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Synthesis of 4-methoxy-1*H*-phenalen-1-one: a subunit related to natural phenalenone-type compounds

Juliana Nanclares [a], Jesús Gil [b], Benjamín Rojano [b], Jairo Saez [a], Bernd Schneider [c,*], Felipe Otálvaro [a,*]

[a] *Instituto de Química-Universidad de Antioquia, Calle 67# 53-108, A.A. 1226 Medellín, Colombia*
[b] *Universidad Nacional de Colombia sede Medellín, Autopista Norte, Calle 64 Cra 65, A.A. 1027 Medellín, Colombia*
[c] *Max-Planck Institut für Chemische Ökologie, Beutenberg Campus, Hans-Knöll-Strasse 8, 07745 Jena, Germany*

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Abstract

4-Methoxy-1*H*-phenalen-1-one (4-methoxyperinaphthenone, **1**), a subunit found in some *Musa* phytoalexins and related natural products from the Haemodoraceae, was synthesized starting from 2-methoxynaphthalene in five steps and an overall yield of 36%. A Heck–Fujiwara coupling between ethyl acrylate and 1-bromonaphthalene afforded the corresponding (*E*)-naphthylpropanoic acid which, after hydrogenolysis, was subjected to a one-pot Friedel–Crafts acylation–DDQ dehydrogenation procedure to furnish **1**.
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Keywords: Friedel–Crafts acylation; Heck coupling; Phenalenones

The search for phytoalexins in *Musa* over the past 15 years resulted in the isolation and structural identification of 9- and 4-phenylphenalenones and related compounds such as dimeric phenylphenalenones, phenylnaphthalic anhydrides, perinaphthenones, and an oxabenzochrysenone.[1] In addition, even more structures of the phenalenone-type have been found in the Haemodoraceae, Pontederiaceae, and Strelitziaceae.[2] Some of these compounds have been tested as antifungal (*Mycosphaerella fijiensis*, *Colletotrichum musae*, *Fusarium oxysporum*), and antiprotozoal agents (*Leishmania donovani*) showing moderate to good activities.[3] Whereas, the bioactivity of 9-phenylphenalenones has been studied in some detail, little information is available about the activity of analogs. This can be explained by the fact that all of these phenalenone-related compounds occur in only minute amounts in plants and efficient syntheses have been developed primarily for 9-phenylphenalenones.[4] Therefore, it is desirable to develop new synthetic routes, especially for the scarcer members of the phenalenone family in order to expand the accessibility of these phenolic compounds for biological assays.

Phenalen-1-ones (perinaphthenones) substituted at the C4 position are common subunits of some of the less abundant natural phenalenone-related compounds. 4-Methoxy-1*H*-phenalen-1-one (4-methoxyperinaphthenone, **1**) is of special interest because of the possibilities that this compound can be used as either starting material for the synthesis of oxabenzochrysenones[5] or to obtain fused dimeric phenylphenalenones by introducing a phenyl ring in the C9 position via a Grignard reaction.[4] Also, it is plausible that 4-phenylphenalenones can be synthesized via cross-coupling reactions using a suitable C4-substituted compound (Scheme 1).[5]

Here, we report the synthesis of **1** using a Heck–Fujiwara coupling and a Friedel–Crafts acylation as the C–C bond forming reactions starting from 2-methoxynaphthalene.

Perinaphthenone can be obtained in one step by condensing 2-naphthol with glycerol, sulphuric acid, and

* Corresponding authors. Tel.: +5742195653; fax: +5742330120 (F.O.); Tel.: +493641571600; fax: +493641571601 (B.S.).
E-mail addresses: schneider@ice.mpg.de (B. Schneider), pipelion@quimica.udea.edu.co (F. Otálvaro).

