

Synthesis of Diospyrin, a Potential Agent Against Leishmaniasis and Related Parasitic Protozoan Diseases

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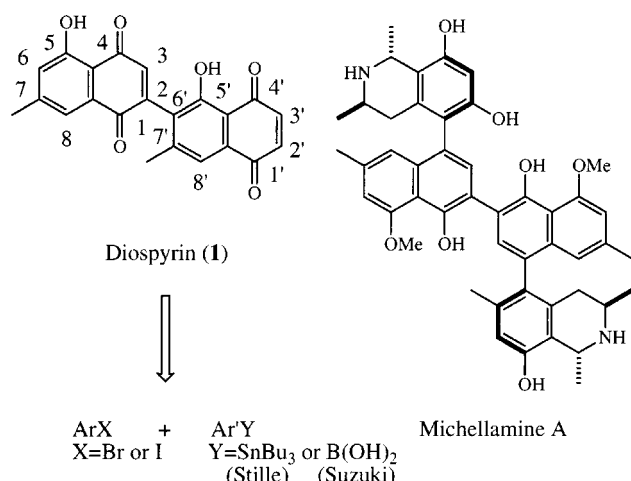
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The first synthesis of diospyrin [2,6'-bis(5-hydroxy-7-methyl-1,4-naphthoquinone), **1**] was achieved by employing Suzuki

coupling between **5** and **14** as the key reaction to connect the two 7-methyljuglone units.

Introduction

Diospyrin was first isolated in 1961 by Kapil and Dhar as an orange-red constituent of *Diospyros montana* Roxb. (*Ebenaceae*), a small or medium-sized tree found throughout India.^[1] Its structure was proposed by Ganguly and Govindachari in 1966 as a dimer of 7-methyljuglone linked between C-2 and C-3'.^[2] Subsequent studies by Sidhu and Pardhasaradhi led to the correct structure of diospyrin as



Scheme 1. Structure and retrosynthetic analysis of diospyrin

depicted in **1** (Scheme 1) with a linkage between C-2 and C-6'.^[3,4] Isolation of diospyrin and its derivatives from *D. montana* was also reported by Musgrave and co-workers.^[5] Waterman and co-workers then examined a number of *Diospyros* species in Africa, and isolated **1** from many of them.^[6,7] Other African plants of the *Euclea* species are also known to produce **1**.^[8,9] Diospyrin (**1**) is optically inactive,^[5] and thus there is no restricted rotation around the connecting bond between C-2 and C-6'.

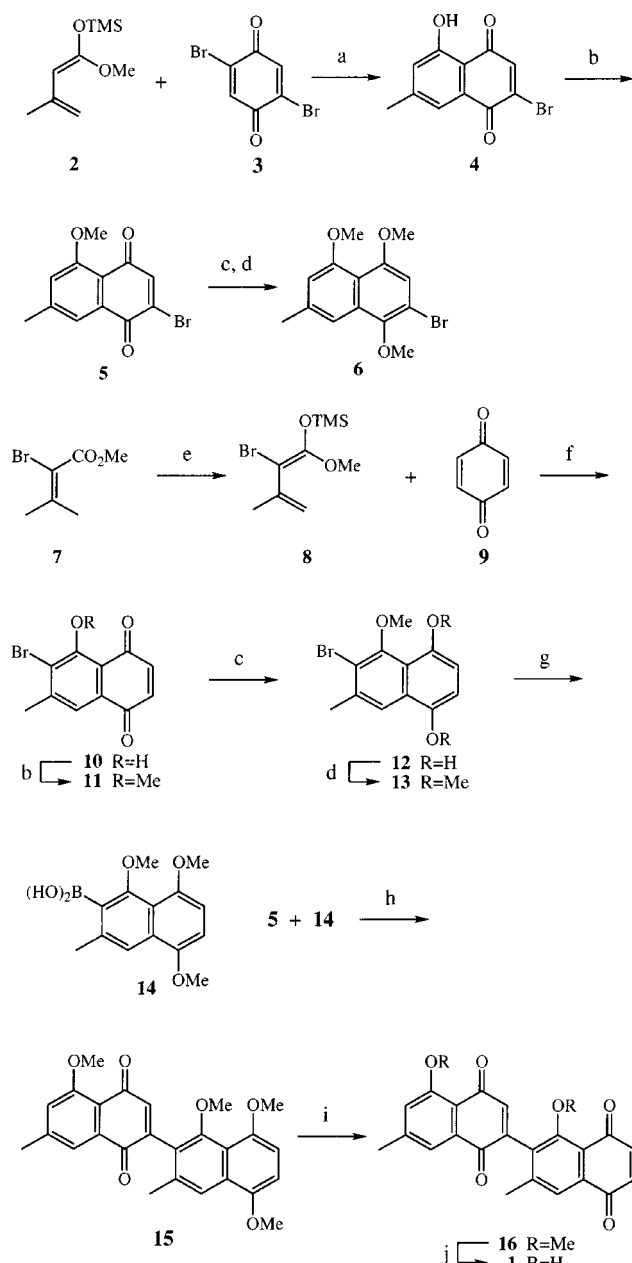
In 1995 Hazra et al. reported the in vitro antiparasitoid effects of diospyrin (**1**), suggesting it to be a useful model for the development of antimalarial drugs.^[10] Then, in 1996 they reported in vitro activity of diospyrin and its derivatives against *Leishmania donovani*, *Trypanosoma cruzi* and *T. bru-*

