Efficient Total Synthesis of (−)-Ilimaquinone†

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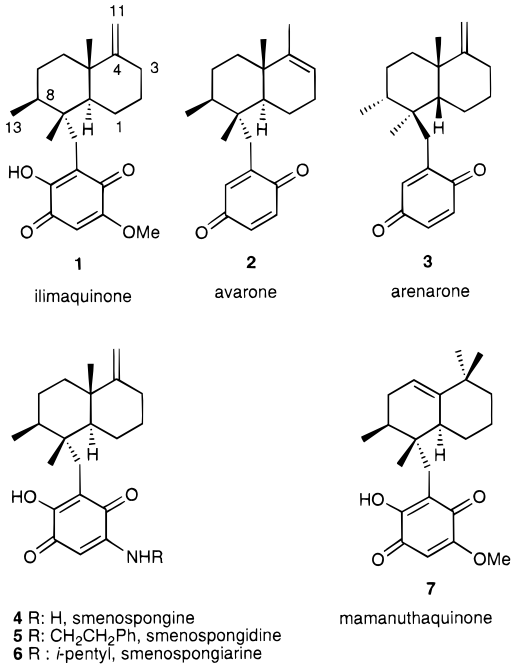
The total synthesis of (−)-ilimaquinone, a metabolite isolated from sea sponges, is described. The key step of the synthesis is the attachment of the quinone moiety to the drimane skeleton. Alkylation of enone **11** obtained in four steps from the readily available diketone **8**, with tetramethoxybenzyl bromide **15** as the alkylating agent, led to addition product **16** in excellent yield. The presence of the tetramethoxybenzyl group induced stereoselective hydrogenation of the exo olefin **18**, leading to the required isomer in a 9:1 ratio. Treatment of compound **21** with ceric ammonium nitrate (CAN) afforded formation of the quinone and deprotection of only one methyl ether in one step to furnish the desired ilimaquinone **1**.

The marine natural products ilimaquinone (**1**)[1] and related sesquiterpene quinones such as avarone (**2**),[2] arenarone (**3**),[3] smenospongine (**4**), smenospongidine (**5**), smenospongiarine (**6**),[4] and mamanuthaquinone (**7**)[5] metabolites isolated from sea sponges have been reported to exhibit a variety of promising biological effects: antimicrobial, antiviral, cytotoxic, and immunomodulatory activities.[6] In addition, ilimaquinone was recently demonstrated to inhibit the toxicity of ricin and diphteria toxin,[7] to reversibly disrupt the Golgi complex,[8] and to provoke the loss of the gap junction plaques and inhibition of intercellular communication in BICR-MIRk and NRK cells.[9] Thus, ilimaquinone appears as a valuable tool for the investigation of some important biological processes.

Only one total synthesis of ilimaquinone has been published to date[10] that has allowed the preparation of analogues of biological interest.[11]

In general, the strategy used for appending the quinone moiety to the drimane skeleton is based upon reductive alkylation of an enone derivative **8** with a benzyl bromide (usually more than 4 equiv), having the appropriate substituents, as the alkylating agent. Ilimaquinone[10] and avarone[12,13] were prepared according to this method. Other methods have been reported in the literature for the construction of the sesquiterpene quinone, including the following: nickel-mediated neopentyl coupling reaction, which was applied to the synthesis of (±)-arenarone,[14] and an exo-Diels−Alder reaction for the synthesis of (±)-mamanuthaquinone.[15]

The two crucial steps in the synthesis of sesquiterpene quinones are the attachment of the benzyl group to the drimane skeleton and the introduction of the appropriate substituents to the quinone moiety, especially in the case of ilimaquinone and related compounds. This latter difficulty was overcome in our synthetic approach (vide infra), which is based on the alkylation of enone **11**, in



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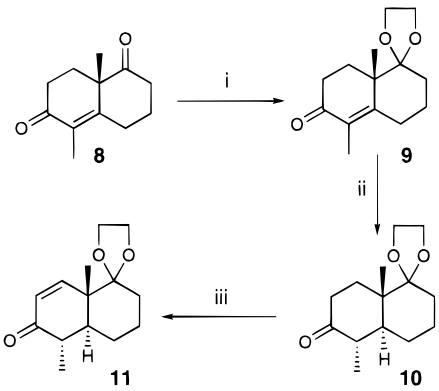
Scheme 1[a]



[a] Key: (i) $HO(CH_2)_2OH$, cat. PTSA, benzene, reflux (91%); (ii) 4 equiv of Li, 1 equiv of H_2O, liquid NH_3, THF, −78 to +30 °C (90%); (iii) (a) 1.2 equiv of LDA, 2 equiv of TMSCl, THF, −78 to 0 °C, (b) 1.1 equiv of $Pd(OAc)_2$, CH_3CN, reflux (95% for two steps).

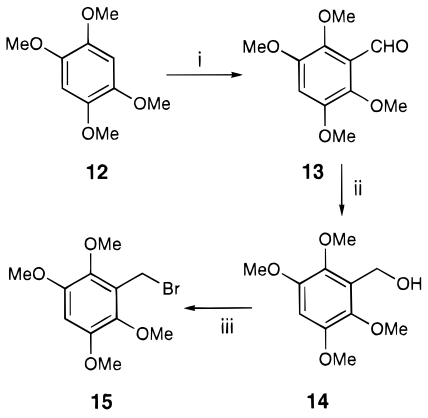
the presence of the tetramethoxybenzyl bromide **15** bearing all substituents required for ilimaquinone.

