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Concise Formal Total Synthesis of Hybocarpone and Related Naturally Occurring Naphthazarins

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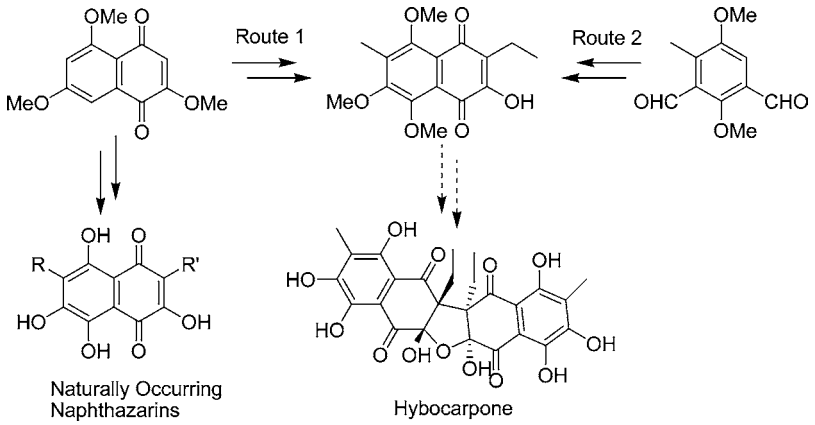

A concise formal total synthesis of the cytotoxic bisnaphthazarin derivative hybocarpone has been completed through the development of routes to the synthetic precursor, 3-ethyl-2-hydroxy-5,7,8-trimethoxy-6-methyl-1,4-naphthoquinone. The oxidation of 3-ethyl-1,2,4,5,7,8-hexamethoxy-6-methylnaphthalene under Rapoport conditions gave 3-ethyl-2-hydroxy-5,7,8-trimethoxy-6-methyl-1,4-naphthoquinone in modest yields after basic hydrolysis. In addition, treatment of 3-ethyl-1,2,4,5,7,8-hexamethoxy-6-methylnaphthalene with boron tribromide provided access to the naturally occurring naphthazarin, boryquinone. The analogous oxidative demethylation of 3,6-dimethyl-1,2,4,5,7,8-hexamethoxynaphthalene and 3-ethyl-1,2,4,5,7,8-hexamethoxynaphthalene resulted in the synthesis of 2,5,7,8-tetrahydroxy-3,6-dimethyl-1,4-naphthoquinone (aureoquinone) and 3-ethyl-2,5,7,8-tetrahydroxy-1,4-naphthoquinone, respectively. An alternative selective synthetic route to 3-ethyl-2-hydroxy-5,7,8-trimethoxy-6-methyl-1,4-naphthoquinone was also developed utilizing an intramolecular Claisen condensation of methyl 2-butyryl-3,5,6-trimethoxy-4-methylphenylacetate with concomitant in situ aerial oxidation.

Introduction

A number of interesting secondary metabolites containing various carboskeletons have been isolated from lichens.[1] The routine screening of lichen cultures for bioactive compounds has facilitated the discovery of new lead compounds with agricultural or therapeutic applications. For instance, compounds isolated from lichens have displayed activity as plant-growth regulators, and the common dibenzofuranoid derivative usnic acid (**1**; Figure 1) has been shown to be particularly active. In addition, the cytotoxicity of usnic acid (**1**) has been well-demonstrated, and it has exhibited antiviral, antiproliferative, anti-inflammatory, and antiprotozoal activity.[2] Polyporic acid (**2**), isolated from the lichen *Pseudocyphellaria colensoi*, has been shown to inhibit the enzyme dihydroorotate dehydrogenase, inhibitors of which have been linked to antitumor and immunomodulating effects.[3] The activity of polyporic acid (**2**) against leukemia L-1210 cells has also been investigated.[4,5] A sulfate of a partially acetylated $\beta(1 \rightarrow 6)$ glucan from the lichen *Umbilicaria esculenta* was shown to inhibit the cytopathic effect

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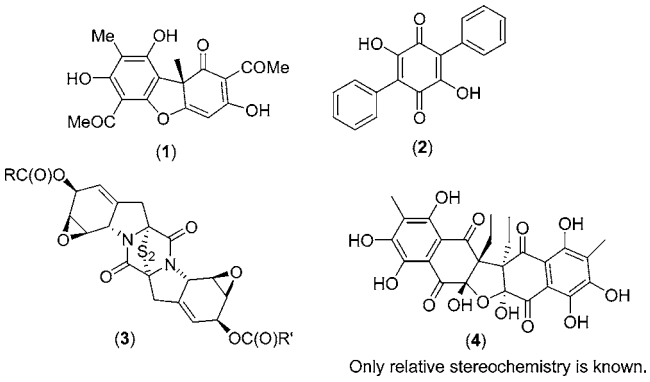

FIGURE 1. Selected bioactive secondary metabolites isolated from lichen sources.

of the HIV virus in vitro,[6] while it has been demonstrated that the scabrosin diesters (**3**), isolated from the lichen *Xanthoparmelia scabrosa*, are potent inhibitors of cellular proliferation.[7]

In 1999, we isolated and identified hybocarpone (**4**), a novel pentacyclic oxido-bridged naphthazarin derivative, from lichen mycobiont cultures of *Lecanora hybocarpa* Tuck.[8] The antiproliferative activity of hybocarpone (**4**) was measured against murine and human cancer cell lines, and the cytotoxicity observed was consistently in the micromolar range. As the exploitation of new lichen metabolites for therapeutic purposes was central to our research interests, hybocarpone (**4**) was regarded as an exciting lead compound. While a number of monomeric and simple dimeric naphthazarins have been isolated from plants, lichen, and marine invertebrates,[9] the dinaphthofurantetraone carbon skeleton of hybocarpone (**4**) is highly unusual and has not been previously observed in nature. Given the potent cytotoxicity of hybocarpone (**4**), we wanted to further investigate its biological properties and ascertain the structural features responsible for the observed bioactivity. A total synthesis of hybocarpone (**4**) would provide access to this unique natural product and allow for further biological studies, given the paucity of material isolated from natural sources.

Nicolaou and Gray have recently reported the only known total synthesis of hybocarpone (**4**) to date.[10,11] The Nicolaou and Gray synthesis of hybocarpone (**4**) involves two key synthetic steps: the formation of the bicyclic core and the oxidative dimerization of the 2-hydroxy-1,4-naphthoquinone precursor (Scheme 1). The construction of the bicyclic framework was initially achieved via a photochemical Diels−Alder reaction of the known 2,4,5-trimethoxy-3,6-dimethylbenzaldehyde (**5**)[12] to access the appropriately functionalized key precursor 3-ethyl-2-hydroxy-5,7,8-trimethoxy-6-methyl-1,4-naphthoquinone (**6**), following functional group installations and interconversions. The next pivotal synthetic sequence involved the oxidative dimerization of naphthoquinone **6** to afford a diastereomeric bisnaphthoquinonoid mixture after a water-mediated ring closure. The diastereomers were subjected to epimerization under acidic conditions, and *O*-methyl ether cleavage gave racemic hybocarpone (**4**).

Our synthetic approaches to naphthoquinone **6** differ significantly from that described by Nicolaou and Gray. This paper details the development and implementation of two alternative synthetic routes to naphthoquinone **6**, which effectively comprise the formal total synthesis of hybocarpone (**4**). In addition, the synthetic pathways developed allow access to various naturally occurring naphthazarins and are readily amenable to the synthesis of structural analogues of hybocarpone (**4**). These results have been previously reported in a communication.[13]

Results and Discussion

Retrosynthetic Analysis. An initial retrosynthetic analysis revealed that naphthoquinone **6** may be derived through the structural elaboration of a bicyclic carbon framework, such as that of the relatively simple 2,5,7-trialkoxy-1,4-naphthoquinone (Scheme 2). The regioselective functionalization of the 2,5,7-trialkoxy-1,4-naphthoquinone may then allow for the synthesis of a symmetrically substituted naphthalene, which would represent the simplest system that contains all of the appropriate oxygen functionality appended to the bicyclic core. The appropriate alkylation and oxidative deprotection of this naphthalene may then give rise to the desired naphthoquinone **6**. Alternatively, a second synthetic route could utilize suitably functionalized benzene derivatives as precursors to naphthoquinone **6**. This approach involves the construction of the bicyclic naphthoquinone system in the final stage of the synthesis via an intramolecular Claisen condensation, followed by in situ aerial oxidation.

