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Synthesis of thio- and oxo-analogues of isopsoralen

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Abstract—A range of novel 5′-substituted 7-oxo and 7-thioisopsoralens were synthesized via a Claisen rearranged allyl aryl ether followed by reductive ozonolysis in the presence of a suitable solvent. In some cases dimethylthiocarbamoyl chloride was used as a protecting group and to introduce the thiol moiety.

1. Introduction

Coumarin derivatives such as psoralens and isopsoralens (angelicin) are a class of natural and synthetic compounds, which exhibit photo-biological and photo-therapeutic properties.[1] This has resulted in the widespread use of these compounds as a treatment for topical skin diseases such as psoriasis and vitiligo,[2,3] as well as probes for nucleic acid structure and function,[4] and have proved to be useful model compounds for mutagenesis and repair studies.[5] They have recently also been shown to be effective against cutaneous T-cell lymphoma and other autoimmune diseases.[6] The biological activity of psoralens is due to their activity towards DNA, to which they are able to bind covalently via photo-addition reactions with the base pairs of the DNA helix, after exposure to UVA radiation (320–400 nm) thus hindering cellular replication.

There has therefore been great interest in the synthesis of these compounds in recent years,[7–9] with emphasis on the synthesis of new analogues with enhanced activity than those which have seen general clinical use, such as 8-methoxypsoralen (8-MOP), 5-methoxypsoralen (5-MOP), and 4,5′,8-trimethylpsoralen. These compounds are photoinduced to form interstrand crosslinks, which have been found to be responsible for the undesired side effects of PUVA (psoralen plus UVA) treatment, namely the risk of skin cancer and skin phototoxicity.[2,10] As a result of these undesired effects, isopsoralen analogues have been studied due to their angular structure, which prevents interstrand crosslinks between the base pairs of the DNA helix. This allows only monoadducts to form, which has been shown to result in the reduction of the unwanted side effects, whilst still maintaining the desired biological activity.[11,12]

Keywords: benzopyrans; rearrangements; ozonolysis.

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2. Results and discussion

Our interest in these compounds lies in developing a new route to the synthesis of 5′-substituted derivatives of 7-oxo- and 7-thioisopsoralen derivatives. The general approach to the 7-oxo-5′-substituted psoralens is outlined in Scheme 1. The allyl aryl coumarins (**3a**,**b**) were isolated in high yields from 7-hydroxycoumarin (**1**), and these molecules were subsequently rearranged under thermal conditions to afford regioselective rearrangement to the 8-position in good yield. 8-Allyl-7-hydroxycoumarin (**4a**) was subsequently treated with ozone, followed by reductive workup with dimethyl sulfide to afford the aldehyde (**5**).

This aldehyde (**5a**) was isolated, as the hemiacetal (**6a**). This underwent nucleophilic substitution in the presence of the solvent methanol, to afford the novel compound 8-methoxy-8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-one (**7a**) in 66% yield, which was characterised by NMR spectroscopy and X-ray diffraction analysis (Fig. 1). From the crystal structure it can be observed that the isopsoralen derivative lies in the monoclinic crystal system with the space group being $P2_1/a$. The two enantiomers are related by a centre of inversion in the space group. The crystal structure also shows the expected planarity of the molecule, and in the solid state the molecules are shown to be packed tightly together in the unit cell, indicating the potential for π-stacking of these compounds and hence the potential for intercalation into the DNA double helix.

The hemiacetal (**6a**) was isolated from reactions carried out in THF, and was shown to be surprisingly stable. Dehydration of the hemiacetal in the presence of *p*-toluene sulfonic acid afforded the known isopsoralen[13] **8a** in high yield. A range of other *o*-substituted nucleophiles was incorporated into the system by making use of various other alcoholic solvents viz. ethanol, isopropanol, and *tert*-butanol. These afforded the isopsoralen derivatives **7b**–**d**.

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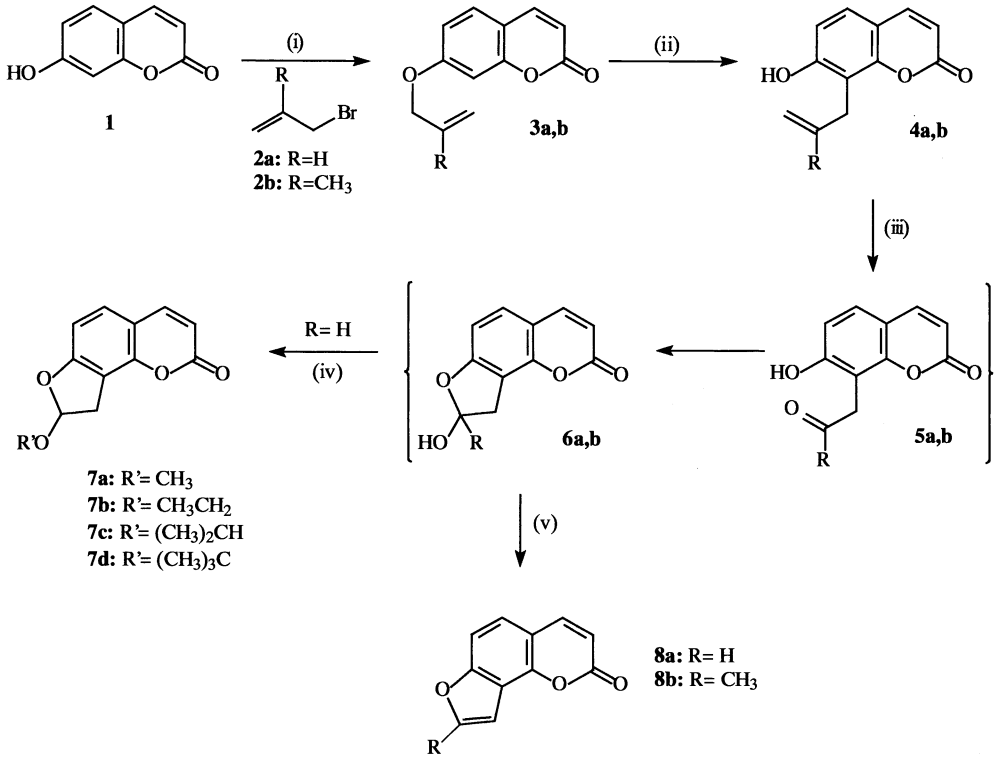


Scheme 1. (i) K_2CO_3, acetone, reflux, 92% **3a** and 86% **3b**; (ii) *N*,*N*-Diethylaniline, reflux, 3 h, 84% **4a** and 77% **4b**; (iii) O_3, THF, −78°C, then dimethyl sulfide, −10°C to rt; (iv) R′OH, 66–75%; (v) *p*-toluene sulfonic acid, toluene, reflux, 100% **8a** and **b**.

