Chromone studies. Part 17. Tricyclic scaffolds from reactions of chromone-3-carbaldehydes and methyl vinyl ketone under Baylis–Hillman conditions

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Reaction of a series of chromone-3-carbaldehydes with methyl vinyl ketone under Baylis–Hillman conditions, using 3-hydroxyquinuclidine in chloroform or DABCO in 1-methyl-2-pyrrolidinone, affords unprecedented tricylic chromone derivatives which, depending on the conditions, may be accompanied by the normal Baylis–Hillman products or their respective tricyclic dimers.

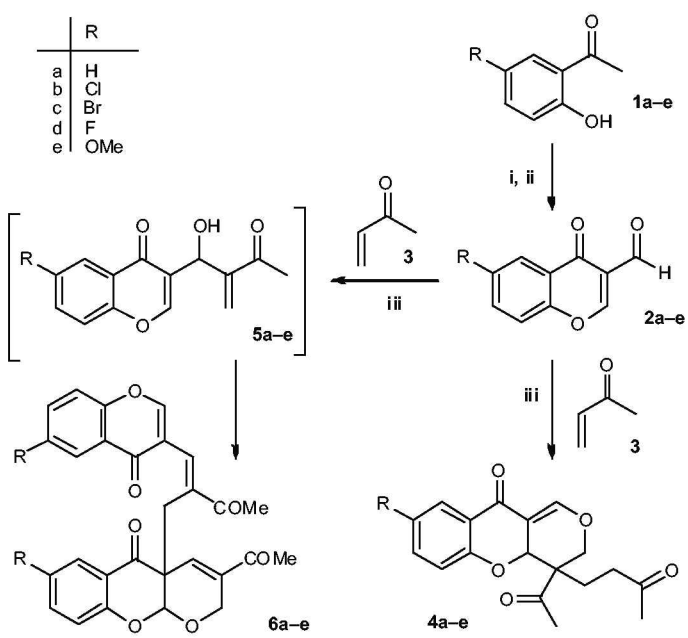
Keywords: Baylis–Hillman reaction, chromone-3-carbaldehydes, methyl vinyl ketone, tricyclic products

Many naturally occurring chromones have been found to exhibit interesting biological activity.[1,2] Examples include khellin, a furochromone with vasodilator and smooth muscle relaxing properties[3] isolated from the fruits and seeds of *Ammi visnaga*[4] and used to treat bronchial asthma,[3-5] and styrylchromone derivatives isolated from the marine cyanophyte, *Hormothamnion enteromorphoides*,[6] which have proved to be potent cytotoxic agents against P388 lymphocytic leukaemia and HL-60 human promyelocytic leukaemia cell lines. As part of ongoing synthetic and physical organic studies of chromone derivatives,[7] we have previously reported the formation of novel dimeric and bis-chromone adducts during 1,4-diazabicyclo[2.2.2]octane (DABCO) catalysed Baylis–Hillman reactions of chromone-3-carbaldehydes with methyl acrylate[8] and acrylonitrile,[9] respectively. In the latter study,[9] treatment of chromone-3-carbaldehyde **2a** (Scheme 1) with methyl vinyl ketone (MVK) in the presence of DABCO afforded the expected Baylis–Hillman product **5a** in very low yield (3%) together with the corresponding condensation dimer **6a** (33%), while a *trace* quantity of a completely different, bis(chromone)–acrylonitrile adduct was isolated from a reaction with acrylonitrile and formulated, on the basis of the HRMS and NMR data, as the polycyclic compound **7**.

Baylis–Hillman reactions are known to be sensitive to variations in the catalyst and solvent system[7] and we now report the results of reactions of a series of chromone-3-carbaldehydes with methyl vinyl ketone conducted using 3-hydroxyquinuclidine in chloroform and DABCO in the solvent, 1-methyl-2-pyrrolidinone (NMP), and in chloroform.

