). The physical characteristics and spectroscopic data for **1** do not match those reported for the natural product eucapsitrione. Unfortunately, we believe the existing, published spectra of eucapsitrione do not permit a reassignment of structure, partly because of uncertainty about whether spurious peaks in the NMR spectra arise from the natural product or significant impurities.

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Given the promising biological activity of the eucapsitrione, another isolation and reinvestigation of its structure is warranted.

During the course of the synthesis of **1**, an unprecedented direct arylation reaction was observed, in which a borono group appears to act as a traceless ortho-activator. At this stage, the reaction appears to have rather specific substrate requirements, but with optimization and broadening of scope, this coupling could prove valuable.

■ EXPERIMENTAL SECTION

Materials and Methods. All solvents were distilled prior to use. Anhydrous THF was obtained from a Pure Solv 5-Mid Solvent Purification System (Innovative Technology Inc.). "Dry DMF" and "dry MeCN" refer to a solvent that was stored over activated 3A molecular sieves for at least 24 h.[90] "Dry acetone" refers to acetone that was stirred over anhydrous $CaSO_4$ for 4 h before being distilled under N_2. Tetramethylethylenediamine (TMEDA) and diisopropylamine were dried over and distilled from CaH_2 under N_2 onto KOH pellets and stored as such under N_2.[77,90] Triisopropyl borate was distilled and stored under N_2. The concentrations of solutions of *n*- and *sec*-BuLi were determined by titration with *N*-benzylbenzamide.[91] 1-Hydroxy-8-acetoxy-9,10-athraquinone was prepared from chrysazin (**2**) by a known method.[18] *N*,*N*-Diethyl-2-methoxybenzamide[92] and *N*,*N*-Diisopropyl-2-methoxybenzamide (**9b**)[93] were prepared by known methods from *o*-anisic acid. Dimethyl 3-hydroxy-6-methyl phthalate[94] was prepared according to a known method. All other reagents and materials were purchased from commercial suppliers and used as received.

All reactions, except for the preparations of 1-hydroxy-8-acetoxy-9,10-anthraquinone and 1-hydroxy-2-iodo-8-acetoxy-9,10-anthraquinone (**3**) were conducted in flame-dried glassware under an atmosphere of N_2 with the use of a syringe and septum-cap techniques. Where indicated, reaction temperatures refer to the temperature of the heating or cooling bath. All organic extracts were dried over $MgSO_4$, filtered, and evaporated under reduced pressure at 40−45 °C. Trace residual solvent was removed under a stream of N_2 or, where indicated, using high vacuum.

Reaction progress was monitored by TLC using Merck aluminum-backed TLC silica gel 60 F_{254} plates, which were also used for preparative TLC. Spots were visualized directly (colored compounds) or by using ultraviolet light. Flash column chromatography was performed using Davisil chromatographic silica media LC60A 40−63 μm.

^{1}H and ^{13}C NMR spectra were acquired using Bruker Avance IIIHD (600 MHz for ^{1}H and 150 MHz for ^{13}C), Bruker Avance IIIHD (500 MHz for ^{1}H and 125 MHz for ^{13}C), and Varian (400 MHz for ^{1}H and 100 MHz for ^{13}C) spectrometers, as indicated. Deuterochloroform ($CDCl_3$) was used as the solvent for NMR samples unless otherwise indicated. Spectra were calibrated against $CHCl_3$ (for ^{1}H spectra; δ 7.26 ppm) or $CDCl_3$ (for ^{13}C spectra; δ 77.16 ppm) peaks. Where d_5-pyridine was used as a solvent, spectra were calibrated against the most upfield peaks of C_5D_4HN (for ^{1}H spectra; δ 7.22 ppm) and C_5D_5N (for ^{13}C spectra; δ 123.90). Where d_6-DMSO was used as a solvent, spectra were calibrated against CD_3SOCD_2H (for ^{1}H spectra; δ 2.50) or $(CD_3)_2SO$ (for ^{13}C spectra; δ 39.52). ^{1}H and ^{13}C NMR assignments were made based upon 2D and NOE NMR experiments, as noted for each assigned compound. Complete atom-numbered structures of each compound synthesized can be found in the Supporting Information.

High resolution mass spectra were recorded on a Waters Liquid Chromatograph Premier mass spectrometer with a time-of-flight mass analyzer, using atmospheric pressure chemical ionization (APCI) in positive or negative mode as indicated. Infrared spectra were recorded on a PerkinElmer Spectrum One FT-IR spectrometer with Attenuated Total Reflectance (ATR) using neat samples. Melting points were determined using a Reichert hot stage melting point apparatus.

Synthesis. *1-Hydroxy-2-iodo-8-acetoxy-9,10-anthraquinone (**3**).*[19] Iodic acid (4.38 g, 24.9 mmol) was added to a stirred mixture of 1-hydroxy-8-acetoxy-9,10-anthraquinone[18] (7.06 g, 25.0 mmol) in water (60 mL) and dioxane (190 mL). Iodine (3.17 g, 12.5 mmol) was added, and the resulting mixture was heated at reflux for 18 h before being cooled to room temperature. The mixture was then poured into water (2 L) and extracted with $CHCl_3$ (3 × 900 mL). The organic extract was washed with 1 M aqueous $Na_2S_2O_3$ solution (500 mL), water (500 mL), and brine (500 mL), dried, and evaporated. The crude solid residue was subjected to flash chromatography. Elution with PhMe gave **3** (2.38 g) as an orange solid. Additionally, impure fractions were recrystallized from PhMe to give **3** as orange needles (2.06 g, total yield 44%), mp 224−226 °C [lit.[19] 222−224 °C]. R_f (PhMe): 0.25. IR (ATR) ν_{max} cm^{-1}: 1765 (OC═O), 1667 (C10═O), 1639 (C9═O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.50 (s, 1H), 8.28 (dd, J = 7.6, 1.2 Hz, 1H), 8.20 (d, J = 8.0 Hz, 1H), 7.84 (dd [app. t], J_1 = J_2 = 8.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.45 (dd, J = 8.0, 1.2 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.8, 181.5, 169.6, 161.4, 150.9, 146.5, 136.1, 135.3, 132.8, 130.6, 126.2, 124.3, 120.5, 116.0, 95.7, 21.3. HRMS (APCI−) *m*/*z*: [M]$^{\bullet-}$ Calcd for $C_{16}H_9IO_5$ 407.9495; found, 407.9510. This compound has been reported previously but only with ^{1}H NMR data provided.[19] The ^{1}H NMR data obtained match those in literature.

