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Synthesis of 7-hydroxy-2-(2-hydroxybenzoyl)benzo[*c*]chromen-6-ones by sequential application of domino reactions of 1,3-bis(silyl enol ethers) with benzopyrylium triflates

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Abstract—The domino, Michael–retro-Michael–aldol, reaction of 2,4-bis(trimethylsilyloxy)penta-1,3-diene with 3-formylchromones afforded 4-(2-hydroxybenzoyl)-2-acetylphenols, which were transformed into 6-(2-hydroxybenzoyl)chromones. The Me_3SiOTf-mediated condensation of the latter with 1,3-bis(silyl enol ethers) and subsequent domino 'retro-Michael–aldol–lactonization' reaction afforded 7-hydroxy-2-(2-hydroxybenzoyl)benzo[*c*]chromen-6-ones.

1. Introduction

Functionalized 6*H*-benzo[*c*]chromen-6-ones (dibenzo[*b*,*d*]-pyran-6-ones) occur in a number of pharmacologically active natural products, such as autumnariol,[1a] autumnariniol,[1b] alternariol[1c] or altenuisol,[1d] and are specific inhibitors of the growth of endothelic cells[2a] and oestrogen receptors.[2b] Dibenzo[*c*,*d*]chromen-6-ones are present in various natural antibiotics and antitumour agents, such as the gilvocarcins, chrysomycins and ravidomycins.[3] The related ellagic and coruleoellagic acids are found in plants.[4] Functionalized benzophenones also occur in a variety of natural products and represent important core structures for the development of pharmaceuticals.[5] For example, the benzophenone phenstatin was discovered as an antitubulin agent (microtubules represent an important target for anticancer therapy).[6] Recently, Hsieh and co-workers reported that cytotoxic 2-hydroxy- and 2-aminobenzophenones represent potent antitubulin agents.[7]

1,3-Bis(silyl enol ethers) represent d^4 synthons and can be regarded as electroneutral equivalents of 1,3-dicarbonyl dianions.[8] In recent years, we have developed a number of domino reactions of 1,3-bis(silyl enol ethers) with pyrylium salts. For example, the Me_3SiOTf-mediated reaction of 3-formylchromones with 1,3-bis(silyl enol ethers) allows the synthesis of 4-(2-hydroxybenzoyl)phenols.[9] The Me_3SiOTf-mediated reaction of 1,3-bis(silyl enol ethers) with chromones provides a facile access to 6*H*-benzo[*c*]-chromen-6-ones.[10] Herein, we report the combination of these two domino reactions based on sequential use of 1,3-bis(silyl enol ethers) at two stages of the synthesis. This strategy allows a convenient synthesis of 7-hydroxy-2-(2-hydroxybenzoyl)benzo[*c*]chromen-6-ones, which combine the structural features of 6*H*-benzo[*c*]chromen-6-ones and 4-(2-hydroxybenzoyl)phenols.

2. Results and discussion

The reaction of 1,3-bis(silyl enol ether) **2** with 3-formylchromones **1a–c** afforded the 4-(2-hydroxybenzoyl)phenols **3a–c** (Scheme 1, Table 1). The syntheses of **3a**[9b] and **3b**,**c**[11] have been previously reported. The formation of the products can be explained by a domino 'Michael–retro-Michael–Aldol' reaction. Compounds **3a–c** were transformed into the novel chromones **4a–c** by treatment with triethyl orthoformate and perchloric acid.[12] The Me_3SiOTf-mediated condensation of **4a–c** with 1,3-bis(silyl enol ethers) **5a–d** gave the 2,3-dihydrobenzopyrans **6a–e**, which were transformed—by treatment with NEt_3—into the novel 7-hydroxy-2-(2-hydroxybenzoyl)benzo[*c*]chromen-6-ones **7a–e**. The formation of these products proceeds by a domino 'retro-Michael–aldol–lactonization' reaction.[10] Notably, the reaction of **4** with **5** generally afforded the 2,3-dihydropyrans **6** together with a small amount of **7**. Therefore, a mixture of these two compounds was separated from polar

