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

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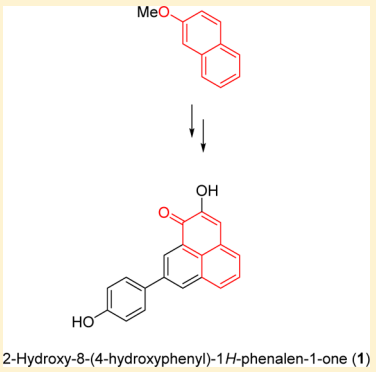
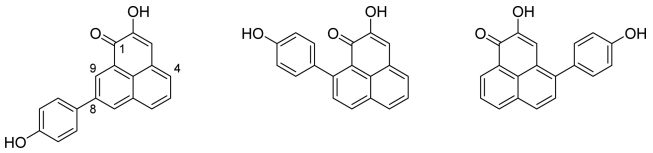
Supporting Information

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**.



2-Hydroxy-8-(4-hydroxyphenyl)-1*H*-phenalen-1-one (**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)



2-Hydroxy-8-(4-hydroxyphenyl)-1*H*-phenalen-1-one (**1**) | Hydroxyanigorufone | Irenolone

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-workers[10] 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-established[12] 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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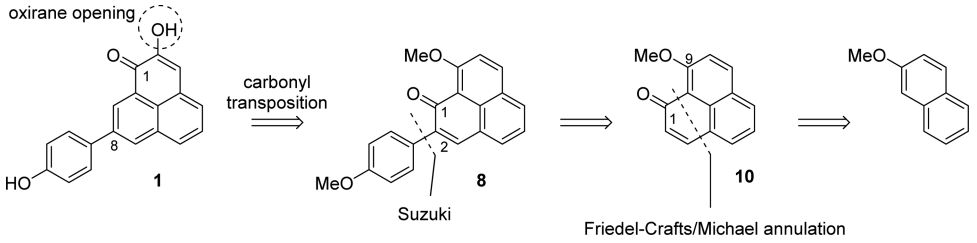
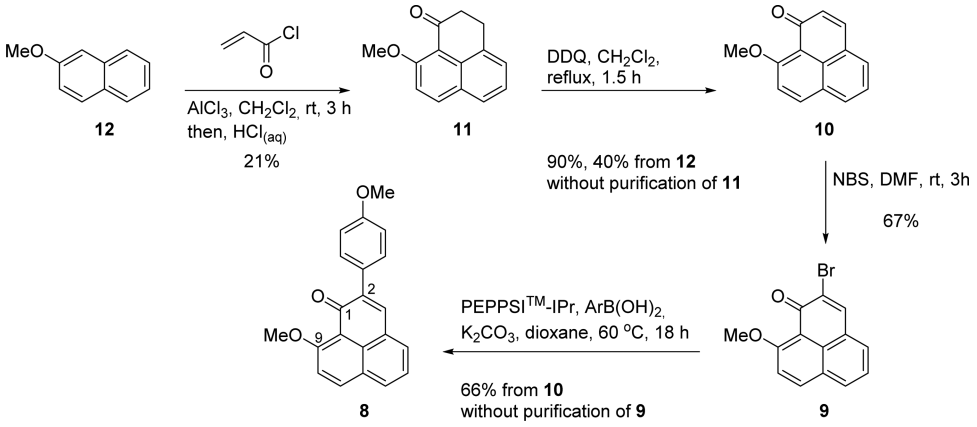
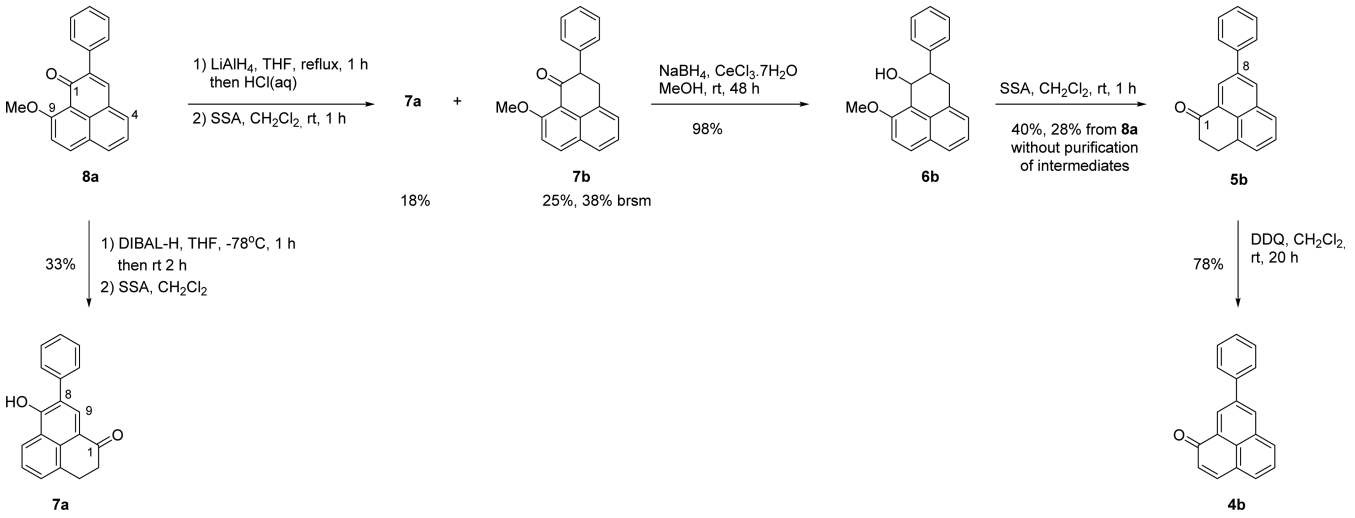
Scheme 1. Retrosynthetic Analysis for 2-Hydroxy-8-(4-hydroxyphenyl)-1*H*-phenalen-1-one (1)