Synthesis of Naphthoquinone 6 via Route 1. The development of route 1 required synthetic access to an appropriate 2,5,7-trialkoxy-1,4-naphthoquinone. Numerous methods for the synthesis of the *O*-methyl ether derivative have been previously reported,[14−16] and our studies were based on the high-yield procedure developed by Brassard and Savard.[17] The Diels−Alder reaction of 2,5-dichloro-1,4-benzoquinone with 1,3-dimethoxy-1-trimethylsilylbuta-1,3-diene gave 2-chloro-5-hydroxy-7-methoxy-1,4-naphthoquinone (**7**), which was subsequently *O*-methylated through treatment with silver(I) oxide and methyl iodide to give 2-chloro-5,7-dimethoxy-1,4-naphthoquinone (**8**) in 58% yield (Scheme 3). The *O*-methylation of naphthoquinone **7** necessitated the use of large amounts of expensive silver(I) oxide. In an effort to circumvent the use of silver(I) oxide, naphthoquinone **7** was treated with ethereal diazomethane. *O*-Methylation at the phenolic C5 position of naphthoquinone **7** did not occur under these conditions; however, 5-hydroxy-7-methoxy-1-methyl-1*H*-benzo[*f*]indazole-4,9-dione (**9**) was isolated as the major product. The tricyclic pyrazole derivative **9** presumably results from a 1,3-dipolar cycloaddition reaction between diazomethane and naphthoquinone **7**, with subsequent

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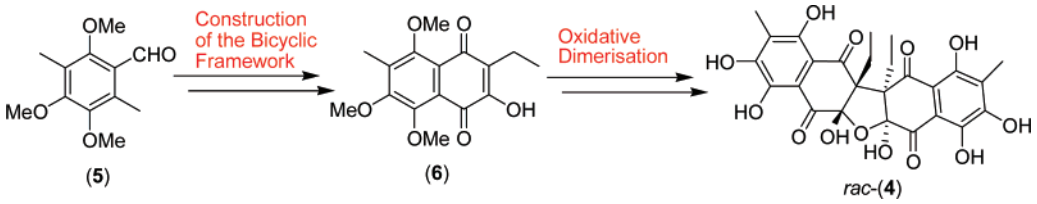
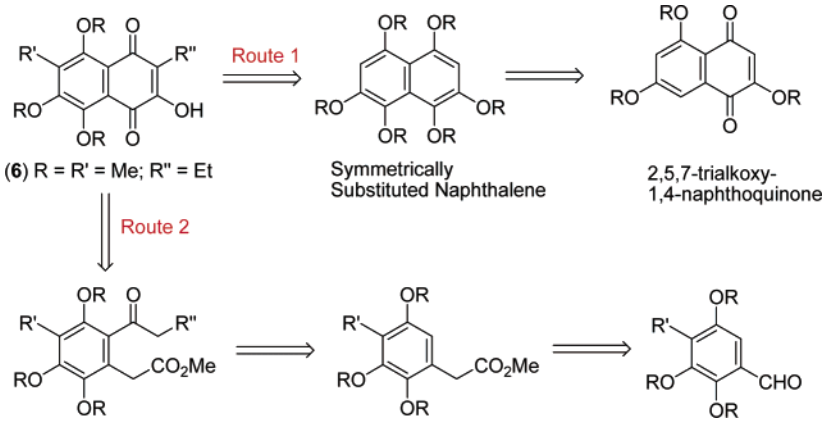
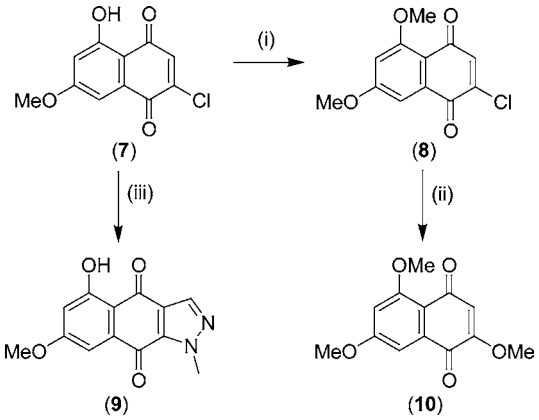
SCHEME 1. Key Features of the Total Synthesis of *rac*-Hybocarpone (4)



SCHEME 2. Retrosynthesis of Naphthoquinone 6



SCHEME 3 [a]



[a] (i) Ag_2O, MeI, $CHCl_3$, 58%; (ii) K_2CO_3, MeOH, 84%; and (iii) CH_2N_2, Et_2O, 80%.

N-methylation. The regioisomeric structure of naphthoquinone **9** was confirmed by X-ray analysis of a single crystal of the corresponding *O*-methyl ether derivative. The conversion of naphthoquinone **8** to 2,5,7-trimethoxy-1,4-naphthoquinone (**10**) was then achieved in 84% yield using anhydrous potassium carbonate in anhydrous methanol (Scheme 3).

Synthesis of Symmetrical Naphthalene 14. Following the successful synthesis of naphthoquinone **10**, the structural elaboration of the bicyclic framework was investigated. The synthesis of the desired symmetrically substituted naphthalene from naphthoquinone **10** required the installation of functionality at the C8 position. As further functionalization would be most readily achieved from a fully aromatic system, naphthoquinone **10** was converted to 1,2,4,5,7-pentamethoxynaphthalene (**11**) in 81% yield using dimethyl sulfate, potassium hydroxide, and sodium dithionite in aqueous THF with tetrabutylammonium bromide as a phase-transfer agent. Alternatively, the reductive methylation of naphthoquinone **10** could be achieved using sodium dithionite with dimethyl sulfate and potassium carbonate in acetone to give naphthalene **11** in comparable yield (Scheme 4).

Following the synthesis of the appropriately *O*-protected naphthalene **11**, attempts were made to functionalize the C8 position. The Vilsmeier−Haack formylation of naphthalene **11** gave the corresponding aromatic 1,2,4,5,7-pentamethoxynaphthalene-8-aldehyde (**12**) in 83% yield when 5 equiv of phosphoryl chloride and 4 equiv of dimethylformamide in anhydrous dichloromethane were used. The definitive requirements for the stoichiometry of the reagents cannot be easily rationalized. The transformation of the newly installed aldehyde functionality into a hydroxyl group, under Baeyer−Villiger conditions, was then sought so as to achieve the desired oxygenation pattern around the naphthalene core. Unfortunately, attempts to oxidize naphthaldehyde **12** with *meta*-chloroperbenzoic acid to give the corresponding formate ester were repeatedly unsuccessful.

Matsumoto et al. reported the synthesis of phenols from aromatic aldehydes in excellent yields using acidic hydrogen peroxide.[18] When aldehyde **12** was treated with hydrogen peroxide in acidic methanol under analogous conditions, 2,5,7,8-tetramethoxy-1,4-naphthoquinone (**13**) was isolated. The spectroscopic and physical data of the naphthoquinone were identical with literature data reported by Natori et al. for naphthoquinone **13**, which they synthesized in low yields through the *O*-methylation of mompain, a naturally occurring naphthazarin.[19] The yields of the hydrogen peroxide oxidation of naphthaldehyde **12** on scales greater than 100 mg were found to be variable. The poor reproducibility of this reaction may be due to inconsistencies in the concentration of hydrogen peroxide and the consequent overoxidation of naphthaldehyde **12**. With naphthoquinone **13** in hand, reductive methylation gave the key symmetrical intermediate 1,2,4,5,7,8-hexamethoxynaphthalene (**14**) in 74% yield (Scheme 4).

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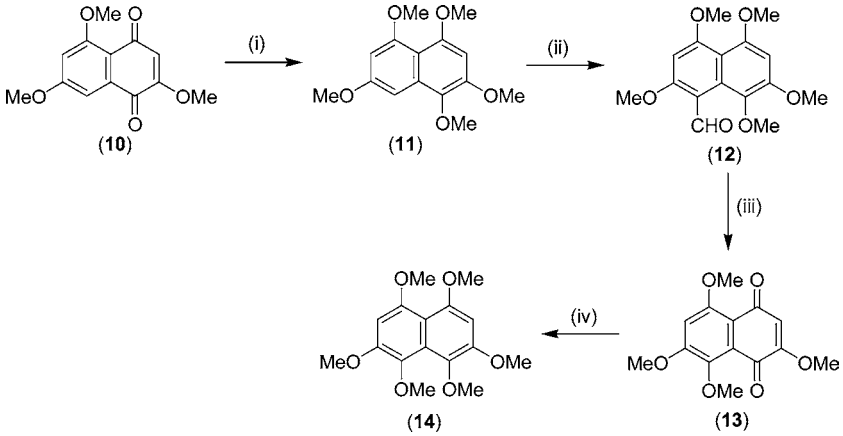
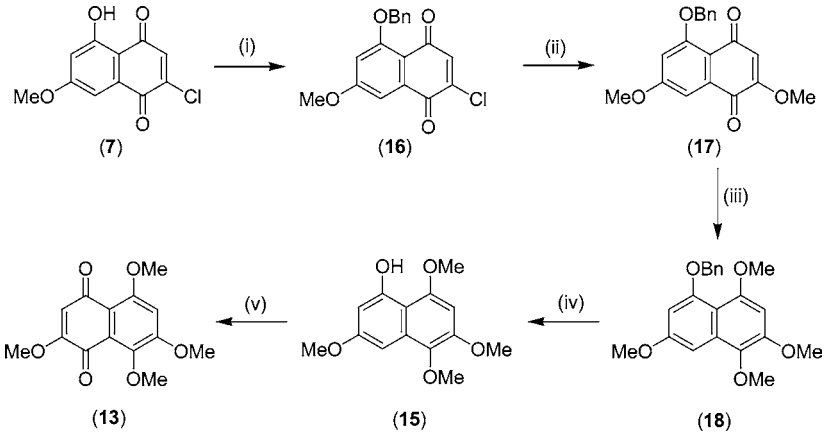
SCHEME 4 [a]



[a] (i) $Na_2S_2O_4$, Me_2SO_4, KOH, NBu_4Br, THF, H_2O, rt, 18 h, 81% or K_2CO_3, Me_2SO_4, $Na_2S_2O_4$, DMF, Me_2CO, reflux, 18 h, 79%; (ii) $POCl_3$, DMF, CH_2Cl_2, then NaOAc, H_2O, 83%; (ii) H_2O_2, H_2SO_4, MeOH, 72%; and (iv) $Na_2S_2O_4$, Me_2SO_4, KOH, NBu_4Br, THF, H_2O, rt, 18 h, 74%.