The chromone-3-carbaldehydes **2a–e**, obtained by "double" Vilsmeier–Haak formylation[10] of the corresponding 2-hydroxyacetophenone precursors **1a–e**, were first reacted with MVK **3** and 3-hydroxyquinuclidine in chloroform for 24 hours.[11] Work-up and purification of the crude products afforded the novel tricyclic adducts **4a–e** (31–52%) and the chromone dimers **6a–e** (12–25%), which contain isomeric tricyclic skeletons. Surprisingly, none of the Baylis–Hillman products **5a–e** appeared to be present after 24 hours,[11] and it was assumed that they had been formed as intermediates but converted *in situ* into the corresponding chromone dimers **6a–e**. The unusual, oxygenated, tricyclic skeleton in the former series (**4a–e**) has been found in natural metallo-β-lactamase inhibitors, such as **8**,[12] and in more complex semaphorin inhibitors.[13]

Use of DABCO, as catalyst, and NMP, as solvent, resulted in the isolation of the tricyclic adducts **4a–e** chemoselectively,



Scheme 1 Reagents and conditions: (i) $POCl_3$, DMF; (ii) H_2O; (iii) 3-hydroxyquinuclidine, $CHCl_3$

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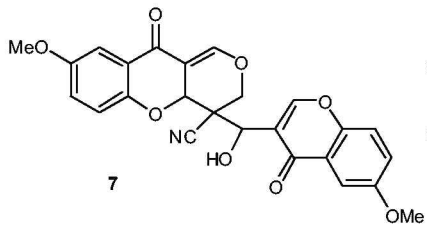

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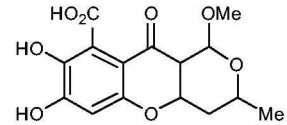

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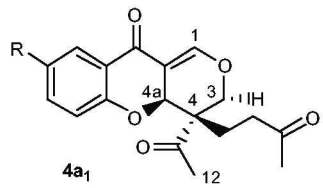
but in slightly lower yield (30–45%).[10] When 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was employed as the catalyst, however, the reaction failed to take place at all, confirming the observation by Aggarwal *et al.*[15] that MVK is not reactive as a Baylis–Hillman substrate in the presence of DBU. When the reactions of the chromone-3-carbaldehydes **2a–c,e** were repeated using 3-hydroxyquinuclidine in chloroform,[14] work-up and chromatography of the crude products afforded the chromone dimers **6a–c,e** (34–72%) and the tricyclic products **4a–c,e** in lower yields (≤ 16%) than those observed earlier.[11] Increasing the relative quantity of MVK (from 1.1 to 2.0 equivalents) failed to improve the yields of the tricyclic adducts **4** but, surprisingly, resulted in the formation of the Baylis–Hillman products **5a–c,e** as competition products instead of the dimers **6a–c,e**. When the chromone-3-carbaldehydes **2a–e** were reacted with MVK using DABCO as catalyst in chloroform for 21 days, work-up and chromatography afforded the chromone dimers **6a–e** in yields (24–49%) comparable to those obtained for dimer **6a** (33%) in our earlier study; [9] however, none of the Baylis–Hillman products were isolated. All products were fully characterised by spectroscopic (IR, 1- and 2-dimensional NMR) and elemental (HREIMS) analysis.

In addition to possessing isomeric tricyclic skeletons, the compounds in both series of products (**4a–e** and **6a–e**) each contain two new stereogenic centres, and diastereomeric products may be expected in each case. Semi-preparative HPLC of the parent tricyclic product **4a** (R = H) afforded two fractions shown to be the diastereomeric products, the relative configurations of which have been assigned following examination of their 2-dimensional n.O.e. (NOESY) spectra. While the stereochemistry of the latter compounds (**6a–e**) is further complicated by *E*- and *Z*-configurational options about the exocyclic double bond, diastereoselective formation of the *E*-products seems likely, based on the NMR spectra and the *E*-configuation observed in the X-ray structure of a diester analogue.[9] The NOESY spectrum of the tricyclic adduct **4a**$_1$ (Fig. 1) reveals interactions between the 1-methine and 12-methyl protons, and between the 4a-methine and one of the 3-methylene protons; however, neither of these interactions provides definitive information pertinent to the stereochemistry of the stereogenic centres C-4 and C-4a. The NOESY spectrum of the diasteromeric tricyclic adduct **4a**$_2$ (Fig. 2), on the other hand, reveals interactions between the 4a-methine and the 13- and 14-methylene protons, clearly indicating that they occupy the same face of the molecule. These observations justify the 4*R*,4a*R* (or 4*S*,4a*S*) configurational assignment(s) to the enantiomers **4a**$_2$ and, by inference, the 4*S*,4a*R* (or 4*R*,4a*S*) configuration(s) to the enantiomers of diastereomer **4a**$_1$.

Semi-preparative HPLC of the brominated and chlorinated analogues **4b** and **4c**, respectively, afforded only one fraction in each case. The brominated analogue **4b** exhibited similar ^{1}H NMR signal patterns to the parent system **4a**$_1$, whereas the chlorinated analogue **4c** exhibited similar ^{1}H NMR signal patterns to the diastereomeric system **4a**$_2$. However, since the reaction and work-up conditions for these transformations have yet to be optimised, generalisations about the relative diastereoselectivities would be premature.

