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Practical First Total Synthesis of the Potent Phytotoxic (±)-Naphthotectone, Isolated from *Tectona grandis*

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Naphthotectone is a quinone isolated recently from teak extracts of *Tectona grandis*. It has been shown to be one of the most abundant compounds and the most active compound isolated form teak. Thus, it has been proposed that naphthotectone is one of the compounds responsible for the allelophathic activity of this plant. An efficient total synthesis of (±)-naphthotectone was achieved in seven steps and 31 % overall yield. The best results were obtained by using an aqueous Wittig reaction as a key step. Other reactions used were the formation of an epoxide ring by the Corey–Chaykovsky method, and an innovative one-pot anodic electrooxidation and demethylation.

Introduction

The allelopathic synergy of the forest species Verbenaceae *Tectona grandis* with agricultural species such as mountain rice, cotton, tapioca, chilli, and ginger, which is seen in teak plantations in Cuba and Venezuela with maize or bean cultures, can be important for the success of the agroforestal system known as taungya.[1] This system involves an allelophathic interaction of crops in young teak plantations,[1,2] and gives excellent harvests, in which fields remain clean and free from competition from undesirable plants.[2a,3]

Evidence of the phytotoxic effects of teak leaf extracts on the germination of monocot species has been found.[4] This phenomenon was recently confirmed when our group reported[5] the isolation and characterization of naphthotectone (**1**; Figure 1) from biologically active leaf extracts of Cuban *Tectona grandis*; **1** was the major component of this highly phytotoxic extract.[1,5] This natural product is an isoprenoid quinone that is structurally similar to alkannin (**2**) and shikonin (**3**; Figure 1), both of which are natural products with interesting biological activities.[6] Our research group has proposed that naphthotectone is one of the major compounds responsible for the allelophathic activity shown by teak, and also that it is involved in other defense mechanisms.[5] This makes naphthotectone an important future target in the development of drugs and ecoherbicides. This gives sufficient reason to develop an efficient synthetic route to this apparently simple structure.

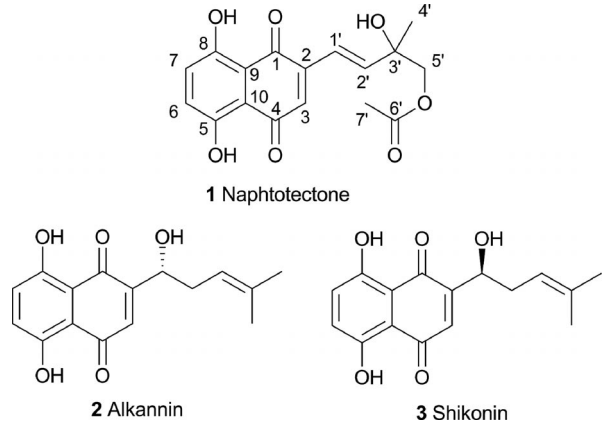

Figure 1. Structures of naphthotectone (**1**), alkannin (**2**), and shikonin (**3**).

Our retrosynthetic analysis of **1** is shown in Scheme 1. The key point of our strategy was the binding of the carbon chain to the naphthoquinone nucleus. For this, we tested various approaches, including Heck, Suzuki, and Sonogashira reactions, but all of these were unsuccessful. A complete analysis of the cause of the unexpected lack of success using these obvious classic reactions is ongoing. Consequently, a linear synthetic strategy was used in which the diol system of **1** was accessed via epoxide **4**. A 1,4,5,8-tetramethoxynaphthalene moiety was used as a precursor to the naphthazarin core, and the side-chain was assembled similarly to previously reported successful syntheses of **2** and **3**.[7] The conjugated double bond was obtained with a high

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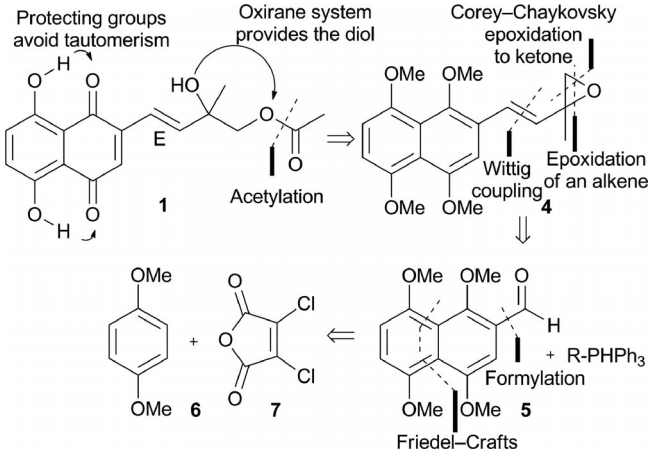
E selectivity in a Wittig reaction between a stabilized ylide and aldehyde **5**, which was synthesized in four high-yielding steps from 1,4-dimethoxybenzene (**6**) and 2,3-dichloromaleic anhydride (**7**).[8] We tried to avoid chromatographic separations to increase the overall yield of the synthesis and also to use Sephadex rather than silica gel where possible, because the substrates are highly unstable on silica gel.



