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A new convenient route to 2-oxoethoxycoumarins: key intermediates in the synthesis of natural products

Stefano Chimichi,[a,*] Marco Boccalini[a] and Barbara Cosimelli[b]

[a] *Centro CNR sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni e Dipartimento di Chimica Organica "U. Schiff", via della Lastruccia 13, I-50019 Sesto F.no (Firenze), Italy*
[b] *Dipartimento di Chimica Organica "A. Mangini", via S. Donato 15, I-40127 Bologna, Italy*

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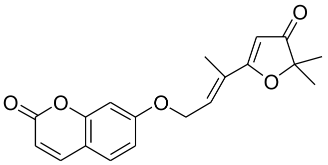
Abstract—A new synthetic route to coumarinyloxyaldehydes starting from hydroxycoumarins is presented; these compounds, useful intermediates in the preparation of natural products such as geiparvarin and psoralens, are now available in excellent yields with a simple workup procedure. Moreover the reported route has been applied to dihydroxycoumarins. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Only two approaches have been reported for the synthesis of 7-(2-oxoethoxy)coumarins[1] starting from the commercially available 7-hydroxycoumarin (umbelliferone). The first one was via ozonolysis of 7-(allyloxy)coumarins (37% overall yield)[1] whereas the other one involved the synthesis of 7-(2,3-dihydroxypropoxy)coumarin from the corresponding allyloxy derivative followed by its reductive cleavage (54% overall yield and long reaction times).[2] Since it has been reported that 7-(2-oxoethoxy)coumarin is a key intermediate for the synthesis of geiparvarin (**1**)[2,3] and in the light of its employment as an intermediate for the synthesis of psoralens (**2**), we wish to report here a new convenient and general procedure leading to 7-(2-oxoethoxy)coumarins that should serve as natural product precursors.



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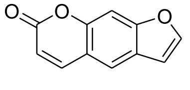

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2. Results and discussion

The synthetic methodology for the preparation of 7-(2-oxoethoxy)coumarins **7a–d** is depicted in Scheme 1. For accomplishing the transformation $RCO_2H \rightarrow RCHO$, the Rosenmund reduction[4] appears the most useful method. The Rosenmund reduction consisting in the selective palladium-catalyzed hydrogenation of an acyl chloride to the corresponding aldehyde was originally carried out by passing hydrogen through a hot solution (xylene or toluene) of the compound in which the catalyst is supported on $BaSO_4$.[4] Although it has often been useful to add catalyst regulators or modifiers to avoid the reduction of the resulting aldehyde,[5,6] it is not necessary to employ these precautions for acyl chlorides **6**; moreover, we observed that these compounds undergo reductive removal of the –COCl group to the corresponding hydrocarbon if xylene replaces toluene as solvent. Thus, 7-hydroxycoumarins were quantitatively converted into coumarin-7-yloxyacetic acids by reaction with ethyl bromoacetate and anhydrous potassium carbonate in freshly distilled acetone,[7] followed by treatment of the esters **4a–d** with sodium hydroxide in ethyl alcohol.[8] The new 7-(2-oxoethoxy)coumarins **7c**,**d** as well as the known compounds[1] **7a**,**b** were synthesized in quantitative yield from coumarin-7-yloxyacetic acids in two steps: first, the acids were converted into the corresponding acyl chlorides with thionyl chloride in chloroform;[9] then the 7-(2-oxoethoxy)coumarins **7a–d** were obtained by catalytic hydrogenation. We wish to point out that whereas in our hands the procedure of Smith et al.[2] gives the hydrate form of 7-(2-oxoethoxy)coumarins **7a–d**, our method gives rise directly to the target (anhydrous) compounds in much higher yields.

Moreover, the described procedure allowed us to synthesize also the new 4-(2-oxoethoxy)coumarin (**7e**) (Scheme 2) starting from 4-hydroxycoumarin (**3e**) in quantitative yield (application of Smith's method[2] gave **7e** in only 22% yield). Through this method the new, racemic, 2-[(coumarin-7-yl)oxy]propanal (**7f**) (Scheme 3) was obtained by reaction of **3a** with ethyl 2-bromopropionate. Good overall yields

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Keywords: hydroxycoumarins; coumarinyloxyaldehydes; Rosenmund reductions; natural product precursors.

[*] Corresponding author. Tel.: +39-055-457-3537; fax: +39-055-457-3568; e-mail: stefano.chimichi@unifi.it

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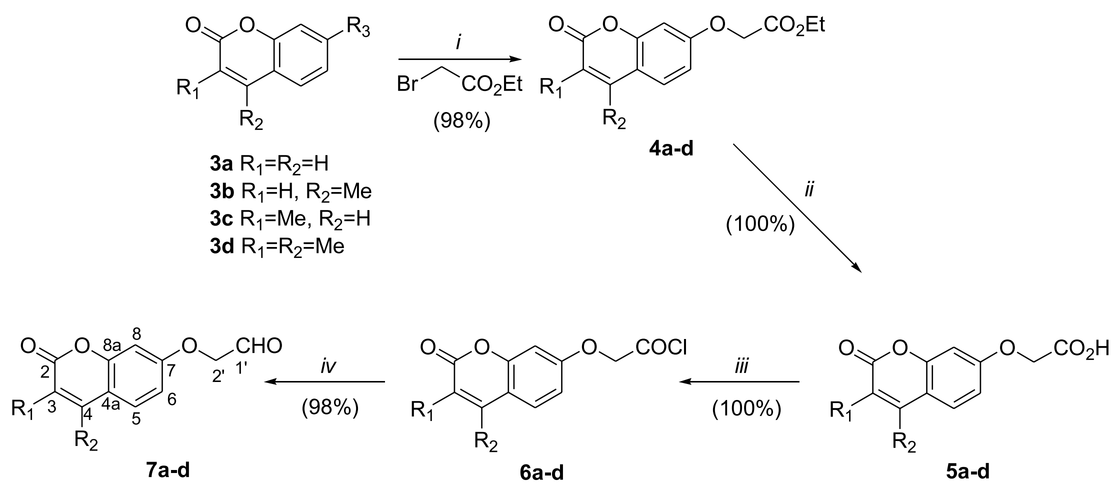
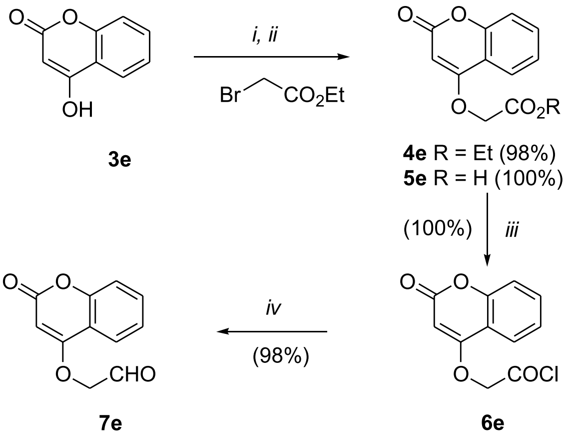
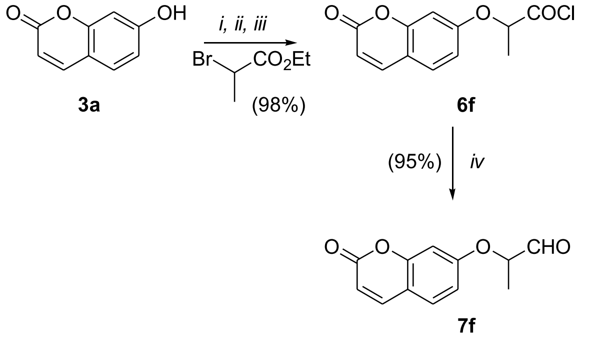


Scheme 1. (i) K_2CO_3, acetone, reflux 5 h; (ii) NaOH then HCl, EtOH; (iii) $SOCl_2$, $CHCl_3$ reflux 2 h; (iv) Rosenmund catalyst, toluene, H_2.