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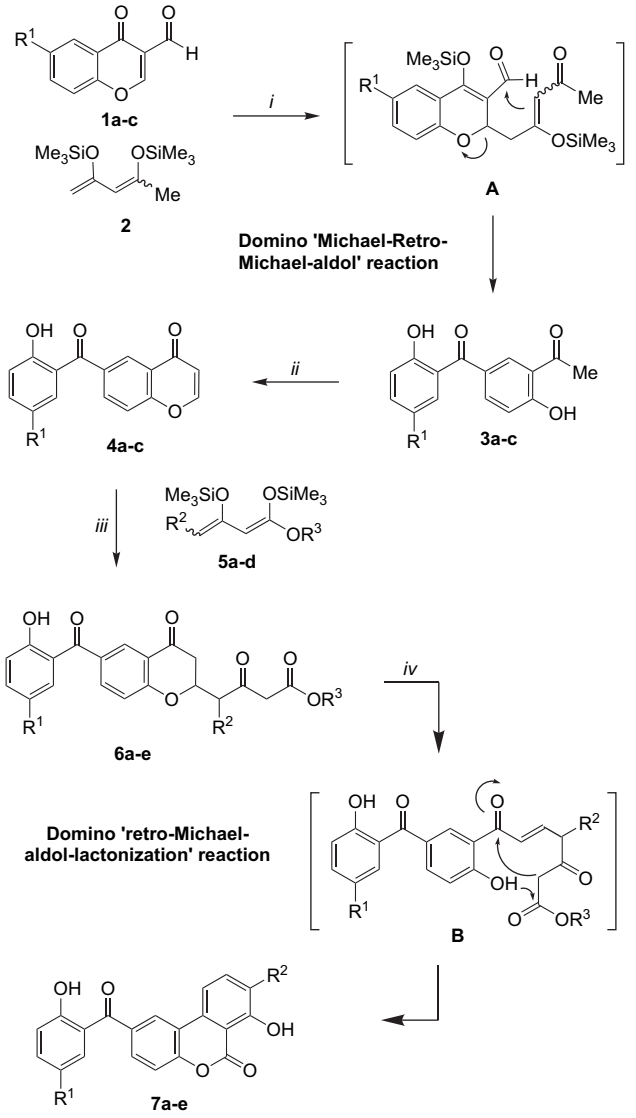
side-products by chromatography and subsequently treated with NEt_3. Notably, the use of hydroxyl protective groups was not required for the transformation of **4a–c** into **7a–e**.



Scheme 1. Synthesis of 7-hydroxy-2-(2-hydroxybenzoyl)benzo[*c*]chromen-6-ones **7a–e**: (i) (1) Me_3SiOTf (0.3 equiv), 0 °C; (2) CH_2Cl_2, then **2**, 0→20 °C, 12 h; (ii) $HC(OEt)_3$, $HClO_4$ (70%), 0→20 °C, 12–20 h; (iii) (1) Me_3SiOTf (1.3 equiv), 0 °C, 1 h; (2) CH_2Cl_2, then **5a–d** (1.3 equiv), 12 h; (3) HCl (10%); (iv) NEt_3, EtOH, 12 h, 20 °C.

Table 1. Products and yields

	R^1	R^2	R^3	**3** (%)[a]	**4** (%)[a]	**7** (%)[a]
a	H	H	Et	43	52	48
b	Cl	H	Me	25	65	70
c	Me	H	Me	29	58	51
d	H	Me	Et	43	52	41
e	H	Et	Me	43	52	23

[a] Yields of isolated products.

The core structure of the products **7** contains 20 carbon atoms out of which 9 carbons are derived from the two 1,3-bis(silyl enol ethers), 10 carbons from the 3-formylchromone and 1 carbon from the orthoformate.

In conclusion, the combination of the Me_3SiOTf-mediated domino Michael–retro-Michael–aldol reaction of 1,3-bis(silyl enol ethers) with 3-formylchromones with the domino 'retro-Michael–aldol–lactonization' reaction of 1,3-bis(silyl enol ethers) with chromones allowed an efficient synthesis of 7-hydroxy-2-(2-hydroxybenzoyl)benzo[*c*]chromen-6-ones. These products combine the structural features of 6*H*-benzo[*c*]chromen-6-ones and 4-(2-hydroxybenzoyl)phenols.