*(E)-Methyl 3′-(8-Acetoxy-1-hydroxy-9,10-anthraquinon-2-yl)-acrylate (**4**).* A mixture of iodide **3** (0.410 g, 1.00 mmol) in MeCN (45 mL) was sparged with N_2 before methyl acrylate (0.29 mL, 3.2 mmol), NEt_3 (0.43 mL, 3.1 mmol), and $Pd(OAc)_2$ (45 mg, 0.20 mmol, 20 mol %) were added. The reaction mixture was then stirred at 70 °C under N_2 for 14 h before being cooled to room temperature. The mixture was diluted with CH_2Cl_2 (200 mL), and the solution was washed with brine (3 × 30 mL), vacuum filtered through Celite, dried, and evaporated. The residue was subjected to flash chromatography. Elution with CH_2Cl_2 afforded **5** (77 mg, 24%) identical with the material described below. Further elution with CH_2Cl_2 gave **4** (52 mg, 14%), which crystallized from EtOAc as red prisms, mp 226−230 °C. R_f (CH_2Cl_2): 0.25. IR (ATR) ν_{max} cm^{-1}: 1765 (OC═O), 1716 (C1′═O), 1667 (C10═O), 1633 (C9═O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.39 (s, 1H), 8.28 (dd, J = 7.6, 1.2 Hz, 1H), 8.00 (d, J = 16.4 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.84 (dd [app. t], J_1 = J_2 = 8.0 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.44 (dd, J = 8.0, 1.2 Hz, 1H), 6.77 (d, J = 16.4 Hz, 1H), 3.84 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.4, 181.4, 169.7, 167.3, 161.7, 150.8, 137.7, 136.0, 135.6, 135.4, 133.2, 130.6, 130.1, 126.2, 124.7, 122.4, 119.0, 116.9, 52.1, 21.3. HRMS (APCI−) *m*/*z*: [M]$^{\bullet-}$ Calcd for $C_{20}H_{14}O_7$ 366.0740; found, 366.0735.

*(E)-Methyl 3′-(1,8-Dihydroxy-9,10-anthraquinon-2-yl)acrylate (**5**).* A mixture of iodide **3** (0.404 g, 0.990 mmol) in dry MeCN (60 mL) was sparged with N_2 before NEt_3 (0.43 mL, 3.1 mmol), methyl acrylate (0.29 mL, 3.2 mmol), and $Pd(OAc)_2$ (42 mg, 0.19 mmol, 19 mol %) were added. The resulting mixture was stirred at 70 °C under N_2 for 5 h, then water (3 mL) was added, and stirring was continued at 70 °C 64 h. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (300 mL), and washed with brine (3 × 50 mL). The organic phase was vacuum filtered through Celite, washed with saturated aqueous citric acid (2 × 100 mL) and brine (100 mL), and then dried and evaporated. The residue was dissolved in CH_2Cl_2, filtered through a plug of silica gel, and washed through with CH_2Cl_2, affording **5** (0.308 g, 96%) as an orange solid, mp 215−218 °C. R_f (CH_2Cl_2): 0.45. IR (ATR) ν_{max} cm^{-1}: 1716 (C1′═O), 1668 (C10═O), 1621 (C9═O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.86 (s, 1H), 11.96 (s, 1H), 8.00 (d, J = 16.4 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.844 (dd, J = 7.2, 1.2 Hz, 1H), 7.842 (d, J = 8.0 Hz, 1H), 7.71 (dd, J = 8.4, 7.6 Hz, 1H), 7.32 (dd, J = 8.6, 1.0 Hz, 1H), 6.77 (d, J = 16.0 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 181.3, 167.2, 162.8, 161.5, 137.7, 137.5, 136.0, 134.2, 133.6, 130.0, 125.0, 122.6, 120.4, 119.7, 116.3, 115.9, 52.1. HRMS (APCI−) *m*/*z*: [M]$^{\bullet-}$ Calcd for $C_{18}H_{12}O_6$ 324.0634; found, 324.0635.

*(E)-3′-(1,8-Dihydroxy-9,10-anthraquinon-2-yl)acrylic Acid (**6**).* 4 M NaOH (0.29 mL) was added to a suspension of acrylate **5** (91 mg, 0.28 mmol) in 3:1 dioxane/MeOH (4 mL), and the resulting purple mixture was heated under reflux for 24 h. The reaction mixture was acidified with 1 M HCl (5 mL), forming an orange precipitate, which was collected by vacuum filtration, washed with water (ca. 300 mL), and dried. The aqueous washes were extracted with EtOAc (3 × 60 mL). The extract was dried and evaporated, giving an orange solid, which was combined with the collected precipitate and triturated with boiling CH_2Cl_2 to give **6** (72 mg, 83%) as a dark orange solid, mp 291−293 °C. R_f (1:49 AcOH/CH_2Cl_2) 0.25. IR (ATR) ν_{max} cm^{-1}: 3200−2400 (CO<u>OH</u>), 1684

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(C1′═O), 1662 (C10═O), 1623 (C9═O); ^{1}H NMR (500 MHz, d_6-DMSO) δ 12.43 (br s, 3H, 3 × OH), 8.23 (d, J = 8.0 Hz, 1H, H3), 7.86 (d, J = 16.2 Hz, 1H, H3′), 7.83 (dd, J = 8.2, 7.7 Hz, 1H, H6), 7.72 (dd, J = 7.5, 1.0 Hz, 1H, H5), 7.69 (d, J = 8.0 Hz, 1H, H4), 7.40 (dd, J = 8.4, 1.0 Hz, 1H, H7), 6.79 (d, J = 16.2 Hz, 1H, H2′); ^{13}C NMR (125 MHz, d_6-DMSO) δ 192.1 (C9), 181.1 (C10), 167.3 (C1′), 161.4 (C8), 160.1 (C1), 137.6 (C6), 136.0 (C3′), 135.5 (C3), 133.7 (C4a), 133.3 (C10a), 129.0 (C2), 124.6 (C7), 123.1 (C2′), 119.4 (C5), 118.6 (C4), 116.4 (C9a), 116.0 (C8a). HRMS (APCI−) m/z: $[M]^{\bullet-}$ Calcd for $C_{17}H_{10}O_6$ 310.0477; found, 310.0480. NMR assignments were made with the assistance of COSY, HQSC, and HMBC experiments.

*(2-(Diisopropylcarbamoyl)-3-methoxyphenyl)boronic Acid (**9a**).*[95] A stirred solution of TMEDA (1.30 mL, 8.67 mmol) in anhydrous THF (30 mL) at −78 °C under N_2 was treated with a 0.96 M solution of *sec*-BuLi in cyclohexane (8.60 mL, 8.26 mmol). To this was added a solution of *N*,*N*-diisopropyl-2-methoxybenzamide[93] (1.76 g, 7.50 mmol) in anhydrous THF (15 mL) dropwise over 10 min. The resulting mixture was stirred at −78 °C for 2 h before being treated with B(O*i*-Pr)$_3$ (5.20 mL, 22.5 mmol) and allowed to warm to room temperature overnight. The mixture was cooled and neutralized with saturated NH_4Cl (10 mL), then most of the THF was evaporated. The residue was diluted with water (30 mL), acidified to pH 3−4 with 1 M HCl (ca. 20 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The extract was evaporated, and the residue was dissolved in Et_2O (150 mL) and extracted with 1 M NaOH (3 × 50 mL). The basic extracts were back-extracted with Et_2O (50 mL), then cooled to 0 °C and acidified to pH 3−4 with 5 M HCl (ca. 35 mL), forming a white suspension, which was extracted with CH_2Cl_2 (5 × 50 mL). The extract was dried and evaporated, affording **9a** (1.49 g, 71%) as a white solid, which did not require further purification, mp 233−234 °C [lit.[96] 149−150 °C]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (dd, J = 7.3, 0.8 Hz, 1H), 7.34 (dd, J = 8.0, 7.5 Hz, 1H), 6.97 (dd, J = 8.3, 0.8 Hz, 1H), 5.91 (s, 2H), 3.81 (s, 3H), 3.61 (sept., J = 6.7 Hz, 1H), 3.52 (sept., J = 6.8 Hz, 1H), 1.57 (d, J = 6.5 Hz, 6H), 1.08 (d, J = 7.0 Hz, 6H). The ^{1}H NMR data match those in the literature.[96]