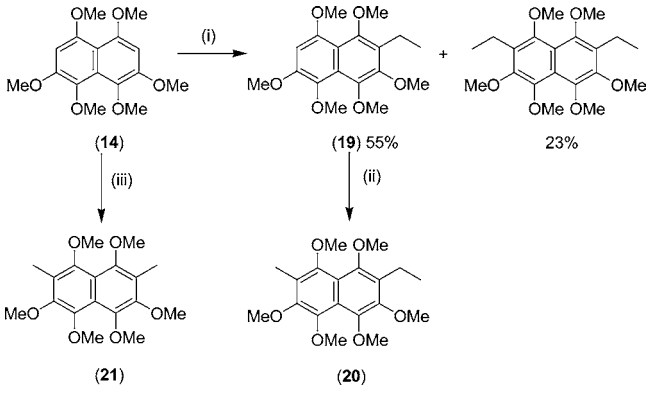
SCHEME 5 [a]



[a] (i) BnBr, Ag_2O, $CHCl_3$, 54%; (ii) K_2CO_3, MeOH, 93%; (iii) $Na_2S_2O_4$, Me_2SO_4, KOH, NBu_4Br, THF, H_2O, rt, 18 h, 56%; (iv) H_2, 10% Pd on C, EtOAc, 80%; and (v) Fremy's salt, MeCN, KH_2PO_4, quantitative.

Alternative Synthesis of Naphthoquinone 13. As naphthoquinone **13** could only be accessed in small quantities, alternative synthetic approaches to this naphthoquinone were explored. It is known that the oxidation of an appropriately substituted naphthol can give rise to the corresponding 1,4-naphthoquinone in good yield. A synthetic route to the appropriately substituted naphthol 5-hydroxy-1,2,4,7-tetramethoxynaphthalene (**15**) was, therefore, designed with the purpose of carrying out an oxidation to afford naphthoquinone **13** (Scheme 5). The first step in this synthetic sequence involved the *O*-benzylation of naphthoquinone **7**, a reaction which proceeded smoothly on treatment with silver(I) oxide and benzyl bromide to give 5-benzyloxy-2-chloro-7-methoxy-1,4-naphthoquinone (**16**) in 54% yield. The treatment of naphthoquinone **16** with potassium carbonate in methanol afforded 5-benzyloxy-2,7-dimethoxy-1,4-naphthoquinone (**17**) with excellent regioselectivity and yield. Naphthoquinone **17** was reductively methylated, and the resultant 5-benzyloxy-1,2,4,7-tetramethoxynaphthalene (**18**) was subjected to hydrogenolysis using 10% palladium on carbon as a catalyst in a hydrogen atmosphere to give naphthol **15** in 80% yield. Oxidation of naphthol **15** with Fremy's salt gave naphthoquinone **13** in quantitative yield (Scheme 5). We have, therefore, successfully developed two viable synthetic routes to naphthoquinone **13**, each comprised of five synthetic steps from naphthoquinone **7**.

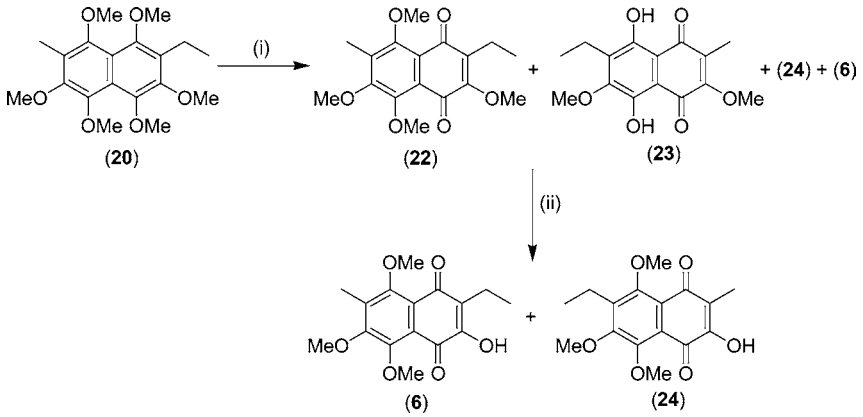
SCHEME 6 [a]



[a] (i) 1.2 equiv *n*-BuLi, 1.2 equiv TMEDA, THF, excess EtI; (ii) 1.2 equiv *n*-BuLi, 1.2 equiv TMEDA, THF, excess MeI, 95%; and (iii) 4.5 equiv *n*-BuLi, 4.5 equiv TMEDA, THF, excess MeI, quantitative.

C Alkylation of the Symmetrical Naphthalene 14. Once synthetic access to naphthalene **14** was achieved, various C-alkylated naphthalenes were identified as appropriate synthetic targets en route to both naphthoquinone **6** and several naturally occurring naphthazarins. Our strategy toward the alkylation of the aromatic naphthalene core involved metalation with an

SCHEME 7 [a]



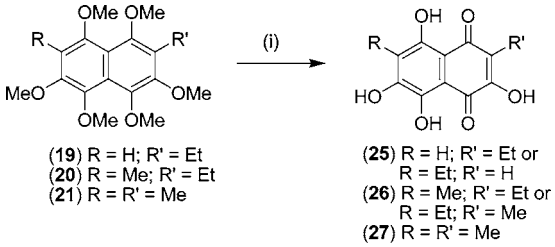
[a] (i) AgO, HNO_3, H_2O, dioxane, sonication, quantitative and (ii) MeOH, 10% NaOH, reflux, 0.5 h, then H_2SO_4, quantitative.

organolithium reagent, followed by the alkylation of the resultant aryllithium with an alkyl halide. Initial attempts to C alkylate naphthalene **14** using a slight excess of *n*-butyllithium and a large excess of ethyl iodide failed to yield any of the desired product, and only starting material was recovered from the reaction mixture. The alkylation was also unsuccessful when other bases such as *tert*-butyllithium and the "superbase" LiCKOR were employed.[20]

The use of basic additives such as tetramethylethylenediamine (TMEDA) to de-aggregate *n*-butyllithium hexamers and, thereby, increase the basicity of *n*-butyllithium is well-documented.[21] When naphthalene **14** was treated with 1.2 equiv of *n*-butyllithium and 1.2 equiv of TMEDA, followed by a large excess of ethyl iodide, 3-ethyl-1,2,4,5,7,8-hexamethoxynaphthalene (**19**) was isolated in 55% yield together with 23% of the dialkylated material and recovered starting material (Scheme 6). The ethylnaphthalene **19** displayed a characteristic proton singlet at 6.62 ppm in the aromatic region of the proton NMR spectrum. Naphthalene **19** can be further C alkylated in excellent yield under comparable reaction conditions using methyl iodide to give the mixed dialkylated 3-ethyl-1,2,4,5,7,8-hexamethoxy-6-methylnaphthalene (**20**). The proton NMR spectrum of naphthalene **20** lacks the aromatic proton signal, and typical C-methyl and C-ethyl resonances were observed. When naphthalene **14** was treated with 4 equiv of *n*-butyllithium and a large excess of methyl iodide, 3,6-dimethyl-1,2,4,5,7,8-hexamethoxynaphthalene (**21**) was isolated in excellent yield.