Scheme 2. (i) K_2CO_3, acetone, reflux 5 h; (ii) NaOH then HCl, EtOH; (iii) $SOCl_2$, $CHCl_3$ reflux 2 h; (iv) Rosenmund catalyst, toluene, H_2.

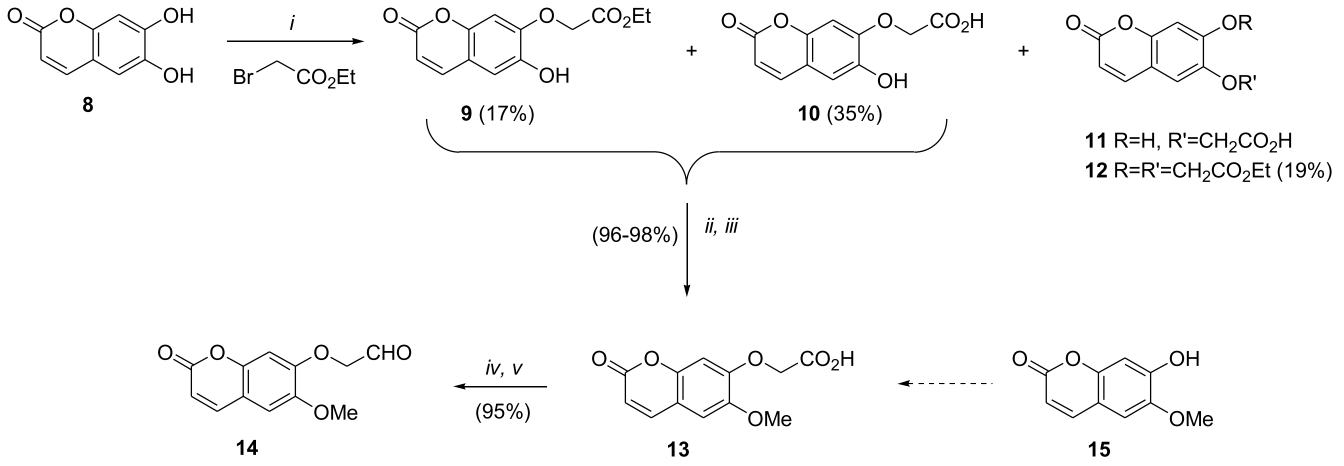


Scheme 3. (i) K_2CO_3, acetone, reflux 5 h; (ii) NaOH then HCl, EtOH; (iii) $SOCl_2$, $CHCl_3$ reflux 2 h; (iv) Rosenmund catalyst, toluene, H_2.

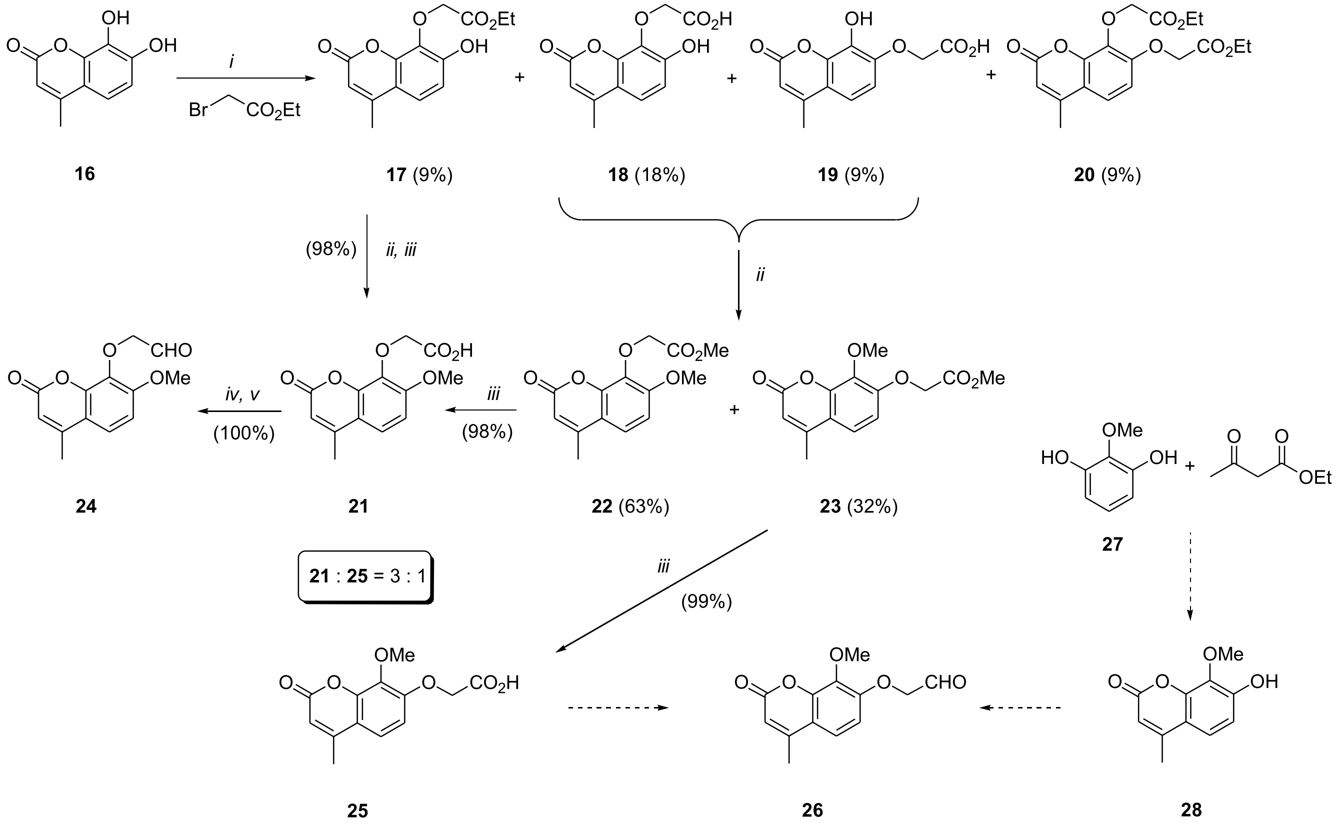
(95%) were achieved when the Rosenmund reduction was performed with: (*a*) absence of impurities such as thionyl chloride in the reaction mixture; (*b*) temperature in the range 125–130°C: for $T<125$°C the acyl chloride was quantitatively recovered; for $T>130$°C the 7-hydroxycoumarin (**3a**) together with traces of 7-allyloxycoumarin and 7-ethoxycoumarin was obtained.

The general applicability and the selectivity of the reported methodology were demonstrated employing dihydroxycoumarins as starting materials. Thus, from the commercially available 6,7-dihydroxycoumarin (esculetin) (**8**) and slightly different experimental conditions (see Section 4) we obtained the 6-methoxy-7-(2-oxoethoxy)coumarinylacetaldehyde (**14**) (50%, overall yield). As depicted in Scheme 4, the first step of the reaction gave a mixture of products from which we recovered the monoester **9** (17%) together with a small quantity of the starting product **8** (8%), the diester **12** (19%) and the monohydroxyacids **10** and **11** (35%) in the ratio 25:1, respectively. Treatment of compounds **9** and **10** with dimethyl sulfate and subsequent hydrolysis of the 6-methoxyesters gave the acid **13** that, by the usual procedure, led to the aldehyde **14**; the regiochemical assignment of this compound was achieved by nOe experiments. Once the complete assignment of protons has been obtained by ^{1}H and ^{13}C NMR mono- and bidimensional experiments, selective irradiation of H-5, showing a positive nOe effect on the methoxy group and on H-4, allowed us to attribute the regiochemistry to the product. It is interesting to note that the aldehyde **14** could also be obtained by the same procedure starting from the expensive 7-hydroxy-6-methoxycoumarin (**15**) (scopoletin).