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 Hall[15] 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-1*H*-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-1*H*-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-workers[16] 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-1*H*-phenalen-1-one into 8-bromo-2,5-di-*tert*-butyl-6-methoxy-1*H*-phenalen-1-one.[16]

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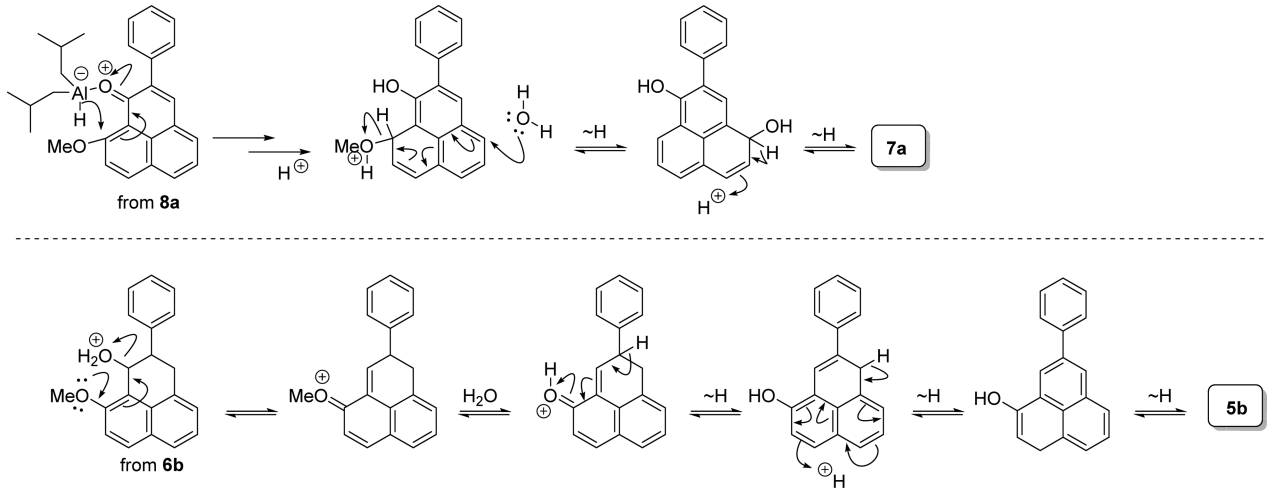
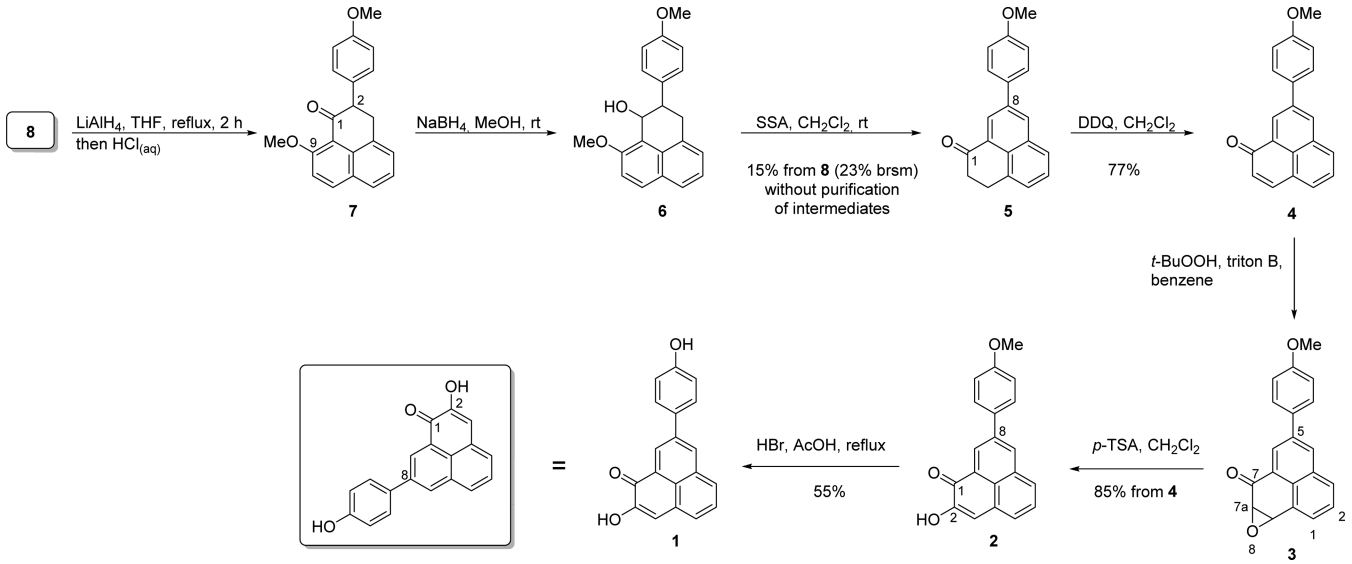
Scheme 4. Mechanistic Rationales for the 8a → 7a and 6b → 5b Conversions



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)-1*H*-phenalen-1-one (**8**) in a gratifying yield of 66% from **10** after column chromatography.

Model studies with 9-methoxy-2-phenyl-1*H*-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 $NaBH_4$ according to Nishida and co-workers[16] 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 CH_2Cl_2 (Scheme 3) allowed for the isolation of 7-hydroxy-8-phenyl-2,3-dihydro-1*H*-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 $LiAlH_4$ in THF allowed 9-methoxy-2-phenyl-2,3-dihydro-1*H*-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 $NaBH_4$ afforded 9-methoxy-2-phenyl-2,3-dihydro-1*H*-phenalen-1-ol (**6b**) (98%); upon treatment with SSA, that was transformed to 8-phenyl-2,3-dihydro-1*H*-phenalen-1-one (**5b**) (40%, 28% from **8a** without purification of intermediates) presumably through tautomerization from 8-phenyl-7,8-dihydro-1*H*-phenalen-1-ol (Scheme 4). Dehydrogenating **5b** with DDQ afforded 8-phenylphenalenone (**4b**) in 78%.

