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Formal Total Synthesis of Hybocarpone Enabled by Visible-Light-Promoted Benzannulation

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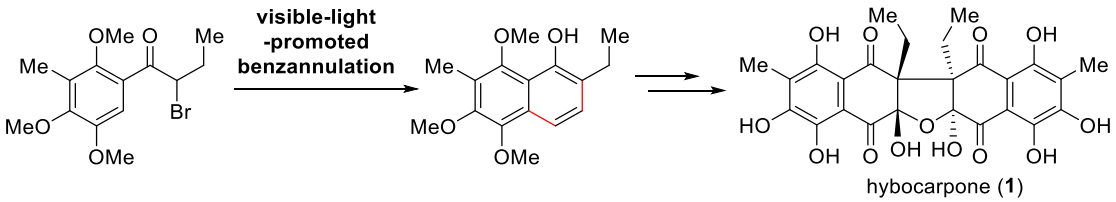


ABSTRACT: The formal total synthesis of hybocarpone was achieved in eight steps from commercially available 1,2,4-trimethoxybenzene. Key transformations include a visible-light-promoted benzannulation to construct the key α-naphthol intermediate, and a modified CAN-mediated dimerization/hydration cascade sequence to generate the vicinal all-carbon quaternary centers in a stereocontrolled manner. The total synthesis of boryquinone was also achieved in seven steps.

Naphthols and naphthoquinones are ubiquitous motifs present in many pharmaceuticals and natural products and have attracted significant attention from the chemical and biological communities.[1,2] Selected examples **1**–**6** are shown in Figure 1. These naphthol and naphthoquinone-based natural products have a broad range of biological activities, such as anti-cancer, anti-HIV, and anti-bacterial activities.[3]

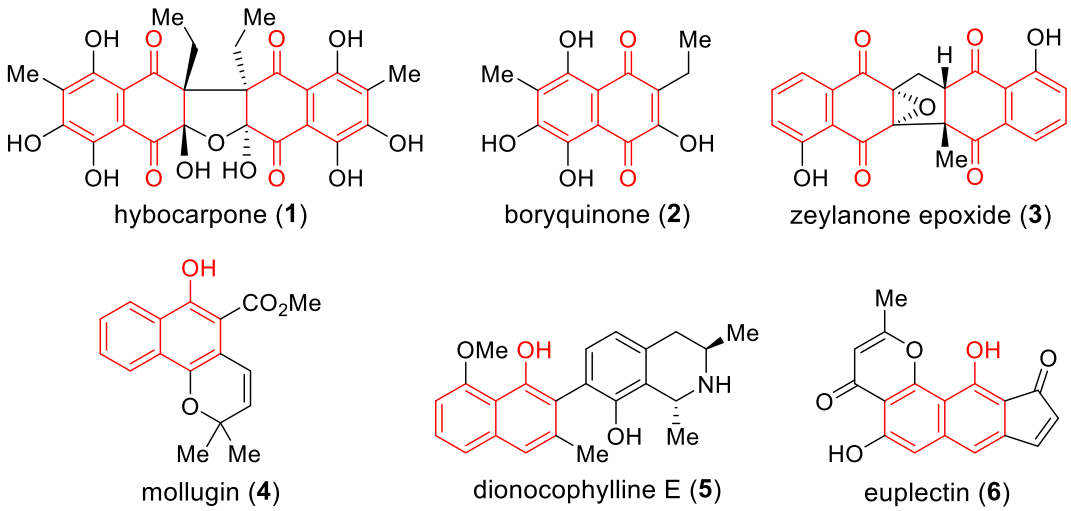


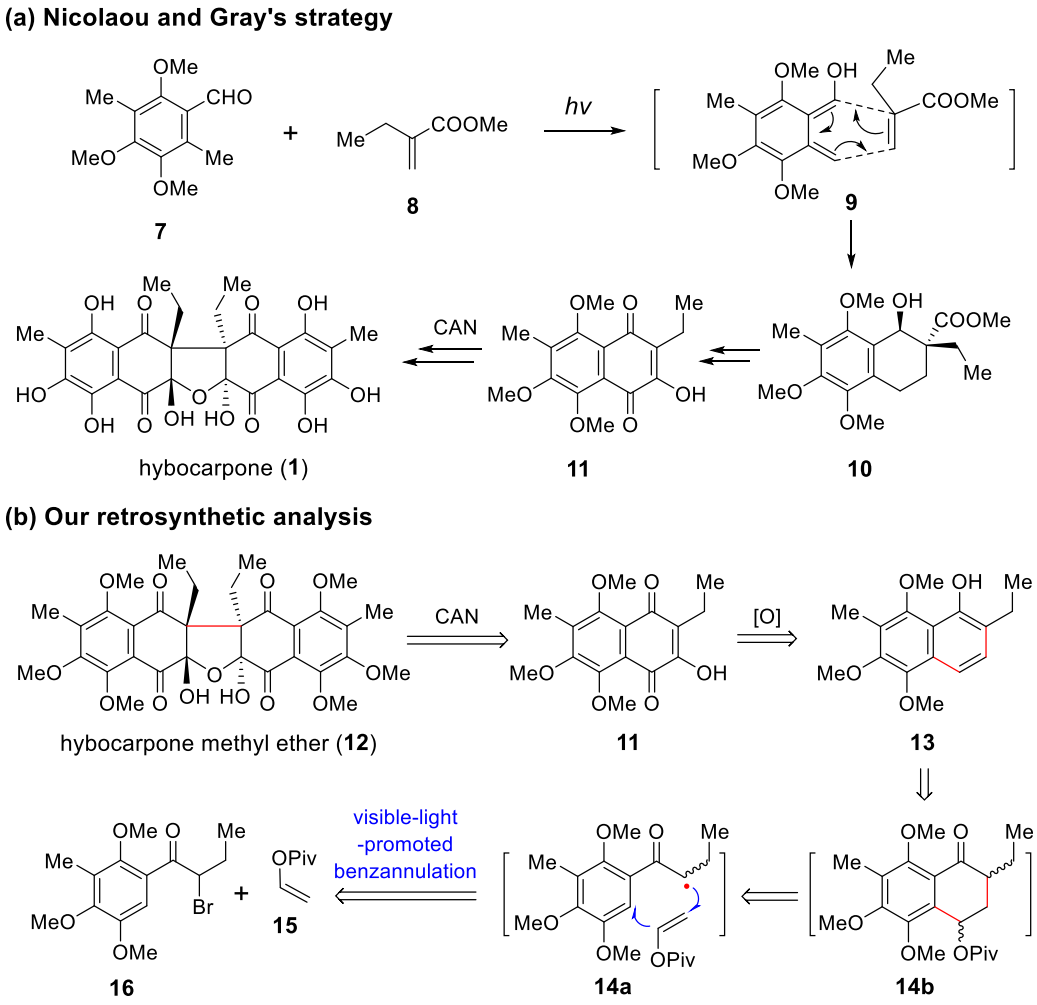
Figure 1. Naturally occurring naphthol and naphthoquinone-based products.

