

# Synthesis of some 3,4-dihydro-2*H*-benzo[*f*]pyrano[2,3-*h*]chromen-6-one derivatives

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Reactions of *o*-quinones **16–18** with ylide **19** afforded compounds **5–7** in moderate to good yields (62–80%), which were further de-ethoxycarbonylated to compounds **28–30** in 53–66% yield. Compounds **6, 7** and **29** were further transformed into compounds **31–35**. The preparation of the novel compounds **10, 11, 16** and **27** is also reported.

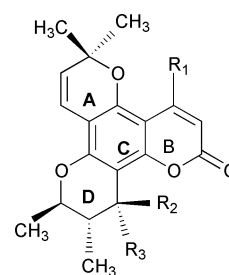
## Introduction

It is well known that calophyllum coumarins, such as the calanolides **1** and **2** and the inophyllums **3, 4** have attracted considerable attention as potent inhibitors of human immune deficiency virus-1 (HIV-1) reverse transcriptase (RT) and several synthetic methods have been reported<sup>3–9</sup> for their preparation as well as for the preparation of compounds modified in their D ring. Our continuing interest in the synthesis of coumarin derivatives through the reaction of the appropriate *o*-quinone with alkoxy carbonylmethylene(triphenyl)phosphoranes<sup>10–13</sup> prompted us to try the synthesis of compounds **6–8**. We therefore studied the reactions of ethoxycarbonylmethylene(triphenyl)phosphorane **19** with the known 2,2-dimethyl-3,4-dihydro-2*H*-benzo[*h*]chromene-5,6-dione ( $\beta$ -lapachone)<sup>14</sup> **17** and 2-methyl-3,4-dihydro-2*H*-benzo[*h*]chromene-5,6-dione<sup>15</sup> **18** and the unknown 2,2,9,9-tetramethyl-2,3,4,7,8,9-hexahydropyrano[3,2-*h*]chromene-5,6-dione **13** respectively, since the A–C–B ring skeleton of the target compounds **6–8** can be considered as similar enough to that of the biologically active calophyllum coumarins.

## Results and discussion

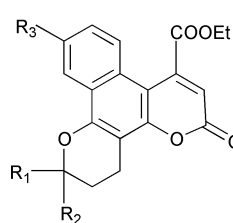
*o*-Quinones **17** and **18** were prepared according to the literature starting from 2-hydroxy-1,4-naphthoquinone (Lausone).<sup>14,15</sup> The synthesis of the unknown *o*-quinone **13** was attempted by applying the method used for the preparation of *o*-quinone **17** (Scheme 1).

Treatment of 2,5-dihydroxy-1,4-benzoquinone **9** with lithium hydride, lithium iodide and two equivalents of 4-bromo-2-methylbut-2-ene afforded 2,5-dihydroxy-3,6-bis(3-methylbut-2-enyl)-1,4-benzoquinone **10** in 30% yield (based on the quinone **9** consumed). When compound **10** was then treated with concentrated sulfuric acid 2,2,7,7-tetramethyl-3,4,8,9-tetrahydropyrano[2,3-*g*]chromene-5(2*H*),10(7*H*)-dione **11** and the unexpected 2,2,9-trimethyl-3,4-dihydro-2*H*-benzo[*h*]chromene-5,6-dione **16** were obtained in 45% and 16% yield, respectively. The expected *o*-quinone **13** was not detected or separated from this reaction mixture. The analytical and spectral data of the major product resembled that of symmetrical isomers **11** and **13**. Reaction of this major product with ylide **19** gave a compound whose mass and spectral data matched that of compound **27** (Scheme 3). Thus the major product was identified as compound **11**. The recorded mass spectrum (*m/z* 256), the <sup>1</sup>H



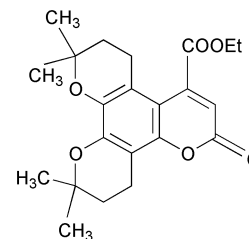
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- 1: R<sub>1</sub>=n-propyl, R<sub>2</sub>=OH, R<sub>3</sub>=H (calanolide A)
- 2: R<sub>1</sub>=n-propyl, R<sub>2</sub>=H, R<sub>3</sub>=OH, (calanolide B)
- 3: R<sub>1</sub>=phenyl, R<sub>2</sub>=OH, R<sub>3</sub>=H (inophyllum B)
- 4: R<sub>1</sub>=phenyl, R<sub>2</sub>=H, R<sub>3</sub>=OH (inophyllum P)



5-7

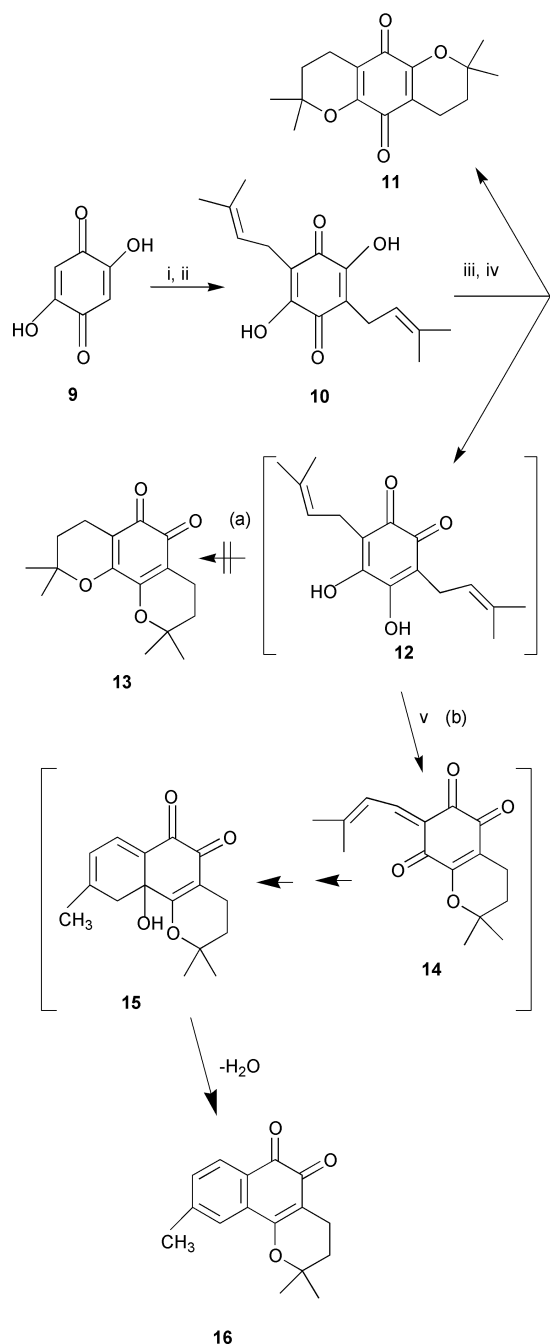
- 5: R<sub>1</sub>=R<sub>2</sub>=R<sub>3</sub>=CH<sub>3</sub>
- 6: R<sub>1</sub>=R<sub>2</sub>=CH<sub>3</sub>, R<sub>3</sub>=H
- 7: R<sub>1</sub>=CH<sub>3</sub>, R<sub>2</sub>=R<sub>3</sub>=H



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NMR spectrum and the <sup>13</sup>C NMR spectrum (three methyl groups, aromatic protons and carbons) of the minor product accord<sup>14</sup> well with the structure **16** suggested for it.