The formation of the bis-MVK tricyclic products **4a–e** and the trace product **7**[9] presents interesting mechanistic possibilities; firm conclusions, however, would be premature at this stage and must await the results of detailed kinetic-mechanistic studies. The tricyclic derivatives **6a–e**, on the other hand, are bis-Baylis–Hillman adducts and are, in fact, analogues of the dimeric products obtained during DABCO-catalysed Baylis–Hillman reactions of chromone-3-carbaldehydes with methyl acrylate.[8] Their formation is presumed to follow the mechanistic sequence proposed earlier,[8] the only difference being the presence of CO.Me rather than CO_2Me moieties. Thus, a pair of the MVK-derived Baylis–Hillman adducts **5** are proposed to combine *via* a six-centred transition state complex, as outlined in Scheme 2, leading to intermediate **9**. Attack of the hemi-acetal hydroxyl oxygen on the α,β-unsaturated carbonyl moiety then results



4a$_1$

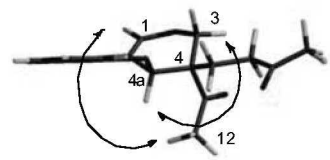
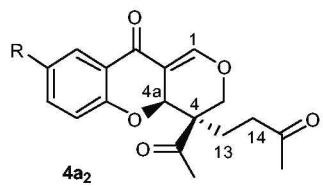


Fig. 1 Assigned relative configuration and computer-modelled structure of diastereomer **4a**$_1$, showing observed n.O.e. interactions.



4a$_2$

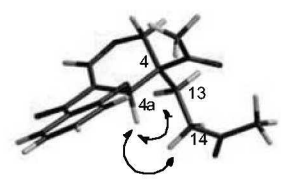
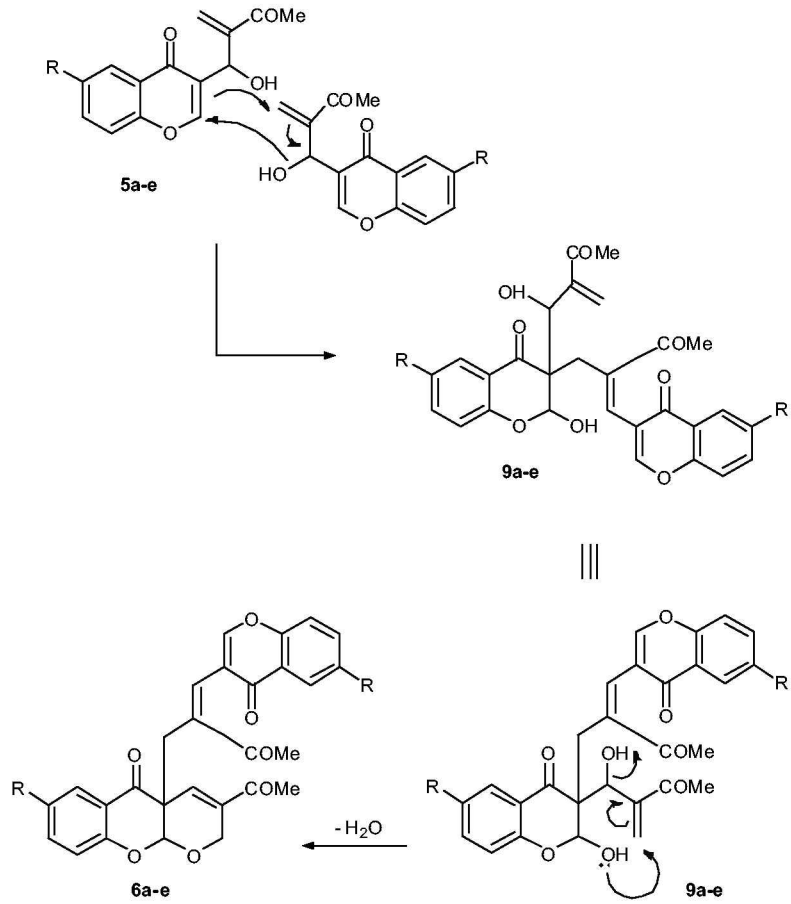


Fig. 2 Assigned relative configuration and computer-modelled structure of diastereomer **4a**$_2$, showing observed n.O.e. interactions.