3. Experimental

3.1. General comments

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For ^1H and ^{13}C NMR spectra the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, H_2O) or electrospray ionization (ESI). For preparative scale chromatography, silica gel (60–200 mesh) was used. The melting points are corrected.

3.2. General procedure for the synthesis of 4-(2-hydroxybenzoyl)phenols 3a–c

To the 3-formylchromone **1** (1.0 equiv) was added Me_3SiOTf (0.3 equiv) at 20 °C. After stirring for 10 min CH_2Cl_2 (8 mL) was added, the solution was cooled to 0 °C and the 1,3-bis(silyl enol ether) (1.3 equiv) was added. The mixture was stirred for 12 h at 20 °C and was subsequently poured into an aqueous solution of hydrochloric acid (10%). The organic and the aqueous layers were separated and the latter was extracted with diethyl ether (3×80 mL). The combined organic layers were washed with water, dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc=10:1→3:1).

3.2.1. 1-[2-Hydroxy-5-(2-hydroxybenzoyl)phenyl]ethanone (3a). The synthesis of **3a** has been previously reported.[9a] Starting with **1a** (200 mg, 1.15 mmol), Me_3SiOTf (77 mg, 0.34 mmol) and 1,3-bis(silyl enol ether) **2a** (365 mg, 1.49 mmol), **3a** was isolated as a colourless solid (127 mg, 43%), mp 129 °C.

3.2.2. 1-[5-Chloro-2-hydroxybenzoyl)-2-hydroxyphenyl]-ethanone (3b). The synthesis of **3b** has been previously reported.[11] Starting with **1b** (202 mg, 1.10 mmol), Me_3SiOTf (75 mg, 0.33 mmol) and 1,3-bis(silyl enol ether) **2a** (350 mg, 1.43 mmol), **3b** was isolated as a colourless solid (80 mg, 25%), mp 145–146 °C. ^1H NMR (250 MHz, $CDCl_3$): δ=12.71 (s, 1H, OH), 11.64 (s, 1H, OH), 8.19 (d, ^4J=2.1 Hz, 1H, Ar), 7.85 (dd, ^3J=8.9 Hz, ^4J=2.1 Hz, 1H, Ar), 7.54 (d, ^4J=2.4 Hz, 1H, Ar), 7.47 (dd, ^3J=8.9 Hz, ^4J=2.4 Hz, 1H, Ar), 7.11 (d, ^3J=8.9 Hz, 1H, Ar), 7.05 (d, ^3J=8.9 Hz, 1H, Ar), 7.05 (d, ^3J=8.9 Hz, 1H, Ar), 2.70 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=204.3 (C=O), 197.7, 165.8 (C–OH), 161.4 (C_{Ar}), 137.2, 136.1, 133.3, 131.6 (CH), 128.0, 123.5 (C), 120.3 (CH), 119.6, 119.3 (C_{Ar}), 118.8 (CH), 26.7 (CH_3).

3.2.3. 1-[(2-Hydroxy-5-methylbenzoyl)-2-hydroxyphenyl]ethanone (3c). The synthesis of **3c** has been previously reported.[11] Starting with **1c** (433 mg, 2.64 mmol), Me_3SiOTf (179 mg, 0.79 mmol) and 1,3-bis(silyl enol ether) **2a** (840 mg, 3.43 mmol), **3c** was isolated as a colourless solid (207 mg, 29%), mp 140–141 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=12.66 (s, 1H, OH), 11.58 (s, 1H, OH), 8.19 (d, ^4J=2.1 Hz, 1H, Ar), 2.28 (s, 3H, CH_3), 7.84 (dd, ^3J=8.9 Hz, ^4J=2.1 Hz, 1H, Ar), 7.31–7.37 (m, 2H, Ar), 7.08 (d, ^3J=8.9 Hz, 1H, Ar), 6.99 (d, ^3J=8.9 Hz, 1H, Ar), 2.68 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=204.4 (C=O), 198.7, 165.4 (C–OH), 160.9, 137.3, 133.1, 132.4 (CH), 128.9, 127.9, 119.2 (C), 118.6, 118.4, 118.3 (CH), 26.7, 20.5 (CH_3).

