Synthesis of Quinonoid Analogues of Diospyrin

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Abstract: Diospyrin and its analogues have been known for their antimycobacterial properties. Significant efforts have been made towards the synthesis of structural analogues of diospyrin with improved biological activities. We report here the synthesis of four novel analogues of diospyrin via a Suzuki cross coupling between bromonaphthoquinones and aryl- or naphthylboronic acids in the presence of tetrakis(triphenylphosphine)palladium(0) as catalyst, followed by selective demethylation of the intermediates.

Key words: quinones, biaryls, boronic acids, diospyrin, Suzuki coupling

Mycobacterium tuberculosis (TB) infection is an acknowledged serious worldwide threat. The WHO estimates that between 2000 and 2020, nearly one billion people will be newly infected, 200 million people will become severely ill, and in the order of 35 million people will die from TB. Present treatment regimes for TB are based on a multidrug therapy in which three or four antituberculosis drugs are administered for six to nine months for sensitive cases and longer for drug resistance TB. These drugs unfortunately have serious side effects and they also do not kill latent bacilli.[1] No new antibiotics have been developed against any mycobacteria causing health problems since the 1970s. Problems for multidrug resistance tubercle bacilli are manifesting themselves for various drug treatment regimes and, thus, there is an urgent need for novel therapeutic agents that can provide reliable and effective treatment regimes against TB.[2]

More than 2000 naturally occurring quinones, viz., anthraquinones, naphthoquinones, and benzoquinones are known to be widely distributed in nature as pigments and as intermediates in cellular respiration and photosynthesis.[3,4] Some quinones play important roles in the biochemistry of energy production and serve as vital links in the respiratory chain of living cells. These compounds act as inhibitors of electron transport, uncouplers of oxidative phosphorylation, and give rise to a wide range of cytostatic and anti-proliferative activities.[5] They essentially provide a defense role as a result of their effectiveness in inhibiting the growth of bacteria, fungi, or parasites[6,7] and this is the reason that a number of them display antimicrobial and anticancer activities.[8]

Diospyrin, an orange-red bisnaphthoquinone that is present in the heartwood of many species of diospyros trees, is well known for its antimycobacterial activity.[9] Sidhu and Pardhasaradhi determined its correct structure, in which a naphthoquinone linkage to the non-quinonoidal aryl ring of another naphthoquinone moiety viz., between C2 and C6′ is apparent (Figure 1).[10,11]

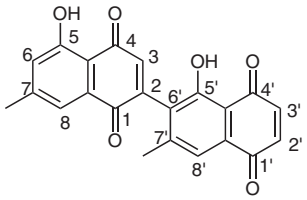

Figure 1 Structure of diospyrin

To date the only synthesis of diospyrin the authors are aware of has been reported by Yoshida and Mori.[12] In addition, diospyrin and its analogues have been investigated for their antimycobacterial properties.[13–15] Thus diospyrin was envisaged to be a potential lead molecule and scaffold for the synthesis of new binaphthalene systems that could eventually be transformed into bisnaphthoquinones with a view to evaluating their biological activity against different strains of *Mycobacterium tuberculosis* and selected cancer cell lines. In addition we also wanted to investigate whether naphthoquinone–benzoquinone systems were able to elicit similar activity and, thus, two targets were chosen for this evaluation. The results of all evaluations, which have demonstrated good promise, will be published elsewhere.

Synthesis of the first bisnaphthoquinone **7a** is summarized in Schemes 1– 3. In achieving this, it was necessary to prepare the naphthalene building blocks **2a** and **5a** (Schemes 1 and 2). Thus for the synthesis of bromonaphthoquinone **2a**, condensation between isoprene and 2,5-dibromo-1,4-benzoquinone,[16] in which the bromine atom is expected to direct the regioselectivity of the Diels–Alder protocol,[17] it was indeed found that the desired non-aromatic adduct **1** was produced in 64% isolated yield. This was followed by aromatization by using a method given by Ho et al.,[18] an equivalent of the oxidant chloranil in boiling benzene afforded bromoquinone **2a** in 75% yield (Scheme 1). For the second naphthalene moiety **5a**, bromoquinone **2a** was reduced using tin(II) chloride[19] to afford the bromonaphthalenediol **3** in which, importantly, the bromine had been retained, and this was followed by methylation with potassium carbonate and dimethyl sulfate in boiling acetone under vigorous stirring to furnish dimethyl ether **4a** in 77% yield (Scheme 1).[20]

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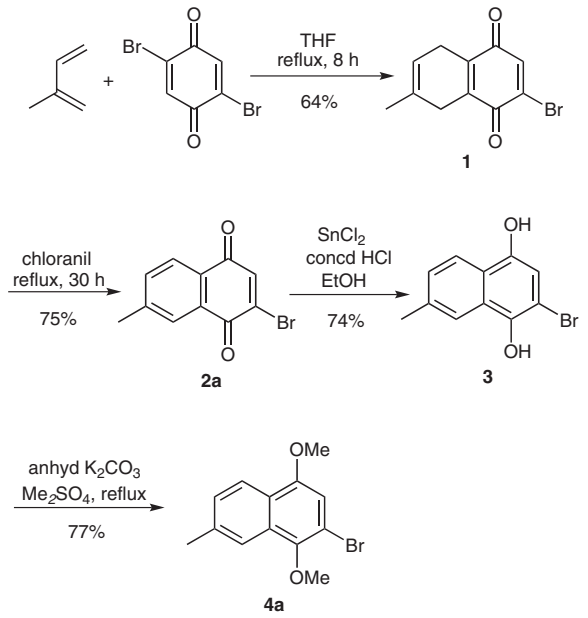
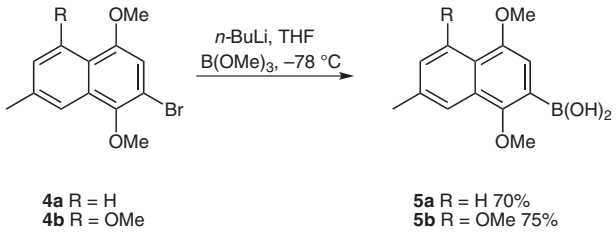