Although the C-alkylation strategy discussed above was successful and allows for the introduction of the alkyl substituents present in the target compounds, the inherent competition between mono- and dialkylation leads to moderate yields of the desired naphthalene **19** at best. An alternative synthesis of naphthalene **19**, involving the acetylation of the naphthalene core followed by the reduction of the acetyl group to the desired ethyl substituent, was also investigated. In principle, the selective installation of the carbon functionality could be achieved via a Friedel−Crafts acylation of naphthalene **14**, given that multiple acylation is unlikely as a result of the deactivation of the resulting aromatic species to further electrophilic aromatic substitution. Initial attempts to perform a Friedel−Crafts acetylation on the symmetrical naphthalene **14** using acetic anhydride and a catalytic amount of perchloric acid resulted in a complex

SCHEME 8 [a]



[a] (i) BBr_3, CH_2Cl_2, −78°C for 1 h, then 72 h at rt, quantitative.

mixture of products. The use of various acylation conditions and reagents including $AlCl_3$/AcCl, $FeCl_3$/Ac_2O, and I_2/Ac_2O resulted in either complex product mixtures or the recovery of starting material. An alternative approach to C acylation would involve the in situ generation of the appropriate aryl lithio species followed by the reaction of the anion thus formed with a suitable electrophile. When naphthalene **14** was treated with *n*-butyllithium at −78 °C followed by the addition of *N*,*N*-dimethylacetamide, however, a complex mixture of products was obtained. Given the difficulties encountered, the selective installation of C-acetyl functionality on the symmetrical naphthalene **14** was not pursued further.

Synthesis of Naphthoquinone 6 and Naturally Occurring Naphthazarins. The treatment of the naphthalene **20** under the classic Rapoport oxidation conditions,[22] using freshly prepared silver(II) oxide and nitric acid, gave a mixture of four products in overall quantitative yield. These reaction products were identified spectroscopically as the two isomeric naphthoquinones **22** and **23** and the corresponding hydrolysis products naphthoquinones **24** and **6**. Treatment of the product mixture under basic conditions gave an inseparable mixture of the 2-hydroxy naphthoquinones **24** and **6** in a 1:1 ratio in quantitative yield (Scheme 7). Given that naphthoquinone **6** was the key precursor used by Nicolaou and Gray, a nonselective formal synthesis of hybocarpone (**4**) was thereby accomplished.

In principle, *O*-methyl cleavage of the various hexamethoxynaphthalenes could also lead to a number of naturally occurring naphthazarins, depending on the selectivity of the ether cleavage. The alkylated naphthalenes **19**, **20**, and **21** were each treated with boron tribromide over 3 days. Under these conditions, the

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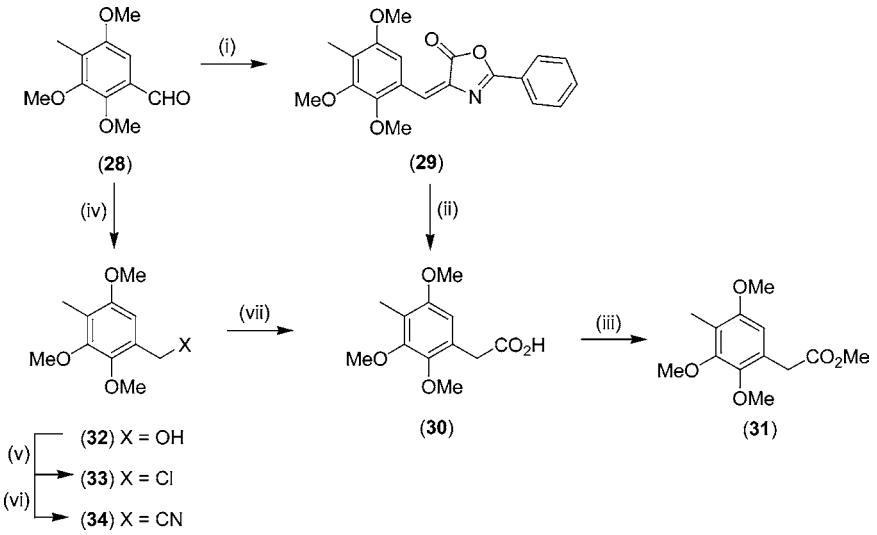
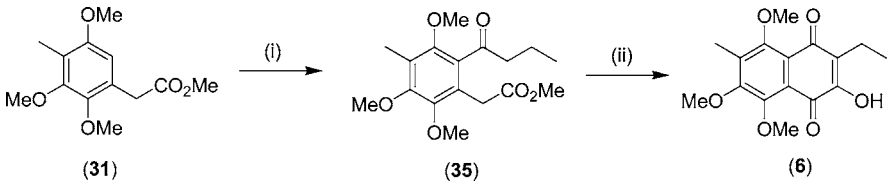
SCHEME 9 [a]



[a] (i) Hippuric acid, Ac_2O, NaOAc, 30%; (ii) 10% NaOH, H_2O_2, 55%; (iii) H_2SO_4, MeOH, 77%; (iv) $NaBH_4$, THF, MeOH, 99%; (v) $SOCl_2$, 96%; (vi) DMSO, KCN, 99%; and (vii) H_2SO_4, AcOH, H_2O, 86%.

SCHEME 10 [a]



[a] (i) Butyric anhydride, $HClO_4$, 85% and (ii) NaOEt, EtOH, air bubbler, 48 h, H_2SO_4, 56%.

methyl ethers were completely cleaved and in situ aerial oxidation ensued to give the deep-purple-red naphthazarins, 3-ethyl-2,7-dihydroxy-1,4-naphthazarin (**25**),[23] 3-ethyl-2,7-dihydroxy-6-methyl-1,4-naphthazarin (**26**),[24] and aureoquinone (**27**),[25] respectively, in quantitative yield (Scheme 8). Two tautomeric forms for each of the isolated naphthazarins are possible, but we were unable to make definitive structural assignments; however, the spectroscopic data were consistent with those reported in the literature for each naphthazarin.[13]

Synthesis of Naphthoquinone 6 via Route 2. As previously outlined, our primary objective was to access synthetic hybocarpone (**4**) for further biological testing, and given that pure naphthoquinone **6** was required, a selective route to naphthoquinone **6** was also developed.

Synthesis of Phenylacetate Derivative 31. The alternative synthesis of naphthoquinone **6** utilized the suitably substituted known 2,3,5-trimethoxy-4-methylbenzaldehyde (**28**)[26] for chain homologation studies. The benzaldehyde **28** was treated with hippuric acid in the presence of acetic anhydride to give azlactone 2-phenyl-4-(2,3,5-trimethoxy-4-methylbenzylidene)-4*H*-oxazol-5-one (**29**) in poor yield. Subsequent hydrolysis and oxidation of azlactone **29** gave 2,3,5-trimethoxy-4-methylphenylacetic acid (**30**), which was then converted into methyl 2,3,5-trimethoxy-4-methylphenylacetate (**31**) through treatment with acidic methanol in 66% yield over the two steps (Scheme 9). Unfortunately, the yields for the azlactone **29** formation were consistently low, and the subsequent rearrangement reaction to phenylacetic acid **30** was not reproducible. This prompted an investigation into an alternative synthesis of the methyl phenylacetate **31**.

An aldehyde can be readily converted into the corresponding aliphatic acid via a one-carbon chain homologation using the cyanide ion as the source of the carbon atom. To examine this approach, it was necessary to reduce benzaldehyde **28** to access the corresponding 2,3,5-trimethoxy-4-methylbenzyl alcohol (**32**). This reduction was achieved in excellent yields using sodium borohydride. The resulting benzyl alcohol **32** was then converted into 2,3,5-trimethoxy-4-methylbenzyl chloride (**33**) through treatment with thionyl chloride. Benzyl chloride **33** was then treated with potassium cyanide to give 2,3,5-trimethoxy-4-methylbenzyl cyanide (**34**), which was subsequently hydrolyzed under acidic conditions to give the corresponding phenylacetic acid **30** in excellent yield. Phenylacetic acid **30** was then esterified under the acidic conditions previously developed to give methyl phenylacetate **31** in good yield (Scheme 9).

Synthesis of Naphthoquinone 6. Treatment of methyl ester **31** with butyric anhydride and perchloric acid gave methyl 2-butyryl-3,5,6-trimethoxy-4-methylphenylacetate (**35**) in good yield. A Claisen condensation reaction was then performed under basic conditions to give naphthoquinone **6** after aerial oxidation and acidic workup (Scheme 10). The spectroscopic data for naphthoquinone **6** were identical to those reported by

(23) Moore, R. E.; Singh, H.; Chang, C. W. J.; Scheuer, P. J. *Tetrahedron* **1967**, *23*, 3271−3305. Moore, R. E.; Singh, H.; Chang, C. W. J.; Scheuer, P. J. *J. Org. Chem.* **1966**, *31*, 3638−3645 and references therein. Moore, R. E.; Singh, H.; Scheuer, P. J. *J. Org. Chem.* **1966**, *31*, 3645−3650.

(24) Huneck, S.; Ahti, T. *Pharmazie* **1982**, *37*, 302.

(25) Berg, A.; Gorls, H.; Dorfelt, H.; Walther, G.; Schlegel, B.; Grafe, U. *J. Antibiot.* **2000**, *53*, 1293−1295.

(26) Kitahara, Y.; Nakahara, S.; Numata, R.; Kubo, A. *Chem. Pharm. Bull.* **1985**, *33*, 2122−2128.