3.3. General procedure for the synthesis of chromones 4a–c

To a solution of 4-(2-hydroxybenzoyl)-2-acetylphenols **3** (1.0 equiv) in triethyl orthoformate (10.0 equiv) was added perchloric acid (60%, 1.3 equiv) at 0 °C. The temperature was allowed to rise slowly to 20 °C and the solution was stirred for additional 12 h. The product was separated from the solution by filtration and purified by column chromatography (silica gel, *n*-heptane/EtOAc=9:1).

3.3.1. 6-(2-Hydroxybenzoyl)chromone (4a). Starting with **3a** (292 mg, 1.14 mmol), triethyl orthoformate (1.35 g, 1.49 mL, 9.08 mmol) and perchloric acid (60%, 240 mg, 0.24 mL, 1.47 mmol), **4a** was isolated (158 mg, 52%) by chromatography (silica gel, hexanes/EtOAc=5:1) as a yellow solid, mp 172 °C. ^1H NMR (DMSO-d_6, 300 MHz): δ=10.27 (s, 1H, OH), 8.36 (d, ^3J=6.2 Hz, 1H, CH), 8.27 (d, ^4J=2.2 Hz, 1H, Ar), 8.16 (dd, ^3J=8.8 Hz, ^4J=2.3 Hz, 1H, Ar), 7.78 (d, ^3J=8.6 Hz, 1H, Ar), 7.47 (m, 1H, Ar), 7.38 (dd, ^3J=7.6 Hz, ^4J=1.6 Hz, 1H, Ar), 6.98 (m, 2H, Ar), 6.42 (d, ^3J=6.2 Hz, 1H, CH). ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ=195.3, 176.1 (C=O), 158.3 (C_{Ar}), 157.4 (CH_{Ar}), 156.4, 134.3 (C_{Ar}), 133.9, 133.3, 130.2, 127.3 (CH_{Ar}), 124.8, 123.7 (C_{Ar}), 119.3, 119.2, 116.7, 112.6 (CH_{Ar}). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3426 (m), 3258 (w), 3175 (w), 3086 (m), 2928 (m), 1656 (s), 1616 (s), 1481 (s), 1443 (s), 1340 (s), 1300 (s), 1247 (s), 1175 (m), 1137 (m), 1027 (w), 959 (w), 846 (m), 800 (w), 762 (m), 724 (w), 624 (w), 545 (m). UV–vis (CH_3CN, nm): λ_{max} (log ε): 338 (3.73), 305 (3.88), 242 (4.35), 216 (4.38). MS (EI, 70 eV): *m*/*z* (%)=266 (M^+, 100), 237 (56), 221 (10), 173 (17), 145 (14), 121 (40), 93 (11), 90 (16), 66 (18). Anal. $C_{16}H_{10}O_4$ (266.3) calcd: C, 72.18; H, 3.79; found: C, 71.92; H, 3.65.

3.3.2. 6-(5-Chloro-2-hydroxybenzoyl)chromone (4b). Starting with **3b** (80 mg, 0.28 mmol), triethyl orthoformate (332 mg, 2.24 mmol) and perchloric acid (70%, 0.05 mL), **4b** was isolated (54 mg, 65%) as a yellow solid; R_f 0.33 (*n*-heptane/EtOAc=1:1). ^1H NMR ($CDCl_3$, 250 MHz): δ=11.69 (s, 1H, OH), 8.50 (d, ^4J=2.4 Hz, 1H, Ar), 8.00 (dd, ^3J=8.5 Hz, ^4J=2.4 Hz, 1H, Ar), 7.92 (d, ^3J=6.1 Hz, 1H, =CH), 7.63 (d, ^3J=8.5 Hz, 1H, Ar), 7.51–7.46 (m, 2H, Ar), 7.06 (d, ^3J=8.5 Hz, 1H, Ar), 6.42 (d, ^3J=6.1 Hz, 1H, =CH). ^{13}C NMR ($CDCl_3$, 63 MHz): δ=198.6, 176.6 (C=O), 161.7, 158.4 (C_{Ar}–O), 155.5, 136.7 (CH_{Ar}), 134.1 (C_{Ar}), 133.8, 131.9, 127.6 (CH_{Ar}), 124.4 (C_{Ar}), 123.7 (C_{Ar}), 120.3 (CH_{Ar}), 119.5 (C_{Ar}), 119.3 (CH_{Ar}), 113.6 (CH_{Ar}). MS (EI, 70 eV): *m*/*z* (%)=302 (M^+, ^{37}Cl, 32), 300 (M^+, ^{35}Cl, 100), 271 (71), 222 (10), 173 (28), 154 (23). HRMS (EI, 70 eV): calcd for $C_{16}H_9ClO_4$ (M^+): 300.01705; found: 300.01839.