Compound **11** is obviously formed by the predominant direct bis-cyclization of compound **10** (Scheme 1). Although a bis-cyclization of the expected tautomeric *o*-quinone **12** could also give the desired *o*-quinone **13** (route a), it can be considered that, instead of that transformation, a mono-cyclization of **12** takes place initially (route b), accompanied by air oxidation to the intermediate **14**, which by further cyclization to the

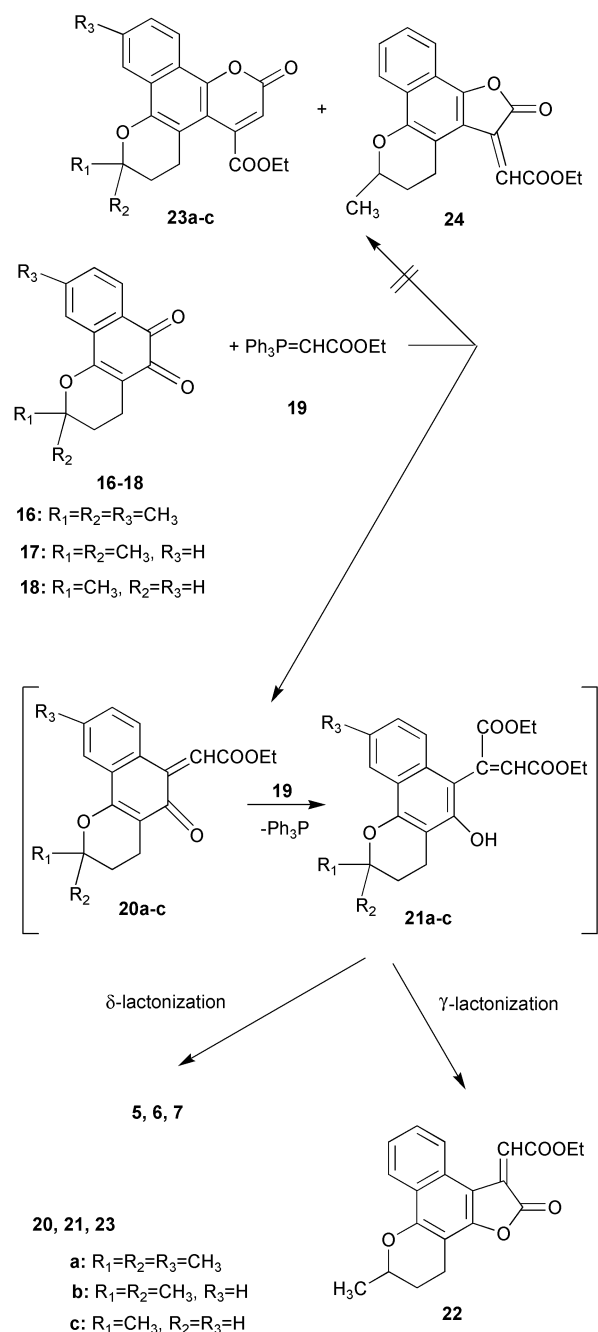


**Scheme 1** Reagents and conditions: i, dry DMSO, LiH,  $-78^\circ\text{C}$ ; ii, LiI,  $\text{CH}_2=\text{CHCH}_2\text{Br}$ ; iii, conc.  $\text{H}_2\text{SO}_4$ ,  $25^\circ\text{C}$ ; iv, ice-water; v, air oxidation.

intermediate **15** and dehydration of the latter can afford the *o*-quinone **16**, obtained from the reaction (Scheme 1).

Our unsuccessful attempts to synthesize *o*-quinone **13** did not allow us to synthesize **8**. However having quinones **16–18** on hand did allow us to synthesize the desired coumarins **5–7** (Scheme 2).

Treatment of quinone **16** with ylide **19** (2 equivalents) in dry DCM under reflux for 5 h and separation of the reaction mixture by column chromatography gave ethyl 2,2,11-trimethyl-6-oxo-3,4-dihydro-2*H*,6*H*-benzo[*f*]pyrano[2,3-*h*]chromene-8-carboxylate **5** in 80% yield. By a similar treatment of quinone **17** with ylide **19** ethyl 2,2-dimethyl-6-oxo-3,4-dihydro-2*H*,6*H*-benzo[*f*]pyrano[2,3-*h*]chromene-8-carboxylate **6** was obtained in 66% yield. In contrast to these reactions treatment of quinone **18** with ylide **19**, under similar conditions, resulted in ethyl 2-methyl-6-oxo-3,4-dihydro-2*H*,6*H*-benzo[*f*]pyrano[2,3-*h*]chromene-8-carboxylate **7** (62%) accompanied by ethyl 2-[2-methyl-6-oxo-3,4,6,7-tetrahydro-2*H*-benzo[*h*]furo[2,3-*f*]chromen-7-ylidene]acetate **22** in 6% yield.



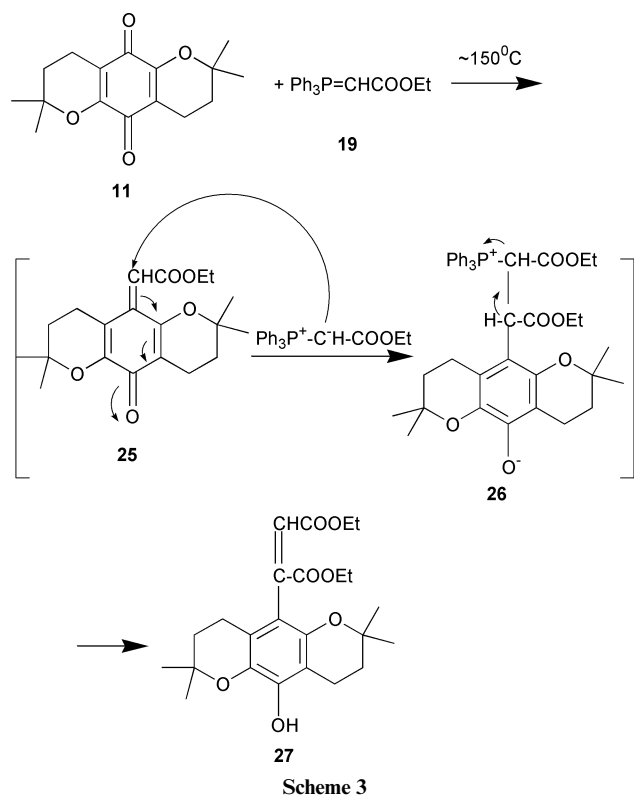
**Scheme 2**

The formation of compounds **5–7** and **22** can be explained by the mechanism suggested<sup>10,11,13</sup> for the formation of similar compounds from reactions of other *o*-quinones with ylide **19**. Wittig mono-olefination of the C-6 carbonyl of *o*-quinones **16–18** followed by Michael addition of a second ylide species to the *o*-quinone methanides **20a–c**, initially formed, accompanied by Hoffmann elimination of triphenylphosphine give the intermediate **21a–c**.  $\delta$ -Lactonization of the latter can afford products **5–7**, while  $\gamma$ -lactonization of **21c** can lead to the formation of product **22** obtained (Scheme 2). Initial Wittig mono-olefination of the 5-carbonyl of quinones used can also lead, *via* a similar reaction sequence, to the formation of products **23a–c** and **24**, isomeric to **5–7** and **22**, respectively.