cei brucei, the causative agents of the protozoan diseases leishmaniasis and trypanosomiasis.^[11] Because we are working on the synthesis of the sex pheromone of the sandfly *Lutzomyia longipalpis*, the vector of *Leishmania* parasites, we have become interested in synthesizing diospyrin (**1**), which directly attacks the parasites themselves.^[12] Another good reason to attempt the synthesis of **1** was to prove unambiguously the correctness of the structure **1**. The structural elucidation of diospyrin depended on its ¹H NMR analysis,^[3,4,13] and there is no reported synthesis of **1** to date.

Scheme 1 shows the retrosynthetic analysis of diospyrin. The two naphthoquinone moieties should be synthesized separately, and then they must be coupled by using either the Stille reaction via organotin intermediates^[14] or Suzuki coupling via organoboronic acid intermediates.^[15] Recent endeavors in the synthesis of michellamine A and related compounds^[16–19] were very instructive to us in designing our own synthesis.

Our synthesis of diospyrin (**1**) is summarized in Scheme 2. The first stage of the synthesis was to prepare the naphthalene building blocks **6** and **13**. A Diels–Alder reaction between the known 1-methoxy-3-methyl-1-trimethylsilyloxy-1,3-butadiene (**2**)^[20] and 2,5-dibromo-1,4-benzoquinone (**3**) afforded **4**. This was methylated with methyl iodide and silver oxide to give **5**, whose reduction with tin(II) chloride^[21] was followed by further methylation of the resulting naphthalenediol to furnish **6**. For the synthesis of **13**, another Diels–Alder reaction was executed. For that purpose, 2-bromo-1-methoxy-3-methyl-1-trimethylsilyloxy-1,3-butadiene (**8**) was prepared from the known methyl 2-bromosenecioate (**7**).^[22] A Diels–Alder reaction between **8** and 1,4-benzoquinone (**9**) proceeded in dichloromethane, and the resulting mixture was treated with dilute hydrochloric acid to remove the partly remaining trimethylsilyl group, giving a mixture of **10** and **11**. This was fully methylated with methyl iodide and silver oxide to afford pure **11**. Reduction of **11** with tin(II) chloride furnished **12**, which was then methylated to give **13**. We first attempted the conversion of **6** or **13** to the corresponding tributyltin derivatives by their lithiation followed by stannylation. These attempts, however, were unsuccessful, and the use of the Stille reaction for the coupling of the two naphthalene units was abandoned.

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Scheme 2. Synthesis of diospyrin (1); reagents: (a) THF, room temp. (44%); (b) MeI, Ag₂O, reflux (quant. for 5; 55% for 11 based on 8); (c) SnCl₂, conc. HCl, EtOH (97%); (d) MeI, NaH, DMF (93% for 6; 92% for 13); (e) LDA, TMSCl, THF (65%); (f) i) CH₂Cl₂, room temp.; ii) 1 N HCl, MeOH; (g) *n*BuLi, THF, B(OMe)₃, -78 °C $\approx$ room temp. (66%); (h) Pd(PPh₃)₄, Na₂CO₃ aq., EtOH, toluene, reflux (53%); (i) Ce(NH₄)₂(NO₃)₆, MeCN, H₂O (quant.); (j) AlCl₃, CH₂Cl₂ (82%).

