The first synthesis of furocoumarin dimers

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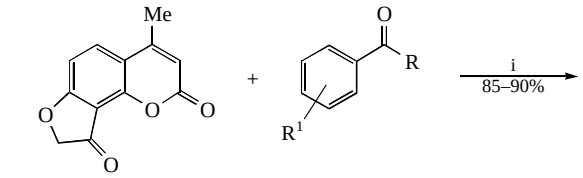
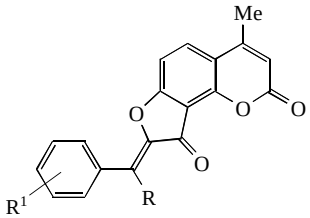
Self-condensation of 4-methyl-2*H*-8,9-dihydrofuro[2,3-*h*]-1-benzopyran-2,9-diones provides the first example of the synthesis of a furocoumarin dimer.

2*H*-Furo-1-benzopyran-2-ones (furocoumarins) are widespread natural products. Many of them are useful in the treatment of human skin diseases.[1–7] The biological activity of these compounds is based on their ability to react with the pyrimidine bases, particularly with thymine, under UV light. 2*H*-Furo[2,3-*g*]-1-benzopyran-2-ones (psoralens) are bifunctional, since they can crosslink with DNA. 2*H*-Furo[2,3-*h*]-1-benzopyran-2-ones (angelicins) are monofunctional, since they cannot crosslink with DNA due to their angular geometry. However, there are no reports concerning the pharmaceutical properties and photoreactivity of furocoumarin dimers. Moreover, furocoumarin dimers have not yet been synthesized.



1a



2

	R	R^1
2a	H	H
2b	H	4′-OH, 3′-OMe
2c	H	4′-NO_2
2d	Me	4′-Me

Scheme 1 *Reagents and conditions*: i, AcOH, HCl, 100 °C, 1 h.

Whilst developing new ways of synthesising furocoumarin derivatives based on the Fries rearrangement of hydroxy-2*H*-1-benzopyran-2-one chloroacetates,[8,9] we have undertaken the first synthesis of an angelicin dimer.

4-Methyl-2*H*-8,9-dihydrofuro[2,3-*h*]-1-benzopyran-2,9-diones **1** possess a definite enolate reactivity. For example, compound **1a** undergoes croton-type condensations with aldehydes and ketones in acetic acid in the presence of HCl. According to spectral data, the condensation products – 8-benzylideno-4-methyl-2*H*-8,9-dihydrofuro[2,3-*h*]-1-benzopyran-2,9-diones **2** – have an enone (croton-type) structure (Scheme 1). Intermediate ketols have not been detected among the condensation products.

Compounds **1** also undergo self-condensation with dimer formation.† However, neither enone **2e** nor intermediate ketol **3** (from compound **1** self-condensation) products have yet been found in the reaction mixtures. Intermediate ketols **3** seem to undergo dehydration with aromatization and furan ring formation. The final products – 9-(4′-methyl-2′*H*-8′,9′-dihydrofuro[2′,3′-*h*]-1′-benzopyran-2′,9′-dione-8′-yl)-4-methyl-2*H*-8,9-dihydrofuro[2,3-*h*]-1-benzopyran-2,9-diones **4** – turn out to be more stable when compared with enone condensation products **2e**.

A small amount of **4a** has also been detected among the 7-chloroacetoxy-4-methylcoumarin Fries rearrangement products.[9] Strong Lewis acids (including $AlCl_3$) are known to catalyse the processes of dehydration and condensation of polycyclic aromatic hydrocarbons and heteroarenes.[10] Its content is increased to a maximum of 5% in the reaction mixture under Fries rearrangement temperatures higher than 120 °C.

According to ^{1}H NMR spectral data, compounds **4** exist in the keto form. However, their enol forms have been isolated as the acetates **5** through acetylation by acetic anhydride in the presence of catalytic amounts of H_2SO_4.