Scheme 1

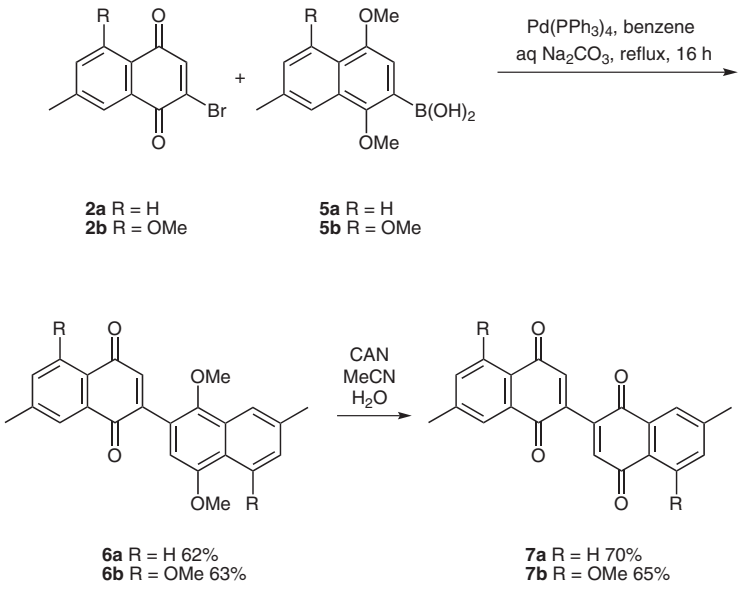
Metal–halogen exchange of **4a** with butyllithium and subsequent reaction with trimethyl borate at –78 °C afforded the corresponding boronic acid **5a** in 70% yield (Scheme 2), which was immediately used in the next stage of the synthesis.[12] It was observed that for optimum yields, addition of aqueous hydrochloric acid to hydrolyze the initial borate has to be very carefully controlled. Suzuki coupling between naphthoquinone **2a** and boronic acid **5a** in the presence of tetrakis(triphenylphosphine)palladium(0) as catalyst and aqueous sodium carbonate under reflux in benzene for 16 hours afforded the binaphthalene product **6a** as red needles in 62% yield (Scheme 3).[21,22] Unfortunately, all attempts to demethylate adduct **6a** with boron tribromide and aluminum trichloride in dichloromethane at low temperature proved to be unsuccessful in our hands and, thus, final oxidative demethylation of **6a** with aqueous cerium(IV) ammonium nitrate was successfully effected to afford the bisnaphthoquinone **7a** in a fair yield of 70%.[23]



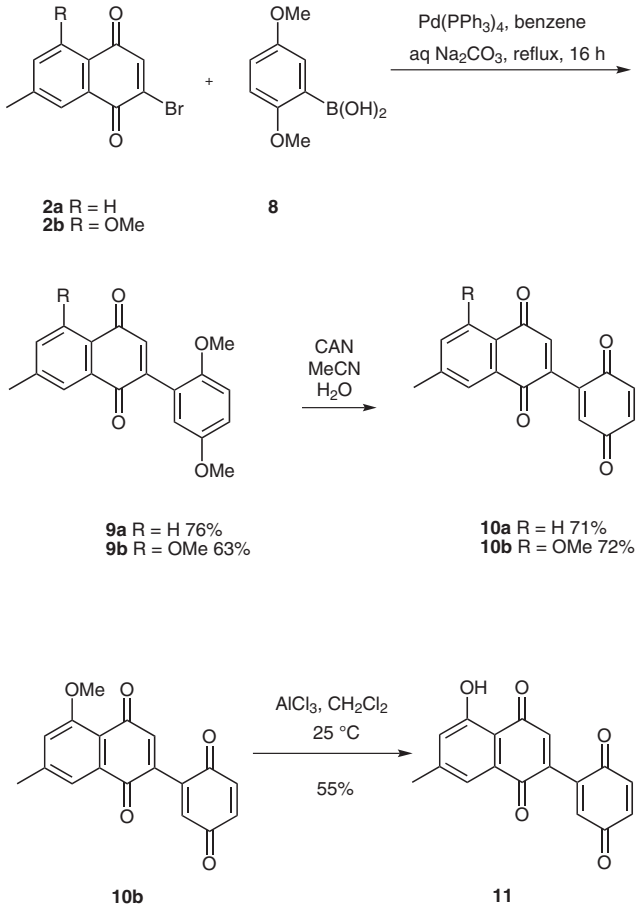
Scheme 2

In the second of our target molecules, treatment of the known 2-bromo-1,4,5-trimethoxy-7-methylnaphthalene (**4b**)[12] with butyllithium and trimethyl borate at –78 °C afforded the expected boronic acid **5b** in a good yield of 75% (Scheme 2) and this compound was immediately used in the coupling protocol described above, with 2-bromo-5-methoxy-7-methyl-1,4-naphthoquinone (**2b**)[12] to produce the binaphthalene **6b** in 63% yield after chromatography. Oxidative demethylation of **6b** using a similar protocol described earlier afforded the bisnaphthoquinone **7b** in 65% yield (Scheme 3). The symmetry of the molecule was exemplified in the rather uncomplicated ^{1}H and ^{13}C NMR spectra.