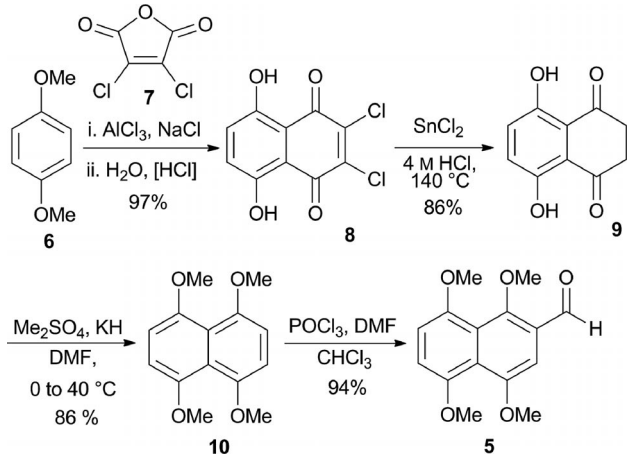
Scheme 1. Retrosynthetic analysis of naphthotectone (**1**).

Results and Discussion

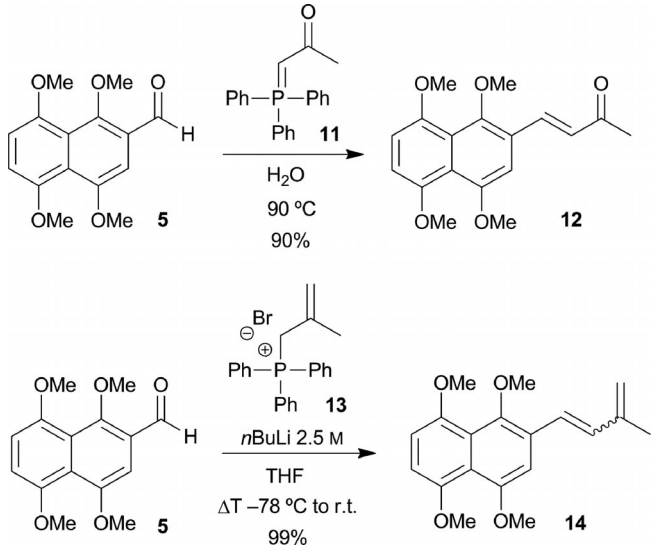
The synthesis started with the large-scale preparation of 2,3-dichloronaphthazarin (**8**) by a double Friedel–Crafts acylation[8] between *p*-dimethoxybenzene (**6**) and 2,3-dichloromaleic anhydride (**7**), followed by reduction of the naphthoquinone core of **8** with anhydrous tin(II) chloride in HCl (4 M) under reflux conditions[8e,8f] to give leuconaphthazarin (**9**).

Protected intermediate 1,4,5,8-tetramethoxynaphthalene (**10**) was obtained by methylation[9] of moderately air-sensitive diketo tautomer[8c] **9** with dimethyl sulfate. Treatment of **10** with $POCl_3$/DMF (Vilsmeier–Haak reaction) gave useful 2-formyl-1,4,5,8-tetramethoxynaphthalene[8e,10] (**5**) (Scheme 2). Purification by column chromatography was not necessary in any of the steps of this large-scale synthetic sequence, since the intermediates were isolated with high purities.

It has been found that when water is used as a reaction medium, Wittig products are formed with high *E* selectivity when a stabilized ylide is used, and (*Z*)-alkene products are obtained with non-stabilized ylides.[11] Indeed, the Wittig reaction between aldehyde **5** and the stabilized ylide derived from acetonylidenetriphenylphosphorane (**11**), in water as solvent at 90 °C, provided α,β-unsaturated ketone **12** with complete *E* selectivity and in high yield on a large scale (Scheme 3). This reaction represents an example of the use of green chemistry.[12] In contrast, under normal conditions,[13] diene **14** was obtained as a very unstable complex 3:1 mixture of *E* and *Z* isomers, and this approach was therefore abandoned.



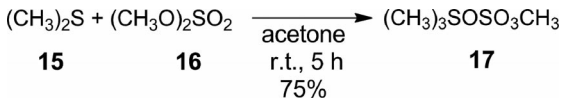
Scheme 2. Synthesis of key aldehyde **5**.