General Procedure for the Suzuki−Miyaura Cross-Couplings. The selected iodide **3** or **10** (1 equiv), boronic acid **9** (or amide in the case of **9b**) (1.3 equiv), K_2CO_3 (4 equiv), and 10 wt % Pd/C (2 mol %) were suspended in water (10 mL/mmol of iodide). The suspension was stirred with heating under reflux under N_2 for 72 h before being cooled to room temperature, acidified with 1 M HCl, diluted with water, and extracted with CH_2Cl_2. The extract was filtered through a pad of Celite, washed with water and brine, dried, and evaporated to give the crude product. Table 1 yields were determined via ^{1}H NMR spectroscopy of the crude product with use of 1,3,5-trimethoxybenzene as the internal standard.

*Suzuki−Miyaura Cross-Coupling of 1-Hydroxy-2-iodo-8-acetoxy-9,10-anthraquinone (**3**) with (2-(Diisopropylcarbamoyl)-3-methoxyphenyl)boronic Acid (**9a**).* The general procedure was used with iodide **3**[19] (1.63 g, 4.00 mmol) and boronic acid **9a**[95] (1.43 g, 5.12 mmol), except that the reaction time was 7 d instead of 72 h. The crude product was subjected to flash chromatography. Elution with 1:199 $MeOH/CH_2Cl_2$ gave a tertiary mixture of **11a**, **12a**, and *N*,*N*-diisopropyl-2-methoxybenzamide (1.69 g, 72% yield of **11a** and **12a** with a 3:1 ratio of **11a**:**12a** by ^{1}H NMR) as an orange solid. A sample of the mixture was subjected to preparative thin-layer chromatography. Development with 2:3 EtOAc/hexanes gave a pure sample of **12a**; the sample of **11a** still contained *N*,*N*-diisopropyl-2-methoxybenzamide, which was removed by crystallization from 1:1 EtOAc/EtOH.

*2′-(1,8-Dihydroxy-9,10-anthraquinon-2-yl)-N,N-diisopropyl-6′-methoxybenzamide (**11a**).* Yellow-orange solid, mp 263−264 °C. R_f (2:3 EtOAc/hexanes): 0.5. IR (ATR) ν_{max} cm^{-1}: 1671 (C10═O), 1623 (C9═O, NC═O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.55 (s, 1H), 12.04 (s, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.87 (dd, J = 7.5, 1.0 Hz, 1H), 7.86 (d, J = 7.5 Hz, 1H), 7.71 (dd [app. t], $J_1 = J_2$ = 8.0 Hz, 1H), 7.39 (dd [app. t], $J_1 = J_2$ = 8.0 Hz, 1H), 7.32 (dd, J = 8.5, 1.0 Hz, 1H), 7.07 (dd, J = 7.8, 0.8 Hz, 1H), 6.97 (dd, J = 8.3, 0.8 Hz, 1H), 3.87 (s, 3H), 3.70 (sept., J = 6.7 Hz, 1H), 3.22 (sept., J = 6.8 Hz, 1H), 1.48 (d, J = 7.0 Hz, 3H), 1.03 (d, J = 7.0 Hz, 3H), 1.02 (d, J = 7.0 Hz, 3H), 0.70 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.4, 181.6, 166.6, 162.8, 160.3, 156.0, 140.3, 137.5, 135.1, 133.9, 133.0, 132.9, 128.4, 128.2, 124.8, 123.0, 120.3, 119.6, 116.1, 115.6, 110.9, 55.9, 51.0, 45.7, 21.0, 20.6, 20.3. HRMS (APCI−) m/z: $[M]^{\bullet-}$ Calcd for $C_{28}H_{27}NO_6$ 473.1838; found, 473.1848.

*5′-(1,8-Dihydroxy-9,10-anthraquinon-2-yl)-N,N-diisopropyl-2′-methoxybenzamide (**12a**).* Red-orange solid, mp 222−223 °C. R_f (2:3 EtOAc/hexanes): 0.4. IR (ATR) ν_{max} cm^{-1}: 1731, 1666 (C10═O), 1621 (C9═O), 1606 (NC═O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.79 (s, 1H), 12.07 (s, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.86 (dd, J = 7.5, 1.0 Hz, 1H), 7.76 (d, J = 7.5 Hz, 1H), 7.72 (dd, J = 8.5, 7.5 Hz, 1H), 7.67 (dd, J = 8.5, 2.5 Hz, 1H), 7.46 (d, J = 2.5 Hz, 1H), 7.33 (dd, J = 8.5, 1.0 Hz, 1H), 7.00 (d, J = 8.5 Hz, 1H), 3.89 (s, 3H), 3.80 (sept., J = 6.7 Hz, 1H), 3.53 (sept., J = 6.7 Hz, 1H), 1.58 (d, J = 6.5 Hz, 3H), 1.56 (d, J = 7.0 Hz, 3H), 1.19 (d, J = 6.5 Hz, 3H), 1.09 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.7, 181.6, 168.1, 162.8, 160.2, 155.5, 137.6, 137.5, 136.6, 133.9, 132.3, 130.6, 128.8, 128.4, 128.1, 124.8, 120.4, 120.2, 116.2, 116.1, 110.8, 55.8, 51.2, 46.0, 20.93, 20.90, 20.7, 20.6. HRMS (APCI−) m/z: $[M]^{\bullet-}$ Calcd for $C_{28}H_{27}NO_6$ 473.1838; found, 473.1841.