Scheme 2 Proposed mechanism for the formation of compounds **6**.

in intramolecular cyclisation *via* an S_N2' (as shown) or a conjugate addition–elimination sequence to afford the dimer **6**; similar treatment of an isolated, methyl acrylate-derived Baylis–Hillman analogue afforded the corresponding dimer.[8]

While variations in reactant concentrations, reaction conditions and, possibly, separation techniques appear to influence the yields and product distribution in these reactions, optimisation of the methodology could well provide efficient access to unusual and complex poly-heterocyclic targets, including analogues of the biologically active semaphorin inhibitors[13] and the metallo-β-lactamase inhibitor **8**.[12]

Experimental

NMR spectra were recorded on Bruker AMX400 or AVANCE 600 MHz spectrometers at 303K in $CDCl_3$ and calibrated using solvent signals. Carbon-13 signal multiplicity assignments are based on DEPT, signal intensity or comparative shift data. In the case of the fluorinated analogues **4d** and **6d**, the cited multiplicities reflect the expected presence (or absence) of ^{13}C–^{1}H coupling; the reported coupling constants (J_{CF}), however, refer to the ^{13}C–^{19}F coupling observed as doublets in the p.n.d. spectra. IR spectra were recorded on a Perkin Elmer FT-IR Spectrum 2000 spectrometer. Low-resolution mass spectra were obtained on Finnigan-Mat GCQ (EI) and LCQ (ES) mass spectrometers; high-resolution (EI) mass spectra were recorded by the Mass Spectrometry Units at the Cape Technikon, the University of the Witwatersrand or the University of the North-West. The structures of the diastereomers $\mathbf{4a}_1$ and $\mathbf{4a}_2$, illustrated in Figs 1 and 2, were modelled at the AM1 level using the software package, PC SPARTAN-*pro*.[16] The chromone-3-carbaldehydes **2a–e** were prepared as described previously.[8-10]

*4-Acetyl-4-(3-oxobutyl)-4,4a-dihydro-3*H*-pyrano[4,3-*b*]benzopyran-10-one* **4a** *and the corresponding dimer* (**6a**): *general procedure*
Methyl vinyl ketone (0.56 mL, 8.6 mmol) was added to a stirred solution of chromone-3-carbaldehyde **2a** (1.0 g, 5.8 mmol) and 3-hydroxyquinuclidine (3.7 g, 29 mmol) in $CHCl_3$ (7.0 mL). The resulting mixture was stirred vigorously at room temperature for 24 h. Evaporation of solvent *in vacuo* gave a brown oily residue which was purified by flash chromatography [on silica; elution with hexane–EtOAc (1:2)] afforded two fractions.

(i) The tricyclic product **4a** as a brown viscous oil (0.67 g, 38%) (Found M^+: 314.1131. $C_{18}H_{18}O_5$ requires, *M*: 314.1154) ν_{max} (KBr)/ cm^{-1}1700, 1665 and 1650 (3 × C=O); δ_H (400 MHz; $CDCl_3$) 1.98 and 2.25 (2H, 2 × m, CH_2CH_2CO), 2.07 (3H, s, $CH_2CH_2COCH_3$), 2.39 (3H, s, $COCH_3$), 2.40 and 2.60 (2H, 2xm, CH_2CH_2CO), 4.59 (1H, dd, J = 17.2 and 1.9 Hz, 3-H_a), 4.79 (1H, dd, J = 17.2 and 1.5 Hz, 3-H_b), 5.13 (1H, s, 4a-H), 7.13 (2H, m, 6-H and 8-H), 7.30 (1H, br s, 1-H), 7.57 (1H, t,, J = 6.9 Hz, 7-H) and 7.90 (1H, d, J = 6.5 Hz, 9-H); δ_C (100 MHz; $CDCl_3$) 24.8 (t), 25.5 (t), 30.0 (q), 37.8 (t), 49.1 (s), 65.9 (t), 99.9 (d), 118.2 (d), 119.5 (s), 123.0 (d), 127.9 (d), 135.4 (d), 136.8 (d), 138.3 (s), 157.6 (s), 192.6 (s), 196.6 (s) and 206.7 (s); *m/z* 314 (M^+, 2%) and 193 (100).