Herein, we report a concise synthesis of ilimaquinone starting from the diketone **8**, which is readily available from an L-phenylalanine-mediated enantioselective Robinson annelation with ee >99%.[16] Thus, the diketone **8** was converted to its monoketal derivative **9**[16] ($HOCH_2$-CH_2OH, PTSA, benzene, reflux, 3 h, 91%), followed by reduction of the double bond (4 equiv of Li, 1 equiv of H_2O, NH_3−THF, −78 °C) to give the saturated ketone **10**[17] as a single isomer (90%). Ketone **10** was subsequently converted to the corresponding enone **11** by reaction of its silyl enol ether (1.2 equiv of LDA, 2 equiv of TMSCl, −78 °C) with 1.1 equiv of $Pd(OAc)_2$[18] in acetonitrile (CH_3CN, reflux, 1 h) in 95% yield over two steps (Scheme 1).

The 2,3,5,6-tetramethoxybenzyl bromide was prepared from the reaction of the lithio derivative of 1,2,4,5-tetramethoxybenzene **12**[19] and DMF (1.1 equiv of *n*-BuLi, 5 equiv of DMF, THF, −78 to 0 °C) to give the benzaldehyde **13**, followed by reduction (1 equiv of $LiAlH_4$, THF, 0 °C), which afforded the benzyl alcohol **14** (89%) (two steps). Bromination of the resulting alcohol (1.2 equiv of CBr_4, 1.3 equiv of Ph_3P, CH_2Cl_2, 0 °C) provided bromo compound **15** in 87% yield (Scheme 2).

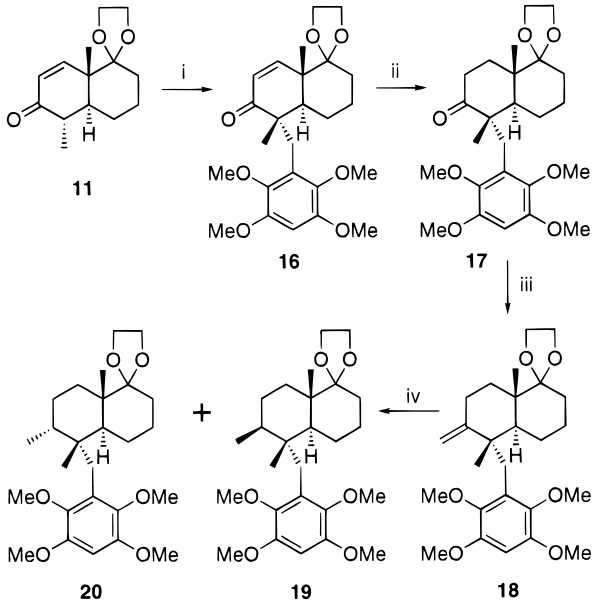
Coupling of **11** through its lithium dienolate (1.2 equiv of LHMDS, THF, −78 °C) in the presence of 1.2 equiv of benzyl bromide **15** cleanly furnished the addition product **16** (91%) as a single isomer. Catalytic hydrogenation of the enone (H_2 balloon, 10% Pd/C, EtOH) gave the saturated ketone **17** in 96% yield, which was submitted to Wittig olefination (9 equiv of Ph_3PCH_3I, 7 equiv of NaH, DMSO, 80 °C) to give the exo olefin **18** in 91% yield. Hydrogenation (H_2 balloon) of the exo olefin **18** over Pd/C in triethylamine[20] afforded a mixture of diastereoisomers that were separated by silica gel chromatography to give compound **19** (81% yield) and its isomer **20** (9% yield) in a ratio of 9:1. Comparison of ^1H NMR data for compound **19** and **20** showed a chemical shift difference between CH_3-13 of **19** (δ CH_3 0.68) and CH_3-13 of **20** (δ CH_3 1.38).

Scheme 2[a]



[a] Key: (i) 1.1 equiv of *n*-BuLi, 5 equiv of DMF, THF, −78 to 20 °C; (ii) 1 equiv of $LiAlH_4$, THF, 0 °C (89% for two steps); (iii) 1.2 equiv of CBr_4, 1.3 equiv of Ph_3P, CH_2Cl_2, 0 °C (87%).

Scheme 3[a]



[a] Key: (i) 1.2 equiv of LiHMDS, **15** (1.2 equiv) (91%), THF, −78 to + 50 °C; (ii) H_2 (balloon), Pd/C 10%, EtOH, 20 °C (96%); (iii) 7 equiv of NaH, 9 equiv of Ph_3PCH_3I, DMSO, 80 °C (91%); (iv) H_2 (balloon), Pd/C 10%, Et_3N, 20 °C (81% for **19** and 9% for **20**).

The latter was influenced by the anisotropic effect of the tetramethoxybenzyl moiety, which shifted the CH_3-13 signal upfield. In addition, the highly selective hydrogenation might be explained by chelation of the methoxy groups of the benzyl moiety on the palladium surface, directing the addition of hydrogen to the α face, favoring the β isomer **19** as the major product[21] (Scheme 3).