*5′-(1,8-Dihydroxy-9,10-anthraquinon-2-yl)-N-isopropyl-2′-methoxybenzamide (**13**).* A tertiary mixture of biaryl amides **11**, **12**, and *N*,*N*-diisopropyl-2-methoxybenzamide was finely divided and then washed with cold 1:1 EtOH/EtOAc, giving a binary mixture of **11** and **12**. This mixture (92 mg, 0.19 mmol, containing 0.078 mmol of **12** by ^{1}H NMR spectroscopy) was treated with conc. H_2SO_4 (2 mL), forming a dark purple mixture. After stirring at 80 °C for 24 h, the resulting mixture was cooled to room temperature, poured into ice/water (40 mL), and extracted with CH_2Cl_2 (5 × 25 mL). The combined extracts were washed with water (30 mL), dried, and evaporated to give an orange solid, which was subjected to flash chromatography. Elution with 3:7 EtOAc/hexanes afforded **13** (11 mg, 33%) as a red-orange solid, mp 232−234 °C. R_f (3:7 EtOAc/hexanes): 0.3. IR (ATR) ν_{max} cm^{-1}: 3331 (N−H), 1664 (C10═O), 1619 (C9═O, NC═O); ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.76 (s, 1H, OH1), 12.06 (s, 1H, OH8), 8.46 (d, J = 2.4 Hz, 1H, H6′), 7.90 (d, J = 7.8 Hz, 1H, H4), 7.86 (dd, J = 7.2, 1.2 Hz, 1H, H5), 7.83 (dd, J = 8.4, 2.4 Hz, 1H, H4′), 7.80 (d, J = 7.8 Hz, 1H, H3), 7.70 (dd, J = 8.4, 7.8 Hz, 1H, H6), 7.69 (br d, J = 7.8 Hz, 1H, N−H), 7.31 (dd, J = 8.4, 0.6 Hz, 1H, H7), 7.08 (d, J = 9.0 Hz, 1H, H3′), 4.31 (m [pseudo oct], J = 6.8 Hz, 1H, NCH), 4.03 (s, 3H, OCH_3), 1.28 (d, J = 6.6 Hz, 6H, 2 × CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.6 (C9), 181.6 (C10), 164.0 (NC = O), 162.7 (C8), 160.2 (C1), 157.6 (C2′), 137.7 (C3), 137.5 (C6), 136.2 (C2), 133.9 (C10a), 133.6 (C4′), 133.3 (C6′), 132.5 (C4a), 129.0 (C5′), 124.7 (C7), 122.2 (C1′), 120.3 (C4), 120.2 (C5), 116.2 (C8a or C9a), 116.1 (C8a or C9a), 111.5 (C3′), 56.3 (OCH_3), 41.8 (NCH), 23.0 (2 × CH_3). HRMS (APCI−) m/z: $[M]^{\bullet-}$ Calcd for $C_{25}H_{21}NO_6$ 431.1369; found, 431.1379. NMR assignments were made with the assistance of COSY, HSQC, HMBC, and NOESY experiments.

Further elution with 1:99 $MeOH/CH_2Cl_2$ afforded 5′-(1,8-dihydroxy-9,10-anthraquinon-2-yl)-2′-methoxybenzamide (**14**) (6.5 mg, 21%) as a red-orange solid, mp 288−290 °C. R_f (1:49 $MeOH/CH_2Cl_2$): 0.2. IR (ATR) ν_{max} cm^{-1}: 3442 (N−H), 3168, 1686 (C═O), 1674 (C═O), 1620 (C9═O); ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.79 (s, 1H, OH), 12.07 (s, 1H, OH), 8.49 (d, J = 2.4 Hz, 1H, H6′), 7.92 (d, J = 7.8 Hz, 1H, H3 or H4), 7.90 (dd, J = 8.4, 2.4 Hz, 1H, H4′), 7.88 (dd, J = 7.5, 0.9 Hz, 1H, H5), 7.81 (d, J = 7.8 Hz, 1H, H3 or H4), 7.74 (br s, 1H, NH), 7.71 (dd, J = 8.4, 7.8 Hz, 1H, H6), 7.32 (dd, J = 8.4, 0.6 Hz, 1H, H7), 7.13 (d, J = 9.0 Hz, 1H, H3′), 5.79 (br s, 1H, NH), 4.06 (s, 3H, OCH_3); ^{1}H NMR (600 MHz, d_5-pyridine) δ 9.03 (d, J = 2.4 Hz, 1H, H6′), 8.62 (br s, 1H, NH), 8.32 (br s, 1H, NH), 7.99 (d, J = 7.8 Hz, 1H, H4), 7.97 (dd, J = 9.0, 2.4 Hz, 1H, H4′), 7.95 (d, J = 7.2 Hz, 1H, H5), 7.80 (d, J = 7.8 Hz, 1H, H3), 7.66 (dd, J = 8.4, 7.8 Hz, 1H, H6), 7.39 (d, J = 8.4 Hz, 1H, H7), 7.19 (d, J = 9.0 Hz, 1H, H3′), 3.85(s, 3H, OCH_3); ^{13}C NMR (150 MHz, d_5-pyridine) δ 193.8 (C9), 181.9 (C10), 167.4 (NC═O), 163.1 (C8), 160.6 (C1), 158.7 (C1′), 138.1 (C3 or C6), 138.0 (C3 or C6), 136.6 (C2), 134.6 (C10a), 134.5 (C4′), 134.1 (C6′), 133.1 (C4a), 129.4 (C5′), 125.1 (C7), 123.7 (this chemical shift is reported based upon the observed correlation to H3′ in the HMBC spectrum, as the signal was obscured by solvent in the ^{13}C NMR spectrum) (C1′), 120.4 (C4), 120.3 (C5), 117.0 (C8a or C9a), 116.9 (C8a or C9a), 112.6 (C3′), 56.5 (OCH_3). HRMS (APCI−) m/z: $[M]^{\bullet-}$ Calcd for $C_{22}H_{15}NO_6$ 389.0899; found, 389.0898. NMR assignments

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were made with the assistance of COSY, HSQC, and HMBC experiments.

*1,8-Dihydroxy-2-iodo-9,10-anthraquinone (**10a**).* Conc. H_2SO_4 (80 mL) was added to 1-hydroxy-8-acetoxy-2-iodo-9,10-anthraquinone (**3**)[19] (2.05 g, 5.02 mmol), and the resulting mixture was stirred for 45 min. The mixture was poured into ice−water (400 mL) and extracted with $CHCl_3$ (3 × 250 mL). The extract was dried and evaporated affording **10a** as an orange solid (1.82 g, 99%), which crystallized from EtOAc as orange needles, mp 200−202 °C. R_f (PhMe): 0.65. IR (ATR) ν_{max} cm^{-1}: 1660 (C10 C═O), 1620 (C9 C═O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.97 (s, 1H, OH), 11.91 (s, 1H, OH), 8.22 (d, *J* = 8.0 Hz, 1H), 7.84 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.71 (dd, *J* = 8.4, 7.6 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H, H3), 7.33 (dd, *J* = 8.4, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 181.4, 162.9, 161.2, 147.0, 137.9, 133.7, 133.6, 125.1, 121.1, 120.4, 115.6, 115.4, 95.3. HRMS (APCI−) *m*/*z*: [M]$^{•-}$ Calcd for $C_{14}H_7IO_4$ 365.9389; found, 365.9376.

*1-Methoxy-2-iodo-8-acetoxy-9,10-anthraquinone (**10b**).* A mixture of 1-hydroxy-2-iodo-8-acetoxy-9,10-anthraquinone (**3**)[19] (0.15 g, 0.37 mmol) and K_2CO_3 were suspended in dry acetone (8 mL). MeOTs (0.24 mL, 1.6 mmol) was then added, and the mixture was heated under reflux under N_2 with stirring for 12 h. Additional dry acetone (2 mL) and MeOTs (0.24 mL, 1.6 mmol) were added, and the mixture was stirred with heating under reflux for a further 24 h. The reaction mixture was cooled to room temperature, filtered, and concentrated under reduced pressure, and the residue was dissolved in CH_2Cl_2 (20 mL). The organic phase was washed with 1 M HCl (3 × 5 mL), water (5 mL), and brine (5 mL), dried, and evaporated. The residue was subjected to flash chromatography. Elution with CH_2Cl_2 gave **10b** (0.11 g, 69%) as a yellow solid, mp 170−173 °C. R_f (CH_2Cl_2): 0.4. IR (ATR) ν_{max} cm^{-1}: 1752 (OC═O), 1668 (C9═O, C10═O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.0 Hz, 1H, H3), 8.19 (dd, *J* = 8.0, 1.2 Hz, 1H, H5), 7.79 (d, *J* = 8.0 Hz, 1H, H4), 7.76 (dd [app. t], *J* = 8.0 Hz, 1H, H6), 7.43 (dd, *J* = 8.0, 1.2 Hz, 1H, H7), 3.92 (s, 3H, OCH_3), 2.49 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.3 (C10), 181.2 (C9), 169.9 (OC═O), 159.8 (C1), 149.9 (C8), 144.7 (C3), 135.1 (C4a), 134.6 (C6), 134.4 (C10a), 130.2 (C7), 126.8 (C9a), 126.2 (C8a), 125.4 (C5), 124.5 (C4), 104.5 (C2), 62.3 (OCH_3), 21.4 (CH_3). HRMS (APCI−) *m*/*z*: [M]$^{•-}$ Calcd for $C_{17}H_{11}IO_5$ 421.9651; found, 421.9643. NMR assignments were made with the assistance of COSY, HSQC, and HMBC experiments.