(ii) The chromone dimer **6a** as a yellow solid (0.32 g, 12%), m.p. 193–195 °C (lit.,[8] 193–194 °C) (Found M^+: 470.1364. $C_{28}H_{22}O_7$ requires *M*: 470.1366); ν_{max} (KBr)/cm^{-1}, 1698, 1669, 1642 and 1606 (4 × C=O); δ_H (400 MHz; $CDCl_3$) 2.29 and 2.42 (6H, 2xs, 2xCH_3), 3.23 (2H, 2x d, J = 14.7 Hz, CH_2), 4.52 (2H, dd, J = 17 and 1.7 Hz, OCH_2), 5.00 (1H, s, OCHO), 6.83–6.90 (2H, m, ArH), 7.17 (1H, s, ArH), 7.27 (1H, m, ArH), 7.40–7.47 (3H, m, C=CH and ArH), 7.69–7.75 (2H, m, ArH), 7.90 (1H, s, ArH), and 8.13 (2H, dd, J = 8.0 and 1.3 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 25.3 (q), 25.8 (t), 25.9 (q), 50.1 (s), 65.9 (t), 99.9 (d), 117.5 (d), 118.1 (d), 120.0 (s), 120.3 (s), 122.9 (d), 123.5 (s), 125.8 (d), 126.1 (d), 128.0 (d), 133.6 (d), 134.2 (d), 136.1 (d), 136.5 (s), 136.7 (d), 139.0 (s), 154.1 (d), 155.9 (s), 157.0 (s), 175.6 (s), 191.5 (s), 196.9 (s) and 199.0 (s); *m/z* 470 (M^+, 24%) and 185 (100).

When DABCO (0.38 g, 2.9 mmol) was used as catalyst and 1-NMP (3 mL) as solvent, work-up afforded compound **4a** as a light brown viscous oil (0.82 g, 45%).

*4-Acetyl-8-chloro-4-(3-oxobutyl)-4,4a-dihydro-3*H*-pyrano[4,3-b]benzopyran-10-one* **4b** *and the corresponding dimer* **6b**

The general procedure was followed, using 6-chlorochromone-3-carbaldehyde **2b**. Work-up and flash chromatography afforded two fractions.

(i) The tricyclic product **4b** as a reddish oil (0.73 g, 44%) (Found MH^+: 349.0843. $C_{18}H_{18}ClO_5$ requires, *M*: 349.0848); ν_{max} (KBr)/cm^{-1} 1717, 1699 and 1674 (3 × C=O); δ_H (400 MHz; $CDCl_3$) 2.13 (3H, s, $CH_2CH_2COCH_3$), 2.15–2.25 (2H, 2 × m, CH_2CH_2CO), 2.31 (3H, s, $COCH_3$), 2.46–2.59 (2H, 2xm, CH_2CH_2CO), 4.48 (1H, dd, J = 17.1 and 2.0 Hz, 3-H_a), 4.63 (1H, dd, J = 17.0 and 1.5 Hz, 3-H_b), 5.40 (1H, s, 4a-H), 6.65 (1H, br s, 1-H), 6.69 (1H, d, J = 8.8 Hz, 6-H), 7.48 (1H, dd, J = 8.8 and 2.7 Hz, 7-H) and 7.80 (1H, d, J = 2.7 Hz, 9-H); δ_C (100 MHz; $CDCl_3$) 25.2 (q), 27.6 (t), 30.0 (q), 37.6 (t), 48.8 (s), 62.7 (t), 99.6 (d), 118.8 (s), 120.0 (d), 126.6 (d), 135.4 (d), 136.9 (d), 139.4 (s), 143.5 (s), 155.9 (s), 192.0 (s), 196.4 (s) and 205.3 (s); *m/z* 349 (MH^+, 9%) and 154 (100).

(ii) The chromone dimer **6b** as a yellow solid (0.45 g, 17%), m.p. 112–114 °C (Found M^+: 538.0587. $C_{28}H_{20}Cl_2O_7$ requires, *M*: 538.0586); ν_{max} (KBr)/cm^{-1}, 1653,1678, 1684 and 1701 (4 × C=O); δ_H (400 MHz; $CDCl_3$) 2.31 and 2.44 (6H, 2xs, 2xCH_3), 3.00 (2H, 2xd, J = 14.7 Hz, CH_2), 5.16 (2H, dd, J = 17 and 1.7 Hz, OCH_2), 5.39 (1H, s, OCHO), 6.93 (1H, s, C=CH), 7.12 (1H, d, J = 8.9 Hz, ArH), 7.30 (1H, s, C=CH), 7.44 (1H, d, J = 8.9 Hz, ArH), 7.45 (1H, d, J = 8.9 and 2.0 Hz, ArH), 7.76 (1H, dd, J = 8.0 and 2.0 Hz, ArH), 8.08 (1H, d, J = 2.0 Hz, ArH), 8.66 (1H, s, ArH), and 8.18 (1H, d, J = 1.3 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 25.4 (q), 25.9 (q), 31.2 (t), 50.5 (s), 66.1(t), 100.2 (d), 116.6 (d), 118.0 (d), 121.6 (s), 122.2 (s), 124.4 (d), 128.4 (d), 128.5 (d), 133.6 (d), 134.0 (s), 136.6 (s), 136.7 (d), 139.3 (s), 141.4 (s), 143.7 (d), 148.6 (s), 154.2 (d), 156.2 (s), 158.5 (s), 174.8 (s), 190.8 (s), 196.9 (s) and 199.0 (s).