Nicolaou and Gray, and this, therefore, constitutes a selective formal total synthesis of hybocarpone (**4**). In principle, numerous analogues of hybocarpone (**4**) can be accessed by varying the anhydride used to form the aryl ketone. This synthetic step could potentially be utilized to access a number of bisnaphthazarin derivatives.

Conclusion

In conclusion, we have successfully accessed naphthoquinone **6** via two synthetic pathways and thus completed the *formal* total synthesis of the cytotoxic bisnaphthazarin hybocarpone (**4**). Furthermore, our synthetic routes also allowed for the synthesis of a number of naturally occurring monomeric naphthazarins and, in principle, are amenable to the synthesis of structural analogues of hybocarpone (**4**).

Experimental Section

Commercially available reagents were used throughout without further purification, unless otherwise stated. All solvents were AR grade, purified by literature procedures, and stored over freshly activated molecular sieves where appropriate. All reactions were carried out under an atmosphere of dry, oxygen-free nitrogen unless otherwise specified. Reactions that involved moisture-sensitive compounds were carried out using oven-dried apparatus and dry solvents. IR spectra were recorded in the range 4000−800 cm^{-1}. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively; *J* values were recorded in hertz. UV/vis spectra were recorded using spectroscopic grade solvents, and the data are displayed as the λ_{max} wavenumber of the absorption peak in nanometers. Melting points are uncorrected. For general reaction protocols, representative procedures are given.

5-Hydroxy-7-methoxy-1-methyl-1*H*-benzo[*f*]indazole-4,9-dione (9). Diazomethane was prepared according to the procedure described by Furniss et al.[27] using diazald glassware. The use of glassware containing ground glass joints should be avoided when preparing and handling solutions of diazomethane, and the use of a blast shield is recommended. To a solution of potassium hydroxide (0.505 g, 9 mmol) in water (1 mL) was added 96% ethanol (2.5 mL), and the solution was warmed to 60−65 °C. A solution of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (2.165 g, 10 mmol) in diethyl ether (25 mL) was then added dropwise, followed by the addition of diethyl ether (30 mL). The ethereal diazomethane solution thus generated was distilled into a solution of 2-chloro-5,7-dimethoxy-1,4-naphthoquinone (**7**; 200 mg, 0.8 mmol) in diethyl ether (10 mL). The reaction vessel was stoppered with a rubber bung and left to stand overnight at room temperature. The solvent was then allowed to evaporate at atmospheric pressure. The resulting residue was purified by flash column chromatography (R_f 0.30, 50% ethyl acetate/petroleum spirits), and 5-hydroxy-7-methoxy-1-methyl-1*H*-benzo[*f*]indazole-4,9-dione (**9**) was isolated in 80% yield. MS (*m*/*z*): 258 (100%, $M^{+\bullet}$), 229 (6%, $M^{+\bullet}$ − NMe), 215 (21%), 187 (23%), 159 (22%), 132 (21%). HRMS (*m*/*z*, $M^{+\bullet}$): calcd for $C_{14}H_{12}N_2O_4$, 258.0641; found, 258.0645. To a solution of 5-hydroxy-7-methoxy-1-methyl-1*H*-benzo[*f*]indazole-4,9-dione (**9**; 100 mg, 0.4 mmol) in acetone (2 mL) was added dry potassium carbonate (80 mg, 0.6 mmol) with stirring. Methyl iodide (0.2 mL, excess) was added to the reaction mixture, and the solution was heated at reflux overnight. The reaction mixture was concentrated in vacuo, and the residue was partitioned between 5% HCl (25 mL) and dichloromethane (25 mL). The aqueous layer was washed with dichloromethane (2 × 25 mL). The combined organic extracts were dried with magnesium sulfate and filtered, and the solvent was removed under reduced pressure to give the crude *O*-methyl derivative, 5,7-dimethoxy-1-methyl-1*H*-benzo[*f*]indazole-4,9-dione. The resulting residue was purified by flash column chromatography (R_f 0.30, 50% ethyl acetate/petroleum spirits) to give the product in 76% yield as an orange solid; mp 201−202 °C. IR ν_{max} (KBr): 3433 (s), 1681 (m), 1589 (w), 1496 (m), 1427 (w), 1272 (m), 1218 (m), 1157 (m), 1041 (s), 802 (w) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.94 (s, 3H), 3.96 (s, 3H), 4.26 (s, 3H), 6.75 (d, J = 3 Hz, 1H), 7.37 (d, J = 3 Hz, 1H), 7.95 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 39.0, 56.0, 56.5, 104.3, 104.7, 115.5, 125.0, 136.1, 137.1, 137.7, 162.8, 164.3, 175.8, 178.6. MS (*m*/*z*): 272 (100%, $M^{+\bullet}$), 243 (86%, $M^{+\bullet}$ − NMe), 241 (52%), 225 (31%). HRMS (*m*/*z*, $M^{+\bullet}$): calcd for $C_{14}H_{12}N_2O_4$, 272.0797; found, 272.0799. The structural assignment was confirmed by X-ray crystallographic analysis.

1,2,4,5,7-Pentamethoxynaphthalene (11). To a stirred solution of 2,5,7-trimethoxy-1,4-naphthoquinone (**10**;[17] 0.5 g, 2.01 mmol) in THF (50 mL) at 0 °C was added tetrabutylammonium bromide (1.7 g, 5.27 mmol). This was followed by the addition of aqueous sodium dithionite (100 mL, 30% w/v), dimethyl sulfate (23.8 mL, 0.25 mol), and finally, the slow addition of aqueous potassium hydroxide (150 mL, 26% w/v) over a period of 5 min. The reaction mixture was stirred at room temperature for 16 h, followed by the addition of ethyl acetate (100 mL). The aqueous layer was isolated and extracted with ethyl acetate (2 × 100 mL). The organic layers were combined, dried with magnesium sulfate, and filtered, and the solvent was removed under reduced pressure. The resultant crude residue was purified by flash column chromatography on SiO_2 using 25% ethyl acetate/petroleum spirits (R_f 0.3) to give naphthalene **11** in 81% yield as a white solid; mp 118 °C. IR ν_{max} (KBr): 2960 (w), 1625 (s), 1614 (m), 1592 (m), 1473 (w), 1379 (m), 1351 (s), 1262 (s), 1231 (s), 1205 (s), 1044 (s), 819 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.87 (s, 3H), 3.91 (s, 6H), 3.92 (s, 3H), 3.96 (s, 3H), 6.36 (d, J = 3 Hz, 1H), 6.49 (s, 1H), 6.96 (d, J = 3 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 55.2, 56.1, 56.6, 57.0, 60.5, 91.7, 94.6, 97.0, 108.9, 132.8, 135.9, 149.0, 154.3, 158.5, 158.7. MS (*m*/*z*): 278 (56%, $M^{+\bullet}$), 263 (100%, $M^{+\bullet}$ − Me), 235 (37%), 220 (11%), 192 (13%), 148 (22%). HRMS (*m*/*z*, $M^{+\bullet}$): calcd for $C_{15}H_{18}O_5$, 278.1154; found, 278.1150. Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.34; H, 6.54.

1,2,4,5,7-Pentahydroxynaphthalene-8-aldehyde (12). *N*,*N*-Dimethylformamide (7.23 mmol, 0.56 mL) was added dropwise at 0 °C to a stirred solution of freshly distilled phosphoryl chloride (9.44 mmol, 0.88 mL) in dry dichloromethane (40 mL). The solution was stirred for 0.5 h at 0 °C, after which time 1,2,4,5,7-pentamethoxynaphthalene (**11**; 0.5 g, 1.80 mmol) was added, and the reaction mixture was stirred for an additional 0.5 h at 0 °C. The reaction mixture was allowed to warm to room temperature, and stirring was continued for an additional 16 h. The reaction was then quenched by the addition of aqueous sodium acetate (50 mL, 10% w/v). The aqueous layer was extracted exhaustively with ethyl acetate (3 × 50 mL), the combined organic fractions were dried with magnesium sulfate and filtered, and the solvent was removed in vacuo to give the aldehyde **12** as the crude product. The aldehyde **12** was purified by flash column chromatography on SiO_2 using 80% ethyl acetate/petroleum spirits (R_f 0.50) to give the product as a white microcrystalline powder (83%); mp 158−159 °C. IR ν_{max} (KBr): 2936 (w), 2839 (w), 1682 (s), 1585 (s), 1516 (w), 1466 (s), 1400 (m), 1369 (m), 1335 (s), 1277 (m), 1215 (s), 1045 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.55 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 3.91 (s, 6H), 6.36 (s, 1H), 6.47 (s, 1H), 10.41 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 56.1, 56.2, 56.7, 59.8, 91.7, 94.5, 108.3, 112.2, 130.8, 135.5, 150.4, 154.9, 156.4, 160.8, 192.4. MS (*m*/*z*): 306 (85%, $M^{+\bullet}$), 291 (93%, $M^{+\bullet}$ − Me), 275 (100%, $M^{+\bullet}$ − CHO), 263 (27%), 248 (19%), 219 (15%). HRMS (*m*/*z*, $M^{+\bullet}$): calcd for $C_{16}H_{18}O_6$, 306.1103; found, 306.1099. Anal. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 63.02; H, 6.04.