The obvious alternative approach was to employ Suzuki coupling,^[15,23] whose application in the synthesis of phytoalexin was recently reported by us.^[24] The desired boronic acid **14** was prepared by lithiation of **13** and subsequent reaction with trimethyl borate. By washing out the accompanying impurities with hot hexane, **14** could be obtained in 66% yield. The coupling of **14** with **6** in the presence of tetrakis(triphenylphosphane)palladium(0), however, failed under the conditions using four different bases (sodium carbonate, barium hydroxide, cesium carbonate and potassium

phosphate). Fortunately, coupling between the bromo-1,4-naphthoquinone **5** and **14** was successful under the standard conditions employing tetrakis(triphenylphosphane)palladium(0) as the catalyst in the presence of sodium carbonate to give the coupling product **15** as orange-red needles in 53% yield.

Oxidative demethylation of **15** with ceric ammonium nitrate^[21,25] furnished diospyrin dimethyl ether (**16**) as yellow needles melting at 256–258 °C (ref.^[3] m.p. 256 °C). Further demethylation of **16** to **1** was problematic, and the attempts with boron tribromide, 47% hydrobromic acid, lithium chloride in DMF, trimethylsilyl iodide, and potassium thiophenolate in diethylene glycol were all unsuccessful. The only fruitful method to achieve the demethylation was to treat **16** with aluminum chloride in dichloromethane at room temperature.^[26] The resultant diospyrin (**1**), m.p. 256–258 °C (ref.^[1] m.p. 258 °C) is identical with the authentic sample provided by Dr. Hazra in every respect including its IR, ¹H NMR, and ¹³C NMR spectra. The overall yield of diospyrin (**1**) was 19% based on **2** (5 steps) or 9% based on **7** (9 steps).

In conclusion, the first and unambiguous synthesis of diospyrin was achieved and its structure was firmly established as **1**. It should be added that the leishmanicidal activity of synthetic diaryl(heteroaryl)ethanes was reported very recently.^[27]

Experimental Section

General: Boiling points: Uncorrected values. – Melting points: Yanaco MP-S3, Uncorrected values. – MS: Hitachi M-80B. – IR: Jasco A-102. – UV/Vis: Shimadzu MPS-2000. – ¹H NMR: Jeol JNM-EX 90A (90 MHz), Jeol JNM-LA 500 (500 MHz) (TMS at δ = 0.00, CHCl₃ at δ = 7.26 as internal standard). – ¹³C NMR: Jeol JNM-LA 400 (100 MHz) (TMS at δ = 0.00, CDCl₃ at δ = 77.0 as an internal standard), Jeol JNM-LA 500 (125 MHz) (TMS at δ = 0.00, CDCl₃ at δ = 77.0 as an internal standard).

2-Bromo-5-hydroxy-7-methyl-1,4-naphthoquinone (4): The known 1-methoxy-3-methyl-1-trimethylsilyloxy-1,3-butadiene (**2**) was prepared from senecioic acid.^[20] To a solution of 2,5-dibromo-1,4-benzoquinone (**3**, 12.8 g, 48.1 mmol) in 80 mL of dry THF at 0 °C under argon was added a solution of **2** (9.87 g, 53.0 mmol) in 45 mL of dry THF dropwise from a syringe pump over 1 h. The resulting solution was stirred at room temperature for 5 h and then concentrated under reduced pressure. The residue was chromatographed on silica gel and then recrystallized from hexane/ethyl acetate to afford 5.62 g (44%) of **4** as orange red needles, m.p. 132.0–133.5 °C. – IR (KBr): $\tilde{\nu}_{\max}$ = 3060 cm⁻¹ (w, C–H), 1670 (m, C=O), 1630 (s, C=O), 1580 (m, Ar), 1560 (m, Ar). – ¹H NMR (90 MHz, CDCl₃): δ = 2.44 (br s, 3 H, 7-Me), 7.11 (br s, 1 H, 8-H), 7.45 (s, 1 H, 3-H), 7.54 (br s, 1 H, 6-H), 11.71 (s, 1 H, 5-OH). – ¹³C NMR (100 MHz, CDCl₃): δ = 22.2, 112.6, 122.4, 124.8, 130.4, 140.4, 140.5, 148.5, 161.9, 177.5, 186.9. – C₁₁H₇BrO₃ (267.1): calcd. C 49.47, H 2.64; found C 49.66, H 2.66.

