Synthesis of Linear and Angular Benzofurocoumarins

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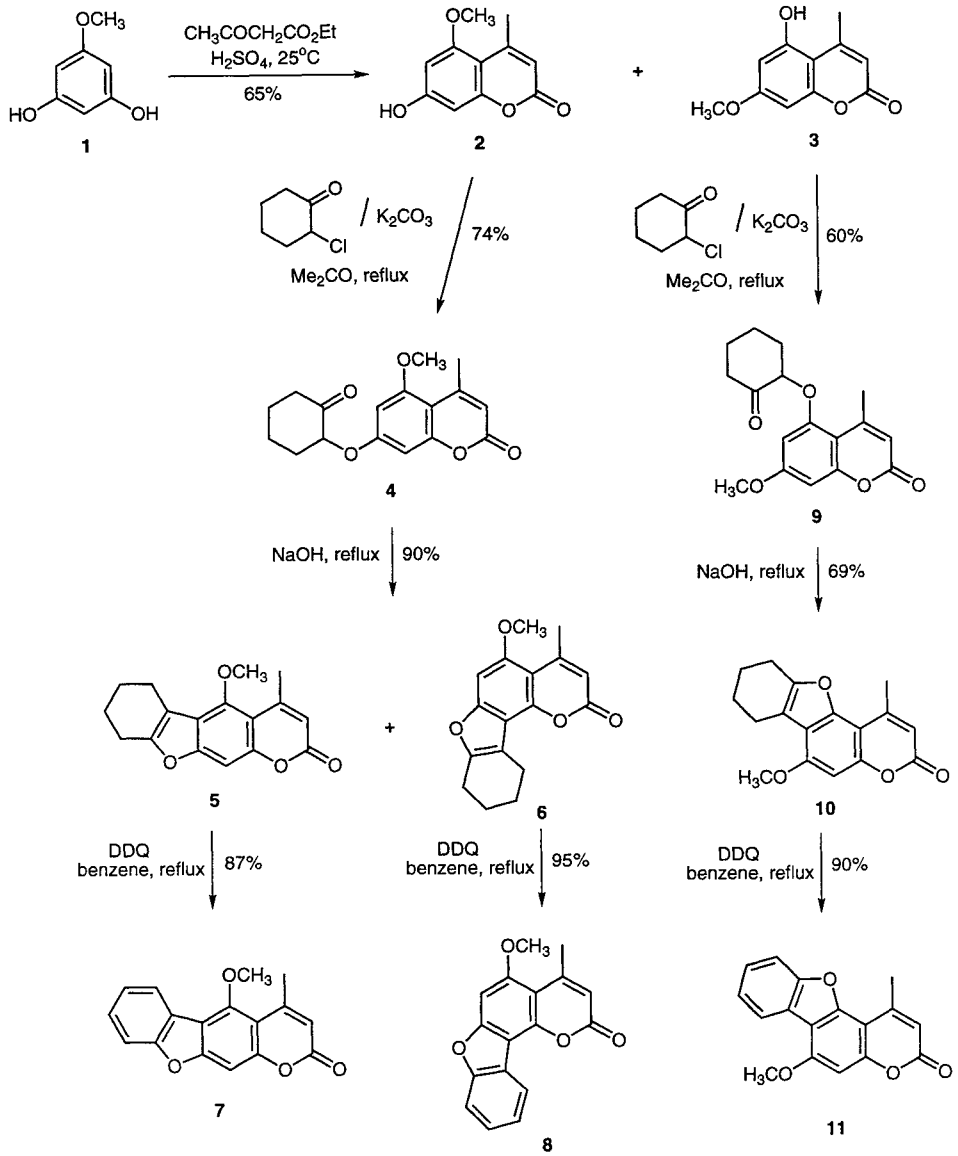
A four-step synthetic approach to substituted linear and angular benzofurocoumarins is described. Starting from 5-methoxyresorcinol, this approach afforded good yields of benzopsoralen (**7**), benzoangelicine (**8**), and benzoallopsoralen (**11**), which bear easily hydrolysed methoxy groups and thus allow access to other substituted compounds with potential as photochemotherapeutic agents.

Furocoumarins are of pharmacological interest due to their capacity to covalently link to DNA[1,2] and other biological macromolecules[3] upon irradiation with long-wavelength UV light (UVA, 320–400 nm). This photoreactivity is generally greatest for linear furocoumarins (psoralens), among which 8-methoxypsoralen (8-MOP), 5-methoxypsoralen (5-MOP), and 4,8,5′-trimethylpsoralen are currently in clinical use in the PUVA (Psoralen + UVA) therapy of various skin diseases.[2,4] In this regard, it has been reported that 5-MOP is less phototoxic than 8-MOP.[5]

Certain adverse side-effects of PUVA therapy have been attributed to the cross-linking of DNA molecules by psoralens through di-adduct formation.[6] To avoid this, monofunctional PUVA agents are sought that retain the high photoreactivity and intercalation capacity of psoralens. An interesting class of such agents is the benzofurocoumarins, in which the reactive double bond of the



Scheme 1

furan ring of the psoralen is deactivated by condensing an aromatic ring across it.[7,8] Initial evaluation of this class of compounds has shown that they are not only much less phototoxic than psoralens, but also have increased capacity to intercalate and photoreact with DNA.[9] Furthermore, some benzofurocoumarins inhibit DNA synthesis even in the dark,[10] suggesting that they may have potential as antitumour agents.