The first of our naphthoquinone–benzoquinone target molecules involved coupling of naphthoquinone **2a** with boronic acid **8** under the normal Suzuki protocol to afford naphthoquinone **9a** in a good 76% yield. Finally, oxidative demethylation of **9a** under conditions used earlier afforded the final biquinone **10a** in 71% yield (Scheme 4). Due to the previous difficulties we experienced in de-



Scheme 3



Scheme 4

methylating bisnaphthoquinone **7b**, in order to evaluate the influence of a *peri*-hydroxy group on activity[15] we chose another simpler example as identified in **11**. Thus coupling between the two partners, namely 2-bromo-5-methoxy-7-methyl-1,4-naphthoquinone (**2b**) and boronic acid **8** afforded the naphthoquinone **9b** in 63% yield. This was followed by oxidative demethylation to produce biquinone **10b** in 72% yield. Finally demethylation of the *peri*-methoxy group employing aluminum trichloride in dichloromethane at 25 °C afforded the hydroxyquinone **11** in 55% yield.[24]

In summary, a reasonably simple protocol has thus been established for the synthesis of naphthoquinone–naphthoquinone as well as naphthoquinone–benzoquinone molecules in which the quinonoidal moieties are directly linked.

Nuclear magnetic resonance spectra were recorded using a Varian 200 MHz spectrometer. All spectra were recorded at 20 °C in $CDCl_3$. Assignments of peaks in ^1H and ^{13}C NMR spectra with the same superscript may be interchanged. Mass spectra were recorded on a Finnigan-Matt Ion Trap Detector spectrometer at 70 eV with automatic gain control. HRMS were recorded on a modified AEI-902 High Resolution Mass Spectrometer at the University of the Witwatersrand, Johannesburg. Infrared spectra were recorded as Nujol mulls on a Perkin Elmer 1000PC Fourier Transform spectrophotometer. Melting points are uncorrected and were recorded on a Fisher-Johns Melting Point Apparatus. Column chromatography was carried out using Merck Kieselgel 60 (70–230 mesh) as dry columns. Pre-adsorption was carried out on Merck Kieselgel 60 (35–70 mesh). PLC was performed on glass plates coated with silica gel with UV254 indicator and as a 1.0 mm thick layer, while TLC was carried out on aluminum plates coated with Merck Kieselgel 60 F_{254}. The residue obtained upon workup refers to material obtained from the dried ($MgSO_4$) organic extract after filtration and solvent removal. Hexane refers to the fraction of boiling point 68–72 °C. All solvents were purified by distillation and, if necessary, were dried according to standard methods.

2-Bromo-7-methyl-5,8-dihydro-1,4-naphthoquinone (1)

To a soln of 2,5-dibromo-1,4-benzoquinone[16] (2.68 g, 10.0 mmol) in THF (20 mL) at 24 °C under an N_2 atmosphere was added a soln of commercially available isoprene (0.68 g, 10.00 mmol) in THF (10 mL) dropwise over 15 min. The resulting soln was heated under reflux for 8 h and then cooled to 24 °C. The residue obtained upon workup was chromatographed (EtOAc–hexane, 1:19) to afford **1** (1.64 g, 64%) as bluish-black needles; mp 73–75 °C (EtOH).

IR (Nujol): 1660 (m, C=O), 1651 (m, C=O), 1601 (w, Ar), 1585 cm^{-1} (w, Ar).

^1H NMR (200 MHz, $CDCl_3$): δ = 1.77 (s, 3 H, 7-CH_3), 3.05 (m, 4 H, H5, H8), 5.48 (m, 1 H, H6), 7.24 (s, 1 H, H3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.9 (CH_3), 25.3 (C5)[a], 29.5 (C8)[a], 116.6 (C6), 130.2 (C2)[b], 137.2 (C7)[b], 137.9 (C3), 139.4 (C4a)[c], 140.2 (C8a)[c], 179.3 (C1)[d], 184.5 (C4)[d].

HRMS: *m/z* $[M]^+$ calcd for $C_{11}H_9BrO_2$: 251.9785; found: 251.9787.

Anal. Calcd for $C_{11}H_9BrO_2$: C, 52.2; H, 3.6. Found: C, 52.4; H, 3.8.

2-Bromo-7-methyl-1,4-naphthoquinone (2a)

A mixture of **1** (1.82 g, 7.10 mmol), chloranil (1.74 g, 7.10 mmol), and benzene (30 mL) was heated under reflux for 30 h. The residue obtained upon workup was chromatographed (EtOAc–hexane, 1:19) to afford **2a** (1.35 g, 75%) as yellow needles; mp 124–126 °C (EtOH).

IR (Nujol): 1674 (s, C=O), 1650 (s, C=O), 1597 (m, Ar), 1587 cm^{-1} (m, Ar).

^1H NMR (200 MHz, $CDCl_3$): δ = 2.51 (s, 3 H, 7-CH_3), 7.49 (s, 1 H, H3), 7.57 (dd, *J* = 8.0, 1.2 Hz, 1 H, H6), 7.96 (d, *J* = 1.2 Hz, 1 H, H8), 7.98 (d, *J* = 8.0 Hz, 1 H, H5).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.9 (CH_3), 127.2 (C3)[a], 128.3 (C6)[a], 129.7 (C2)[b], 131.0 (C7)[b], 135.2 (C5)[c], 139.9 (C4a)[d], 140.5 (C8)[c], 145.6 (C8a)[d], 179.0 (C1)[e], 182.4 (C4)[e].

HRMS: *m/z* $[M]^+$ calcd for $C_{11}H_7BrO_2$: 251.9629; found: 251.9631.

Anal. Calcd for $C_{11}H_7BrO_2$: C, 52.6; H, 2.8. Found: C, 52.8; H, 2.6.