Hybocarpone (**1**), which is isolated from mycobiont cultures derived from the lichen *Lecanora hybocarpa*, is a dimer of naphthazarin bearing a highly substituted pentacyclic ring and two vicinal quaternary stereocenters. Hybocarpone was reported to be a potent cytotoxic agent against a murine mastocytoma cell line, with an IC_{50} value of 0.27 μM.[3a]

The first total synthesis of **1** was accomplished in 12 steps from a commercially available starting material by Nicolaou and Gray in 2001 (Scheme 1a).[4] The key steps in their elegant total synthesis are a UV-light-promoted Diels-Alder reaction of substituted 6-methylbenzaldehyde **7** with methyl 2-methylenebutanoate **8**, resulting in the formation of substituted tetrahydronaphthalene **10**, followed by a ceric ammonium nitrate (CAN)-mediated oxidative dimerization of substituted 3-hydroxy-naphthalene-1,4-dione **11** for the formation of the hybocarpone core (**1**). The Chai group[5] and Pettus group[6] reported different approaches for the construction of the key intermediate **11**.

Recently, visible-light-mediated photoredox catalysis has emerged as a powerful tool for synthesizing structurally diverse organic compounds.[7] As part of our program aimed at forming the core structures of biologically important natural products *via* visible-light-promoted reactions,[8] we became interested in

applying photoredox-catalyzed cascade radical cyclization as a key step in the total synthesis of hybocarpone (**1**). As shown in our retrosynthetic analysis (Scheme 1b), visible-light-promoted benzannulation of α-bromocarbonyl **16** with vinyl pivalate **15** was envisioned for constructing naphthol **13**, which could be converted to the key intermediate **11** through a global oxidation event. Finally, CAN-mediated oxidative dimerization of **11** could furnish hybocarpone methyl ether (**12**), facilitating the formal total synthesis of hybocarpone (**1**).

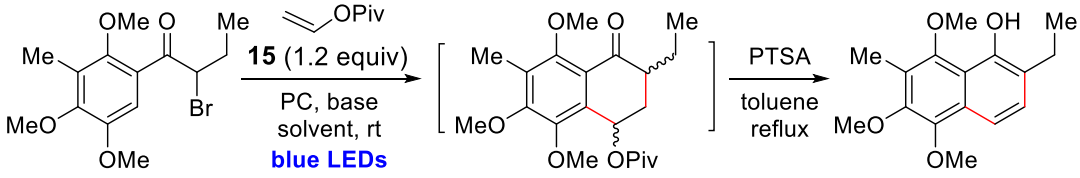


Scheme 1. Synthetic analysis of hybocarpone.

Our synthesis began with the development of a concise method for constructing naphthol **13**. Naphthols are important intermediates in organic synthesis, and hence, intense effort has been devoted to their synthesis.[9] The emergence of visible-light photoredox catalysis has enabled the productive use of lower-

energy radiation, leading to structurally diverse polycyclic compounds,[10] which has attracted our attention. Substituted α-bromoketone has a tendency to generate α-ketone radicals under photoredox catalysis. The radicals can couple with alkene to form functionalized building blocks.[11] Therefore, we envisage generating radical **14a** through irradiation of α-bromoketone **16** under visible light in the presence of a photosensitizer. This radical couples with vinyl pivalate **15** followed by benzannulation through intermediate **14b** to produce naphthol **13** (Scheme 1b).

Table 1. Optimized reaction conditions.[a]



16 (1.0 equiv) **14b** (without isolation) **13**

entry	PC	base	solvent	yield (%)[b]
1	eosin Y	NEt_3	MeCN	< 5
2	eosin Y	Na_2CO_3	MeCN	< 5
3	$[Ru(bpy)_3]Cl_2•6H_2O$	Na_2CO_3	MeCN	< 5
4	$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	Na_2CO_3	MeCN	15
5	*fac*-Ir(ppy)$_3$	Na_2CO_3	MeCN	58
6	*fac*-Ir(ppy)$_3$	K_2CO_3	MeCN	66
7	*fac*-Ir(ppy)$_3$	Na_2HPO_4	MeCN	43
8	*fac*-Ir(ppy)$_3$	K_2CO_3	DMF	30
9[c]	*fac*-Ir(ppy)$_3$	K_2CO_3	MeCN	0
10	-	K_2CO_3	MeCN	0

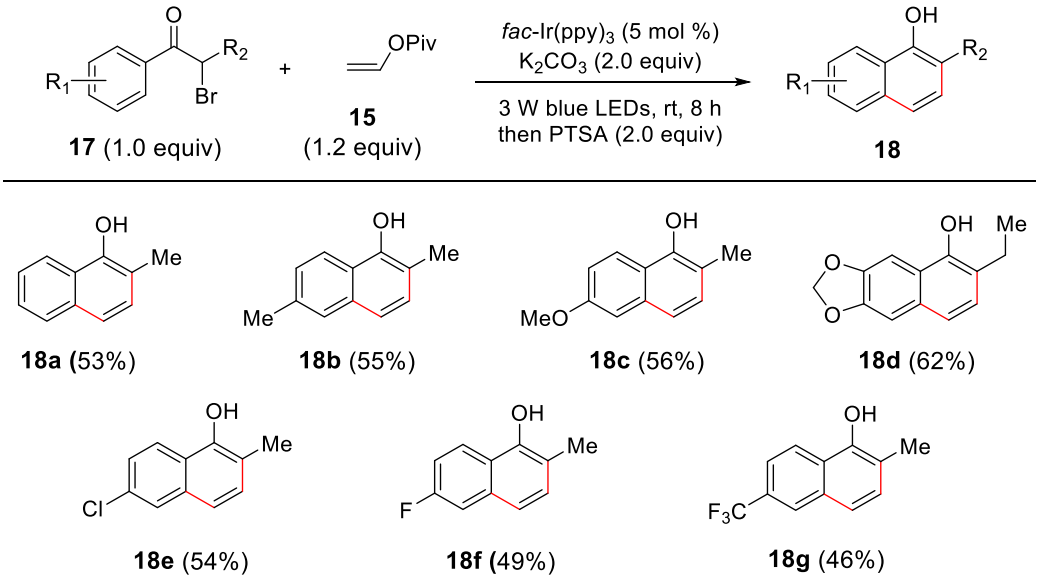
[a]Reaction conditions: **16** (50 mg, 0.15 mmol), vinyl pivalate **15** (0.18 mmol, 1.2 equiv), PC (5 mol %), base (2.0 equiv), and solvent (1.0 mL). The reaction was stirred at rt for 8 h under irradiation with a 3 W blue LED. The product **14b** was subjected to reflux with PTSA (2.0 equiv) in toluene without further isolation. [b]Isolated yield after flash column chromatography over two steps. [c]In absence of light.

