

Total Synthesis and Biological Evaluation of an Antifungal Tricyclic *o*-Hydroxy-*p*-Quinone Methide Diterpenoid

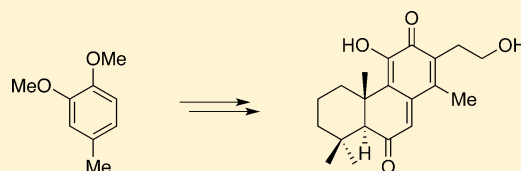
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S Supporting Information

ABSTRACT: A convergent route has been developed to synthesize an antifungal tricyclic *o*-hydroxy-*p*-quinone methide diterpenoid and analogues. A Li/naphthalene-mediated reductive alkylation was employed for coupling β -cyclocitral and the corresponding benzyl chloride, while a BBr₃-mediated one-pot bis-demethylation and intramolecular Friedel–Crafts alkylation was used to assemble the tricyclic molecular skeleton. The structure–activity relationship of the diterpenoid was assessed on the basis



of antiproliferation assays of the natural product and analogues against strains of pathogenic yeasts and filamentous fungi.

INTRODUCTION

Quinone methides are typically reactive electrophilic species that are formed as transient intermediates in chemical transformations.¹ However, in the presence of stabilizing structural elements, such as extended conjugation, relatively stable quinone methides may be formed. Indeed, a number of *o*-hydroxy-*p*-quinone methide diterpenoids and triterpenoids, such as fuerstion (1), taxodione (2) and its dimer (4), pristimerin (5), celastrol (6), and tingenone (7), many of which show interesting biological activities, have been isolated from nature (Figure 1).² As part of our efforts in investigating natural products with useful pharmacological properties,³ we became interested in 3, an unnamed quinone methide diterpenoid isolated from the root bark of *Bobgunnia madagascariensis*.⁴ In particular, we were intrigued by its reported potent antifungal activity, which even rivals that of

the clinical drugs amphotericin B and fluconazole. Our interest was partially fueled by the increasing demand for new antifungal drugs.⁵ The increasing incidence of invasive fungal infections associated with substantial mortality and high financial burden, especially among immunocompromised patient populations, rendered it increasingly important to develop new classes of drugs to combat fungal infection.

RESULTS AND DISCUSSION

Whereas a number of approaches have been reported for the synthesis of taxodione and related compounds,⁶ many employing linear synthetic routes starting from natural precursors, no total synthesis had been reported for 3 since its isolation in 2000.^{5a} To fully explore the biomedical potential of 3, we envisioned a convergent synthetic approach that not only would enable access of the natural product but also allow the preparation of analogues for structure–activity relationship (SAR) and mode-of-action studies. In this regard, we envisioned that the *o*-hydroxy-*p*-quinone methide moiety of 3 could be prepared by oxidation of catechol 8 (Scheme 1). An intramolecular Friedel–Crafts alkylation would be relied upon to build the tricyclic core of 8. The corresponding precursor 9 would be assembled by coupling of benzyl chloride 10 and commercially available β -cyclocitral. Herein we describe the results of our study, which led to the first synthesis of (\pm)-3 and elucidation of its preliminary SAR.

Our synthesis started from the known bromobenzene 11, available in four steps from commercial 3,4-dimethoxytoluene (Scheme 2).⁷ Stille coupling of 11 and tributylvinyltin was envisioned for introducing the ethylene group as a precursor to the 2-hydroxyethyl functionality of 3. After extensive screening of reaction conditions, the coupling was achieved using Pd₂(dba)₃ and P(*t*-Bu)₃ to give 12 in 98% yield.⁸ The

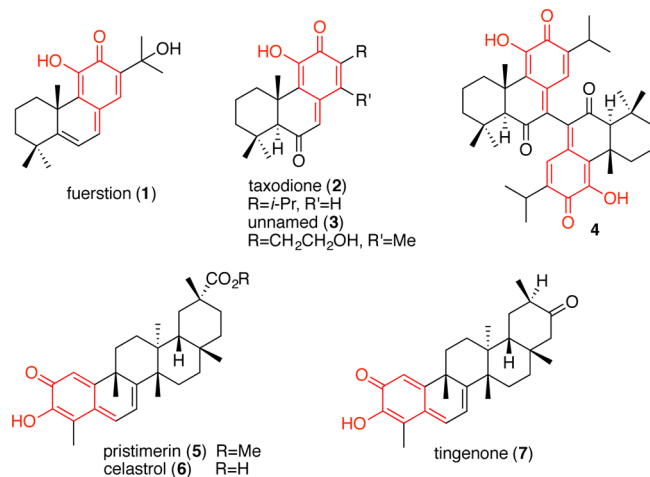
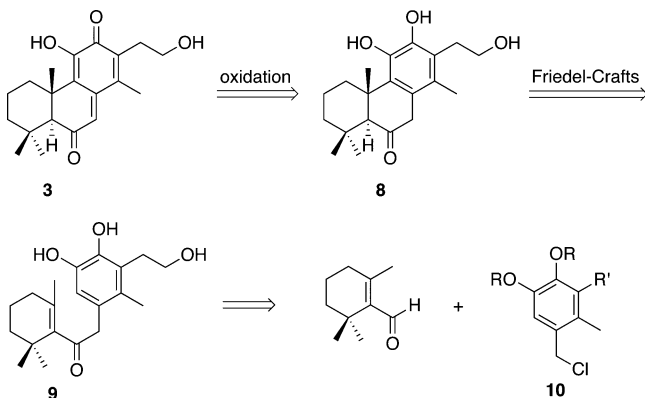


Figure 1. Some *o*-hydroxy-*p*-quinone methide natural products.

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Scheme 1. Synthetic Design

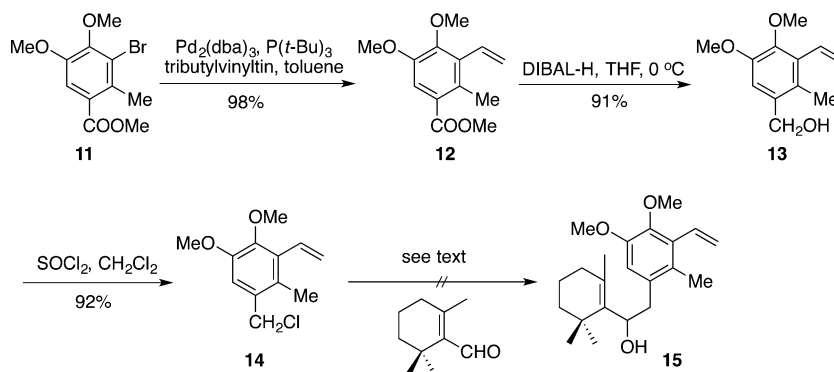


reduction of ester **12** with DIBAL-H yielded benzyl alcohol **13**, which was converted to benzyl chloride **14** upon treatment with SOCl_2 . Whereas complex mixtures were obtained when Li/naphthalene was used for coupling benzyl chloride **14** and β -cyclocitral,^{6c} no desired product (i.e., **15**) could be isolated from our attempts of coupling through the corresponding Grignard and organolithium reagents of **14**.