When DABCO (0.31 g, 2.4 mmol) was used as the catalyst and 1-NMP (3 mL) as solvent, work-up afforded compound **4b** as a light brown viscous oil (0.67 g, 40%).

*4-Acetyl-8-bromo-4-(3-oxobutyl)-4,4a-dihydro-3*H*-pyrano[4,3-b]benzopyran-10-one* **4c** *and the corresponding dimer* **6c**

The general procedure was followed, using 6-bromochromone-3-carbaldehyde **2c**. Work-up and flash chromatography afforded two fractions.

(i) The tricyclic product **4c** as a reddish oil (0.81 g, 52%) (Found: M^+, 392.0257. $C_{18}H_{17}{}^{79}BrO_5$ requires, *M*: 392.0259), ν_{max} (KBr)/cm^{-1}, 1600, 1674 and 1716 (3 × C=O); δ_H (400 MHz; $CDCl_3$) 1.94–2.24 (2H, 2xm, CH_2CH_2CO), 2.08 (3H, s, $CH_2CH_2COCH_3$), 2.26–2.58 (2H, m, CH_2CH_2CO), 2.39 (3H, s, $COCH_3$), 4.58 (1H, dd, J = 17.2 and 1.7 Hz, 3-H_a), 4.79 (1H, dd, J = 17.2 and 1.5 Hz, 3-H_b), 5.11 (1H, s, 4a-H), 6.73 (1H, m, 1-H), 7.02 (1H, d, J = 8.81 Hz, 6-H), 7.64 (1H, dd, J = 8.8 and 2.5 Hz, 7-H) and 7.99 (1H, d, J = 2.4 Hz, 9-H); δ_C (100 MHz; $CDCl_3$) 24.7 (t), 25.5 (q), 30.0 (q), 37.6 (t), 49.0 (s), 65.9 (t), 100.0 (d), 118.1 (s), 120.2 (d), 130.3 (d), 134.8 (d), 139.4 (d), 138.4 (s), 143.5 (s), 156.5 (s), 191.4 (s), 196.4 (s) and 206.5 (s); *m/z* 392 (M^+, 2%) and 194 (100).

(ii) The chromone dimer **6c** as a yellow oil (0.53 g, 21%) (Found M^+: 625.9579. $C_{28}H_{20}{}^{79}Br_2O_7$ requires, *M*: 625.9576); ν_{max} (KBr)/cm^{-1}, 1600, 1670, 1675 and 1710 (4 × C=O); δ_H (400 MHz; $CDCl_3$) 2.31 and 2.44 (6H, 2 × s, 2xCH_3), 3.50 (2H, 2xd, J = 14.7 Hz, CH_2), 5.17 (2H, dd, J = 17 and 1.7 Hz, OCH_2), 5.81 (1H, s, 9a-H), 7.16 (1H, s, C=CH), 7.28 (1H, s, C=CH), 7.38 (1H, d, J = 8.9 Hz, ArH), 7.61 (1H, d, J = 8.9 Hz, ArH), 7.62 (1H, d, J = 8.9 and 2.0 Hz, ArH), 7.79 (1H, s, ArH), 8.00 (1H, dd, J = 8.0 and 2.0 Hz, ArH), 8.35 (1H, d, J = 2.0 Hz, ArH), and 8.32 (1H, d, J = 1.3 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 25.4 (q), 25.89 (q), 25.91 (t), 50.0 (s), 66.0 (t), 99.8 (d), 115.9 (s), 118.3 (d), 119.4 (d), 120.0 (d), 120.4 (s), 121.2 (s), 124.6 (s), 128.7 (d), 130.4 (d), 133.3 (d), 136.2 (d), 136.5 (s), 137.3 (d), 138.8 (d), 139.4 (s), 154.1 (s), 154.5 (s), 155.9 (s), 174.1 (s), 190.3 (s), 196.8 (s) and 198.9 (s); m/z 626 (M^+, 16%) and 136 (100).