2-Bromo-5-methoxy-7-methyl-1,4-naphthoquinone (5): A mixture of **4** (4.00 g, 15.0 mmol), powdered Ag₂O (5.22 g, 22.5 mmol), and methyl iodide (80 mL) was stirred and heated under reflux for 1 h. The mixture was then filtered through Celite and the filter cake was washed with chloroform. The filtrate and the washings were

combined and evaporated to afford 4.25 g (quant.) of **5** as a yellow solid. The crude product was used in the next reaction without further purification. An analytical sample of **5** was obtained by recrystallization from hexane/chloroform as yellow needles, m.p. 168.5–170.0 °C. – IR (KBr): $\tilde{\nu}_{\max}$ = 3100 cm⁻¹ (w, C–H), 3020 (w, C–H), 3000 (w, C–H), 2950 (w, C–H), 2850 (w, C–H), 1665 (s, C=O), 1640 (s, C=O), 1600 (s, Ar). – ¹H NMR (90 MHz, CDCl₃): δ = 2.48 (br s, 3 H, 7-Me), 3.99 (s, 3 H, 5-OMe), 7.12 (br s, 1 H, 8-H), 7.36 (s, 1 H, 3-H), 7.63 (br s, 1 H, 6-H). – ¹³C NMR (100 MHz, CDCl₃): δ = 22.3, 56.5, 117.0, 118.8, 121.5, 132.8, 136.6, 142.4, 146.7, 160.1, 178.5, 181.3. – C₁₂H₉BrO₃ (281.11): calcd. C 51.27, H 3.23; found C 51.29, H 3.24.

2-Bromo-1,5,8-trimethoxy-3-methylnaphthalene (6): To a stirred suspension of **5** (2.00 g, 7.11 mmol) in ethanol (80 mL) at 50 °C was added a solution of tin(II) chloride (4.72 g, 24.9 mmol) in concentrated HCl (5.0 mL). After 30 min at the same temperature, it was then poured into cold water (300 mL). The precipitated product was collected by filtration and washed with water. The resulting crude product (1.94 g, 97%), isolated as a white solid, was used in the next reaction without further purification. – IR (KBr): $\tilde{\nu}_{\max}$ = 3360 cm⁻¹ (br s, OH), 3020 (w, C–H), 2970 (w, C–H), 2950 (w, C–H), 2840 (w, C–H), 1625 (m, Ar), 1605 (s, Ar). – ¹H NMR (90 MHz, CDCl₃): δ = 2.49 (s, 3 H, 7-Me), 4.04 (s, 3 H, 5-OMe), 5.45 (s, 1 H, 1-OH or 4-OH), 6.67 (br s, 1 H, 8-H), 6.85 (s, 1 H, 3-H), 7.59 (br s, 1 H, 6-H), 8.90 (s, 1 H, 4-OH or 1-OH).

To a stirred suspension of sodium hydride (60% dispersion in mineral oil, 297 mg, 7.41 mmol) in DMF (30 mL) at room temperature under argon was added a solution of the reduction product (700 mg, 2.47 mmol) in DMF (10 mL). The mixture was stirred at room temperature for 45 min. After cooling to 0 °C, methyl iodide (0.46 mL, 7.41 mmol) was added and the resulting mixture was stirred at room temperature for 6 h. It was then diluted with chloroform. The chloroform solution was washed with water and brine, dried with MgSO₄, and concentrated under reduced pressure. The residue was chromatographed on silica gel (40 g, hexane/ethyl acetate 10:1) to afford 718 mg (93%) of **6** as a colorless solid. An analytical sample of **6** was obtained by recrystallization from hexane as colorless needles, m.p. 95.0–96.0 °C. – IR (KBr): $\tilde{\nu}_{\max}$ = 3000 cm⁻¹ (w, C–H), 2950 (w, C–H), 2930 (w, C–H), 2840 (w, C–H), 1620 (m, Ar), 1585 (s, Ar). – ¹H NMR (90 MHz, CDCl₃): δ = 2.50 (s, 3 H, 7-Me), 3.91 (s, 6 H, 4-OMe, 5-OMe), 3.95 (s, 3 H, 1-OMe), 6.72 (br s, 1 H, 8-H), 6.83 (s, 1 H, 3-H), 7.46 (br s, 1 H, 6-H). – ¹³C NMR (100 MHz, CDCl₃): δ = 22.2, 56.4, 56.7, 61.1, 108.8, 108.9, 112.7, 113.8, 115.7, 131.7, 137.7, 146.2, 153.8, 157.3. – C₁₄H₁₅BrO₃ (311.2): calcd. C 54.04, H 4.86; found C 54.18, H 4.80.