2-Bromo-7-methylnaphthalene-1,4-diol (3)

To a stirred suspension of **2a** (1 g, 3.98 mmol) in EtOH (40 mL) at 50 °C was added a soln of $SnCl_2$ (3.1 g, 13.90 mmol) in concd HCl (5 mL). The mixture was stirred at this temperature for 45 min, it was poured into cold H_2O (150 mL), and the solid material was filtered and washed with H_2O to afford **3** (0.74g, 74%) as white needles; mp ~115 °C (dec.) (benzene).

IR (Nujol): 3297 (m, OH), 1595 cm^{-1} (m, Ar).

^1H NMR (200 MHz, $CDCl_3$): δ = 2.54 (s, 3 H, 7-CH_3), 5.56 (s, 1 H, OH), 6.81 (s, 1 H, H3), 7.36 (dd, *J* = 8.5, 1.6 Hz, 1 H, H6), 7.95 (d, *J* = 1.6 Hz, 1 H, H8), 7.97 (d, *J* = 8.5 Hz, 1 H, H5).

^1H NMR (200 MHz, acetone-d_6): δ = 2.50 (s, 3 H, 7-CH_3), 6.92 (s, 1 H, H3), 7.36 (dd, *J* = 8.4, 1.6 Hz, 1 H, H6), 7.77 (s, 1 H, 1-OH)[a], 7.98 (d, *J* = 1.6 Hz, 1 H, H8), 8.07 (d, *J* = 8.4 Hz, 1 H, H5), 8.83 (s, 1 H, 4-OH)[a].

^{13}C NMR (50 MHz, acetone-d_6): δ = 12.9 (CH_3), 95.4 (C2), 101.8 (C3)[a], 113.0 (C6)[a], 114.2 (C5)[a], 115.4 (C8)[a], 118.4 (C7)[a], 119.3 (C4a)[b], 128.0 (C8a)[b], 133.8 (C1)[c], 138.9 (C4)[c].

HRMS: *m/z* [M]$^+$ calcd for $C_{11}H_9BrO_2$: 251.9785; found: 251.9782.

Anal. Calcd for $C_{11}H_9BrO_2$: C, 52.2; H, 3.6. Found: C, 52.5; H, 3.4.

2-Bromo-1,4-dimethoxy-7-methylnaphthalene (4a)

To a soln of **3** (0.73 g, 2.89 mmol) in anhyd acetone (20 mL) was added anhyd K_2CO_3 (4.79 g, 34.68 mmol). Me_2SO_4 (1.82 g, 1.36 mL, 14.40 mmol) was then added in one portion and the mixture was heated and vigorously stirred under reflux for 20 h. It was then cooled to 25 °C and filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in Et_2O (50 mL) and Et_3N (1.46 g, 2.0 mL, 14.40 mmol) was added. The mixture was stirred at 25 °C for 20 min and the soln was washed with 1 M HCl (2 × 20 mL) and H_2O (1 × 25 mL). The residue obtained upon workup was chromatographed (EtOAc–hexane, 1:5) to afford **4a** (0.62g, 77%) as colorless needles; mp 73–74 °C (EtOH).

IR (Nujol): 1626 (w, Ar), 1587 cm^{-1} (m, Ar).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.54 (s, 3 H, 7-CH_3), 3.94 (s, 3 H, OMe), 3.96 (s, 3 H, OMe), 6.81 (s, 1 H, H3), 7.33 (dd, *J* = 8.4, 1.6 Hz, 1 H, H6), 7.81 (d, *J* = 1.6 Hz, 1 H, H8), 8.09 (d, *J* = 8.4 Hz, 1 H, H5).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.0 (CH_3), 55.9 (OMe), 61.4 (OMe), 107.3 (C3), 112.1 (C2), 121.0 (C6)[a], 122.6 (C5)[a], 124.1 (C7)[a], 128.0 (C8)[a], 129.3 (C4a)[b], 137.4 (C8a)[b], 150.6 (C1)[c], 152.4 (C4)[c].

HRMS: *m/z* [M]$^+$ calcd for $C_{13}H_{13}BrO_2$: 280.0098; found: 280.0099.

Anal. Calcd for $C_{13}H_{13}BrO_2$: C, 55.5; H, 4.7. Found: C, 55.8; H, 4.4.

1,4-Dimethoxy-7-methylnaphthalen-2-ylboronic Acid (5a); Typical Procedure

A 1.28 M soln of BuLi (1.67 mL, 2.14 mmol, 1.2 equiv) was added dropwise to a stirred soln of **4a** (500 mg, 1.78 mmol) in anhyd THF (10 mL) at –78 °C. The mixture was stirred at this temperature under an N_2 atmosphere for 15 min, during which time the mixture color went from colorless to lime green. $B(OMe)_3$ (1.0 mL, 0.92 g, 8.90 mmol, 5.0 mol equiv) was then added dropwise causing the mixture to become clear again. The mixture was stirred at –78 °C for a further 30 min and then allowed to warm to 24 °C over 20 h. The mixture was then cooled to 0 °C and 5% aq HCl was added until the pH was ~6. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) to afford **5a** (308 mg, 70%), which was immediately used in the next reaction.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.52 (s, 3 H, 7-CH_3), 3.55 (s, 3 H, OMe), 3.81 (s, 3 H, OMe), 5.58 [s, 2 H, $B(OH)_2$], 6.57 (s, 1 H, H3), 7.57 (dd, *J* = 8.0, 1.2 Hz, 1 H, H6), 7.97 (d, *J* = 1.2 Hz, 1 H, H8), 8.02 (d, *J* = 8.0 Hz, 1 H, H5).

