

Synthesis of 8-Phenylphenalenones: 2-Hydroxy-8-(4-hydroxyphenyl)-1*H*-phenalen-1-one from *Eichhornia crassipes*

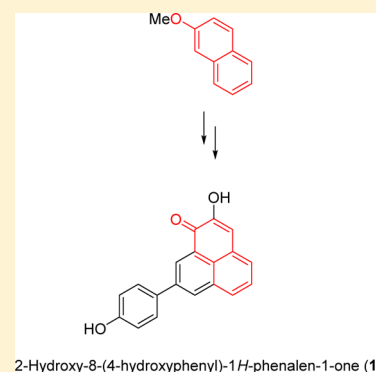
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S Supporting Information

ABSTRACT: 2-Hydroxy-8-(4-hydroxyphenyl)-1*H*-phenalen-1-one (**1**), the first reported 8-phenylphenalenone from the roots of *Eichhornia crassipes* (water hyacinth), was synthesized starting from 2-methoxynaphthalene in 11 steps and with an overall yield of 2%. A cascade Friedel–Crafts/Michael annulation reaction between acryloyl chloride and 2-methoxynaphthalene afforded 9-methoxyperinaphthanone that, after transformation to 9-methoxy-2-(4-methoxyphenyl)-1*H*-phenalen-1-one by means of standard Suzuki–Miyaura methodology, was subjected to a reductive carbonyl transposition to afford 8-(4-methoxyphenyl)perinaphthanone. Dehydrogenation, epoxidation, and demethylation of the latter afforded **1**.



In 2005, Hölscher and Schneider reported the isolation of the first 8-phenylphenalenones from the roots of *Eichhornia crassipes* (water hyacinth), a pantropical freshwater weed characterized by its invasive nature.¹ The biosynthesis of these novel phenylphenalenones was suggested to involve an unusual 1,2-aryl migration similar to that known to occur in the biosynthesis of isoflavonoids.¹ This work added another group of phenylphenalenones, namely 8-phenylphenalenones, to the well-known isomeric 4- and 9-phenylphenalenones (Figure 1)

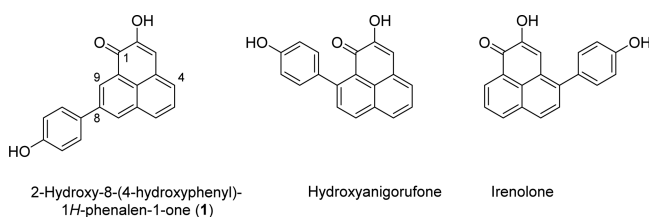


Figure 1. Examples of natural isomeric phenylphenalenones: 2-hydroxy-8-(4-hydroxyphenyl)-1*H*-phenalen-1-one (**1**),¹ hydroxyanigorufone,^{3,4} and irenolone.²

occurring in the plant kingdom.^{1–8} 4-Phenylphenalenones seem to be exclusive to Musaceae,^{2–4} and 9-phenylphenalenones are common in Hemodoraceae,^{5,6} Musaceae,^{2–4} and Pontederiaceae.⁸ Interestingly, 2-phenyl-1*H*-phenalen-1-one (fuliginone) has been reported for the first time as a natural product from *Macropidia fuliginosa* (Hemodoraceae).⁹

A biological evaluation of isomeric phenylphenalenones reveals a striking contrast in some activities.^{10,11} For example, Rosquete and co-workers¹⁰ reported a differential in vitro antiprotozoal activity among three isomeric 3-, 4-, and 9-(4-

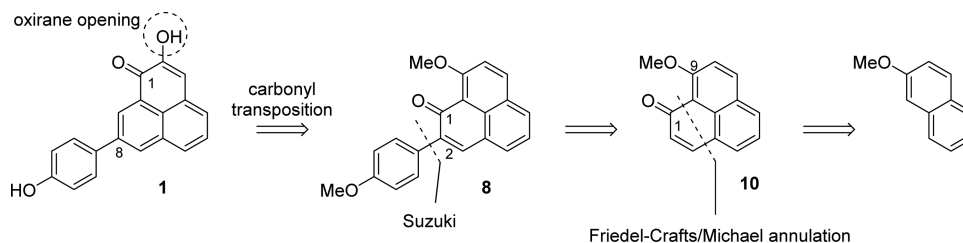
methoxyphenyl)phenalenones, with the 3-isomer being inactive against *Leishmania amazonensis* and *Trypanosoma cruzi*, the 4-isomer being active against the same protozoa, and the 9-isomer active only against *L. amazonensis*. In addition, activity in the submicrogram range was observed against *Plasmodium falciparum* for the 3-isomer with a 15-fold difference with respect to its 9-phenylphenalenone counterpart.¹¹ These findings indicate the importance of the spatial positioning of the 4-methoxyphenyl group in relation to the carbonyl group, as noticed by Gutiérrez and co-workers.¹¹

While the synthesis of several 4- and 9-phenylphenalenones is well-established¹² and the bioactivity of natural and synthetic compounds of these types has been studied somewhat,^{10,11,13} nothing is known about the biological activity or ecological role of 8-phenylphenalenones and their structure–activity relationship (SAR). Accordingly, the development of synthetic routes to 8-phenylphenalenones seems desirable for conducting systematic studies among phenylphenalenones.

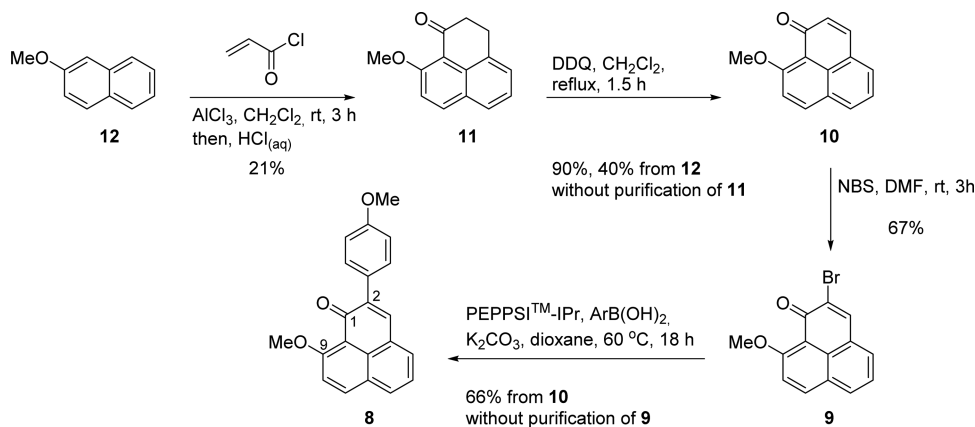
Ideal synthetic strategies toward **1** would exploit a late functionalization of the commercially accessible perinaphthenone at position C-8. Unfortunately, perinaphthenone seems to be prone only to electrophilic substitution at position C-2 or to the addition of strong nucleophiles at C-9.^{14,12} However, position C-2 in perinaphthenone can be viewed as a latent C-8 position if somehow the carbonyl group can be transposed to position C-9. Thus, a 1,2 reduction of 2-(4-methoxyphenyl)-9-methoxyperinaphthenone (**8**) should in principle provide 8-(4-methoxyphenyl)phenalenone (**4**) after an acidic workup (Scheme 1). Such a process closely resembles the 1,2 addition