3.3.3. 6-(2-Hydroxy-5-methylbenzoyl)chromone (4c). Starting with **3c** (207 mg, 0.81 mmol), triethyl orthoformate (960 mg, 6.48 mmol) and perchloric acid (70%, 0.15 mL), **4c** was isolated (132 mg, 58%) by chromatography (silica gel, *n*-heptane/EtOAc) as a colourless solid; R_f 0.38 (*n*-heptane/EtOAc=1:1). ^1H NMR ($CDCl_3$, 250 MHz): δ=11.64 (s, 1H, OH), 8.50 (d, ^4J=2.1 Hz, 1H, Ar), 8.02 (dd, ^3J=8.5 Hz, ^4J=2.1 Hz, 1H, Ar), 7.91 (d, ^3J=6.1 Hz, 1H, =CH), 7.61 (d, ^3J=8.5 Hz, 1H, Ar), 7.38–7.29 (m, 2H, Ar), 7.00 (d, ^3J=8.5 Hz, 1H, Ar), 6.42 (d, ^3J=6.1 Hz, 1H, =CH), 2.25 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 63 MHz): δ=199.4, 176.8 (C=O), 161.2, 158.1 (C_{Ar}–O), 155.5, 137.9 (CH_{Ar}), 134.9 (C_{Ar}), 134.0, 132.7 (CH_{Ar}), 128.2 (C_{Ar}), 127.5 (CH_{Ar}), 124.2 (C_{Ar}), 119.0 (CH_{Ar}), 118.5 (C_{Ar}), 118.4, 113.5 (CH_{Ar}), 20.5 (CH_3). MS (EI, 70 eV): *m*/*z* (%)=280.0 (M^+, 100), 279.0 (83), 251.0 (45), 235.1 (12), 173.0 (14), 135.0 (28). HRMS (EI, 70 eV): calcd for $C_{17}H_{12}O_4$ (M^+): 280.07301; found: 280.07231.

3.4. General procedure for the synthesis of 7-hydroxy-2-(2-hydroxybenzoyl)benzo[*c*]chromen-6-ones 7a–e

To chromone **4** (1.0 equiv) was added Me_3SiOTf (1.3 equiv) at 20 °C and the mixture was stirred for 1 h at 20 °C. Subsequently, dichloromethane (8 mL/mmol) was added and the solution was cooled to 0 °C. The 1,3-bis(silyl enol ether) **3** (1.3 equiv) was added, the temperature was allowed to warm slowly to 20 °C and the solution was stirred for 12 h. To the mixture was added hydrochloric acid (10%), the organic and the aqueous layers were separated and the latter was extracted with dichloromethane (3×50 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by a rapid flash chromatography (silica gel, *n*-heptane/EtOAc=5:1) to remove polar side-products. The 2,3-dihydrobenzopyran **6** (together with some amount of **7**) was dissolved in dry ethanol (10 mL/mmol), triethylamine (3.0 equiv) was added and the solution was stirred for 12 h at 20 °C. To the solution was added hydrochloric acid (10%) and diethyl ether. After stirring for 30 min, the organic and the aqueous layers were separated and the latter was extracted with diethyl ether (3×80 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, *n*-heptane/EtOAc=20:1) to give the product **7**.