The dioxolane protecting group of compound **19** was removed (THF−1 N HCl 4:1, 20 °C) and the resulting ketone subjected to Wittig olefination (7 equiv of Ph_3-PCH_3Br, 6.4 equiv of *n*-BuLi, dioxane, reflux), providing olefin **21** in 93% yield (two steps). Finally, olefin **21** was

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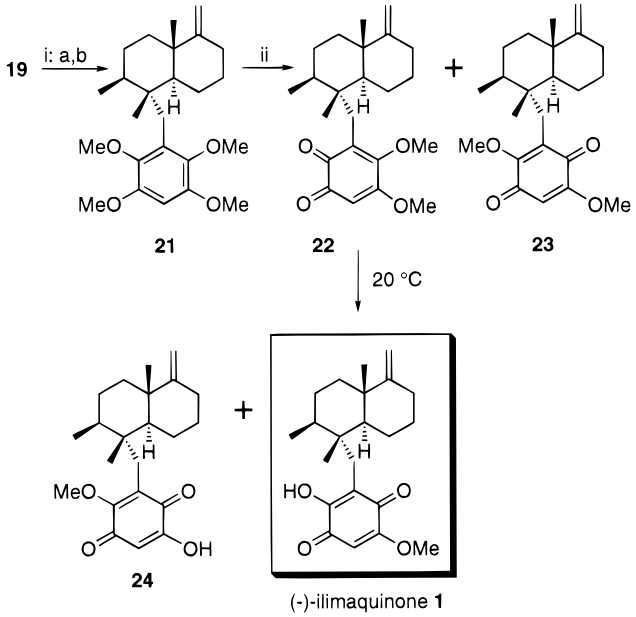
(21) Catalytic hydrogenation of olefin **18** over PtO_2 provided **19** and **20** in a ratio of 4:1, and in addition, the reduction of exo-olefin having a 1,4-dimethoxybenzene side chain over Pd/C furnished a mixture of β/α in a ratio of 3:2 (see ref 13), which is the result of steric hindrence as reported. We reasoned that in addition of steric effects due to drimane skeleton, the tetramethoxybenzene moiety could have an interaction with the catalyst surface during the reduction of olefin **18** over Pd/C favoring the β-isomer **19** as a major product.

Scheme 4[a]



[a] Key: (i) (a) THF−1 N HCl (4:1), 20 °C (100%); (b) 6.4 equiv of *n*-BuLi, 7 equiv of Ph_3PCH_3Br, dioxane 110 °C (93%); (ii) 2.5 equiv of CAN, CH_3CN-H_2O, −5 to +20 °C (54% for **1**, 10% for **23**, and 34% for **24**).

treated with ceric ammonium nitrate to accomplish deprotection of methyl ether and formation of the quinone system. Thus, slow addition of a solution of ceric ammonium nitrate (2.5 equiv, CH_3CN-H_2O, −5 °C) to compound **21** resulted in immediate formation of *o*-quinone **22** accompanied by a small amount of *p*-quinone **23**[22] (10%). At the end of the addition, the reaction was allowed to stir at room temperature, and smooth demethylation of the more hindered methyl group occurred, providing the desired ilimaquinone **1** (54%), along with its isomer **24** (34%)[23] (Scheme 4).

Due to the acidity[24] of the reaction medium, longer reaction time provided a lower yield of compound **1**, leading to a mixture of very polar products that could not be isolated and identified. For this reason, it is important to respect the reaction time once the quinone compound **22** has disappeared (TLC, 10 h). The synthetic ilimaquinone obtained here was identical in all respects ($[\alpha]_D$, NMR, IR, TLC) with natural ilimaquinone. The total synthesis of ilimaquinone described above requires 11 steps and proceeds in 25% overall yield from the readily available diketone **8**.

This preparation of sesquiterpene quinones offers marked improvements: enone **11** derivative could be coupled with an appropriate alkylating agent bearing suitable functionalities, using only an equimolar (1.2 equiv) amount of reagent under mild conditions, allowing an easy access to the synthesis of other naturally occurring sesquiterpene quinones. The tetramethoxybenzyl appendage favors the highly selective hydrogenation of the exo olefin (9:1), and CAN oxidation provides the formation of quinone and deprotection of only one methyl ether, in one step. This latter reaction could be applied to the synthesis of other natural products that share the same 2-hydroxy-5-methoxy-1,4-benzoquinone.[25]

In summary, we have described a concise synthesis of ilimaquinone that offers a new route to the preparation of potentially useful analogues through enone **11** (drimane skeleton) and **15** (quinone moiety) for evaluation of biological activities.

Experimental Section

All the reactions were carried out under an argon atmosphere. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 300 MHz spectrometer. Chemical shifts (δ) are expressed in ppm from Me_4Si as internal standard. Mass spectra were recorded on a Kratos MS 50 instrument at 70 eV (EI) or Nermag 10−10 (CI, NH_3). IR spectra were recorded on a Nicholet (impact 400D) FT IR. All reagents were obtained from commercial suppliers and used without further purification. THF, dioxane, and benzene were freshly distilled from sodium benzophenone. Methylene chloride and triethylamine were distilled from CaH_2. DMSO was dried and stored over 4 Å molecular sieves. Flash chromatography was carried out using silica gel 60 (Merck) with mixtures of ethyl acetate and hexane as eluent unless specified otherwise. TLC analyses were performed on thin-layer analytical plates 60F254 (Merck). Elementary analyses were carried out in the Institut de Chimie des Substances Naturelles, Gif-sur-Yvette.