1′,4′-Dimethoxy-7,7′-dimethyl-2,2′-binaphthalene-1,4-dione (6a); Typical Procedure

A mixture of **2a** (314 mg, 1.25 mmol) and $Pd(PPh_3)_4$ (150 mg, 0.13 mmol) in benzene (20 mL) was stirred for 0.5 h at 24 °C under an N_2 atmosphere. Aq 2 M Na_2CO_3 (1.0 mL) and **5a** (307 mg, 1.25 mmol) in benzene (20 mL) were added successively. The mixture was heated under reflux for 16 h with vigorous stirring. The cooled resulting mixture was extracted with CH_2Cl_2 and the residue obtained upon workup was chromatographed (EtOAc–hexane, 3:7) to afford **6a** (290 mg, 62%) as red crystals; mp 141–143 °C (EtOAc–hexane).

IR (Nujol): 1664 (s, C=O), 1657 (m, C=O), 1597 cm^{-1} (m, Ar).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.53 (s, 3 H, 7′-CH_3), 2.55 (s, 3 H, 7-CH_3), 3.74 (s, 3 H, OMe), 3.97 (s, 3 H, OMe), 6.56 (s, 1 H, H3′), 7.17 (s, 1 H, H3), 7.38 (dd, *J* = 8.4, 1.4 Hz, 1 H, H6′), 7.59 (dd, *J* = 7.6, 1.0 Hz, 1 H, H6), 7.87 (d, *J* = 1.4 Hz, 1 H, H8′), 8.00 (d, *J* = 1.0 Hz, 1 H, H8), 8.05 (d, *J* = 7.6 Hz, 1 H, H5), 8.16 (d, *J* = 8.4 Hz, 1 H, H5′).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.9 (CH_3), 22.0 (CH_3), 55.7 (OMe), 62.4 (OMe), 104.0 (C3′), 108.8 (C2′), 118.0 (C2), 121.5 (C6)[a], 122.4 (C6′)[a], 126.3 (C5′)[b], 127.4 (C8′)[b], 128.7 (C3)[b], 130.0 (C7′)[c], 130.3 (C4a′)[c],132.5 (C8a′)[c], 134.5 (C5)[d], 136.8 (C7)[d], 137.5 (C8)[d], 145.0 (C1′)[e], 147.7 (C4a)[e], 147.9 (C8a)[e], 151.7 (C4′)[e], 184.4 (C1)[f], 185.1 (C4)[f].

HRMS: *m/z* [M]$^+$ calcd for $C_{24}H_{20}O_4$: 372.1361; found: 372.1299.

Anal. Calcd for $C_{24}H_{20}O_4$: C, 77.4; H, 5.4. Found: C, 77.6; H, 5.2.

7,7′-Dimethyl-2,2′-binaphthalene-1,1′,4,4′-tetrone (7a); Typical Procedure

A suspension of **6a** (200 mg, 0.54 mmol) in a mixture of MeCN (18 mL) and H_2O (8 mL) was cooled to 0 °C. Over the course of 10 min a cooled soln of CAN (1.10 g, 2.00 mmol) in a mixture of MeCN (12 mL) and H_2O (12 mL) was added to the suspension. The mixture was stirred for 20 min and allowed to warm to 24 °C over 30 min. The mixture was diluted with H_2O (100 mL) and extracted with CH_2Cl_2. The residue obtained upon workup was chromatographed (EtOAc–hexane, 2:3) to afford **7a** (138 mg, 70%) as yellow crystals; mp 179–181 °C (EtOH).

IR (Nujol): 1668 (s, C=O), 1657 (s, C=O), 1599 (m, Ar), 1587 cm^{-1} (m, Ar).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.52 (s, 3 H, 7′-CH_3)[a], 2.54 (s, 3 H, 7-CH_3)[a], 6.93(s, 1 H, H3′)[b], 7.26 (s, 1 H, H3)[b], 7.60 (dd, *J* = 8.2, 2.0 Hz, 2 H, H6′, H6), 7.93 (d, *J* = 2.0 Hz, 1 H, H8′)[c], 8.01 (d, *J* = 8.2 Hz, 1 H, H5′)[d], 8.03 (d, *J* = 2.0 Hz, 1 H, H8)[c], 8.05 (d, *J* = 8.2 Hz, 1 H, H5)[d].

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.9 (CH_3), 29.7 (CH_3), 126.7 (C3′)[a], 127.4 (C3)[a], 127.6 (C6′)[a], 128.2 (C6)[a], 129.2 (C2′)[b], 129.8 (C2)[b], 131.0 (C7′)[c], 131.7 (C7)[c], 135.0 (C5′)[d], 135.4 (C5)[d],137.8 (C4a′)[e], 138.1 (C8a′)[e], 140.0 (C4a)[e], 144.3 (C8a)[e], 145.5 (C8′)[f], 145.8 (C8)[f], 177.3 (C1′)[g], 180.0 (C4′)[g], 182.0 (C1)[g], 183.8 (C4)[g].

(HRMS: *m/z* [M]$^+$ calcd for $C_{22}H_{14}O_4$: 342.0892; found: 342.0888.

Anal. Calcd for $C_{22}H_{14}O_4$: C, 77.2; H, 4.1. Found: C, 77.3; H, 4.3.

1,4,5-Trimethoxy-7-methylnaphthalen-2-ylboronic Acid (5b)

Following the typical procedure for **5a** using 1.32 M soln of BuLi (2.90 mL, 3.88 mmol, 1.1 equiv), **4b**[12] (1.1 g, 3.53 mmol), anhyd THF (15 mL), and $B(OMe)_3$ (2.0 mL, 1.83 g, 17.65 mmol, 5.0 equiv) gave **5b** (0.73 g, 75%), which was immediately used without further purification.