*1-Methoxy-2-iodo-8-hydroxy-9,10-anthraquinone (**10c**).* Conc. H_2SO_4 (1.5 mL) was added to acetate **10b** (63 mg, 0.15 mmol), and the mixture was stirred for 45 min, then poured into ice/water (15 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The extract was dried and evaporated, giving a yellow-green solid, which was subjected to flash chromatography. Elution with 7:3 PhMe/hexanes afforded **10c** (43 mg, 75%) as a yellow solid, mp 164−166 °C. R_f (7:3 PhMe:hexanes): 0.25. IR (ATR) ν_{max} cm^{-1}: 1672 (C10═O), 1636 (C9═O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.77 (s, 1H, OH), 8.28 (d, *J* = 8.0 Hz, 1H, H3), 7.86 (d, *J* = 8.0 Hz, 1H, H4), 7.80 (dd, *J* = 7.5, 1.0 Hz, 1H, H5), 7.67 (dd, *J* = 8.5, 7.5 Hz, 1H, H6), 7.33 (dd, *J* = 8.5, 1.0 Hz, 1H, H7), 3.98 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.9 (C9), 182.1 (C10), 162.8 (C8), 160.3 (C1), 145.7 (C3), 136.7 (C6), 136.0 (C4a), 132.7 (C10a), 125.6 (C9a), 125.3 (C4), 125.2 (C7), 119.3 (C5), 116.7 (C8a), 105.0 (C2), 62.0 (OCH_3). HRMS (APCI−) *m*/*z*: [M]$^{•-}$ Calcd for $C_{15}H_9IO_4$ 379.9546; found, 379.9556. NMR assignments were made with the assistance of COSY, HSQC, and HMBC experiments.

*(2-(Diethylcarbamoyl)-3-methoxyphenyl)boronic acid (**9c**).*[36] A 0.96 M solution of *sec*-BuLi in cyclohexane (17.0 mL, 16.3 mmol) was added to a solution of TMEDA (2.50 mL, 16.7 mmol) in anhydrous THF (40 mL) at −78 °C under N_2. To this, a solution of *N*,*N*-diethyl-2-methoxybenzamide[92] (3.08 g, 14.8 mmol) in anhydrous THF (20 mL) was added dropwise over 20 min with stirring. The resulting mixture was stirred at −78 °C for 1 h then treated with B(O*i*-Pr)$_3$ (11.5 mL, 49.8 mmol). The reaction mixture was allowed to warm to room temperature, and stirring was continued overnight. The reaction mixture was cooled and neutralized with saturated NH_4Cl (15 mL), and most of the THF was evaporated. The residue was diluted with water (60 mL), acidified to pH 3−4 with 1 M HCl, and extracted with $CHCl_3$ (3 × 100 mL). The extract was evaporated, and the residue was dissolved in Et_2O and extracted with 1 M NaOH (2 × 50 mL). The basic extract was back-extracted with Et_2O (50 mL), then cooled to 0 °C, and acidified with 1 M HCl to pH 3−4. The resulting mixture was extracted with $CHCl_3$ (3 × 100 mL), and the combined extracts were dried and evaporated, affording **9c** as a white solid (1.85 g, 50%), which was used as such without further purification. A sample crystallized from EtOAc/hexanes as colorless microneedles, mp 106−108 °C. IR (ATR) $\nu_{max}$$^{-1}$: 3355 (OH), 1606 (NC═O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 7.0, 1.0 Hz, 1H), 7.37 (dd [app. t], *J* = 8.5, 7.5 Hz, 1H), 6.98 (dd, *J* = 8.0, 1.0 Hz, 1H), 5.97 (s, 2H), 3.82 (s, 3H), 3.61 (q, *J* = 7.0 Hz, 2H), 3.12 (q, *J* = 7.0 Hz, 2H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.02 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 154.6, 130.5, 129.8, 127.7, 113.0, 55.6, 43.4, 39.6, 13.8, 12.8. HRMS (APCI−) *m*/*z*: [M−H]$^-$ Calcd for $C_{12}H_{17}BNO_4$ 250.1251; found, 250.1247. This compound has been reported previously,[36] but the free boronic acid has not been characterized.

*2′-(1,8-Dihydroxy-9,10-anthraquinon-2-yl)-N,N-diethyl-6′-methoxybenzamide (**11c**).* The general procedure was used with iodide **3**[19] (1.63 g, 4.00 mmol), boronic acid **9c**[36] (1.31 g, 5.22 mmol), and 10% Pd/C (125 mg, 3 mol %). The crude product was subjected to flash chromatography. Elution with CH_2Cl_2 gave a binary mixture of **11c** and the byproduct *N*,*N*-diethyl-2-methoxybenzamide as a red gum. The residue was heated under high vacuum to give **11c** (1.46 g, 82%) as an orange solid, mp 212−214 °C. R_f ($CHCl_3$): 0.1. IR (ATR) ν_{max} cm^{-1}: 1669 (C10═O), 1629 (C9═O), 1615 (NC═O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.50 (s, 1H), 12.03 (s, 1H), 7.86 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.84 (AB, *J* = 8.0 Hz, 2H), 7.71 (dd, *J* = 8.4, 7.6 Hz, 1H), 7.42 (dd, *J* = 8.4, 8.0 Hz, 1H), 7.31 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.05 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.00 (dd, *J* = 8.4, 0.8 Hz, 1H), 3.88 (s, 3H), 3.73 (m [pseudo sextet], *J* = 6.8 Hz, 1H), 3.25 (m [pseudo sextet], *J* = 7.0 Hz, 1H), 2.96 (m [pseudo sextet], *J* = 7.0 Hz, 1H), 2.92 (m [pseudo sextet], *J* = 7.1 Hz, 1H), 0.96 (dd [app. t], $J_1 = J_2$ = 7.2 Hz, 3H), 0.75 (dd [app. t], $J_1 = J_2$ = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 181.6, 167.0, 162.8, 160.2, 156.0, 139.6, 137.6, 135.3, 134.1, 133.9, 133.0, 129.1, 126.7, 124.8, 122.9, 120.3, 119.7, 116.1, 115.7, 110.9, 55.8, 42.7, 38.1, 13.7, 12.2. HRMS (APCI−) *m*/*z*: [M]$^{•-}$ Calcd for $C_{26}H_{23}NO_6$ 445.1525; found, 445.1514.