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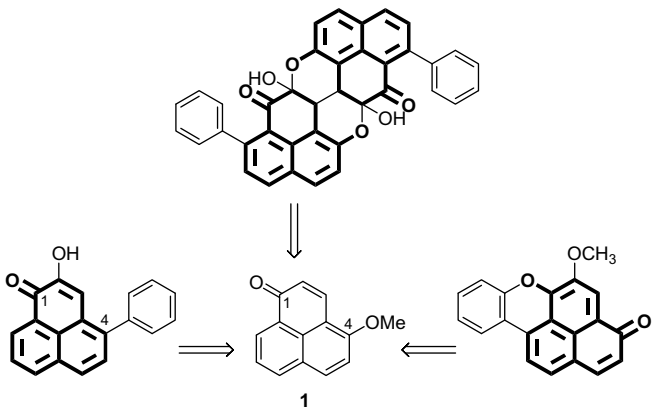
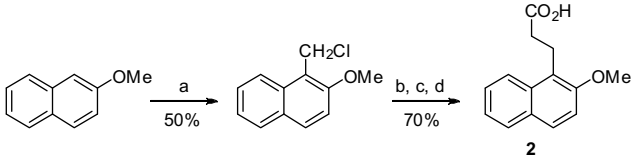


Scheme 1. 4-Methoxy-1*H*-phenalen-1-one (4-methoxyperinaphthenone, **1**) as a plausible retrosynthetic intermediate of natural phenylphenalenone-related compounds.

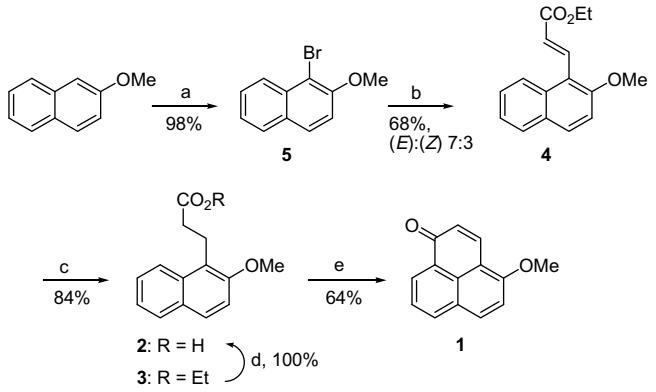
a mild oxidizing agent.[6] This procedure, applied to 2,7-dihydroxynaphthalene, gives 6-hydroxyperinaphthenone. However, in both the cases the yields are low, and complex mixtures result.[6] Applying conditions reported by Cooke et al.[6] to 1,6-dihydroxynaphthalene, a suitable substrate for obtaining 4-hydroxy-1*H*-phenalen-1-one (4-hydroxyperinaphthenone), afforded unsatisfactory results, as mixtures were formed in which the desired compound was not detected by ^{1}H NMR spectroscopy. No attempt was made to optimize this strategy.

4-Methoxy-1*H*-phenalen-1-one (4-methoxyperinaphthenone, **1**) and other perinaphthenones alike can be prepared by the cyclization of β-1-naphthylpropanoic acids obtained by the malonic ester synthesis, using 1-halogenomethyl naphthalenes as starting materials (Scheme 2).[6] This strategy has been recognized as the most versatile synthesis of phenalenes, 2,3-dihydrophenalenes, and 2,3-dihydrophenalenones.[6] However, 3-(2-methoxy-1-naphthyl)propanoic acid (**2**), the direct precursor of **1**, is formed in only moderate yield,[7] and moreover, in our hands the chloromethylation and malonate condensation steps required careful handling for reproducible yields to be achieved. Therefore, a different strategy was explored in the preparation of **2**.

Thus, following a procedure slightly modified from that in the literature,[8] the solvent-free bromination of 4-methoxynaphthalene with NBS/Al_2O_3 afforded 1-bromo-2-methoxynaphthalene (**5**) with suitable purity for synthetic purposes. Standard Heck–Fujiwara treatment[9] of **5** in the 4 mmol scale afforded acrylate **4** in 70% yield as a single (*E*)-diastereomer. Interestingly, scaling this process up just 4-fold led to a 68% yield of an inseparable mixture of (*E*)- and (*Z*)-diastereomers with a 7:3 ratio in favor of the (*E*)-diastereomer. The diminished stereoselectivity was of no consequence, as hydrogenation of the mixture with hydrogen over palladium–charcoal transformed both isomers into ethyl 3-(2-methoxy-1-naphthyl)propanoate (**3**) in an 85% yield.[10] Ester **3** was then refluxed with aqueous NaOH solution (2 M, 120 °C, 3 h) to obtain **2** in quantitative yield after acidic workup.