Reduction of the compounds **4** by $NaBH_4$ in dioxane–methanol leads to the corresponding alcohols **6**, which upon dehydration in H_2SO_4 gave the 4-methylangelicin 2,3′-bifuran dimers **7** (Scheme 2).

The melting points and spectral data of new compounds are listed below.‡

† *Self-condensation of* 4-*methyldihydrofuro*[2,3-*h*]*coumarin-9-ones* **1** (*general procedure*). A mixture of compound **1** (4.6 mmol), glacial acetic acid (12 ml) and concentrated HCl (6 ml) was refluxed for 3 h. Product **4** was filtrated off, washed with hot acetone and recrystallized from DMSO.

‡ ^{1}H NMR spectra were recorded on a Varian Gemini-200 spectrometer (USA) at 200 MHz using TMS as internal standard. Chemical shifts are given in ppm. Mass spectra were scanned on a SSQ-710 (Finnigan MAT) spectrometer (USA) at an energy of ionising electrons equal to 70 eV.

2a: mp 286–287 °C; ^{1}H NMR (200 MHz, [$^2H_6$]acetone), δ: 2.55 (d, 3H, 4-Me, $J_{3,Me}$ 1.2 Hz), 6.34 (q, 1H, 3-H, $J_{Me,3}$ 1.2 Hz), 6.93 [s, 1H, =(Ph)C–H], 7.48 (d, 1H, 6-H, $J_{5,6}$ 8.7 Hz), 7.50 (m, 3H, 3′-H, 4′-H and 5′-H), 8.05 (m, 2H, 2′-H and 6′-H), 8.20 (d, 1H, 5-H, $J_{6,5}$ 8.7 Hz); MS, *m*/*z*: 304 (M^+, 61%), calc. for $C_{19}H_{12}O_4$: 304.

2b: mp 330–331 °C; ^{1}H NMR (200 MHz, [$^2H_6$]DMSO), δ: 2.44 (d, 3H, 4-Me, $J_{3,Me}$ 0.9 Hz), 3.86 (s, 3H, OMe), 6.35 (q, 1H, 3-H, $J_{Me,3}$ 0.9 Hz), 6.85 (d, 1H, 5′-H, $J_{6',5'}$ 8.5 Hz), 6.90 [s, 1H, =(Ph)C–H], 7.48 (d, 1H, 6-H, $J_{5,6}$ 9.0), 7.49 (dd, 1H, 6′-H, $J_{5',6'}$ 8.5 Hz, $J_{2',6'}$ 0.9 Hz), 7.54 (d, 1H, 2′-H, $J_{6',2'}$ 0.9 Hz), 8.09 (d, 1H, 5-H, $J_{6,5}$ 9.0 Hz), 9.94 (s, 1H, OH); MS, *m*/*z*: 350 (M^+, 100%), calc. for $C_{20}H_{14}O_6$: 350.

2c: mp 354–355 °C; ^{1}H NMR (200 MHz, [$^2H_6$]DMSO), δ: 2.50 (d, 3H, 4-Me, $J_{3,Me}$ 0.9 Hz), 6.38 (q, 1H, 3-H, $J_{Me,3}$ 0.9 Hz), 7.08 [s, 1H, =(Ph)C–H], 7.50 (d, 1H, 6-H, $J_{5,6}$ 9.0 Hz), 8.18 (d, 2H, 2′-H, $J_{3',2'}$ 8.5 Hz), 8.23 (d, 1H, 5-H, $J_{6,5}$ 9.0 Hz), 8.30 (d, 2H, 3′-H, $J_{2',3'}$ 8.5 Hz); MS, *m*/*z*: 349 (M^+, 100%), calc. for $C_{19}H_{11}NO_6$: 349.