While for the 6,7-dihydroxycompound **8** the most reactive OH group is that one at position 7, it is worthy note that for 7,8-dihydroxy-4-methylcoumarin (**16**),[10] the most reactive group is now that one at position 8 (ratio of acids **21** and **25** is 3:1). Thus, operating as depicted in Scheme 5, we obtained a crude product in which **17** and **18** are the predominant compounds. In particular, in the first step of the reaction we recovered after flash chromatography some unreacted **16** (41%); in spite of the high quantity of this material, the reported experimental conditions are the best ones to minimize the formation of the diester **20** (9%). Together with the monoester **17** (9%) we also obtained a mixture of the isomeric hydroxyacids **18** and **19**, ratio 2:1, respectively (27%). As before, compound **17** was treated with dimethyl sulfate and then hydrolyzed to give the acid **21** (98%), whereas methylation of **18** and **19** with dimethyl sulfate gave the corresponding esters **22** and **23** which were separated by flash-chromatography and then hydrolyzed to



Scheme 4. (i) K_2CO_3, DMF, rt 4 h, then HCl; (ii) $(MeO)_2SO_2$, K_2CO_3, acetone, reflux 5 h, then HCl; (iii) NaOH, EtOH, reflux 2 h then HCl; (iv) $SOCl_2$, $CHCl_3$, reflux 2 h; (v) Rosenmund catalyst, toluene, H_2.



Scheme 5. (i) NaOH, EtOH, rt overnight, then HCl; (ii) $(MeO)_2SO_2$, K_2CO_3, acetone, reflux 5 h, then HCl; (iii) NaOH, EtOH, reflux 2 h then HCl; (iv) $SOCl_2$, $CHCl_3$, reflux 2 h; (v) Rosenmund catalyst, toluene, H_2.

give an additional amount of **21** (18%) and the acid **25**, respectively. Structures of these isomeric compounds were once again attributed via ^{1}H NMR NOEDIF experiments. Finally, the acid **21** was converted into the corresponding acyl chloride to give the aldehyde **24**. Thus, whereas this procedure allows compound **24** to be obtained from 7,8-dihydroxycoumarin **16** in 25% overall yield, the isomeric aldehyde **26** could be more conveniently prepared with the reported methodology starting from the available 2-(methyloxy)-1,3-benzendiol (2-*O*-methylpyrogallol) (**27**)[11] through compound **28**.[12]

3. Conclusions

A new versatile synthetic route to 2-oxoethoxycoumarins is described. Besides the high yields for the syntheses of 7-coumarinyloxyaldehydes (compounds **7a–d**, **f**) and

4-coumarinyloxyacetaldehyde (**7e**), this methodology constitutes also a method for the preparation of mono aldehydes (**14**, **24** and **26**) starting from 6,7- and 7,8-dihydroxycoumarins.

4. Experimental

Melting points were measured using a Büchi apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 (operating at 50.29 MHz for ^{13}C), on Varian Gemini 300 (operating at 75.43 MHz for ^{13}C) and on Varian Mercury 400 (operating at 100.58 MHz for ^{13}C) instruments in the Fourier transform mode at 21±0.5°C in CDCl$_3$ or DMSO-d_6. Chemical shifts (δ) are in ppm relative to TMS as secondary internal reference standard; coupling constants are in Hz. Attributions of ^{13}C NMR resonances were performed on the basis of 'gated decoupled' or DEPT experiments. Mass spectra were registered with a Carlo Erba QMD 1000 instrument at 70 eV. IR spectra were recorded with a Perkin–Elmer 881 spectrophotometer in KBr pellets or nujol mull. Elemental analyses were obtained by Elemental Analyzer Perkin–Elmer 240C apparatus. Silica gel plates (Merck F$_{254}$) and silica gel 60 (Merck 230–400 mesh) were used for analytical tlc and for flash chromatographies, respectively. Solvents were removed under reduced pressure. Toluene was distilled from sodium; acetone and chloroform were distilled from phosphorous pentoxide.

4.1. Ethyl coumarinyloxyacetates 4a–f

Potassium carbonate (0.8 g, 5.8 mmol) was added to a solution of the requisite hydroxycoumarin (5.7 mmol) and ethyl bromoacetate or ethyl 2-bromopropionate (for **4f**) (5.7 mmol) in acetone (25 mL) and the reaction mixture was refluxed for 5 h. After filtration, the solution was concentrated under reduced pressure, dried in vacuo and the solid obtained was crystallized from ethanol.

4.1.1. Ethyl 2-[(2-oxo-2*H*-chromen-7-yl)oxy]acetate 4a. Colourless needles; 1.38 g (98%); mp 108.5–109.5°C [lit.[7] 113–115°C].

4.1.2. Ethyl 2-[(4-methyl-2-oxo-2*H*-chromen-7-yl)oxy]-acetate 4b. Colourless needles; 1.47 g (98%); mp 102–103°C [lit.[13] 101–103°C]; IR (KBr) 3061, 2984, 1745, 1711, 1611 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.46 (1H, d, ^{3}J=8.8 Hz, H-5), 6.84 (1H, dd, ^{3}J=8.8 Hz, ^{4}J=2.5 Hz, H-6), 6.71 (1H, d, ^{4}J=2.5 Hz, H-8), 6.09 (1H, q, ^{4}J=1.3 Hz, H-3), 4.63 (2H, s, 2′-CH$_2$), 4.23 (2H, q, ^{3}J=7.1 Hz, CH_2CH$_3$), 2.34 (3H, d, ^{4}J=1.3 Hz, 4-CH$_3$), 1.26 (3H, t, ^{3}J=7.1 Hz, CH$_2$$CH_3$); ^{13}C NMR (75.43 MHz, CDCl$_3$) δ 167.8 (s, C-1′), 160.9 (s, C-2), 160.5 (s, C-7), 154.9 (s, C-8a), 152.3 (s, C-4), 125.7 (d, C-5), 114.4 (s, C-4a), 112.4 (d, C-3), 112.4 (d, C-6), 101.6 (d, C-8), 65.2 (t, C-2′), 61.6 (t, CH_2CH$_3$), 18.5 (q, 4-CH$_3$), 14.0 (q, CH$_2$$CH_3$); EI-MS m/z (%) 262 (M$^+$, 92), 189 (37), 159 (39), 147 (100).

4.1.3. Ethyl 2-[(3-methyl-2-oxo-2*H*-chromen-7-yl)oxy]-acetate 4c. Colourless needles; 1.47 g (98%); mp 125–126°C; IR (KBr) 3072, 2942, 1756, 1696, 1611 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 7.45 (1H, q, ^{4}J=1.1 Hz, H-4), 7.33 (1H, d, ^{3}J=8.8 Hz, H-5), 6.87 (1H, dd, ^{3}J=8.8 Hz, ^{4}J=2.6 Hz, H-6), 6.77 (1H, d, ^{4}J=2.6 Hz, H-8), 4.66 (2H, s, 2′-CH$_2$), 4.28 (2H, q, ^{3}J=7.1 Hz, CH_2CH$_3$), 2.18 (3H, d, ^{4}J=1.1 Hz, 3-CH$_3$), 1.31 (3H, t, ^{3}J=7.1 Hz, CH$_2$$CH_3$); ^{13}C NMR (50.29 MHz, CDCl$_3$) δ 167.8 (s, C-1′), 162.1 (s, C-2), 159.6 (s, C-7), 154.4 (s, C-8a), 138.9 (d, C-4), 125.7 (d, C-5), 122.7 (s, C-3), 113.4 (s, C-4a), 112.4 (d, C-6), 101.4 (d, C-8), 65.4 (t, C-2′), 61.5 (t, CH_2CH$_3$), 16.9 (q, 3-CH$_3$), 14.1 (q, CH$_2$$CH_3$); EI-MS m/z (%) 262 (M$^+$, 100), 324 (19), 189 (55), 175 (13), 159 (35), 147 (76). Anal. calcd for C$_{14}$H$_{14}$O$_5$: C, 64.12; H, 5.38. Found: C, 64.09; H, 5.62.