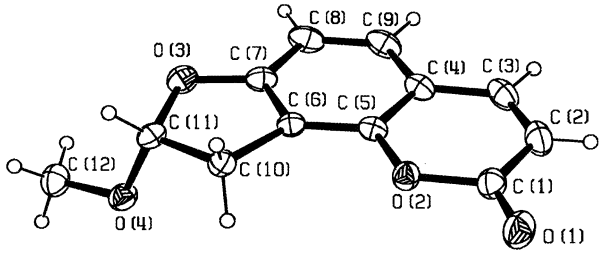


Figure 1.

Extension of this work to include other moieties at the 5′-position was also carried out, by making use of 3-bromo-2-methylpropene (**2b**) instead of allyl bromide (**2a**). In the case where R=CH_3, cyclisation of the ketone (**5b**) to the hemiacetal (**6b**) initially failed to take place (!). This may be attributed to the electron releasing methyl group resulting in a less electrophilic carbonyl. However, cyclisation of the ketone intermediate (**5b**) was induced in refluxing toluene containing *p*-toluene sulfonic acid as a catalyst, this then afforded the dehydrated product and known isopsoralen[14] **8b** in quantitative yield. The success of this reaction may be attributed to the formation of the carbocation intermediate (**9**) formed by the protonation of the carbonyl by the *p*-toluene sulfonic acid (Fig. 2). This carbocation would then undergo rapid cyclisation and dehydration to afford the expected product.

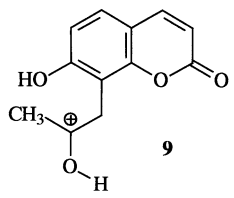
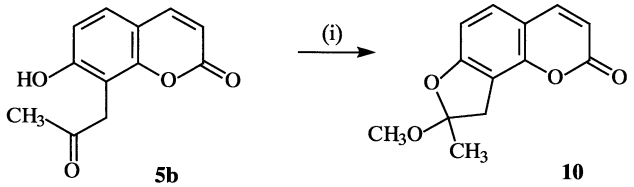


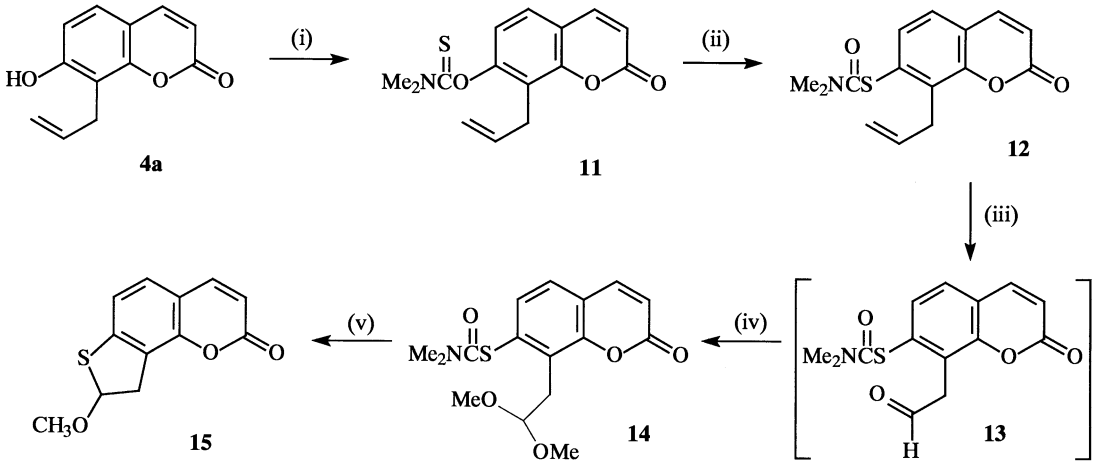
Figure 2.

The cyclisation reaction was then repeated in the presence of methanol (Scheme 2) in order to bring about the nucleophilic substitution of the methoxy group, which should occur more readily than the dehydration reaction. This procedure afforded the expected isopsoralen derivative (**10**) in quantitative yield.



Scheme 2. (i) Methanol, *p*-TSA, 4 Å molecular sieve, reflux, 100%.

Attention has subsequently been directed towards extending this approach to include a sulfur heteroatom into the isopsoralen ring system. This was successfully achieved by the method outlined in Scheme 3. Methods exist in the literature by which the alcohol moiety may be converted into a thiol;[15] however, if one converts the hydroxyl moiety directly into the thiol, it has been shown that during the Claisen rearrangement the thiol reacts with the alkene to afford a variety of undesired products.[16] As a result of this problem, dimethylthiocarbamoyl chloride was utilised, thus allowing for the conversion of the alcohol moiety into a



Scheme 3. (i) DMF, NaH, then Me_2NCSCl, 96%; (ii) 240°C, 86%; (iii) THF, O_3, −78°C, then dimethyl sulfide, −10°C to rt; (iv) MeOH, *p*-TSA, reflux, 84%; (v) CH_3OH, KOH, reflux, then H^+, H_2O, 29%.

protected thiol. Subsequent deprotection could then be performed only after the terminal alkene had been cleaved via ozonolysis. In this approach the alcohol moiety of the Claisen rearranged allyl aryl ether was converted into the dimethylcarbamothioate (**11**), which was subsequently thermally rearranged to afford *S*-(8-allyl-2-oxo-2*H*-chromen-7-yl) *N*,*N*-dimethylcarbamothioate (**12**).

Ozonolysis in THF followed by reductive workup with dimethyl sulfide, afforded the aldehyde (**13**), which was subsequently protected as the acetal (**14**). Deprotection and cleavage of the dimethylcarbamothioate group in methanol afforded the crystalline thio-isopsoralen, 8-methoxy-8,9-dihydro-2*H*-thieno[2,3-*h*]chromen-2-one (**15**) in 29% yield.

3. Conclusion

In conclusion, a range of novel oxo-analogues and one thio-analogue of isopsoralen have been synthesized in moderate to good yields. Various investigations into the observed regioselectivity and extention of this approach to include selenium heteroatoms are currently under investigation.

