# Synthesis and Photooxygenation of the 2*H*-4,8,9-Trimethylfuro[2′,3′:5,6]naphtho[1,2-*b*]-pyran-2-one, an Unnatural Furocoumarin with a Benzene Spacer

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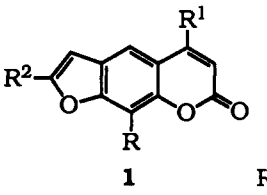
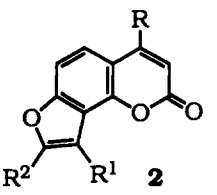
Furocoumarins such as psoralens 1 are photoactive drugs, which are extensively used in the PUVA therapy (psoralen plus UVA radiation) for the treatment of skin diseases, e.g., psoriasis and vitiligo.[1,2] The potency and effectiveness of these photochemotherapeutic agents depend on their photobinding ability with DNA. The latter is the consequence of two successive events: (a) intercalation of the furocoumarin between the base pairs of the nucleic acid[3] and (b) photocycloaddition with the pyrimidine bases, particularly thymine.[4] A marked disadvantage of the usual psoralens is their propensity to form interstrand crosslinks with DNA,[5,6] a consequence of their bifunctional nature (photoactive α-pyrone and furan sites). Thus, undesirable side effects of the PUVA therapy are mutagenicity and carcinogenicity.[7] For this reason, considerable efforts have been expended to develop furocoumarins which only permit monofunctional photobinding with DNA and thereby diminish undesirable side effects. To date, this has been accomplished in two different ways: (a) the use of angular furocoumarins such as angelicins **2**, which on account of their geometry cannot crosslink with DNA,[8] and (b) blocking of the photoreactive α-pyrone double bond by appropriate substituents, e.g., **3**,[9] or by annelation of an additional aromatic ring, e.g., pyridopsoralen **4**.[10]

While the success of these approaches toward monofunctional photobinding furocoumarins has been variable,[1] we decided to probe the novel strategy of enlarging the space between the photoactive double bonds of the α-pyrone and furan through an additional benzene ring. Inspection of molecular models suggests that such furonaphthopyrones no longer permit proper alignment for [2 + 2] photocycloaddition of both its α-pyrone and furan double bonds with thymines on the two opposite DNA strands. Furthermore, extension of the heteroaromatic ring system assures a bathochromic shift in its absorption characteristics, and thereby more benign longer wavelength light needs to be employed in the photochemistry with such potential photoactive materials.



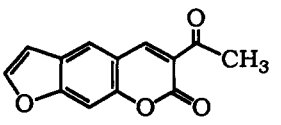
**1**



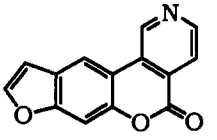
**2**

**1a**: R, $R^1$, $R^2$=H
**1b**: R=$OCH_3$; $R^1$, $R^2$=H
**1c**: R, $R^1$, $R^2$=$CH_3$

**2a**: R, $R^1$, $R^2$=H
**2b**: R, $R^1$=$CH_3$; $R^2$=H
**2c**: R, $R^2$=$CH_3$; $R^1$=H



**3**



**4**

We report here on the synthesis of the new furocoumarin **7** with a benzene spacer, which should serve as potential monofunctional, photobinding agent. Since it has been reported that furocoumarins serve as photosensitizers for molecular oxygen[11] and themselves react with the *in situ* generated singlet oxygen ($^1O_2$) to give biologically active products,[12] we have also investigated the photooxygenation of the novel furonaphthopyrone **7**.

## Results and Discussion

The synthetic methodology for the preparation of the furonaphthopyrone is displayed in Scheme I. Thus, the 1,5-naphthalenediol was converted in 78% yield to the naphthopyrone **5** by Pechmann condensation[13] with ethyl acetoacetate in $H_2SO_4$. The naphthopyrone **5** showed characteristic peaks at δ 6.35 (d, $J$ = 1,2 Hz) in the $^1H$ NMR for 3-H and δ 159.4 (s) in the $^{13}C$ NMR and $\nu$ = 1680 $cm^{-1}$ in the IR for the α-pyrone carbonyl group. The reaction of **5** with 3-chloro-2-butanone in 2-butanone in the presence of $K_2CO_3$ gave **6** in 72% yield at 50% conversion. The absence of the HO group absorption in the IR, the presence of carbonyl group resonance at δ 210.0 (s) in $^{13}C$ NMR for C-2′, and the aliphatic proton resonances at δ 1.65 (d, $J$ = 6.8 Hz), 2.20 (s), and 4.85 (q, $J$ = 6.8 Hz) for 4′-H, 1′-H, and 3′-H confirm the ether group in **6**. The cyclization of **6** in $POCl_3$ gave the furonaphthopyrone **7** in 72% yield. Its structure was confirmed by the presence of the furan carbon resonances of C-8 and C-6b at δ 149.7 and 151.9. Our three-step synthesis displayed in Scheme I constitutes in convenience and efficiency a much improved preparation of furonaphthopyrones, of which prior to our efforts several derivatives have been made by elaborate synthetic methods from naphthopyrones as starting materials.[14]