We began exploring this synthetic transformation to produce the proposed chemistry. To this end, we synthesized α-bromoketone **16** in two steps from commercially available 1,2,4-trimethoxybenzene (see

the Experimental Section). First, we examined this transformation with organic photoredox catalyst eosin Y ($*E_{1/2}^{ox}$ = -1.08 V vs SCE)[12] as the photocatalyst (PC). However, the desired bicyclic product **13** was only observed at trace levels (Table 1, entries 1 and 2). We then evaluated other typical photosensitizers (entries 3–5). Among them, *fac*-Ir(ppy)$_3$, with its lower redox potential ($*E_{1/2}^{ox}$ = -1.73 V *vs* SCE)[13], produced the best result (58%, entry 5). The yield slightly improved (66%, entry 6) when the base was changed to potassium carbonate (K_2CO_3). In contrast, a decreased yield was observed when Na_2HPO_4 was used as a base (43%, entry 7). When using DMF as a solvent, only 30% yield of the desired product **13** could be isolated (entry 8). Control experiments revealed that the reaction did not proceed in the absence of a photocatalyst or visible light irradiation (entries 9 and 10). Notably, this reaction could be carried out on gram scale with a slightly decreased yield (see the Experimental Section).

With the optimized conditions in hand, the generality and scope of this visible-light-promoted benzannulation were explored. The results are listed in Table 2.

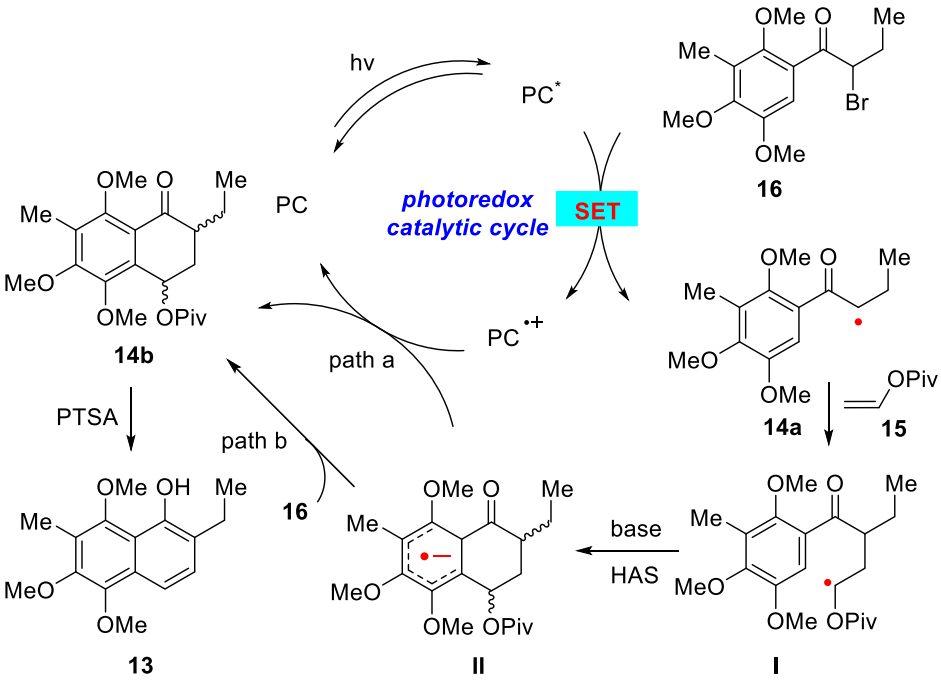
Table 2. Substrate scope of visible-light-promoted benzannulation.[a]



[a]The reaction was conducted on a 100 mg scale. All yields are those for isolated products over two steps.

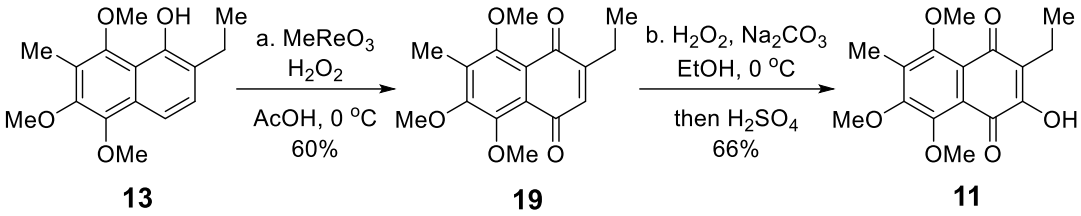
As shown in Table 2, all the selected substrates could produce the expected naphthols (**18a–18g)** in moderate to high yields, and substrates with electron-donating groups on their aromatic ring produced higher yields (**18b**–**18d**) than those with electron-withdrawing groups (**18e**–**18g**).

A proposed mechanism was depicted in Scheme 2. Initially, the excited state photocatalyst is generated from *fac*-Ir(ppy)$_3$ under the visible light irradiation. The oxidative quenching may happen in presence of *α*-bromoketone **16** *via* a single-electron-transfer (SET) process and the resultant radical intermediate **14a** (an electron deficient radical species) subsequently add to the electron rich double bond of vinyl pivalate **15**. The generated radical intermediate **I** can cyclize onto the aromatic ring system through a homolytic-aromatic-substitution (HAS) process[14] in presence of base to deliver the arene radical anion **II**. Oxidation of **II** by the oxidized-state photocatalyst ($E_{1/2}^{Ir(IV)/Ir(III)}$= + 0.77 V *vs* SCE) [13] will regenerate the ground-state photocatalyst and afford the tetralone product **14b** (path a). Alternatively, **14b** can be obtained *via* a chain-propagating electron transfer[15] from another equivalent of substrate **16** (path b). Finally, under the assistance of PTSA, **14b** can be easily converted to the desired naphthol product **13**.



Scheme 2. Proposed mechanism.