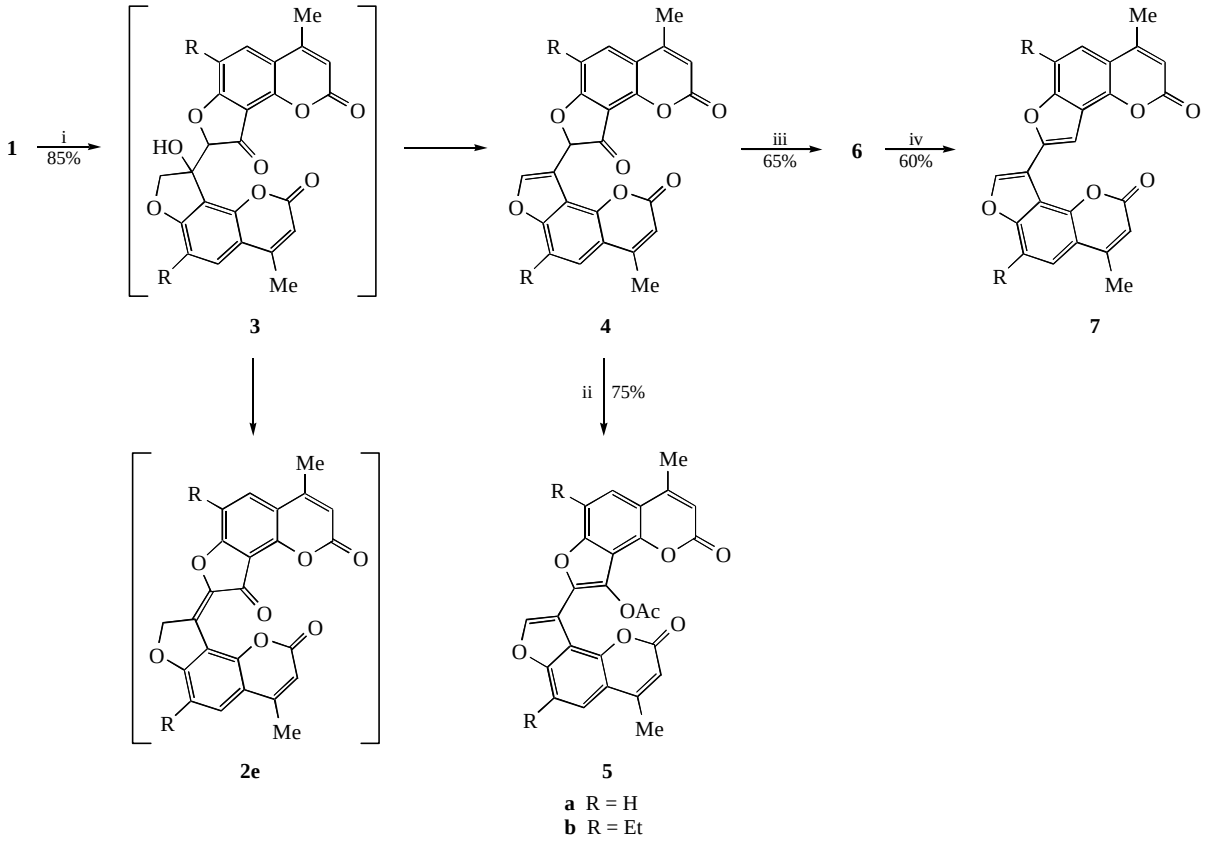
2d: mp 263–264 °C; ^{1}H NMR (200 MHz, [$^2H_6$]DMSO), δ: 2.40 (s, 3H, 4′-Me), 2.50 (d, 3H, 4-Me, $J_{3,Me}$ 1.0 Hz), 2.69 [s, 3H, =(Ph)C–Me], 6.26 (q, 1H, 3-H, $J_{Me,3}$ 1.0 Hz), 7.20 (d, 1H, 6-H, $J_{5,6}$ 8.5 Hz), 7.30 (d, 2H, 3′-H, $J_{2',3'}$ 8.4 Hz), 7.65 (d, 2H, 2′-H, $J_{3',2'}$ 8.4 Hz), 8.06 (d, 1H, 5-H, $J_{6,5}$ 8.5 Hz); MS, *m*/*z*: 332 (M^+, 86%), calc. for $C_{21}H_{16}O_4$: 332.