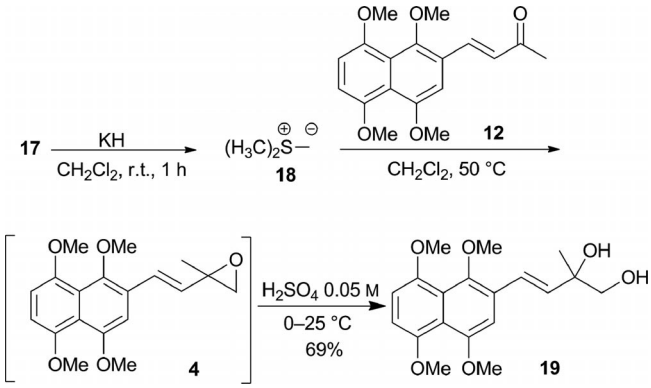
Scheme 3. *E*-Selective synthesis of enone **12** by a Wittig reaction in water, and non-selective synthesis of **14** in THF.

A cheap, easy, and accessible preparation of trimethylsulfonium methylsulfate[14] (**17**) was achieved with a mixture of dimethyl sulfide (**15**) and dimethyl sulfate (**16**) in acetone, which gave a very hygroscopic white solid (Scheme 4). Homologation of the side-chain of naphthotectone was achieved by the known Corey–Chaykovsky reaction[15] (Scheme 5). Intermediate epoxide **4** was obtained in a one-pot procedure by the selective addition of a methylene group to the carbonyl group of **12**. A solution of dimethylsulfoniomethylide (**18**) could be generated in situ from salt **17** and potassium hydride in dry dichloromethane under argon. A dichloromethane solution of ketone **12** was then added at room temperature, and this was followed by heating at reflux for 24 h. The intermediate epoxide (i.e., **4**) was not isolated, but controlled treatment with acid led to neutralization of the reaction mixture and opening of the epoxide ring of **4** to furnish theand light; it reacts to give the

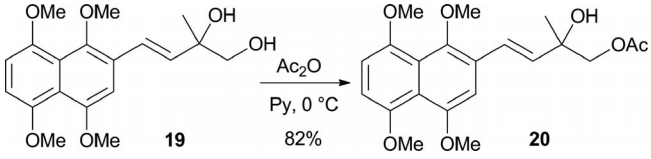
corresponding aldehyde at position C-5′. This problem was overcome by selective acetylation of the primary alcohol of **19** under basic conditions to give **20** (Scheme 6).



Scheme 4. Synthesis of trimethylsulfonium methylsulfate (**17**).

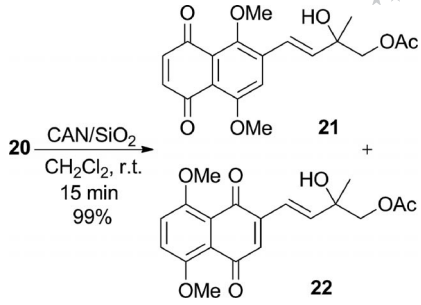


Scheme 5. One-pot synthesis of diol **19** by Corey–Chaykovsky epoxidation.



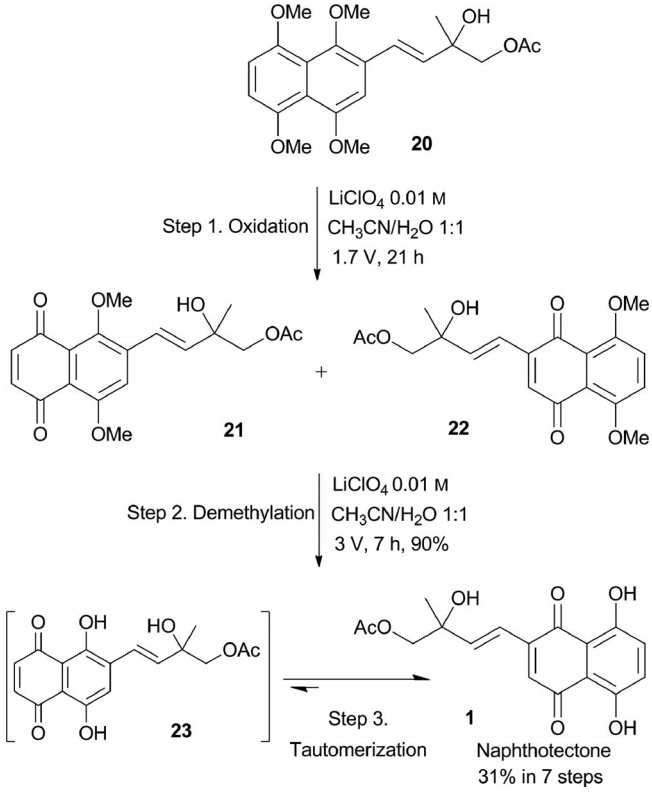
Scheme 6. Selective acetylation of diol **19**.