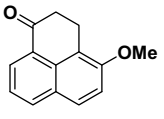


Scheme 2. Reagents and conditions: (a) *p*-formaldehyde, AcOH, $HCl_{(g)}$, 0 °C for 5 min then rt, 2 h; (b) $NaOEt_{(s)}$, THF, diethyl malonate, reflux, 2 h; (c) $NaOH_{(aq)}$ (6 M), 1 h reflux then H_2SO_4 98% until pH ~ 4; (d) 190 °C.



Scheme 3. Reagents and conditions: (a) NBS, neutral Al_2O_3, 90 °C, 1 h; (b) $Pd(OAc)_2$, P(*o*-tolyl)$_3$, DMF, ethyl acrylate, Et_3N, reflux under N_2, 6 h; (c) $H_{2(g)}$, 10% Pd/C, MeOH, 25 °C, 24 h; (d) NaOH (2 M), reflux, 3 h then HCl 10% until pH ~ 2; (e) $SOCl_2$ (4 mL), 30 °C until dryness then CH_2Cl_2 (25 mL), $AlCl_3$ (400 mg, 3 equiv) 10 min, DDQ (304 mg, 1.3 equiv) 15 min.

Typically, substrates like **2** are cyclized using Friedel–Crafts conditions which, after dehydrogenation, afford perinaphthenones in good yields.[11] Therefore, the attractive variant reported by Sarvani and Sharghi[12] was tested; **2** (0.5 mmol) was mixed with *p*-TSA·H_2O (0.09 mmol) and graphite (0.15 g) at 140 °C. By using these conditions, we obtained 10% of 4-methoxy-1*H*-phenalen-1-one (4-methoxyperinaphthenone, **1**) as the only product (48% based on recovered **2**) after careful purification by preparative TLC (*n*-hexane/diethyl ether 1:1.5). Changing the temperature from 110 to 190 °C did not improve the yield, nor did the varying *p*-TSA·H_2O in the range of 0.01–0.1 mmol. Therefore, a more conventional strategy was explored using a 'one pot' procedure (Scheme 3). Treating **2** with thionyl chloride followed by adding CH_2Cl_2 and $AlCl_3$ at 30 °C afforded a mixture of 2,3-dihydro-4-methoxy-1*H*-phenalen-1-one (4-methoxyperinaphthanone, **6**) and 4-methoxy-1*H*-phenalen-1-one (4-methoxyperinaphthenone, **1**).[13] Adding DDQ to the previous slurry completely transformed the 2,3-dihydro compound **6** to **1**, which, after purification by column chromatography, was obtained in 64% overall yield.



For identification purposes, 2,3-dihydro-4-methoxy-1*H*-phenalen-1-one (4-methoxyperinaphthanone, **6**) was obtained using the above mentioned procedure for compound **1** without adding DDQ and purified by column chromatography using CH_2Cl_2 as an eluent (54% yield).[14] The product slowly decomposed to **1** in open air atmosphere at 30 °C.

In summary, we have developed a five-step synthesis of 4-methoxy-1*H*-phenalen-1-one (4-methoxyperinaphthenone, **1**) starting from 2-methoxynaphthalene in a 36% global yield. The use of a Heck–Fujiwara coupling and the one-pot cyclization procedure significantly improved the previously reported methods. Further studies focusing on the use of **1** in the synthesis of natural phenylphenalenones or structural analogs are currently underway.