4.1.4. Ethyl 2-[(3,4-dimethyl-2-oxo-2*H*-chromen-7-yl)-oxy]acetate 4d. Colourless needles; 1.54 g (98%); mp 136–137°C; IR (KBr) 3071, 2984, 1757, 1704, 1607, 1211 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 7.52 (1H, d, ^{3}J=8.8 Hz, H-5), 6.90 (1H, dd, ^{3}J=8.8 Hz, ^{4}J=2.6 Hz, H-6), 6.76 (1H, d, ^{4}J=2.6 Hz, H-8), 4.67 (2H, s, 2′-CH$_2$), 4.28 (2H, q, ^{3}J=7.1 Hz, CH_2CH$_3$), 2.37 (3H, s, 4-CH$_3$), 2.19 (3H, s, 3-CH$_3$), 1.31 (3H, t, ^{3}J=7.1 Hz, CH$_2$$CH_3$); ^{13}C NMR (50.29 MHz, CDCl$_3$) δ 167.9 (s, C-1′), 162.0 (s, C-2), 159.4 (s, C-7), 153.2 (s, C-8a), 145.9 (s, C-4), 125.4 (d, C-5), 119.4 (s, C-3), 114.9 (s, C-4a), 112.2 (d, C-6), 101.4 (d, C-8), 65.4 (t, C-2′), 61.6 (t, CH_2CH$_3$), 15.0 (q, 4-CH$_3$), 14.1 (q, CH$_2$$CH_3$) 13.1 (q, 3-CH$_3$); EI-MS m/z (%) 276 (M$^+$, 74), 161 (100), 117 (51), 115 (40). Anal. calcd for C$_{15}$H$_{16}$O$_5$: C, 65.21; H, 5.84. Found: C, 65.19; H, 5.86.

4.1.5. Ethyl 2-[(2-oxo-2*H*-chromen-4-yl)oxy]acetate 4e. Colourless crystals; 1.39 g (98%); mp 97–98°C; IR (KBr) 3087, 2984, 1746, 1705, 1623 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 7.94–7.90 (1H, m), 7.61–7.53 (1H, m), 7.36–7.26 (2H, m), 5.58 (1H, s, H-3), 4.78 (2H, s, 2′-CH$_2$), 4.32 (2H, q, ^{3}J=7.2 Hz, CH_2CH$_3$), 1.33 (3H, t, ^{3}J=7.2 Hz, CH$_2$$CH_3$); ^{13}C NMR (50.29 MHz, CDCl$_3$) δ 166.2 (s, C-1′), 164.5 (s, C-4), 162.2 (s, C-2), 153.2 (s, C-8a), 132.6 (d), 123.9 (d), 123.1 (d), 116.6 (d), 115.1 (s, C-4a), 91.1 (d, C-3), 65.2 (t, C-2′), 61.9 (t, CH_2CH$_3$), 14.1 (q, CH$_2$$CH_3$); EI-MS m/z (%) 248 (M$^+$, 100), 175 (72), 133 (78), 89 (83). Anal. calcd for C$_{13}$H$_{12}$O$_5$: C, 62.90; H, 4.87. Found: C, 62.98; H, 4.90.

4.1.6. Ethyl 2-[(2-oxo-2*H*-chromen-7-yl)oxy]propanoate 4f. Colourless crystals; 1.47 g (98%); mp 107–108°C; IR (KBr) 3053, 2972, 1742, 1710, 1613 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 7.63 (1H, d, ^{3}J=9.5 Hz, H-4), 7.38 (1H, d, ^{3}J=8.6 Hz, H-5), 6.80 (1H, dd, ^{3}J=8.6 Hz, ^{4}J=2.5 Hz, H-6), 6.74 (1H, d, ^{4}J=2.5 Hz, H-8), 6.26 (1H, d, ^{3}J=9.5 Hz, H-3), 4.79 (1H, q, ^{3}J=6.8 Hz, CHCH$_3$), 4.24 (1H, q, ^{3}J=7.1 Hz, CH_2CH$_3$), 1.66 (3H, d, ^{3}J=6.8 Hz, CHCH_3), 1.28 (3H, t, ^{3}J=7.1 Hz, CH$_2$$CH_3$); ^{13}C NMR (50.29 MHz, CDCl$_3$) δ 171.1 (s, C-1′), 161.0 (s, C-2), 160.6 (s, C-7), 155.6 (s, C-8a), 143.2 (d, C-4), 128.9 (d, C-5), 113.6 (d, C-6), 113.1 (d, C-3), 113.1 (s, C-4a), 102.0 (d, C-8), 72.8 (d, C-2′), 61.7 (t, CH_2CH$_3$), 18.4 (q, CHCH_3), 14.1 (q, CH$_2$$CH_3$); EI-MS m/z (%) 262 (M$^+$, 64), 189 (100), 162 (35), 134 (80). Anal. calcd for C$_{14}$H$_{14}$O$_5$: C, 64.12; H, 5.38. Found: C, 64.15; H, 5.60.

4.2. General procedure for the preparation of the acids 5a–f

A solution of the acetate **4** (2.7 mmol) and sodium hydroxide 5% (2.16 mL) in ethanol (15 mL) was stirred under reflux for 2 h. After removal of the solvent, the residue was dissolved in water and acidified with HCl 6 M. The white solid collected by filtration was washed with cool water, dried and crystallized from ethanol.

4.2.1. 2-[(2-Oxo-2*H*-chromen-7-yl)oxy]acetic acid 5a. White powder; 0.59 g (quantitative yield); mp 208–209°C [lit.[7] 209–213°C].

4.2.2. 2-[(4-Methyl-2-oxo-2*H*-chromen-7-yl)oxy]acetic acid 5b. White powder; 0.63 g (quantitative yield); mp 205–206°C; IR (KBr) 3200–2500, 1735, 1608 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.69 (1H, d, ^3J=8.5 Hz, H-5), 6.97 (2H, m, H-6 and H-8), 6.22 (1H, q, ^4J=1.1 Hz, H-3), 4.82 (2H, s, 2′-CH$_2$), 2.39 (3H, d, ^4J=1.1 Hz, 4-CH$_3$); ^{13}C NMR (50.29 MHz, DMSO-d_6) δ 169.6 (s), 160.8 (s), 160.0 (s), 154.5 (s), 153.3 (s), 126.5 (d), 113.5 (d), 112.2 (d), 111.3 (s), 101.5 (d), 64.9 (t), 18.1 (q); EI-MS *m/z* (%) 234 (M$^+$, 62), 206 (47), 147 (100), 103 (11). Anal. calcd for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30. Found: C, 61.70; H, 4.42.