Evidence in favour of structures **5–7** for the products in question is their strong fluorescence, a property characteristic of coumarins substituted with an alkoxy substituent<sup>16</sup> at the 7-position and not at the 6-position of their skeleton. The suggested structure **6** was further supported by NOE experiments on its derivative **29** (see Scheme 4), as we will see in the following. The analytical and spectral data of the products obtained

are consistent with the structures suggested for them. The coumarin derivatives **5–7** exhibited absorptions at 1725–1720 and 1710–1680  $\text{cm}^{-1}$  in their IR spectra and a singlet at  $\delta$  6.33–6.39 in their  $^1\text{H}$  NMR spectra for the 7-H (3-H of pyranone ring), in contrast to the IR and  $^1\text{H}$  NMR spectra of compound **22**, which exhibited an absorption at 1780  $\text{cm}^{-1}$ , characteristic of a five-membered lactone carbonyl<sup>10</sup> and a singlet at  $\delta$  7.01.

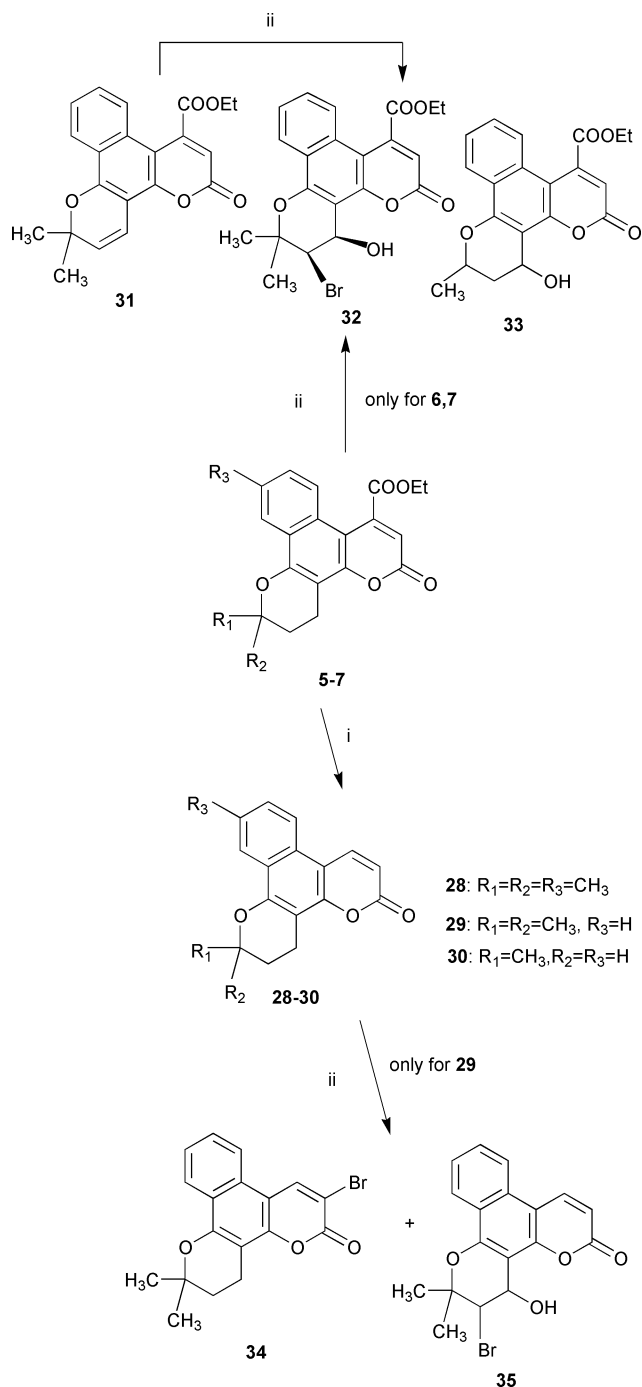
When quinone **11** was treated with ylide **19** under the conditions described above no reaction was observed, even under refluxing in ethyl acetate or toluene, as indicated by TLC examination after prolonged heating. When the mixture was then heated without solvent at  $\sim 150^\circ\text{C}$  (melted) for 1 h, diethyl 2-(10-hydroxy-2,2,7,7-tetramethyl-2,3,4,7,8,9-hexahydropyrano[2,3-*g*]chromen-5-yl)but-2-enedioate **27** was obtained in 69% yield, *via* the intermediates **25**, **26** (Scheme 3).<sup>17,18</sup> The stability of the product in question, under the con-



ditions applied for its preparation is strong evidence that the hydroxy group of this product is well separated from the ester groups, in agreement with the product expected<sup>17,18</sup> from the *p*-quinone **11**, since the formation of an *o*-hydroxy butenedioate intermediate, similar to **21**, from the isomeric *o*-quinone **13** ought to undergo a  $\delta$ -, and/or  $\gamma$ -lactonization.

De-ethoxycarbonylation of compounds **5–7** with copper powder in dry quinoline at 190–235  $^\circ\text{C}$  for 4–14 h gave 2,2,11-trimethyl-3,4-dihydro-2*H*-benzo[*f*]pyrano[2,3-*h*]chromen-6-one **28** (61%), 2,2-dimethyl-3,4-dihydro-2*H*-benzo[*f*]pyrano[2,3-*h*]chromen-6-one **29** (59–66%, three attempts) and 2-methyl-3,4-dihydro-2*H*-benzo[*f*]pyrano[2,3-*h*]chromen-6-one **30** (53%), respectively (Scheme 4). NOE experiments on the de-ethoxycarbonylation product of compound **6** showed an interaction between 8-H (8.41 ppm) and 9-H (8.13 ppm, 13.5%) and between 4-H (3.02 ppm) and 3-H (1.97 ppm, 7%) in agreement with structure **29** suggested for it. This proves beyond any doubt the identity of the structures **5–7** and **22**.

Treatment of compound **6** with NBS and a catalytic amount of benzoyl peroxide in refluxing carbon tetrachloride for 6 h and separation of the reaction mixture by column chromatography gave ethyl 2,2-dimethyl-6-oxo-2*H*,6*H*-benzo[*f*]pyrano[2,3-*h*]chromene-8-carboxylate **31** and ethyl 3-bromo-4-hydroxy-



**Scheme 4** Reagents and conditions: i, Cu, dry quinoline, 190–235  $^\circ\text{C}$ , 4–14 h; ii, NBS,  $\text{CCl}_4$ ,  $(\text{C}_6\text{H}_5\text{CO})_2\text{O}_2$ , reflux.

2,2-dimethyl-6-oxo-3,4-dihydro-2*H*,6*H*-benzo[*f*]pyrano[2,3-*h*]chromene-8-carboxylate **32** in 23% and 64% yield, respectively. By a similar treatment of compound **7** with NBS ethyl 4-hydroxy-2-methyl-6-oxo-3,4-dihydro-2*H*,6*H*-benzo[*f*]pyrano[2,3-*h*]chromene-8-carboxylate **33** was obtained in 67% yield.