4. Experimental

4.1. General

NMR spectra were obtained from $CDCl_3$ or CD_3OD solutions on a Varian Unity-Inova 500 MHz spectrometer and are referenced using the solvent signals (δ_H 7.26 and δ_C 77.0 ppm for $CDCl_3$). Low-resolution mass spectra were recorded by a Hewlett Packard 5890 mass spectrometer and high-resolution data on a Kratos MS80RF double-focusing magnetic sector instrument (Cape Technikon Mass Spectrometry Unit). Melting points were recorded using a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer spectrum one. All solvents were dried prior to use. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh; particle size 0.040–0.063 nm).

4.1.1. 7-(Allyloxy)-2*H*-chromen-2-one (3a). 3-Bromo-1-propene (**2a**) (5.71 ml, 66 mmol) was added dropwise under dry nitrogen to a stirred mixture of 7-hydroxy-coumarin (5.0 g, 30 mmol) and anhydrous K_2CO_3 (5.8 g, 41 mmol) in dry acetone (150 ml). The resulting mixture was then boiled under reflux for 5 h, after which it was allowed to cool, and the K_2CO_3 filtered off and washed with fresh acetone. The solvent was removed in vacuo and the resulting crystals recrystallised from methanol to afford, as pale, cream-yellow crystals, 7-(allyloxy)-2*H*-chromen-2-one (**3a**) (5.62 g, 92%), mp 78–79°C (from methanol) (lit.,[14] 93–93.5°C) Found: M^+ 202.06349, $C_{12}H_{10}O_3$ requires *M*, 202.06299; ν_{max}(KBr) cm^{-1} 1723 and 1614; δ_H (500 MHz, $CDCl_3$) 4.60 (2H, d, $J_{1',2'}$= 5.3 Hz, 1′-CH_2), 5.34 (1H, dd, J_{cis}=10.4 and J_{gem}=1.2 Hz, C=C*H*) and 5.44 (1H, dd, J_{trans}=17.2 and J_{gem}=1.2 Hz, C=C*H*), 6.05 (1H, ddt, J_{trans}=17.2, J_{cis}=10.4 and $J_{2',1'}$= 5.3 Hz, 2′-H), 6.26 (1H, d, $J_{3,4}$=9.4 Hz, 3-H), 6.83 (1H, d, $J_{8,6}$=2.3 Hz, 8-H), 6.87 (1H, dd, $J_{6,8}$=2.3 and $J_{6,5}$=8.5 Hz, 6-H), 7.38(1H, d, $J_{5,6}$=8.6 Hz, 5-H) and 7.64 (1H, d, $J_{4,3}$= 9.4 Hz, 4-H); δ_C (125 MHz, $CDCl_3$) 69.9 (C-1′), 102.4 (C-8), 113.2 (C-4a), 113.80 (C-3), 113.86 (C-6), 119.2 (C-3′), 129.4 (C-5), 132.8 (C-2′), 114.0 (C-4), 156.5 (C-8a), 161.8 (C-7) and 162.4 (C-2); *m*/*z* 202 (M^+, 100%) and 187 (71).

4.1.2. 8-Allyl-7-hydroxy-2*H*-chromen-2-one (4a). 7-(Allyloxy)-2*H*-chromen-2-one (**3a**) (5.0 g, 24.7 mmol) was dissolved in *N*,*N*-diethylaniline (50 ml) in a two-necked flask attached to a nitrogen line and boiled under reflux at ca. 220°C for 3 h. The reaction mixture was then cooled, during which precipitation of some of the product occurred; hexane (40 ml) was added in order to precipitate out the remaining product. The precipitate was filtered, washed with hexane, dried by vacuum filtration, and recrystallised from ethyl acetate to yield, as cream crystals, 8-allyl-7-hydroxy-2*H*-chromen-2-one (**4a**) (4.2 g, 84%), mp 151–153°C (from ethyl acetate) (lit.,[14] 165–166°C) Found: M^+ 202.06313, $C_{12}H_{10}O_3$ requires *M*, 202.06299; ν_{max}(KBr) cm^{-1} 3332, 1699 and 1600; δ_H (500 MHz, $CDCl_3$) 2.81 (1H, s, OH), 2.81 (1H, s, OH), 3.61 (2H, d, $J_{1',2'}$=6.2 Hz, 1′-CH_2), 5.0 (1H, dd, J_{cis}=10.1 and J_{gem}=1.8 Hz, C=C*H*) and 5.12 (1H, dd, J_{trans}=17.2 and J_{gem}=1.8 Hz, C=C*H*), 6.01 (1H, ddt, J_{trans}=17.2,

J_{cis}=10.1 and $J_{2',1'}$=6.2 Hz, 2′-H), 6.20 (1H, d, $J_{3,4}$=9.6 Hz, 3-H), 6.80 (1H, d, $J_{6,5}$=8.5 Hz, 6-H), 7.21 (1H, d, $J_{5,6}$=8.5 Hz, 5-H) and 7.64 (1H, d, $J_{4,3}$=9.6 Hz, 4-H); δ_C (125 MHz, $CDCl_3$) 27.3 (C-1′), 112.2 (C-3), 112.7 (C-4a), 113.2 (C-6), 114.7 (C-8), 115.9 (C-3′), 127.2 (C-5), 135.7 (C-2′), 145.1 (C-4), 154.2 (C-8a), 159.5 (C-7) and 162.9 (C-2); *m/z* 202 (M^+, 100%) and 187 (75).

4.1.3. 8-Methoxy-8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-one (7a). 8-Allyl-7-hydroxy-2*H*-chromen-2-one (**4a**) (2.0 g, 9.9 mmol) was dissolved in THF (60 ml) and placed in a three-necked flask fitted with a reflux condenser and attached to an ozone generator and two traps containing acidified 1.1 M KI solution to mop up any unreacted ozone. The flask was cooled to −78°C in a solid CO_2/acetone bath. Ozone was passed through the mixture for 100 min at a rate of ca. 1 ml/min, after which analysis by TLC showed no starting material to be present. Dimethyl sulfide (0.9 ml, 12.4 mmol) was added, the reaction mixture warmed to −10°C (salt/ice bath), and stirred for 3 h, allowing the mixture to slowly warm to room temperature. Methanol (30 ml) was then added, and the mixture was boiled under reflux for 3 h and left stirring overnight. The solvent was removed in vacuo to leave a dark orange oil from which the product crystallized out as orange crystals. This was then recrystallised from methanol to afford 8-methoxy-8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-one (**7a**) (1.43 g, 66%), mp 144–145°C (from methanol) Found: M^+ 218.05846, $C_{12}H_{10}O_4$ requires *M*, 218.05791; ν_{max}(KBr) cm^{-1} 1724 and 1615; δ_H (500 MHz, $CDCl_3$) 3.24 (1H, dd, J_{gem}=17.1 and $J_{9a,8}$=2.3 Hz, 9-CH_a) and 3.45 (1H, dd, J_{gem}=17.1 and $J_{9b,8}$=6.6 Hz, 9-CH_b), 3.56 (3H, s, CH_3), 5.80 (1H, dd, $J_{8,9a}$=2.3 and $J_{8,9b}$=6.6 Hz, 8-H), 6.22 (1H, d, $J_{3,4}$=9.6 Hz, 3-H), 6.81 (1H, d, $J_{6,5}$=8.2 Hz, 6-H), 7.30 (1H, d, $J_{5,6}$=8.2 Hz, 5-H) and 7.64 (1H, d, $J_{4,3}$=9.6 Hz, 4-H); δ_C (125 MHz, $CDCl_3$) 34.28 (9-CH_2), 56.93 (1′-CH_3), 107.9 (C-6), 109.8 (C-8), 113.1 (C-9a), 113.2 (C-3), 114.1 (C-4a), 129.4 (C-5), 144.9 (C-4), 151.9 (C-9b), 161.7 (C-2) and 162.8 (C-6a); *m/z* 218 (M^+, 100%) and 187 (60).