Once the rapidly assembled key naphthol intermediate **13** was obtained, we investigated the preparation of advanced intermediate **11** (Scheme 3). To this end, naphthol **13** was treated with methyltrioxorhenium (VII)[16] in the presence of hydrogen peroxide (H_2O_2) and acetic acid in an aqueous solution; the substituted 1,4-diquinone derivative **19** was obtained with 60% yield. Further oxidation of **19** with H_2O_2 in the presence of Na_2CO_3 in EtOH followed by the treatment with H_2SO_4[17] afforded hydroxynaphthoquinone **11** with 66% overall yield. This is the key intermediate in the total synthesis of hybocarpone (**1**), as reported by Nicolaou group.[4]



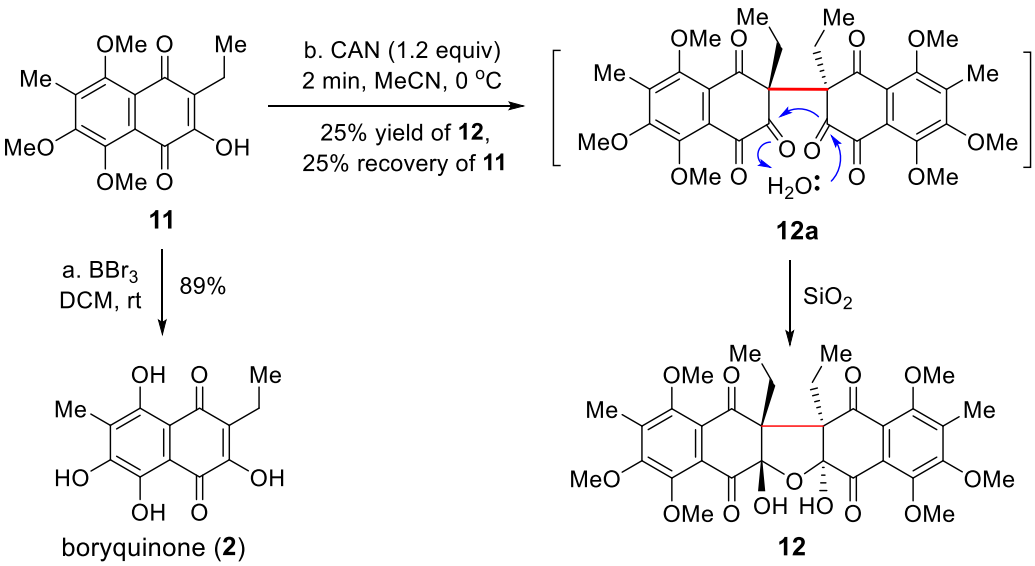
13 **19** **11**

Scheme 3. Synthesis of advanced intermediate **11**.

With **11** in hand, we proceeded toward the total synthesis of hybocarpone (**1**). To this end, we first removed the three methyl ether groups from substrate **11** through treatment with BBr_3 in methylene chloride at room temperature for 24 h, thus producing boryquinone (**2**) with 89% yield (Scheme 4). Actually, compound **2** is a naturally occurring solid product with a deep red color, and the spectral data for the synthesized compound were identical to those reported in the literature.[3b,5]

We then attempted to directly synthesize hybocarpone (**1**) from boryquinone (**2**) under different oxidative coupling conditions. However, the desired hybocarpone (**1**) product could not be obtained (see the Supporting Information for details). We believe that this transformation could be attributed to polyphenol groups in **2**, which could be decomposed through oxidation.[18] Therefore, we decided to use hydroxynaphthoquinone **11** as the substrate for constructing the pentacyclic core of compound **12**, thus realizing the formal total synthesis of hybocarpone (**1**). A modified version of the Nicolaou and Gray's method was used to isolate dimer product **12** as a single isomer with 25% yield together with 25%

recovered starting material **11** and some unidentified products (Scheme 4). We could even isolated intermediate **12a** using preparative thin layer chromatography (PTLC). Interestingly, **12a** was found to undergo a cascade hydration process, thus generating pentacycle product **12** in $CDCl_3$ (see the Supporting Information for details). Nicolaou and Gray used **12** as a key intermediate in the total synthesis of hybocarpone (**1**).[4] Thus, we have achieved a formal total synthesis of hybocarpone (**1**) in eight steps from commercially available starting compound.



Scheme 4. Synthesis of boryquinone and advanced intermediate **12**.

In conclusion, we developed a visible-light-promoted benzannulation strategy for a concise total synthesis of boryquinone (**2**) in seven steps. We also used a modified CAN-mediated oxidative dimerization/hydration cascade reaction to construct the sterically congested pentacyclic core of hybocarpone (**1**), realizing a formal total synthesis of hybocarpone (**1**) in eight steps from commercially available 1,2,4-trimethoxybenzene.

EXPERIMENTAL SECTION

General Experimental Information. Reagents were purchased at the highest commercial quality (>95%) and used without further purification, unless otherwise stated. Anhydrous tetrahydrofuran (THF),

toluene (PhMe) were distilled from sodium-benzophenone, dichloromethane (DCM), acetonitrile (MeCN), and dimethylformamide (DMF) were distilled from calcium hydride. All reactions were carried out with magnetic stirring, and if moisture or air sensitive, under an argon gas atmosphere with dry solvents. External bath temperatures were used to record all reaction temperatures. Low temperature reactions were carried out in a Dewar vessel filled with acetone/dry ice (–78 °C) or distilled water/ice (0 °C). 3 W blue LEDs (λ_{max} = 465 nm, model 12V 5050, purchased from Greenthink Co., Ltd.) was used for light irradiation. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Tsingdao silica gel glass-backed plates (60F-254) and visualized under UV light at 254 nm. Staining was performed with an ethanolic solution of phosphomolybdic acid and heat as developing agents. Tsingdao silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Yields refer to chromatographically, unless otherwise specified. NMR spectra were recorded on Brüker Advance 500 (^{1}H: 500 MHz, ^{13}C 125 MHz), Brüker Advance 400 (^{1}H: 400 MHz, ^{13}C 100 MHz) and Brüker Advance 300 (^{1}H: 300 MHz, ^{13}C 75 MHz). The spectra were reported as followed: chemical shift δ in ppm (multiplicity, coupling constant *J* in Hz, number of protons) for ^{1}H NMR spectra and chemical shift δ in ppm for ^{13}C NMR spectra. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, or combinations thereof. Residual solvent peaks of $CDCl_3$ (δ H = 7.26 ppm, δ C = 77.16 ppm) or CD_3OD (δ H = 3.31 ppm, δ C = 48.00 ppm) was used as an internal reference, unless otherwise stated. High resolution mass spectrometric (HRMS) data were recorded on Q-TOF-MS instruments (Brüker Apex IV RTMS and VG Auto Spec-3000), respectively. Infrared spectra (IR) were recorded on an IR Prestige-21 FTIR spectrometer with a KBr disc. Melting points (m.p.) are uncorrected and were recorded on a SGWX-4B apparatus.