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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-1*H*-phenalen-1-one (**5**) (15%, 23% brsm) together with 2-(4-methoxyphenyl)-1*H*-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 $CeCl_3{\cdot}7H_2O$. 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)-1*H*-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)-1*H*-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)-1*H*-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-F_{254}) 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 (^{1}H) and 125.75 MHz (^{13}C). Chemical shifts are reported relative to residual solvent signals. Signals were assigned with the aid of HMQC, HMBC, and ^{1}H−^{1}H 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-Methoxyperinaphthenone (**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% $HCl_{(aq)}$ solution (20 mL, slow addition, gas evolution!) and the mixture partitioned between CH_2Cl_2 (3 × 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 55−68 °C): 800 mg (40% yield); yellow solid; mp 79−81 °C (uncorrected); ^{1}H NMR (C_2D_6CO) 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); ^{13}C NMR (C_2D_6CO) 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) $[M + H]^+$ calcd for $C_{14}H_{11}O_2$ *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; ^{1}H 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); ^{13}C 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) $[M + H]^+$ calcd for $C_{14}H_{13}O_2$ *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 × 100 mL) and H_2O (200 mL). The organic phase was dried to afford crude 2-bromo-9-methoxy-1*H*-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 210−212 °C (uncorrected); ^{1}H NMR (C_2D_6CO) 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); ^{13}C NMR (C_2D_6CO) 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) $[M + H]^+$ calcd for $C_{14}H_{10}BrO_2$ *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 × 100 mL) and H_2O (200 mL) followed by drying of the organic phase afforded 9-methoxy-2-(4-methoxyphenyl)-1*H*-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 134−136 °C (uncorrected); ^{1}H NMR (C_2D_6CO) 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); ^{13}C NMR (C_2D_6CO) 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) $[M + H]^+$ calcd for $C_{21}H_{17}O_3$ *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 × 100 mL) and 5% $HCl_{(aq)}$ (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 × 100 mL) and H_2O (200 mL), and the organic phase was concentrated. The mixture was treated with silica sulfuric acid[20] (SSA, 1.0 g) in CH_2Cl_2 (15 mL) for 24 h and adsorbed on silica gel for subsequent column

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chromatography [2:1 petroleum ether/CH_2Cl_2; R_f (**5**, CH_2Cl_2) = 0.6]: 35 mg (15% yield from **8**); brown oil; ^{1}H NMR (C_2D_6CO) 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, ~d, J = 9.0 Hz, H-3′-5′), 7.51 (1H, ~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, ~d, J = 9.0 Hz, H-2′-6′), 7.95 (1H, ~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 (C_2D_6CO) 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 $C_{20}H_{17}O_2$ 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**).* ^{1}H NMR (C_2D_6CO) 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, ~d, J = 8.8 Hz, H-3′-5′), 7.19 (2H, ~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 (C_2D_6CO) 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 $C_{21}H_{19}O_3$ m/z 319.1329, found m/z 319.1326.

(1S,2S*)-9-Methoxy-2-(4-methoxyphenyl)-2,3-dihydro-1H-phenalen-1-ol (**6**).* ^{1}H NMR (C_2D_6CO) 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, ~d, J = 8.8 Hz, H-3′-5′), 7.29 (2H, ~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 (C_2D_6CO) 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) $[M + Na]^+$ calcd for $C_{21}H_{20}NaO_3$ m/z 343.1305, found m/z 343.1307.

2-(4-Methoxyphenyl)-1*H*-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); ^{1}H NMR (C_2D_6CO) δ 3.86 (3H, s, -OMe), 7.02 (2H, ~d, J = 8.8 Hz, H-3′-5′), 7.70 (2H, ~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 (C_2D_6CO) 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 $C_{20}H_{15}O_2$ 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); ^{1}H NMR (C_2D_6CO) δ 3.87 (3H, s, -OMe), 6.65 (1H, d, J = 9.9 Hz, H-2), 7.11 (2H, ~d, J = 8.8 Hz, H-3′-5′), 7.69 (1H, dd, J = 7.0 and 8.3 Hz, H-5), 7.82 (2H, ~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 (C_2D_6CO) 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 $C_{20}H_{15}O_2$ 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 × 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 × 100 mL) and H_2O (200 mL), followed by rotary evaporation of the organic phase, afforded 2-hydroxy-8-(4-methoxyphenyl)-1*H*-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); ^{1}H NMR ($CDCl_3$) δ 3.90 (3H, s, -OMe), 7.07 (2H, ~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, ~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 $C_{20}H_{15}O_3$ 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**).* ^{1}H NMR (C_2D_6CO) 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, ~d, J = 8.8 Hz, H-3′-5′), 7.67 (1H, dd, J = 8.4 and 7.0 Hz, H-2), 7.82 (2H, ~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 (C_2D_6CO) 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), 130.1$_8$ (C-3a), 130.2$_2$ (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 $C_{20}H_{15}O_3$ 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 × 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)-1*H*-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] ^{1}H NMR (Figure S35) and ^{1}H−^{1}H 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 phenalenone 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; ^{1}H NMR (C_2D_6CO) δ 7.05 (2H, ~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, ~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