(4a*S*)-2,3,4,4a,5,6,7,8-Octahydro-1,4a*β*-dimethyl-5-(1,3-dioxolan-2-yl)naphthalen-2-one (9). This compound was prepared according to the literature as follows:[26] A mixture of dry benzene (200 mL) and ethylene glycol (27.1 g, 436 mmol) was heated under reflux with vigorous stirring until all the water was removed. To this mixture was added dropwise a solution of anhydrous toluene-*p*-sulfonic acid (0.7 mmol) and diketone **8** (5.76 g, 30 mmol) in dry benzene (20 mL). The reaction was heated under reflux for 2 h, cooled, and worked up to afford an oily residue, which was purified over silica gel using hexanes−ethyl acetate (8:2) to give the enone **9** (6.450 g, 91%) as a colorless oil: $[\alpha]_D$ +111.5 (*c* 1.39, CH_3OH) lit.[12] $[\alpha]_D$ +114 (*c* 1.1, $CHCl_3$)]; MS *m*/*z* (CI) 237 (MH^+); IR (neat) 2950, 2880, 1670, 1620, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.01−3.91 (m, 4H), 2.74 (m, 1H), 2.52−2.34 (m, 2H), 2.14 (m, 2H), 1.97−1.72 (m, 2H), 1.78 (d, J = 1.3 Hz, 3H), 1.70−1.54 (m, 3H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 198.6, 160.1, 130.0, 112.7, 65.2, 65.0, 45.2, 33.6, 29.6, 26.4, 26.3, 21.3, 20.8, 11.4.

(1*S*, 4a*S*)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-1α,4a*β*-dimethyl-5-(1,3-dioxolan-2-yl)naphthalen-2-one (10). A solution of compound **9** (6.136 g, 26 mmol) and H_2O (0.468 mL, 26 mmol) in dry THF (50 mL) was added dropwise to a stirred solution of Li (0.7 g, 100 mmol) in liquid ammonia (100 mL) at −78 °C over 30 min. The cooling bath was removed, and the reaction was stirred for 1 h. Solid ammonium chloride was added, and NH_3 was allowed to evaporate. Water was added, and the mixture was extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified over silica gel using hexanes−EtOAc (4:1) as eluent to give **10** (5.57 g, 90%) as a colorless oil: R_f 0.4 (4:1 hexane−AcOEt); $[\alpha]_D$ −8.7 (*c* 3.0, $CHCl_3$); MS *m*/*z* (CI) 239 (MH^+); IR (neat) 2956, 2874,

(22) The structure of *p*-quinone **23** was proved by methylation of either ilimaquinone **1** or compound **24** using diazomethane (CH_2N_2) to provide a methylated product that was identical in all respects (TLC, NMR, IR) with compound **23**.

(23) It has been reported that *o*-quinone derivatives could be transformed to *p*-quinone on heating in acetic acid (see Reinaud, O.; Capdevielle, P.; Maumy, M. *Tetrahedron* **1987**, *43*, 4167 and references therein). In our case, regarding to the acidity of the reaction medium (pH = 1.3), it was sufficient to cause transformation of compound **22**. In addition, it was reported that simple acid hydrolysis, using $HClO_4$, extruded the more hindered methoxy group of 2,5-dimetoxy-1,4-benzoquinone substituted with a simple alkyl chain (see Kubo, I.; Kim, M.; Ganjian, I. *Tetrahedron* **1987**, *43*, 2653). Treatment of compound **23** with $HClO_4$ (few drops) led to the total destruction of starting material within a few minutes.

(24) The pH of the reaction measured in the beginning as we have mentioned was 1.3, and at the end of reaction, it dropped to ∼0.7.

(25) Manuscript in preparation.

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1710, 1455, 1189, 1086 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.98−3.85 (m, 4H), 2.50−2.21 (m, 3H), 1.91 (dt, 1H), 1.80−1.46 (m, 8H), 1.24 (s, 3H), 0.99 (d, 3H); ^{13}C NMR ($CDCl_3$) δ 208.4, 112.5, 65.0, 64.9, 48.0, 44.9, 42.3, 37.5, 30.6, 29.9, 24.9, 22.6, 14.1, 11.6. Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.76; H, 9.37.

(1*S*,4a*S*)-1,2,4a,5,6,7,8,8a-Octahydro-1α,4a*β*-dimethyl-5-(1,3-dioxolan-2-yl)naphthalen-2-one (11). To a solution of LDA (4.8 mmol, prepared from *n*-BuLi 1.6 M in hexane and diisopropylamine at 0 °C) in dry THF (10 mL) was added a solution of **10** (952 mg, 4 mmol) in dry THF (10 mL) at −78 °C. The mixture was stirred for 1 h at −78 °C. TMSCl (1 mL, 8 mmol) was added. The reaction was stirred for 30 min at −78 °C and then allowed to warm at room temperature. The THF was evaporated under reduced pressure and the residue diluted with ether, washed with water and saturated NaCl, dried over $MgSO_4$, and concentrated in vacuo. The crude silyl enol was dissolved in CH_3CN (16 mL), $Pd(OAc)_2$ (986 mg, 4.4 mmol) was added, and the mixture was heated under reflux for 1 h. The mixture was filtered and the solvent removed under reduced pressure. The residue was subjected to flash column chromatography using hexanes−EtOAc (8:2) as eluent to give compound **11** (897 mg, 95%) as colorless needles: mp 79 °C; R_f 0.31 (4:1 hexane−AcOEt); $[\alpha]_D$ −30.8 (*c* 3.0, $CHCl_3$); MS *m*/*z* (CI) 237 (MH^+); IR (KBr) 2929, 1660, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.97 (d, 1H), 5.83 (d, 1H), 4.02−3.88 (m, 4H), 2.22 (m, 1H), 2.03 (dt, 1H), 1.69−1.41 (m, 5H), 1.22 (m, 1H), 1.13 (s, 3H), 1.06 (d, 3H); ^{13}C NMR ($CDCl_3$) δ 201.4, 155.3, 127.4, 111.4, 65.1, 64.6, 45.6, 45.2, 41.9, 29.0, 23.7, 22.5, 16.0, 12.2. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.78; H, 8.96.