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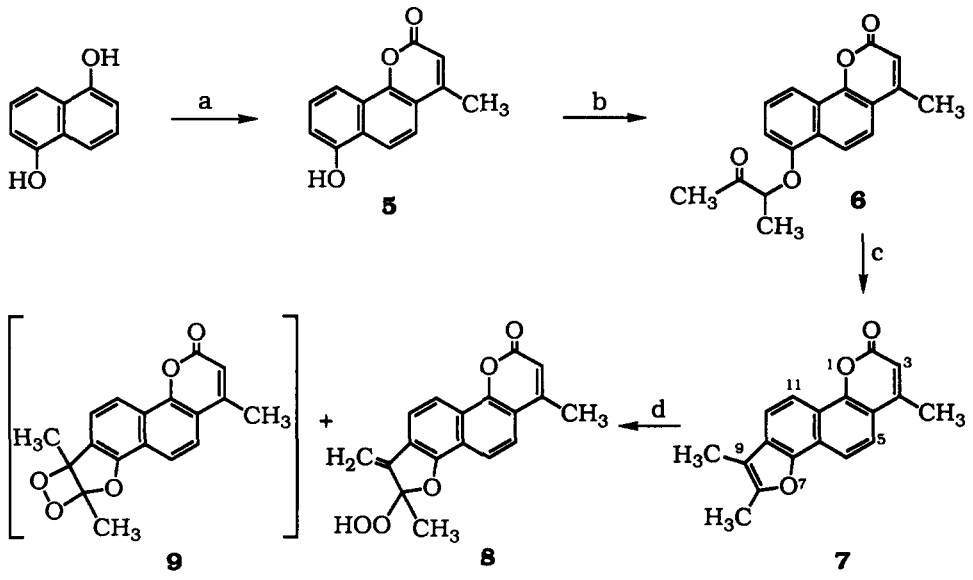
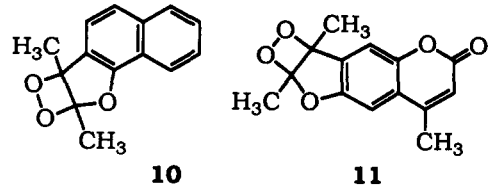
**Scheme I**[a]




[a] Key: (a) $CH_3COCH_2COOC_2H_5$, $H_2SO_4$, 20 °C, 3 h; (b) $CH_3COCH(Cl)CH_3$, $K_2CO_3$, $CH_3COC_2H_5$, reflux, 2 d; (c) $POCl_3$, $CCl_4$, reflux, 1.5 h; (d) $O_2$, TPP, $h\nu$, $CH_2Cl_2$, −20 °C, 1 h.

The photooxygenation of the furonaphthopyrone **7** in methylene chloride and tetraphenylporphine (TPP) as sensitizer at −20 °C gave the allylic hydroperoxide **8** and the dioxetane **9** as a 55:45 mixture. In the absence of TPP photooxidation of **7** was not observed. The stable allylic hydroperoxide **8** was isolated and fully characterized. It showed the expected proton resonances at $\delta$ 5.35 and 5.75 and the carbon resonance at $\delta$ 105.7 (s) for the methylene group and the hydroperoxy stretching band at $\nu$ = 3500–3100 $cm^{-1}$ in the IR. The dioxetane **9** could be detected by NMR at low temperature (−20 °C); however, it was too labile for isolation and purification.