The analytical and spectral data of the products in question accord well the structures suggested for them. The recorded  $^1\text{H}$  NMR spectrum of compound **32** exhibited two doublets at  $\delta$  4.27 (1H, d,  $J = 4.6$  Hz, exchangeable with  $\text{D}_2\text{O}$ ) and 4.41 (1H, d,  $J = 4.6$  Hz) and a triplet at  $\delta$  5.50 (1H, t,  $J = 4.6$  Hz) indicative of the  $-\text{OH}$  and the two protons of the pyran ring, with the hydroxy and bromo substituents in aa, ae or ea positions. The recorded  $^1\text{H}$  NMR spectrum of product **33** exhibited absorptions at  $\delta$  1.85 (1H, ddd,  $J = 3.8, 3.8, 14.0$  Hz), 2.26 (1H, d,  $J = 14.0$  Hz), 3.15 (br s, 1H), 4.62 (1H, dq,  $J = 3.8, 6.4$  Hz) and 5.32 (1H, d,  $J = 3.8$  Hz) for the  $-\text{OH}$  and the pyran protons, in agreement with the structure **33** suggested for it.

Obviously, compound **31** is formed *via* an initial benzylic bromination of **6**, followed by dehydrobromination, while compound **32** can be formed by further addition of hypobromous acid (HOBr) formed *in situ* from the NBS and H<sub>2</sub>O,<sup>19</sup> to compound **31**, with the –OH group being introduced into the 4-position, due to the more stable benzylic carbonium intermediate formed after the addition of the Br<sup>+</sup>. When, in a control experiment, compound **31** was treated with NBS under the conditions applied for the reaction of the latter with compound **6**, compound **32** was obtained in 63% yield. The formation of compound **33** can be explained by assuming a further substitution of the bromine of the 4-bromo derivative, initially formed, by the hydroxy group.

Treatment of compound **29** with NBS, under the same conditions, gave 7-bromo-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*f*]pyrano[2,3-*h*]chromen-6-one **34** and 3-bromo-4-hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*f*]pyrano[2,3-*h*]chromen-6-one **35**, in 30% and 12% yield, respectively. The <sup>1</sup>H NMR spectrum of compound **35** is very similar to that of compound **32**, with two absorptions at δ 4.41 (1H, d, *J* = 5.1 Hz) and 5.52 (1H, d, *J* = 5.1 Hz). The <sup>1</sup>H NMR of the major product showed a singlet at δ 8.73 for its 8-H and two triplets at δ 3.00 (2H, t, *J* = 6.8 Hz) and 1.97 (2H, t, *J* = 6.8 Hz) without any absorption for 7-H at δ ~ 6.4, in agreement with the structure **34** suggested for it. A similar bromination of the 3-position of the coumarin skeleton has also been reported in the case of the treatment of coumarin with NBS.<sup>20</sup>

In conclusion, the title compounds can be easily prepared in moderate to good yields, starting from the appropriate *o*-quinones, by using the reactions depicted in Schemes 2 and 4, and can further transformed into other derivatives modified in their pyran ring.

## Experimental

Mps were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were obtained with a Perkin–Elmer 1310 spectrophotometer as Nujol mulls. NMR spectra were recorded on a Bruker AM 300 (300 MHz and 75 MHz for <sup>1</sup>H and <sup>13</sup>C respectively, using CDCl<sub>3</sub> as the solvent and TMS as an internal standard. *J* values are reported in Hz. Mass spectra were determined on a VG-250 spectrometer at 70 eV under electron impact (EI) conditions, or on a Perkin Elmer API 100 Sciex Simple Quadrupole under electrospray ionization (ESI) conditions. High resolution mass spectra (HRMS) were recorded on an Ionspec mass spectrometer under matrix-assisted laser desorption-ionization Fourier transform mass spectrometer (MALDI-FTMS) conditions with 2,5-dihydroxybenzoic acid (DHB) as the matrix. Microanalyses were determined on a Perkin–Elmer 2400-II Element analyser. Silica gel No. 60, Merck AG was used for column chromatography. Compounds **17**<sup>14</sup> and **18**<sup>15</sup> were prepared according to the literature.

### 2,5-Dihydroxy-3,6-bis(3-methylbut-2-enyl)-1,4-benzoquinone **10**

Lithium hydride (1.192 g, 144.9 mmol) was added to a stirred solution of 2,5-dihydroxy-1,4-benzoquinone **9** (10.0 g, 71.38 mmol) in dry DMSO (83 cm<sup>3</sup>) at –78 °C and the mixture was heated gradually up to 25 °C. When the hydrogen gas evolution ceased, anhydrous lithium iodide (4.777 g, 35.7 mmol) was added, followed by 3,3-dimethylallyl bromide (21.276 g, 16.45 cm<sup>3</sup>, 142.76 mmol). The mixture was then heated at 45 °C for 7 h and left at 25 °C for 15 h. A mixture of ice (95 g) and water (35 cm<sup>3</sup>) was then added and the initial red colour was discharged within 5 min. The mixture was treated with concentrated hydrochloric acid (35 cm<sup>3</sup>) and then stirred with ethyl acetate (240 cm<sup>3</sup>) for 5 min. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 × 200 cm<sup>3</sup>). The combined organic extracts were washed with 5%

sodium bicarbonate solution (4 × 100 cm<sup>3</sup>). The combined aqueous layers were acidified accurately to pH = 2, by addition of concentrated hydrochloric acid and the unreacted quinone **9** was precipitated (3.2 g, 22.84 mmol, 32%). The organic extracts were concentrated on a rotary evaporator, ether (250 cm<sup>3</sup>) was added to the residue, the mixture was filtered and the filtrate was washed with 2 M sodium hydroxide solution (3 × 150 cm<sup>3</sup>). The combined alkaline extractions were then acidified accurately to pH = 2 by addition of concentrated hydrochloric acid and cooled in an ice–water bath to give a precipitate of compound **10** (3.965 g, 14.38 mmol, 20%), mp 176–178 °C (from ethanol) (Found: C, 69.8; H, 7.1. C<sub>16</sub>H<sub>20</sub>O<sub>4</sub> requires C, 69.5; H, 7.3%);  $\nu_{\max}/\text{cm}^{-1}$  3305, 1610;  $\delta_{\text{H}}$  1.68 (s, 6H), 1.73 (s, 6H), 3.11 (d, 4H, *J* = 7.6), 5.13 (t, 2H, *J* = 7.6), 7.61 (s, 2H, –OH, exchanged with D<sub>2</sub>O);  $\delta_{\text{C}}$  17.7, 21.5, 25.7, 102.2, 119.4, 133.7, 149.3, 175.1; EI MS: *m/z* 276 (M<sup>+</sup>, 65%), 261 (68), 220 (100), 205 (40), 55 (70); ESI MS: *m/z* 277 [M + H]<sup>+</sup>, 275 [M – H]<sup>+</sup>.