When DABCO (0.26 g, 2.0 mmol) was used as the catalyst and 1-NMP (3 mL) as solvent, work-up afforded compound **4c** as a light-brown viscous oil (0.51 g, 33%).

*4-Acetyl-8-fluoro-4-(3-oxobutyl)-4,4a-dihydro-3*H*-pyrano[4,3-b]benzopyran-10-one* **4d** *and the corresponding dimer* **6d**

The general procedure was followed, using 6-fluorochromone-3-carbaldehyde **2d**. Work-up and flash chromatography afforded two fractions.

(i) The tricyclic product **4d** as a light brown oil (0.53 g, 31%) (Found: M^+, 332.1051. $C_{18}H_{17}FO_5$ requires, *M*: 332.1060), ν_{max} (KBr)/cm^{-1}, 1674, 1687 and 1699 (3 × C=O); δ_H (400 MHz; $CDCl_3$) 1.97–2.23 (2H, 2xm, CH_2CH_2CO), 2.08 (3H, s, $CH_2CH_2COCH_3$), 2.35–2.45 (2H, 2xm, CH_2CH_2CO), 2.39 (3H, s, $COCH_3$), 4.57 (1H, dd, J = 17.2 and 1.9 Hz, 3-H_a), 4.79 (1H, dd, J = 17.2 and 1.7 Hz, 3-H_b), 5.11 (1H, s, 4a-H), 7.12 (1H, dd, J = 9.1 and 4.2 Hz, 6-H), 7.27 (1H, br s, 1-H), 7.30 (1H, m, 7-H) and 7.54 (1H, dd, J = 8.0 and 3.1 Hz, 9-H); δ_C (100 MHz; $CDCl_3$) 24.7 (t), 25.5 (q), 30.0 (q), 37.6 (t), 49.0 (s), 65.9 (t), 100.1 (d), 113.0 (J_{CF} = 23.6 Hz, C-7, d), 120.0 (J_{CF} = 7.7 Hz, C-6, d), 120.2 (J_{CF} = 6.5 Hz, C-10, s), 124.4 (J_{CF} = 24.7 Hz, C-9, d), 126.2 (s), 134.9 (d), 153.8 (s), 158.0 (J_{CF} = 244.1 Hz, C-8, s), 191.9 (s), 196.5 (s) and 206.5 (s).

(ii) The chromone dimer **6d** as a yellow solid oil (0.37 g, 21%) (Found MH^+: 507.1251. $C_{28}H_{20}F_2O_7$ requires, *M* + *1*: 507.1255); ν_{max} (KBr)/cm^{-1}, 1674, 1683, 1699 and 1717 (4 × C=O); δ_H (400 MHz; $CDCl_3$) 2.32 and 2.45 (6H, 2 × s, 2xCH_3), 3.52 (2H, 2xd, J = 14.7 Hz, CH_2), 5.18 (2H, dd, J = 17 and 1.7 Hz, OCH_2), 5.85 (1H, s, OCHO), 7.17 (1H, s, C=CH), 7.26 (1H, d, J = 8.9 and 2.0 Hz, ArH), 7.30 (1H, s, C=CH), 7.48 (1H, d, J = 8.9 Hz, ArH), 7.72 (1H, d, J = 8.9 Hz, ArH), 7.64 (1H, dd, J = 8.0 and 2.0 Hz, ArH), 7.93 (1H, s, ArH), 7.94 (1H, d, J = 2.0 Hz, ArH), and 7.96 (1H, d, J = 1.3 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 25.3 (q), 25.79 (t), 25.85 (q), 49.9 (s), 66.0 (t), 99.9 (d), 110.8 (J_{CF} = 23.8 Hz, d), 113.1 (J_{CF} = 23.6 Hz, d), 119.3 (J_{CF} = 8.1 Hz, d), 119.7 (s), 120.3 (J_{CF} = 8.1 Hz, d), 120.6 (J_{CF} = 6.6 Hz, s), 122.7 (J_{CF} = 25.1 Hz, d), 123.6 (J_{CF} = 24.8 Hz, d), 124.6 (J_{CF} = 7.4 Hz, s), 133.4 (d), 136.0 (d), 136.7 (s), 139.3 (s), 152.0 (s), 153.1 (s), 154.2 (d), 157.8 (J_{CF} = 244.8 Hz, s), 159.8 (J_{CF} = 248.7 Hz, s), 174.8 (s), 190.7 (s), 196.8 (s) and 198.8 (s).