2,3,5,6-Tetramethoxybenzyl Alcohol (14). To a solution of 1,2,4,5-tetramethoxybenzene (3.01 g, 15.2 mmol) in dry THF (75 mL) was added *n*-BuLi (1.6 M in hexane, 10 mL, 16 mmol) dropwise at −78 °C over 30 min. The reaction was warmed to −10 °C over 1 h and stirred at this temperature for an additional 1 h. The mixture was cooled to −78 °C, and dry DMF (5.84 mL, 76 mmol) was added in one portion. The reaction was allowed to warm to 0 °C over 1 h. THF was removed under reduced pressure, water was added, and the residue was extracted with ether (2×). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give the crude benzaldehyde **13** (3.39 g), which was used for the next step without further purification. To a solution of the crude benzaldhyde **13** (3.39 g) in dry THF (70 mL) was added $LiAlH_4$ (577 mg, 15.2 mmol) in small portions at 0 °C. The reaction was stirred for 1 h at 0 °C. EtOAc was added to destroy the excess of $LiAlH_4$ and the mixture concentrated in vacuo. The residue was extracted with CH_2Cl_2, washed successively with 1 N HCl, water, and brine, dried over $MgSO_4$, and concentrated. The residue was subjected to flash column chromatography using hexanes−EtOAc (1:1) as eluent to give compound **14** (3.1 g, 89%): white solid; mp 86 °C; MS *m*/*z* (EI) 228 (M^+); IR (KBr) 3400, 3000, 2942, 2840, 1600, 1499, 1350, 1250, 813, 640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.52 (s, 1H), 4.73 (d, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 2.81 (t, 1H); ^{13}C NMR ($CDCl_3$) δ 148.7, 140.8, 128.3, 98.8, 61.3, 56.2, 55.6. Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.97; H, 7.08. Found: C, 57.89; H, 7.01.

2,3,5,6-Tetramethoxybenzyl Bromide (15). To a solution of alcohol **14** (2.97 g, 13 mmol) in dry CH_2Cl_2 (60 mL) was added CBr_4 (5.173 g, 15.6 mmol) at −7 °C (salt ice bath), followed by addition of Ph_3P (4.427 g, 16.9 mmol, 1.3 equiv) in small portion. The mixture was stirred at this temperature for an additional 15 min. The CH_2Cl_2 was removed under reduced pressure, ether was added, and the mixture was filtered. The filter cake was washed with ether (3×). The filtrate was washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was purified over silica gel (hexanes−EtOAc 7:3) to give **15** (3.3 g, 87%) as a white solid: mp 127 °C; MS *m*/*z* (EI) 290−292 (M^+); IR (KBr) 3000, 2942, 2840, 1595, 1502, 1340, 1255, 813, 590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.54 (s, 1H), 4.65 (s, 2H), 3.92 (s, 3H), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.8, 141.1, 126.4, 100.0, 61.0, 56.4, 22.7. Anal. Calcd for $C_{11}H_{15}BrO_4$: C, 45.61; H, 5.33. Found: C, 45.36; H, 5.15.

(1*R*,4a*S*)-1,2,4a,5,6,7,8,8a-Octahydro-1α-[(2,3,5,6-tetramethoxybenzene)methyl]-1*β*,4a*β*-dimethyl-5-(1,3-dioxolan-2-yl)naphthalen-2-one (16). To a solution of LiHMDS (3.6 mmol, prepared from *n*-BuLi, 1.6 M in hexane, and hexamethyldisilazane at 0 °C) in dry THF (10 mL) was added a solution of enone **11** (708 mg, 3 mmol) in dry THF (5 mL) at −78 °C. The mixture was allowed to warm to 0 °C over 30 min and then cooled to −78 °C, and a solution of bromobenzyl **15** (1.047 g, 3.6 mmol) in dry THF (10 mL) was added dropwise. The mixture was allowed to warm to room temperture over 30 min and heated at 50 °C for an additional 1 h. The mixture was cooled and solvent removed in vacuo. The residue was extracted with CH_2Cl_2, washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (hexanes−EtOAc 1:1) gave compound **16** (1.217 g, 91%) as white crystals: mp 136 °C; R_f: 0.16 (7:3 hexane−AcOEt); $[\alpha]_D$ −1.2 (*c* 1.7, $CHCl_3$); MS *m*/*z* (EI) 446 (M^+); IR (KBr) 2963, 2922, 1665, 1598, 1490, 814 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.86 (d, 1H), 6.47 (s, 1H), 6.01 (d, 1H), 3.95−3.84 (m, 4H), 3.82 (s, 6H), 3.64 (s, 6H), 3.19 (d, 1H), 2.85 (d, 1H), 2.18−2.13 (dd, 1H), 1.56−1.23 (m, 6H), 1.18 (s, 3H), 1.16 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 202.7, 152.6, 148.6, 141.9, 127.7, 126.4, 111.8, 98.8, 64.9, 64.5, 59.9, 56.5, 47.9, 45.1, 42.6, 34.5, 29.6, 22.7, 22.6, 20.9, 19.3. Anal. Calcd for $C_{25}H_{34}O_7$: C, 67.24; H, 7.67. Found: C, 67.48; H, 7.88.