### Transformation of compound **10** to 2,2,7,7-tetramethyl-3,4,8,9-tetrahydropyrano[2,3-*g*]chromene-5(2*H*),10(7*H*)-dione **11** and 2,2,9-trimethyl-3,4-dihydro-2*H*-benzo[*h*]chromene-5,6-dione **16**

A mixture of quinone **10** (0.82 g, 2.97 mmol) in concentrated sulfuric acid (6 cm<sup>3</sup>) was stirred at 25 °C for 1 h and then poured into an ice–water mixture (100 g). The yellow precipitate formed was filtered off, washed with water, dried and recrystallized from ethanol to give compound **11** (0.24 g). The filtrate was concentrated and the residue was separated by column chromatography (DCM) to give an additional amount of compound **11** (0.132 g, total amount 0.372 g, 45%), mp 246–247 °C (sealed tube) (from ethanol);  $\nu_{\max}/\text{cm}^{-1}$  1635, 1590;  $\delta_{\text{H}}$  1.38 (s, 12H), 1.73 (t, 4H, *J* = 6.6), 2.42 (t, 4H, *J* = 6.6);  $\delta_{\text{C}}$  15.9, 26.4, 31.5, 78.2, 114.5, 152.9 181.3; ESI MS: *m/z* 277 [M + H]<sup>+</sup>, 299 [M + Na]<sup>+</sup>; MALDI HRMS (DHB): *m/z* 277.1424 [M + H]<sup>+</sup>. C<sub>16</sub>H<sub>21</sub>O<sub>4</sub> requires *m/z* 277.1434.

Compound **16** was eluted next (0.122 g, 16%), mp 172–174 °C (from ethanol);  $\nu_{\max}/\text{cm}^{-1}$  1680, 1630, 1565;  $\delta_{\text{H}}$  1.47 (s, 6H), 1.85 (t, 2H, *J* = 6.4), 2.46 (s, 3H), 2.56 (t, 2H, *J* = 6.4), 7.29 (d, 1H, *J* = 7.6), 7.59 (s, 1H), 7.95 (d, 1H, *J* = 7.6);  $\delta_{\text{C}}$  16.2, 22.1, 26.7, 31.7, 79.1, 112.6, 124.6, 127.9, 128.9, 131.2, 132.6, 146.0, 162.0, 174.4, 178.9; ESI MS: *m/z* 257 [M + H]<sup>+</sup>, 255 [M – H]<sup>+</sup>, 279 [M + Na]<sup>+</sup>; MALDI HRMS (DHB): *m/z* 257.1176 [M + H]<sup>+</sup>. C<sub>16</sub>H<sub>17</sub>O<sub>3</sub> requires *m/z* 257.1172.

### Ethyl 2,2,11-trimethyl-6-oxo-3,4-dihydro-2*H*,6*H*-benzo[*f*]pyrano[2,3-*h*]chromene-8-carboxylate **5**

A solution of quinone **16** (59 mg, 0.23 mmol) and ylide **19** (77 mg, 0.51 mmol) in dry DCM (5 cm<sup>3</sup>) was refluxed for 5 h and the solvent was removed on a rotary evaporator. Separation of the residue by column chromatography (hexane–ethyl acetate 10 : 1) gave compound **5** (67 mg, 80%), mp 161–163 °C (ether–hexane);  $\nu_{\max}/\text{cm}^{-1}$  3050, 1725, 1680, 1578;  $\delta_{\text{H}}$  1.40 (t, 3H, *J* = 7.6), 1.48 (s, 6H), 1.96 (t, 2H, *J* = 6.4), 2.53 (s, 3H), 2.99 (t, 2H, *J* = 6.4), 4.52 (q, 2H, *J* = 7.6), 6.33 (s, 1H, 7-H), 7.36 (d, 1H, *J* = 8.9), 7.65 (d, 1H, *J* = 8.9), 8.07 (s, 1H);  $\delta_{\text{C}}$  13.8, 17.1, 21.4, 26.6, 31.6, 62.7, 76.5, 103.1, 105.9, 110.3, 121.9, 123.0, 123.7, 125.2, 129.5, 135.0, 146.7, 153.9, 154.7, 160.4, 167.9; ESI MS: *m/z* 367 [M + H]<sup>+</sup>, 365 [M – H]<sup>+</sup>, 389 [M + Na]<sup>+</sup>; MALDI HRMS (DHB): *m/z* 367.1528 [M + H]<sup>+</sup>. C<sub>22</sub>H<sub>23</sub>O<sub>3</sub> requires 367.1540.

### Ethyl 2,2-dimethyl-6-oxo-3,4-dihydro-2*H*,6*H*-benzo[*f*]pyrano[2,3-*h*]chromene-8-carboxylate **6**

A. A solution of β-lapachone **17** (0.478 g, 1.975 mmol) and ylide **19** (2.062 g, 5.93 mmol) in dry DCM (25 cm<sup>3</sup>) was heated under reflux for 1 h, until the quinone was consumed. The solvent was evaporated off on a rotary evaporator and the residue was separated by column chromatography (hexane–ethyl acetate 10 : 1) to give, after the elution of triphenylphosphine (0.367 g, 71%), compound **6** (0.459 g, 66%).

**B.** A solution of **17** (0.484 g, 2 mmol) and ylide **19** (1.462 g, 4.20 mmol) in dry DCM (15 cm<sup>3</sup>) was stirred at room temperature for 14 h to give compound **6** (0.367 g, 53%), mp 137–138 °C (ether–hexane) (Found: C, 71.4; H, 5.7. C<sub>21</sub>H<sub>20</sub>O<sub>5</sub> requires C, 71.6; H, 5.7%);  $\nu_{\max}/\text{cm}^{-1}$  1725, 1710, 1690;  $\delta_{\text{H}}$  1.40 (t, 3H,  $J = 7.6$ ), 1.47 (s, 6H), 1.96 (t, 2H,  $J = 6.4$ ), 3.00 (t, 2H,  $J = 6.4$ ), 4.52 (q, 2H,  $J = 7.6$ ), 6.36 (s, 1H, 7-H), 7.46–7.56 (m, 2H), 7.76 (d, 1H,  $J = 7.6$ ), 8.31 (d, 1H,  $J = 7.6$ );  $\delta_{\text{C}}$  13.9, 17.1, 26.6, 31.5, 62.7, 103.1, 105.9, 110.4, 122.7, 123.1, 123.6, 125.1, 127.2, 127.6, 146.7, 154.3, 155.2, 160.3, 167.9; EI MS:  $m/z$  352 (M<sup>+</sup>, 100%), 297 (33), 296 (58), 268 (61), 240 (20), 223 (18), 167 (20), 139 (26).