1′,4′,5,5′-Tetramethoxy-7,7′-dimethyl-2,2′-binaphthalene-1,4-dione (6b)

Following the typical procedure for **6a** using **2b**[12] (800 mg, 2.90 mmol), $Pd(PPh_3)_4$ (340 mg, 0.30 mmol), and benzene (30 mL) and aq 2 M Na_2CO_3 (3.0 mL), **5b** (780 mg, 2.80 mmol), and benzene (20 mL); chromatography (EtOAc–hexane, 1:1) afforded **6b** (782 mg, 63%) as reddish brown needles; mp 84–86 °C (EtOAc–hexane).

IR (Nujol): 1668 (m, C=O), 1651 (m, C=O), 1599 cm^{-1} (m, Ar).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.50 (s, 6 H, 7′-CH_3, 7-CH_3), 3.68 (s, 3 H, OMe), 3.94 (s, 3 H, OMe), 3.97 (s, 3 H, OMe), 4.03 (s, 3 H, OMe), 6.61 (s, 1 H, H3′), 6.76 (d, *J* = 1.2 Hz, 1 H, H6′), 7.07 (s, 1 H, H3), 7.13 (d, *J* = 1.0 Hz, 1 H, H6), 7.50 (d, *J* = 1.0 Hz, 1 H, H8), 7.66 (d, *J* = 1.2 Hz, 1 H, H8′).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.3 (CH_3), 22.4 (CH_3), 56.6 (OMe), 56.8 (OMe), 57.0 (OMe), 62.1 (OMe), 106.6 (C3′)[a], 110.1

(C6′)[a], 114.6 (C8′)[a], 117.5 (C2′)[b], 118.0 (C2)[b], 118.2 (C3)[a], 120.8 (C6)[a], 122.8 (C7′)[c], 131.4 (C7)[c], 134.7 (C4a′)[c], 137.2 (C8a′)[c], 139.6 (C8)[a], 145.2 (C4a)[d], 146.4 (C8a)[d], 147.8 (C5′)[d], 153.4 (C1′)[e], 157.4 (C4′)[e], 159.8 (C5)[e], 184.3 (C1)[f], 184.5 (C4)[f].

HRMS: *m/z* $[M]^+$ calcd for $C_{26}H_{24}O_6$: 432.1572; found: 432.1546.

Anal. Calcd for $C_{26}H_{24}O_6$: C, 72.2; H, 5.6. Found: C, 72.0; H, 5.8.

5,5′-Dimethoxy-7,7′-dimethyl-2,2′-binaphthalene-1,1′,4,4′-tetrone (7b)

Following the typical procedure for **7a** using **6b** (250 mg, 0.58 mmol), MeCN (18 mL), and H_2O (8 mL) with addition of CAN (1.0 g, 1.80 mmol), MeCN (10 mL), and H_2O (10 mL) over 20 min; chromatography (EtOAc–hexane, 1:1) afforded **7b** (151 mg, 65%) as yellow crystals; mp 219 °C (dec) (EtOAc–hexane).

IR (Nujol): 1668 (m, C=O), 1652 cm^{-1} (m, C=O).

^1H NMR (200 MHz, $CDCl_3$): δ = 2.49 (s, 6 H, 7′-CH_3, 7-CH_3), 4.02 (s, 6 H, 2 OMe), 6.94 (d, *J* = 1.0 Hz, 2 H, H6′, H6), 7.13 (s, 2 H, H3′, H3), 7.58 (d, *J* = 1.0 Hz, 2 H, H8′, H8).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.5 (7′-CH_3, 7-CH_3), 56.6 (2 OMe), 118.6 (C6′, C6)[a], 120.8 (C3′, C3)[a], 131.0 (C2′, C2)[b], 135.1 (C7′, C7)[b], 139.8 (C8′, C8), 141.1 (C4a′, 4a)[c], 146.9 (C8a′, 8a)[c], 160.0 (C5′, C5), 183.2 (C1′, C1)[d], 183.5 (C4′, C4)[d].

HRMS: *m/z* $[M]^+$ calcd for $C_{24}H_{18}O_6$: 402.1103; found: 402.1247.

Anal. Calcd for $C_{24}H_{18}O_6$: C, 71.6; H, 4.5. Found: C, 71.8; H, 4.6.

2,5-Dimethoxyphenylboronic Acid (8)

Following the typical procedure for **5a** using 1.32 M soln of BuLi (3.84 mL, 5.06 mmol, 1.1 equiv), 2-bromo-1,4-dimethoxybenzene (1.0g, 4.60 mmol), and THF (10 mL), but stirring the mixture for 10 min, and $B(OMe)_3$(2.58 mL, 2.39 g, 23.00 mmol, 5.0 equiv) with the mixture allowed to warm to 24 °C over 2 h. **8** (671 mg, 80%) was obtained as white crystals; mp 86–87 °C (benzene) (Lit.[25] 91–93 °C).

IR (Nujol): 3227 (s, OH), 1503 cm^{-1} (s, Ar).

^1H NMR (200 MHz, $CDCl_3$): δ = 3.81 (s, 3 H, OMe), 3.88 (s, 3 H, OMe), 6.38 [br s, 2 H, $B(OH)_2$], 6.85 (d, *J* = 8.6 Hz, 1 H, H6), 6.99 (dd, *J* = 8.6, 2.8 Hz, 1 H, H5), 7.39 (d, *J* = 2.8 Hz, 1 H, H3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.8 (OMe), 56.1 (OMe), 111.3, 118.7, 120.8 (C2, C3, C5, C6), 153.9 (C1)[a], 158.9 (C4)[a].