Ceric ammonium nitrate (CAN) has gained widespread popularity as an effective oxidizing agent, especially for the formation of quinone structures.[16] We found that the use of silica-gel-supported CAN[17] with an organic solution of **20** gave a clean mixture of regioisomeric dimethoxynaphthoquinones **21** and **22** after simple filtration of the reaction mixture. This approach limits the production of waste water contaminated with cerium metal[18] (Scheme 7). This high-yielding reaction was faster (15 min) than the same reaction carried out in a mixture of H_2O/CH_3CN (2 h). Despite its greater efficiency, only a modest regioselectivity[17] was obtained in favor of the desired compound (i.e., **22**; the regioisomers were separated by reverse-phase HPLC using a mixture of H_2O/CH_3CN to provide 40% of **22** and 25% of **21**). Further demethylation of **21** and **22** by treatment with AgO and HNO_3[16c,16d] in acetone[17] or dioxane[19a] or with $AlCl_3$[16c,16d,17,19b,19c] or BBr_3[16c,19c–19e] did not efficiently generate the desired target molecule.



Scheme 7. Synthesis of **21** and **22** by using simple silica-gel-supported CAN.

Next, we investigated the formation of the quinone moiety from compound **20** using a new anodic electrooxidation method.[7a,20] This two-step approach involved a simple experimental set-up with graphite electrodes under argon by using mixtures of $LiClO_4$ (0.01 M) in H_2O/CH_3CN (1:1) as the electrolyte (Scheme 8). The first oxidation step, carried out at 1.7 V for 21 h, led to the complete conversion of **20** into a mixture of **21** and **22**, as shown by TLC analysis. A second oxidation step, carried out at 3 V for 7 h, led to the clean conversion into our desired target naphthotectone in 90% yield by demethylation of intermediates **21** and **22** followed by tautomerization of **23**. Naphthotectone (**1**) could be easily purified by using a Sephadex LH-20 column with isocratic H_2O/CH_3CN mixtures.



Scheme 8. Oxidation, demethylation, and tautomerization reaction; one-pot synthesis of naphthotectone from **20** by anodic electrochemistry.

Conclusions

Naphthotectone, a potent phytotoxic isoprenoid naphthoquinone, was synthesized in seven steps and 31% overall yield from readily available starting materials. This approach avoided the need for chromatographic separations in the first four steps. The naphthoquinone nucleus was efficiently obtained in a one-pot reaction by a new anodic electrooxidation and demethylation method. Naphthotectone was isolated as a chiral compound, and this synthetic route will allow the preparation of new derivatives in order to gain insights into the structural requirements for biological activity, as well as the preparation of the natural enantiomer, and this work is ongoing.

Experimental Section

General Information: IR spectra (KBr) were recorded with Perkin–Elmer FTIR Spectrum 1000 or Matton 5020 spectrophotometers. NMR spectra were recorded with Agilent INOVA-400 and Varian INOVA 500 spectrometers. Chemical shifts are given in ppm; ^{1}H NMR spectra were calibrated to the residual solvent signal of $CDCl_3$ (δ = 7.26 ppm), and ^{13}C NMR spectra were calibrated to the solvent signal (δ = 77.0 ppm). HRMS data were recorded with a Waters SYNAPT G2 mass spectrometer (70 eV). HPLC was carried out by using a Merck–Hitachi instrument, with RI detection, using Merck LiChrospher columns: SI 60 (5 μm, 250 × 4 mm). Melting points were recorded with a Logen Scientific-LS melting point apparatus. Commercially available reagents and solvents were analytical grade, or were purified by standard procedures before use. Compounds were analyzed by IR spectroscopy, NMR spectroscopy (^{1}H, ^{13}C, and ^{31}P), and high-resolution ESI mass spectrometry, which gave data consistent with the proposed structures.