2-Bromo-1-methoxy-3-methyl-1-trimethylsilyloxy-1,3-butadiene (8): The known methyl 2-bromo-senecioate (**7**) was prepared from senecioic acid.^[21] A solution of lithium diisopropylamide (LDA) was prepared from 13.1 mL (93.2 mmol) of diisopropylamine in 120 mL of dry THF and 37.0 mL of a 2.52 M solution of *n*-butyllithium in hexane. The LDA solution was cooled to –78 °C and a solution of **7** (15.0 g, 77.7 mmol) in 90 mL of dry THF was added dropwise over 1 h. The mixture was stirred for 0.5 h at the same temperature and trimethylsilyl chloride (11.8 mL, 93.2 mmol) was then added. The temperature was allowed to rise to room temperature, stirring was continued for 2 h, the solvent was then removed under reduced pressure, and the residue redissolved in hexane. The solution was filtered to remove the precipitated LiCl, the solvent removed from the filtrate in vacuo, and the residue distilled to afford 14.1 g (65%) of **8** as a colorless oil, b.p. 54.0–56.0 °C/1.5 Torr. – IR (film): $\tilde{\nu}_{\max}$ = 1615 cm⁻¹. – ¹H NMR (90 MHz, CDCl₃): δ = 0.24 (s, 9 H, 1-OTMS), 1.95 (s, 3 H, 3-Me), 3.65 (s, 3 H, 1-OMe), 5.00–5.12 (m,

1 H, 4*cis*-H), 5.18 (br s, 1 H, 4*trans*-H). This oil was employed immediately for the next step.

6-Bromo-5-hydroxy-7-methyl-1,4-naphthoquinone (10): To a solution of **8** (13.2 g, 47.4 mmol) in 300 mL of dry dichloromethane at room temperature under argon was added 1,4-benzoquinone (**9**, 10.2 g, 94.8 mmol). The resulting solution was stirred at room temperature for 12 h, concentrated under reduced pressure, and the residue was dissolved in 300 mL of methanol. After addition of 1 N HCl (4 mL), the solution was stirred for 1 h at 0 °C, and again concentrated under reduced pressure. The residue was dissolved in chloroform and ethyl acetate, dried with MgSO₄ and concentrated under reduced pressure. The residue was chromatographed on silica gel (500 g, hexane/ethyl acetate 30:1) to afford 7.06 g (56%) of a mixture of **10** and **11** as an orange/red solid. The crude product was used in the next reaction without further purification. – ¹H NMR (90 MHz, CDCl₃): δ = 2.56 (s, 3 H, 7-Me), 6.95 (s, 2 H, 2-H, 3-H), 7.52 (s, 1 H, 8-H), 12.64 (s, 1 H, 5-OH).

6-Bromo-5-methoxy-7-methyl-1,4-naphthoquinone (11): A mixture of **10** and **11** (7.06 g), powdered Ag₂O (9.18 g, 39.6 mmol), and methyl iodide (120 mL) was stirred and heated under reflux for 1 h. The mixture was then filtered through Celite and the filter cake was washed with chloroform. The filtrate and the washings were combined and evaporated to afford 7.29 g (55% from **8**) of **11** as a yellow solid. The crude product was used in the next reaction without further purification. An analytical sample of **11** was obtained by recrystallization from hexane/chloroform as a yellow solid, m.p. 152.0–153.5 °C. – IR (KBr): $\tilde{\nu}_{\max}$ = 3050 cm⁻¹ (w, C–H), 3000 (w, C–H), 2950 (w, C–H), 2860 (w, C–H), 1665 (s, C=O), 1610 (m, Ar), 1575 (s, Ar). – ¹H NMR (90 MHz, CDCl₃): δ = 2.56 (s, 3 H, 7-Me), 3.93 (s, 3 H, 5-OMe), 6.89 (s, 2 H, 2-H, 3-H), 7.80 (s, 1 H, 8-H). – ¹³C NMR (100 MHz, CDCl₃): δ = 24.4, 61.5, 122.7, 124.6, 130.1, 131.7, 136.7, 140.3, 146.7, 156.9, 183.3, 184.6. – C₁₂H₉BrO₃ (281.1): calcd. C 51.27, H 3.23; found C 51.34, H 3.16.