2-Chloro-5-benzyloxy-7-methoxy-1,4-naphthoquinone (16). To a solution of 2-chloro-5-hydroxy-7-methoxy-1,4-naphthoquinone (**7**; 0.85 g, 3.6 mmol) in chloroform (10 mL) was added benzyl

(27) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Longman Scientific and Technical: London, 1989.

bromide (0.85 mL, excess) and silver(I) oxide (3.3 g, 14.2 mmol), and the reaction mixture was stirred at room temperature for 96 h. The suspension was filtered through Celite, and the solvent was removed in vacuo to give the crude product mixture, which was then purified by column chromatography (R_f 0.42, 15% ethyl acetate/petroleum spirits) to give 2-chloro-5-benzyloxy-7-methoxy-1,4-naphthoquinone (**16**) in 54% yield; mp 121.5−123.5 °C. IR ν_{max} (KBr): 3418 (w), 1682 (s), 1645 (s), 1593 (s), 1556 (w), 1454 (w), 1438 (w), 1385 (w), 1328 (s), 1302 (m), 1294 (m), 1276 (s), 1259 (s), 1233 (m), 1203 (m), 1170 (m), 1141 (m), 1090 (w), 1027 (w) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.89 (s, 3H), 5.23 (s, 2H), 6.77 (d, J = 3 Hz, 1H), 7.04 (s, 1H), 7.29 (d, J = 3 Hz, 1H), 7.30−7.55 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 56.0, 70.8, 105.0, 105.9, 114.0, 126.5, 127.9, 128.6, 135.0, 135.6, 138.0, 142.6, 160.8, 164.5, 178.3, 180.4. MS (*m*/*z*): 330 (2%, M$^{+\bullet}$, $C_{18}H_{13}O_4{}^{37}Cl$), 328 (16%, M$^{+\bullet}$, $C_{18}H_{13}O_4{}^{35}Cl$), 272 (31%), 238 (34%), 203 (19%), 175 (7%), 91 (100%). HRMS (*m*/*z*, M$^{+\bullet}$): calcd for $C_{18}H_{13}O_4{}^{37}Cl$, 330.0473; found, 330.0473. HRMS (*m*/*z*, M$^{+\bullet}$): calcd for $C_{18}H_{13}O_4{}^{35}Cl$, 328.0502; found, 328.0500. Anal. Calcd for $C_{18}H_{13}ClO_4$: C, 65.76; H, 3.99. Found: C, 65.33; H, 4.11.

5-Hydroxy-1,2,4,7-tetramethoxynaphthalene (15). To a solution of 1,2,4,7-tetramethoxy-5-benzyloxynaphthalene (**18**; 115 mg, 0.33 mmol) in ethyl acetate (20 mL) was added 10% palladium on carbon (12 mg), and the reaction mixture was stirred at room temperature under a hydrogen atmosphere for 96 h. The resultant suspension was then poured through Celite, and the volume of the filtrate was concentrated under reduced pressure. The crude product was purified chromatographically (R_f 0.19, 15% ethyl acetate/petroleum spirits) to give the desired naphthol **15** in 80% yield; mp 115−116 °C. IR ν_{max} (KBr): 3384 (s), 2935 (m), 1634 (s), 1618 (m), 1452 (m), 1384 (s), 1354 (m), 1274 (m), 1229 (w), 1150 (s), 1122 (m), 1109 (m), 1043 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.86 (s, 3H), 3.88 (s, 3H), 3.96 (s, 3H), 4.01 (s, 3H), 6.41 (d, J = 2 Hz, 1H), 6.43 (s, 1H), 6.88 (d, J = 2 Hz, 1H), 9.21 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 55.3, 56.3, 57.1, 60.6, 91.9, 92.8, 100.2, 106.9, 132.5, 136.9, 148.6, 153.1, 155.9, 159.8. MS (*m*/*z*): 264 (68%, M$^{+\bullet}$), 249 (100%, M$^{+\bullet}$ − Me), 221 (33%, M$^{+\bullet}$ − Me − CO), 206 (14%), 175 (6%), 135 (7%). HRMS (*m*/*z*, M$^{+\bullet}$): calcd for $C_{14}H_{16}O_5$, 264.0998; found, 264.1001. Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.64; H, 6.00.

2,5,7,8-Tetramethoxy-1,4-naphthoquinone (13). Method 1: To a stirred solution of 1,2,4,5,7-pentahydroxynaphthalene-8-aldehyde (**12**; 0.2 g, 0.65 mmol) in methanol (35 mL) was added 30% aqueous hydrogen peroxide (1 mL) and concentrated sulfuric acid (6.5 μL). The reaction mixture was stirred at room temperature for 1.5 h, poured onto cold, aqueous sodium bicarbonate (50 mL, 10% w/v), and immediately extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried with magnesium sulfate and filtered, and the solvent was removed in vacuo to give the deep red naphthoquinone **13**. Recrystallization from ethyl acetate/petroleum spirits then gave naphthoquinone **13** as red needles in 72% yield. Method 2: To a solution of 5-hydroxy-1,2,4,7-tetramethoxynaphthalene (**15**; 26 mg, 0.1 mmol) in acetonitrile (2 mL) was added potassium nitrosodisulfonate (30 mg, 0.11 mmol) and potassium dihydrogen phosphate (15 mg, 0.11 mmol) in water (0.5 mL) with sonication. The reaction mixture was then stirred for 16 h without further sonication at room temperature. The solvent was concentrated in vacuo, and the resultant residue was purified by flash column chromatography (R_f 0.12, 80% ethyl acetate/petroleum spirits) to give naphthoquinone **13** in quantitative yield; mp 162 °C (lit. 169−171 °C).[18] IR ν_{max} (KBr): 3418 (w), 2946 (w), 2848 (w), 1679 (m), 1644 (s), 1627 (s), 1578 (w), 1548 (m), 1471 (m), 1353 (m), 1313 (m), 1259 (s), 1233 (s), 1216 (s), 1177 (m), 1094 (m), 1034 (s), 846 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.80 (s, 3H), 3.84 (s, 3H), 3.95 (s, 3H), 3.96 (s, 3H), 5.96 (s, 1H), 6.75 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 56.1, 56.2, 56.7, 61.2, 102.1, 110.8, 112.5, 125.6, 144.1, 157.4, 158.7, 159.1, 179.6, 183.6. MS (*m*/*z*): 280 (22%, M$^{+\bullet}$ + 2H), 278.0 (100%, M$^{+\bullet}$), 265 (31%), 263 (17%, M$^{+\bullet}$ − Me), 217 (24%), 207 (16%), 189 (11%), 149 (12%). HRMS (*m*/*z*, M$^{+\bullet}$): calcd for $C_{14}H_{14}O_6$, 278.0790; found, 278.0785.

3-Ethyl-1,2,4,5,7,8-hexamethoxynaphthalene (19). To a solution of 1,2,4,5,7,8-hexamethoxynaphthalene (**14**; 0.1 g, 0.32 mmol) in dry THF (2 mL) in a two-necked 10 mL round-bottomed flask was added *n*-butyllithium (0.21 mL, 0.38 mmol) under nitrogen at −78 °C with stirring. TMEDA (0.06 mL, 0.38 mmol) was added to the reaction mixture, and the solution was stirred for 1 h at −78 °C before it was warmed to room temperature. The reaction mixture was then cooled to −78 °C, ethyl iodide (0.1 mL, excess) was added, and the solution was stirred for 1 h at −78 °C, followed by warming to room temperature. The reaction mixture was quenched with water and extracted with ethyl acetate (3 × 10 mL). The organic extracts were combined, dried with magnesium sulfate, and filtered, and the solvent was removed in vacuo to afford the crude monoethylated naphthalene **19**, diethylated naphthalene, and 1,2,4,5,7,8-hexamethoxynaphthalene (**14**) in a 5:4:1 ratio. The compounds were then separated using flash column chromatography with 15% ethyl acetate/petroleum spirits (R_f 0.28, 0.81, and 0.1, respectively). Naphthalene **19** was isolated in 55% yield as a white solid; mp 45 °C. ^{1}H NMR ($CDCl_3$): δ 1.21 (t, J = 7 Hz, 3H), 2.77 (q, J = 7 Hz, 2H), 3.76 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 3.97 (s, 3H), 3.98 (s, 3H), 4.00 (s, 3H), 6.62 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 15.5, 17.9, 56.7, 56.9, 61.1, 61.6, 61.8, 62.5, 95.9, 114.4, 125.1, 128.4, 136.6, 143.3, 149.2, 150.3, 150.9, 152.7. MS (*m*/*z*): 336 (100%, M$^{+\bullet}$), 321 (83%, M$^{+\bullet}$ − Me), 306 (21%, M$^{+\bullet}$ − Et), 289 (40%), 275 (12%), 263 (27%), 233 (11%). HRMS (*m*/*z*, M$^{+\bullet}$): calcd for $C_{18}H_{24}O_6$, 336.1573; found, 336.1570.