4.2.3. 2-[(3-Methyl-2-oxo-2*H*-chromen-7-yl)oxy]acetic acid 5c. White powder; 0.63 g (quantitative yield); mp 162–163°C; IR (KBr) 3665–2064, 1711, 1605 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.81 (1H, q, ^4J=1.1 Hz, H-4), 7.54 (1H, d, ^3J=9.9 Hz, H-5), 6.95–6.91 (2H, m, H-6 and H-8), 4.80 (2H, s, 2′-CH$_2$), 2.06 (3H, d, ^4J=1.1 Hz, 3-CH$_3$); ^{13}C NMR (50.29 MHz, DMSO-d_6) δ 169.6 (s), 161.4 (s), 159.8 (s), 154.1 (s), 139.6 (d), 128.4 (d), 121.4 (d), 113.2 (s), 112.4 (s), 101.2 (d), 64.8 (t), 14.7 (q); EI-MS *m/z* (%) 234 (M$^+$, 60), 147 (100), 103 (42). Anal. calcd for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30. Found: C, 61.65; H, 4.32.

4.2.4. 2-[(3,4-Dimethyl-2-oxo-2*H*-chromen-7-yl)oxy]-acetic acid 5d. White powder; 0.67 g (quantitative yield); mp 171–172°C; IR (KBr) 3694–2467, 1730, 1675, 1606 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.65 (1H, d, ^3J=8.4 Hz, H-5), 6.92–6.68 (2H, m, H-6 and H-8), 4.78 (2H, s, 2′-CH$_2$), 2.31 (3H, s, 4-CH$_3$), 2.03 (3H, s, 3-CH$_3$); ^{13}C NMR (50.29 MHz, DMSO-d_6) δ 169.5 (s), 161.0 (s), 159.5 (s), 152.6 (s), 146.5 (s), 128.4 (d), 121.4 (d), 113.2 (s), 112.4 (s), 101.2 (d), 64.8 (t), 14.7 (q); EI-MS *m/z* (%) 248 (M$^+$, 37), 220 (13), 161 (100), 115 (17). Anal. calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 62.77; H, 4.95.

4.2.5. 2-[(2-Oxo-2*H*-chromen-4-yl)oxy]acetic acid 5e. White powder; 0.59 g (quantitative yield); mp 219–220°C; IR (KBr) 3795–2402, 1715, 1624 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.87–7.83 (1H, m), 7.73–7.64 (1H, m), 7.44–7.36 (2H, m), 5.89 (1H, s, H-3), 5.00 (2H, s, 2′-CH$_2$); ^{13}C NMR (50.29 MHz, DMSO-d_6) δ 168.3 (s), 164.1 (s), 161.3 (s), 152.6 (s), 132.8 (d), 124.2 (d), 122.8 (d), 116.4 (d), 115.0 (s), 91.2 (d), 65.4 (t); EI-MS *m/z* (%) 220 (M$^+$, 21), 147 (32), 133 (29), 84 (49), 57 (100). Anal. calcd for $C_{11}H_8O_5$: C, 60.01; H, 3.66. Found: C, 60.28; H, 3.87.

4.2.6. 2-[(2-Oxo-2*H*-chromen-7-yl)oxy]propanoic acid 5f. Colourless crystals; 0.63 g (quantitative yield); mp 150–151°C; IR (KBr) 3700–2362, 1730, 1682, 1607 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.98 (1H, d, ^3J=9.3 Hz, H-4), 7.63 (1H, d, ^3J=8.4 Hz, H-5), 6.94–6.89 (2H, m, H-6 and H-8), 6.30 (1H, d, ^3J=9.3 Hz, H-3), 5.04 (1H, q, ^3J=6.7 Hz, 2′-CH), 1.53 (3H, d, ^3J=6.7 Hz, 3′-CH$_3$); ^{13}C NMR (50.29 MHz, DMSO-d_6) δ 172.2 (s), 160.4 (s), 160.0 (s), 155.0 (s), 144.0 (d), 129.4 (d), 115.5 (s), 112.7 (d), 112.6 (d), 101.6 (d), 71.9 (d), 18.0 (q); EI-MS *m/z* (%) 234 (M$^+$, 24), 189 (23), 162 (45), 134 (100). Anal. calcd for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30. Found: C, 61.45; H, 4.58.

4.3. General procedure for the preparation of the aldehydes 7a–f

A mixture of the acid **5** (1 mmol) and thionyl chloride (0.5 mL, 7 mmol) was refluxed for 2 h in dry chloroform (25 mL). Excess of thionyl chloride and chloroform are then removed under reduced pressure to obtain the pure acyl chlorides **6** (quantitative yield). Anhydrous toluene (6 mL) and 5% palladium–barium sulfate catalyst (0.032 g) were placed in a round-bottom flask equipped with a reflux condenser and a gas inlet tube. A slow stream of hydrogen was passed through the stirred mixture while the temperature was raised to reflux for 30 min. After cooling to room temperature, the acyl chloride (1 mmol) was added. The mixture was then refluxed for 4 h under hydrogen flow. After the reaction had cooled to room temperature, the suspension was diluted with ethyl acetate and filtered on celite to remove the catalyst. Removal of the solvent gave the pure aldehydes **7**.

4.3.1. 2-[(2-Oxo-2*H*-chromen-7-yl)oxy]acetaldehyde 7a. Yellowish powder; 0.20 g (97%); mp 125–127°C [lit.[2] 124–127°C].

4.3.2. 2-[(4-Methyl-2-oxo-2*H*-chromen-7-yl)oxy]acetaldehyde 7b. Yellowish powder; 0.21 g (97%); mp 144–146°C (lit.[1] 150–152°C); IR (KBr) 2835, 1715, 1615 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 9.85 (1H, t, ^3J=0.8 Hz, CHO), 7.53 (1H, d, ^3J=8.8 Hz, H-5), 6.89 (1H, dd, ^3J=8.8 Hz, ^4J=2.6 Hz, H-6), 6.77 (1H, d, ^4J=2.6 Hz, H-8), 6.16 (1H, q, ^4J=1.1 Hz, H-3), 4.66 (2H, d, ^3J=0.8 Hz, 2′-CH$_2$), 2.39 (3H, d, ^4J=1.1 Hz, 4-CH$_3$). ^{13}C NMR (50.29 MHz, CDCl$_3$) δ 197.2 (d, C-1′), 160.8 (s, C-2), 160.2 (s, C-7), 155.1 (s, C-8a), 152.2 (s, C-4), 125.9 (d, C-5), 114.6 (s, C-4a), 112.7 (d, C-3), 112.2 (d, C-6), 101.9 (d, C-8), 72.7 (t, C-2′), 18.7 (q, 4-CH$_3$); EI-MS *m/z* (%) 218 (M$^+$, 100), 189 (42), 159 (67), 147 (69), 103 (81), 77 (69). Anal. calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.35; H, 4.43.

4.3.3. 2-[(3-Methyl-2-oxo-2*H*-chromen-7-yl)oxy]acetaldehyde 7c. Yellowish powder; 0.21 g (98%); mp 90–91°C; IR (KBr) 3032, 2928, 2888, 1714, 1611 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 9.87 (1H, t, ^3J=0.8 Hz, CHO), 7.47 (1H, q, ^4J=1.5 Hz, H-4), 7.36 (1H, d, ^3J=8.6 Hz, H-5), 6.86 (1H, dd, ^3J=8.6 Hz, ^4J=2.6 Hz, H-6), 6.79 (1H, d, ^4J=2.6 Hz, H-8), 4.65 (2H, d, ^3J=0.8 Hz, 2′-CH$_2$), 2.19 (3H, d, ^4J=1.5 Hz, 3-CH$_3$). ^{13}C NMR (50.29 MHz, CDCl$_3$) δ 197.4 (d, C-1′), 162.2 (s, C-2), 159.4 (s, C-7), 154.6 (s, C-8a), 139.0 (d, C-4), 128.2 (d, C-5), 123.1 (s, C-3), 114.2 (s, C-4a), 112.2 (d, C-6), 101.6 (d, C-8), 72.7 (t, C-2′), 16.9 (q, 3-CH$_3$); EI-MS *m/z* (%) 218 (M$^+$, 48), 189 (26), 103 (34), 84 (100). Anal. Calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.25; H, 4.56.