6-Bromo-5-methoxy-7-methyl-1,4-naphthalenediol (12): To a stirred suspension of **11** (4.02 g, 14.3 mmol) in ethanol (160 mL) at 50 °C was added a solution of tin(II) chloride (9.45 g, 50.1 mmol) in concentrated HCl (10.0 mL). After 30 min at the same temperature, it was poured into cold water (600 mL). The precipitated product was separated by filtration and washed with water. The resulting crude product **12** (3.94 g, 97%) was obtained as a white solid and was used in the next reaction without further purification. – IR (KBr): $\tilde{\nu}_{\max}$ = 3420 cm⁻¹ (s, OH), 3380 (s, OH), 3275 (s, OH), 3000 (w, C–H), 2950 (w, C–H), 2850 (w, C–H), 1630 (m, Ar), 1600 (s, Ar). – ¹H NMR (90 MHz, CDCl₃): δ = 2.57 (d, *J* = 0.8 Hz, 3 H, 7-Me), 4.04 (s, 3 H, 5-OMe), 6.73 (s, 2 H, 2-H, 3-H), 7.86 (d, *J* = 0.8 Hz, 1 H, 8-H), 8.86 (s, 1 H, -OH).

2-Bromo-1,5,8-trimethoxy-3-methylnaphthalene (13): To a stirred suspension of sodium hydride (60% dispersion in mineral oil, 1.72 g, 42.9 mmol) in DMF (160 mL) at room temperature under argon was added a solution of **12** (3.94 g, 13.9 mmol) in DMF (40 mL). The mixture was then stirred at room temperature for 45 min. After cooling to 0 °C, methyl iodide (2.60 mL, 41.7 mmol) was added and the resulting mixture was stirred at room temperature for 12 h. It was then diluted with chloroform, washed with water and brine, dried with MgSO₄, and concentrated under reduced pressure. The residue was chromatographed on silica gel (200 g, hexane/ethyl acetate 10:1) to afford 4.08 g (92% based on **11**) of **13** as a colorless solid. An analytical sample of **13** was obtained by recrystallization from hexane as colorless needles, m.p. 123–125 °C. – IR (KBr): $\tilde{\nu}_{\max}$ = 3000 cm⁻¹ (w, C–H), 2950 (w, C–H), 2910 (m, C–H), 2850 (m, C–H), 1620 (m, Ar), 1590 (s, Ar). –

^1H NMR (90 MHz, CDCl_3): δ = 2.56 (s, 3 H, 3-Me), 3.88 (s, 3 H, 1-OMe), 3.94 (s, 6 H, 5-OMe, 8-OMe), 6.73 (s, 2 H, 6-H, 7-H), 7.92 (s, 1 H, 4-H). – ^{13}C NMR (125 MHz, CDCl_3): δ = 24.0, 55.8, 57.1, 61.6, 104.2, 106.5, 118.8, 120.29, 120.32, 127.2, 136.4, 149.20, 149.25, 152.9. – $\text{C}_{14}\text{H}_{15}\text{BrO}_3$ (311.2): calcd. C 54.04, H 4.86; found C 54.01, H 4.77.

1,5,8-Trimethoxy-3-methylnaphthalene-2-boronic Acid (14): A solution of **13** (1.90 g, 6.11 mmol) in dry THF (200 mL) under argon was cooled to -78°C . Over the course of 10 min, a 1.54 M solution of *n*-butyllithium in hexane (4.36 mL, 6.72 mL) was added, and the reaction mixture was stirred for 1 h to give a yellow solution. Trimethyl borate (3.43 mL, 30.6 mmol) was then added, and the reaction mixture was allowed to warm to room temperature for about 12 h. The mixture was diluted with water (100 mL), and extracted with dichloromethane. The combined organic extracts were dried with MgSO_4 and concentrated under reduced pressure. The residue was refluxed with hexane and the insoluble residue was collected on a filter to give **14** (1.11 g, 66%) as a white solid, m.p. 122–124 $^\circ\text{C}$. – IR (KBr): $\tilde{\nu}_{\text{max}}$ = 3340 cm^{-1} (s, OH), 3000 (m, C–H), 2970 (m, C–H), 2950 (m, C–H), 2850 (m, C–H), 1625 (s, Ar), 1600 (s, Ar), 1580 (s, Ar). – ^1H NMR (90 MHz, CDCl_3): δ = 2.60 (s, 3 H, 3-Me), 3.85 (s, 3 H, 1-OMe), 3.95 (s, 6 H, 5-OMe, 8-OMe), 5.90 [s, 2 H, B(OH) $_2$], 6.71 (s, 2 H, 6-H, 7-H), 7.92 (s, 1 H, 4-H). – ^{13}C NMR (125 MHz, CDCl_3): δ = 23.2, 55.8, 56.3, 63.8, 104.6, 104.7, 117.8, 118.8, 129.6, 140.1, 140.4, 149.1, 149.5, 161.3. – $\text{C}_{14}\text{H}_{17}\text{BO}_5$ (276.1): calcd. C 60.90, H 6.21; found C 58.60, H 6.01. Due to the hygroscopic nature of **14**, correct combustion analytical data could not be obtained. – $\text{C}_{14}\text{H}_{17}\text{BO}_5$: calcd. 276.1169; found 276.1185 (HRMS).