HRMS: *m/z* $[M]^+$ calcd for $C_8H_{11}BO_4$: 182.0752; found: 182.0755.

Anal. Calcd for $C_8H_{11}BO_4$: C, 52.8; H, 6.1. Found: C, 52.9; H, 6.0.

2-(2,5-Dimethoxyphenyl)-7-methyl-1,4-naphthoquinone (9a)

Following the typical procedure for **6a** using **2a** (700 mg, 2.80 mmol), $Pd(PPh_3)_4$ (335 mg, 0.29 mmol), and benzene (30 mL) and aq 2 M Na_2CO_3 (3.0 mL), **8** (500 mg, 2.74 mmol), and benzene (20 mL); chromatography (EtOAc–hexane, 1:5) afforded **9a** (652 mg, 76%) as reddish brown crystals; mp 63–64 °C (EtOH).

IR (Nujol): 1663 (s, C=O), 1655 (m, C=O), 1599 cm^{-1} (s, Ar).

^1H NMR (200 MHz, $CDCl_3$): δ = 2.51 (s, 3 H, 7-CH_3), 3.74 (s, 3 H, OMe), 3.79 (s, 3 H, OMe), 6.81 (d, *J* = 2.6 Hz, 1 H, H3′), 6.94 (s, 1 H, H3)[a], 6.94 (m, 1 H, H6′)[a], 6.97 (m, 1 H, H5′)[a], 7.56 (dd, *J* = 8.2, 2.0 Hz, 1 H, H6), 7.94 (d, *J* = 2.0 Hz, 1 H, H8), 8.01 (d, *J* = 8.2 Hz, 1 H, H5).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.8 (CH_3), 55.8 (OMe), 56.4 (OMe), 112.6 (C3′)[a], 115.9 (C6′)[a], 116.1 (C5′)[a], 124.4 (C2′)[b], 126.2 (C3)[c], 127.3 (C6)[c], 130.0 (C2)[b], 132.5 (C7)[b], 134.3 (C8)[c], 136.8 (C5)[c], 144.8 (C4a)[d], 147.8 (C8a)[d], 151.5 (C1′)[e], 153.5 (C4′)[e], 183.7 (C1)[f], 185.1 (C4)[f].

HRMS: *m/z* $[M]^+$ calcd for $C_{19}H_{16}O_4$: 308.1048; found: 308.1049.

Anal. Calcd for $C_{19}H_{16}O_4$: C, 74.0; H, 5.2. Found: C, 74.2; H, 5.0.

2-(3,6-Dioxocyclohexa-1,4-dienyl)-7-methyl-1,4-naphthoquinone (10a)

Following the typical procedure for **7a** using **9a** (450 mg, 1.45 mmol), MeCN (40 mL), and H_2O (16 mL) with the addition of CAN (2.4 g, 4.37 mmol), MeCN (25 mL), and H_2O (25 mL) over 20 min. Extraction was with CH_2Cl_2 (3 × 30 mL) and chromatography (EtOAc–hexane, 1:4) afforded **10a** (290 mg, 71%) as yellow crystals; mp 155–157 °C (EtOH).

IR (Nujol): 1668 (s, C=O), 1658 (m, C=O), 1599 (s, Ar), 1580 cm^{-1} (m, Ar).

^1H NMR (200 MHz, $CDCl_3$): δ = 2.52 (s, 3 H, 7-CH_3), 6.89 (br s, 3 H, H3′, H5′, H6′), 6.97 (s, 1 H, H3), 7.59 (dd, *J* = 8.0, 2.0 Hz, 1 H, H6), 7.92 (d, *J* = 2.0 Hz, 1 H, H8), 8.01(d, *J* = 8.0 Hz, 1 H, H5).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.9 (CH_3), 126.6 (C5′)[a], 127.4 (C6′)[a], 129.8 (C2′)[b], 131.8 (C2)[b], 135.0 (C3′)[c], 135.5 (C6)[c], 136.6 (C8)[c], 136.9 (C5)[c], 138.0 (C3)[c], 141.3 (C4a)[d], 142.2 (C8a)[d], 145.6 (C7)[d], 182.9 (C1′)[e], 183.8 (C4′)[e], 184.6 (C1)[e], 186.4 (C4)[e].

HRMS: *m/z* $[M]^+$ calcd for $C_{17}H_{10}O_4$: 278.0579; found: 278.0570.

Anal. Calcd for $C_{17}H_{10}O_4$: C, 73.4; H, 3.6. Found: C, 73.2; H, 3.8.

2-(3,6-Dioxocyclohexa-1,4-dienyl)-5-methoxy-7-methyl-1,4-naphthoquinone (9b)

Following the typical procedure for **6a** using **2b** (760 mg, 2.70 mmol), $Pd(PPh_3)_4$ (320 mg, 0.28 mmol), and benzene (30 mL) and aq 2 M Na_2CO_3 (3.0 mL), **8** (500 mg, 2.70 mmol), and benzene (20 mL); chromatography (EtOAc–hexane, 3:7) afforded **9b** (575 mg, 63%) as reddish brown crystals; mp 147–149 °C (EtOH).

IR (Nujol): 1668 (m, C=O), 1649 (s, C=O), 1603 cm^{-1} (m, Ar).