The furonaphthopyrone dioxetane **9** is structurally related to the dioxetanes **10** and **11** derived from the naphthofuran and the furocoumarin, which show a marked




difference in their thermal stability. For example, while the naphthofuran dioxetane **10** decomposed readily already at −40 °C, the furocoumarin dioxetane **11** persisted sufficiently at −10 °C to enable isolation.[15] Thus, in its thermal properties, the dioxetane **9** more closely resembles that of the naphthofuran dioxetane **10**.

Comparison of the UV–vis absorption and fluorescence spectral data of the furonaphthopyrone **7** with those of psoralen **1a** (Table I) exhibits pronounced similarities between the furonaphthopyrone **7** and furocoumarin **1a**. For example, they possess three similar absorption bands[16] in the UV region and, as expected, the furonaphthopyrone **7** is bathochromically shifted (ca. 16 nm). Also, the fluorescence bands are similar and all display the usually large Stokes shifts, which are attributed to intermolecular charge transfer in the excited singlet state.[17] The furonaphthopyrone **7** absorbs somewhat more strongly in the UV–vis region than the furocoumarin **1a**; however, large differences are observed in their fluorescence quantum yields; i.e., for **7** it is ca. 100-fold larger than for **1a**.

**Table I. Absorption and Fluorescence Spectral Properties of the Furocoumarin 1a and the Furonaphthopyrone 7**

| compd | absorpn $\lambda_{max}$ (nm)[log $\epsilon$] | fluorescence $\lambda_{max}$ (nm)[$\Phi^{fl}$][a] |
|---|---|---|
| **1a** | 326 [3.760][b] | 445 [0.0016][b] |
| **7** | 340 [4.372][c] | 424 [0.29][c] |

[a] Determined relative to quinone sulfate.[19] [b] In methanol.[17] [c] In ethanol.

These spectral properties of the furonaphthopyrone **7** are advantageous for the photobinding to DNA, provided that these heteroarenes also exhibit intercalation. In collaboration with Dall'Acqua's group (Padova, Italy) it has been attempted to determine the intercalation efficiency of **7**. Unfortunately, the water solubility of furonaphthopyrone **7** is too low to employ the usual methods, e.g., linear flow dichroism measurements,[18] for determining its DNA intercalation ability. Synthesis of water-soluble derivatives of furonaphthopyrone will be required to assess the propensity for intercalation into and photobinding with DNA of such unnatural furocoumarins.

## Experimental Section

Commercial reagents and solvents were purchased from standard chemical suppliers and purified to match the reported physical and spectra data. For absorption spectra benzene-free absolute ethanol was used; the accuracy of the peak wavelengths was ±1 nm, and the error in the extinction coefficients was ±5%. Fluorescence spectra were recorded on a Perkin-Elmer LS 50 luminescence spectrometer; the fluorescence quantum yields were determined relative to quinine sulfate in sulfuric acid as standard ($\Phi^{fl}$ = 0.54) by using published procedures;[19] the error was ±10%. $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker AC 200 or

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AC 250 spectrometers with $CDCl_3$ or TMS as internal standard. Column chromatography was performed by using silica gel (60–230 mesh) from Woelm or silylated silica gel 60 from Merck. The solutions were dried over $MgSO_4$, and for the removal of the solvent, unless otherwise stated, a rotary evaporator (20 °C/17 Torr) was used.

**4-Methyl-7-hydroxynaphtho[1,2-*b*]pyran-2-one (5).** To a mixture of 2.00 g (12.5 mmol) of 1,5-naphthalenediol and 1.80 g (14.2 mmol) of ethyl acetoacetate was added 5 mL of concd $H_2SO_4$ (98%) during 20 min at 0 °C. The mixture was stirred for 3 h and after the addition of ice/water (100 mL) extracted with ether (3 × 200 mL), washed with water (3 × 20 mL), and dried, and the solvent was removed to give 1.10 g (78% at 56% conversion) of **5** as yellow needles: mp 271–272 °C (acetone); IR (KBr) 3170, 1680, 1630, 1610, 1570, 1475, 1410, 1385, 1300, 1280 $cm^{-1}$; UV (ethanol) $\lambda_{max,\ nm}$ (log $\epsilon$) 218 (4.724), 285 (4.565), 371 (4.015); Fl (ethanol) $\lambda_{max,\ nm}$ 450, $\Phi^{fl} = 0.05$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 2.45 (d, $J$ = 1.2 Hz, 3H, 4-$CH_3$), 6.35 (d, $J$ = 1.2 Hz, 1H, 3-H), 7.05 (dd, $J_{AX}$ = 7.8 Hz, $J_{AB}$ = 0.8 Hz, 1H, 8-H), 7.40 (dd, $J_{XB}$ = 8.9 Hz, $J_{XA}$ = 7.8 Hz, 1H, 9-H), 7.55 (d, $J$ = 9.0 Hz, 1H, 5-H), 7.80 (d, $J$ = 9.0 Hz, 1H, 6-H), 8.0 (dd, $J_{BX}$ = 8.90 Hz, $J_{BA}$ = 0.80 Hz, 1H, 10-H), 10.35 (s, 1H, –OH); $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 18.3 (q, 4-$CH_3$), 110.4 (d, C-3), 111.7 (d, C-8), 113.3 (d, C-9), 114.5 (s, C-4a), 117.8 (d, C-6), 118.4 (d, C-5), 123.3 (s, C-6a), 125.2 (s, C-10a), 127.1 (d, C-10), 149.2 (s, C-4), 152.9 (s, C-7), 153.2 (s, C-10b), 159.4 (s, C-2). Anal. Calcd for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46. Found: C, 74.26; H, 4.41.