*2′-Hydroxy-N,N-diisopropyl-3-methoxy-[1,1′-biphenyl]-2-carboxamide (**11d**).* The general procedure was used with iodide **10d** (0.113 g, 0.514 mmol) and boronic acid **9a**[95] (0.185 g, 0.663 mmol). The crude product was subjected to flash chromatography. Elution with 1:4 EtOAc/hexanes gave **11d** (85 mg, 51%) as a white powder, mp 189−191 °C. R_f (1:4 EtOAc/hexanes): 0.30. IR (ATR) ν_{max} cm^{-1}: 3400−2900 (OH), 1610 (NC═O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.37 (dd, *J* = 8.3, 7.8 Hz, 1H), 7.24 (ddd, *J* = 8.1, 7.4, 1.9 Hz, 1H), 7.06 (br d, *J* = 7.5 Hz), 7.02 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.92 (dd, *J* = 8.3, 0.8 Hz, 1H), 6.92 (ddd [app. td], *J* = 7.4, 1.3 Hz, 1H), 6.86 (dd, *J* = 7.8, 0.8 Hz), 3.86 (s, 3H), 3.59 (sept, *J* = 6.7 Hz, 1H), 3.28 (sept, *J* = 6.8 Hz, 1H), 1.49 (d, *J* = 6.5 Hz, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.78 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 154.7, 154.3, 137.3, 130.8, 129.9, 129.8, 129.7, 127.3, 123.7, 120.6, 120.2, 109.8, 55.8, 51.5, 46.2, 20.6, 20.5, 20.4, 19.7. HRMS (APCI+) *m*/*z*: [M + H]$^+$ Calcd for $C_{20}H_{26}NO_3^+$ 328.1913; found, 328.1917.

*2-Iodo-4-nitrophenol (**10e**).*[97] I_2 (5.08 g, 20.0 mmol) was dissolved in saturated aqueous KI (200 mL), and the resulting solution was added dropwise to a solution of 4-nitrophenol (2.78 g, 20.0 mmol) in 25% aqueous NH_3 (150 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 4 d. Additional I_2 (1.67 g, 6.58 mmol) in saturated aqueous KI (150 mL) was added dropwise, and the reaction mixture was stirred at room temperature for a further 2 d. A third portion of I_2 (1.02 g, 4.02 mmol) in saturated aqueous KI (40 mL) was added dropwise, followed by fresh 25% aqueous NH_3 (150 mL), and the reaction mixture was stirred for a further 17 d, after which time thin-layer chromatography still showed incomplete consumption of 4-nitrophenol. The reaction mixture was acidified with 6 M HCl to ∼pH 3, and the resulting suspension was extracted with Et_2O (3 × 300 mL). The extract was washed with 0.5 M $Na_2S_2O_3$ (2 × 200 mL), water (200 mL), and brine, and then dried and evaporated. The crude residue was subjected to flash chromatography. Elution with CH_2Cl_2 afforded **10e** (3.86 g, 73%) as a yellow solid, mp 89−91 °C [lit.[98] 85−87]. ^{1}H NMR

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(400 MHz, $CDCl_3$) δ 8.60 (d, J = 2.4 Hz, 1H), 8.18 (dd, J = 9.0, 2.4 Hz, 1H), 7.07 (d, J = 9.2 Hz, 1H), 6.06 (s, 1H). The ^{1}H NMR data match those in the literature.[98]

*Dimethyl 3-Hydroxy-4-iodo-6-methyl phthalate (**10f**).* A mixture of dimethyl 3-hydroxy-6-methyl phthalate[94] (1.11 g, 4.97 mmol), $NaIO_4$ (1.09 g, 5.08 mmol), and NaCl (0.59 g, 10 mmol) was dissolved in 9:1 AcOH/water (20 mL), and KI (0.84 g, 5.06 mmol) was added portionwise. The mixture was stirred at room temperature for 15 min, then sealed, and stirred at 50 °C for 21 h before being cooled to room temperature and poured into water (150 mL). The resulting suspension was extracted with CH_2Cl_2 (3 × 100 mL), and the extract was washed with 0.2 M $Na_2S_2O_3$ (2 × 50 mL), water (2 × 50 mL), and brine (50 mL). The organic phase was dried and evaporated to give **10f** as an off-white solid (1.68 g, 97%) which required no further purification, mp 89−92 °C. R_f (CH_2Cl_2) 0.6. IR (ATR) ν_{max} cm^{-1}: 3136 (OH), 1721 (C8=O), 1678 (C10=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.63 (s, 1H, OH), 7.84 (s, 1H, H5), 3.94 (s, 3H, 3 × H11), 3.89 (s, 3H, 3 × H9), 2.19 (s, 3H, 3 × H7); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1 (C10), 168.9 (C8), 158.6 (C3), 146.6 (C5), 135.3 (C1), 127.7 (C6), 109.1 (C2), 87.1 (C4), 53.5 (C11), 52.6 (C9), 18.2 (C7). HRMS (APCI−): [M−H]$^-$ Calcd for $C_{11}H_{10}IO_5^-$ 348.9578; found, 348.9578. NMR assignments were made with the assistance of HSQC and HMBC experiments.

*2′-(Diisopropylcarbamoyl)-2-hydroxy-3′-methoxy-5-methyl-[1,1′-biphenyl]-3,4-dicarboxylic Acid (**11f**).* The general procedure was used with iodide **10f** (0.175 g, 0.50 mmol) and boronic acid **9a**[95] (0.183 g, 0.66 mmol). Repeated crystallization from Et_2O/CH_2Cl_2/hexanes afforded a pure sample of **11f** as white granules, mp >300 °C. R_f (1:4:45 TFA/MeOH/CH_2Cl_2): 0.25. IR (ATR) ν_{max} cm^{-1}: 3000−2700 (OH), 2700−2250 (OH), 2100−1850, 1672 (C8=O), 1648 (C7=O), 1616 (NC=O); ^{1}H NMR (500 MHz, MeOD) δ 7.46 (d, J = 0.4 Hz, 1H, H6), 7.37 (dd, J = 8.3, 7.8 Hz, 1H, H5′), 7.06 (dd, J = 8.3, 0.8 Hz, 1H,), 7.04 (dd, J = 7.8, 0.8 Hz, 1H,), 3.87 (s, 3H, OCH_3), 3.68 (sept, J = 6.6 Hz, 1H, NCH), 3.34 (sept, J = 6.8 Hz, 1H, NCH), 2.23 (d, J = 0.4 Hz, 3H, 3 × H9), 1.47 (d, J = 6.8 Hz, 3H, CH_3), 1.07 (d, J = 6.8 Hz, 3H, CH_3), 1.02 (d, J = 6.6 Hz, 3H, CH_3), 0.69 (d, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, MeOD), δ 173.0 (C8), 172.7 (C7), 169.7 (C7′), 158.7 (C2), 157.3 (C3′), 139.8 (C6), 137.9 (C4), 135.3 (C1′), 129.7 (C5′), 129.2 (C1 or C3), 128.5 (C2′), 124.9 (C5), 124.7 (C6′), 111.4 (C4′), 110.8 (C1 or C3), 56.2 (C8′), 52.4, 46.9, 21.0, 20.8, 20.3, 20.2, 18.5 (C9). HRMS (APCI−): [M−H]$^-$ Calcd for $C_{23}H_{26}NO_7^-$ 428.1715; found, 428.1725. NMR assignments were made with the assistance of COSY, HSQC, and HMBC experiments.