When DABCO (0.26 g, 2.0 mmol) was used as catalyst and 1-NMP (3 mL) as solvent, work-up afforded compound **4d** as a light brown viscous oil (0.40 g, 30%).

*4-Acetyl-8-methoxy-4-(3-oxobutyl)-4,4a-dihydro-3*H*-pyrano[4,3-b]benzopyran-10-one* **4e** *and the corresponding dimer* **6e**

The general procedure was followed, using 6-bromochromone-3-carbaldehyde **2e**. Work-up and flash chromatography afforded two fractions.

(i) The tricyclic product **4e** as a reddish oil (0.57 g, 34%) (Found: M^+, 344.1252. $C_{19}H_{20}O_6$ requires, *M*: 344.1259), ν_{max} (KBr)/cm^{-1}, 1652, 1665 and 1674 (3 × C=O); δ_H (400 MHz; $CDCl_3$) 2.09–2.23 (2H, 2xm, CH_2CH_2CO), 2.15 (3H, s, $CH_2CH_2COCH_3$), 2.39–2.51 (2H, 2xm, CH_2CH_2CO), 2.44 (3H, s, $COCH_3$), 3.91 (3H, s, 6-OCH_3), 4.55 (1H, dd, 3-H_a and H_b), 4.94 (1H, s, 4a-H), 6.69 (1H, br s, 1-H), 7.08 (1H, d, J = 9.11 Hz, 6-H), 7.33 (1H, dd, J = 2.32 and 9.11 Hz, 7-H) and 7.85 (1H, d, J = 2.32 Hz, 9-H); δ_C (100 MHz; $CDCl_3$) 24.7 (t), 25.5 (q), 30.0 (q), 37.6 (t), 50.1 (s), 55.9 (q), 65.9 (t), 99.8 (d), 118.5 (s), 119.4 (d), 124.1 (d), 133.9 (d), 137.3 (d), 139.0 (s), 143.5 (s), 154.8 (s), 191.4 (s), 197.1 (s) and 199.2 (s); *m/z* (M^+, 33%) and 193 (100).

(ii) The chromone dimer **6e** as a yellow oil (0.49 g, 19%) (Found M^+: 530.1578. $C_{30}H_{26}O_9$ requires, *M*:530.1576); ν_{max} (KBr)/cm^{-1}, 1653, 1674, 1677 and 1700 (4 × C=O); δ_H (400 MHz; $CDCl_3$) 2.28 and 2.33 (6H, 2x s, 2xCH_3), 3.14 (2H, 2xd, J = 14.7 Hz, CH_2), 3.68 and 3.80 (6H, 2xs, 2xOCH_3), 5.09 (2H, dd, J = 17 and 1.7 Hz, OCH_2), 5.25 (1H, s, OCHO), 6.95 (1H, s, C=CH), 6.98 (1H, d, J = 8.9 Hz, ArH), 7.27 (1H, s, C=CH), 7.44 (1H, d, J = 8.9 and 2.0 Hz, ArH), 7.64 (1H, d, J = 8.9 Hz, ArH), 7.73 (1H, dd, J = 8.0 and 2.0 Hz, ArH), and 8.16 (1H, d, J = 1.3 Hz, ArH), 8.33 (1H, d, J = 2.0 Hz, ArH), and 8.70 (1H, s, ArH); δ_C (100 MHz; $CDCl_3$) 25.4 (q), 25.86 (t), 25.93 (q), 50.1 (s), 55.5 (q), 55.9 (q), 65.8 (t), 99.7 (d), 105.0 (d), 108.1 (d), 118.5 (d), 119.2 (s), 119.3 (d), 119.8 (s), 124.05 (s), 124.13 (d), 125.1 (d), 133.9 (d), 136.0 (s), 137.3 (s), 139.0 (d), 150.6 (s), 157.4 (s), 153.8 (d), 154.7 (s), 157.2 (s), 175.3 (s), 191.4 (s), 197.1 (s) and 199.2 (s); *m/z* 548 (M^+, 5%) and 43 (100).

When DABCO (0.32 g, 2.5 mmol) was used as the catalyst and 1-NMP (3 mL) as solvent, work-up afforded compound **4e** as a light brown viscous oil (0.6 g, 37%).

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