**4-Methyl-7-[(2′-oxobutan-3′-yl)oxy]naphtho[1,2-*b*]pyran-2-one (6).** A mixture of 2.00 g (8.80 mmol) of **5**, 2 mL (19.8 mmol) of 3-chloro-2-butanone, and 1.40 g (10.6 mmol) of $K_2C\ O_3$ in 50 mL of 2-butanone was refluxed for 2 d. After the removal of the solvent and addition of 100 mL of water, the resulting mixture was extracted with a 6:1 mixture of ether/petroleum ether (3 × 120 mL). The organic layer was washed with water (3 × 10 mL) and dried, and the solvent was removed to afford 800 mg (72% at 50% conversion) of **6** as colorless needles: mp 177–179 °C (ether); IR (KBr) 2900, 1760, 1630, 1570, 1400, 1280, 1190, 1135, 870 $cm^{-1}$; UV(ethanol) $\lambda_{max,\ nm}$ (log $\epsilon$) 216 (4.828), 283 (4.756), 360 (4.987); Fl (ethanol) $\lambda_{max,\ nm}$ 445, $\Phi^{fl} = 0.14$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.65 (d, $J$ = 6.8 Hz, 3H, 4′-$CH_3$), 2.20 (s, 3H, 1′-$CH_3$), 2.55 (d, $J$ = 1.2 Hz, 3H, 4-$CH_3$), 4.85 (q, $J$ = 6.8 Hz, 1H, 3′-CH), 6.35 (d, $J$ = 1.2 Hz, 1H, 3-H), 6.75 (d, $J$ = 7.7 Hz, 1H, 8-H), 7.45 (dd, $J$ = 7.70 and 8.9 Hz, 1H, 9-H), 7.60 (d, $J$ = 8.6 Hz, 1H, 6-H), 8.10 (d, $J$ = 8.60 Hz, 1H, 5-H), 8.15 (d, $J$ = 8.9 Hz, 1H, 10-H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 17.4 (q, 4′-$CH_3$), 19.1 (q, 4-$CH_3$), 24.4 (q, 1′-$CH_3$), 79.4 (d, C-3′), 108.1 (d, C-3), 114.7 (d, C-8), 115.5 (d, C-9), 115.7 (s, C-4a), 118.1 (d, C-6), 119.8 (d, C-5), 124.4 (s, C-6a), 126.7 (s, C-10a), 127.1 (d, C-10), 150.0 (s, C-4), 152.8 (s, C-7), 153.1 (s, C-10b), 160.6 (s, C-2), 210.0 (s, C-2′). Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.82; H, 5.37.