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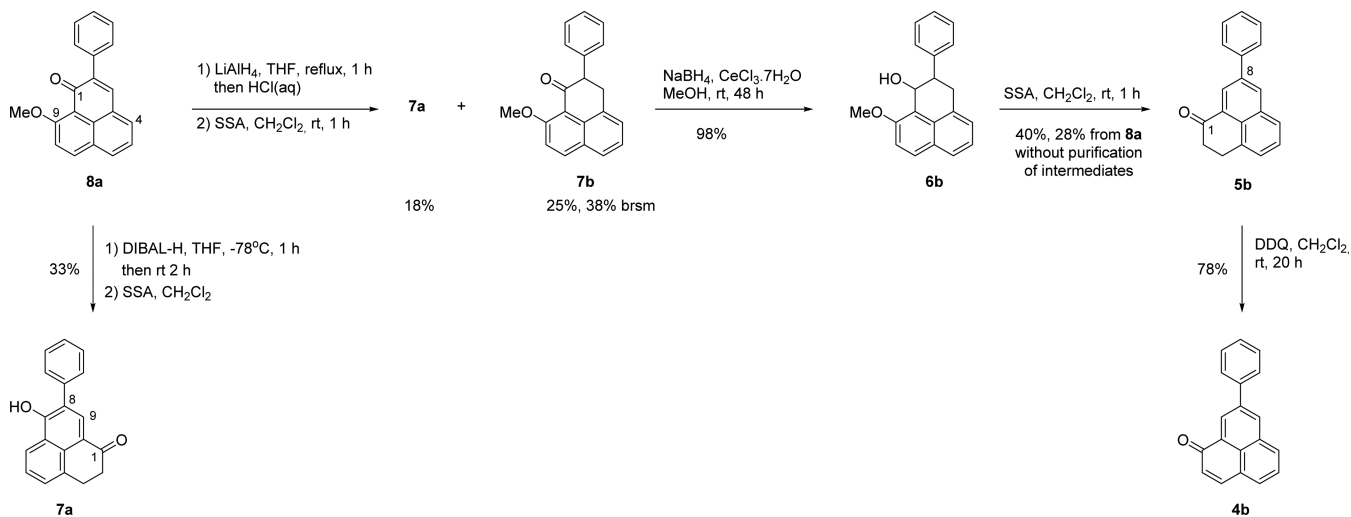
Scheme 1. Retrosynthetic Analysis for 2-Hydroxy-8-(4-hydroxyphenyl)-1H-phenalen-1-one (1)



Scheme 2. Synthesis of Key Substrate 8



Scheme 3. Model Studies toward Carbonyl Transposition



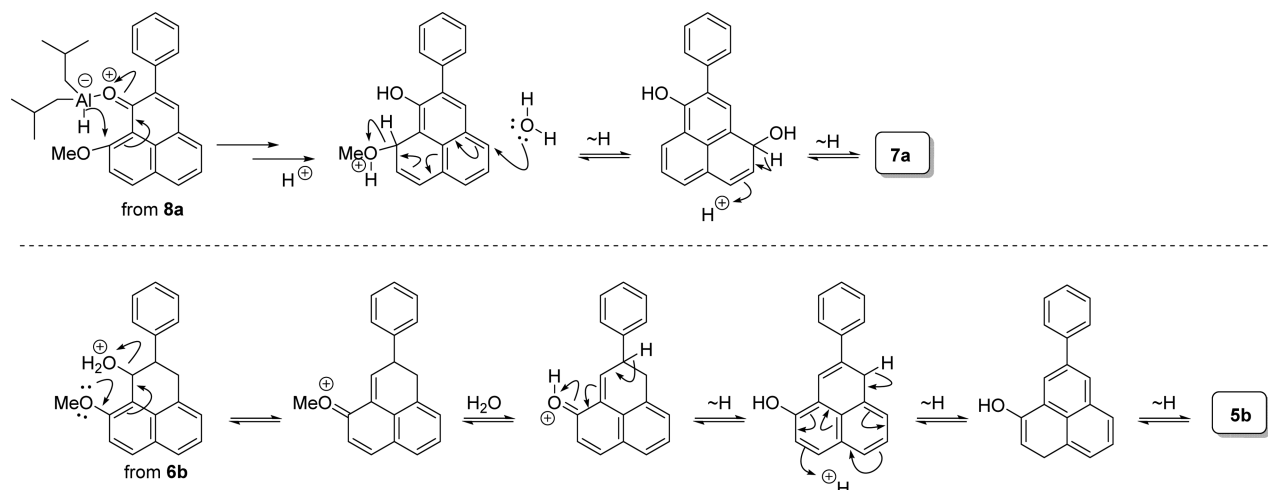
of nucleophiles to enol ethers of cyclohexane-1,3-diones that was first reported by Frank and Hall¹⁵ and applied recently in a similar context.¹⁶ Disconnection of the aryl moiety in **4** via Suzuki–Miyaura coupling points to the use of 9-methoxyperinaphthenone (**10**) as the initial substrate.

Compound **10** was prepared by a reportedly difficult methylation of 9-hydroxyperinaphthenone,¹⁷ which can be obtained by condensation between 2-methoxynaphthalene and cinnamoyl chloride followed by aromatization through elimination of benzene.^{12,18} In our case, it was postulated that a cascade process mediated by Lewis acid and involving 2-methoxynaphthalene and acryloyl chloride could provide **10** in a straightforward way (Scheme 1).

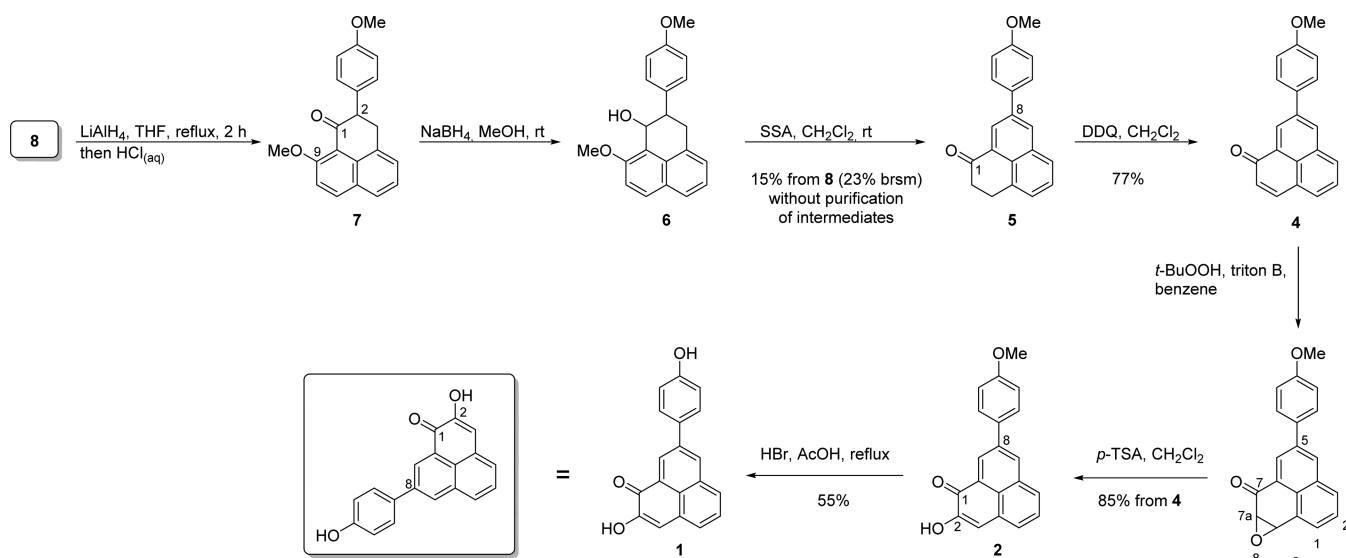
Treatment of 2-methoxynaphthalene with acryloyl chloride in the presence of AlCl_3 in dichloromethane afforded 9-