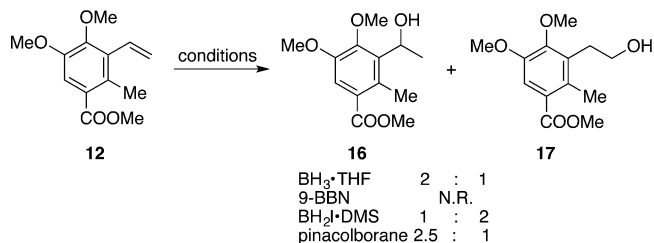
We speculated that the extended conjugation of **14** might be responsible for the difficulty of the coupling. Thus, we explored the possibility of furnishing the 2-hydroxyethyl group prior to the coupling reactions. However, attempts to introduce the 2-hydroxyethyl group of **17** through hydroboration/oxidation of **12** was only partially successful, as the undesired regioisomer (i.e., **16**) was formed as the major product under all conditions except when $\text{BH}_2\text{I}\cdot\text{Me}_2\text{S}$ was used,⁹ which gave the desired regioisomeric product **17** somewhat preferentially (2:1) (Scheme 3).

In order to improve the efficiency of the synthesis, we turned to the allyl-substituted benzyl chloride **19**, which was expected to be compatible with the coupling reaction (Scheme 4). The previously employed Stille reaction conditions also proved to be effective for the coupling of **11** and allyltributyltin to give **18**. DIBAL-H reduction followed by chlorination with SOCl_2 converted **18** into benzyl chloride **19**. As we had expected, the coupling of benzyl chloride **19** and β -cyclocitral went smoothly to give **20** (79% yield), which was converted to the α,β -unsaturated ketone **21** through oxidation with IBX. After oxidative cleavage of the alkene of **21** through OsO_4 -catalyzed dihydroxylation and subsequent oxidative cleavage of the vicinal diol with NaIO_4 , aldehyde **22** was obtained in 85% yield. Selective reduction of the aldehyde in the presence of α,β -

Scheme 2. Synthesis of 14



Scheme 3. Hydroboration/Oxidation of 12

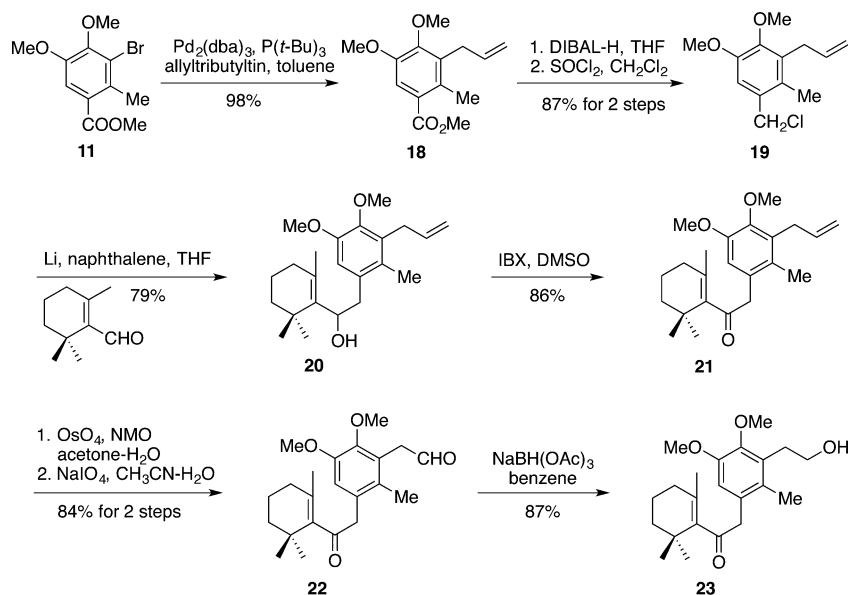


unsaturated ketone was achieved with $\text{NaBH}(\text{OAc})_3$ to give the primary alcohol **23**.

The generation of the tricyclic molecular skeleton of **3** by an intramolecular Friedel–Crafts alkylation reaction is challenging, because it requires simultaneous dearomatization and the formation of an all-carbon quaternary center. Thus, to evaluate the feasibility and to elucidate the nuance of this transformation, we used **25** as a model substrate to test various conditions for the cyclization. This substrate (i.e., **25**) was synthesized through Li/naphthalene-mediated coupling of the known benzyl chloride **24** and β -cyclocitral followed by oxidation with IBX (Scheme 5).^{6j}

A number of achiral and chiral Brønsted/Lewis acids were evaluated for the intramolecular Friedel–Crafts alkylation of **25**. The combination of formic acid and phosphoric acid was reported to be suitable for cyclizing **25** into **26** in 41% yield at 115 °C (not shown).^{6f} Interestingly, an extended reaction under such conditions led to formation of the undesired *cis*-isomeric **28** as the major product (Table 1, entry 1), suggesting its thermodynamic nature. The BINOL-based chiral phosphoric acid **31c** was also effective for the cyclization (entry 2), but no enantioselectivity was observed under the harsh conditions necessary for the reaction to proceed. A number of Lewis acids were also tested (see the Supporting Information for a complete list). Treatment of **25** with BBr_3 led to one-pot bis-demethylation, and an intramolecular Friedel–Crafts alkylation gave **27** (entry 3),¹⁰ which could be oxidized with Ag_2O to give taxodione (i.e., **2**, not shown).^{6a} On the other hand, the starting material was recovered when **25** was treated with $\text{BF}_3\cdot\text{Et}_2\text{O}$ (entry 4). Surprisingly, the one-pot demethylation and Friedel–Crafts cyclization of **25** with TMSI led to diastereoselective formation of the *cis*-isomeric product **30**, with only one of the methoxyl groups hydrolyzed (entry 5). In order to impose enantioselection during the cyclization, the oxazaborolidine-based Lewis acid **32** was also used.¹¹ However, the cyclization proceeded with low yield and low enantioselectivity

Scheme 4. Synthesis of 23



Scheme 5. Synthesis of 25

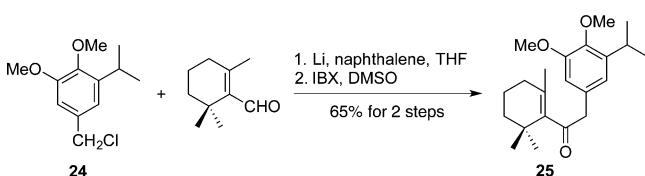
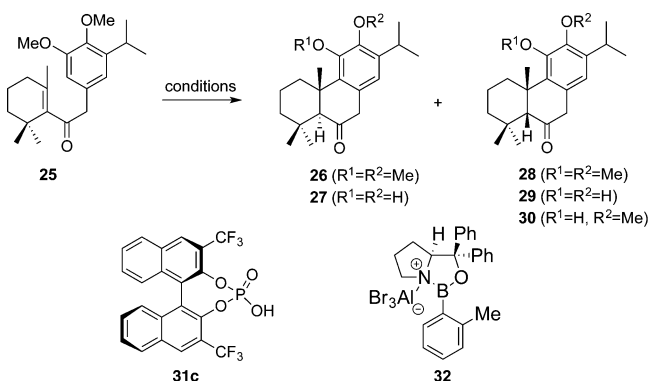


Table 1. Intramolecular Friedel–Crafts Alkylation of 25



| entry | conditions | T (°C) | time | product | yield (%) [ee] |
|-------|---|-----------|--------|---------|-------------------|
| 1 | HCO ₂ H, H ₃ PO ₄ | 115 | 12 h | 26 + 28 | 18 + 38 |
| 2 | HCO ₂ H, 31c | 110 | 96 h | 26 + 28 | 43 + 14 |
| 3 | BBr ₃ , CH ₂ Cl ₂ | -78 to 0 | 30 min | 27 | 45 |
| 4 | BF ₃ ·Et ₂ O, CH ₂ Cl ₂ | -78 to rt | 2 h | 27 | 0 |
| 5 | TMSI, toluene | 70 | 4 h | 30 | 54 |
| 6 | 32, BBr ₃ , CH ₂ Cl ₂ | 0 | 20 min | 27 | 20 [<20] |

(entry 6). A series of chiral Brønsted and Lewis acidic conditions were also tested (see the Supporting Information). However, no enantioselection was observed for the cyclization.