4.1.4. 8-Ethoxy-8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-one (7b). 8-Allyl-7-hydroxy-2*H*-chromen-2-one (**4a**) (0.80 g, 3.96 mmol) was dissolved in THF (40 ml) and ozone was passed through the system for ca. 80 min at −78°C. Dimethyl sulfide (0.4 ml, 5.5 mmol) was added, and following the procedure outlined for the synthesis of 8-methoxy-8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-one (**7a**) yielded, as yellow crystals, 8-ethoxy-8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-one (**7b**) (0.62 g, 67%) mp 107–109°C (from ethanol) Found: M^+ 232.07441, $C_{13}H_{12}O_4$ requires *M*, 232.07356; ν_{max}(KBr) cm^{-1} 1726 and 1613; δ_H (500 MHz, $CDCl_3$) 1.26 (3H, t, $J_{2',1'}$=7.1 Hz, 2′-CH_3), 3.23 (1H, dd, J_{gem}=16.9 and $J_{9a,8}$=2.5 Hz, 9-CH_a) and 3.45 (1H, dd, J_{gem}=16.9 and $J_{9b,8}$=6.7 Hz, 9-CH_b), 3.69 and 3.95 (2H, 2×dq, J_{gem}=9.4 and $J_{1',2'}$=7.1 Hz, 1′-CH_2), 5.91 (1H, dd, $J_{8,9a}$=2.5 and $J_{8,9b}$=6.7 Hz, 8-H), 6.21 (1H, d, $J_{3,4}$=9.4 Hz, 3-H), 6.79 (1H, d, $J_{6,5}$=8.2 Hz, 6-H), 7.29 (1H, d, $J_{5,6}$=8.2 Hz, 5-H) and 7.64 (1H, d, $J_{4,3}$=9.4 Hz, 4-H); δ_C (125 MHz, $CDCl_3$) 15.68 (2′-CH_3), 34.38 (9-CH_2), 65.45 (1′-CH_2), 107.91 (C-6), 108.67 (C-8), 113.08 (C-3), 113.14 (C-9a), 113.96 (C-4a), 129.37 (C-5), 144.72 (C-4),151.99 (C-9b), 61.72 (C-2) and 162.84 (C-6a); *m/z* 232 (M^+, 79%) and 175 (100).

4.1.5. 8-Isopropoxy-8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-one (7c). 8-Allyl-7-hydroxy-2*H*-chromen-2-one (**4a**) (0.80 g, 3.96 mmol) was dissolved in THF (40 ml) and ozone was passed through the system for ca. 80 min at −78°C. Dimethyl sulfide (0.4 ml, 5.5 mmol) was added, and following the procedure outlined for the synthesis of 8-methoxy-8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-one (**7a**) yielded, as an orange oil from which yellow crystals crystallised out, 8-isopropoxy-8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-one (**7c**) (0.73 g, 75%) mp 117–119°C (from isopropanol) Found: M^+ 246.08952, $C_{14}H_{14}O_4$ requires *M*, 246.08921; ν_{max}(KBr) cm^{-1} 3419, 1625 and 1715; δ_H (500 MHz, $CDCl_3$) 1.20–1.25 [6H, 2×d, *J*=6.1 Hz, $CH(CH_3)_2$], 3.23 (1H, dd, J_{gem}=16.9 and $J_{9a,8}$=2.4 Hz, 9-CH_a) and 3.45 (1H, dd, J_{gem}=16.9 and $J_{9b,8}$=6.9 Hz, 9-CH_b), 4.08 (1H, heptet, *J*=6.2 Hz, 1′-H), 6.01 (1H, dd, $J_{8,9a}$=2.4 and $J_{8,9b}$=6.9 Hz, 8-H), 6.23 (1H, d, $J_{3,4}$=9.4 Hz, 3-H), 6.79 (1H, d, $J_{6,5}$=8.2 Hz, 6-H), 7.29 (1H, d, $J_{5,6}$=8.2 Hz, 5-H) and 7.64 (1H, d, $J_{4,3}$=9.4 Hz, 4-H); δ_C (125 MHz, $CDCl_3$) 22.0 and 23.6 [$CH(CH_3)_2$], 34.2 (9-CH_2), 71.8 (C-1′), 106.2 (C-8), 107.4 (C-6), 107.6 (C-4a), 112.5 (C-3), 112.8 (C-9a), 128.9 (C-5), 144.3 (C-4), 151.6 (C-9b), 160.8 (C-6a) and 162.4 (C-2); *m/z* 246 (M^+, 53%), 204 (44) and 175 (100).