methoxy-2,3-dihydro-1H-phenalen-1-one (**11**) after an acidic workup. This reaction probably proceeds via sequential Friedel–Crafts/Michael addition in that order.¹⁸ Direct treatment of **11** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) effected dehydrogenation to afford 9-methoxyperinaphthenone (**10**) in a 40% combined yield after column chromatography (Scheme 2). Bromination of **10** with *N*-bromosuccinimide (NBS) afforded 2-bromo-9-methoxy-1H-phenalen-1-one (**9**) with suitable purity for synthetic purposes. Attempts to transpose the carbonyl group in **9** by means of NaBH_4 according to Nishida and co-workers¹⁶ afforded 9-methoxyperinaphthenone (**10**) as the major product. Interestingly, those conditions are reported to effectively transform 2-bromo-5,8-di-*tert*-butyl-4,9-dimethoxy-1H-phenalen-1-one into 8-bromo-2,5-di-*tert*-butyl-6-methoxy-1H-phenalen-1-one.¹⁶

Scheme 4. Mechanistic Rationales for the 8a → 7a and 6b → 5b Conversions



Scheme 5. Completion of the Synthesis of 1



Therefore, installation of the aryl moiety prior to a reductive carbonyl transposition seemed to be adequate. In this regard, reaction of **9** and 4-methoxyphenylboronic acid mediated by [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride (PEPPSI-IPr) using a standard protocol afforded 9-methoxy-2-(4-methoxyphenyl)-1H-phenalen-1-one (**8**) in a gratifying yield of 66% from **10** after column chromatography.

Model studies with 9-methoxy-2-phenyl-1H-phenalen-1-one (**8a**) (prepared in a manner similar to that of **8**) demonstrated the recalcitrant properties of this compound toward reduction. In fact, treatment of **8a** with NaBH₄ according to Nishida and co-workers¹⁶ did not provide any detectable product of reduction or carbonyl transposition. The addition of cerium(III) chloride did not improve the situation. Moreover, treating **8a** with diisobutylaluminum hydride (DIBAL-H) at room temperature generated an unidentified compound that rapidly reverted to the starting material in the open air. Treating the DIBAL-H product with silica sulfuric acid (SSA) in wet CH₂Cl₂ (Scheme 3) allowed for the isolation of 7-hydroxy-8-phenyl-2,3-dihydro-1H-phenalen-1-one (**7a**) (33% yield), suggesting that the DIBAL-H reduction introduced the hydride into

position C-9 in **8a** followed by SSA-mediated conjugate substitution of the methoxyl by water at position C-4. Scheme 4 provides a mechanistic rationale for this process. Refluxing **8a** with excess LiAlH₄ in THF allowed 9-methoxy-2-phenyl-2,3-dihydro-1H-phenalen-1-one (**7b**) in 25% yield [38% based on recovered starting material (brsm)] to be isolated from a reaction mixture that also contained the same product that was obtained in the DIBAL-H reduction (Scheme 3). Although **7b** was not the expected product, molecular modeling of this compound revealed a dihedral angle of 28.27° defined by the O, C-1, C-9a, and C-9 atoms.¹⁹ This result shows that the carbonyl group in **7b** is not part of a conjugated system and therefore should be accessible to reduction. Fortunately, this proved to be the case, and reduction of **7b** with NaBH₄ afforded 9-methoxy-2-phenyl-2,3-dihydro-1H-phenalen-1-ol (**6b**) (98%); upon treatment with SSA, that was transformed to 8-phenyl-2,3-dihydro-1H-phenalen-1-one (**5b**) (40%, 28% from **8a** without purification of intermediates) presumably through tautomerization from 8-phenyl-7,8-dihydro-1H-phenalen-1-ol (Scheme 4). Dehydrogenating **5b** with DDQ afforded 8-phenylphenalenone (**4b**) in 78%.

With the route established for **4b**, we decided to conduct the final steps toward the natural product **1** (Scheme 5). Thus, the sequential reduction of **8** with LiAlH_4 and NaBH_4 followed by SSA treatment (Scheme 5) afforded 8-(4-methoxyphenyl)-2,3-dihydro-1H-phenalen-1-one (**5**) (15%, 23% brsm) together with 2-(4-methoxyphenyl)-1H-phenalen-1-one (12%) after preparative TLC. The formation of the latter compound, presumably the product of a conjugate hydride addition at position C-9, was detected after the addition of NaBH_4 and could not be suppressed by the addition of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$. Moreover, this unexpected process was not detected during the model study of the synthesis of **4b**. Treating **5** with DDQ effected dehydrogenation to produce 8-(4-methoxyphenyl)-1H-phenalen-1-one (**4**, 77%). The installation of the hydroxyl group in **4** was achieved through the epoxidation of the enone followed by an acid-catalyzed oxirane opening to produce 2-hydroxy-8-(4-methoxyphenyl)-1H-phenalen-1-one (**2**) in 85% combined yield. Demethylating **2** with HBr (55%, 90% brsm) afforded compound **1**, which was identical in all respects with the natural product.

In summary, we have developed an 11-step synthesis of 2-hydroxy-8-(4-hydroxyphenyl)-1H-phenalen-1-one (**1**) starting from 2-methoxynaphthalene in a 2% global yield using a reductive carbonyl transposition as a key step. The use of a Friedel–Crafts/Michael annulation reaction for the construction of 9-methoxyperinaphthanone is also noteworthy.

EXPERIMENTAL SECTION

General Experimental Procedures. All reactions were monitored by thin-layer chromatography (TLC) conducted on 0.25 mm Merck silica gel plates (60-F₂₅₄) using UV light (254 nm) as a visualizing agent and a 98% sulfuric acid/methanol (9:1) solution and heat as developing agents. NMR spectroscopic analyses were performed on a 500 MHz NMR spectrometer operating at 500.13 MHz (¹H) and 125.75 MHz (¹³C). Chemical shifts are reported relative to residual solvent signals. Signals were assigned with the aid of HMQC, HMBC, and ¹H–¹H COSY spectra. HRESIMS was conducted in positive ion mode on an UPLC–MS/MS system consisting of an Ultimate 3000 series RSLC (Dionex, Idstein, Germany) system and an Orbitrap mass spectrometer. Yields refer to weighed chromatographically homogeneous samples.