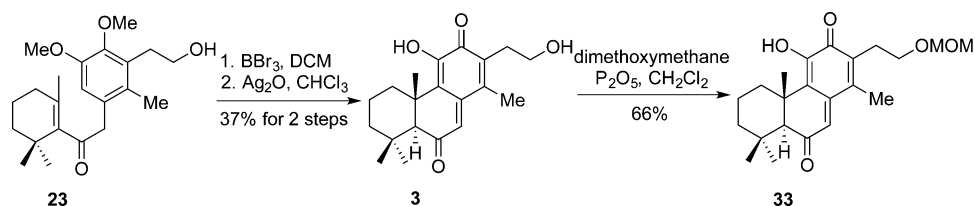
The application of the BBr₃-mediated one-pot reaction conditions allowed the completion of the synthesis of 3. Thus, treatment of 23 with BBr₃ led to one-pot bis-demethylation and cyclization to form a tricyclic catechol, which was subjected to oxidation with Ag₂O to give 3 (Scheme 6). Comparison of the

¹H and ¹³C NMR and MS spectra with those reported for the natural product confirmed the identity of synthetic 3. Selective monoetherification of 3 with dimethoxymethane gave the analogue 33.

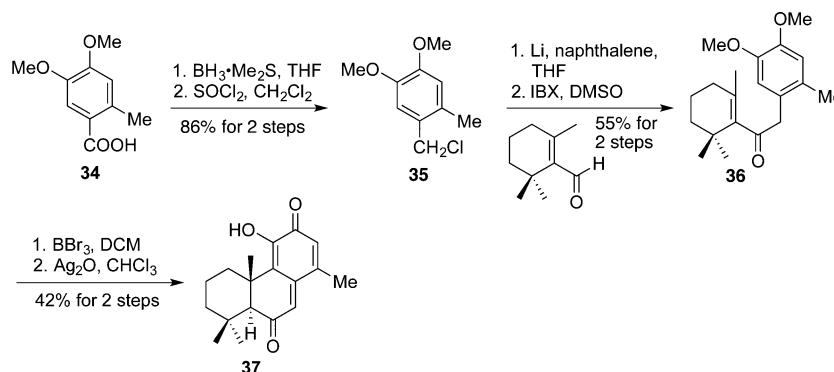
To evaluate the effect of the 2-hydroxyethyl group of 3 on the antifungal activity, we also prepared analogue 37 from the known carboxylic acid 34⁷ (Scheme 7). Thus, reduction of 34 with borane–dimethyl sulfide complex followed by chlorination with SOCl₂ provided benzyl chloride 35. The coupling of 35 and β-cyclocitral went smoothly with Li/naphthalene to give the corresponding allyl alcohol, which was oxidized with IBX to give enone 36. Compound 37 was obtained by BBr₃-mediated one-pot bis-demethylation and intramolecular Friedel–Crafts alkylation followed by oxidation of the resulting catechol with Ag₂O.

With the compounds synthesized above in hand, we evaluated their antifungal activity against strains of pathogenic yeasts (*Candida* spp. and *Cryptococcus* spp.) and the mold *Aspergillus fumigatus*. *Candida*, *Cryptococcus*, and *Aspergillus* species are the major fungal pathogens of global significance (Table 2).¹² The strains were chosen because of existing data on their susceptibility to fluconazole or itraconazole,^{13,14} two azole drugs that are commonly used clinically to treat infections caused by yeast and mold, respectively. Consistent with the original report, the synthetic *o*-hydroxy-*p*-quinone methide 3 indeed was found to be potently cytotoxic toward all the yeast strains tested, with MIC₁₀₀ values ranging from 0.4 to 6.4 mg/L. Interestingly, the values of MIC₁₀₀ were found to be similar to those of MFC (minimal fungicidal concentration). In contrast, MFCs are often much higher than MICs for fungistatic drugs such as fluconazole (Table 2). This finding indicates the fungicidal rather than fungistatic nature of these compounds. Compounds 3 and 37 are particularly effective against all the yeast strains, including the *Candida glabrata*, *Candida krusei*, and *Candida parapsilosis* strains that are resistant to the commonly used antifungal fluconazole (Table 2).¹⁴ The lack of any apparent correlation between the fungal susceptibility against these new compounds and that against azole drugs suggests that these compounds might differ in their mode of action against fungi from the known drug fluconazole.

Scheme 6. Synthesis of 3 and 33



Scheme 7. Synthesis of 37

Table 2. Taxodione (2), 3, and Analogues Exhibiting Fungicidal Effects (mg/L)^a

| yeast/fungal strain | 3 | | 37 | | 2 | | 33 | | azole | |
|---|--------------------|------------------|--------------------|------|--------------------|-------|--------------------|-------|-------------------|------|
| | MIC ₁₀₀ | MFC ^a | MIC ₁₀₀ | MFC | MIC ₁₀₀ | MFC | MIC ₁₀₀ | MFC | MIC ₉₀ | MFC |
| <i>Cryptococcus gattii</i> R265 | 0.4 | 0.4 | 0.8 | 0.8 | 0.8 | 0.8 | 6.4 | 12.8 | 4 | |
| <i>Cryptococcus neoformans</i> H99 α | 0.4 | 0.8 | 0.8 | 0.8 | 1.6 | 1.6 | 6.4 | 12.8 | 1 | 8 |
| <i>Candida albicans</i> SC5314 | 6.4 | 12.8 | 3.2 | 6.4 | 6.4 | >12.8 | >12.8 | >100 | 0.2 | 64 |
| <i>Candida glabrata</i> PAT2ISO3 | 1.6 | 6.4 | 1.6 | 3.2 | 3.2 | >6.4 | 6.4 | >12.8 | 8 | >64 |
| <i>Candida krusei</i> DUMC132.91 | 1.6 | 1.6 | 1.6 | 3.2 | 3.2 | 6.4 | 12.8 | >12.8 | 64 | 64 |
| <i>Candida parapsilosis</i> MMRL1594 | 3.2 | 6.4 | 1.6 | 3.2 | 6.4 | 12.8 | 12.8 | >100 | >64 | >64 |
| <i>Aspergillus fumigatus</i> Af293 | 25.6 | 25.6 | 17.1 | 17.1 | >100 | >100 | 100 | >100 | 0.4 | 12.8 |
| <i>Aspergillus fumigatus</i> CEA10 | 25.6 | 25.6 | 17.1 | 17.1 | >100 | >100 | 100 | >100 | 0.5 | - |

^aMFC is defined as the lowest drug concentration at which at least 99% of cells were killed in comparison to the original inocula. Suspensions from the microdilution assays after 24 h (for *Candida* species and *Aspergillus fumigatus* strains) or 48 h (for strains of *Cryptococcus* species) of incubation were plated on a drug-free medium to obtain the values of colony forming units (CFU) to determine the minimal fungicidal concentration (MFC). Successive 2 \times serial dilutions of the compounds were used. The data on the susceptibility of these strains against azole drugs (itraconazole for the mold *A. fumigatus* and fluconazole for all yeast species) were obtained from previous studies.^{13–15}

Taxodione (2) showed potent activity as well. However, the methoxymethyl ether of 3 (i.e., 33) significantly diminished the growth inhibition activity. None of these compounds were found to be effective against the mold *A. fumigatus*. It appears that the cytotoxicity of these compounds is correlated with the fungal growth mode (yeast versus mold) rather than their evolutionary relatedness, given that *Candida* (yeast) and *Aspergillus* (mold) spp. are closely related and their common ancestors diverged from that of *Cryptococcus* (yeast) spp. about one billion years ago. The cause of the differential cytotoxicities of these compounds against yeasts and the filamentous fungal stains is currently unknown.