3-Ethyl-2,5,7,8-tetrahydroxy-6-methyl-1,4-naphthoquinone (Boryquinone, 26). To a stirred solution of 3-ethyl-1,2,4,5,7-pentamethoxy-6-methylnaphthalene (**20**; 10 mg, 0.03 mmol) in dry dichloromethane (1 mL) was added boron tribromide (1 M in dichloromethane, 0.15 mL) at −78 °C. The reaction mixture was warmed to room temperature and stirred for 48 h, after which time water (2 mL) was added prior to the addition of dichloromethane (5 mL). The organic layer was isolated, and the aqueous layer was extracted with dichloromethane (2 × 5 mL). The organic layers were combined, dried with magnesium sulfate, and filtered, and the solvent was removed in vacuo to afford the deep-red-purple solid; mp 178−181 °C (lit. 180−184 °C).[24] IR ν_{max} (KBr): 3395 (s), 2932 (s), 1735 (s), 1658 (s), 1388 (s), 1303 (s), 1180 (s), 1095 (m), 810 (w) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.14 (t, J = 8 Hz, 3H), 2.14 (s, 3H), 2.67 (q, J = 8 Hz, 2H), 6.66 (s, 1H), 6.68 (s, 1H), 11.74 (s, 1H), 13.47 (s, 1H). MS (*m*/*z*): 264 (100%, M$^{+\bullet}$), 249.0 (15%), 221.0 (52%), 190 (6%), 167 (5%), 137 (10%). HRMS (*m*/*z*, M$^{+\bullet}$): calcd for $C_{13}H_{12}O_6$, 264.06334; found, 264.06335. UV/vis (MeOH): 234, 264, 323, 510, 550 nm.

2-Phenyl-4-(2,3,5-trimethoxy-4-methylbenzylidene)-4*H*-oxazol-5-one (29). A stirred mixture of 2,3,5-trimethoxy-4-methylbenzaldehyde (**28**;[28] 0.5 g, 2.70 mmol), hippuric acid (0.51 g, 2.85 mmol), acetic anhydride (0.82 mL), and anhydrous sodium acetate (0.24 g, 2.90 mmol) was heated at 100 °C for 2 h. The reaction mixture was cooled to room temperature, diluted with ethanol (4 mL), and filtered to give an orange/yellow powder (0.190 g, 0.53 mmol). The solid was purified by recrystallization from ethyl acetate/petroleum spirits to give the desired compound in 30% yield as yellow prisms; mp 153−154 °C. IR ν_{max} (KBr): 3441 (s), 2939 (w), 1790 (m), 1651 (s), 1589 (s), 1458 (w), 1411 (w), 1319 (w), 1280 (s), 1226 (w), 1164 (m), 1110 (s), 1018 (w) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.19 (s, 3H), 3.82 (s, 3H), 3.88 (s, 3H), 3.95 (s, 3H), 7.46−7.62 (m, 3H), 7.69 (s, 1H), 8.06−8.12 (m, 2H), 8.24 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 9.5, 55.6, 60.4, 61.9, 107.6, 124.7, 125.7, 126.5, 127.6, 128.0, 128.9, 132.4, 133.1, 148.6, 151.7, 154.3, 162.7, 167.7. MS (*m*/*z*): 353 (58%, M$^{+\bullet}$), 205 (2%), 167 (3%), 105 (100%), 77 (32%). HRMS (*m*/*z*, M$^{+\bullet}$): calcd for $C_{20}H_{19}NO_5$, 353.1263; found, 353.1266.

2,3,5-Trimethoxy-4-methylbenzyl Alcohol (32). To a solution of 2,3,5-trimethoxy-4-methylbenzaldehyde (**28**;[26] 1.17 g, 5.90 mmol) in dry THF (15 mL) and methanol (4 mL) was added sodium

borohydride (0.06 g, 1.59 mmol) at 0 °C. The solution was stirred for 1.5 h at 0 °C prior to the addition of 5% aqueous hydrochloric acid (50 mL) and ethyl acetate (50 mL). The organic layer was isolated, and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were dried with magnesium sulfate and filtered, and the solvent was removed in vacuo to givea pale oil in 99% yield. IR ν_{max} (KBr): 3392 (s), 2937 (s), 1486 (s), 1463 (s), 1407 (s), 1242 (m), 1130 (s), 1091 (m), 1033 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.10 (s, 3H), 3.77 (s, 3H), 3.79 (s, 3H), 3.82 (s, 3H), 4.64 (s, 2H), 6.58 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 8.7, 55.5, 60.1, 60.7, 60.8, 105.1, 120.0, 131.2, 144.4, 151.4, 154.0. MS (*m*/*z*): 212 (100%, $M^{+\bullet}$), 197 (48%, $M^{+\bullet} - Me$), 182 (23%), 154 (40%), 137 (89%), 122 (15%), 109 (30%). HRMS (*m*/*z*, $M^{+\bullet}$): calcd for $C_{11}H_{16}O_4$, 212.1049; found, 212.1047. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.41; H, 7.54.

2,3,5-Trimethoxy-4-methylbenzyl Chloride (33). A solution of 2,3,5-trimethoxy-4-methylbenzyl alcohol (**32**; 1.24 g, 5.84 mmol) in thionyl chloride (1.36 g, 11.43 mmol) was stirred at room temperature for 1 h. The excess thionyl chloride was removed in vacuo, and the residue was partitioned between ethyl acetate (20 mL) and water (20 mL). The organic layer was separated and washed with brine (20 mL). The organic fraction was then dried with magnesium sulfate and filtered, and the solvent was removed in vacuo. The product was purified by flash column chromatography (R_f 0.42, 15% ethyl acetate/petroleum spirits) to give 2,3,5-trimethoxy-4-methylbenzyl chloride (**33**) as a pale yellow oil in 96% yield. IR ν_{max} (KBr): 2938 (s), 2836 (m), 1486 (s), 1464 (s), 1407 (s), 1336 (m), 1266 (m), 1243 (m), 1132 (s), 1091 (s), 1033 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.11 (s, 3H), 3.79 (s, 3H), 3.80 (s, 3H), 3.87 (s, 3H), 4.62 (s, 2H), 6.59 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 9.0, 41.5, 55.6, 60.2, 61.2, 106.6, 122.0, 128.1, 145.3, 151.9, 154.1. MS (*m*/*z*): 232 (33%, $C_{11}H_5{}^{37}ClO_3$), 230 (100%, $M^{+\bullet}$, $C_{11}H_5{}^{35}ClO_3$), 215 (86%, $M^{+\bullet} - Me$), 195 (27%, $M^{+\bullet} - {}^{35}Cl$), 180 (38%), 165 (9%), 152 (23%). HRMS (*m*/*z*, $M^{+\bullet}$): calcd for $C_{11}H_{15}O_3{}^{37}Cl$, 230.0680; found, 232.0681. HRMS (*m*/*z*, $M^{+\bullet}$): calcd for $C_{11}H_{15}O_3{}^{35}Cl$, 230.0710; found, 230.0713. Anal. Calcd for $C_{11}H_{15}ClO_3$: C, 57.27; H, 6.55. Found: C, 57.26; H, 6.48.

2,3,5-Trimethoxy-4-methylphenylacetic Acid (30). Method 1: A solution of 2-phenyl-4-(2,3,5-trimethoxy-4-methylbenzylidene)-4*H*-oxazol-5-one (**29**; 1.26 g, 3.57 mmol) in 10% sodium hydroxide (7.7 mL) was heated under reflux for 5 h. The reaction mixture was cooled to 0 °C and diluted with ice-cold 10% sodium hydroxide (2 mL). To this was added, with stirring, a 15% hydrogen peroxide solution (1 mL), and the temperature was kept below 15 °C. The reaction mixture was stirred at room temperature overnight and then acidified with concentrated hydrochloric acid. The resultant solution was then extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried with magnesium sulfate and filtered, and the solvent was removed in vacuo to give the crude phenylacetic acid **30**. Method 2: To a solution of 2,3,5-trimethoxy-4-methylbenzyl cyanide (**34**; 1.27 g, 5.74 mmol) in glacial acetic acid (25 mL) was added water (8 mL) and concentrated sulfuric acid (2.5 mL). The reaction mixture was heated to reflux for 22 h and then cooled to room temperature. The mixture was poured onto ice, and the resultant solution was extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were washed with brine (30 mL), dried with magnesium sulfate, and filtered, and the solvent was concentrated under reduced pressure prior to purification via flash column chromatography (R_f 0.46, 25% ethyl acetate/petroleum spirits) to give phenylacetic acid **30** as a colorless oil in 86% yield. IR ν_{max} (KBr): 3456 (w), 2939 (s), 1736 (s), 1597 (s), 1466 (s), 1404 (s), 1319 (m), 1242 (s), 1126 (s), 1087 (m), 1034 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.09 (s, 3H), 3.64 (s, 2H), 3.76 (s, 3H), 3.79 (s, 3H), 3.80 (s, 3H), 6.45 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 9.0, 35.8, 55.8, 60.3, 60.7, 107.3, 120.6, 124.3, 145.3, 151.8, 154.0, 177.8. MS (*m*/*z*): 240 (100%, $M^{+\bullet}$), 225 (90%, $M^{+\bullet} - Me$), 207 (24%), 181 (68%), 137 (38%), 109 (26%). HRMS (*m*/*z*, $M^{+\bullet}$): calcd for $C_{12}H_{16}O_5$, 240.0998; found, 240.1000.