4.1.6. 8-(*tert*-Butoxy)-8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-one (7d). 8-Allyl-7-hydroxy-2*H*-chromen-2-one (**4a**) (0.80 g, 3.96 mmol) was dissolved in THF (40 ml) and ozone was passed through the system for 80 min at −78°C. Dimethyl sulfide (0.4 ml, 5.5 mmol) was added, and following the procedure outlined for the synthesis of 8-methoxy-8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-one (**7a**) yielded, as an orange oil from which the product crystallised out as yellowish crystals, 8-(*tert*-butoxy)-8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-one (**7d**) (0.74 g, 71%) mp 119–122°C (from *tert*-butanol) Found: M^+ $-C(CH_3)_3$, 204.04375, $C_{11}H_7O_4$ requires *M*, 203.03443; ν_{max}(KBr) cm^{-1} 3385, 1729 and 1621; δ_H (500 MHz, $CDCl_3$) 1.25 (9H, s, $C(CH_3)_3$), 3.24 (1H, dd, J_{gem}=17.0 and $J_{9a,8}$=2.3 Hz, 9-CH_a) and 3.43 (1H, dd, J_{gem}=17.0 and $J_{9b,8}$=6.6 Hz, 9-CH_b), 5.79 (1H, dd, $J_{8,9a}$=2.3 and $J_{8,9b}$=6.6 Hz, 8-H), 6.21 (1H, d, $J_{3,4}$=9.6 Hz, 3-H), 6.80 (1H, d, $J_{6,5}$=8.2 Hz, 6-H), 7.29 (1H, d, $J_{5,6}$=8.2 Hz, 5-H) and 7.64 (1H, d, $J_{4,3}$=9.6 Hz, 4-H); δ_C (125 MHz, $CDCl_3$) 29.9 [$C(CH_3)_3$], 33.8 (9-CH_2), 102.7 (C-1′), 107.5 (C-6), 109.3 (C-8), 112.7 (C-3), 113.6 (C-4a), 125.1 (C-9a), 129.0 (C-5), 144.3 (C-5), 151.5 (C-9b), 161.3 (C-6a) and 162.3 (C-2); *m/z* 260 (M^+, 16%), 204 (67) and 176 (100).

4.1.7. 8-Hydroxy-8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-one (6a). 8-Allyl-7-hydroxy-2*H*-chromen-2-one (**4a**) (1.0 g, 4.95 mmol) was dissolved in THF (40 ml) and ozone was passed through the system for 80 min at −78°C. Dimethyl sulfide (0.45 ml, 6.2 mmol) was added, the reaction mixture taken to −10°C (salt/ice bath), and stirred overnight, allowing the mixture to slowly warm to room temperature. The solvent was then removed in vacuo and the resulting residue was passed through a column (50:50 ethyl acetate/hexane as a running solvent) to yield, as white crystals, 8-hydroxy-8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-one (**6a**) (0.52 g, 51%), mp 137–139°C (from ethyl acetate) Found: M^+ 204.0426, $C_{11}H_8O_4$ requires *M*, 204.04226; ν_{max}(KBr) cm^{-1} 3302, 1689 and 1614; δ_H (500 MHz, CD_3OD) 3.19 (2H, d,

$J_{9,8}$=5.3 Hz, 9-CH_2), 4.89 (1H, t, $J_{8,9}$=5.3 Hz, 8-H), 6.21 (1H, d, $J_{3,4}$=9.4 Hz, 3-H), 6.88 (1H, d, $J_{6,5}$=8.5 Hz, 6-H), 7.31 (1H, d, $J_{5,6}$=8.5 Hz, 5-H) and 7.78 (1H, d, $J_{4,3}$=9.4 Hz, 4-H); δ_C (125 MHz, CD_3OD) 30.9 (9-CH_2), 98.2 (C-8), 111.5 (C-3), 111.9 (C-4a), 112.7 (C-9a), 113.8 (C-6), 127.7 (C-5), 145.9 (C-4), 154.4 (C-9b), 160.5 (C-6a) and 163.5 (C-2); *m/z* 204 (M^+, 34%), 174 (100) and 146 (75).

4.1.8. 2*H*-Furo[2,3-*h*]chromen-2-one (8a). 8-Hydroxy-8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-one (**6a**) (0.03 g, 0.15 mmol) was placed in a two-necked round bottomed flask containing THF (20 ml) and connected to a reflux condenser and a nitrogen line. *p*-Toluene sulfonic acid (0.01 g) and some 3 Å molecular sieve were added to the flask and the reaction mixture was boiled under reflux for 2 h. The mixture was then passed through a plug of silica gel to remove the catalyst, and the solvent removed under vacuum to afford 2*H*-furo[2,3-*h*]chromen-2-one (**8a**) (0.028 g, 100%), mp 131–132°C (from methanol) (lit.,[10] 137–137.5°C); ν_{max}(KBr) cm^{-1} 3385, 1709 and 1620; δ_H (500 MHz, CD_3OD) 6.35 (1H, d, $J_{3,4}$=9.4 Hz, 3-H), 6.59 (1H, d, $J_{9,8}$=2.2 Hz, 9-H), 6.98 (1H, d, $J_{8,9}$=2.2 Hz, 8-H), 7.21 (1H, d, $J_{5,6}$=8.3 Hz, 5-H), 7.39 (1H, d, $J_{6,5}$=8.3 Hz, 6-H) and 8.06 (1H, d, $J_{4,3}$=9.4 Hz, 4-H); δ_C (125 MHz, $CDCl_3$) 98.4 (C-9), 106.8 (C-6), 113.2 (C-3), 114.1 (C-4a), 117.6 (C-9a), 125.2 (C-5), 146.1 (C-4), 146.2 (C-8), 147.9 (C-9b), 156.8 (C-6a) and 161.2 (C-2); *m/z* 186 (M^+, 100%), 158 (94) and 102 (28).

4.1.9. 7-[(2-Methyl-2-propenyl)oxy]-2*H*-chromen-2-one (3b). 3-Bromo-2-methyl-1-propene (**2a**) (5 ml, 49.6 mmol) was added dropwise under nitrogen to a stirred mixture of 7-hydroxy coumarin (**1**) (4.02 g, 24.3 mmol) and K_2CO_3 (4.66 g) in dry acetone (130 ml). The mixture was then boiled under reflux for 5 h, allowed to cool, and the K_2CO_3 filtered and washed with fresh acetone. The solvent was then removed in vacuo and the residue recrystallised from methanol to afford 7-[(2-methyl-2-propenyl)oxy]-2*H*-chromen-2-one (**3b**) (4.55 g, 86%), mp 59–60°C (from methanol) Found: M^+ 216.07878, $C_{13}H_{12}O_3$ requires *M*, 216.07864; ν_{max}(KBr) cm^{-1} 1734, 1609 and 3454; δ_H (500 MHz, $CDCl_3$) 1.82 (3H, s, CH_3), 4.49 (2H, s, 1′-CH_2), 5.02 and 5.09 (2H, 2×s, 3′-CH_2), 6.24 (1H, d, $J_{3,4}$=9.6 Hz, 3-H), 6.81 (1H, d, $J_{8,6}$=2.4 Hz, 8-H), 6.86 (1H, d, $J_{6,5}$=8.7 and $J_{6,8}$=2.4 Hz, 6-H), 7.36 (1H, d, $J_{5,6}$=8.7 Hz, 5-H) and 7.63 (1H, d, $J_{4,3}$=9.6 Hz, 4-H); δ_C (125 MHz, $CDCl_3$) 19.9 (CH_3), 72.9 (1′-CH_2), 102.4 (C-8), 113.3 (C-4a), 113.7 (C-6), 113.8 (C-3), 114.2 (3′-CH_2), 129.4 (C-5), 140.4 (C-2′), 144.1 (C-4), 156.5 (C-8a), 161.9 (C-7) and 162.6 (C-2); *m/z* 216 (M^+, 100%) and 201 (61).