CONCLUSION

In summary, we completed the first total synthesis of the antifungal tricyclic *o*-hydroxy-*p*-quinone methide diterpenoid 3. A Stille reaction was used to introduce the allyl group as a masked 2-hydroxyethyl side chain, whereas a Li/naphthalene-mediated reductive alkylation was employed for coupling benzyl chloride 19 and β -cyclocitral. We developed a BBr₃-

mediated one-pot bis-demethylation/intramolecular Friedel–Crafts alkylation to assemble the tricyclic molecular skeleton and completed the synthesis of 3. Taxodione 2 and analogues of 3 were also synthesized. Compounds 3, 37, and 2 showed potent cytotoxicity against various strains of pathogenic yeasts tested, but etherification of the 2-hydroxyethyl group led to significantly attenuated activity. Surprisingly, these compounds were found to be ineffective against the fungal strain *Aspergillus fumigatus*. The cause of this discrepancy of activity against the yeasts versus filamentous fungi is currently unknown.

EXPERIMENTAL SECTION

General Information. All moisture-sensitive reactions were carried out in flame-dried flasks under a nitrogen atmosphere. Dichloromethane and diethyl ether were dried using an activated molecular sieve solvent purification system. Tetrahydrofuran was freshly distilled over sodium and benzophenone. All other commercial reagents were used as received. Reactions were monitored by TLC performed on precoated glass-backed TLC plates, silica gel 60 F254 (EMD 250 μ m thickness). Spots were visualized with UV or through staining with an ethanolic solution of phosphomolybdic acid. Flash

column chromatography was performed using 60 Å silica gel (230–400 mesh) as the stationary phase. ^1H NMR chemical shifts are reported as δ values in ppm relative to CDCl_3 (7.26 ppm) or acetone- d_6 (2.05 ppm), coupling constants (J) are reported in Hertz (Hz), and multiplicities follow the normal convention. CDCl_3 (77.0 ppm) or acetone- d_6 (29.84 ppm) served as the internal standard for ^{13}C NMR spectra. Infrared (IR) spectra resonance frequencies are given as wavenumbers in cm^{-1} . HRMS spectra were recorded using a tandem TOF spectrometer.

Methyl 4,5-Dimethoxy-2-methyl-3-vinylbenzoate (12). To a suspension of ester **11** (1.57 g, 5.45 mmol), $\text{Pd}_2(\text{dba})_3$ (113 mg, 0.11 mmol), and tributylvinyltin (1.75 mL, 6.0 mmol) in toluene (11 mL) was added $\text{P}(t\text{-Bu})_3$ (0.22 mL, 0.22 mmol, 1 M in toluene) under nitrogen. The reaction was stirred at 60 °C overnight. When the reaction was complete on the basis of TLC, the solution was treated with KF (4 g), Et_2O (30 mL), and activated carbon (4 g). The mixture was stirred for 5 min before it was filtered through a short pad of silica gel (washed with ethyl acetate). After concentration, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether 1/5) to provide **12** (1.26 g, 98%) as a yellow oil: IR (film, cm^{-1}) 2999, 2955, 2842, 1723, 1590, 1478, 1427, 1324, 1199, 1167, 1110, 983; ^1H NMR (500 MHz, CDCl_3) δ 7.32 (s, 1H), 6.71 (dd, $J = 17.9, 11.6$ Hz, 1H), 5.61 (dd, $J = 11.6, 2.0$ Hz, 1H), 5.52 (dd, $J = 17.9, 2.0$ Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.79 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 168.4, 150.0, 149.7, 133.8, 131.2, 131.1, 126.3, 121.1, 112.9, 60.3, 55.9, 52.0, 17.6; HRMS molecular ion not observed.

(4,5-Dimethoxy-2-methyl-3-vinylphenyl)methanol (13). To a stirred solution of ester **12** (1.24 g, 5.25 mmol) in THF (30 mL) was added DIBAL-H (1 M in hexanes, 15.75 mL, 15.75 mmol) at 0 °C under nitrogen. The mixture was stirred at 0 °C for 2 h before it was quenched with ethyl acetate (3 mL) and saturated aqueous Rochelle salt (30 mL). The mixture was stirred for another 1 h at room temperature. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4 . After concentration, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether 1/1) to provide **13** (992 mg, 91%) as a colorless oil: IR (film, cm^{-1}) 2934, 1587, 1475, 1318, 1235, 1116, 974, 921, 944; ^1H NMR (500 MHz, CDCl_3) δ 6.92 (s, 1H), 6.74 (dd, $J = 17.9, 11.7$ Hz, 1H), 5.58 (dd, $J = 11.7, 2.1$ Hz, 1H), 5.54 (dd, $J = 17.9, 2.1$ Hz, 1H), 4.67 (s, 2H), 3.86 (s, 3H), 3.75 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 150.4, 146.3, 134.6, 132.9, 131.5, 126.6, 120.5, 111.2, 63.9, 60.2, 55.9, 15.1; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{16}\text{O}_3$ [$\text{M} + \text{Li}^+$] 215.1259, found 215.1266.

1-(Chloromethyl)-4,5-dimethoxy-2-methyl-3-vinylbenzene (14). To a solution of alcohol **13** (832 mg, 4.0 mmol) in CH_2Cl_2 (20 mL) was added SOCl_2 (0.35 mL, 4.8 mmol) dropwise at 0 °C under nitrogen. The reaction mixture was stirred at room temperature for 30 min before it was carefully quenched with saturated aqueous NaHCO_3 and taken into CH_2Cl_2 . The organic layer was separated, washed with water and brine, and dried over Na_2SO_4 . After concentration, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether 1/20) to provide **14** (832 mg, 92%) as a yellow oil: IR (film, cm^{-1}) 3005, 2970, 2934, 2837, 1590, 1478, 1318, 1238, 1116, 1045, 980, 927, 853; ^1H NMR (500 MHz, CDCl_3) δ 6.84 (s, 1H), 6.73 (dd, $J = 17.9, 11.7$ Hz, 1H), 5.60 (dd, $J = 11.7, 2.0$ Hz, 1H), 5.54 (dd, $J = 17.9, 2.1$ Hz, 1H), 4.62 (s, 2H), 3.88 (s, 3H), 3.76 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 150.5, 147.4, 133.4, 131.3, 131.2, 128.2, 120.7, 113.0, 60.2, 55.9, 45.8, 15.4; HRMS molecular ion not observed.