**2*H*-4,8,9-Trimethylfuro[2′,3′:5,6]naphtho[1,2-*b*]pyran-7-one (7).** To a solution of 500 mg (1.69 mmol) of **6** in 10 mL of $CCl_4$ was added 10 mL of $POCl_3$ dropwise at room temperature. The mixture was refluxed for 1.5 h and cooled to room temperature, and after the addition of 100 mL of ice/water, the solid material was collected by filtration and 360 mg (72%) of **7** as yellow needles was obtained: mp 259–260 °C (ethyl acetate); IR (KBr) 2900, 1725, 1600, 1480, 1380, 1250, 1150, 1030, 1000, 970, 950, 840 $cm^{-1}$; UV (ethanol) $\lambda_{max,\ nm}$ (log $\epsilon$) 251 (4.666), 284 (4.605), 340 (4.372), 362 (sh, 4.348), 378 (sh, 4.323); Fl (ethanol) $\lambda_{max,\ nm}$ 424, $\Phi^{fl} = 0.29$; $^1H$ NMR ($CF_3COOD$) $\delta$ 2.20 (s, 3H, 3-$CH_3$), 2.43 (s, 3H, 2-$CH_3$), 2.50 (d, $J$ = 1.0 Hz, 3H, 9-$CH_3$), 6.33 (d, $J$ = 1.0 Hz, 1H, 3-H), 7.35 (d, $J$ = 8.7 Hz, 1H, 11-H), 7.40 (d, $J$ = 8.6 Hz, 1H, 6-H), 7.61 (d, $J$ = 8.7 Hz, 1H, 10-H), 7.78 (d, $J$ = 8.6 Hz, 1H, 5-H); $^{13}C$ NMR ($CF_3COOD$) $\delta$ 7.9 (q, 9-$CH_3$), 12.0 (q, 8-$CH_3$), 20.0 (q, 4-$CH_3$), 111.7 (d, C-3), 113.5 (s, C-9), 116.4 (s, C-4a), 117.8 (d, C-11), 119.7 (d, C-6), 120.2 (s, C-9a), 121.2 (d, C-10), 121.5 (d, C-5), 123.8 (s, C-6a), 131.4 (s, C-11a), 149.7 (s, C-8), 151.9 (s, C-6b), 155.3 (s, C-4), 162.6 (s, C-11), 168.1 (s, C-2). Anal. Calcd for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07. Found: C, 77.73; H, 4.89.

**2*H*-8,9-Dihydro-8-hydroperoxy-8-methyl-9-methylenefuro[2′,3′:5,6]naphtho[1,2-*b*]pyran-7-one (8).** A solution of 300 mg (1.10 mmol) of **7** and 5 mg of tetraphenylporphine (TPP) in 50 mL of $CH_2Cl_2$ was irradiated externally by means of a sodium lamp (150 W) at –20 °C for 1 h while passing a continuous slow stream of dry oxygen gas through the solution. After the removal of the solvent and recrystallization from $CHCl_3$, 160 mg (48%) of thermally stable hydroperoxide **8** was obtained as orange needles: mp 161–162 °C (ethyl acetate); IR (KBr) 3500–3100, 2900, 1710 (sh), 1685 (sh), 1670, 1555, 1370, 1300, 1220 $cm^{-1}$; UV (ethanol) $\lambda_{max,\ nm}$ (log $\epsilon$) 234 nm (4.391), 245 (4.400), 253 (4.406), 283 (4.549), 385 (4.114), 402 (sh, 4.050); Fl (ethanol) $\lambda_{max,\ nm}$ 459, $\Phi^{fl} = 0.38$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 1.70 (s, 3H, 8-$CH_3$), 2.55 (d, $J$ = 1.2 Hz, 3H, 4-$CH_3$), 5.35 (s, 1H, =$CH_2$), 5.70 (s, 1H, =$CH_2$), 6.50 (d, $J$ = 1.2 Hz, 1H, 3-H), 7.59 (s, 1H, –OOH), 7.76 (d, $J$ = 8.8 Hz, 1H, 11-H), 7.83 (d, $J$ = 7.7 Hz, 1H, 6-H), 7.84 (d, $J$ = 7.7 Hz, 1H, 5-H), 7.92 (d, $J$ = 8.8 Hz, 1H, 10-H); $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 18.6 (q, 8-$CH_3$), 27.1 (q, 4-$CH_3$), 105.7 (t, = $CH_2$), 111.1 (s, C-8), 114.0 (d, C-3), 114.1 (d, C-11), 115.8 (s, C-4a), 117.6 (d, C-6), 120.6 (s, C-9a), 120.7 (d, C-5), 121.2 (d, C-10), 123.5 (s, C-6a), 148.7 (s, C-9), 150.0 (s, C-11), 154.0 (s, C-4), 154.8 (s, C-6), 159.4 (s, C-11), 168.4 (s, C-2). Anal. Calcd for $C_{18}H_{14}O_5$: C, 69.67; H, 4.55. Found: C, 69.60; H, 4.68.

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