4.1.10. 7-Hydroxy-8-(2-methyl-2-propenyl)-2*H*-chromen-2-one (4b). 7-[(2-Methyl-2-propenyl)oxy]-2*H*-chromen-2-one (**3b**) (3.80 g, 17.6 mmol) was dissolved in *N*,*N*-diethyl-aniline (40 ml) in a flask fitted with a reflux condenser and nitrogen line and boiled under reflux for 3 h. The reaction mixture was then left to cool and hexane (40 ml) was added to precipitate out the product, which was then recrystallised from ethyl acetate to afford 7-hydroxy-8-(2-methyl-2-propenyl)-2*H*-chromen-2-one (**4b**) (2.95 g, 77%), mp 123–125°C (from ethyl acetate) Found: M^+ 216.07875, $C_{13}H_{12}O_3$ requires *M*, 216.07864; ν_{max}(KBr) cm^{-1} 3442, 1684 and 1603; δ_H (500 MHz, $CDCl_3$) 1.77 (3H, s, CH_3), 3.64 (2H, s, 1′-CH_2), 4.81 and 4.90 (2H, 2×s, 3′-CH_2), 6.25 (1H, d, $J_{3,4}$=9.4 Hz, 3-H), 6.56 (1H, br. s, OH), 8.86 (1H, d, $J_{6,5}$=8.5 Hz, 6-H), 7.27 (1H, d, $J_{5,6}$=8.5 Hz, 5-H) and 7.66 (1H, d, $J_{4,3}$=9.4 Hz, 4-H); δ_C (125 MHz, $CDCl_3$) 22.5 (CH_3), 31.4 (1′-CH_2), 112.5 (3′-CH_2), 112.6 (C-3), 112.8 (C-4a), 113.2 (C-8), 113.5 (C-6), 127.4 (C-5), 143.6 (C-2′), 144.6 (C-4), 153.7 (C-8a), 159.1 (C-7) and 162.1 (C-2); *m/z* 216 (M^+, 87%) and 201 (100).

4.1.11. 7-Hydroxy-8-(2-oxopropyl)-2*H*-chromen-2-one (5b). 7-Hydroxy-8-(2-methyl-2-propenyl)-2*H*-chromen-2-one (**4b**) (0.8 g, 3.7 mmol) was dissolved in dry methanol (40 ml) in a three necked round bottomed flask, cooled to −78°C (dry ice/acetone) and ozone was passed through the system for ca. 80 min. Dimethyl sulfide (0.33 ml, 4.57 mmol) was then added and the reaction mixture stirred overnight under nitrogen while allowing to warm to room temperature. The solvent was then removed in vacuo to leave an orange oil from which the final product crystallised out. This was then recrystallised from methanol to yield, as orange crystals, 7-hydroxy-8-(2-oxopropyl)-2-*H*chromen-2-one (**5b**) (0.56 g, 68%), mp 188–190°C (from methanol); Found: M^+ 218.05768, $C_{12}H_{10}O_4$ requires *M*, 218.05791; ν_{max}(KBr) cm^{-1} 3317, 1729 and 1614; δ_H (500 MHz, CD_3OD) 2.29 (3H, s, 3′-CH_3), 3.99 (2H, s, 1′-CH_2), 6.19 (1H, d, $J_{3,4}$=9.4 Hz, 3-H), 6.85 (1H, d, $J_{6,5}$=8.5 Hz, 6-H), 7.33 (1H, d, $J_{5,6}$=8.5 Hz, 5-H) and 7.75 (1H, d, $J_{4,3}$=9.4 Hz, 4-H); δ_C (125 MHz, CD_3OD) 29.4 (3′-CH_3), 37.8 (2′-CH_2), 109.5 (C-8), 111.3 (C-3), 112 (C-4a), 112.6 (C-6), 127.9 (C-5), 145.2 (C-4), 153.8 (C-8a), 159.9 (C-2), 162.7 (C-7) and 207.5 (C-2′); *m/z* 218 (M^+, 100%) and 187 (52).

4.1.12. 8-Methyl-2*H*-furo[2,3-*h*]chromen-2-one (8b). 7-Hydroxy-8-(2-oxopropyl)-2*H*-chromen-2-one (**5b**) (0.25 g, 1.25 mmol), and *p*-toluene sulfonic acid (0.05 g) were dissolved in toluene (20 ml) in a two necked round bottomed flask fitted with a Dean and Stark apparatus containing 4 Å molecular sieve, and a nitrogen line. The mixture was refluxed for 4 h to afford, on removal of solvent and after passing through a silica gel plug, a quantitative yield of 8-methyl-2*H*-furo[2,3-*h*]chromen-2-one (**8b**) as white crystals, mp 124–126°C (from toluene) (lit.,[14] 153–154°C) Found: M^+ 200.04702, $C_{12}H_8O_3$ requires *M*, 200.04734; ν_{max}(KBr) cm^{-1} 3317, 1705 and 1614; δ_H (500 MHz, CD_3OD) 2.38 (3H, s, 1′-CH_3), 6.39 (1H, d, $J_{3,4}$=9.1 Hz, 3-H), 6.78 (1H, s, 9-H), 7.40 (1H, d, $J_{6,5}$=8.5 Hz, 6-H), 7.43 (1H, d, $J_{5,6}$=8.5 Hz, 5-H) and 8.04 (1H, d, $J_{4,3}$=9.1 Hz, 4-H); δ_C (125 MHz, CD_3OD) 20.1 (1′-CH_3), 99.2 (C-9), 108.2 (C-6), 113.1 (C-3), 113.8 (C-4a), 118.1 (C-9a), 123.2 (C-5), 145.8 (C-4), 147.4 (C-9b), 157.4 (C-8), 157.5 (C-6a) and 161.9 (C-2); *m/z* 200 (M^+, 100%) and 171 (73).