Synthesis of 1,2,4-trimethoxy-3-methylbenzene. To a solution of 1,2,4-trimethoxybezene(14.9 mL, 100 mmol, 1.00 equiv) in THF (400 mL) was added ^{n}BuLi (50.0 mL of 2.5 M soln in hexanes, 125 mmol,

1.25 equiv) dropwise over 5 min at -78 °C under an argon atmosphere. After 15 min stirring at this temperature, the reaction was allowed to warm to room temperature and keep stirring for another 1 h. Then the reaction was cooled to -78 °C again and MeI (9.40 mL, 150 mmol, 1.50 equiv) was added. The mixture was allowed to warm to room temperature again over 2 h and quenched with sat. aq. NH_4Cl (200 mL) solution. The aqueous layer was extracted with Et_2O (3 x 250 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (19:1 hexanes:EtOAc) to afford 1,2,4-trimethoxy-3-methylbenzene (18.2 g, 99%) as a colorless oil. R_f = 0.75 (silica gel, EtOAc/hexanes= 1/16). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.71 (d, *J* = 8.9 Hz, 1H), 6.55 (d, *J* = 8.9 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.79 (s, 3H), 2.17 (s, 3H). The spectroscopic data was identical to the one reported in the literature.[19]

Synthesis of 2-bromo-1-(2,4,5-trimethoxy-3-methylphenyl)butan-1-one (16). (*Strategy A: one-step synthesis*): To a stirred solution of $AlBr_3$ (221 mg, 0.83 mmol, 1.50 equiv) in DCM (3.0 mL) was added 2-bromobutanoyl chloride (76.5 μL, 0.66 mmol, 1.20 equiv) at 0 °C under an argon atmosphere, the resultant mixture was stirred at this temperature for 10 min. A solution of 1,2,4-trimethoxy-3-methylbenzene (100 mg, 0.55 mmol, 1.00 equiv) in DCM (2.0 mL) was added dropwise and the reaction was allowed to warm to room temperature and stirring was continued for 2 h. The reaction mixture was quenched with sat. aq. NH_4Cl (5.0 mL). The aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (19:1 hexanes:EtOAc) to afford **16** (81.6 mg, 45%) as a brown oil. (*Strategy B: multi-gram scale synthesis*): 1,2,4-trimethoxy-3-methylbenzene (15.5 g, 85.0 mmol, 1.00 equiv) and *n*-butyric acid (9.4 mL, 102 mmol, 1.20 equiv) were added into polyphosphate acid (PPA, 100 g) and the reaction mixture was

stirred at 65 °C for 5 h. Ice water (500 mL) was poured into the mixture and extracted with DCM (3 x 300 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, the residue was filtered through a short plug of silica gel (eluent: 10% EtOAc in hexanes) to give the crude product as a yellow oil. The crude product was submitted to the next step without further purification. To a solution of the crude product in ether (100 mL) was added Br_2 (4.1 mL, 85.0 mmol, 1.00 equiv) via addition funnel over 30 min at room temperature. When the reddish color disappeared (about 2 h), the organic solvent was removed under reduced pressure. The residue was diluted with DCM (100 mL) and washed with sat. aq. $NaHCO_3$ (50 mL) and brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (19:1 hexanes:EtOAc) to afford the **16** (20.3 g, 72 % yield over two steps) as a brown oil. R_f = 0.58 (silica gel, EtOAc/hexanes= 1/8). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (s, 1H), 5.37 (dd, *J* = 7.8, 6.2 Hz, 1H), 3.86 (s, 3H), 3.86 (s, 3H), 3.72 (s, 3H), 2.21 (s, 3H), 2.17 (dt, *J* = 14.6, 1H), 2.04 (dt, *J* = 14.6, 7.4 Hz, 1H), 1.07 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 152.4, 152.0, 149.6, 126.3, 125.9, 111.0, 62.8, 60.5, 56.1, 54.6, 27.6, 12.4, 9.7; IR ν_{max} (film) 2966, 1681, 1628, 1404, 1275, 1087, 1002; HRMS (ESI) m/z calcd for $C_{14}H_{20}O_4Br$ $[M+H]^+$:331.0539; found:331.0541.

General procedure for bromide precursor synthesis: [20] To a stirred solution of commercially available ketones (10.0 mmol, 1.00 equiv) in AcOH (50 mL) was added Br_2 (0.48 mL, 10.0 mmol, 1.00 equiv) dropwise. When the reddish color disappeared (about 1-2 h), the organic solvent was removed under reduced pressure. The residue was diluted with DCM (50 mL) and washed with sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under

reduced pressure. The crude product was purified by silica gel flash chromatography (20:1 hexanes:EtOAc) to afford the corresponding precursors **17**. Note: **17a** was commercially available and purchased from Aldrich (CAS No: 2114-00-3)

2-bromo-1-(*p*-tolyl)propan-1-one (17b). 17b was synthesized following the general procedure. After purification by silica gel flash chromatography, **17b** was provided as a white solid (1.60 g, 71% yield from 1-(*p*-tolyl)propan-1-one). R_f = 0.65 (silica gel, DCM/hexanes= 1/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 5.28 (q, *J* = 6.6 Hz, 1H), 2.42 (s, 3H), 1.89 (d, *J* = 6.6 Hz, 3H). The spectroscopic data was identical to the one reported in the literature.[20c]

2-bromo-1-(4-methoxyphenyl)propan-1-one (17c). 17c was synthesized following the general procedure. After purification by silica gel flash chromatography, **17c** was provided as a light yellow solid (2.40 g, > 98% yield from 1-(4-methoxyphenyl)propan-1-one). R_f = 0.68 (silica gel, DCM/hexanes= 1/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 9.0 Hz, 2H), 7.06 – 6.86 (m, 2H), 5.26 (q, *J* = 6.6 Hz, 1H), 3.87 (s, 3H), 1.88 (d, *J* = 6.6 Hz, 3H).The spectroscopic data was identical to the one reported in the literature.[20a]

1-(benzo[*d*][1,3]dioxol-5-yl)-2-bromobutan-1-one (17d). 17d was synthesized following the general procedure. After purification by silica gel flash chromatography, **17d** was provided as a white solid (2.04 g, 85% yield from 1-(benzo[*d*][1,3]dioxol-5-yl)butan-1-one). R_f = 0.88 (silica gel, DCM/hexanes= 1/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.48 (d, *J* = 1.7 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.06 (s, 2H), 4.99 (dd, *J* = 7.7, 6.5 Hz, 1H), 2.31 – 1.99 (m, 2H), 1.06 (t, *J* = 7.3 Hz, 3H).The spectroscopic data was identical to the one reported in the literature.[20b]