Methyl 2-Butyryl-3,5,6-trimethoxy-4-methylphenylacetate (35). To a solution of methyl 2,3,5-trimethoxy-4-methylphenyl acetate (**31**; 0.92 g, 3.60 mmol) in butyric anhydride (3.5 mL) was added 40% aqueous perchloric acid (0.02 mL) at room temperature. The reaction mixture was stirred for 16 h prior to the slow addition of 5% sodium hydrogen carbonate (10 mL). The solution was extracted with ethyl acetate (3 × 20 mL), the combined organic extracts were dried with magnesium sulfate and filtered, and the solvent was removed under reduced pressure to give the crude product. The residue was then purified using column chromatography (R_f 0.34, 50% ethyl acetate/petroleum spirits) to give the ketone **35** as a colorless oil in 85% yield. IR ν_{max} (KBr): 1740 (s), 1697 (m), 1578 (w), 1458 (m), 1404 (m), 1327 (w), 1261 (m), 1169 (s), 1092 (s), 1018 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.94 (t, J = 7 Hz, 3H), 1.66 (h, J = 7 Hz, 2H), 2.16 (s, 3H), 2.80 (t, J = 7 Hz, 2H), 3.61 (s, 3H), 3.66 (s, 2H), 3.77 (s, 3H), 3.79 (s, 3H), 3.81 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 13.7, 17.1, 31.6, 46.6, 52.0, 60.2, 60.3, 60.4, 62.2, 123.0, 125.3, 132.2, 148.2, 151.6, 152.3, 171.8, 207.4. MS (*m*/*z*): 324 (84%, $M^{+\bullet}$), 288 (42%), 281 (67%), 265 (35%), 254 (92%), 253 (100%), 239 (43%). HRMS (*m*/*z*, $M^{+\bullet}$): calcd for $C_{17}H_{24}O_6$, 324.1573; found, 324.1575.

2-Ethyl-3-hydroxy-5,6,8-trimethoxy-7-methyl-1,4-naphthoquinone (6). Method 1: To a solution of 3,6-diethyl-1,2,4,5,7,8-hexamethoxynaphthalene (**20**; 67 mg, 0.2 mmol) in freshly distilled, dry dioxane (2 mL) was added freshly prepared silver(II) oxide (0.185 g, 0.8 mmol). The reaction mixture was then subjected to sonication for 1 min to give a uniform dispersal of the oxidant. A freshly prepared solution of aqueous 6 N nitric acid (0.2 mL) was added, and the reaction mixture was stirred at room temperature for 2 min. A chloroform/water (8:2 mL) mixture was then added. The organic layer was isolated, washed with further aliquots of water (2 × 5 mL), dried with magnesium sulfate, and filtered, and the solvent was removed in vacuo. The residue was dissolved in methanol (2 mL), and 10% aqueous sodium hydroxide (1 mL) was added. The reaction mixture was stirred at room temperature for 0.5 h, after which time the solution was acidified with 5% hydrochloric acid. The reaction mixture was then extracted with ethyl acetate (3 × 5 mL), the combined organic extracts were dried with magnesium sulfate and filtered, and the solvent was removed under reduced pressure to give an inseparable mixture of naphthoquinone **6** and the regioisomeric 7-ethyl-3-hydroxy-5,6,8-trimethoxy-2-methyl-1,4-naphthoquinone (**24**) in equimolar amounts. Method 2: A solution of ketone **35** (0.40 g, 1.25 mmol) in dry ethanol (7 mL) was added dropwise to a solution of sodium ethoxide, freshly prepared from sodium (0.067 g, 2.91 mmol) in ethanol (7 mL). The reaction mixture was heated to reflux and stirred for 20 min. Air was then bubbled through the solution overnight at room temperature, after which the solvent was removed in vacuo. To the residue was added 1 N sulfuric acid (5 mL) and ethyl acetate (10 mL). The organic layer was then separated, and the aqueous layer was washed with aliquots of ethyl acetate (2 × 10 mL). The combined organic extracts were dried with magnesium sulfate and filtered, and the solvent was removed under reduced pressure to give the orange naphthoquinone **6**. The quinone was then purified by flash column chromatography (R_f 0.35, 25% ethyl acetate/petroleum spirits) to give the product in 56% yield; mp 105−106 (lit. 106−108 °C).[11,12] IR ν_{max} (KBr): 3338 (m), 2935 (m), 1661 (m), 1644 (s), 1634 (m), 1461 (s), 1402 (s), 1352 (s), 1283 (s), 1255 (m), 1154 (m), 1024 (w) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.10 (t, J = 8 Hz, 3H), 2.26 (s, 3H), 2.54 (t, J = 8 Hz, 2H), 3.80 (s, 3H), 3.88 (s, 3H), 3.91 (s, 3H), 7.37 (s, 1H). ^{13}C NMR ($CDCl_3$, 500 MHz): δ 10.1, 12.7, 16.8, 60.9, 61.1, 61.2, 121.1, 121.4, 125.2, 136.9, 150.6, 151.6, 156.2, 157.1, 180.4, 183.7. MS (*m*/*z*): 306 (100%, $M^{+\bullet}$), 291 (59%, $M^{+\bullet} - CH_2$), 277 (38%, $M^{+\bullet} - Et$), 263 (26%), 233 (19%), 168 (22%), 168 (23%). HRMS (*m*/*z*, $M^{+\bullet}$): calcd for $C_{16}H_{18}O_6$, 306.1103; found, 306.1101. Anal. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.57; H, 6.23.

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Supporting Information Available: Experimental details for the preparation of 1,2,4,5,7,8-hexamethoxynaphthalene (**14**), 5-benzyloxy-2,7-dimethoxy-1,4-naphthoquinone (**17**), 5-benzyloxy-1,2,4,7-tetramethoxynaphthalene (**18**), 3-ethyl-1,2,4,5,7,8-hexamethoxy-6-methylnaphthalene (**20**), 3,6-dimethyl-1,2,4,5,7,8-hexamethoxynaphthalene (**21**), 3-ethyl-2,5,7,8-tetrahydroxy-1,4-naphthoquinone (**25**), 2,5,7,8-tetrahydroxy-3,6-dimethyl-1,4-naphthoquinone (**27**), 2,3,5-trimethoxy-4-methylbenzyl cyanide (**34**), and methyl 2,3,5-trimethoxy-4-methylphenylacetate (**31**) and ^{1}H and ^{13}C NMR spectra for 1,2,4,5,7-pentamethoxynaphthalene (**11**), 8-formyl-1,2,4,5,7-pentahydroxynaphthalene (**12**), 2,5,7,8-tetramethoxy-1,4-naphthoquinone (**13**), 1,2,4,5,7,8-hexamethoxynaphthalene (**14**), 5-hydroxy-1,2,4,7-tetramethoxynaphthalene (**15**), 2-chloro-5-benzyloxy-7-methoxy-1,4-naphthoquinone (**16**), 3,6-diethyl-1,2,4,5,7,8-hexamethoxynaphthalene, 3-ethyl-1,2,4,5,7,8-hexamethoxy-6-methylnaphthalene (**20**; ^{1}H NMR only), 3,6-dimethyl-1,2,4,5,7,8-hexamethoxynaphthalene (**21**; ^{1}H NMR only), 2,3,5-trimethoxy-4-methylbenzaldehyde (**28**),[26] 2-phenyl-4-(2,3,5-trimethoxy-4-methylbenzylidene)-4*H*-oxazol-5-one (**29**), 2,3,5-trimethoxy-4-methylbenzyl alcohol (**32**), 2,3,5-trimethoxy-4-methylbenzyl chloride (**33**), methyl 2-butyryl-3,5,6-trimethoxy-4-methylphenylacetate (**35**), and 2-ethyl-3-hydroxy-5,6,8-trimethoxy-7-methyl-1,4-naphthoquinone (**6**). Crystallographic data was obtained to support the structural assignment of 5,7-dimethoxy-1-methyl-1*H*-benzo[*f*]indazole-4,9-dione. This material is available free of charge via the Internet at http://pubs.acs.org.

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