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(C_2D_6CO) δ 115.5 (C-3), 117.9 (C-3′-5′), 124.8 (C-9b), 129.5 (C-5), 130.3 (C-9a), 130.3_8 (C-9), 130.4_0 (C-2′-6′), 130.5 (C-3a), 131.3_6 (C-6), 131.4_1 (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 $C_{19}H_{13}O_3$ m/z 289.0859, found m/z 289.0857.

*9-Methoxy-2-phenyl-1H-phenalen-1-one (**8a**).* 2-Bromo-9-methoxy-1*H*-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 $Na_2CO_{3(aq)}$ (0.8 mL, 2 M). The mixture was refluxed for 4 h. Partitioning between AcOEt and H_2O followed by column chromatography (1:1 petroleum ether/CH_2Cl_2) afforded 110 mg of **8a**: 110 mg (74% yield); orange solid; mp: 157−158 °C (uncorrected); R_f = 0.4 (CH_2Cl_2); ^{1}H NMR (C_2D_6CO) 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); ^{13}C NMR (C_2D_6CO) 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 $C_{20}H_{15}O_2$ 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 NH_4Cl (2 mL). Partitioning between AcOEt and H_2O (150 mL each) and evaporation of the organic phase afforded crude material that was picked in CH_2Cl_2 (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/CH_2Cl_2, five rounds) afforded 22 mg of **7a**: 27 mg (33% yield); R_f = 0.5 (CH_2Cl_2); ^{1}H NMR (C_2D_6CO) 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); ^{13}C NMR (C_2D_6CO) 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 $C_{19}H_{15}O_2$ m/z 275.1067, found m/z 275.1065.

*8-Phenyl-2,3-dihydro-1H-phenalen-1-one (**5b**). Part 1.* $LiAlH_4$ (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 H_2O (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 $CeCl_3{\cdot}7H_2O$ (145.2 mg, 0.4 mmol), followed by $NaBH_4$ (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 CH_2Cl_2 and H_2O (50 mL each). The aqueous phase was further extracted with CH_2Cl_2 (2 × 50 mL) and the organic phase concentrated and picked in CH_2Cl_2 (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/CH_2Cl_2) to afford 19 mg of **5b** (R_f = 0.5 in CH_2Cl_2): 19 mg (25% yield, 38% brsm); ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_{19}H_{15}O$ 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 (CH_2Cl_2); ^{1}H NMR (C_2D_6CO) δ 3.67 (2H, ddd for each proton, J_{set_a} = 16.5, 9.2, and 0.7 Hz, J_{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); ^{13}C NMR (C_2D_6CO) δ 30.6 ($C\text{-}3_{from\ HMQC}$), 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 ($C\text{-}9b_{from\ HMBC}$), 135.7 (C-6), 141.4 ($C\text{-}1'_{from\ HMBC}$), 156.7 ($C\text{-}9_{from\ HMBC}$), 198.9 ($C\text{-}1_{from\ HMBC}$); HRMS (ESI) $[M + H]^+$ calcd for $C_{20}H_{17}O_2$ 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 (CH_2Cl_2); ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 CH_2Cl_2 (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/CH_2Cl_2, two runs) of the reaction mixture afforded 14 mg of compound **4b**: 14 mg (78% yield); R_f = 0.3 (CH_2Cl_2); yellow solid; mp 96−97 °C (uncorrected); ^{1}H NMR (C_2D_6CO) 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); ^{13}C NMR (C_2D_6CO) 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 $C_{19}H_{13}O$ 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.

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

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Notes

The authors declare no competing financial interest.

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