4a: mp 310 °C (decomp.); ^{1}H NMR (200 MHz, [$^2H_6$]DMSO), δ: 2.42 (d, 3H, 4′-Me, $J_{3',Me'}$ 0.9 Hz), 2.50 (d, 3H, 4-Me, $J_{3,Me}$ 0.9 Hz), 6.10 (q, 1H, 3′-H, $J_{Me',3'}$ 0.9 Hz), 6.27 (s, 1H, 8′-H), 6.30 (q, 1H, 3-H, $J_{Me,3}$ 0.9 Hz), 7.16 (d, 1H, 6′-H, $J_{5',6'}$ 8.9 Hz), 7.64 (d, 1H, 6-H, $J_{5,6}$ 9.0 Hz), 7.74 (d, 1H, 5-H, $J_{6,5}$ 9.0 Hz), 8.10 (d, 1H, 5′-H, $J_{6',5'}$ 8.9 Hz), 8.45 (s, 1H, 8-H); MS, *m*/*z*: 414 (M^+, 100%), calc. for $C_{24}H_{14}O_7$: 414.

4b: mp 275 °C (decomp.); ^{1}H NMR (200 MHz, [$^2H_6$]DMSO), δ: 1.15 (t, 3H, Me′, $J_{CH_2',Me'}$ 7.7 Hz), 1.33 (t, 3H, Me, $J_{CH_2,Me}$ 7.6 Hz), 2.42 (d, 3H, 4′-Me, $J_{3',Me'}$ 0.9 Hz), 2.50 (d, 3H, 4-Me, $J_{3,Me}$ 0.9 Hz), 2.71 (q, 2H, CH_2′, $J_{Me',CH_2'}$ 7.7 Hz), 2.94 (q, 2H, CH_2, J_{Me,CH_2} 7.6 Hz), 6.10 (q, 1H, 3′-H, $J_{Me',3'}$ 0.9 Hz), 6.32 (s, 1H, 8′-H), 6.33 (q, 1H, 3-H, $J_{Me,3}$ 0.9 Hz), 7.57 (s, 1H, 5-H), 7.96 (s, 1H, 5′-H), 8.56 (s, 1H, 8-H); MS, *m*/*z*: 470 (M^+, 100%), calc. for $C_{28}H_{22}O_7$: 470.

5a: mp 313–314 °C; ^{1}H NMR (200 MHz, [$^2H_6$]DMSO), δ: 2.42 (s, 3H, OAc), 2.52 (2d, 6H, 4-Me and 4′-Me), 6.37 (2q, 2H, 3-H and 3′-H), 7.61 (d, 1H, 6′-H, $J_{5',6'}$ 8.7 Hz), 7.72 (d, 1H, 6-H, $J_{5,6}$ 8.7 Hz), 7.80 (d, 1H, 5-H, $J_{6,5}$ 8.7 Hz), 7.84 (d, 1H, 5′-H, $J_{6',5'}$ 8.7 Hz), 8.54 (s, 1H, 8-H); MS, *m*/*z*: 456 (M^+, 2%), calc. for $C_{26}H_{16}O_8$: 456.

5b: mp 277–278 °C (decomp.); ^{1}H NMR (200 MHz, [$^2H_6$]DMSO), δ: 1.35 (2t, 6H, Me and Me′), 2.42 (s, 3H, OAc), 2.52 (2d, 6H, 4-Me and 4′-Me), 2.97 (2q, 4H, CH_2 and CH_2′), 6.37 (2q, 2H, 3-H and 3′-H), 7.60 (s, 1H, 5-H), 7.66 (s, 1H, 5′-H), 8.60 (s, 1H, 8-H); MS, *m*/*z*: 512 (M^+, 2%), calc. for $C_{30}H_{24}O_8$: 512.