(1*R*,4a*S*)-Decahydro-1*β*,4a*β*-dimethyl-1α-[(2,3,5,6-tetramethoxybenzene)methyl]-naphthalen-2-one (17). A mixture of enone **16** (1.12 g, 2.511 mmol) and 10% Pd/C (110 mg) in EtOH (20 mL) was stirred at room temperature under 1 atm of hydrogen for 4 h. The reaction was filtered through Celite and the filtrate concentrated in vacuo. Flash chromatography (hexanes−EtOAc 1:1) gave compound **17** (1.08 g, 96%) as a white solid: mp 95 °C; R_f 0.24 (7:3 hexane−AcOEt); $[\alpha]_D$ +29.8 (*c* 1.98, $CHCl_3$); MS *m*/*z* (EI) 448 (M^+); IR (KBr) 2934, 1703, 1598, 1492, 1466, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.46 (s, 1H), 3.92 (m, 4H), 3.82 (s, 6H), 3.66 (s, 6H), 3.15 (d, 1H), 2.79 (d, 1H), 2.73 (m, 1H), 2.32 (m, 1H), 2.22−2.08 (m, 2H), 1.65−1.28 (m, 7H), 1.03 (s, 3H), 1.00 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 206.1, 148.4, 141.9, 125.7, 112.8, 98.9, 64.9, 64.6, 59.9, 56.5, 50.5, 46.0, 42.1, 34.3, 34.1, 29.9, 28.6, 22.7, 22.5, 20.5, 17.2. Anal. Calcd for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 66.81; H, 8.32.

(1*R*,4a*S*)-Decahydro-1α-[(2,3,5,6-tetramethoxybenzene)-methyl]-1*β*,4a*β*-dimethyl-2-methylene-5-(1,3-dioxolan-2-yl)-naphthalene (18). NaH (60% oil dispersion; 0.456 g, 11.4 mmol) was washed with several portions of hexane. Dry DMSO (10 mL) was introduced and the mixture heated at 80 °C for 45 min. The resulting solution of methylsulfinyl carbanion was cooled to 0 °C (ice−water bath), and a solution of methyltriphenylphosphonium iodide (5.9 g, 14.6 mmol) in warm DMSO (15 mL) was added dropwise over 30 min. The reaction mixture was stirred at room temperature for an additional 30 min, and a solution of ketone (725 mg, 1.62 mmol) in dry DMSO (5 mL) was added dropwise over 1 min. The reaction mixture was heated at 75−80 °C for 24 h, cooled to 0 °C, diluted with water (20 mL), and extracted with ether (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (hexanes−EtOAc 8:2) gave compound **18** (658 mg, 91%) as a white solid: mp 56 °C; R_f 0.35 (4:1 hexane−AcOEt); $[\alpha]_D$ +63.8 (*c* 0.83, $CHCl_3$); MS *m*/*z* (EI) 446 (M^+); IR (KBr) 1640, 1598, 1480, 890, 813 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.39 (s, 1H), 4.59 (s, 1H), 4.09 (d, 1H), 4.00−3.85 (m, 4H), 3.79 (s, 6H), 3.64 (s, 6H), 2.77 (d, 1H), 2.60 (d, 1H), 2.43 (m, 1H), 2.17−1.93 (m, 3H), 1.69−1.06 (m, 7H), 1.00 (s, 3H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 153.7, 148.1, 142.1, 126.5, 113.8, 106.9, 97.3, 64.9, 64.4, 60.3, 56.2, 47.7, 44.2, 42.9, 35.4, 32.1, 29.4, 23.4, 23.0, 21.0, 19.2. Anal. Calcd for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58. Found: C, 69.84; H, 8.81.

(1*R*,2*S*,4a*S*)-Decahydro-1*β*,2*β*,4a*β*-trimethyl-1α-[(2,3,5,6-tetramethoxybenzene)methyl]-5-(1,3-dioxolan-2-yl)naphthalene (19) and (1*R*,2*R*,4a*S*)-Decahydro-1*β*,2α,4a*β*-tri-

methyl-1α-[(2,3,5,6-tetramethoxybenzene)methyl]-5-(1,3-dioxolan-2-yl)naphthalene (20). A mixture of exo olefin **18** (625 mg, 1.4 mmol), 10% Pd/C (700 mg), and MeOH (1 drop) in triethylamine was stirred at room temperature under 1 atm of hydrogen (balloon) for 12 h. The reaction was filtered through Celite and the filtrate concentrated in vacuo. Flash chromatography (hexanes−EtOAc 4:1) gave the less polar compound **20** (56 mg, 9%) and the more polar compound **19** (508 mg, 81%).