#### Ethyl 2-methyl-6-oxo-3,4-dihydro-2H,6H-benzo[*f*]pyrano[2,3-*h*]chromene-8-carboxylate **7**

A solution of quinone **18** (0.55 g, 2.41 mmol) and ylide **19** (2.098 g, 6.03 mmol) in dry DCM (20 cm<sup>3</sup>) was stirred at room temperature for 1 h during which time the quinone was consumed. The solvent was evaporated off on a rotary evaporator and the residue was chromatographed on a column (hexane–ethyl acetate 6 : 1) to give, after the elution of compound **22**, compound **7** (0.509 g, 62%), mp 170–172 °C (ethyl acetate–hexane) (Found: C, 70.8; H, 5.3. C<sub>20</sub>H<sub>18</sub>O<sub>5</sub> requires C, 71.0; H, 5.4%);  $\nu_{\max}/\text{cm}^{-1}$  3060, 1720, 1690, 1580;  $\delta_{\text{H}}$  1.42 (t, 3H,  $J = 7.2$ ), 1.60 (d, 3H,  $J = 6.3$ ), 1.82–1.90 (m, 1H), 2.20–2.28 (m, 1H), 2.91–2.99 (m, 1H), 3.13–3.19 (m, 1H), 4.40–4.46 (m, 1H), 4.55 (q, 2H,  $J = 7.2$ ), 6.39 (s, 1H, 7-H), 7.51–7.58 (m, 2H), 7.75 (d, 1H,  $J = 7.6$ ), 8.30 (d, 1H,  $J = 7.6$ );  $\delta_{\text{C}}$  13.9, 19.1, 20.9, 27.8, 62.7, 73.6, 103.4, 106.9, 110.6, 122.6, 123.1, 123.2, 125.2, 127.1, 127.6, 146.7, 155.1, 155.2, 160.2, 167.8; ESI MS:  $m/z$  339 [M + H]<sup>+</sup>, 361 [M + Na]<sup>+</sup>.

#### Ethyl 2-[2-methyl-6-oxo-3,4,6,7-tetrahydro-2H-benzo[*h*]furo[2,3-*f*]chromen-7-ylidene]acetate **22**

Acetate **22** was obtained from the reaction between compounds **18** and **19** described above (0.052 g, 6%), mp 181–182 °C (DCM–hexane);  $\nu_{\max}/\text{cm}^{-1}$  3060, 1780, 1705, 1590;  $\delta_{\text{H}}$  1.39 (t, 3H,  $J = 7.6$ ), 1.55 (d, 3H,  $J = 6.4$ ), 1.72–1.86 (m, 1H), 2.10–2.23 (m, 1H), 2.71–2.98 (m, 2H), 4.32–4.50 (m, 3H), 7.01 (s, 1H), 7.41 (t, 1H,  $J = 7.6$ ), 7.56 (t, 1H,  $J = 7.6$ ), 7.87 (d, 1H,  $J = 8.9$ ), 8.23 (d, 1H,  $J = 8.9$ );  $\delta_{\text{C}}$  14.0, 18.8, 21.0, 27.7, 61.7, 73.7, 103.3, 105.6, 121.8, 122.8, 123.5, 124.3, 125.5, 127.7, 128.8, 129.2, 154.5, 155.4, 165.2, 165.6; EI MS:  $m/z$  338 (M<sup>+</sup>, 100%), 310 (14), 293 (22), 268 (51), 267 (13), 266 (52), 251 (14), 167 (51), 139 (53); MALDI HRMS (DHB):  $m/z$  339.1228 [M + H]<sup>+</sup>. C<sub>20</sub>H<sub>19</sub>O<sub>5</sub> requires 339.1227.

#### Diethyl 2-(10-hydroxy-2,2,7,7-tetramethyl-2,3,4,7,8,9-hexahydropyrano[2,3-*g*]chromen-5-yl)but-2-enedioate **27**

A solution of quinone **11** (0.2 g, 0.72 mmol) and ylide **19** (0.707 g, 2.03 mmol) was heated in an oil bath at ~150 °C for 1 h after which the reaction mixture was separated by column chromatography (hexane–ethyl acetate 10 : 1) to give compound **27** (0.214 g, 69%), yellow oil;  $\nu_{\max}/\text{cm}^{-1}$  3430, 1720, 1710, 1620, 1590;  $\delta_{\text{H}}$  1.13 (t, 3H,  $J = 7.2$ ), 1.19 (s, 3H), 1.22 (s, 3H), 1.28 (t, 3H,  $J = 7.2$ ), 1.31 (s, 3H), 1.37 (s, 3H), 1.72–1.79 (m, 4H), 2.36–2.43 (m, 1H), 2.50–2.55 (m, 1H), 2.67–2.71 (m, 2H), 4.0–4.09 (m, 2H), 4.19–4.30 (m, 2H), 5.70 (s, 1H), 6.99 (s, 1H);  $\delta_{\text{C}}$  13.9, 14.1, 17.1, 20.4, 25.5, 26.0, 26.9, 27.5, 32.1, 33.1, 60.3, 61.3, 73.5, 74.3, 105.9, 112.4, 117.8, 129.3, 133.4, 141.4, 142.8, 144.4, 165.3, 167.1; ESI MS:  $m/z$  433 [M + H]<sup>+</sup>, 431 [M – H]<sup>+</sup>, 455 [M + Na]<sup>+</sup>; MALDI HRMS (DHB):  $m/z$  432.2142 [M]<sup>+</sup>. C<sub>24</sub>H<sub>32</sub>O<sub>7</sub> requires 432.2142. Unreacted starting quinone **11** was eluted next (16 mg, 8%).

#### De-ethoxycarbonylation of compounds **5–7**

**Synthesis of compounds 28–30: general procedure.** A mixture of the ester **5–7** (0.5 mmol) and copper powder (220 mg, 3.5

mmol) in dry quinoline (10 cm<sup>3</sup>) was heated at 195–235 °C under a nitrogen atmosphere for 4–14 h. Ethyl acetate (3 × 10 cm<sup>3</sup>) was then added to the cooled mixture and this was filtered. The combined filtrates were treated with 10% hydrochloric acid (4 × 15 cm<sup>3</sup>) and the organic layer was washed with water (2 × 10 cm<sup>3</sup>), dried with anhydrous sodium sulfate and concentrated on a rotary evaporator. The residue was separated by column chromatography (hexane–ethyl acetate 15 : 1) to give the products **28–30**.

**2,2,11-Trimethyl-3,4-dihydro-2H-benzo[*f*]pyrano[2,3-*h*]chromen-6-one **28.** This was obtained from compound **5** which was heated at 190–195 °C for 5 h, (90 mg, 61%), mp 211–212 °C (ethyl acetate–hexane) (Found: C, 77.75; H, 6.2. C<sub>19</sub>H<sub>18</sub>O<sub>3</sub> requires C, 77.5; H, 6.2%);  $\nu_{\max}/\text{cm}^{-1}$  3060, 1710, 1560, 1510;  $\delta_{\text{H}}$  1.48 (s, 6H), 1.96 (t, 2H,  $J = 6.9$ , 3-H), 2.55 (s, 3H), 3.01 (t, 2H,  $J = 6.9$ , 4-H), 6.35 (d, 1H,  $J = 9.5$ , 7-H), 7.47 (d, 1H,  $J = 8.6$ ), 8.02 (d, 1H,  $J = 8.6$ ), 8.05 (s, 1H), 8.39 (d, 1H,  $J = 9.5$ , 8-H);  $\delta_{\text{C}}$  16.9, 21.6, 26.7, 31.7, 76.2, 105.8, 106.3, 110.7, 120.9, 121.8, 123.2, 126.3, 129.9, 135.0, 139.7, 153.0, 153.7, 162.0; EI MS:  $m/z$  294 (M<sup>+</sup>, 75%), 238 (100), 210 (35), 84 (90).**