Ethyl 3-Allyl-4,5-dimethoxy-2-methylbenzoate (18). To a suspension of ester **11** (2.88 g, 10 mmol), $\text{Pd}_2(\text{dba})_3$ (275 mg, 0.30 mmol), and allyltributyltin (3.72 mL, 12 mmol) in toluene (15 mL) was added $\text{P}(t\text{-Bu})_3$ (1 M in toluene, 0.60 mL, 0.60 mmol) under nitrogen. The reaction mixture was stirred at 60 °C overnight. When the reaction was complete (monitored by TLC, ethyl acetate/petroleum ether 1/10 for two to three times), KF (5 g) was added followed by Et_2O (30 mL) and activated carbon (5 g). The mixture was stirred for 5 min, and then it was filtered through a short pad of

silica (washed with ethyl acetate). After concentration, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether 1/5) to provide **18** (2.59 g, 98%) as a yellow oil: IR (film, cm^{-1}) 2949, 2842, 1717, 1596, 1484, 1330, 1211, 1099, 1045, 989; ^1H NMR (500 MHz, CDCl_3) δ 7.29 (s, 1H), 5.95–5.89 (m, 1H), 5.00 (dd, $J = 10.2, 1.8$ Hz, 1H), 4.86 (dd, $J = 17.1, 1.8$ Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.83 (s, 3H), 3.49 (dt, $J = 5.6, 1.8$ Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 168.6, 150.2, 150.0, 136.0, 133.3, 132.1, 126.1, 115.1, 112.2, 60.9, 55.7, 51.9, 30.8, 16.1; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{18}\text{O}_4$ [$\text{M} + \text{H}^+$] 251.1283, found 251.1274.

3-Allyl-1-(chloromethyl)-4,5-dimethoxy-2-methylbenzene (19). To a solution of ester **18** (2.50 g, 10 mmol) in THF (50 mL) was added DIBAL-H (1 M in hexanes, 30 mL, 30 mmol) at 0 °C under nitrogen. The mixture was stirred at 0 °C for 4 h before it was treated with ethyl acetate (5 mL) and saturated aqueous Rochelle salt (50 mL). The mixture was stirred for another 1 h at room temperature. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4 . After concentration, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether 1/1) to provide allyl alcohol **S1** (2.01 g, 90%) as a colorless oil: IR (film, cm^{-1}) 3414, 2937, 1640, 1599, 1487, 1309, 1232, 1111, 1042, 906, 850; ^1H NMR (500 MHz, CDCl_3) δ 6.87 (s, 1H), 5.92 (ddt, $J = 17.1, 10.1, 5.8$ Hz, 1H), 4.99 (dd, $J = 10.2, 1.8$ Hz, 1H), 4.90 (dd, $J = 17.1, 1.9$ Hz, 1H), 4.64 (d, $J = 4.5$ Hz, 2H), 3.84 (s, 3H), 3.78 (s, 3H), 3.47 (dt, $J = 5.8, 1.8$ Hz, 2H), 2.18 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 150.4, 146.7, 136.5, 134.4, 132.6, 127.5, 115.0, 110.5, 63.9, 60.9, 55.7, 30.9, 13.9; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{18}\text{O}_3$ [$\text{M} + \text{Li}^+$] 229.1416, found 229.1406.

To a solution of **S1** (1.85 g, 8.32 mmol) in CH_2Cl_2 (40 mL) was added SOCl_2 (0.73 mL, 9.99 mmol) dropwise at 0 °C under nitrogen. The reaction mixture was maintained at room temperature for 30 min before it was carefully quenched with saturated aqueous NaHCO_3 . The mixture was taken into CH_2Cl_2 . The organic layer was separated, washed with water and brine, and dried over Na_2SO_4 . After concentration, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether 1/10) to provide **19** (1.93 g, 97%) as a white amorphous solid: IR (film, cm^{-1}) 2940, 1602, 1484, 1330, 1226, 1108, 1045, 986, 912; ^1H NMR (500 MHz, CDCl_3) δ 6.79 (s, 1H), 5.92 (ddt, $J = 17.1, 10.2, 5.8$ Hz, 1H), 5.01 (dd, $J = 10.2, 1.8$ Hz, 1H), 4.89 (dd, $J = 17.1, 1.8$ Hz, 1H), 4.60 (s, 2H), 3.86 (s, 3H), 3.80 (s, 3H), 3.48 (dt, $J = 5.8, 1.8$ Hz, 2H), 2.26 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 150.5, 147.7, 136.2, 133.1, 131.0, 129.1, 115.1, 112.2, 60.9, 55.7, 45.9, 31.0, 14.3; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{17}\text{ClO}_2$ [$\text{M} + \text{H}^+$] 241.0995, found 241.1003.

2-(3-Allyl-4,5-dimethoxy-2-methylphenyl)-1-(2,6,6-trimethylcyclohex-1-en-1-yl)ethanol (20). A mixture of naphthalene (3.61 g, 28.13 mmol) and lithium (196 mg, 28.13 mmol) in THF (30 mL) was stirred at room temperature under nitrogen for 1.5 h. The mixture was then treated with a solution of β -cyclocitral (1.26 g, 8.25 mmol) and benzyl chloride **19** (1.80 g, 7.50 mmol) in THF (10 mL) dropwise via syringe at 0 °C. After it was stirred at room temperature for 2 h, the mixture was diluted with ether and treated with saturated aqueous NH_4Cl . The organic phase was separated. The aqueous phase was extracted with EtOAc . The combined organic layers were washed with brine and dried over Na_2SO_4 . After concentration, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether 1/4) to provide **20** (2.13 g, 79%) as a colorless liquid: IR (film, cm^{-1}) 3500, 2931, 1593, 1484, 1291, 1229, 1111, 1048, 989, 906; ^1H NMR (500 MHz, CDCl_3) δ 6.70 (s, 1H), 5.94 (dd, $J = 17.1, 10.1$ Hz, 1H), 5.01 (dq, $J = 10.1, 1.7$ Hz, 1H), 4.93 (dq, $J = 17.1, 1.8$ Hz, 1H), 4.45 (dd, $J = 10.0, 4.3$ Hz, 1H), 3.87 (s, 3H), 3.80 (s, 3H), 3.49 (ddd, $J = 5.8, 3.9, 1.9$ Hz, 2H), 3.19 (dd, $J = 14.2, 10.0$ Hz, 1H), 2.88 (dd, $J = 14.2, 4.3$ Hz, 1H), 2.24 (s, 3H), 2.03–1.99 (m, 2H); 2.02 (s, 3H), 1.65–1.54 (m, 2H), 1.46–1.44 (m, 2H), 1.11 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 150.3, 146.0, 139.3, 136.7, 133.3, 132.4, 132.0, 128.3, 114.9, 113.0, 71.2, 60.9, 55.8, 40.5, 40.0, 34.8, 34.2, 31.2, 28.5, 28.3, 21.4, 19.3, 15.2;

HRMS (ESI) calcd for $C_{23}H_{34}O_3$ [$M + Na^+$] 381.2406, found 381.2388.