^1H NMR (200 MHz, $CDCl_3$): δ = 2.46 (s, 3 H, CH_3), 3.71 (s, 3 H, OMe), 3.77 (s, 3 H, OMe), 3.98 (s, 3 H, OMe), 6.79 (dd, *J* = 2.4, 0.6 Hz, 1 H, H3′), 6.86 (s, 1 H, H3), 6.90 (m, 2 H, H5′, H6′), 7.08 (d, *J* = 2.0 Hz, 1 H, H6), 7.58 (d, *J* = 2.0 Hz, 1 H, H8).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.2 (CH_3), 55.7 (OMe), 56.3 (2 OMe), 112.5 (C3′)[a], 115.7 (C5′)[a], 116.0 (C6′)[a], 117.7 (C2′), 117.9 (C6)[b], 120.4 (C8)[b], 123.9 (C2)[c], 134.6 (C7)[c], 138.8 (C3)[b], 145.3 (C4a)[d], 146.1 (C8a)[d], 151.4 (C1′)[e], 153.4 (C4′)[e], 159.5 (C5)[e], 183.8 (C1)[f], 184.2 (C4)[f].

HRMS: *m/z* $[M]^+$ calcd for $C_{20}H_{18}O_5$: 338.1154; found: 338.1143.

Anal. Calcd for $C_{20}H_{18}O_5$: C, 71.0; H, 5.4. Found: C, 71.3; H, 5.6.

2-(3,6-Dioxocyclohexa-1,4-dienyl)-5-methoxy-7-methyl-1,4-naphthoquinone (10b)

Following the typical procedure for **7a** using **9a** (290 mg, 0.86 mmol), MeCN (25 mL), and H_2O (10 mL) and CAN (1.44 g, 2.62 mmol), MeCN (15 mL), and H_2O (15 mL); chromatography (EtOAc–hexane, 2:3) afforded **10b** (191 mg, 72%) as orange crystals; mp >300 °C (EtOH).

IR (Nujol): 1667 (m, C=O), 1646 (w, C=O), 1597 (w, Ar), 1577 cm^{-1} (m, Ar).

^1H NMR (200 MHz, DMSO-d_6): δ = 2.42 (s, 3 H, 7-CH_3), 3.90 (s, 3 H, 5-OMe), 7.03 (dd, *J* = 8.8, 2.6 Hz, 1 H, H5′), 7.34 (d, *J* = 2.0 Hz, 1 H, H6), 7.39 (d, *J* = 2.6 Hz, 1 H, H3′), 7.48 (s, 1 H, H3), 7.66 (d, *J* = 8.8 Hz, 1 H, H6′), 9.91 (d, *J* = 2.0 Hz, 1 H, H8).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 21.7 (CH_3), 56.3 (OMe), 106.3 (C5′)[a], 113.5 (C6′)[a], 116.7 (C2′)[b], 118.3 (C3′)[a], 119.4 (C2)[b], 119.8 (C3)[c], 120.8 (C7)[c], 122.9 (C6)[c], 134.9 (C8)[c], 146.9 (C4a)[d], 149.5 (C8a)[d], 154.7 (C5), 155.8 (C1′)[e], 160.5 (C4′)[e], 173.4 (C1)[f], 180.8 (C4)[f].

HRMS: *m/z* $[M]^+$ calcd for $C_{18}H_{12}O_5$: 308.0684; found: 308.0611.

Anal. Calcd for $C_{18}H_{12}O_5$: C, 70.1; H, 3.9. Found: C, 70.2; H, 4.0.

2-(3,6-Dioxocyclohexa-1,4-dienyl)-5-hydroxy-7-methyl-1,4-naphthoquinone (11)

To a soln of **10b** (150 mg, 0.49 mmol) in anhyd CH_2Cl_2 (20 mL) at 25 °C under an N_2 atmosphere was added $AlCl_3$ (2.61 g, 19.60 mmol). The mixture was stirred at 25 °C for 24 h, poured into H_2O, then acidified with dil HCl, and extracted with CH_2Cl_2. The residue obtained upon workup was chromatographed (EtOAc–hexane, 1:5) to afford **11** (78 mg, 55%) as red crystals; mp >300 °C (EtOAc–hexane).

IR (Nujol): 3400 (s, OH), 1650 (w, C=O), 1643 (m, C=O), 1565 cm^{-1} (w, Ar).

^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.40 (s, 3 H, CH_3), 7.09 (dd, *J* = 9.0, 2.4 Hz, 1 H, H5′), 7.15 (d, *J* = 2.0 Hz, 1 H, H6), 7.43 (d, *J* = 2.4 Hz, 2 H, H3′, overlaid by H3), 7.72 (d, *J* = 9.0 Hz, 1 H, H6′), 9.97 (d, *J* = 2.0 Hz, 1 H, H8), 11.77 (s, 1 H, 5-OH).

^{1}H NMR (200 MHz, acetone-d_6): δ = 2.48 (s, 3 H, CH_3), 7.16 (s, 1 H, H3), 7.22 (dd, *J* = 9.2, 2.4 Hz, 1 H, H5′), 7.56 (d, *J* = 2.2 Hz, 1 H, H6), 7.62 (d, *J* = 2.4 Hz, 1 H, H3′), 7.68 (d, *J* = 9.2 Hz, 1 H, H6′), 8.93 (d, *J* = 2.2 Hz, 1 H, H8), 11.99 (s, 1 H, 5-OH).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 21.5 (CH_3), 106.1 (C5′)[a], 113.0 (C2′), 113.7 (C6′)[a], 119.3 (C3′)[b], 120.4 (C3)[b], 123.0 (C6)[c], 123.3 (C2)[a], 124.0 (C7)[c], 133.0 (C8), 148.4 (C4a)[d], 150.1 (C8a)[d], 153.5 (C5), 156.0 (C1′)[e], 161.4 (C4′)[e], 178.9 (C1)[f], 180.3 (C4)[f].

HRMS: *m*/*z* $(M]^+$ calcd for $C_{17}H_{10}O_5$: 294.0528; found: 294.0571.

Anal. Calcd for $C_{17}H_{10}O_5$: C, 69.4; H, 3.4. Found: C, 69.2; H, 3.6.

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