*2′-(1,8-Dimethoxy-9,10-anthraquinon-2-yl)-N,N-diethyl-6′-methoxybenzamide (**16**).* MeI (3.2 mL, 51 mmol) was added to a mixture of amide **11c** (1.12 g, 2.51 mmol) and K_2CO_3 (6.22 g, 45.0 mmol) in dry DMF (50 mL). The resulting mixture was flushed with N_2, sealed, and stirred at 60 °C for 48 h. The mixture was poured into water (200 mL) and extracted with EtOAc (6 × 100 mL) until the extracts were colorless. The extract was washed with water (8 × 200 mL) and brine (6 × 200 mL), dried, and evaporated. The crude residue was filtered through a plug of silica, alternating washes with hexanes and CH_2Cl_2 until the washes were colorless. Elution with 9:1 CH_2Cl_2/MeOH afforded **16** as a yellow solid (1.09 g, 92%), mp 183−185 °C. R_f (1:49 MeOH/CH_2Cl_2): 0.4. IR (ATR) ν_{max} cm^{-1}: 1673 (C9=O, C10=O), 1624 (NC=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.0 Hz, 1H, H4), 7.86 (dd, J = 7.6, 1.2 Hz, 1H, H5), 7.66 (dd, J = 8.6, 7.8 Hz, 1H, H6), 7.59 (br s, 1H, H3), 7.38 (dd, J = 8.2, 7.8 Hz, 1H, H4′), 7.31 (dd, J = 8.6, 1.0 Hz, 1H, H7), 7.02 (dd, J = 7.8, 0.6 Hz, 1H, H3′), 6.96 (dd, J = 8.6, 1.0 Hz, 1H, H5′), 4.01 (s, 3H, 3 × H3″), 3.86 (s, 3H, 3 × H1″), 3.75 (s, 3H, 3 × H2″), 3.71 (m [pseudo sextet], J = 7.0 Hz, 1H, NCH_2), 3.35 (m [pseudo sextet], J = 7.0 Hz, 1H, NCH_2), 3.10 (br m, 1H, NCH_2), 3.00 (br m, 1H, NCH_2), 1.08 (dd [app. t], J_1 = J_2 = 6.8 Hz, 3H, CH_3), 0.80 (br s, 3H, CH_3); ^{13}C (100 MHz, $CDCl_3$) δ 183.5, 183.0, 167.0, 159.6, 157.9, 155.7, 141.5, 136.0, 135.7 (br, C3), 135.2, 134.3 (C6), 134.2, 129.0 (C4′), 128.4, 126.7, 124.1, 122.9 (C3′), 121.9 (C4), 119.2 (C5), 118.1 (C7), 110.3 (C5′), 62.6 (C2″), 56.7 (C3″), 55.6 (C1″), 42.8, 37.8, 13.6, 12.1. HRMS (APCI−) m/z: [M]$^{\bullet-}$ 473.1841; $C_{28}H_{27}NO_6^{\bullet-}$ Calcd 473.1838. NMR assignments were made with the assistance of COSY, HSQC, and NOESY experiments.

*2′-(1,8,9,10-Tetramethoxyanthracen-2-yl)-N,N-diethyl-6′-methoxy-benzamide (**17**).* Tetra-n-butylammonium chloride hydrate (0.320 g, 1.15 mmol) and anthraquinone **16** (1.12 g, 2.36 mmol) were dissolved in THF (110 mL). The orange solution was treated with a solution of $Na_2S_2O_4$ (2.47 g, 14.2 mmol) in water (20 mL) and stirred for 1 h. A solution of NaOH (2.83 g, 70.8 mmol) in water (20 mL) was added, and the resulting dark red mixture was stirred for 30 min. MeOTs (14.5 mL, 96.1 mmol) was added, and the reaction mixture was stirred under N_2 for 24 h. The resulting yellow mixture was poured into water (300 mL) and extracted with CH_2Cl_2 (3 × 200 mL). The extract was dried and evaporated, and the residue was filtered through a plug of silica, washing with CH_2Cl_2 to remove excess MeOTs, then eluting with EtOAc. The filtrate was evaporated, and the resulting orange film was subjected to high vacuum, affording **17** (1.12 g, 94%) as a yellow foam, mp 88−92 °C. R_f (EtOAc): 0.6. IR (ATR) ν_{max} cm^{-1}: 1621 (NC=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 9.2 Hz, 1H), 7.86 (dd, J = 8.8, 1.2 Hz, 1H), 7.41−7.36 (br m, 1H), 7.39 (dd, J = 8.4, 7.6 Hz, 1H), 7.38 (dd, J = 8.8, 7.6 Hz, 1H), 7.11 (br d, J = 7.2 Hz, 1H), 6.96 (dd, J = 8.4, 0.8 Hz, 1H), 6.80 (d, J = 7.2 Hz, 1H), 4.07 (s, 3H), 4.04 (s, 3H), 3.92 (s, 3H), 3.88 (s, 3H), 3.76 (s, 3H), 3.70 (m [pseudo sextet], J = 6.8 Hz, 1H), 3.49 (br s, 1H), 2.97 (br s, 1H), 2.88 (br m, 1H), 1.06 (dd [app. t], J_1 = J_2 = 6.4 Hz, 3H) 0.56 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 157.4, 155.7 (br), 153.6, 149.9, 148.3, 138.1, 129.6, 129.1 (br), 128.7, 127.6, 127.5, 127.0, 125.8, 123.3, 120.7, 119.6, 117.6, 114.9, 109.7, 104.3, 64.0, 63.2 (br), 62.9, 56.6, 55.6, 42.8, 37.7, 13.8, 12.1. HRMS (APCI+) m/z: [M + H]$^+$ Calcd for $C_{30}H_{34}NO_6^+$ 504.2386; found, 504.2381.

*1,5,6,7,11-Pentamethoxy-13H-indeno[1,2-b]anthracen-13-one (**18**).* A solution of anhydrous i-Pr_2NH (1.03 mL, 7.35 mmol) in anhydrous THF (20 mL) under N_2 was cooled to −50 °C and treated with a 1.2 M solution of n-BuLi in hexanes (5.4 mL, 6.5 mmol). The resulting mixture was stirred for 30 min before a solution of amide **17** (0.531 g, 1.05 mmol) in THF (12 mL) was added dropwise over 10 min, whereupon a deep orange color developed. The reaction mixture was stirred at −50 °C for 2 h, then allowed to slowly warm to room temperature, and stirring was continued for 60 h, before being quenched with saturated NH_4Cl (90 mL) and water (30 mL). The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the extract was dried and evaporated to give **18** as a red gum, which formed a red foam (0.506 g) under high vacuum. Attempts at purification led to the decomposition of **18**, so the ^{1}H NMR data reported are for the crude product. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.86 (dd, J = 8.7, 0.9 Hz, 1H), 7.84 (dd, J = 7.2, 0.6 Hz, 1H), 7.58 (dd, J = 8.4, 7.8 Hz, 1H), 7.44 (dd, J = 8.7, 7.5 Hz, 1H), 6.90 (d, J = 7.8 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 4.091 (s, 3H), 4.089 (s, 3H), 4.04 (s, 3H), 4.03 (s, 3H), 3.98 (s, 3H).