(3*E*)-4-(1,4,5,8-Tetramethoxy-2-naphthyl)but-3-en-2-one (12):[11] A mixture of 2-formyl-1,4,5,8-tetramethoxynaphthalene (**5**; 0.79 g, 2.86 mmol) and acetylmethylenetriphenylphosphorane (1.63 g, 5.14 mmol, 1.8 equiv.) in water (28 mL) was heated at reflux at 90 °C for 3 h. $CHCl_3$ (29 mL) was added to the reaction mixture. The organic phase was separated, and the aqueous phase was extracted with $CHCl_3$ (3 × 30 mL). The combined organic extracts were dried with Na_2SO_4 and filtered, and the solvents were evaporated. The crude material was purified by silica gel column chromatography (ethyl acetate/hexanes, 1:1) to give recovered starting material **5** (0.08 g, 9%; silica gel TLC R_f = 0.48 in ethyl acetate/hexanes, 1:1) and product **12** (0.81 g, 90%; silica gel TLC R_f = 0.43 in ethyl acetate/hexanes, 1:1) as a yellow solid. M.p. 122–123 °C. IR (neat): $\tilde{\nu}$ = 2926 (C–H), 2850 (O–CH_3), 1662 (C=O), 1598 (C=C–C=O), 1458 (CH_3–CO), 1372 (–CH_3), 1262 (C–O), 1072 (–CH_3) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, J = 16.6 Hz, 1 H, 1′-H), 6.92 (d, J = 8.7 Hz, 1 H, 7-H), 6.89 (d, J = 8.7 Hz, 1 H, 6-H), 6.72 (d, J = 16.6 Hz, 1 H, 2′-H), 4.04 (s, 3 H, 1a-OCH_3), 3.96 (s, 3 H, 4a-OCH_3)*, 3.90 (s, 3 H, 5a-OCH_3)*, 3.80 (s, 3 H, 8a-OCH_3)*, 2.44 (s, 3 H, 4′-CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.1 (C-3′), 153.6 (C-5), 151.6 (C-1), 151.2 (C-8), 151.0 (C-4), 138.5 (C-1′), 128.3 (C-2′), 124.7 (C-10), 122.9 (C-2), 122.1 (C-9), 110.8 (C-7), 108.9 (C-3), 103.6 (C-6), 63.8 (C-1a), 58.1 (C-5a)*, 57.2 (C-8a)*, 57.1 (C-4a)*, 27.0 (C-4′) ppm. *Assignments may be interchanged. HRMS (ESI): calcd. for $C_{18}H_{20}O_5Na$ [M + Na]$^+$ 339.1208; found 339.1216.

(2-Methylprop-2-en-1-yl)triphenylphosphonium Bromide (13): Triphenylphosphane (2.62 g, 10 mmol) and dry toluene (20 mL) were placed in a flame-dried round-bottomed flask under argon. Methylallyl bromide (1 mL, 10 mmol) was added, and the mixture was heated at reflux at 120 °C for 18 h. The precipitate was filtered off under vacuum, washed with dry diethyl ether, and dried in an oven to give **13** (3.75 g, 95%) as a white solid. M.p. 187–189 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83–7.69 (m, 9 H, 3′-H, 3′′-H, 3′′′-H, 4′-H, 4′′-H, 4′′′-H, 5′-H, 5′′-H, 5′′′-H), 7.66–7.57 (m, 6 H, 2′-H, 2′′-H, 2′′′-H, 6′-H, 6′′-H, 6′′′-H), 5.01–4.94 (m, 1 H, 3a-H), 4.83 (dt, J = 5.2, 1.0 Hz, 1 H, 3b-H), 4.58 (d, J = 15.3 Hz, 2 H, 1-H), 1.52 (dd, J = 2.9, 1.3 Hz, 3 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.1 (C-4′′, C-4′′′), 135 (C-4′), 134 (C-2′′, C-2′′′), 133.9 (C-2′), 132.6 (C-2), 132.5 (C-2), 130.3 (C-3′′, C-3′′′), 130.2 (C-3′), 121.6 (C-1′′, C-1′′′)*, 121.5 (C-1′)*, 117.7 (C-3), 31.9 (C-1), 24.7 (C-4), 24.7 (C-4) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 20.13 ppm.

1,4,5,8-Tetramethoxy-2-[(1*E* and 1*Z*)-3-methylbuta-1,3-dien-1-yl]-naphthalene (14): A mixture of (2-methylprop-2-en-1-yl)triphenylphosphonium bromide (**13**; 216 mg, 0.54 mmol) and dry THF (1 mL) was placed in a flame-dried round-bottomed flask at 0 °C. *n*BuLi (2.5 M in hexanes; 0.13 mL, 0.33 mmol, 1.2 equiv.) was added, and the mixture was stirred for 30 min. A solution of 2-formyl-1,4,5,8-tetramethoxynaphthalene (**5**; 75 mg, 0.27 mmol) in dry THF (1 mL) was added dropwise over 5 min. The mixture was warmed to room temp. and stirred for 3 h. The solvent was evaporated, and water (10 mL) was added to the residue. The aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (ethyl acetate/hexanes, 40%) to give **14** [mixture of products *E*/*Z* (3:1); 85 mg, 99%; silica gel TLC: R_f = 0.63 in ethyl acetate/hexanes, 40%] as a yellow solid. M.p. 65–71 °C.

Data for *E* Isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (d, J = 16.3 Hz, 1 H, 1′-H), 7.07 (s, 1 H, 3-H), 6.94 (d, J = 16.3 Hz, 1 H, 2′-H), 6.86–6.78 (m, 2 H, 7-H, 6-H), 5.14 (d, J = 24.4 Hz, 2 H, 4′-H), 3.98 (s, 3 H, -OCH_3), 3.94 (s, 3 H, -OCH_3), 3.76 (s, 3 H, -OCH_3), 3.76 (s, 3 H, -OCH_3), 2.05 (s, 3 H, 5′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.3 (C-5), 151.6 (C-1), 150.9 (C-8), 148.3 (C-4), 142.8 (C-3′), 132.49 (C-1′), 127.5 (C-9), 123.5 (C-2′), 123.3 (C-3), 117.4 (C-4′), 110.2 (C-10), 108.8 (C-7)*, 108.7 (C-6)*, 108.5 (C-2), 104.9 (C-3), 62.1 (C-1a), 57.9 (C-5a), 57.4 (C-4a), 57.3 (C-8a), 18.9 (C-5′) ppm. *Assignments may be interchanged.