Synthetic Procedures. **9-Methoxyperinaphthanone (10).** A solution of 2-methoxynaphthalene (1.5 g, 9.5 mmol) in CH_2Cl_2 (25 mL, rotovaporated from MgSO_4) was cooled to -10°C (salt/ice bath). AlCl_3 (1.9 g, 14.5 mmol) was then added and the mixture agitated for 15 min (solution turns green). To this mixture was slowly added acryloyl chloride (850 μL , 9.9 mmol) (1 min addition, solution turns red), and the reaction mixture was allowed to warm to room temperature (25°C in 30 min) with further stirring (3 h). Reaction progress was checked by TLC [CH_2Cl_2 , R_f (**11**) = 0.6]. The reaction was quenched with a 18% $\text{HCl}_{(\text{aq})}$ solution (20 mL, slow addition, gas evolution!) and the mixture partitioned between CH_2Cl_2 (3 \times 200 mL) and H_2O (200 mL). The organic phase was evaporated, dissolved in CH_2Cl_2 (50 mL), and refluxed with DDQ (2.2 g, 9.5 mmol) for 1.5 h. Reaction progress was checked by TLC [CH_2Cl_2 , R_f (**10**) = 0.3]. After cooling, the reaction mixture was adsorbed in silica gel, and compound **10** was purified by isocratic column chromatography (CH_2Cl_2) prior to stabilization of the stationary phase with petroleum ether (bp $55\text{--}68^\circ\text{C}$): 800 mg (40% yield); yellow solid; mp $79\text{--}81^\circ\text{C}$ (uncorrected); ¹H NMR ($\text{C}_2\text{D}_6\text{CO}$) δ 4.16 (3H, s, -OMe), 6.58 (1H, d, J = 9.9 Hz, H-2), 7.58 (1H, d, J = 9.2 Hz, H-8), 7.71 (1H, dd, J = 8.1 and 7.3 Hz, H-5), 8.23 (1H, d, J = 9.9 Hz, H-3), 8.24 (1H, d, J = 9.2 Hz, H-7), 8.28 (1H, dd, J = 8.1 and 1.3 Hz, H-4), 8.53 (1H, dd, J = 7.3 and 1.3 Hz, H-6); ¹³C NMR ($\text{C}_2\text{D}_6\text{CO}$) δ 58.0 (-OMe), 114.7 (C-9a), 115.8 (C-8), 126.7 (C-5), 128.8 (C-2), 129.8 (C-6a), 130.5 (C-9b), 131.0 (C-3a), 132.3 (C-6), 136.5 (C-4), 136.6 (C-7), 136.9 (C-3),

160.9 (C-9), 185.7 (C-1); HRMS (ESI) [$\text{M} + \text{H}$]⁺ calcd for $\text{C}_{14}\text{H}_{11}\text{O}_2$ m/z 211.0754, found m/z 211.0752.

For identification purposes, compound **11** was isolated by column chromatography (CH_2Cl_2) using the same procedure as described above without treatment with DDQ.

9-Methoxy-2,3-dihydro-1H-phenalen-1-one (11). 424 mg (21% yield, rapidly decomposes); brown oil; ¹H NMR (CDCl_3) δ 2.91 (2H, t, J = 7.4 Hz, H-2), 3.37 (2H, t, J = 7.4 Hz, H-3), 3.98 (3H, s, -OMe), 7.31 (1H, d, J = 9.0 Hz, H-8), 7.41 (1H, dd, J = 8.0 and 7.1 Hz, H-5), 7.80 (1H, d, J = 9.0 Hz, H-7), 7.99 (1H, d, J = 8.0 Hz, H-4), 8.15 (1H, d, J = 7.1 Hz, H-6); ¹³C NMR (CDCl_3) δ 21.5 (C-3), 37.6 (C-2), 56.1 (-OMe), 113.2 (C-8), 117.6 (C-9a), 123.1 (C-4), 125.6 (C-5), 127.6 (C-6), 128.6 (C-9b), 129.0 (C-6a), 132.9 (C-3a), 134.0 (C-7), 154.5 (C-9), 198.9 (C-1); HRMS (ESI) [$\text{M} + \text{H}$]⁺ calcd for $\text{C}_{14}\text{H}_{13}\text{O}_2$ m/z 213.0910, found m/z 213.0916.

2-Bromo-9-methoxy-1H-phenalen-1-one (9). In a round-bottom flask, covered with aluminum foil, were mixed compound **10** (252 mg, 1.2 mmol), NBS (281 mg, 1.6 mmol), and N,N -dimethylformamide (DMF, 4 mL) in that order. The mixture was stirred at room temperature for 3 h, and the crude material was partitioned between CH_2Cl_2 (2 \times 100 mL) and H_2O (200 mL). The organic phase was dried to afford crude 2-bromo-9-methoxy-1H-phenalen-1-one (**9**) at a suitable purity [R_f (**9**) = 0.4 (CH_2Cl_2)] for the next step. Compound **9** was further purified by column chromatography (petroleum ether/ CH_2Cl_2) using a gradient elution scheme (10:1 to 9:2 to 8:3 to 7:4 to 6:5) accounting for a total of 10 fractions (100 mL each): 233 mg (67% yield); yellow solid; mp $210\text{--}212^\circ\text{C}$ (uncorrected); ¹H NMR ($\text{C}_2\text{D}_6\text{CO}$) δ 4.21 (3H, s, -OMe), 7.63 (1H, d, J = 9.2 Hz, H-8), 7.77 (1H, dd, J = 7.9 and 7.5 Hz, H-5), 8.33 (1H, d, J = 9.2 Hz, H-7), 8.37 (1H, dd, J = 7.9 and 1.3 Hz, H-6), 8.64 (1H, dd, J = 7.5 and 1.3 Hz, H-4), 8.67 (1H, s, H-3); ¹³C NMR ($\text{C}_2\text{D}_6\text{CO}$) δ 58.3 (-OMe), 114.8 (C-9a), 116.0 (C-8), 125.2 (C-3a), 127.2 (C-5), 129.6 (C-6a), 129.7 (C-9b), 130.0 (C-2), 134.2 (C-4), 137.6 (C-6), 138.0 (C-7), 138.4 (C-3), 161.3 (C-9), 179.0 (C-1); HRMS (ESI) [$\text{M} + \text{H}$]⁺ calcd for $\text{C}_{14}\text{H}_{10}\text{BrO}_2$ m/z 288.9859, found m/z 288.9841.

9-Methoxy-2-(4-methoxyphenyl)-1H-phenalen-1-one (8). Compound **9** (all crude material from previous step), K_2CO_3 (561 mg, 4.0 mmol), [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride (PEPPSI-IPr, 17 mg, 0.025 mmol), (4-methoxyphenyl)boronic acid (216 mg, 1.4 mmol), and dioxane (4 mL) were mixed in that order in a 25 mL round-bottom flask. The mixture was stirred under argon at 60°C for 18 h. Partitioning the mixture between CH_2Cl_2 (2 \times 100 mL) and H_2O (200 mL) followed by drying of the organic phase afforded 9-methoxy-2-(4-methoxyphenyl)-1H-phenalen-1-one [**8**; R_f = 0.4 (CH_2Cl_2)] after column chromatography (2:1 petroleum ether/ CH_2Cl_2): 250 mg (66% yield from **10**); orange solid; mp $134\text{--}136^\circ\text{C}$ (uncorrected); ¹H NMR ($\text{C}_2\text{D}_6\text{CO}$) δ 3.86 (3H, s, 4'-OMe), 4.19 (3H, s, 9-OMe), 7.01 (2H, ~d, J = 9.0 Hz, H-3'-5'), 7.62 (1H, d, J = 9.2 Hz, H-8), 7.69 (2H, ~d, J = 9.0 Hz, H-2'-6'), 7.75 (1H, dd, J = 7.9 and 7.5 Hz, H-5), 8.24 (1H, d, J = 9.2 Hz, H-7), 8.31 (1H, dd, J = 7.9 and 1.3 Hz, H-6), 8.31 (1H, s, H-3), 8.63 (1H, dd, J = 7.5 and 1.3 Hz, H-4); ¹³C NMR ($\text{C}_2\text{D}_6\text{CO}$) δ 56.5 (9-OMe), 58.1 (4'-OMe), 115.1 (C-3'-5'), 115.9 (C-8), 126.8 (C-5), 132.1 (C-2'-6'), 133.1 (C-4), 133.4 (C-6), 136.2 (C-7), 136.5 (C-3), 161.0 (C-9), 161.4 (C-4'), 184.5 (C-1); HRMS (ESI) [$\text{M} + \text{H}$]⁺ calcd for $\text{C}_{21}\text{H}_{17}\text{O}_3$ m/z 317.1172, found m/z 317.1169.