2-bromo-1-(4-chlorophenyl)propan-1-one (17e). 17e was synthesized following the general procedure. After purification by silica gel flash chromatography, **17e** was provided as a white solid (2.24 g, 91% yield from2-bromo-1-(4-chlorophenyl)propan-1-one). R_f = 0.85 (silica gel, DCM/hexanes= 1/1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 7.89 (m, 2H), 7.53 – 7.38 (m, 2H), 5.22 (q, *J* = 6.6 Hz, 1H), 1.90 (d, *J* = 6.6 Hz, 3H).The spectroscopic data was identical to the one reported in the literature.[20c]

2-bromo-1-(4-fluorophenyl)propan-1-one (17f). 17f was synthesized following the general procedure. After purification by silica gel flash chromatography, **17f** was provided as a colorless oil (2.06 g, 90% yield from 1-(4-fluorophenyl)propan-1-one). R_f = 0.68 (silica gel, DCM/hexanes= 1/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 7.87 (m, 2H), 7.11 (dd, *J* = 11.8, 5.4 Hz, 2H), 5.23 (q, *J* = 6.6 Hz, 1H), 1.86 (d, *J* = 6.6 Hz, 3H).The spectroscopic data was identical to the one reported in the literature.[20c]

2-bromo-1-(4-(trifluoromethyl)phenyl)propan-1-one (17g). 17g was synthesized following the general procedure. After purification by silica gel flash chromatography, **17g** was provided as a colorless oil (2.28 g, 82% yield from 1-(4-(trifluoromethyl)phenyl)propan-1-one). R_f = 0.70 (silica gel, DCM/hexanes= 1/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (t, *J* = 6.5 Hz, 2H), 7.75 (t, *J* = 7.5 Hz, 2H), 5.26 (qd, *J* = 6.6, 2.1 Hz, 1H), 1.92 (t, *J* = 6.0 Hz, 3H).The spectroscopic data was identical to the one reported in the literature.[20a]

General procedure for visible-light-promoted benzannulation. A mixture of α-bromocarbonyl **17a-17g** (100 mg, 1.00 equiv), vinyl pivalate **15** (1.20 equiv), K_2CO_3 (2.00 equiv), *fac*-Ir(ppy)$_3$ (5 mol %) was charged with MeCN (2 mL) in round-bottom flask under an argon atmosphere, the resultant mixture was stirred at room temperature for 8 h under irradiation with visible light from a 3 W blue LEDs at a distance of 5.0 cm. Upon completion of the reaction by TLC monitor, the reaction mixture was filtered through a pad of silica gel (eluent: EtOAc). The organic layer was washed with brine and dried over anhydrous Na_2SO_4, which was removed under reduced pressure and the resultant residue was dissolved in toluene (2 mL). PTSA (2.00 equiv) was added and the reaction was refluxed for 2-3 h with a Dean-stark apparatus. When starting material was totally consumed (monitored by TLC), the reaction mixture was allowed to cool to room temperature and neutralized with sat. aq. $NaHCO_3$, then extracted

with DCM (2 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography to obtain the corresponding naphthols **18a-18g**.

2-ethyl-5,6,8-trimethoxy-7-methylnaphthalen-1-ol (**13**). The synthesis of naphthol **13** was carried out on 1.0 g scale following the general procedure above but 1 mol % *fac*-Ir(ppy)$_3$ was used and the reaction time was prolonged to 24 h. After purification by silica gel flash chromatography (50:1 hexanes:EtOAc), **13** was provided as a brown oil (446 mg, 53% yield from **16**). R_f = 0.68 (silica gel, EtOAc/hexanes= 1/8). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.27 (d, *J* = 8.8 Hz, 1H), 3.95 (s, 3H), 3.95 (s, 3H), 3.89 (s, 3H), 2.79 (q, *J* = 7.6 Hz, 2H), 2.35 (s, 3H), 1.28 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 149.6, 147.7, 144.1, 128.4, 124.6, 121.9, 114.8, 112.3, 105.4, 62.4, 61.0, 60.7, 23.0, 14.5, 9.8; IR ν_{max} (film) 2995, 1769, 1759, 1376, 1247, 1241, 1058; HRMS (ESI) m/z calcd for $C_{16}H_{21}O_4$ $[M+H]^+$: 277.1434; found: 277.1433.

2-methylnaphthalen-1-ol (18a). 18a was synthesized following the general procedure. After purification by silica gel flash chromatography (20:1→10:1 hexanes:EtOAc), **18a** was provided as a brown powder (16.8 mg, 53% yield from **17a**). R_f = 0.45 (silica gel, EtOAc/hexanes= 1/8). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.3 Hz, 1H), 7.78 (d, *J* = 7.9 Hz, 1H), 7.51 – 7.41 (m, 2H), 7.38 (d, *J* = 8.3 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 5.11 (s, 1H), 2.42 (s, 3H). The spectroscopic data was identical to the one reported in the literature.[20]

2,6-dimethylnaphthalen-1-ol (**18b**). **18b** was synthesized following the general procedure. After purification by silica gel flash chromatography (20:1→10:1 hexanes:EtOAc), **18b** was provided as a brown powder (18.9 mg, 55% yield from **17b**). m.p.: 75-77 °C. R_f = 0.5 (silica gel, EtOAc/hexanes= 1/8). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.6 Hz, 1H), 7.55 (s, 1H), 7.35 – 7.27 (m, 2H), 7.21 (d, *J* = 8.3 Hz, 1H), 5.05 (s, 1H), 2.50 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.7, 135.1,

133.9, 129.2, 127.7, 126.9, 122.7, 120.9, 119.7, 115.6, 21.7, 15.7; IR ν_{max} (film) 2995, 1755, 1249, 1240, 764, 748; HRMS (ESI) m/z calcd for $C_{12}H_{11}O$ $[M-H]^-$: 171.0815; found: 171.0813.

6-methoxy-2-methylnaphthalen-1-ol (**18c**). **18c** was synthesized following the general procedure. After purification by silica gel flash chromatography (20:1→10:1 hexanes:EtOAc), **18c** was provided as a yellow solid (21.1 mg, 56% yield from **17c**). m.p.: 83-85 ºC. R_f = 0.53 (silica gel, EtOAc/hexanes= 1/8). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 9.1 Hz, 1H), 7.27 (d, *J* = 7.9 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 1H), 7.12 (dd, *J* = 9.1, 2.5 Hz, 1H), 7.08 (d, *J* = 2.5 Hz, 1H), 5.04 (s, 1H), 3.91 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 149.0, 134.9, 129.8, 122.9, 119.9, 119.2, 118.0, 114.2, 106.0, 55.4, 15.5; IR ν_{max} (film) 2995, 1595, 1275, 1259, 764, 749; HRMS (ESI) m/z calcd for $C_{12}H_{13}O_2[M+H]^+$: 189.0910; found: 189.0910.