Data for *Z* Isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.07 (s, 1 H, 3), 6.86–6.78 (m, 2 H, 7-H, 6-H), 6.73 (d, J = 12.3 Hz, 1 H, 1′-H), 6.28 (d, J = 12.4 Hz, 1 H, 2′-H), 5.01 (d, J = 9.7 Hz, 2 H, 4′-H), 3.98 (s, 3 H, -OCH_3), 3.93 (s, 3 H, -OCH_3), 3.88 (s, 3 H, -OCH_3), 3.76 (s, 3 H, -OCH_3), 1.78 (s, 3 H, 5′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.2 (C-5), 151.4 (C-1), 150.7 (C-8), 148.1 (C-4), 142.1 (C-3′), 133.2 (C-1′), 128.9 (C-9), 125.8 (C-2′), 120.3 (C-3), 117.3 (C-4′), 110.4 (C-10), 108.8 (C-7)*, 108.7 (C-6)*, 108 (C-2), 104.9 (C-3), 62.8 (C-1a), 57.8 (C-5a), 57.4 (C-4a), 57.2 (C-8a), 22.4 (C-5′) ppm. *Assignments may be interchanged. HRMS (ESI): calcd. for $C_{19}H_{22}O_4$ [M]$^+$ 314.1518; found 314.1518.

(3*E*)-2-Methyl-4-(1,4,5,8-tetramethoxy-2-naphthyl)but-3-ene-1,2-diol (19):[14,15] Potassium hydride (30% dispersion in mineral oil; 0.51 mmol) was placed in a 25 mL two-necked round-bottomed reaction vessel and washed four times with hexane (10 mL) by swirling, allowing the hydride to settle, and decanting, in order to remove the mineral oil. In another 25 mL two-necked round-bottomed reaction vessel, dry CH_2Cl_2 (1 mL) was added to trimethylsulfonium methylsulfate (**17**; 0.51 mmol) under argon. This solution was then added to the first vessel, and the mixture was stirred

at room temp. for 1 h to obtain dimethylsulfoniomethylide. A solution of (3*E*)-4-(1,4,5,8-tetramethoxy-2-naphthyl)but-3-en-2-one (**12**; 53.6 mg, 0.17 mmol) in dry CH_2Cl_2 (1.8 mL) was added, and the reaction mixture was heated at reflux at 60 °C for 24 h under argon to generate the epoxide intermediate. Sulfuric acid (0.05 M aq.; 13.5 mL) was added at 0 °C. Stirring was continued at room temp. for 3 d. After the epoxide-opening reaction was complete, $NaHCO_3$ (0.11 g) was added, and the solution was stirred for 30 min. The organic phase was decanted, and the aqueous phase was extracted with dichloromethane (3× 50 mL). The combined organic extracts were washed with brine and dried with anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified on Sephadex LH-20 (CH_2Cl_2/hexane, 95%) to give **19** (40.5 mg, 68%; silica gel TLC R_f = 0.22 in ethyl acetate/hexanes, 1:1) as a yellow oil. IR (neat): $\tilde{\nu}$ = 3464 (–OH), 2930 (C–H), 2838 (O–CH_3), 2062 (Ar), 1686 (C=O), 1602 (C=C–C–O), 1462 (CH_3–CO), 1366 (–CH_3), 1260 (C–O), 1072 (–CH_3) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.2 (d, J = 16.3 Hz, 1 H, 1′-H), 6.94 (s, 1 H, 3-H), 6.83–6.79 (m, 2 H, 6-H, 7-H), 6.30 (dd, J = 16.3 Hz, 1 H, 2′-H), 3.91 (s, 6 H, 5a-OCH_3, 8a-OCH_3)*, 3.87 (s, 3 H, 4a-OCH_3)* 3.71 (s, 3 H, 1a-OCH_3)*, 3.65 (d, J = 10.8, 1 H, 5′a-H), 3.55 (d, J = 10.8, 1 H, 5′b-H), 1.41 (s, 3 H, 4′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.3 (C-5), 151.5 (C-1), 150.8 (C-8), 148 (C-4), 134.5 (C-10), 131 (C-2), 126.7 (C-2′), 124.2 (C-1′), 120.6 (C-9), 108.9 (C-3), 108.6 (C-6), 105.2 (C-7), 73.9 (C-3′), 70.2 (C-5′), 62.7 (C-1a), 57.9 (C-5a)*, 57.4 (C-8a)*, 57.3 (C-4a)*, 24.6 (C-4′) ppm. *Assignments may be interchanged. HRMS (ESI): calcd. for $C_{19}H_{24}O_6Na$ $[M + Na]^+$ 371.1471; found 371.1469.