2-(1',4',5'-Trimethoxy-7'-methylnaphthalen-6'-yl)-5-methoxy-7-methyl-1,4-naphthoquinone (15): To a stirred mixture of $\text{Pd}(\text{PPh}_3)_4$ (124 mg, 0.11 mmol) and **5** (300 mg, 1.07 mmol) in toluene (5 mL) were added successively an aqueous Na_2CO_3 solution (2 M, 0.93 mL) and **14** (325 mg, 1.18 mmol) in ethanol (1.3 mL) under argon. The mixture was refluxed for 3 h with vigorous stirring. The resulting mixture was extracted with chloroform. The extract was washed with brine, dried with MgSO_4 , and concentrated under reduced pressure. The residue was chromatographed on silica gel (20 g, benzene/ethyl acetate 10:1) to afford 245 mg (53%) of **15** as an orange/red solid. An analytical sample of **15** was obtained by recrystallization from benzene/ethyl acetate as orange red needles, m.p. 195.0–196.0 $^\circ\text{C}$. – IR (KBr): $\tilde{\nu}_{\text{max}}$ = 2950 cm^{-1} (w, C–H), 2840 (w, C–H), 1655 (s, C=O), 1630 (m, C=O), 1600 (s, Ar), 1460 (m), 1425 (m), 1340 (m), 1300 (m), 1260 (m), 1235 (m), 1110 (m), 1070 (s), 1045 (m). – ^1H NMR (90 MHz, CDCl_3): δ = 2.27 (d, J = 0.9 Hz, 3 H, 7'-Me), 2.49 (s, 3 H, 7-Me), 3.64 (s, 3 H, 5'-OMe), 3.92 (s, 3 H, 1'-OMe or 4'-OMe), 3.96 (s, 3 H, 4'-OMe or 1'-OMe), 4.03 (s, 3 H, 5-OMe), 6.73 (s, 2 H, 2'-H, 3'-H), 6.86 (s, 1 H, 3-H), 7.13 (br s, 1 H, 6-H), 7.62 (br s, 1 H, 8-H), 7.93 (d, J = 0.9 Hz, 1 H, 8'-H). – ^{13}C NMR (100 MHz, CDCl_3): δ = 20.6, 22.4, 55.9, 56.41, 56.44, 62.7, 104.5, 105.0, 118.1, 118.5, 118.8, 120.7, 126.7, 128.3, 128.8, 134.28, 134.34, 139.9, 145.3, 146.3, 149.2, 149.8, 153.7, 159.7, 184.2, 184.8. – $\text{C}_{26}\text{H}_{24}\text{O}_6$ (432.5): calcd. C 72.21, H 5.91; found C 72.35, H 5.96.

2,6'-Bis(5-methoxy-7-methyl-1,4-naphthoquinone) (16): A suspension of **15** (378 mg, 0.87 mmol) in a mixture of acetonitrile (25 mL) and water (10 mL) was cooled to 0 $^\circ\text{C}$. Over the course of 10 min, a cooled solution of ceric ammonium nitrate (1.44 g, 2.62 mmol) in a mixture of acetonitrile (15 mL) and water (15 mL) was added to the suspension. The reaction mixture was stirred at 0 $^\circ\text{C}$ for 20 min, and allowed to warm to room temperature over 30 min. The mixture was diluted with water, and extracted with chloroform.