6-ethylnaphtho[2,3-d][1,3]dioxol-5-ol (**18d**). **18d** was synthesized following the general procedure. After purification by silica gel flash chromatography (20:1→10:1 hexanes:EtOAc), **18d** was provided as a brown solid (26.8 mg, 62% yield from **17d**). m.p.: 108-110 ºC. R_f = 0.48 (silica gel, EtOAc/hexanes= 1/8). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 7.11 (d, *J* = 8.3 Hz, 1H), 7.05 (s, 1H), 6.02 (s, 2H), 4.98 (s, 1H), 2.73 (q, *J* = 7.6 Hz, 2H), 1.30 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.9, 147.5, 130.6, 125.8, 121.8, 121.2, 119.8, 103.9, 101.1, 98.3, 23.0, 14.5; IR ν_{max} (film) 2993, 1754, 1279, 1259, 764, 749; HRMS (ESI) m/z calcd for $C_{13}H_{13}O_3$ $[M+H]^+$: 217.0859; found: 217.0860.

6-chloro-2-methylnaphthalen-1-ol (**18e**). **18e** was synthesized following the general procedure. After purification by silica gel flash chromatography (20:1→10:1 hexanes:EtOAc), **18e** was provided as a brown solid (20.7 mg, 54% yield from **17e**). m.p.: 118-123 ºC. R_f = 0.53 (silica gel, EtOAc/hexanes= 1/8). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 9.0 Hz, 1H), 7.74 (d, *J* = 2.0 Hz, 1H), 7.39 (dd, *J* = 9.0, 2.1 Hz, 1H), 7.31 – 7.23 (m, 2H), 5.09 (s, 1H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.0, 134.3,

131.6, 130.4, 126.4, 126.2, 123.3, 122.8, 119.5, 116.7, 15.7; IR ν_{max} (film) 2989, 1275, 1261, 1241, 764, 749; HRMS (ESI) m/z calcd for $C_{11}H_8OCl$ $[M-H]^-$: 191.0269; found: 191.0268.

6-fluoro-2-methylnaphthalen-1-ol (**18f**). **18f** was synthesized following the general procedure. After purification by silica gel flash chromatography (20:1→10:1 hexanes:EtOAc), **18f** was provided as a brown oil (17.2 mg, 49% yield from **17f**). R_f = 0.55 (silica gel, EtOAc/hexanes= 1/8). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 9.2, 5.7 Hz, 1H), 7.37 (dd, *J* = 10.0, 2.5 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.25 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.22 (dd, *J* = 8.9, 2.5 Hz, 1H), 5.12 (s, 1H), 2.39 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.9, -116.2 ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9 (d, $^1J_{CF}$ = 243.8 Hz, C-F), 149.1, 134.5 (d, $^3J_{CF}$ = 8.8 Hz, CH),130.46, 124.1 (d, $^3J_{CF}$ = 8.8 Hz, CH), 121.7, 119.6 (d, $^4J_{CF}$ = 5.0 Hz, CH), 115.9, 115.6 (d, $^2J_{CF}$ = 25.0 Hz, CH), 110.7 (d, $^2J_{CF}$ = 21.3 Hz, CH), 15.5; IR ν_{max} (film) 1275, 1261, 1241, 764, 749; HRMS (ESI) m/z calcd for $C_{11}H_8OF$ $[M-H]^-$: 175.0564; found: 175.0565.

2-methyl-6-(trifluoromethyl)naphthalen-1-ol (18g). 18g was synthesized following the general procedure. After purification by silica gel flash chromatography (20:1→10:1 hexanes:EtOAc), **18g** was provided as a brown solid (20.8 mg, 46% yield from **17g**). m.p.: 87-90 °C. R_f = 0.50 (silica gel, EtOAc/hexanes= 1/8). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.8 Hz, 1H), 8.07 (s, 1H), 7.62 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.46 (d, *J* = 8.3 Hz, 1H), 7.34 (d, *J* = 8.3 Hz, 1H), 5.15 (s, 1H), 2.44 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.3; ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.9, 132.4, 130.5, 127.6, 125.7, 125.5 (q, $^2J_{CF}$ = 24.5 Hz, C-CF_3), 123.6, 122.6, 121.2, 121.0 (q, $^1J_{CF}$ = 237.5 Hz, CF_3), 118.8, 15.9; IR ν_{max} (film) 1318, 1274, 1261, 1105, 1095, 764, 749; HRMS (ESI) m/z calcd for $C_{12}H_8OF_3$ $[M-H]^-$: 225.0532; found: 225.0538.

Synthesis of 2-ethyl-5,6,8-trimethoxy-7-methylnaphthalene-1,4-dione (19). To a stirred solution of **13** (318 mg, 1.15 mmol, 1.00 equiv) and methyltrioxorhenium(VII) $MeReO_3$ (15 mg, 0.06 mmol, 5 mol %) in AcOH (5. 0 mL) was added 30% aqueous hydrogen peroxide H_2O_2 (0.6 mL, 5.75 mmol, 5.00

equiv) dropwise at 0 °C. The reaction was allowed to warm to room temperature and stirring was continued for 3 h, quenched with sat. aq. Na_2SO_3 (10 mL) and subsequently extracted with DCM (3 x 20 mL). The combined organic layer was washed with sat. aq. $NaHCO_3$ (2 x 10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (15:1→10:1 hexanes:EtOAc) to afford 1,4-naphthoquinone **19** (200 mg, 60%) as a yellow oil. R_f = 0.55 (silica gel, EtOAc/hexanes= 1/4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (t, *J* = 1.5 Hz, 1H), 3.95 (s, 3H), 3.87 (s, 3H), 3.83 (s, 3H), 2.54 (qd, *J* = 7.4, 1.5 Hz, 2H), 2.27 (s, 3H), 1.16 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.9, 184.5, 158.4, 156.3, 152.7, 149.9, 134.6, 134.0, 124.6, 121.7, 61.5, 61.4, 61.0, 22.5, 11.9, 10.0; IR ν_{max} (film) 2995, 1770, 1383, 1247, 1058, 749; HRMS (ESI) m/z calcd for $C_{16}H_{19}O_5[M+H]^+$:291.1227; found:291.1222.