(3*E*)-2-Hydroxy-2-methyl-4-(1,4,5,8-tetramethoxy-2-naphthyl)but-3-en-1-yl Acetate (20): Acetic anhydride (34 μL, 0.31 mmol) was added to a stirred, cooled solution of **19** (0.11 g, 0.31 mmol) in dry pyridine (400 μL). The mixture was stirred for 6 h, and then it was concentrated under vacuum. The residue was purified on Sephadex LH-20 (CH_2Cl_2/hexane, 95%) to give **20** (0.1 g, 82%; silica gel TLC R_f = 0.44 in ethyl acetate/hexanes, 80%) as a yellow oil. IR (neat): $\tilde{\nu}$ = 3472 (–OH), 2932 (C–H), 2838 (O–CH_3), 2064 (Ar), 1740 (C=O), 1602 (C–O), 1458 (–CH_3–C–O), 1370 (CH_3), 1260 (C–O), 1074 (–CH_3) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, J = 16.3 Hz, 1 H, 1′-H), 6.95 (s, 1 H, 3-H), 6.85 (d, J = 8.6 Hz, 1 H, 7-H), 6.82 (d, J = 8.6 Hz, 1 H, 6-H), 6.3 (d, J = 16.3 Hz, 1 H, 2′-H), 4.23 (d, J = 11.2 Hz, 1 H, 5′a-H), 4.10 (d, J = 11.2 Hz, 1 H, 5′b-H), 3.95 (s, 3 H, 8a-OCH_3)*, 3.93 (s, 3 H, 5a-OCH_3)*, 3.89 (s, 3 H, 4a-OCH_3)*, 3.73 (s, 3 H, 1a-OCH_3), 2.10 (s, 3 H, 7′-H), 1.46 (s, 3 H, 4′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2 (C-6′), 153.4 (C-5), 151.5 (C-1), 150.8 (C-8), 148.1 (C-4), 133.8 (C-2′), 126.6 (C-10), 124.3 (C-1′), 123.2 (C-2), 120.7 (C-9), 109.0 (C-7), 108.6 (C-6), 105.2 (C-3), 72.8 (C-3′), 71.2 (C-5′), 62.7 (C-1a), 57.9 (C-5a)*, 57.4 (C-4a)*, 57.3 (C-8a)*, 25.1 (C-4′), 21.1 (C-7′) ppm. *Assignments may be interchanged. HRMS (ESI): calcd. for $C_{21}H_{26}O_7Na$ $[M + Na]^+$ 413.1576; found 413.1581.

(3*E*)-4-(1,4-Dimethoxy-5,8-dioxo-5,8-dihydronaphthalen-2-yl)-2-hydroxy-2-methylbut-3-en-1-yl Acetate (21) and (3*E*)-4-(5,8-Dimethoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2-hydroxy-2-methylbut-3-en-1-yl Acetate (22):[18] A solution of CAN (0.12 g, 0.23 mmol) in water (0.40 mL) was added dropwise with continuous stirring to chromatography-grade silica gel (0.4 g) in a 10 mL round-bottomed flask fitted with a rubber septum. The silica gel was stirred for approximately 5 min after the addition was complete, and a free-flowing yellow solid was obtained. A solution of **20** (0.030 g, 0.076 mmol) in CH_2Cl_2 (1.2 mL) was added to the stirred reaction mixture. The reaction mixture changed from yellow to dark orange immediately upon addition of the starting material. After the reaction was complete (approximately 15 min according to TLC), the mixture was filtered under reduced pressure through a sintered-glass funnel. The solid was washed with CH_2Cl_2 (ca. 50 mL). The solvent was removed under reduced pressure by using a rotary evaporator to give a mixture of products **21** and **22** (quantitative) as a yellow/orange oil. The mixture was purified by reverse-phase HPLC D7000 (acetonitrile/water, 40%). Pure **21** (10.0 mg, 40%; silica gel TLC R_f = 0.37 in acetonitrile/water, 60%) was obtained as an orange oil, along with **22** (6.9 mg, 25%; silica gel TLC R_f = 0.25 in acetonitrile/water, 60%) as a red oil.