*1,5,7-Trimethoxy-6H-indeno[1,2-b]anthracene-6,11,13-trione (**19**).* Crude fluorenone **18** synthesized as described above from amide **17** (143 mg, 0.283 mmol) was dissolved in 1,4-dioxane (10 mL) and treated with AgO (0.175 g, 1.41 mmol). The resulting mixture was stirred under N_2 for 5 min, then 4 M HNO_3 (3 mL) was added dropwise over 5 min. The resulting dark orange solution was stirred under N_2 for 30 min before being diluted with water (20 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The extract was dried and evaporated, and the residue was subjected to flash chromatography. Elution with 1:199 MeOH/CH_2Cl_2 gave **19** (74 mg, 66% over 2 steps) as an orange solid, mp 277−279 °C. R_f (1:199 MeOH/CH_2Cl_2): 0.25. IR (ATR) ν_{max} cm^{-1}: 1704 (C13=O), 1671 (C6=O, C11=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.87 (dd, J = 7.8, 1.3 Hz, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.69 (dd, J = 8.0, 7.0 Hz, 1H), 7.57 (dd, J = 8.5, 7.5 Hz, 1H), 7.34 (dd, J = 8.5, 1.0 Hz, 1H), 6.96 (d, J = 8.0 Hz, 1H), 4.11 (s, 3H), 4.04 (s, 3H), 4.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.6, 182.9, 182.7, 159.7, 158.7, 155.9, 144.0, 140.7, 139.2, 138.0, 136.4, 135.0, 134.8, 133.6, 123.6, 120.6, 119.5, 118.3, 118.2, 118.1, 114.3, 62.4, 56.8, 56.2. HRMS (APCI−) m/z: [M]$^{\bullet-}$ Calcd for $C_{24}H_{16}O_6$ 400.0947; found, 400.0935.

*1,5,7-Trihydroxy-6H-indeno[1,2-b]anthracene-6,11,13-trione (**1**). Method 1.* Crude fluorenone **18** synthesized as described above from amide **17** (125 mg, 0.248 mmol) was treated with $AlCl_3$ (1.68 g, 12.6 mmol) and nitrobenzene (15 mL). The resulting dark green mixture was stirred at 60 °C under N_2 for 6.5 days before being poured into a mixture of ice (75 g), water (30 mL), and 10 M HCl (45 mL). The resulting mixture was stirred for 3 d before being extracted with Et_2O (3 × 60

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mL). The extract was diluted with hexanes (~200 mL) resulting in a dark red precipitate, which was collected by vacuum filtration, washed with hexanes, and air-dried. The aqueous phase was allowed to stand for 3 d, and the resulting precipitate was collected by vacuum filtration, washed with water, and air-dried. The precipitates were combined and crystallized from pyridine to give **1** as burgundy microcrystals (27 mg, 30%), identical with the product described below.

Method 2. A stirred suspension of fluorenone **19** (73 mg, 0.18 mmol) in glacial AcOH (20 mL) was treated with 48% aq. HBr (15 mL) and then heated under reflux under N_2 for 4.5 days. More glacial AcOH (10 mL) and 48% aq. HBr (7.5 mL) were added, and the mixture was refluxed under N_2 for a further 2.5 days before being cooled to room temperature and poured into water (100 mL). The resulting precipitate was collected by vacuum filtration, washed with water, and air-dried, giving **1** as a dark red solid (59 mg, 91%), mp >295 °C. R_f (1:99 AcOH/CH_2Cl_2): 0.45. IR (ATR) ν_{max} cm^{-1}: 3380 (OH), 1696 (C13═O), 1669 (C11═O), 1628 (C6═O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.48 (s, 1H, OH), 11.95 (s, 1H, OH), 8.39 (br s, 1H, OH1), 8.16 (s, 1H, H12), 7.89 (dd, J = 7.5, 1.5 Hz, 1H, H10), 7.75 (dd, J = 8.5, 7.5 Hz, 1H, H9), 7.60 (dd, J = 7.0, 0.5 Hz, 1H, H4), 7.49 (dd, J = 8.5, 7.0 Hz, 1H, H3), 7.35 (dd, J = 8.3, 1.3 Hz, 1H, H8), 6.88 (dd, J = 8.5, 0.5 Hz, 1H, H2); ^{1}H NMR (500 MHz, d_5-pyridine) δ 8.34 (s, 1H, H12), 7.91 (dd, J = 7.5, 0.5 Hz, 1H, H10), 7.78 (d, J = 7.0 Hz, 1H, H4), 7.67 (dd [app. t], J_1 = J_2 = 8.0 Hz, 1H, H9), 7.51 (dd, J = 8.3, 7.3 Hz, 1H, H3), 7.39 (d, J = 8.0 Hz, 1H, H8), 7.13 (d, J = 8.5 Hz, 1H, H2); ^{13}C NMR (125 MHz, d_5-pyridine) δ 193.7 (C6), 191.0 (C13), 181.3 (C11), 163.2 (C7), 159.0 (C1), 158.3 (C5), 143.6 (C4a), 141.7 (C11a or C12a),[99] (C4b), 134.4 (C10a), 125.2 (C8), 121.7 (C2), 121.6 (C5a), 120.5 (C10), 119.0 (C13a), 118.0 (C4), 116.8 (C6a), 114.5 (C12). HRMS (APCI−) m/z: $[M]^{\bullet-}$ Calcd for $C_{21}H_{10}O_6$ 358.0477; found, 358.0488. NMR assignments were made with the assistance of COSY, HSQC, and HMBC experiments (S53, S54, and S55, respectively).

^{13}C NMR Chemical Shift Calculations. Calculations conducted at the HF 6-31G* level of theory were carried out using the Spartan 08 software package.[100] Those performed at the HF/6-311+G(2d,p), B3LYP/6-31G*, and B3LYP/6-311+G(2d,p) levels of theory were conducted using the Gaussian 09 software package.[101] Where two different levels of theory are noted, the ^{13}C NMR shifts were predicted at the first level of theory, and the structure was optimized at the second. Where only one level of theory is noted, both the structure optimization and ^{13}C NMR chemical shift prediction were conducted using that level of theory. All calculations were conducted with solvation modeled in DMSO. Shifts are reported based on a tetramethylsilane reference calculated at the same level of theory as the structure optimization.

The calculated shifts were sorted in numerical order and then directly compared to the experimentally determined shifts (also sorted in numerical order) for the molecule in question (chrysazin in d_6-DMSO[11] for Table 2, and **1** in d_5-pyridine for Table S2). The mean of the absolute value of the shift differences is reported, along with the absolute value of the largest shift difference at the foot of Table 2, Figure 2, and Table S2. For Table S2, the ^{13}C NMR resonance of C11a or C12a in **1** could not be experimentally observed (see experimental procedures for **1**) and so was excluded from these shift difference calculations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00863.

Additional ^{13}C and ^{1}H NMR data, ^{13}C NMR chemical shift predictions, and ^{1}H and ^{13}C NMR spectra of new and known compounds (PDF)

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Notes

The authors declare no competing financial interest.

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