The extract was washed with brine, dried with MgSO_4 , and evaporated to afford 352 mg (quant.) of **16** as a yellow solid. The crude product was used in the next reaction without further purification. An analytical sample of **16** was obtained by recrystallization from petroleum ether/dichloromethane as yellow needles, m.p. 256–258 $^\circ\text{C}$ (ref.^[3] 256 $^\circ\text{C}$). – IR (KBr): $\tilde{\nu}_{\text{max}}$ = 3050 cm^{-1} (w, C–H), 3000 (w, C–H), 2950 (w, C–H), 2850 (w, C–H), 1655 (s, C=O), 1630 (m, C=O), 1600 (s, Ar), 1580 (s, Ar), 1455 (m), 1405 (w), 1350 (m), 1335 (m), 1305 (s), 1290 (m), 1280 (m), 1260 (s, C–O), 1165 (w), 1135 (w), 1100 (m), 1075 (w), 1050 (s, C–O), 855 (m). – ^1H NMR (90 MHz, CDCl_3): δ = 2.30 (d, J = 0.7 Hz, 3 H, 7'-Me), 2.50 (s, 3 H, 7-Me), 3.69 (s, 3 H, 5'-OMe), 4.03 (s, 3 H, 5-OMe), 6.77 (s, 1 H, 3-H), 6.89 (s, 1 H, 2'-H or 3'-H), 6.90 (s, 1 H, 3'-H or 2'-H), 7.16 (br s, 1 H, 6-H), 7.57–7.63 (m, 1 H, 8-H), 7.84 (d, J = 0.7 Hz, 1 H, 8'-H). – ^{13}C NMR (125 MHz, CDCl_3): δ = 20.8, 22.4, 56.5, 62.5, 117.7, 118.5, 120.7, 121.6, 124.4, 133.6, 133.9, 135.9, 136.7, 139.9, 140.5, 143.4, 144.8, 146.8, 158.1, 159.9, 183.3, 183.7, 184.1, 184.8. – $\text{C}_{24}\text{H}_{18}\text{O}_6$ (402.4): calcd. C 71.63, H 4.51; found C 71.35, H 4.38.

2,6'-Bis(5-hydroxy-7-methyl-1,4-naphthoquinone) (1) [Diospyrin]: To a solution of **16** (50.0 mg, 0.12 mmol) in dry dichloromethane (10 mL) at room temperature under argon was added aluminum trichloride (628 mg, 4.71 mmol). The mixture was stirred at room temperature for 24 h, poured into water, then acidified with dil. HCl, and extracted with chloroform. The extracted was dried with MgSO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel and refluxed with acetone. The insoluble residue gave 38 mg (82%) of **1** as an orange/red solid. An analytical sample of **1** was obtained by recrystallization from chloroform as orange plates, m.p. 256–258 $^\circ\text{C}$ (ref.^[1] 258 $^\circ\text{C}$); authentic **1**, m.p. 256–258 $^\circ\text{C}$; mixture m.p. 256–258 $^\circ\text{C}$. – EI-MS (70 eV); m/z (%): 374 (100)[M^+], 359 (16), 357 (11), 356 (12), 328 (10), 187 (9), 163 (8), 135 (10), 134 (10), 106 (13), 99 (10). – IR (KBr): $\tilde{\nu}_{\text{max}}$ = 3350 cm^{-1} (br w, C–H), 1670 (m, C=O), 1645 (s, C=O), 1610 (m, Ar), 1595 (m, Ar), 1385 (m), 1360 (m), 1335 (m), 1260 (s, C–O), 1210 (m), 1090 (m), 1050 (w), 855 (m). – UV/Vis (MeOH): λ_{max} (log ϵ) = 252 nm (4.34), 432 (3.90); (+NaOH) 260, 546. – ^1H NMR (500 MHz, CDCl_3): δ = 2.31 (s, 3 H, 7'-Me), 2.46 (s, 3 H, 7-Me), 6.90 (s, 1 H, 3-H), 6.96 (s, 2 H, 2'-H, 3'-H), 7.13 (s, 1 H, 6-H), 7.51 (s, 1 H, 8-H), 7.57 (s, 1 H, 8'-H), 11.88 (s, 1 H, 5-OH), 12.14 (s, 1 H, 5'-OH). – ^{13}C NMR (100 MHz, CDCl_3): δ = 21.1, 22.3, 113.0, 113.2, 120.8, 121.3, 124.3, 128.9, 131.4, 131.6, 138.81, 138.84, 139.5, 145.8, 146.5, 148.7, 159.2, 161.7, 182.6, 184.1, 188.9, 189.8. – $\text{C}_{22}\text{H}_{15}\text{O}_6 \cdot \text{H}_2\text{O}$ (392.4): calcd. C 67.35, H 4.11; found C 67.24, H 4.09. – $\text{C}_{22}\text{H}_{15}\text{O}_6$: calcd. 374.0790; found 374.0806 (HRMS).

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