4.3.4. 2-[(3,4-Dimethyl-2-oxo-2*H*-chromen-7-yl)oxy]-acetaldehyde 7d. Yellowish powder; 0.23 g (98%); mp 148–149°C; IR (KBr) 3007, 2977, 2957, 1707, 1607 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.87 (1H, t, ^3J=0.9 Hz, CHO), 7.54 (1H, d, ^3J=8.9 Hz, H-5), 6.89 (1H, dd, ^3J=8.9 Hz, ^4J=2.4 Hz, H-6), 6.77 (1H, d, ^4J=2.4 Hz, H-8), 4.65 (2H, d, ^3J=0.9 Hz, 2′-CH_2), 2.38 (3H, s, 4-CH_3), 2.19 (3H, s, 3-CH_3); ^{13}C NMR (75.43 MHz, $CDCl_3$) δ 197.6 (s, C-1′), 162.1 (s, C-2), 159.2 (s, C-7), 153.4 (s, C-8a), 145.9 (s, C-4), 125.7 (d, C-5), 119.8 (s, C-3), 115.3 (s, C-4a), 112.0 (d, C-6), 101.7 (d, C-8), 72.7 (t, C-2′), 15.1 (q, 4-CH_3), 13.2 (q, 3-CH_3); EI-MS *m*/*z* (%) 232 (M^+, 34), 204 (14), 161 (100), 117 (50). Anal. calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.45; H, 5.21.

4.3.5. 2-[(2-Oxo-2*H*-chromen-4-yl)oxy]acetaldehyde 7e. White powder; 0.20 g (98%); mp 157–158°C; IR (KBr) 3032, 2984, 1715, 1618 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.89 (1H, t, ^3J=0.7 Hz, CHO), 7.93 (1H, dd, ^3J=7.8 Hz, ^4J=1.6 Hz, H-5 or H-8), 7.60 (1H, m, H-7 or H-6), 7.35 (1H, m, H-8 or H-5), 7.32 (1H, m, H-6 or H-7), 5.60 (1H, s, H-3), 4.80 (2H, d, ^3J=0.7 Hz, 2′-CH_2); ^{13}C NMR (100.58 MHz, $CDCl_3$) δ 194.6 (d, C-1′), 164.4 (s, C-4), 162.2 (s, C-2), 153.4 (s, C-8a), 132.9 (d), 124.2 (d), 123.0 (d), 116.9 (d), 115.0 (s, C-4a), 91.5 (d, C-3), 72.5 (t, C-2′); EI-MS *m*/*z* (%) 204 (M^+, 40), 162 (12), 105 (16), 89 (100). Anal. Calcd for $C_{11}H_8O_4$: C, 64.71; H, 3.95. Found: C, 64.84; H, 3.87.

4.3.6. 2-[(2-Oxo-2*H*-chromen-7-yl)oxy]propanal 7f. Yellowish waxy solid; 0.21 g (95%); IR (nujol) 2925, 2857, 1713, 1614 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.71 (1H, d, ^3J=1.5 Hz, CHO), 7.64 (1H, d, ^3J=9.5 Hz, H-4), 7.41 (1H, d, ^3J=8.6 Hz, H-5), 6.85 (1H, dd, ^3J=8.6 Hz, ^4J=2.4 Hz, H-6), 6.79 (1H, d, ^4J=2.4 Hz, H-8), 6.29 (1H, d, ^3J=9.5 Hz, H-3), 4.74 (1H, qd, ^3J=7.0 Hz, ^3J=1.5 Hz, *CH*CH_3), 1.55 (3H, d, ^3J=7.0 Hz, CH*CH_3*); ^{13}C NMR (50.29 MHz, $CDCl_3$) δ 200.0 (d, C-1′), 160.7 (s, C-2), 160.1 (s, C-7), 155.4 (s, C-8a), 143.1 (d, C-4), 129.0 (d, C-5), 113.5 (d, C-3), 113.2 (s, C-4a), 112.7 (d, C-6), 102.3 (d, C-8), 78.0 (d, C-2′), 15.0 (q, CH*CH_3*); EI-MS *m*/*z* (%) 218 (M^+, 16), 189 (48), 133 (38), 105 (39), 89 (100). Anal. calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.00; H, 4.55.

4.4. Reaction of 6,7-dihydroxycoumarin (8) with ethyl bromoacetate

To a solution of 6,7-dihydroxycoumarin (**8**) (0.50 g, 2.8 mmol) and ethyl bromoacetate (0.3 mL, 2.8 mmol) in DMF (15 mL) potassium carbonate (0.39 g) was added and the reaction mixture was maintained at room temperature for 4 h under stirring. Removal of the solvent left a yellow residue that was dissolved in water (10 mL) and acidified with 6 M HCl under cooling. The white precipitate was collected by filtration, washed with cooled water and dried in vacuo. The obtained material resulted in a mixture of compounds **9–12** that were separated by flash-chromatography (petroleum ether/ethyl acetate=1:2, as eluant). The fastest running band gave ethyl 2-[(6-(2-ethoxy-2-oxoethoxy)-2-oxo-2*H*-chromen-7-yl)oxy]acetate **12** (0.18 g, 0.52 mmol, 19%), the second band was identified as ethyl 2-[(6-hydroxy-2-oxo-2*H*-chromen-7-yl)oxy]-acetate **9** (0.12 g, 0.47 mmol, 17%); some starting material **8** (0.039 g, 8%) was recovered from the slowest moving fraction. A mixture of compounds **10** and **11** (0.23 g, 0.98 mmol, 35%, 25:1) was then obtained by eluting with methanol.

4.4.1. Ethyl 2-[(6-hydroxy-2-oxo-2*H*-chromen-7-yl)-oxy]acetate 9. Colourless crystals; mp 155–156°C; IR (KBr) 3480–3000, 1752, 1685 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.60 (1H, d, ^3J=9.5 Hz, H-4), 7.03 (1H, s, H-5), 6.81 (1H, s, H-8), 6.32 (1H, d, ^3J=9.5 Hz, H-3), 4.73 (2H, s, 2′-CH_2), 4.30 (2H, q, ^3J=7.3 Hz, *CH_2*CH_3), 1.33 (3H, t, ^3J=7.3 Hz, CH_2*CH_3*); EI-MS *m*/*z* (%) 264 (M^+, 30), 218 (62), 190 (49), 162 (100). Anal. calcd for $C_{13}H_{12}O_6$: C, 59.09; H, 4.58. Found: C, 59.22; H, 4.66.

4.4.2. Ethyl 2-[(6-(2-ethoxy-2-oxoethoxy)-2-oxo-2*H*-chromen-7-yl)oxy]acetate 12. Colourless crystals; mp 111–112°C; IR (KBr) 3062, 1747, 1615 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.60 (1H, d, ^3J=9.5 Hz, H-4), 7.01 (1H, s, H-5), 6.76 (1H, s, H-8), 6.30 (1H, d, ^3J=9.5 Hz, H-3), 4.76 (2H, s, OCH_2), 4.73 (2H, s, OCH_2), 4.28 (2H, q, ^3J=7.3 Hz, *CH_2*CH_3), 4.27 (2H, q, ^3J=7.3 Hz, *CH_2*CH_3), 1.32 (3H, t, ^3J=7.3 Hz, CH_2*CH_3*), 1.30 (3H, t, ^3J=7.3 Hz, CH_2*CH_3*); EI-MS *m*/*z* (%) 350 (M^+, 40), 277 (30), 203 (100). Anal. calcd for $C_{17}H_{18}O_8$: C, 58.28; H, 5.18. Found: C, 58.42; H, 5.16.