Compound 19: white solid; mp 72 °C; R_f 0.31 (4:1 hexane−AcOEt); $[\alpha]_D$ +1.6 (*c* 2.93, $CHCl_3$); MS *m*/*z* (EI) 448 (M^+); IR (KBr) 2942, 2874, 1591, 1489, 1240, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.46 (s, 1H), 3.89−3.86 (m, 4H), 3.84 (s, 6H), 3.70 (s, 6H), 2.70 (d, 1H), 2.54 (d, 1H), 1.81−1.22 (m, 12H), 1.04 (s, 3H), 0.81 (s, 3H), 0.68 (d, 3H); ^{13}C NMR ($CDCl_3$) δ 148.5, 142.8, 129.0, 113.6, 98.1, 65.2, 64.8, 60.0, 56.5, 47.3, 44.0, 42.6, 38.8, 36.6, 30.8, 29.7, 28.1, 23.3, 22.4, 18.5, 16.7, 15.9. Anal. Calcd for $C_{26}H_{40}O_6$: C, 69.61; H, 8.99. Found: C, 69.25; H, 8.87.

Compound 20: white solid; mp 127 °C; R_f 0.41 (4:1 hexane−AcOEt); $[\alpha]_D$ −11.0 (*c* 2.23, $CHCl_3$); MS *m*/*z* (EI) 448 (M^+); IR (KBr) 2942, 2874, 1598, 1489, 1240, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.55 (s, 1H), 4.16−3.98 (m, 4H), 3.96 (s, 6H), 3.85 (s, 6H), 2.86 (d, 1H), 2.72 (d, 1H), 1.97−1.43 (m, 12H), 1.38 (d, 3H), 1.24 (s, 3H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.5, 142.2, 129.1, 114.0, 96.8, 65.2, 64.8, 60.2, 56.1, 44.5, 42.3, 40.9, 37.5, 30.5, 30.4, 25.5, 24.1, 23.4, 20.9, 19.7, 18.8, 16.1. Anal. Calcd for $C_{26}H_{40}O_6$: C, 69.61; H, 8.99. Found: C, 69.81; H, 8.78.

(1*R*,2*S*,4a*S*)-Decahydro-1*β*,2α,4a*β*-trimethyl-5-methylene-1α-(2,3,5,6-tetramethoxybenzene)methylnaphthalene (21). A solution of **19** (448 mg, 1 mmol) in THF (8 mL) and aqueous HCl (1 N, 2 mL) was stirred at room temperature for 2 h. A saturated solution of $NaHCO_3$ (20 mL) was added in one portion, and the aqueous layer was extracted with ether (3×). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to give a ketone (404 mg, 100%), which was subjected to a Wittig reaction without further purification. To a solution of methyltriphenylphosphonium bromide (2.5 g, 7 mmol) in dry 1,4-dioxane (25 mL) was added *n*-BuLi (1.6 M in hexane, 4 mL, 6.4 mmol). The resulting orange solution was stirred at room temperature for 1 h. To this was added a solution of the above ketone (404 mg, 1 mmol) in dry 1,4-dioxane (10 mL), and the mixture was heated at 110 °C for 4 h. The mixture was cooled to 0 °C, water (10 mL) was added, and the excess dioxane removed in vacuo. More water (40 mL) was added, and the aqueous solution was extracted with ether (3×). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to flash chromatography using hexanes−EtOAc (4:1) as eluent to give the olefin **21** (374 mg, 93%) as a white solid: mp 84 °C; R_f: 0.58 (4:1 hexane−AcOEt); $[\alpha]_D$ −24.8 (*c* 1.47, $CHCl_3$); MS *m*/*z* (EI) 402 (M^+); IR (KBr) 1640, 1591, 1480, 890 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.43 (s, 1H), 4.40 (m, 2H), 3.82 (s, 6H), 3.65 (s, 6H), 2.60 (d, 1H), 2.51 (d, 1H), 2.31 (dt, 1H), 2.08−1.79 (m, 3H), 1.53−1.26 (m, 8H), 1.02 (s, 3H), 0.84 (s, 3H), 0.74 (d, 3H); ^{13}C NMR ($CDCl_3$) δ 160.7, 148.5, 142.6, 128.5, 102.3, 97.6, 59.9, 56.3, 51.4, 43.1, 40.6, 38.2, 36.5, 36.0, 33.1, 28.6, 28.4, 23.7, 20.4, 18.6, 16.7. Anal. Calcd for $C_{25}H_{38}O_4$: C, 74.37; H, 9.59. Found: C, 74.59; H, 9.51.