4.1.13. 8-Methoxy-8-methyl-8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-one (10). 7-Hydroxy-8-(2-oxopropyl)-2*H*-chromen-2-one (**5b**) (0.25 g, 1.25 mmol), and *p*-toluene sulfonic acid (0.02 g) were dissolved in dry methanol in a two necked round bottomed flask fitted with a condenser and containing 4 Å molecular sieve. The mixture was then refluxed for 5 h under nitrogen, and was then passed through a plug of silica gel to remove the catalyst. Removal of the solvent then afforded, as white crystals, 8-methoxy-8-methyl-8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-one (**10**)

(0.29 g, 100%), mp 121–122°C (from methanol) Found: M^+ 232.07352, $C_{13}H_{12}O_4$ requires *M*, 232.073562; ν_{max}(KBr) cm^{-1} 2941, 1728 and 1615; δ_H (500 MHz, $CDCl_3$) 1.73 (3H, s, CH_3), 3.20 and 3.42 (2H, 2×d, J_{gem}=17.1 Hz, 9-CH_2), 3.32 (3H, s, OCH_3), 6.20 (1H, d, $J_{3,4}$=9.6 Hz, 3-H), 6.75 (1H, d, $J_{6,5}$=8.2 Hz, 6-H), 7.28 (1H, d, $J_{5,6}$=8.2 Hz, 5-H) and 7.63 (1H, d, $J_{4,3}$=9.6 Hz, 4-H); δ_C (125 MHz, $CDCl_3$) 24.2 (CH_3), 37.1 (9-CH_2), 50.2 (OCH_3), 106.8 (C-6), 112.3 (C-3), 112.9 (C-8), 113.0 (C-4a), 114.2 (C-9a), 128.8 (C-5), 144.1 (C-4), 151.1 (C-9b), 160.9 (C-6a) and 162.1 (C-2); *m/z* 232 (M^+, 100%), 201 (68) and 171 (52).

4.1.14. *O*-(8-Allyl-2-oxo-2*H*-chromen-7-yl) *N*,*N*-dimethylcarbamothioate (11). 8-Allyl-7-hydroxy-2*H*-chromen-2-one (**4a**) (2.0 g, 9.9 mmol) was dissolved in dry DMF (20 ml) in a two-necked flask fitted with a thermometer, reflux condenser, and nitrogen line, and NaH (0.53 g of a 50% oil dispersion, 11 mmol) was added. Once the evolution of hydrogen gas had ceased, dimethylthiocarbamoyl chloride (1.29 g, 10.5 mmol) was added and the reaction mixture was heated at 60°C for 30 min. The reaction mixture was then poured onto 50 ml cold water and the precipitate obtained was filtered, dried, and recrystallised from ethanol to afford, as cream crystals, *O*-(8-allyl-2-oxo-2*H*-chromen-7-yl) *N*,*N*-dimethylcarbamothioate (**11**) (2.71 g, 96%), mp 103–104°C (from ethanol) Found: M^+ 289.07775, $C_{15}H_{15}O_3SN$ requires *M*, 289.07727; ν_{max}(KBr) cm^{-1} 1723 and 1671; δ_H (500 MHz, $CDCl_3$) 3.38 and 3.47 (6H, 2×s, N(CH_3)$_2$), 3.54 (2H, d, $J_{1',2'}$=6.3 Hz, 1′-CH_2), 5.03 (1H, dd, J_{cis}=10 and J_{gem}=1.5 Hz, C=C*H*) and 5.08 (1H, dd, J_{trans}=17.1 and J_{gem}=1.6 Hz, C=C*H*), 5.95 (1H, ddt, J_{trans}=17.1, J_{cis}=10.0 and $J_{2',1'}$=6.3 Hz, 2′-H), 6.40 (1H, d, $J_{3,4}$=9.6 Hz, 3-H), 7.03 (1H, d, $J_{6,5}$=8.4 Hz, 6-H), 7.38 (1H, d, $J_{5,6}$=8.4 Hz 5-H) and 7.69 (1H, d, $J_{4,3}$=9.6 Hz, 4-H); δ_C (125 MHz, $CDCl_3$) 28.7 (C-1′), 39.5 and 44.1 [N(CH_3)$_2$], 116.5 (C-3), 116.8 (C-3′), 117.5 (C-4a), 121.1 (C-6), 122.4 (C-8), 126.5 (C-5), 135.1 (C-2′), 144.1 (C-4), 153.5 (C-8a), 155.4 (C-7), 161.2 (C-2) and 187.1 (*C*=S); *m/z* 289 (M^+, 24%) and 217 (100).

4.1.15. *S*-(8-Allyl-2-oxo-2*H*-chromen-7-yl) *N*,*N*-dimethylcarbamothioate (12). *O*-(8-Allyl-2-oxo-2*H*-chromen-7-yl)*N*,*N*-dimethylcarbamothioate (**11**) (2.7 g, 9.34 mmol) was heated neat in a two-necked flask containing a thermometer and nitrogen line to ca. 230°C for 40 min, cooled, and the residue recrystallised from ethanol to afford the rearranged product, *S*-(8-allyl-2-oxo-2*H*-chromen-7-yl) *N*,*N*-dimethylcarbamothioate (**12**) (2.32 g, 86%) mp 101–105°C (from EtOH) Found: M^+ 289.07765, $C_{15}H_{15}O_3SN$ requires *M*, 289.07727); ν_{max}(KBr) cm^{-1} 1723 and 1603; δ_H (500 MHz, $CDCl_3$) 3.02 and 3.14 (6H, 2×s, N(CH_3)$_2$), 3.81 (2H, d, $J_{1',2'}$=6.2 Hz, 1′-CH_2), 5.01–5.04 (2H, m, 3′-CH_2), 5.97 (1H, ddt, J_{trans}=17.6, J_{cis}=9.8 and $J_{2',1'}$=6.2 Hz, 2′-H), 6.44 (1H, d, $J_{3,4}$=9.6 Hz, 3-H), 7.36 (1H, d, $J_{6,5}$=8.2 Hz, 6-H), 7.46 (1H, d, $J_{5,6}$=8.2 Hz, 5-H) and 7.69 (1H, d, $J_{4,3}$=9.6 Hz, 4-H); δ_C (125 MHz, $CDCl_3$) 32.1 (1′-CH_2), 37.3 [N(CH_3)$_2$], 116.5 (3′-CH_2), 117.5 (C-3), 119.8 (C-4a), 125.8 (C-6), 132.8 (C-8), 133.4 (C-5), 133.5 (C-7), 135.1 (C-2′), 143.6 (C-4), 152.3 (C-8a), 160.6 (C-1) and 165.7 [N*C*(O)S]; *m/z* 289 (M^+, 30%) and 217 (100).