In this work we report the synthesis of angular and linear benzofurocoumarins with a methoxy substituent on the central benzene ring, C-5 (i.e. in an analogous position to the methoxy of 5-MOP) in compounds **7** and **8**, and at C-10 in compound **11**. We are interested in these compounds as models for studying the effects of the additional ring on the photochemotherapeutic properties of angular and linear furocoumarins, and as base compounds for the preparation of a series of benzofurocoumarins bearing side-chains of various natures, which we plan to introduce by hydrolysis and subsequent modification of the methoxy group.

The synthetic approach used here is similar to one previously used to obtain furocoumarins.[11,12] It consists the cyclization of a suitable phenol to a coumarin or benzopyrone upon which the furan ring is then constructed, and it is easily generalizable to the synthesis of compounds with diverse substituents by varying the starting β-oxo ester and/or phenol. Here, starting from 5-methoxyresorcinol **(1)** and ethyl acetoacetate, we obtained benzopsoralen **(7)**, benzoangelicine **(8)**, and benzoallopsoralen **(11)** as follows. Pechmann reaction of **1** with ethyl acetoacetate in sulfuric acid gave a 53:47 mixture of isomeric hydroxycoumarins **2** and **3** in 65% combined yield.[13] Williamson reaction of **2** and **3** with 2-chlorocyclohexanone in acetone/K_2CO_3 gave, after 15 h at reflux, the corresponding oxo ethers **4** and **9** in 74% and 60% yield, respectively. Cyclization of oxo ether **4** by heating it in strongly alkaline solution afforded a ca. 2:3 mixture of tetrahydrobenzofurocoumarins **5** and **6** in 90% combined yield. Analogous cyclization of oxo ether **9** gave **10** in 69% yield. Compounds **5** and **6** were distinguished by NOE spectroscopy,[14] by virtue of the fact that, for compound **5**, irradiation of the methoxy protons enhanced the signals due to both the methyl group and the nearby allylic protons of the cyclohexene ring. Finally, this ring of tetrahydrobenzofurocoumarins **5,6**, and **10** was aromatized by treating each with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing benzene, which afforded benzofurocoumarins **7,8**, and **11** in 87%, 95%, and 90% yields, respectively.

Evaluation of the photochemical and biological properties of series comprising these and related compounds is in progress.

Melting points are uncorrected and were determined in a Reichert Kofler thermopan or in capillary tubes in a Büchi 510 apparatus. IR spectra were recorded in a Perkin-Elmer 1640FT spectrometer (ν in cm^{-1}). ^1H NMR spectra (300 MHz) and ^{13}C NMR spectra (75.47 MHz) were recorded in a Bruker AMX spectrometer, using TMS as internal standard (chemical shifts in δ values, J in Hz). Mass spectrometry was carried out in a Hewlett Packard 5988A spectrometer. Elemental analyses were performed by a Perkin-Elmer 240B microanalyser (C $\pm$ 0.29, H $\pm$ 0.28). Flash chromatography (FC) was performed on silica gel (Merck 60, 230–400 mesh); analytical TLC was performed on pre-coated silica gel plates (Merck 60 F254, 0.25 mm).

5-Methoxy-4-methyl-7-(2-oxocyclohexanyloxy)coumarin (4):
A mixture of 7-hydroxycoumarin (**2**; 20 g, 142.8 mmol), 2-chlorocyclohexanone (37.91 g, 214.2 mmol), and K_2CO_3 (29.55 g, 214.2 mmol) in anhyd acetone (2 L) was heated at reflux for 48 h. The mixture was cooled, the precipitate was filtered, and the solvent was evaporated under reduced pressure. The residue was purified by FC with 8:2 hexane/EtOAc as eluant, which gave pure **4**. Yield: 21.80 g, (74%); mp 195–196°C.

IR (KBr): ν = 2933, 1718, 1706, 1605, 1335, 1163, 1117, 1087, 825 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.04–1.40 (m, 5H, H4′+H5′+1H6′), 2.35 (m, 2H, H6′ and 1H3′), 2.47 (d, 3H, J = 1.05, CH_3), 2.69 (td, 2H, J = 13.40 and 6.00, 1H3′), 3.35 (s, 3H, OCH_3), 5.21 (dd, 1H, J = 10.20 and 6.40, H1′), 5.99 (q, 1H, J = 1.05, H3), 6.46 (d, 1H, J = 2.35, H6), 6.50 (d, 1H, J = 2.35, H8).