Acknowledgments

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8. Imanzadeh, G.; Zamanloo, M.; Eskandari, H.; Shayesteh, K. *J. Chem. Res.* **2006**, 151–153; *Experimental procedure*: NBS (1.8 g, 10 mmol), neutral Al_2O_3 (8.2 g, flame dried), and 2-methoxynaphthalene (954 mg, 6 mmol) were mixed in a mortar until a uniform color was perceived. The mixture was transferred to a round-bottomed flask and then heated to 90 °C for one hour. Extraction with CH_2Cl_2 followed by solvent evaporation afforded 1-bromo-2-methoxynaphthalene (**5**) (1.4 g, 98%).
9. *Experimental procedure*: A 100 mL three-necked round-bottomed flask equipped with a condenser was charged with $PdCl_2$ (161.6 mg, 0.72 mmol), tri-*o*-tolylphosphine (895 mg, 2.94 mmol), 1-bromo-2-methoxynaphthalene (3.4 g, 14.5 mmol) and DMF (50 mL). The mixture was refluxed under nitrogen for 6 h at 160 °C. DMF was removed under vacuum and the crude mixture subjected to column chromatography (*n*-hexane–diethyl ether is 9:1) to give an (*E*,*Z*)-mixture of ethyl 3-(2-methoxy-1-naphthyl)acrylate (**4**) as a brown oil. (68%, (*E*):(*Z*) ratio is 7:3); (*E*)-diastereomer: ^{1}H NMR (C_3D_6O, 500.13 MHz) δ 8.33 (d, $J = 16.2$ Hz, H-3), 8.18 (d, $J = 8.6$ Hz, H-8′), 8.00 (d, $J = 9.2$ Hz, H-4′), 7.86 (d, $J = 8.1$ Hz, H-5′), 7.59 (dd, $J = 8.6$, 8.5 Hz, H-7′), 7.51 (d, $J = 9.2$ Hz, H-3′), 7.42 (dd, $J = 8.5$, 8.1 Hz, H-6′), 6.75 (d, $J = 16.2$ Hz, H-2), 4.27 (q, $J = 7.2$ Hz, –OCH_2CH_3), 4.07 (s, –OCH_3), 1.33 (t, $J = 7.2$ Hz, –OCH_2CH_3); ^{13}C NMR (C_3D_6O, 125.75 MHz) δ 167.8 (C-1), 158.0 (C-2′), 137.8 (C-3), 133.5 (C-8a′), 132.7 (C-4′), 130.0 (C-4a′), 129.6 (C-5′), 128.4 (C-7′), 124.7 (C-6′), 124.0 (C-2), 123.6 (C-8′), 116.8 (C-1′), 114.0 (C-3′), 60.7 (–OCH_2-CH_3), 56.7 (–OCH_3), 14.7 (–OCH_2CH_3). HREIMS *m*/*z* 256.111221 (calcd for $C_{16}H_{16}O_3$, 256.109945).
10. *Experimental procedure*: A balloon filled with hydrogen was fitted to a 25 mL round-bottomed flask charged with the catalyst (1 g) and a solution of **4** (2.2 g, 14 mmol) in MeOH (10 mL). The mixture was stirred at 25 °C for 24 h, the catalyst filtered and the solvent evaporated. Ethyl 3-(2-methoxy-1-naphthyl)propanoate (**3**): White powder, ^{1}H NMR (C_3D_6O, 500.13 MHz) δ 8.01 (d, $J = 8.6$ Hz, H-8′), 7.84 (d, $J = 8.1$ Hz, H-5′), 7.83 (d, $J = 9.0$ Hz, H-4′), 7.50 (dd, $J = 8.6$, 8.5 Hz, H-7′), 7.42 (d, $J = 9.0$ Hz, H-3′), 7.34 (dd, $J = 8.5$, 8.1 Hz, H-6′), 4.10 (q, $J = 7.2$ Hz, –OCH_2CH_3), 3.98 (s, –OCH_3), 3.38 (t, $J = 8.2$ Hz, H-3), 2.54 (t, $J = 8.2$ Hz, H-2), 1.20 (t, $J = 7.2$ Hz, –OCH_2CH_3); ^{13}C NMR (C_3D_6O, 125.75 MHz) δ 173.2 (C-1), 155.5 (C-2′), 133.4 (C-8a′), 130.2 (C-4a′), 129.4 (C-5′), 129.0 (C-4′), 127.3 (C-7′), 124.0 (C-6′), 123.5 (C-8′), 122.1 (C-1′), 114.1 (C-3′), 60.6 (–OCH_2CH_3), 56.7 (–OCH_3), 34.8 (C-2), 21.3 (C-3), 14.5 (–OCH_2-CH_3). HREIMS *m*/*z* 258.124791 (calcd for $C_{16}H_{18}O_3$, 258.125595).
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13. *Experimental procedure*: To a 50 mL round-bottomed flask charged with **2** (242 mg, 1 mmol) was added $SOCl_2$ (1 mL). After gas evolution had ceased, the flask was air-dried and the $SOCl_2$ addition repeated three times. The product was dissolved in CH_2Cl_2 (25 mL) and $AlCl_3$ (400 mg) was added in one portion (the solution turns red). DDQ (304 mg, 1.3 equiv) was added after 10 min and the mixture maintained at 30 °C for 15 min. Finally, silica gel (5 g) was added and the mixture was dried at 30 °C. Column chromatography (1:1 *n*-hexane–CH_2Cl_2) afforded 4-methoxy-1*H*-phenalen-1-one (4-methoxyperinaphthenone, **1**) (134 mg, 64%): Orange powder, ^{1}H NMR (C_3D_6O, 500.13 MHz) δ 8.50 (d, $J = 7.5$ Hz, H-9), 8.30 (d, $J = 7.9$ Hz, H-7), 8.25 (d, $J = 9.2$ Hz, H-6), 8.25 (d, $J = 10.0$ Hz, H-3), 7.72 (dd, $J = 7.5$, 7.9 Hz, H-8), 7.60 (d, $J = 9.2$ Hz, H-5), 6.58 (d, $J = 10.0$ Hz, H-2), 4.17 (s, –OCH_3); ^{13}C NMR (C_3D_6O, 125.75 MHz) δ 184.7 (C-1), 159.9 (C-4), 140.0 (C-3), 135.9 (C-6), 135.6 (C-7), 131.3 (C-9), 130.1 (C-9a), 129.0 (C-6a), 127.9 (C-2), 125.7 (C-8), 124.4 (C-9 b), 114.9 (C-5), 113.8 (C-3a), 57.1 (–OCH_3). HREIMS *m*/*z* 210.067280 (calcd for $C_{14}H_{10}O_2$, 210.068080).
14. *Experimental procedure*: 2,3-Dihydro-4-methoxy-1*H*-phenalen-1-one (4-methoxyperinaphthanone, **6**) was synthesized from **2** (92 mg) by treatment with $SOCl_2$ (3 × 0.5 mL), dissolving the residue in CH_2Cl_2