4.1.16. *S*-[8-(2,2-Dimethoxyethyl)-2-oxo-2*H*-chromen-7-yl] *N*,*N*-dimethylcarbamothioate (14). *S*-(8-Allyl-2-oxo-2*H*-chromen-7-yl) *N*,*N*-dimethylcarbamothioate (**12**) (1.0 g, 3.46 mmol), was dissolved in dry THF, cooled to −78°C, and ozone was passed through for 80 min until analysis by TLC showed the disappearance of starting material. Dimethyl sulfide (0.3 ml, 4.15 mmol) was then added and the mixture stirred at −10°C for 3 h while allowing to warm to room temperature. Methanol (20 ml), *p*-toluene sulfonic acid (20 mg) and some 4 Å molecular sieve were then added and the reaction mixture boiled under reflux for 4 h until TLC showed there was no starting material left. The volatile components were removed in vacuo and the final product purified via radial chromatography (50:50 ethyl acetate/hexane as a running solvent) to afford *S*-[8-(2,2-dimethoxyethyl)-2-oxo-2*H*-chromen-7-yl]-*N*,*N*-dimethylcarbamothioate (**14**) (0.99 g, 84%) mp 96–99°C (from methanol) Found: M^+ 337.09877, $C_{16}H_{19}O_5SN$ requires *M*, 337.09839; ν_{max}(KBr) cm^{-1} 2948, 1727 and 1654; δ_H (500 MHz, $CDCl_3$) 3.00 and 3.12 [6H, 2×s, N(CH_3)$_2$], 3.34 (6H, s, 2×OCH_3), 3.40 (2H, d, $J_{1',2'}$=5.7 Hz, 1′-CH_2), 4.69 (1H, t, $J_{2',1'}$=5.7 Hz, 2′-H), 6.43 (1H, d, $J_{3,4}$=9.4 Hz, 3-H), 7.35 (1H, d, $J_{6,5}$=8.2 Hz, 6-H), 7.45 (1H, d, $J_{5,6}$=8.2 Hz, 5-H) and 7.68 (1H, d, $J_{4,3}$=9.4 Hz, 4-H); δ_C (125 MHz, $CDCl_3$) 31.9 (1′-CH_2), 36.9 [N(CH_3)$_2$], 53.9 (2eOCH_3), 104 (C-2′), 117 (C-3), 119.2 (C-4a), 125.6 (C-6), 129.8 (C-8), 133.2 (C-5), 134.5 (C-7), 143.3 (C-4), 152.3 (C-8a), 160.1 (C-2) and 165.5 [N*C*(O)S]; *m/z* 337 (M^+, 28%), 234 (28) and 203 (100).

4.1.17. 8-Methoxy-8,9-dihydro-2*H*-thieno[2,3-*h*]chromen-2-one (15). *S*-[8-(2,2-Dimethoxyethyl)-2-oxo-2*H*-chromen-7-yl]-*N*,*N*-dimethylcarbamothioate (**14**) (0.8 g, 2.3 mmol) was added to a mixture of dry methanol containing KOH (0.168 g, 3 mmol) and heated under reflux for ca. 4 h, monitoring with TLC. The reaction mixture was then acidified with HCl and boiled under reflux for another two hours. Water (5 ml) was then added and the product was then extracted with ether (3×30 ml). The organic layer was dried with magnesium sulfate and removed under vacuum to yield, as an orange oil from which the product crystallised out, 8-methoxy-8,9-dihydro-2*H*-thieno[2,3-*h*]chromen-2-one (**15**) (0.156 g, 29%) mp 141–143°C (from methanol); Found: M^+ 234.03381, $C_{12}H_{10}O_3S$ requires *M*, 234.03507; ν_{max}(KBr) cm^{-1} 1718 and 1603; δ_H (500 MHz, $CDCl_3$) 3.38 (3H, s, CH_3), 3.51 (1H, dd, J_{gem}=17.3 and $J_{9a,8}$=5.5 Hz, 9-CH_a) and 3.78 (1H, d, J_{gem}=17.3 Hz, 9-CH_b), 5.54 (1H, d, $J_{8,9a}$=5.5 Hz, 8-H), 6.30 (1H, d, $J_{3,4}$=9.6 Hz, 3-H), 7.18 (1H, d, $J_{6,5}$=8.0 Hz, 6-H), 7.29 (1H, d, $J_{5,6}$=8.0 Hz, 5-H) and 7.66 (1H, d, $J_{4,3}$=9.6 Hz, 4-H); δ_C (125 MHz, $CDCl_3$) 40.1 (9-CH_2), 56.3 (1′-CH_3), 92.7 (C-8), 114.5 (C-3), 115.9 (C-9a), 118.8 (C-6), 125.3 (C-4a), 127.6 (C-5), 143.6 (C-4), 145.7 (C-6a), 150.6 (C-9b) and 160.6 (C-2); *m/z* 234 (M^+, 92%) and 203 (100).

4.2. X-Ray crystallography

The crystallographic measurements on 8-methoxy-8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-one (**7a**) were made using a Philips X-ray Generator with a 3 KW X-ray Tube and an Enraf Nonius CAD 4 diffractometer. The structure was solved using the direct methods program SHELXS-97,[17] as implemented by the crystallographic program OSCAIL.[18] The final model was plotted using ORTEP.[19] Detailed crystallographic data for compound **7a** have been deposited

at the Cambridge Crystallographic Data Centre (No. CCDC 169113) and are available on request.

Crystal data of compound **7a**. $C_{12}H_{10}O_4$, M=218.20, T=293(2) K, λ=0.71073 Å, monoclinic a=7.902(3), b=7.2686(14), c=17.500(5) Å, α=90.031(19)°, β=99.44(3)°, γ=90.00(3)°, V=991.6(5) Å^3, space group $P2_1/a$, Z=4, D_x=1.462 mg m^{-3}, μ=0.111 mm^{-1}, $F(000)$=456. Crystal size 1.40×0.80×0.25 mm^3; θ range for data collection 2.36–27.96°; index range $-10<h<10$, $-3<k<9$, $-4<l<23$; reflections collected 3555; independent reflections 2339 [$R_{(int)}$=0.0221]; refinement method full-matrix least-squares on F^2; data/restraints/parameters 2339:0:152; goodness-of-fit on F^2 1.209; $R(F)$ [$I>2(I)$]=0.0812; wR_2=0.3114; largest diff. peak and hole 0.594 and −0.419 e Å^{-3}

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