^{13}C NMR (DMSO-d_6): δ = 23.4, 24.0, 27.2, 34.1, C-3′ (overlapped by DMSO), 56.6, 79.9, 94.8, 96.7, 104.3, 110.9, 154.6, 156.5, 159.2, 160.1, 161.5, 206.7.

6,7,8,9-Tetrahydro-5-methoxy-4-methylbenzofuro[3,2-*g*]coumarin (5) and 8,9,10,11-tetrahydro-5-methoxy-4-methylbenzofuro[2,3-*h*]coumarin (6):
Oxo ether **4** (15 g, 49 mmol) was heated at reflux in 1 N NaOH (300 mL) for 3 h. The mixture was cooled, acidified with 1 N HCl, and the precipitate formed was collected, washed with H_2O and purified by FC with 9:1 toluene/EtOAc as eluant, which afforded in order of elution, **6** yield: 7.47 g (52.7%) and **5** yield: 5.27 g, (37.2%).

Compound **5**: Mp 167–168°C.

IR (KBr): ν = 2934, 1718, 1706, 1569, 1458, 1146, 1069 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.85 (m, 2H, H7), 1.94 (m, 2H, H8), 2.65 (d, 3H, J = 1.20, CH_3), 2.73 (m, 2H, H6), 2.83 (m, 2H, H9), 3.88 (s, 3H, OCH_3), 6.10 (q, 1H, J = 1.20, H3), 7.16 (s, 1H, H11).

^{13}C NMR ($CDCl_3$): δ = 22.51, 22.8, 23.2, 23.4, 23.8, 64.9, 97.1, 110.2, 111.8, 114.3, 120.4, 151.6, 152.1, 153.7, 155.5, 157.1, 161.4.

MS: m/z (%) = 285 (MH^+, 19), 284 (M^+, 100), 269 (34), 256 (16), 241 (18).

Compound **6**: Mp 212–214°C.

IR (KBr): ν = 2949, 2840, 1716, 1599, 1432, 1108, 1088, 832 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.94–1.81 (m, 4H, H9+H10), 2.60 (d, 3H, J = 1.10, CH_3), 2.70 (m, 2H, H11), 2.95 (m, 2H, H8), 3.89 (s, 3H, OCH_3), 6.05 (q, 1H, J = 1.10, H3), 6.80 (s, 1H, H6).

^{13}C NMR ($CDCl_3$): δ = 22.3, 22.9, 23.0, 23.7, 25.3, 56.4, 91.5, 106.6, 111.4, 112.5, 113.0, 149.5, 153.6, 155.9, 155.9, 156.9, 161.3.

MS: m/z (%) = 285 (MH^+, 19), 284 (M^+, 100), 269 (34), 256 (16), 241 (18).

5-Methoxy-4-methylbenzofuro[3,2-*g*]coumarin (7):
A solution of tetrahydrobenzopsoralen (**5**; 2 g, 7.04 mmol) and DDQ (4 g, 17.60 mmol) in benzene (500 mL) was heated at reflux for 4 h. The mixture was cooled, the precipitate was filtered, and the solvent was evaporated under reduced pressure. The residue was purified by FC with 9:1 toluene/EtOAc as eluant, which gave benzopsoralen **(7)**. Yield: 1.70 g (87%); mp 214°C (dec).

IR (KBr): ν 3057, 2931, 1723, 1599, 1148, 1068, 749 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.74 (d, 3H, J = 1.15, CH_3), 4.00 (s, 3H, OCH_3), 6.13 (q, 1H, J = 1.15, H3), 7.33 (s, 1H, H11), 7.42 (td, 1H, J = 7.30 and 1.25, H7), 7.50 (m, 1H, J = 7.30 and 1.35, H8), 7.57 (dd, 1H, J = 8.20 and 1.25, H9), 8.03 (dd, 1H, J = 7.30 and 1.35, H6).

^{13}C NMR ($CDCl_3$): δ = 22.9, 62.0, 97.1, 110.3, 111.7, 114.2, 115.3, 121.7, 122.6, 123.8, 127.5, 153.0, 153.5, 154.6, 156.4, 158.4, 160.3.

MS: m/z (%) = 281 (MH^+, 63), 280 (M^+, 55), 252 (27), 237 (100).

Methoxy-4-methylbenzofuro[2,3-*h*]coumarin (8):
This compound was prepared from **6** (2 g) in an analogous manner

to **7**. The crude product was purified by FC with 1:1 hexane/CH_2Cl_2 as eluant, which gave pure **8**. Yield: 1.87 g (95%); mp 215°C (dec).