4.4.3. 2-[(6-Methoxy-2-oxo-2*H*-chromen-7-yl)oxy]acetic acid 13. (a) To a solution of compound **9** (0.30 g, 1.1 mmol) and dimethyl sulfate (0.24, 2.5 mmol) in acetone (15 mL) potassium carbonate (0.28 g) was added and the mixture was refluxed for 5 h. Removal of the solvent left a white solid which was suspended in water, collected by filtration and dried. To a solution of this product (0.30 g) in ethanol (10 mL), was added NaOH 5% (1.3 mL) and the mixture was stirred under reflux for 2 h. Removal of the solvent left a residue that was dissolved in water and acidified with 6 M HCl to give the acid **13** as a white solid (0.26 g, 96%); mp 218–220°C; IR (KBr) 3600–1900, 1743, 1684 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 7.96 (1H, d, ^3J=9.5 Hz, H-4), 7.30 (1H, s, H-5), 6.99 (1H, s, H-8), 6.31 (1H, d, ^3J=9.5 Hz, H-3), 4.84 (2H, s, 2′-CH_2), 3.82 (3H, s, OCH_3); EI-MS *m*/*z* (%) 206 (M^+-44, 100), 191 (45), 178 (23), 163 (41). Anal. calcd for $C_{12}H_{10}O_6$: C, 57.61; H, 4.03. Found: C, 57.55; H, 4.35.

(b) Operating as above starting from the acid **10** (0.26 g, 1.1 mmol) compound **13** was obtained in 98% yield.

4.4.4. 2-[(6-Methoxy-2-oxo-2*H*-chromen-7-yl)oxy]acetaldehyde 14. Operating as for **5a–f**, starting from compound **13** (0.23 g, 0.92 mmol), the aldehyde **14** (0.20 g, 95%) was obtained as a white powder: mp 138–140°C; IR (KBr) 3063, 1723, 1615 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.89 (1H, t, ^3J=0.9 Hz, CHO), 7.62 (1H, d, ^3J=9.5 Hz, H-4), 6.92 (1H, s, H-5), 6.74 (1H, s, H-8), 6.32 (1H, d, ^3J=9.5 Hz, H-3), 4.71 (2H, d, ^3J=0.9 Hz, 2′-CH_2), 3.94 (3H, s, OCH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$) δ 197.2 (d, C-1′), 160.9 (s, C-2), 150.1 (s), 149.4 (s), 146.6 (s), 142.9 (d, C-4), 114.5 (d, C-3), 112.8 (s, C-4a), 109.0 (d, C-5), 102.2 (d, C-8), 73.6 (t, C-2′), 56.4 (q, OCH_3); EI-MS *m*/*z*

(%) 234 (M$^+$, 100), 205 (6), 190 (79). Anal. calcd for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30. Found: C, 61.49; H, 4.55.

4.5. Reaction of 7,8-dihydroxy-4-methylcoumarin (16) with ethyl bromoacetate

Ethyl bromoacetate (0.26 mL, 2.5 mmol) and NaOH 5% (2.0 mL) were added to a solution of 7,8-dihydroxy-4-methylcoumarin (**16**) (0.49 g, 2.5 mmol) in ethanol (15 mL) and the reaction mixture was stirred at room temperature overnight. Removal of the solvent left a yellow residue that was dissolved in water (10 mL) and acidified with HCl 6 M under cooling. The white precipitate was collected by filtration, washed with water and dried in vacuo to give a mixture of compounds **16–20** that were separated by flash-chromatography (petroleum ether/ethyl acetate=1:1, as eluant). The fastest running band gave compound **17** (0.06 g, 0.23 mmol, 9%), the second band was identified as the diester **20** (0.08 g, 0.22 mmol, 9%) and the third one resulted to be the starting material **16** (0.20 g, 1 mmol). A mixture of monoacids **18** and **19** (0.17 g, 0.68 mmol, 27%, 2:1) was then recovered by eluting with methanol.

4.5.1. Ethyl 2-[(7-hydroxy-4-methyl-2-oxo-2*H*-chromen-8-yl)oxy]acetate 17. Colourless crystals; mp 103–104°C; IR (KBr) 3400–3000, 1727, 1606 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 8.81 (s, OH), 7.28 (1H, d, ^3J=8.8 Hz, H-5), 6.93 (1H, d, ^3J=8.8 Hz, H-6), 6.12 (1H, q, ^4J=1.1 Hz, H-3), 4.81 (2H, s, 2$'$-CH$_2$), 4.28 (2H, q, ^3J=7.0 Hz, CH_2CH$_3$), 2.38 (3H, d, ^4J=1.1 Hz, 4-CH$_3$), 1.30 (3H, t, ^3J=7.0 Hz, CH$_2$$CH_3$); ^{13}C NMR (100.58 MHz, CDCl$_3$) δ 173.1 (s, C-1$'$), 160.3 (s, C-2), 153.3 (s, C-4), 153.2 (s, C-7), 147.4 (s, C-8a), 133.6 (s, C-8), 121.2 (d, C-5), 113.8 (s, C-4a), 113.3 (d, C-6), 111.5 (d, C-3), 70.9 (t, C-2$'$), 62.5 (t, CH_2CH$_3$), 18.9 (q, 4-CH$_3$), 14.0 (q, CH$_2$$CH_3$); EI-MS *m/z* (%) 278 (M$^+$, 28), 232 (41), 205 (75), 204 (82), 176 (100). Anal. calcd for $C_{14}H_{14}O_6$: C, 60.43; H, 5.07. Found: C, 60.50; H, 5.16.

4.5.2. 2-[(7-Hydroxy-4-methyl-2-oxo-2*H*-chromen-8-yl)-oxy]acetic acid 18. Analytical sample obtained by alkaline hydrolysis of ester **17**: white powder; mp 269–270°C; IR (KBr) 3600–2100, 3511, 3414, 1740, 1666, 1604 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.37 (1H, d, ^3J=9.0 Hz, H-5), 6.88 (1H, d, ^3J=9.0 Hz, H-6), 6.17 (1H, q, ^4J=1.2 Hz, H-3), 4.68 (2H, s, 2$'$-CH$_2$), 2.37 (3H, d, ^4J=1.2 Hz, 4-CH$_3$); EI-MS *m/z* (%) 250 (M+, 1), 232 (30), 205 (10), 204 (60), 176 (100). Anal. calcd for $C_{12}H_{10}O_6$: C, 57.60; H, 4.03. Found: C, 57.43; H, 4.25.

4.5.3. 2-[(8-Hydroxy-4-methyl-2-oxo-2*H*-chromen-7-yl)-oxy]acetic acid 19 (mixture with 18). ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.20 (1H, d, ^3J=8.8 Hz, H-5), 6.33 (1H, d, ^3J=8.8 Hz, H-6), 6.22 (1H, q, ^4J=1.0 Hz, H-3), 4.82 (2H, s, 2$'$-CH$_2$), 2.36 (3H, d, ^4J=1.0 Hz, 4-CH$_3$).