8-(4-Methoxyphenyl)-2,3-dihydro-1H-phenalen-1-one (5). To a suspension of LiAlH_4 (101.4 mg, 2.7 mmol) in dry THF (9 mL) was added compound **8** (262 mg, 0.8 mmol), and the mixture was refluxed for 2 h. After cooling, the crude reaction was quenched with ethyl acetate (AcOEt , dropwise until gas evolution ceased) and then the mixture partitioned between AcOEt (2 \times 100 mL) and 5% $\text{HCl}_{(\text{aq})}$ (150 mL). The organic phase was dried and reconstituted with MeOH (5 mL). To this solution was added NaBH_4 (263 mg, 7 mmol), and the mixture was stirred for 45 min at room temperature. The mixture was dried and partitioned between CH_2Cl_2 (3 \times 100 mL) and H_2O (200 mL), and the organic phase was concentrated. The mixture was treated with silica sulfuric acid²⁰ (SSA, 1.0 g) in CH_2Cl_2 (15 mL) for 24 h and adsorbed on silica gel for subsequent column

chromatography [2:1 petroleum ether/ CH_2Cl_2 ; R_f (5, CH_2Cl_2) = 0.6]: 35 mg (15% yield from 8); brown oil; ^1H NMR ($\text{C}_2\text{D}_6\text{CO}$) δ 2.96 (2H, t, J = 7.2 Hz, H-2), 3.47 (2H, t, J = 7.2 Hz, H-3), 3.88 (3H, s, -OMe), 7.11 (2H, \sim d, J = 9.0 Hz, H-3'-5'), 7.51 (1H, \sim dd, J = 7.0 and 1.3 Hz, H-4), 7.56 (1H, dd, J = 8.1 and 7.0 Hz, H-5), 7.80 (2H, \sim d, J = 9.0 Hz, H-2'-6'), 7.95 (1H, \sim dd, J = 8.1 and 1.3 Hz, H-6), 8.36 (1H, d, J = 2.0 Hz, H-9), 8.43 (1H, d, J = 2.0 Hz, H-7); ^{13}C NMR ($\text{C}_2\text{D}_6\text{CO}$) δ 29.9 (C-3), 40.1 (C-2), 56.7 (-OMe), 116.4 (C-3'-5'), 124.9 (C-9), 127.1 (C-4), 128.2 (C-6), 128.7 (C-5), 130.1 (C-2'-6'), 132.1 (C-7), 132.2 (C-6a), 132.2 (C-9b), 134.0 (C-1'), 135.5 (C-3a), 136.1 (C-9a), 139.6 (C-8), 161.8 (C-4'), 199.0 (C-1); HRMS (ESI) $[M + H]^+$ calcd for $\text{C}_{20}\text{H}_{17}\text{O}_2$ m/z 289.1223, found m/z 289.1224.

For identification purposes, compounds 6 and 7 were isolated by preparative TLC (CH_2Cl_2) using the same procedure without treatment with NaBH_4 and SSA or SSA (R_f values of 0.6 and 0.4, respectively).

9-Methoxy-2-(4-methoxyphenyl)-2,3-dihydro-1H-phenalen-1-one (7). ^1H NMR ($\text{C}_2\text{D}_6\text{CO}$) δ 3.63 (2H, m, H-3), 3.74 (3H, s, 4'-OMe), 4.03 (3H, s, 9-OMe), 4.13 (1H, dd, J = 8.8 and 6.6 Hz, H-2), 6.83 (2H, \sim d, J = 8.8 Hz, H-3'-5'), 7.19 (2H, \sim d, J = 8.8 Hz, H-2'-6'), 7.47 (1H, dd, J = 8.1 and 7.2 Hz, H-5), 7.54 (1H, d, J = 9.2 Hz, H-8), 7.96 (1H, d, J = 9.2 Hz, H-7), 8.06 (1H, dd, J = 7.2 and 1.3 Hz, H-4), 8.12 (1H, dd, J = 8.1 and 1.3 Hz, H-6); ^{13}C NMR ($\text{C}_2\text{D}_6\text{CO}$) δ 30.5 (C-3), 53.3 (C-2), 56.4 (4'-OMe), 57.6 (9-OMe), 115.5 (C-3'-5'), 115.6 (C-8), 118.7 (C-9a), 125.0 (C-5), 127.7 (C-4), 129.7 (C-7), 130.6 (C-6a), 130.9 (C-3a), 131.1 (C-2'-6'), 133.2 (C-1'), 134.3 (C-9b), 135.6 (C-6), 156.7 (C-9), 160.6 (C-4'), 199.1 (C-1); HRMS (ESI) $[M + H]^+$ calcd for $\text{C}_{21}\text{H}_{19}\text{O}_3$ m/z 319.1329, found m/z 319.1326.

(1S*,2S*)-9-Methoxy-2-(4-methoxyphenyl)-2,3-dihydro-1H-phenalen-1-ol (6). ^1H NMR ($\text{C}_2\text{D}_6\text{CO}$) δ 3.06 (1H, m, H-2), 3.06 and 3.42 (2H, m, H-3), 3.78 (3H, s, 4'-OMe), 3.94 (3H, s, C-9-OMe), 4.20 (1H, d, J = 6.2 Hz, -OH), 5.10 (1H, dd, J = 10.8 and 6.2 Hz, H-1), 6.88 (2H, \sim d, J = 8.8 Hz, H-3'-5'), 7.29 (2H, \sim d, J = 8.8 Hz, H-2'-6'), 7.34 (1H, dd, J = 8.2 and 7.2 Hz, H-5), 7.39 (1H, d, J = 9.0 Hz, H-8), 7.70 (1H, d, J = 7.2 Hz, H-4), 7.73 (1H, d, J = 8.2 Hz, H-6), 7.80 (1H, d, J = 9.0 Hz, H-7); ^{13}C NMR ($\text{C}_2\text{D}_6\text{CO}$) δ 31.6 (C-3), 48.7 (C-2), 56.4 (4'-OMe), 57.4 (9-OMe), 74.5 (C-1), 114.6 (C-8), 115.5 (C-3'-5'), 121.3 (C-9a), 124.5 (C-4), 125.5 (C-5), 128.4 (C-6), 128.8 (C-7), 130.5 (C-6a), 130.9 (C-2'-6'), 131.8 (C-9b), 137.5 (C-1'), 140.3 (C-3a), 154.8 (C-9), 160.3 (C-4'); HRMS (ESI) $[M + \text{Na}]^+$ calcd for $\text{C}_{21}\text{H}_{20}\text{NaO}_3$ m/z 343.1305, found m/z 343.1307.