**2,2-Dimethyl-3,4-dihydro-2H-benzo[*f*]pyrano[2,3-*h*]chromen-6-one **29.** This was obtained from compound **6** which was heated at 230–235 °C for 4 h, (93 mg, 66%), mp 144–145 °C (ether–hexane) (Found: C, 77.15; H, 5.4. C<sub>18</sub>H<sub>16</sub>O<sub>3</sub> requires C, 77.1; H, 5.75%);  $\nu_{\max}/\text{cm}^{-1}$  3030, 1715, 1575, 1560, 1510;  $\delta_{\text{H}}$  1.47 (s, 6H), 1.97 (t, 2H,  $J = 6.5$ , 3-H), 3.02 (t, 2H,  $J = 6.5$ , 4-H), 6.36 (d, 1H,  $J = 9.7$ , 7-H), 7.51 (t, 1H,  $J = 7.6$ ), 7.63 (t, 1H,  $J = 7.6$ ), 8.13 (d, 1H,  $J = 7.6$ , 9-H), 8.28 (d, 1H,  $J = 7.6$ ), 8.41 (d, 1H,  $J = 9.7$ , 8-H);  $\delta_{\text{C}}$  16.8, 26.6, 31.5, 76.2, 105.7, 106.1, 110.6, 120.8, 122.5, 123.0, 125.0, 127.8, 128.1, 139.5, 153.3, 154.0, 161.6; EI MS:  $m/z$  280 (M<sup>+</sup>, 100%), 265 (7), 225 (35), 224 (83), 196 (58), 139 (30), 115 (18), 114 (15).**

**2-Methyl-3,4-dihydro-2H-benzo[*f*]pyrano[2,3-*h*]chromen-6-one **30.** This was obtained from compound **7** which was heated at 190–195 °C for 14 h, (71 mg, 53%), mp 195–196 °C (ethyl acetate–hexane) (Found: C, 76.9; H, 5.2. C<sub>17</sub>H<sub>14</sub>O<sub>3</sub> requires C, 76.7; H, 5.3%);  $\nu_{\max}/\text{cm}^{-1}$  3040, 1705, 1575, 1555, 1505;  $\delta_{\text{H}}$  1.57 (d, 3H,  $J = 6.9$ ), 1.74–1.92 (m, 1H), 2.19–2.28 (m, 1H), 2.82–2.99 (m, 1H), 3.07–3.19 (m, 1H), 4.31–4.45 (m, 1H), 6.35 (d, 1H,  $J = 9.5$ , 7-H), 7.51 (t, 1H,  $J = 8.6$ ), 7.63 (t, 1H,  $J = 8.6$ ), 8.11 (d, 1H,  $J = 8.6$ ), 8.27 (d, 1H,  $J = 8.6$ ), 8.38 (d, 1H,  $J = 9.5$ , 8-H);  $\delta_{\text{C}}$  18.9, 21.0, 27.9, 73.4, 106.5, 106.8, 111.0, 120.9, 122.5, 122.7, 125.2, 128.0, 128.1, 139.6, 154.1, 154.4, 161.7; EI MS:  $m/z$  266 (M<sup>+</sup>, 100%), 251 (12), 237 (20), 224 (70), 196 (65).**

#### Ethyl 2,2-dimethyl-6-oxo-2H,6H-benzo[*f*]pyrano[2,3-*h*]chromene-8-carboxylate **31**

A mixture of compound **6** (0.332 g, 0.942 mmol), NBS (0.168 g, 0.943 mmol) and benzoyl peroxide (3 mg, 0.0095 mmol) in carbon tetrachloride (20 cm<sup>3</sup>) was heated under reflux for 3 h. Additional amounts of NBS (0.168 g, 0.943 mmol) and benzoyl peroxide (3 mg) were then added and the mixture was heated for a further 3 h and then cooled to room temperature. The precipitated succinimide was filtered off and washed with carbon tetrachloride (5 cm<sup>3</sup>). The filtrate was concentrated on a rotary evaporator and the residue was separated by column chromatography (hexane–ethyl acetate 10 : 1 up to 4 : 1) to give first compound **31** (76 mg, 23%), yellow crystals, mp 112–113 °C (from hexane) (Found: C, 72.0; H, 5.1. C<sub>21</sub>H<sub>18</sub>O<sub>5</sub> requires C, 72.0; H, 5.2%);  $\nu_{\max}/\text{cm}^{-1}$  3050, 1730, 1690;  $\delta_{\text{H}}$  1.40 (t, 3H,  $J = 7.2$ ), 1.58 (s, 6H), 4.53 (q, 2H,  $J = 7.2$ ), 5.79 (d, 1H,  $J = 10.0$ ), 6.38 (s, 1H, 7-H), 6.99 (d, 1H,  $J = 10.0$ ), 7.50–7.59 (m, 2H), 7.74 (d, 1H,  $J = 8.5$ ), 8.30 (d, 1H,  $J = 7.9$ );  $\delta_{\text{C}}$  13.9, 28.2, 62.9, 78.8, 106.4, 107.3, 111.3, 115.6, 123.0, 123.2, 123.4, 125.5, 126.6, 128.3, 129.5, 146.7, 152.2, 153.5, 160.0, 167.7; EI MS:  $m/z$  350 (M<sup>+</sup>, 100%), 336 (14), 335 (78), 307 (8), 261 (8), 235 (7), 205 (5), 178 (8).

### Ethyl 3-bromo-4-hydroxy-2,2-dimethyl-6-oxo-3,4-dihydro-2H,6H-benzof[*f*]pyrano[2,3-*h*]chromene-8-carboxylate **32**

A. Compound **32** [0.257 g, 64%, yellow crystals, mp 71–73 °C (ether–hexane)] was eluted after compound **31** from the reaction of **6** described above.

B. A mixture of compound **31** (60 mg, 0.17 mmol), NBS (31 mg, 0.17 mmol) and a few crystals of benzoyl peroxide in carbon tetrachloride (3 cm<sup>3</sup>) was refluxed for 2 h. TLC examination of the reaction mixture showed the presence of unreacted starting quinone **31**. An additional amount of NBS (31 mg, 0.17 mmol) was then added and the mixture was refluxed for a further 2 h, after which time the starting material was consumed. The reaction mixture was cooled, the precipitated succinimide was filtered off, the filtrate was concentrated on a rotary evaporator and the residue was separated by column chromatography (hexane–ethyl acetate 7 : 1 up to 4 : 1) to give compound **32**, identical with that obtained by method A, (48 mg, 63%) (Found: C, 56.5; H, 4.15. C<sub>21</sub>H<sub>19</sub>BrO<sub>6</sub> requires C, 56.4; H, 4.3%;  $\nu_{\max}/\text{cm}^{-1}$  3450, 3050, 1715, 1690;  $\delta_{\text{H}}$  1.40 (t, 3H,  $J = 7.3$ ), 1.67 (s, 3H), 1.74 (s, 3H), 4.27 (d, 1H,  $J = 4.6$ , exchangeable with D<sub>2</sub>O), 4.41 (d, 1H,  $J = 4.6$ ), 4.53 (q, 2H,  $J = 7.3$ ), 5.50 (t, 1H,  $J = 4.6$ ), 6.42 (s, 1H, 7-H), 7.53–7.63 (m, 2H), 7.78 (d, 1H,  $J = 8.3$ ), 8.35 (d, 1H,  $J = 8.3$ );  $\delta_{\text{C}}$  13.9, 25.4, 25.9, 57.2, 63.0, 67.3, 79.6, 104.9, 106.9, 111.3, 123.3, 123.6, 125.9, 128.4, 128.8, 133.8, 147.0, 153.0, 155.5, 159.8, 167.4; EI MS:  $m/z$  448/446 (M<sup>+</sup>, 100%), 432 (11), 430 (14), 367 (11), 350 (35), 349 (11), 336 (44), 312 (96), 284 (89), 256 (46), 126 (76).