2-(3-Allyl-4,5-dimethoxy-2-methylphenyl)-1-(2,6,6-trimethylcyclohex-1-en-1-yl)ethanone (21). A solution of alcohol **20** (910 mg, 2.54 mmol) and IBX (1.07 g, 3.81 mmol) in DMSO (5 mL) was stirred at room temperature for 3 h. The reaction was quenched with H_2O (5 mL) at 0 °C. The mixture was filtered, and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4 . After concentration in vacuo, the residue was purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether 1/1) to provide **21** (780 mg, 86%) as a yellow oil: IR (film, cm^{-1}) 2937, 1691, 1596, 1487, 1285, 1226, 1113, 1048, 995; 1H NMR (500 MHz, $CDCl_3$) δ 6.56 (s, 1H), 5.93 (ddt, $J = 17.1, 10.2, 5.7$ Hz, 1H), 4.99 (dq, $J = 10.1, 1.7$ Hz, 1H), 4.91 (dq, $J = 17.1, 1.9$ Hz, 1H), 3.87 (s, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 3.48 (dt, $J = 5.7, 1.8$ Hz, 2H), 2.11 (s, 3H), 1.99 (t, $J = 6.5$ Hz, 2H), 1.72–1.67 (m, 2H), 1.63 (s, 3H), 1.48–1.46 (m, 2H), 1.11 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.8, 150.3, 146.4, 143.1, 136.6, 132.4, 129.5, 129.1, 128.4, 114.9, 112.9, 60.8, 55.8, 50.8, 39.0, 33.4, 31.3, 31.2, 28.8, 21.2, 18.9, 15.4; HRMS (ESI) calcd for $C_{23}H_{32}O_3$ [$M + H^+$] 357.2430, found 357.2423.

2-(2,3-Dimethoxy-6-methyl-5-(2-oxo-2-(2,6,6-trimethylcyclohex-1-en-1-yl)ethyl)phenyl)acetaldehyde (22). To a solution of alkene **21** (530 mg, 1.49 mmol) in acetone/ H_2O (4/1, 15 mL) was added NMO (262 mg, 2.23 mmol) and OsO_4 (2.5 wt % solution in *t*-BuOH, 758 mg, 7.45% mmol). After being stirred at room temperature overnight, the mixture was concentrated in vacuo. The residue was taken into EtOAc, washed with H_2O and brine, and dried over Na_2SO_4 . After concentration in vacuo, the crude reaction product was dissolved in CH_3CN/H_2O (1/1, 16 mL) and treated with NaIO₄ (478 mg, 2.24 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 1 h before it was filtered through a short pad of silica gel (eluted with EtOAc). The filtrate was washed with H_2O and brine and dried over Na_2SO_4 . After concentration in vacuo, the residue was purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether 1/5) to provide **22** (446 mg, 84% for two steps) as a white amorphous solid: IR (film, cm^{-1}) 2937, 1720, 1697, 1484, 1279, 1229, 1108, 1066; 1H NMR (500 MHz, $CDCl_3$) δ 9.68 (s, 1H), 6.62 (s, 1H), 3.89 (s, 2H), 3.84 (s, 3H), 3.81 (d, $J = 2.0$ Hz, 2H), 3.78 (s, 3H), 2.07 (s, 3H), 2.00 (t, $J = 6.5$ Hz, 2H), 1.72–1.66 (m, 2H), 1.64 (s, 3H), 1.49–1.46 (m, 2H), 1.12 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.6, 199.7, 150.2, 146.6, 143.0, 129.7, 129.2, 128.8, 125.7, 114.2, 60.5, 55.8, 50.8, 42.7, 38.9, 33.5, 31.3, 28.8, 21.2, 18.8, 16.1; HRMS (ESI) calcd for $C_{22}H_{30}O_4$ [$M + Li^+$] 365.2304, found 365.2312.

2-(3-(2-Hydroxyethyl)-4,5-dimethoxy-2-methylphenyl)-1-(2,6,6-trimethylcyclohex-1-en-1-yl)ethanone (23). To a solution of aldehyde **22** (423 mg, 1.18 mmol) in benzene (10 mL) was added $NaBH(OAc)_3$ (376 mg, 1.77 mmol) and acetic acid (0.70 mL). After it was stirred at room temperature under nitrogen for 6 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ at 0 °C. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4 . After concentration in vacuo, the residue was purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether 1/1) to provide **23** (370 mg, 87%) as a white amorphous solid: IR (film, cm^{-1}) 3446, 2934, 1694, 1596, 1492, 1300, 1229, 1116, 1048; 1H NMR (500 MHz, $CDCl_3$) δ 6.55 (s, 1H), 3.88 (s, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.77 (t, $J = 6.7$ Hz, 2H), 3.00 (t, $J = 6.8$ Hz, 2H), 2.16 (s, 3H), 2.00 (t, $J = 6.4$ Hz, 2H), 1.72–1.67 (m, 2H), 1.64 (s, 3H), 1.49–1.46 (m, 2H), 1.12 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.8, 150.1, 146.5, 143.0, 131.1, 129.6, 128.8, 128.8, 113.1, 62.7, 60.5, 55.7, 50.9, 38.9, 33.5, 31.3, 30.7, 28.8, 21.2, 18.8, 15.7; HRMS (ESI) calcd for $C_{22}H_{32}O_4$ [$M + Li^+$] 367.2461, found 367.2469.

2-(3-Isopropyl-4,5-dimethoxyphenyl)-1-(2,6,6-trimethylcyclohex-1-en-1-yl)ethanone (25). A mixture of naphthalene (4.92 g, 38.35 mmol) and lithium (266 mg, 38.35 mmol) in THF (40 mL) was stirred at room temperature for 1.5 h before it was treated with a solution of β -cyclocitral (1.28 g, 8.44 mmol) and benzyl chloride **24** (1.75 g, 7.67 mmol) in THF (10 mL) dropwise at 0 °C. The resulting

mixture was stirred at room temperature for 2 h, diluted with ether, and then treated with saturated aqueous NH_4Cl . The organic phase was separated, and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4 . After concentration, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether 1/5) to provide allyl alcohol **S2** (2.26 g, 85%) as a light yellow liquid: 1H NMR (500 MHz, $CDCl_3$) δ 6.70 (d, $J = 1.9$ Hz, 1H), 6.66 (d, $J = 1.9$ Hz, 1H), 4.42 (dd, $J = 10.1, 3.6$ Hz, 1H), 3.87 (s, 3H), 3.80 (s, 3H), 3.34 (dt, $J = 13.9, 6.9$ Hz, 1H), 3.06 (dd, $J = 13.9, 10.1$ Hz, 1H), 2.82 (dd, $J = 13.9, 3.5$ Hz, 1H), 2.05–1.94 (m, 2H), 1.96 (s, 3H), 1.62–1.53 (m, 2H), 1.46–1.42 (m, 2H), 1.23 (s, 3H), 1.22 (s, 3H), 1.10 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.5, 144.9, 142.4, 138.9, 135.5, 131.8, 118.9, 110.7, 72.3, 60.9, 55.7, 43.4, 39.9, 34.8, 34.1, 28.6, 28.1, 26.8, 23.6, 23.5, 21.4, 19.3.