2-(4-Methoxyphenyl)-1H-phenalen-1-one was also found at the end of this sequence in a yield of 12% from 8 [R_f = 0.4 (CH_2Cl_2): mp: 136–137 °C (uncorrected); ^1H NMR ($\text{C}_2\text{D}_6\text{CO}$) δ 3.86 (3H, s, -OMe), 7.02 (2H, \sim d, J = 8.8 Hz, H-3'-5'), 7.70 (2H, \sim d, J = 8.8 Hz, H-2'-6'), 7.72 (1H, dd, J = 8.1 and 7.0 Hz, H-5), 7.90 (1H, dd, J = 8.2 and 7.2 Hz, H-8), 8.01 (1H, d, J = 7.0 Hz, H-4), 8.03 (1H, s, H-3), 8.18 (1H, d, J = 8.1 Hz, H-6), 8.40 (1H, dd, J = 8.1 and 1.3 Hz, H-7), 8.62 (1H, dd, J = 7.3 and 1.3 Hz, H-9); ^{13}C NMR ($\text{C}_2\text{D}_6\text{CO}$) δ 56.6 (-OMe), 115.2 (C-3'-5'), 128.7 (C-9b), 129.0 (C-5), 129.2 (C-8), 130.1 (C-9a), 130.9 (C-1'), 131.7 (C-3a), 132.0 (C-9), 132.2 (C-2'-6'), 133.0 (C-6), 133.4 (C-4), 134.1 (C-6a), 136.6 (C-7), 140.1 (C-2), 140.2 (C-3), 161.6 (C-4'), 185.2 (C-1); HRMS (ESI) $[M + H]^+$ calcd for $\text{C}_{20}\text{H}_{15}\text{O}_2$ m/z 287.1067, found m/z 287.1068.

8-(4-Methoxyphenyl)-1H-phenalen-1-one (4). To a solution of compound 5 (35 mg, 0.1 mmol) in CH_2Cl_2 (10 mL) was added DDQ (62 mg, 0.3 mmol). The mixture was refluxed for 10 h. The adsorption of the mixture in a silica gel was followed by column chromatography [2:1 petroleum ether/ CH_2Cl_2 ; R_f (4, CH_2Cl_2) = 0.4]: 22 mg (77% yield); orange solid; mp 102–104 °C (uncorrected); ^1H NMR ($\text{C}_2\text{D}_6\text{CO}$) δ 3.87 (3H, s, -OMe), 6.65 (1H, d, J = 9.9 Hz, H-2), 7.11 (2H, \sim d, J = 8.8 Hz, H-3'-5'), 7.69 (1H, dd, J = 7.0 and 8.3 Hz, H-5), 7.82 (2H, \sim d, J = 8.8 Hz, H-2'-6'), 7.90 (1H, d, J = 7.0 Hz, H-4), 7.93 (1H, d, J = 9.9 Hz, H-3), 8.21 (1H, d, J = 8.3 Hz, H-6), 8.56 (1H, d, J = 2.0 Hz, H-7), 8.72 (1H, d, J = 2.0 Hz, H-9); ^{13}C NMR ($\text{C}_2\text{D}_6\text{CO}$) δ 56.7 (-OMe), 116.4 (C-3'-5'), 128.0 (C-9b), 129.2 (C-5), 129.5 (C-3a), 129.8 (C-9), 130.3 (C-2'-6'), 130.6 (C-2), 131.6 (C-9a), 133.1 (C-4), 133.3 (C-7), 133.6 (C-1'), 133.9 (C-6), 134.9 (C-6a), 141.2

(C-8), 143.6 (C-3), 161.9 (C-4'), 186.4 (C-1); HRMS (ESI) $[M + H]^+$ calcd for $\text{C}_{20}\text{H}_{15}\text{O}_2$ m/z 287.1067, found m/z 287.1068.

2-Hydroxy-8-(4-methoxyphenyl)-1H-phenalen-1-one (2). A solution of compound 4 (50 mg, 0.2 mmol) in benzene (4 mL) was treated with triton B (24 μL , 40% in MeOH) and *t*-BuOOH (24 μL , 70% in H_2O) and stirred at 0 °C for 0.5 h. The ice bath was removed and stirred continually for an additional 1 h followed by another addition of triton B (24 μL , 40% in MeOH) and *t*-BuOOH (24 μL , 70% in H_2O). Agitation for an additional 1 h, followed by CH_2Cl_2 (2 \times 100 mL)/ H_2O (200 mL) partitioning, afforded 50 mg of crude material after rotary evaporation of the organic phase. The crude material was dissolved in CH_2Cl_2 (4 mL) and treated with the soluble fraction of *p*-toluenesulfonic acid (*p*-TSA, 10 mg) in diethyl ether (2 mL) for 2 h. The addition of another portion of *p*-TSA (10 mg) was followed by stirring for an additional 13 h. Partitioning the crude extract between CH_2Cl_2 (2 \times 100 mL) and H_2O (200 mL), followed by rotary evaporation of the organic phase, afforded 2-hydroxy-8-(4-methoxyphenyl)-1H-phenalen-1-one (2) in suitable purity for the next step: R_f (2, CH_2Cl_2) = 0.4; 51 mg (85% yield); red solid; mp 222–224 °C (uncorrected); ^1H NMR (CDCl_3) δ 3.90 (3H, s, -OMe), 7.07 (2H, \sim d, J = 8.6 Hz, H-3'-5'), 7.17 (1H, s, H-3), 7.60 (1H, dd, J = 8.1 and 7.0 Hz, H-5), 7.69 (1H, d, J = 7.0 Hz, H-4), 7.75 (2H, \sim d, J = 8.6 Hz, H-2'-6'), 7.97 (1H, d, J = 8.1 Hz, H-6), 8.41 (1H, s, H-7), 8.96 (1H, s, H-9); ^{13}C NMR (CDCl_3) δ 55.4 (O-Me), 113.8 (C-3), 114.6 (C-3'-5'), 123.1 (C-9b), 127.5 (C-5), 127.7 (C-3a), 128.2 (C-9a), 128.6 (C-2'-6'), 129.9 (C-6), 130.0 (C-9), 130.2 (C-4), 131.8 (C-1'), 132.5 (C-6a), 133.4 (C-7), 139.5 (C-8), 149.5 (C-2), 159.8 (C-4'), 180.6 (C-1); HRMS (ESI) $[M + H]^+$ calcd for $\text{C}_{20}\text{H}_{15}\text{O}_3$ m/z 303.1016, found m/z 303.1015.

For identification purposes, an aliquot of the crude material was taken prior to treatment with *p*-TSA.

5-(4-Methoxyphenyl)-7a,8a-dihydro-7H-phenaleno[1,2-b]oxiren-7-one (3). ^1H NMR ($\text{C}_2\text{D}_6\text{CO}$) δ 3.88 (3H, s, -OMe), 4.13 (1H, d, J = 3.9 Hz, H-8a), 4.78 (1H, d, J = 3.9 Hz, H-7a), 7.12 (2H, \sim d, J = 8.8 Hz, H-3'-5'), 7.67 (1H, dd, J = 8.4 and 7.0 Hz, H-2), 7.82 (2H, \sim d, J = 8.8 Hz, H-2'-6'), 8.02 (1H, dd, J = 7.0 and 1.1 Hz, H-1), 8.15 (1H, dd, J = 8.4 and 1.1 Hz, H-3), 8.54 (1H, d, J = 2.0 Hz, H-4), 8.55 (1H, d, J = 2.0 Hz, H-6); ^{13}C NMR ($\text{C}_2\text{D}_6\text{CO}$) δ 56.7 (-OMe), 58.3 (C-8a), 58.5 (C-7a), 116.4 (C-3'-5'), 128.1 (C-6), 128.5 (C-2), 129.2 (C-8c), 129.5 (C-8c), 130.1₈ (C-3a), 130.2₂ (C-2'-6'), 131.3 (C-1), 131.8 (C-3), 133.2 (C-4), 133.4 (C-1'), 135.8 (C-8b), 140.6 (C-5), 162.0 (C-4'), 193.7 (C-7); HRMS (ESI) $[M + H]^+$ calcd for $\text{C}_{20}\text{H}_{15}\text{O}_3$ m/z 303.1016, found m/z 303.1017.