### Ethyl 4-hydroxy-2-methyl-6-oxo-3,4-dihydro-2H,6H-benzof[*f*]pyrano[2,3-*h*]chromene-8-carboxylate **33**

A mixture of compound **7** (0.3 g, 0.887 mmol), NBS (0.174 g, 0.976 mmol) and benzoyl peroxide (2.7 mg, 0.00855 mmol) in carbon tetrachloride (15 cm<sup>3</sup>) was heated under reflux for 3 h. Additional amounts of NBS (0.174 g, 0.976 mmol) and benzoyl peroxide (2.7 mg, 0.00855 mmol) were added and the mixture was heated for an additional 6 h. The mixture was cooled at room temperature and the precipitated succinimide was filtered off and washed with carbon tetrachloride (5 cm<sup>3</sup>). The solvent was removed on a rotary evaporator and the residue was separated by column chromatography (hexane–ethyl acetate 10 : 1) to give yellow crystals of compound **33** (0.21 g, 67%), mp 171–173 °C (ether–hexane) (Found: C, 67.7; H, 5.0. C<sub>20</sub>H<sub>18</sub>O<sub>6</sub> requires C, 67.8; H, 5.1%;  $\nu_{\max}/\text{cm}^{-1}$  3350, 3060, 1715, 1690;  $\delta_{\text{H}}$  1.39 (t, 3H,  $J = 7.6$ ), 1.63 (d, 3H,  $J = 6.4$ ), 1.85 (ddd, 1H,  $J_1 = 3.8$ ,  $J_2 = 3.8$ ,  $J_3 = 14.0$ ), 2.26 (d, 1H,  $J = 14.0$ ), 3.15 (br s, 1H), 4.51 (q, 2H,  $J = 7.6$ ), 4.62 (dq, 1H,  $J_1 = 3.8$ ,  $J_2 = 6.4$ ), 5.32 (d, 1H,  $J = 3.8$ ), 6.37 (s, 1H, 7-H), 7.49–7.59 (m, 2H), 7.75 (d, 1H,  $J = 7.6$ ), 8.35 (d, 1H,  $J = 7.6$ );  $\delta_{\text{C}}$  13.9, 20.8, 36.6, 58.3, 62.8, 69.7, 103.7, 109.0, 111.0, 123.2, 123.3, 123.4, 125.5, 128.1, 128.5, 146.9, 155.4, 155.9, 159.9, 167.6; EI MS:  $m/z$  354 (M<sup>+</sup>, 100%), 336 (10), 321 (29), 286 (50), 284 (83), 256 (59), 183 (48), 127 (91).

### 7-Bromo-2,2-dimethyl-3,4-dihydro-2H-benzof[*f*]pyrano[2,3-*h*]chromen-6-one **34**

A mixture of compound **29** (0.117 g, 0.417 mmol), NBS (0.074 g, 0.417 mmol) and benzoyl peroxide (1 mg, 0.0042 mmol) in carbon tetrachloride (10 cm<sup>3</sup>) was refluxed for 30 min and additional amounts of NBS (0.038 g, 0.213 mmol) and benzoyl peroxide (1 mg, 0.0042 mmol) were then added. The reaction mixture was refluxed for further 30 min, cooled to room temperature and the precipitated succinimide was filtered off and washed with carbon tetrachloride (2 cm<sup>3</sup>). The filtrate was concentrated on a rotary evaporator and the residue was separated by column chromatography (hexane–ethyl acetate 15 : 1 up to 4 : 1) to give compound **34** (45 mg, 30%), mp 226–228 °C (ethyl acetate–hexane);  $\nu_{\max}/\text{cm}^{-1}$  3050, 1710, 1570;  $\delta_{\text{H}}$  1.48 (s, 6H),

1.97 (t, 2H,  $J = 6.8$ ), 3.00 (t, 2H,  $J = 6.8$ ), 7.53 (t, 1H,  $J = 7.8$ ), 7.64 (t, 1H,  $J = 7.8$ ), 8.08 (d, 1H,  $J = 7.8$ ), 8.28 (d, 1H,  $J = 7.8$ ), 8.73 (s, 1H, 8-H);  $\delta_{\text{C}}$  16.9, 26.7, 31.6, 78.6, 105.6, 105.8, 107.0, 120.9, 121.2, 122.8, 123.3, 125.5, 127.5, 128.3, 141.1, 153.9, 158.0; EI MS:  $m/z$  360/358 (M<sup>+</sup>, 100%), 343 (48), 341 (33), 304 (51), 302 (41), 223 (17), 152 (33), 139 (97); MALDI HRMS (DHB):  $m/z$  359.0288 [M + H]<sup>+</sup>. C<sub>18</sub>H<sub>16</sub>BrO<sub>3</sub> requires 359.0277.

### 3-Bromo-4-hydroxy-2,2-dimethyl-3,4-dihydro-2H-benzof[*f*]pyrano[2,3-*h*]chromen-6-one **35**

The hydroxy bromide **35** was obtained from the reaction of compound **29** with NBS, described above (eluted after compound **34**), (18 mg, 12%), mp 210–212 °C (ethyl acetate–hexane);  $\nu_{\max}/\text{cm}^{-1}$  3320, 3070, 1730, 1580;  $\delta_{\text{H}}$  1.65 (s, 3H), 1.75 (s, 3H), 2.18 (br s, 1H), 4.41 (d, 1H,  $J = 5.1$ ), 5.52 (d, 1H,  $J = 5.1$ ), 6.42 (d, 1H,  $J = 10.2$ , 7-H), 7.57 (t, 1H,  $J = 8.9$ ), 7.71 (t, 1H,  $J = 8.9$ ), 8.15 (d, 1H,  $J = 8.9$ ), 8.32 (d, 1H,  $J = 8.9$ ), 8.43 (d, 1H,  $J = 10.2$ , 8-H);  $\delta_{\text{C}}$  24.7, 26.1, 57.4, 67.4, 79.5, 106.3, 106.8, 107.5, 111.6, 121.1, 122.7, 123.5, 125.8, 129.2, 139.8, 152.1, 154.0, 160.9; EI MS:  $m/z$  376/374 (M<sup>+</sup>, 23%), 278 (8), 277 (16), 263 (15), 240 (100), 212 (70), 184 (23), 128 (35); MALDI HRMS (DHB):  $m/z$  375.0228 [M + H]<sup>+</sup>. C<sub>18</sub>H<sub>16</sub>BrO<sub>4</sub> requires 375.0226.

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