Scheme 2 *Reagents and conditions*: i, AcOH, HCl, 100 °C, 3 h; ii, Ac_2O, H_2SO_4, 120 °C, 1 h; iii, $NaBH_4$, dioxane, MeOH, 20 °C, 2 h; iv, 20% H_2SO_4, EtOH, 80 °C, 3 h.

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6a: mp 283–284 °C; ^{1}H NMR (200 MHz, [$^2H_6$]DMSO), δ: 2.42 (d, 3H, 4′-Me, $J_{3',Me'}$ 1.0 Hz), 2.52 (d, 3H, 4-Me, $J_{3,Me}$ 1.0 Hz), 5.63 (d, 1H, 9′-OH, $J_{9',9\text{-}OH'}$ 7.2 Hz), 5.86 (dd, 1H, 9′-H, $J_{9\text{-}OH',9'}$ 7.2 Hz, $J_{8',9'}$ 7.1 Hz), 6.17 (dd, 1H, 8′-H, $J_{9',8'}$ 7.1 Hz, $J_{8,8'}$ 1.2 Hz), 6.21 (q, 1H, 3′-H, $J_{Me',3'}$ 1.0 Hz), 6.39 (q, 1H, 3-H, $J_{Me,3}$ 1.0 Hz), 7.04 (d, 1H, 6′-H, $J_{5',6'}$ 8.7 Hz), 7.63 (d, 1H, 6-H, $J_{5,6}$ 8.8 Hz), 7.74 (d, 1H, 5-H, $J_{6,5}$ 8.8 Hz), 8.77 (d, 1H, 5′-H, $J_{6',5'}$ 8.7 Hz), 8.09 (d, 1H, 8-H, $J_{8',8}$ 1.2 Hz); MS, *m*/*z*: 416 (M^+, 29%), calc. for $C_{24}H_{16}O_7$: 416.

6b: mp 297–298 °C; ^{1}H NMR (200 MHz, [$^2H_6$]DMSO), δ: 1.27 (t, 3H, Me′, $J_{CH_2',Me'}$ 7.7 Hz), 1.35 (t, 3H, Me, $J_{CH_2,Me}$ 7.6 Hz), 2.44 (d, 3H, 4′-Me, $J_{3',Me'}$ 1.0 Hz), 2.52 (d, 3H, 4-Me, $J_{3,Me}$ 1.0 Hz), 2.73 (q, 2H, CH_2′, $J_{Me',CH_2'}$ 7.7 Hz), 2.96 (q, 2H, CH_2, J_{Me,CH_2} 7.6 Hz), 5.58 (d, 1H, 9′-OH, $J_{9',9'\text{-}OH}$ 7.2 Hz), 5.84 (dd, 1H, 9′-H, $J_{9'\text{-}OH,9'}$ 7.2 Hz, $J_{8',9'}$ 7.1 Hz), 6.15 (dd, 1H, 8′-H, $J_{9',8'}$ 7.1 Hz, $J_{8,8'}$ 1.1 Hz), 6.19 (q, 1H, 3′-H, $J_{Me',3'}$ 1.0 Hz), 6.36 (q, 1H, 3-H, $J_{Me,3}$ 1.0 Hz), 7.55 (s, 1H, 5-H), 7.57 (s, 1H, 5′-H), 8.09 (d, 1H, 8-H, $J_{8',8}$ 1.1 Hz); MS, *m*/*z*: 472 (M^+, 28%), calc. for $C_{28}H_{24}O_7$: 472.