2-Hydroxy-8-(4-hydroxyphenyl)-1H-phenalen-1-one (1). Compound 2 (34 mg, 0.1 mmol) was dissolved in glacial acetic acid (AcOH, 4 mL) followed by addition of HBr (47 μL , 48% in water). The mixture was refluxed for 7 h and then partitioned between CH_2Cl_2 (2 \times 100 mL) and H_2O (200 mL). The organic phase was dried and subjected to preparative TLC (CH_2Cl_2 , four runs) to give 2-hydroxy-8-(4-hydroxyphenyl)-1H-phenalen-1-one (1) along with recovered 2. Compound 1 displays an R_f of 0.1 in 3:1 petroleum ether/AcOEt.

The NMR data are in full agreement with those reported for the natural product.¹ ^1H NMR (Figure S35) and ^1H - ^1H COSY spectra (Figure S37) exhibited the spin system of a 4-substituted aryl ring (δ 7.05 and 7.78, J = 8.8 Hz), a three-spin system of H-4–H-6 (d 7.81, dd 7.67, d 8.11), a singlet of H-3 (δ 7.21), and doublets at δ 8.62 (H-7) and 8.86 (H-9) with J = 2.0 Hz. This 4J coupling (2.0 Hz) indicates that a substituent must be located at the position between these two protonated carbon atoms. A complete set of HSQC (Figure S38) and HMBC (Figure S39) correlations confirmed the structure of compound 1. Correlations of H-3 and H-9 with δ 182.0 assigned the carbonyl carbon atom to C-1. Most importantly, attachment of the 4-hydroxyphenyl substituent to the phenalene nucleus was confirmed by HMBC cross signals of the H-2'–H-6' doublet with C-8 (δ 141.5): 16 mg (55% yield); red solid; mp 160–161 °C dec; ^1H NMR ($\text{C}_2\text{D}_6\text{CO}$) δ 7.05 (2H, \sim d, J = 8.8 Hz, H-3'-5'), 7.21 (1H, s, H-3), 7.67 (1H, dd, J = 8.1 and 7.0 Hz, H-5), 7.78 (2H, \sim d, J = 8.8 Hz, H-2'-6'), 7.81 (1H, d, J = 7.0 Hz, H-4), 8.11 (1H, d, J = 8.1 Hz, H-6), 8.62 (1H, d, J = 2.0 Hz, H-7), 8.86 (1H, d, J = 2.0 Hz, H-9); ^{13}C NMR

(C₂D₆CO) δ 115.5 (C-3), 117.9 (C-3'-5'), 124.8 (C-9b), 129.5 (C-5), 130.3 (C-9a), 130.3₈ (C-9), 130.4₀ (C-2'-6'), 130.5 (C-3a), 131.3₆ (C-6), 131.4₁ (C-4), 132.4 (C-1'), 134.5 (C-7), 134.8 (C-6a), 141.5 (C-8), 152.3 (C-2), 159.8 (C-4'), 182.0 (C-1); HRMS (ESI) [M + H]⁺ calcd for C₁₉H₁₃O₃ m/z 289.0859, found m/z 289.0857.

9-Methoxy-2-phenyl-1H-phenalen-1-one (8a). 2-Bromo-9-methoxy-1H-phenalen-1-one (**10**, 150 mg, 0.5 mmol), phenylboronic acid (74 mg, 0.6 mmol), and bis(triphenylphosphine)palladium(II) dichloride (18 mg, 5 mol %) were dissolved in dioxane (7 mL) and treated with Na₂CO_{3(aq)} (0.8 mL, 2 M). The mixture was refluxed for 4 h. Partitioning between AcOEt and H₂O followed by column chromatography (1:1 petroleum ether/CH₂Cl₂) afforded 110 mg of **8a**: 110 mg (74% yield); orange solid; mp: 157–158 °C (uncorrected); R_f = 0.4 (CH₂Cl₂); ¹H NMR (C₂D₆CO) δ 4.20 (3H, s, -OMe), 7.34 (1H, tt, J = 7.5 and 1.3 Hz, H-4'), 7.45 (2H, m, -Ph), 7.63 (1H, d, J = 9.2 Hz, H-8), 7.72 (2H, m, -Ph), 7.76 (1H, dd, J = 8.0 and 7.4 Hz, H-5), 8.27 (1H, d, J = 9.2 Hz, H-7), 8.33 (1H, dd, J = 8.0 and 1.3 Hz, H-6), 8.36 (1H, s, H-3), 8.64 (1H, dd, J = 7.4 and 1.3 Hz, H-4); ¹³C NMR (C₂D₆CO) δ 58.1 (-OMe), 114.9 (C-9a), 115.9 (C-8), 126.9 (C-5), 129.4 (C-4'), 129.6 (C-9b), 129.7 (C-3'-5'), 130.0 (C-6a), 130.9 (C-2'-6'), 131.5 (C-3a), 133.1 (C-4), 134.6 (C-3), 136.6 (C-6 and C-7), 138.9 (C-2), 139.5 (C-1'), 161.3 (C-9), 184.2 (C-1); HRMS (ESI) [M + H]⁺ calcd for C₂₀H₁₅O₂ m/z 287.1067, found m/z 287.1068.

7-Hydroxy-8-phenyl-2,3-dihydro-1H-phenalen-1-one (7a). Compound **8a** (96.1 mg, 0.3 mmol) was dissolved in dry THF (5 mL) and the solution cooled to -78 °C. To this solution was added DIBAL-H (1 M in THF) (0.75 mL, 2 equiv, color change from orange to red), and the solution was stirred for 1 h. The cooling bath was removed, and the solution was left to warm for an additional 2 h. The reaction was quenched with 1 mL of AcOEt (slow addition) followed by saturated NH₄Cl (2 mL). Partitioning between AcOEt and H₂O (150 mL each) and evaporation of the organic phase afforded crude material that was picked in CH₂Cl₂ (5 mL, not dry) and treated with SSA (201 mg) for 1 h at room temperature. Preparative TLC of the reaction mixture (1:1 petroleum ether/CH₂Cl₂, five rounds) afforded 22 mg of **7a**: 27 mg (33% yield); R_f = 0.5 (CH₂Cl₂); ¹H NMR (C₂D₆CO) δ 2.87 (2H, t, J = 7.3 Hz, H-2), 3.44 (2H, t, J = 7.3 Hz, H-3), 7.41 (1H, tt, J = 7.3 and 1.3 Hz, H-4'), 7.51 (2H, m~t, J = 7.3 Hz, H-3'-5'), 7.55 (2H, ~d, J = 5.5 Hz, H-4 and H-6), 7.60 (2H, m, H-2'-6'), 8.06 (1H, s, H-9), 8.29 (1H, m~t, J = 5.5 Hz, H-5); ¹³C NMR (C₂D₆CO) δ 30.2 (C-3), 39.7 (C-2), 122.5 (C-5), 124.5 (C-8), 124.8 (C-6a), 126.5 (C-9a), 127.6 (C-4), 127.8 (C-6), 129.5 (C-4'), 130.1 (C-9), 130.7 (C-3'-5'), 131.6 (C-2'-6'), 134.3 (C-9b), 135.4 (C-3a), 139.5 (C-1'), 156.3 (C-7), 197.6 (C-1); HRMS (ESI) [M + H]⁺ calcd for C₁₉H₁₅O₂ m/z 275.1067, found m/z 275.1065.