Synthesis of 2-ethyl-3-hydroxy-5,6,8-trimethoxy-7-methylnaphthalene-1,4-dione (11). To a solution of **19** (800 mg, 2.76 mmol, 1.00 equiv) in EtOH (20 mL) was added 30% aqueous hydrogen peroxide H_2O_2 (5.6 mL, 55.2 mmol, 20.0 equiv) dropwise at 0-5 °C. A solution of Na_2CO_3 (292 mg, 2.76 mmol, 1.00 equiv) in cold water (3.0 mL) was added and the reaction mixture was allowed to stir until the yellow color disappeared (about 3 h), then quenched with sat. aq. Na_2SO_3 (10 mL) and subsequently extracted with DCM (3 x 20 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product as a deep yellow oil. The crude product was submitted to the next step without further purification. The sulfuric acid (5.0 mL) was added into the flask containing the crude product and resulted bright red solution, stirred at 0-5 °C for 20 min. The reaction mixture was slowly added to chilled water and extracted with DCM (3 x 30 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (15:1 →8:1 hexanes:EtOAc) to afford naphthazarin **11** (554 mg, 66%) as a reddish solid. m.p.: 105-107 °C. R_f

= 0.48 (silica gel, EtOAc/hexanes= 1/4). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (s, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.82 (s, 3H), 2.56 (q, *J* = 7.5 Hz, 2H), 2.28 (s, 3H), 1.12 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.8, 180.6, 157.3, 156.4, 151.8, 150.9, 137.0, 125.4, 121.7, 121.4, 61.4, 61.3, 61.0, 17.0, 12.8, 10.2; IR ν_{max} (film) 2995, 1768, 1759, 1383, 1247, 1057; HRMS (ESI) m/z calcd for $C_{16}H_{19}O_6[M+H]^+$:307.1176; found:307.1175.

Synthesis of boryquinone (2). To a stirred solution of **11** (100 mg, 0.33 mmol, 1.00 equiv) in dry DCM (5.0 mL) was added BBr_3 (1.65 mL of 1 M soln in DCM, 1.65 mmol, 5.00 equiv) under an argon gas atmosphere at -78 °C. The reaction mixture was allowed to warm to room temperature and stirred for 24 h, then quenched with chilled water (5.0 mL) and subsequently extracted with DCM (3 x 10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (1:1 hexanes:EtOAc) to give boryquinone **2** (76.7 mg, 89%) as a reddish solid, which was sparingly soluble in $CDCl_3$ and totally soluble in EtOAc or CD_3OD. m.p.: 179-182 °C (lit. 180-184 °C)[5]. R_f = 0.45 (silica gel, EtOAc/hexanes= 1/1). ^{1}H NMR (500 MHz, $CDCl_3$/EtOAc) δ 13.47 (s, 1H), 11.75 (s, 1H), 6.76 (s, 1H), 6.72 (s, 1H), 2.68 (q, *J* = 7.5 Hz, 2H), 2.15 (s, 3H), 1.15 (t, *J* = 7.5 Hz, 3H); ^{1}H NMR (400 MHz, CD_3OD) δ 2.65 (q, *J* = 7.4 Hz, 2H), 2.15 (s, 3H), 1.12 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$/EtOAc) δ 173.7, 173.0, 171.2 ($CH_3\underline{C}(O)OCH_2CH_3$), 164.6, 164.4, 151.5, 151.2, 128.5, 122.9, 108.4, 104.1, 60.5 ($CH_3C(O)O\underline{C}H_2CH_3$), 21.1 ($\underline{C}H_3C(O)OCH_2CH_3$), 16.8, 14.4 ($CH_3C(O)OCH_2\underline{C}H_3$), 12.8, 8.6; ^{13}C NMR (100 MHz, CD_3OD) δ 173.7, 172.7, 166.0, 165.6, 153.8, 153.4, 127.5, 121.8, 109.0, 103.5, 16.2, 12.1, 7.4; IR ν_{max} (film) 2995, 1769, 1755, 1247, 1055; HRMS (ESI) m/z calcd for $C_{13}H_{13}O_6[M+H]^+$: 265.0707; found: 265.0709.

Synthesis of hybocarpone methyl ether (12). Under an argon gas atmosphere, a solution of CAN (113 mg, 0.21 mmol, 1.20 equiv) in MeCN (2.0 mL) was stirred at 0 °C. In a separated flask, hydroxyl quinone

11(52 mg, 0.17 mmol, 1.00 equiv) was dissolved in degassed MeCN (2.0 mL) and cooled to 0 °C. This solution was then added to the solution of CAN in one portion and the reaction mixture was stirred for 2 min. During this time, the color of the reaction mixture changed from black to a light yellow. Water (2.0 mL) was added to the reaction mixture and subsequently extracted with DCM (3 x 5.0 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was carefully purified by silica gel flash chromatography (10:1→5:1→2:1, hexanes:EtOAc) to give **12** (13 mg, 25%) as colorless oil, and the starting material **11** (13 mg, 25%). Notably, **12** was isolated as a single isomer. R_f = 0.15 (silica gel, EtOAc/hexanes= 1/3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.11 (s, 2H), 3.95 (s, 6H), 3.92 (s, 6H), 3.81 (s, 6H), 2.36 (dq, *J* = 12.9, 7.3 Hz, 2H), 2.31 (s, 6H), 1.88 (dq, *J* = 12.9, 7.3 Hz, 2H), 0.59 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 192.0, 157.8, 156.0, 149.4, 136.6, 128.2, 123.8, 101.9, 70.0, 62.8, 62.1, 61.6, 26.5, 11.1, 10.5; IR ν_{max} (film) 2995, 1769, 1383, 1247, 1058, 913, 744; HRMS (ESI) m/z calcd for $C_{32}H_{36}O_{13}Na[M+Na]^+$: 651.2048; found: 651.2053.

2,2'-diethyl-5,5',6,6',8,8'-hexamethoxy-7,7'-dimethyl-[2,2'-binaphthalene]-1,1',3,3',4,4'(2H,2'H)-hexaone (12a). **12a** was isolated for characterization purpose by taking an aliquot from the above reaction mixture and filtering it through a short plug of silica (eluent: EtOAc), followed by concentration under reduced pressure and the residue was purified by PTLC (silica gel, 1:1 hexanes:EtOAc, with two drops of NEt_3) to give **12a** as a colorless oil. **12a** was observed to undergo hydration to give the pentacycle product **12** in $CDCl_3$ (See the Supporting Information for details). R_f = 0.45 (silica gel, EtOAc/hexanes= 1/3). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.97 (s, 6H), 3.95 (s, 6H), 3.69 (s, 6H), 2.59 (dq, *J* = 15.3, 7.6 Hz, 2H), 2.38 – 2.27 (dq, *J* = 15.3, 7.6 Hz, 2H), 2.24 (s, 6H), 0.73 (t, *J* = 7.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.7, 191.5, 179.3, 158.2, 154.6, 150.5, 136.2, 126.5, 124.8, 73.3, 62.4, 62.3, 61.1,

27.9, 10.8, 10.5; IR ν_{max} (film) 2995, 1769, 1247, 1058, 913, 743; HRMS (ESI) m/z calcd for $C_{32}H_{35}O_{12}[M+H]^+$:611.2123; found:611.2123.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI: Full spectroscopic data for all new compounds and crystallographic data (PDF)

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