4.5.4. Ethyl 2-[(8-(2-ethoxy-2-oxoethoxy)-4-methyl-2-oxo-2*H*-chromen-7-yl)oxy]acetate 20. Colourless crystals; mp 88–89°C [lit.[13] 84–85°C]; ^{1}H NMR (200 MHz, CDCl$_3$) δ 7.28 (1H, d, ^3J=9.2 Hz, H-5), 6.81 (1H, d, ^3J=9.2 Hz, H-6), 6.18 (1H, q, ^4J=1.1 Hz, H-3), 4.85 (2H, s, OCH$_2$), 4.80 (2H, s, OCH$_2$), 4.26 (2H, q, ^3J=7.0 Hz, CH_2CH$_3$), 4.25 (2H, q, ^3J=6.9 Hz, CH_2CH$_3$), 2.38 (3H, d, ^4J=1.1 Hz, 4-CH$_3$), 1.29 (3H, t, ^3J=7.0 Hz, CH$_2$$CH_3$), 1.28 (3H, t, ^3J=6.9 Hz, CH$_2$$CH_3$); EI-MS *m/z* (%) 364 (M$^+$, 50), 291 (41), 217 (100).

4.5.5. 2-[(7-Methoxy-4-methyl-2-oxo-2*H*-chromen-8-yl)-oxy]acetic acid 21. (a) Operating as for **13** starting from compound **17** the acid **21** was obtained as a white precipitate (98%): mp 222–224°C; IR (KBr) 3700–2000, 1760, 1677, 1602 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.49 (1H, d, ^3J=9.0 Hz, H-5), 7.12 (1H, d, ^3J=9.0 Hz, H-6), 6.24 (1H, q, ^4J=1.1 Hz, H-3), 4.63 (2H, s, 2$'$-CH$_2$), 3.90 (3H, s, OCH$_3$), 2.39 (3H, d, ^4J=1.1 Hz, 4-CH$_3$); ^{13}C NMR (50.29 MHz, DMSO-d_6) δ 169.7 (s), 159.5 (s), 154.2 (s), 153.3 (s), 146.4 (s), 133.2 (s), 120.2 (d), 114.1 (s), 111.4 (d), 108.8 (d), 68.7 (t), 56.4 (q), 18.2 (q); EI-MS *m/z* (%) 264 (M$^+$, 78), 219 (18), 205 (78), 177 (100).). Anal. calcd for $C_{13}H_{12}O_6$: C, 59.09; H, 4.58. Found: C, 59.19; H, 4.70

(b) A solution of the ester **22** (0.33 g, 1.17 mmol) and NaOH 5% (0.94 mL) in ethanol (15 mL) was stirred under reflux for 2 h. After removal of the solvent, the residue was dissolved in water and acidified with 6 M HCl. The white solid collected by filtration was washed with water, dried and crystallized from ethanol to give the acid **21** (0.30 g, 98%).

4.5.6. 2-[(7-Methoxy-4-methyl-2-oxo-2*H*-chromen-8-yl)-oxy]acetaldehyde 24. Operating as for **5a–f**, starting from the acid **21** (0.20 g, 0.76 mmol) the aldehyde **24** was quantitatively obtained as a yellow powder: mp 124–125°C; IR (KBr) 1723, 1606 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 10.01 (1H, t, ^3J=1.3 Hz, CHO), 7.34 (1H, d, ^3J=9.0 Hz, H-5), 6.90 (1H, d, ^3J=9.0 Hz, H-6), 6.16 (1H, q, ^4J=1.2 Hz, H-3), 4.62 (2H, d, ^3J=1.3 Hz, 2$'$-CH$_2$), 3.94 (3H, s, OCH$_3$), 2.40 (3H, d, ^4J=1.2 Hz, 4-Me); ^{13}C NMR (100.58 MHz, CDCl$_3$) δ 200.4 (d, C-1$'$), 160.0 (s, C-2), 154.5 (s, C-7/C-4), 152.4 (s, C-4/C-7), 147.1 (s, C-8a), 134.6 (s, C-8), 120.1 (d, C-5), 114.8 (s, C-4a), 112.6 (d, C-3), 108.0 (d, C-6), 76.6 (t, C-2$'$), 56.3 (q, OCH$_3$), 18.8 (q, 4-CH$_3$); EI-MS *m/z* (%) 248 (M$^+$, 100), 219 (77), 205 (89), 177 (89). Anal. calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 62.97; H, 4.78.

4.6. Preparation of esters 22 and 23

To a solution of compounds **18** and **19** (0.34 g, 1.36 mmol) and dimethyl sulfate (0.2 mL, 2.12 mmol) in acetone (15 mL) potassium carbonate (0.50 g) was added and the reaction mixture was refluxed for 5 h. Removal of the solvent left a white solid which was suspended in water, collected by filtration and dried in vacuo. Chromatographic workup (petroleum ether/ethyl acetate=1:1, as eluant) of the solid gave the esters **22** (0.24 g, 63%) and **23** (0.12 g, 32%).

4.6.1. Methyl 2-[(7-methoxy-4-methyl-2-oxo-2*H*-chromen-8-yl)oxy]acetate 22. Colourless crystals; mp 158–159°C; ^{1}H NMR (200 MHz, CDCl$_3$) δ 7.32 (1H, d, ^3J=8.8 Hz, H-5), 6.88 (1H, d, ^3J=8.8 Hz, H-6), 6.15 (1H, q, ^4J=1.1 Hz, H-3), 4.79 (2H, s, 2$'$-CH$_2$), 3.94 (3H, s, OCH$_3$), 3.81 (3H, s, OCH$_3$), 2.39 (3H, d, ^4J=1.1 Hz, 4-CH$_3$); EI-MS *m/z* (%) 278 (M$^+$, 15), 219 (16), 205 (37), 84 (100). Anal. calcd for $C_{14}H_{14}O_6$: C, 60.43; H, 5.07. Found: C, 60.52; H, 5.20.

4.6.2. Methyl 2-[(8-methoxy-4-methyl-2-oxo-2*H*-chromen-7-yl)oxy]acetate 23. Colourless crystals; mp 114–115°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.27 (1H, d, ^3J=8.9 Hz, H-5), 6.80 (1H, d, ^3J=8.9 Hz, H-6), 6.18 (1H, q, ^4J=1.2 Hz, H-3), 4.81 (2H, s, 2′-CH_2), 4.02 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 2.39 (3H, d, ^4J=1.2 Hz, 4-CH_3) EI-MS *m*/*z* (%) 278 (M^+, 100), 219 (43), 205 (52), 177 (57). Anal. calcd for $C_{14}H_{14}O_6$: C, 60.43; H, 5.07. Found: C, 60.49; H, 5.18.

4.6.3. 2-[(8-Methoxy-4-methyl-2-oxo-2*H*-chromen-7-yl)-oxy]acetic acid 25. Operating as in (b) for compound **21**, starting from the ester **23** (0.26 g, 0.93 mmol) the acid **25** was obtained as white powder (0.24 g, 99%): mp 199–200°C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.46 (1H, d, ^3J=9.0 Hz, H-5), 7.03 (1H, d, ^3J=9.0 Hz, H-6), 6.25 (1H, q, ^4J=1.1 Hz, H-3), 4.90 (2H, s, 2′-CH_2), 3.86 (3H, s, OCH_3), 2.39 (3H, d, ^4J=1.1 Hz, 4-CH_3); ^{13}C NMR (50.29 MHz, DMSO-d_6) δ 169.6 (s), 159.5 (s), 153.4 (s), 153.3(s), 147.0 (s), 135.3 (s), 120.0 (d), 114.4 (s), 111.6 (d), 109.5 (d), 65.0 (t), 60.7 (q), 18.2 (q); EI-MS *m*/*z* (%) 264 (M^+, 71), 219 (6), 205 (39), 177 (100). Anal. calcd for $C_{13}H_{12}O_6$: C, 59.09; H, 4.58. Found: C, 59.25; H, 4.42.

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