7a: mp 319–320 °C; ^{1}H NMR (200 MHz, [$^2H_6$]DMSO), δ: 2.51 (2d, 6H, 4-Me and 4′-Me), 6.34 (q, 1H, 3′-H, $J_{Me',3'}$ 1.0 Hz), 6.44 (q, 1H, 3-H, $J_{Me,3}$ 1.0 Hz), 7.54 (d, 1H, 6′-H, $J_{5',6'}$ 8.7 Hz), 7.64 (d, 1H, 6-H, $J_{5,6}$ 8.9 Hz), 7.66 (d, 1H, 5-H, $J_{6,5}$ 8.9 Hz), 7.78 (d, 1H, 5′-H, $J_{6',5'}$ 8.7 Hz), 7.91 (s, 1H, 9′-H), 8.65 (s, 1H, 8-H); MS, *m*/*z*: 398 (M^+, 100%), calc. for $C_{24}H_{14}O_6$: 398.

7b: mp 315–316 °C; ^{1}H NMR (200 MHz, [$^2H_6$]DMSO), δ: 1.36 (2t, 6H, Me and Me′), 2.51 (2d, 6H, 4-Me and 4′-Me), 2.99 (2q, 4H, CH_2 and CH_2′), 6.31 (q, 1H, 3′-H, $J_{Me',3'}$ 0.9 Hz), 6.40 (q, 1H, 3-H, $J_{Me,3}$ 0.9 Hz), 7.47 (s, 1H, 5-H), 7.59 (s, 1H, 5′-H), 7.86 (s, 1H, 9′-H), 8.67 (s, 1H, 8-H); MS, *m*/*z*: 454 (M^+, 100%), calc. for $C_{28}H_{22}O_6$: 454.

References

1 F. Dall'Acqua, D. Vedaldi, S. Caffieri, A. Guiotto, P. Rodighiero, F. Baccichetti, F. Carlassare and F. Bordin, *J. Med. Chem.*, 1981, **24**, 178.
2 A. Guiotto, P. Rodighiero, P. Manzini, G. Pastorini, F. Bordin, F. Baccichetti, F. Carlassare, D. Vedaldi, F. Dall'Acqua, M. Tamaro, G. Recchia and M. Cristofolini, *J. Med. Chem.*, 1984, **27**, 959.
3 F. Bordin, F. Carlassare, F. Baccichetti, A. Guiotto, P. Rodighiero, D. Vedaldi and F. Dall'Acqua, *Photochem., Photobiol.*, 1979, **29**, 1063.
4 F. Dall'Acqua, D. Vedaldi, A. Guiotto, P. Rodighiero, F. Carlassare, F. Baccichetti and F. Bordin, *J. Med. Chem.*, 1981, **24**, 806.
5 A. Guiotto, P. Rodighiero, G. Pastorini, P. Manzini, F. Bordin, F. Baccichetti, F. Carlassare, D. Vedaldi and F. Dall'Acqua, *Eur. J. Med. Chem.-Chim. Ther.*, 1981, **16**, 489.
6 F. Dall'Acqua, D. Vedaldi, F. Bordin, F. Baccichetti, F. Carlassare, M. Tamaro, P. Rodighiero, G. Pastorini, A. Guiotto, G. Recchia and M. Cristofolini, *J. Med. Chem.*, 1983, **26**, 870.
7 D. Vedaldi, F. Dall'Acqua, F. Baccichetti, F. Carlassare, F. Bordin, P. Rodighiero, P. Manzini and A. Guiotto, *Farmaco.*, 1991, **46**, 1381.
8 V. F. Traven, D. V. Kravtchenko and T. A. Chibisova, *Mendeleev Commun.*, 1995, 21.
9 V. F. Traven, D. V. Kravtchenko, T. A. Chibisova, S. V. Shorshnev, R. Eliason and D. H. Wakefield, *Heterocyclic Commun.*, 1996, **2**, 345.
10 H. Wang and L. D. Kispert, *J. Chem. Soc., Perkin Trans. 2*, 1989, 1463.

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