8-Phenyl-2,3-dihydro-1H-phenalen-1-one (5b). Part 1. LiAlH₄ (111 mg, 3 mmol) was suspended in dry THF (6 mL) and treated with compound **8a** (73.1 mg, 0.3 mmol). After the change in color (green), the suspension was refluxed for 2 h. The reaction mixture was cooled to room temperature, treated with AcOEt (1 mL, slow addition), and partitioned between AcOEt and H₂O (75 mL each). The aqueous phase was washed with AcOEt (2 × 50 mL), and the combined organic extracts were concentrated and picked with 6 mL of MeOH.

Part 2. The methanolic solution was treated with CeCl₃·7H₂O (145.2 mg, 0.4 mmol), followed by NaBH₄ (172.7 mg, 4.6 mmol, slow addition, gas evolution!), color change from orange to pale yellow). The mixture was agitated for 15 h, concentrated, and partitioned between CH₂Cl₂ and H₂O (50 mL each). The aqueous phase was further extracted with CH₂Cl₂ (2 × 50 mL) and the organic phase concentrated and picked in CH₂Cl₂ (5 mL).

Part 3. The dichloromethane solution mentioned above was treated with SSA (201 mg). Addition of SSA was repeated after 1 h (550 mg) and the mixture agitated for a further 24 h. The mixture is adsorbed in silica gel and subjected to column chromatography (1:1 petroleum ether/CH₂Cl₂) to afford 19 mg of **5b** (R_f = 0.5 in CH₂Cl₂): 19 mg (25% yield, 38% brsm); ¹H NMR (CDCl₃) δ 3.03 (2H, t, J = 7.1 Hz, H-2), 3.47 (2H, t, J = 7.1 Hz, H-3), 7.47 (5H, m), 7.77 (2H, m), 7.86 (1H, d, J = 8.1 Hz, H-6), 8.29 (1H, d, J = 1.5 Hz, H-6), 8.49 (1H, d, J

= 1.5 Hz, H-7); ¹³C NMR (CDCl₃) δ 28.5 (C-3), 38.6 (C-2), 124.5 (C-9), 125.5 (C-4), 126.5 (C-6), 126.7 (C-5), 127.4 (C-3'-5'), 127.9 (C-4'), 129.0 (C-2'-6'), 130.2 (C-6a), 130.8 (C-9b), 131.5 (C-7), 133.2 (C-1'), 133.9 (C-3a), 138.5 (C-9a), 140.0 (C-8), 198.6 (C-1); HRMS (ESI) [M + H]⁺ calcd for C₁₉H₁₅O m/z 259.1117, found m/z 259.1115.

For identification purposes, compounds **7b** and **6b** were isolated after parts 1 and 2, respectively.

9-Methoxy-2-phenyl-2,3-dihydro-1H-phenalen-1-one (7b). R_f = 0.8 (CH₂Cl₂); ¹H NMR (C₂D₆CO) δ 3.67 (2H, ddd for each proton, $J_{\text{set a}}$ = 16.5, 9.2, and 0.7 Hz, $J_{\text{set b}}$ = 16.5, 6.2, and 0.6 Hz, H-3), 4.04 (3H, s, -OMe), 4.21 (1H, dd, J = 9.2 and 6.2 Hz, H-2), 7.26 (5H, m, -Ph), 7.49 (1H, dd, J = 8.1 and 7.2 Hz, H-5), 7.56 (1H, d, J = 9.0 Hz, H-8), 7.98 (1H, d, J = 9.0 Hz, H-7), 8.08 (1H, dd, J = 7.2 and 1.3 Hz, H-4), 8.15 (1H, dd, J = 8.1 and 1.3 Hz, H-6); ¹³C NMR (C₂D₆CO) δ 30.6 (C-3_{from HMBC}), 54.2 (C-2), 57.6 (-OMe), 115.7 (C-8), 118.7 (C-9a), 125.0 (C-5), 127.7 (C-4), 128.6 (C-4'), 129.8 (C-7), 130.1 (C-3'-5'), 130.2 (C-2'-6'), 130.6 (C-6a), 134.4 (C-9b_{from HMBC}), 135.7 (C-6), 141.4 (C-1'_{from HMBC}), 156.7 (C-9_{from HMBC}), 198.9 (C-1_{from HMBC}); HRMS (ESI) [M + H]⁺ calcd for C₂₀H₁₇O₂ m/z 289.1223, found m/z 289.1226.

9-Methoxy-2-phenyl-2,3-dihydro-1H-phenalen-1-ol (6b). R_f = 0.4 (CH₂Cl₂); ¹H NMR (CDCl₃) δ 3.44 (3H, m, H-2 and H-3), 4.02 (3H, s, -OMe), 5.16 (1H, ~s, H-1), 7.44 (8H, m), 7.84 (2H, m); ¹³C NMR (CDCl₃) δ 22.9 (C-3), 44.8 (C-2), 56.4 (-OMe), 73.0 (C-1), 113.2 (C-8), 119.9 (C-9a), 123.4 (C-4), 125.9 (C-5), 126.9 (C-6), 127.1 (C-7), 128.3 (C-3'-5'), 128.6 (C-2'-6'), 129.0 (C-6a), 129.3 (C-9b), 135.6 (C-1'), 142.5 (C-3a), 153.5 (C-9).

8-Phenyl-1H-phenalen-1-one (4b). Compound **5b** (18 mg, 0.07 mmol) in CH₂Cl₂ (2 mL) was treated with DDQ (22 mg, 0.12 mmol). The DDQ addition (7 mg, 0.03 mmol) was repeated after 3 h and the mixture refluxed for 20 h. Column chromatography (1:1 petroleum ether/CH₂Cl₂, two runs) of the reaction mixture afforded 14 mg of compound **4b**: 14 mg (78% yield); R_f = 0.3 (CH₂Cl₂); yellow solid; mp 96–97 °C (uncorrected); ¹H NMR (C₂D₆CO) δ 6.66 (1H, d, J = 9.7 Hz, H-2), 7.47 (1H, tt, J = 7.3 and 1.3 Hz, H-4'), 7.57 (2H, m, -Ph), 7.72 (1H, dd, J = 8.4 and 7.0 Hz, H-5), 7.88 (2H, m, -Ph), 7.93 (1H, d, J = 7.0 Hz, H-4), 7.94 (1H, d, J = 9.7 Hz, H-3), 8.25 (1H, d, J = 8.4 Hz, H-6), 8.63 (1H, d, J = 2.0 Hz, H-7), 8.76 (1H, d, J = 2.0 Hz, H-9); ¹³C NMR (C₂D₆CO) δ 128.4 (C-9b), 129.2 (C-3'-5'), 129.3 (C-5), 129.6 (C-3a), 130.0 (C-4'), 130.1 (C-9), 130.7 (C-2), 131.0 (C-2'-6'), 131.7 (C-9a), 133.4 (C-4), 134.0 (C-6), 134.1 (C-7), 134.9 (C-6a), 141.4 (C-1'), 141.5 (C-8), 143.6 (C-3), 186.2 (C-1); HRMS (ESI) [M + H]⁺ calcd for C₁₉H₁₃O m/z 257.0961, found m/z 257.0959.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02559.

¹H and ¹³C NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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