IR (KBr): ν = 1723, 1604, 1440, 1194 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.63 (d, 3H, J = 1.15, CH_3), 3.98 (s, 3H, OCH_3), 6.13 (q, 1H, J = 1.15, H3), 6.93 (s, 1H, H6), 7.39 (td, 1H, J = 7.25 and 1.50, H10), 7.43 (td, 1H, J = 7.25 and 1.80, H9), 7.54 (m, 1H, J = 7.25, 1.50 and 0.55, H8), 8.32 (m, 1H, J = 7.25, 1.80 and 0.60, H11).

^{13}C NMR ($CDCl_3$): δ = 24.7, 56.2, 91.1, 106.4, 106.6, 111.1, 112.6, 122.3, 122.7, 123.8, 126.3, 150.7, 155.1, 155.9, 158.6, 158.7, 160.3.

MS: m/z (%) = 280 (M^+, 12), 166 (29), 149 (100).

7-Methoxy-4-methyl-5-(2-oxocyclohexanyloxy)coumarin (9):
This compound was prepared from **3** (20 g) in an analogous manner to **4**. The crude product was purified by FC with 8:2 hexane/EtOAc as eluant, which gave pure **9**. Yield: 17.60 g (60%); mp 217–219°C.

IR (KBr): ν = 3068, 2956, 1732, 1716, 1654, 1606, 1167, 1120 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.05–1.55 (m, 5H, H4′+H5′+1H6′), 2.30 (m, 1H, 1H6′), 2.42 (m, 1H, 1H3′), 2.48 (d, 3H, J = 1.10, CH_3), 2.65 (td, 1H, J = 13.30 and 6.10, 1H3′), 3.78 (s, 3H, OCH_3), 5.29 (dd, 1H, J = 10.70 and 6.40, H1′), 6.01 (q, 1H, J = 1.10, H3), 6.36 (d, 1H, J = 2.30, H6), 6.56 (d, 1H, J = 2.30, H8).

^{13}C NMR (DMSO-d_6): δ = 23.4, 24.2, 27.3, 34.1, C-3′ (overlapped by DMSO), 56.2, 80.7, 93.9, 97.4, 104.4, 111.1, 154.8, 156.7, 157.5, 160.0, 162.8, 206.8.

6,7,8,9-Tetrahydro-10-methoxy-4-methylbenzofuro[2,3-*f*]coumarin (10):
This compound was prepared from **9** (15 g) in an analogous manner to **5** and **6**. The crude product was purified by FC with 9:1 toluene/EtOAc as eluant, which gave **10**. Yield: 9.60 g (69%); mp 277–280°C.

IR (KBr): ν = 2940, 2850, 1716, 1603, 1386, 1109, 840 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.92–1.84 (m, 4H, H7+H8), 2.68 (d, 3H, J = 1.10, CH_3), 2.73 (m, 2H, H9), 2.80 (m, 2H, H6), 3.92 (s, 3H, OCH_3), 6.08 (q, 1H, J = 1.10, H3), 6.60 (s, 1H, H11).

^{13}C NMR ($CDCl_3$): δ = 22.4, 22.4, 23.1, 23.2, 23.9, 56.2, 93.9, 102.3, 111.4, 113.1, 115.8, 151.2, 152.7, 153.3, 153.5, 156.8, 162.0.

MS: m/z (%) = 285 (MH^+, 19), 284 (M^+, 100), 256 (21), 241 (16), 227 (12).

10-Methoxy-4-methylbenzofuro[2,3-*f*]coumarin (11):
This compound was prepared from **10** (2 g) in an analogous manner to **7**. The crude product was purified by FC with 1:1 hexane/CH_2Cl_2 as eluant, which gave **11**. Yield: 1.75 (90%); mp 279°C.

IR (KBr): ν = 1734, 1611, 1386, 1166, 739 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.81 (d, 3H, J = 0.70, CH_3), 4.09 (s, 3H, OCH_3), 6.15 (q, 1H, J = 0.70, H3), 6.77 (s, 1H, H11), 7.40 (m, 1H, J = 7.50 and 1.00, H8), 7.44 (m, 1H, J = 8.20 and 1.40, H7), 7.59 (dd, 1H, J = 8.20 and 1.00, H6), 8.11 (dd, 1H, J = 7.50 and 1.40, H9).

^{13}C NMR ($CDCl_3$): δ = 22.1, 56.2, 94.3, 101.9, 110.6, 111.2, 111.6, 122.4, 122.5, 123.6, 126.1, 152.2, 153.2, 155.3, 155.7, 157.7, 161.0.

MS: m/z (%) = 281 (MH^+, 19), 280 (M^+, 100), 237 (12), 181 (17), 152 (14).

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