[1*R*-(1α,2*β*,4a*β*,8aα)]-3-(Decahydro-1,2,4a-trimethyl-5-methylene-1-naphthalenyl)methyl]-2-hydroxy-5-methoxy-2,5-cyclohexadiene-1,4-dione, (−) Ilimaquinone (1), [1*R*-(1α,2*β*,4a*β*,8aα)]-3-(Decahydro-1,2,4a-trimethyl-5-methylene-1-naphthalenyl)methyl]-2,5-dimethoxy-2,5-cyclohexadiene-1,4-dione (23), and [1*R*-(1α,2*β*,4a*β*,8aα)]-3-(Decahydro-1,2,4a-trimethyl-5-methylene-1-naphthalenyl)methyl]-5-hydroxy-2-methoxy-2,5-cyclohexadiene-1,4-dione (24). To a solution of olefin **21** (67 mg, 0.166 mmol) in CH_3CN (2.5 mL) was added a solution of ammonium cerium(IV) nitrate (228 mg, 0.415 mmol) in CH_3CN-H_2O (2 mL, 1:1) dropwise at −7 °C (salt ice bath) over 1 h. The reaction was allowed to stir at room temperature for 10 h and diluted with ether. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified over silica gel using hexanes−EtOAc (7:3) as eluent to give compounds **23** (6 mg, 10%) and ilimaquinone (**1**) (32 mg, 54%). Further elution with methanol gave compound **24** as its Fe complex (deep-red solid),[27] which was dissolved in ether, washed with 0.1 N HCl, water, and brine, dried over Na_2SO_4, and concentrated in vacuo to give pure compound **24** as a yellow oil (20 mg, 34%).

Ilimaquinone 1: yellow solid; mp 108−110 °C (pentane) [lit.[1a] mp 112−113 °C (hexane)]; R_f: 0.34 (7:3 hexane−AcOEt); $[\alpha]_D$ −23.8 (*c* 1.47, $CHCl_3$) [lit. $[\alpha]_D$ −23.2 (*c* 1.12, $CHCl_3$)]; MS *m*/*z* (CI) 369 (MH^+); IR (KBr) 3320, 1728, 1640, 1602 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.85 (s, 1H), 4.44 (d, 1H), 4.43 (d, 1H), 3.86 (s, 3H), 2.54 (d, 1H), 2.46 (d, 1H) AB syst., 2.31 (dt, 1H), 2.08−1.83 (m, 3H), 1.57−1.11 (m, 8H), 1.04 (s, 3H), 0.97 (d, 3H), 0.84 (s, 3H), 0.76 (dd, 1H); ^{13}C NMR ($CDCl_3$) δ 182.3, 182.0, 161.7, 160.5, 153.3, 117.3, 102.5, 102.0, 86.8, 50.1, 43.3, 40.4, 38.0, 36.6, 32.9, 32.3, 28.6, 27.9, 23.1, 20.5, 17.8, 17.3. HRMS (CI) calcd for $C_{22}H_{31}O_4$ (MH^+) 359.2222, found 359.2212.

Compound 23: yellow solid; mp 130−132 °C (pentane); R_f: 0.58 (7:3 hexane−AcOEt); $[\alpha]_D$ −41.0 (*c* 2.49, $CHCl_3$); MS *m*/*z* (CI) 373 (MH^+); IR (KBr) 3080, 1666, 1653, 1634, 1588, 1210, 1040; ^1H NMR ($CDCl_3$) δ 5.73 (s, 1H), 4.44 (d, 1H), 4.43 (d, 1H), 4.01 (s, 3H), 3.81 (s, 3H), 2.53 (d, 1H), 2.44 (d, 1H) AB syst, 2.37−2.26 (dt, 1H), 2.09−1.80 (m, 3H), 1.53−1.10 (m, 7H), 1.03 (s, 3H), 0.92 (d, 3H), 0.83 (s, 3H), 0.73 (dd, 1H); ^{13}C NMR ($CDCl_3$) δ 183.2, 182.5, 160.1, 159.2, 157.4, 128.8, 105.1, 102.6, 60.8, 56.4, 50.5, 43.5, 40.4, 38.1, 36.5, 32.9, 32.7, 28.4, 27.9, 23.3, 20.5, 17.9, 17.1; HRMS (CI) calcd for $C_{23}H_{33}O_4$ (MH^+) 373.2378, found 373.2384.

Compound 24: yellow oil; R_f: 0.1 (7:3 hexane−AcOEt); $[\alpha]_D$ −2.6 (*c* 0.5; $CHCl_3$); MS *m*/*z* (CI) 359 (MH^+); IR (neat) 3350, 1728, 1635, 1591, 1100; ^1H NMR ($CDCl_3$) δ 5.88 (s, 1H), 4.45 (d, 1H), 4.43 (d, 1H), 4.09 (s, 3H), 2.51 (d, 1H), 2.43 (d, 1H) AB syst., 2.31 (m, 1H), 2.08−1.83 (m, 3H), 1.59−1.10 (m, 8H), 1.25 (s, 3H), 0.92 (d, 3H), 0.83 (s, 3H), 0.71 (dd, 1H); ^{13}C NMR ($CDCl_3$) δ 183.7, 182.5, 159.9, 154.6, 125.3, 105.1, 102.9, 61.4, 50.5, 43.5, 40.5, 38.2, 36.5, 32.9, 30.3, 29.7, 27.9, 23.4, 22.7, 20.5, 18.0, 17.2; HRMS (CI) calcd for $C_{22}H_{31}O_4$ (MH^+) 359.2222, found 359.2215.

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Supporting Information Available: ^1H and ^{13}C NMR of ilimaquinone and all new compounds (30 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(27) Compound **24** was eluted from silica gel with methanol, although its R_f was 0.1 in hexane−AcOEt (7:3). We believe that **24** formed a complex with Fe (0.02% contained in silica gel) or with silica, and the deep red color might be attributed to its complex (see: Sodeoka, M.; Sampe R., Kagamizono, T.; Osada, H. *Tetrahedron Lett.* **1996**, *37*, 8775).