To a solution of **S2** (370 mg, 1.07 mmol) in DMSO (4 mL) was added IBX (449 mg, 1.60 mmol) at room temperature. The resulting mixture was stirred at room temperature for 3 h before it was treated with H_2O (5 mL) at 0 °C. The mixture was filtered, and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4 . After concentration, the residue was purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether 1/5) to provide **25** (285 mg, 77%) as a yellow amorphous solid: 1H NMR (500 MHz, $CDCl_3$) δ 6.66 (d, $J = 2.0$ Hz, 1H), 6.64 (d, $J = 2.0$ Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.79 (s, 2H), 3.33 (dt, $J = 13.9, 6.9$ Hz, 1H), 1.99–1.96 (m, 2H), 1.69–1.67 (m, 2H), 1.56 (s, 3H), 1.47–1.44 (m, 2H), 1.20 (s, 3H), 1.19 (s, 3H), 1.08 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3, 145.1, 143.1, 142.0, 129.7, 129.6, 119.7, 111.3, 60.9, 55.7, 52.2, 38.9, 33.4, 31.2, 28.8, 26.7, 23.5, 21.2, 18.8.

o-Hydroxy-*p*-quinone Methide Diterpenoid 3. To a solution of alcohol **23** (301 mg, 0.84 mmol) in dichloromethane (8 mL) was added a freshly prepared solution of BBr_3 (1 M in dichloromethane, 5.04 mL, 5.04 mmol) dropwise at –78 °C under nitrogen. The reaction mixture was stirred for 30 min, warmed to 0 °C, and stirred for another 2 h. The reaction was carefully quenched with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4 . After concentration in vacuo, the residue was taken into $CHCl_3$ (10 mL) and treated with Ag_2O (223 mg, 0.90 mmol). The mixture was stirred at 50 °C for 30 min and filtered through a cotton plug. The filtrate was concentrated and purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether 1/1) to provide **3** (103 mg, 37% for 2 steps) as an orange amorphous solid: IR (film, cm^{-1}) 3325, 2925, 1670, 1610, 1377, 1223, 1185, 1146, 1045; 1H NMR (500 MHz, acetone- d_6) δ 8.32 (s, 1H), 6.50 (s, 1H), 3.75 (t, $J = 5.7$ Hz, 1H), 3.63–3.59 (m, 2H), 3.05–3.02 (m, 1H), 2.85–2.81 (m, 2H), 2.65 (s, 1H), 2.34 (s, 3H), 1.76–1.70 (m, 2H), 1.59–1.54 (m, 1H), 1.40–1.36 (m, 1H), 1.29–1.26 (m, 1H), 1.27 (s, 3H), 1.24 (s, 3H), 1.10 (s, 3H); 1H NMR (500 MHz, acetone- $d_6 + D_2O$) δ 6.52 (s, 1H), 3.59 (t, $J = 7.1$ Hz, 2H), 3.03 (d, $J = 11.8$ Hz, 1H), 2.83 (t, $J = 7.2$ Hz, 2H), 2.66 (s, 1H), 2.33 (s, 3H), 1.73–1.66 (m, 2H), 1.56–1.53 (m, 1H), 1.37 (d, $J = 11.7$ Hz, 1H), 1.26 (s, 3H), 1.23 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (125 MHz, acetone- d_6) δ 201.1, 182.3, 146.4, 145.1, 142.0, 134.8, 131.3, 127.0, 62.3, 61.2, 43.0, 42.9, 37.7, 33.4, 33.3, 31.0, 22.2, 21.6, 19.3, 15.9; HRMS (ESI) calcd for $C_{20}H_{26}O_4$ [$M - H^+$] 329.1753, found 329.1738.

(4bS,8aS)-4-Hydroxy-2-(2-(methoxymethoxy)ethyl)-1,4b,8,8-tetramethyl-4b,5,6,7,8,8a-hexahydrophenanthrene-3,9-dione (33). To a solution of alcohol **3** (9.9 mg, 0.03 mmol) in dichloromethane (2 mL) was added dimethoxymethane (0.027 mL, 0.3 mmol) and P_2O_5 (43 mg, 0.15 mmol). The solution was stirred at room temperature for 2 h before it was diluted with dichloromethane, washed with saturated aqueous $NaHCO_3$, and then dried over Na_2SO_4 . After concentration, the residue was purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether 1/5) to provide **33** (7.4 mg, 66%) as a yellow liquid: IR (film, cm^{-1}) 3322, 2934, 1670, 1611, 1380, 1152, 1116, 1025; 1H NMR (500 MHz, $CDCl_3$) δ 7.53 (s, 1H), 6.51 (s, 1H), 4.60 (s, 2H), 3.62 (t, $J = 6.9$ Hz, 2H), 3.33 (s, 3H), 2.98–2.95 (m, 1H), 2.93–2.88 (m, 2H), 2.59 (s,

1H), 2.29 (s, 3H), 1.74–1.70 (m, 2H), 1.62–1.59 (m, 2H), 1.44–1.40 (m, 1H), 1.28 (s, 3H), 1.26 (s, 3H), 1.13 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 201.2, 181.5, 146.1, 143.7, 141.1, 133.5, 131.1, 126.6, 96.3, 65.9, 62.2, 55.2, 42.6, 42.4, 37.1, 33.2, 32.7, 27.2, 21.9, 21.7, 18.6, 15.8; HRMS (ESI) calcd for C₂₂H₃₀O₅ [M + Li⁺] 381.2248, found 381.2262.

(4bS,8aR)-4-Hydroxy-2-isopropyl-3-methoxy-4b,8,8-trimethyl-4b,5,6,7,8,8a-hexahydrophenanthren-9(10H)-one (30).

A mixture of hexamethyldisilazane (0.25 mL, 1.2 mmol) and iodine (305 mg, 1.2 mmol) was heated at 65 °C for 20 min under nitrogen. After the mixture was cooled to room temperature, a solution of ketone **25** (69 mg, 0.2 mmol) in toluene (1 mL) was added. The reaction mixture was stirred at 70 °C for 4 h before it was concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether 1/5) to provide **30** (35.9 mg, 54%) as a yellow amorphous solid: IR (film, cm⁻¹) 3414, 2955, 2931, 1694, 1448, 1418, 1300, 1229, 1057, 1033, 998; ¹H NMR (500 MHz, CDCl₃) δ 6.67 (s, 1H), 5.77 (s, 1H), 3.80 (s, 3H), 3.65 (d, J = 22.9, 1.1 Hz, 1H), 3.47 (d, J = 22.9 Hz, 1H), 3.27 (dt, J = 13.9, 6.9 Hz, 1H), 3.03–2.99 (m, 1H), 1.98 (s, 1H), 1.61–1.15 (m, 5H), 1.26 (d, J = 6.9 Hz, 3H), 1.24 (d, J = 6.9 Hz, 3H), 1.24 (s, 3H), 0.94 (s, 3H), 0.30 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 213.1, 145.8, 144.9, 133.7, 130.4, 126.4, 122.3, 68.5, 61.9, 44.0, 42.2, 40.1, 37.4, 34.4, 32.4, 31.9, 27.2, 22.8, 22.5, 22.4, 20.2; HRMS (ESI) calcd for C₂₁H₃₀O₃ [M + H⁺] 331.2268, found 331.2264.

1-(Chloromethyl)-4,5-dimethoxy-2-methylbenzene (35). To a solution of carboxylic acid **34** (1.0 g, 5.10 mmol) in THF (9 mL) was added a solution of borane–dimethyl sulfide complex (2 M in THF, 4.08 mL, 8.15 mmol) at 0 °C. The solution was warmed to room temperature and stirred overnight. The reaction mixture was carefully quenched with H₂O, and the resulting mixture was diluted with EtOAc. The organic phase was separated, washed with H₂O, and dried over Na₂SO₄. After concentration, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether 1/1) to provide the benzyl alcohol (836 mg, 90%) as a white amorphous solid.