Data for Compound 21: IR (neat): $\tilde{\nu}$ = 3462 (–OH), 3014, 2940 (C–H), 2844 (O–CH_3), 2362, 2344 (Ar), 1740 (O–C=O), 1654 (C=O), 1586 (C=C–C=O), 1478, 1462 (–OCH_3), 1260 (C–O), 1048 (–CH_3) cm^{-1}. ^1H NMR (50 MHz, CD_3OD): δ = 7.59 (s, 1 H, 3-H), 7.09 (d, J = 16.3 Hz, 1 H, 2′-H), 6.8 (s, 2 H, 6-H, 7-H), 6.64 (d, J = 16.3 Hz, 1 H, 1′-H), 4.15 (d, J = 11.1 Hz, 1 H, 5′a-H), 4.05 (d, J = 11.1 Hz, 1 H, 5′b-H), 3.99 (s, 3 H, 1a-OCH_3), 3.78 (s, 3 H, 4a-OCH_3), 2.07 (s, 3 H, 7′-H), 1.42 (s, 3 H, 4′-H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 186.2 (C-8), 185.8 (C-5), 172.6 (C-6′), 157.6 (C-1), 152.5 (C-4), 141.9 (C-2), 140.9 (C-1′), 140.1 (C-7), 139.2 (C-6), 127 (C-9), 123.2 (C-2′), 120.7 (C-10), 117.5 (C-3), 73.2 (C-3′), 71.5 (C-5′), 62.4 (C-4a)*, 57 (C-1a)*, 25 (C-4′), 20.8 (C-7′) ppm. HRMS (ESI): calcd. for $C_{19}H_{20}O_7Na$ $[M + Na]^+$ 383.1107; found 383.1123.

Data for Compound 22: IR (neat): $\tilde{\nu}$ = 3482 (–OH), 2924 (C–H), 2854 (O–CH_3), 2366, 2342 (Ar), 1738 (O–C=O), 1656 (C=C–C=O), 1464 (–OCH_3), 1246 (C–O), 1054 (–CH_3) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.52 (s, 2 H, 6-H, 7-H), 6.83 (d, J = 0.86 Hz, 1 H, 1′-H), 6.82 (d, J = 0.79 Hz, 1 H, 3-H), 6.81 (dd, J = 16.3 Hz, 1 H, 1′-H), 6.72 (d, J = 16.3 Hz, 1 H, 2′-H), 4.09 (d, J = 11.03 Hz, 1 H, 5′a-H), 4.02 (d, J = 11.03 Hz, 1 H, 5′b-H), 3.93 (s, 3 H, 5a-OCH_3)*, 3.92 (s, 3 H, 8a-OCH_3)*, 2.1 (s, 3 H, 4′-H), 1.4 (s, 3 H, 7′-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 186.5 (C-1), 185.8 (C-4), 172.6 (C-6′), 155.2 (C-5), 154.8 (C-8), 145.3 (C-2), 143.9 (C-2′), 132.4 (C-1′), 122.3 (C-3), 122.2 (C-9), 122.1 (C-6), 122 (C-7), 121.6 (C-10), 73.2 (C-3′), 71.4 (C-5′), 57.2 (C-5a)*, 57.1 (C-8a)*, 24.8 (C-4′), 20.7 (C-7′) ppm. *Assignments may be interchanged. HRMS (ESI): calcd. for $C_{19}H_{20}O_7Na$ $[M + Na]^+$ 383.1107; found 383.1106.

(±)-Naphthotectone (1):[20] A mixture of compound **20** (20.8 mg, 0.053 mmol) and lithium perchlorate (159.6 mg, 1.50 mmol) in aqueous acetonitrile (50%; 15 mL) was introduced into an undivided electrolytic cell with graphite electrodes under argon. The solution was electrolyzed in two steps. *First step, oxidation:* Electrolysis at 1.71 V for 21 h generated a mixture of products **21** and **22** (quantitative). *Second step, demethylation and tautomerization:* Electrolysis at 3.09 V for 7 h transformed the mixture of **21** and **22** into the desired naphthotectone (**1**). The solvent was removed under reduced pressure at 45 °C until the volume of the solution was 5 mL, and the resulting solution was extracted with chloroform (6× 10 mL). The combined organic extracts were washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed, and the residue was purified on Sephadex LH-20 (acetonitrile/water, 60%) to give pure naphthotectone (**1**) (16.0 mg, 90%; silica gel TLC R_f = 0.5 in acetonitrile/water, 60%) as an amorphous red solid. The spectroscopic data of **1** are in good agreement with those previously reported for the natural product.[5] HRMS (ESI): calcd. for $C_{17}H_{16}O_7Na$ $[M + Na]^+$ 355.0794; found 355.0805.

Supporting Information (see footnote on the first page of this article): Complete experimental procedures and copies of ^1H and ^{13}C NMR spectra for known compounds **8**, **9**, **10**, **5**, and **17**, and detailed experimental procedures, characterization, and copies of ^1H,

^{13}C, ^{31}P, COSY, HSQC, and HMBC NMR spectra of new compounds.

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