(5 mL) and adding $AlCl_3$ (180 mg) according to the procedure which was used to prepare **1**. After adding silica gel (2 g) and column chromatography (CH_2Cl_2), compound **6** was obtained as a pale yellow oil (46 mg, 54%) which in open air atmosphere at 30 °C slowly decomposed to **1**. The compound was solidified by means of slow evaporation of a CH_2Cl_2 solution under N_2: Pale yellow powder, ^1H NMR (C_3D_6O, 500.13 MHz) δ 8.12 (dd, $J = 8.2$, 1.3 Hz, H-7), 8.06 (dd, $J = 7.1$, 1.3 Hz, H-9), 7.94 (d, $J = 9.0$ Hz, H-6), 7.51 (d, $J = 9.0$ Hz, H-5), 7.47 (dd, $J = 7.1$, 8.2 Hz, H-8), 4.03 (s, $-OCH_3$), 3.36 (2H, t, $J = 7.4$ Hz, H-3), 2.85 (2H, t, $J = 7.4$ Hz, H-2); ^{13}C NMR (C_3D_6O, 125.75 MHz) δ 198.0 (C-1), 155.6 (C-4), 134.7 (C-7), 133.7 (C-9b), 130.0 and 129.8 (C-9a and C-6a), 128.7 (C-6), 125.8 (C-9), 123.8 (C-8), 118.2 (C-3a), 114.5 (C-5), 56.6 ($-OCH_3$), 38.1 (C-2), 22.2 (C-3). HREIMS m/z 212.082985 (calcd for $C_{14}H_{12}O_2$, 212.083730).