The benzylic alcohol (1.82 g, 10 mmol) was taken into CH₂Cl₂ (20 mL) and treated with SOCl₂ (0.87 mL, 12 mmol) dropwise at 0 °C under nitrogen. The mixture was stirred at room temperature for 30 min before it was carefully quenched with saturated aqueous NaHCO₃. The organic phase was separated, and the aqueous phase was extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether 1/5) to provide **35** (1.90 g, 95%) as a yellow oil: IR (film, cm⁻¹) 2963, 2934, 1611, 1519, 1466, 1338, 1282, 1226, 1105, 998; ¹H NMR (500 MHz, CDCl₃) δ 6.84 (s, 1H), 6.71 (s, 1H), 4.60 (s, 2H), 3.89 (s, 6H), 2.38 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 149.1, 147.0, 129.8, 127.3, 113.7, 113.0, 56.0, 55.9, 45.2, 18.4; HRMS (ESI) calcd for C₁₀H₁₃O₂Cl [M + H⁺] 201.0682, found 201.0692.

2-(4,5-Dimethoxy-2-methylphenyl)-1-(2,6,6-trimethylcyclohex-1-en-1-yl)ethanone (36). A mixture of naphthalene (5.77 g, 45 mmol) and lithium (313 mg, 45 mmol) in THF (50 mL) was stirred at room temperature under nitrogen for 1.5 h. To this mixture was added a solution of β-cyclocitral (1.51 g, 9.9 mmol) and benzyl chloride **35** (1.80 g, 9 mmol) in THF (10 mL) via syringe at 0 °C. The mixture was then stirred at room temperature for 2 h before it was diluted with ether and treated with saturated aqueous NH₄Cl. The organic phase was separated, and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na₂SO₄. After concentration, the residue was purified by flash column chromatography (silica gel, eluted with ethyl acetate/petroleum ether 1/5) to provide allyl alcohol **S3** (2.17 g, 76%) as a light yellow amorphous solid: IR (film, cm⁻¹) 3538, 2934, 1608, 1513, 1466, 1270, 1226, 1102, 998; ¹H NMR (500 MHz, CDCl₃) δ 6.74 (s, 1H), 6.69 (s, 1H), 4.44 (dd, J = 10.2, 4.1 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.14 (dd, J = 14.2, 10.2 Hz, 1H), 2.79 (dd, J = 14.2, 4.1 Hz, 1H), 2.33 (s, 3H), 2.03–1.94 (m, 2H), 2.00 (s, 3H), 1.62–1.53 (m, 2H), 1.45–1.42 (m, 2H), 1.10 (s, 3H), 0.94 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) 147.3, 147.0, 139.3, 131.9, 129.6, 128.8, 113.8, 113.7, 71.4, 56.1, 55.9,

40.0, 39.5, 34.8, 34.2, 28.5, 28.3, 21.4, 19.6, 19.3; HRMS (ESI) calcd for C₂₀H₃₀O₃ [M + Li⁺] 325.2355, found 325.2339.

A solution of **S3** (960 mg, 3.03 mmol) in DMSO (6 mL) was treated with IBX (1.27 g, 4.55 mmol) and stirred at room temperature for 2 h. The reaction mixture was treated with H₂O (6 mL) at 0 °C and filtered. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na₂SO₄. After concentration in vacuo, the residue was purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether 1/3) to provide **36** (701 mg, 73%) as a light yellow amorphous solid: IR (film, cm⁻¹) 2931, 1700, 1516, 1460, 1270, 1229, 1108, 1039, 998; ¹H NMR (500 MHz, CDCl₃) δ 6.71 (s, 1H), 6.61 (s, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.82 (s, 2H), 2.23 (s, 3H), 1.99 (t, J = 6.4 Hz, 2H), 1.71–1.66 (m, 2H), 1.62 (s, 3H), 1.48–1.46 (m, 2H), 1.11 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 208.0, 147.8, 146.8, 143.0, 129.5, 129.4, 124.5, 113.7, 113.6, 56.0, 55.8, 49.7, 38.9, 33.4, 31.2, 28.8, 21.1, 19.6, 18.8; HRMS (ESI) calcd for C₂₀H₂₈O₃ [M + H⁺] 317.2117, found 317.2126.

(4bS,8aS)-4-Hydroxy-1,4b,8,8-tetramethyl-4b,5,6,7,8,8a-hexahydrophenanthrene-3,9-dione (37). To a solution of ketone **36** (95 mg, 0.30 mmol) in CH₂Cl₂ (3 mL) was added a freshly prepared solution of BBr₃ (1 M in CH₂Cl₂, 1.80 mL, 1.80 mmol) dropwise at –78 °C under nitrogen. The reaction mixture was stirred for 30 min, warmed to 0 °C, and further stirred for 3 h. The reaction was carefully quenched with saturated aqueous NaHCO₃. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na₂SO₄. After concentration in vacuo, the residue was taken into CHCl₃ (10 mL) and treated with Ag₂O (104 mg, 0.45 mmol). The mixture was stirred at 50 °C for 30 min and filtered through a plug of cotton. The filtrate was concentrated and purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether 1/4) to provide **37** (35.9 mg, 42% for 2 steps) as an orange amorphous solid: IR (film, cm⁻¹) 3432, 2925, 1673, 1626, 1413, 1380, 1356, 1223, 1146, 773; ¹H NMR; δ 7.42 (s, 1H), 6.43 (s, 1H), 6.42 (d, J = 1.2 Hz, 1H), 2.97–2.94 (m, 1H), 2.59 (s, 1H), 2.26 (d, J = 1.3 Hz, 3H), 1.77–1.66 (m, 2H), 1.62–1.57 (m, 1H), 1.43–1.39 (m, 1H), 1.27 (s, 3H), 1.26 (s, 3H), 1.24–1.16 (m, 1H), 1.12 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 201.1, 181.6, 150.3, 144.5, 140.9, 131.3, 126.9, 126.4, 62.4, 42.9, 42.4, 37.1, 33.2, 32.8, 21.9, 21.7, 19.8, 18.6; HRMS (ESI) calcd for C₁₈H₂₂O₃ [M – H⁺] 285.1496, found 285.1501.

Taxodione (2). To a solution of ketone **25** (103 mg, 0.30 mmol) in CH₂Cl₂ (3 mL) was added a freshly prepared solution of BBr₃ (1 M in CH₂Cl₂, 1.80 mL, 1.80 mmol) at –78 °C under nitrogen. The reaction mixture was stirred for 30 min, warmed to 0 °C, and stirred for another 30 min. The reaction was carefully quenched with saturated aqueous NaHCO₃. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na₂SO₄. After concentration in vacuo, the residue was taken into CHCl₃ (10 mL) and treated with Ag₂O (104 mg, 0.45 mmol). The mixture was stirred at 50 °C for 30 min before it was filtered through a plug of cotton. The filtrate was concentrated and purified by column chromatography (silica gel, eluted with ethyl acetate/petroleum ether 1/4) to provide **2** (36.8 mg, 39% for two steps) as an orange amorphous solid.

■ ASSOCIATED CONTENT

📄 Supporting Information

Figures giving some other conditions tested for the Friedel–Crafts alkylation of **26** and ¹H and ¹³C NMR spectra of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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