3.4.1. 7-Hydroxy-2-(2-hydroxybenzoyl)benzo[*c*]chromen-6-one (7a). Starting with **4a** (252 mg, 0.95 mmol), Me_3SiOTf (274 mg, 0.22 mL, 1.24 mmol) and **5a** (340 mg, 1.24 mmol) (first step), and triethylamine (435 mg, 4.3 mmol) and ethanol (10 mL) (second step), **7a** was isolated (151 mg, 48%) as a colourless solid, mp 220 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ=11.85 (s, 1H, OH), 11.24 (s, 1H, OH), 8.41 (d, ^4J=1.9 Hz, 1H, Ar), 7.83 (dd, ^3J=8.5 Hz, ^4J=2.0 Hz, 1H, Ar), 7.77 (t, ^3J=8.1 Hz, 1H, Ar), 7.59 (m, 3H, Ar), 7.51 (d, ^3J=8.5 Hz, 1H, Ar), 7.15 (m, 2H, Ar), 6.93 (m, 1H, Ar). ^{13}C NMR ($CDCl_3$, 75.5 MHz):

δ=199.7 (C=O), 164.8, 163.3, 162.6, 152.7 (C_{Ar}–O), 137.7, 136.8 (CH_{Ar}), 134.9, 134.3 (C_{Ar}), 133.1, 131.4, 125.1, 119.0 (CH_{Ar}), 118.9 (C_{Ar}), 118.8 (CH_{Ar}), 118.6 (C_{Ar}), 117.9, 117.5, 112.6 (CH_{Ar}), 106.1 (C_{Ar}). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3122 (m), 3052 (m), 1683 (s), 1626 (s), 1593 (s), 1484 (m), 1447 (s), 1347 (m), 1302 (m), 1276 (s), 1243 (s), 1206 (s), 1139 (m), 1072 (m), 994 (w), 840 (w), 760 (m), 710 (m). UV–vis (CH_3CN, nm): λ_{max} (log ε): 349 (4.09), 338 (4.10), 261 (4.37), 231 (4.42), 217 (4.39). Fluorescence (CH_3CN, nm): Fλ_{max} (λ_{Ex}): 485 (340). MS (EI, 70 eV): *m*/*z* (%)=332 (M^+, 8), 256 (71), 241 (10), 212 (18), 163 (24), 148 (21), 121 (100), 105 (22), 66 (31).

3.4.2. 7-Hydroxy-2-(5-chloro-2-hydroxybenzoyl)-[*c*]chromen-6-one (7b). Starting with **4b** (54 mg, 0.18 mmol), Me_3SiOTf (51 mg, 0.23 mmol) and **5b** (60 mg, 0.23 mmol) in CH_2Cl_2 (1.8 mL) (first step), and triethylamine (85 mg, 0.85 mmol) in ethanol (1.5 mL) (second step), **7b** was isolated (46 mg, 70%) as a slightly yellow solid; R_f 0.66 (*n*-heptane/EtOAc=1:1). ^{1}H NMR ($CDCl_3$, 250 MHz): δ=11.72 (s, 1H, OH), 11.22 (s, 1H, OH), 8.40 (d, ^4J=2.1 Hz, 1H, Ar), 7.84–7.75 (m, 2H, Ar), 7.64 (d, ^3J=8.2 Hz, 1H, Ar), 7.57–7.49 (m, 3H, Ar), 7.17 (d, ^3J=8.2 Hz, 1H, Ar), 7.09 (d, ^3J=8.2 Hz, 1H, Ar). ^{13}C NMR (DMSO, 63 MHz): δ=193.7 (C=O) 163.6, 161.1, 154.7, 152.9 (C_{Ar}–O), 137.8 (CH_{Ar}), 134.2, 133.9, 133.7 (C_{Ar}), 132.4, 131.8, 129.1 (CH_{Ar}), 126.8 (C_{Ar}), 125.0 (CH_{Ar}), 122.8 (C_{Ar}), 118.4 (CH_{Ar}), 118.0 (C_{Ar}), 117.6, 116.8, 113.1 (CH_{Ar}). MS (EI, 70 eV): *m*/*z* (%)=368 (M^+, ^{37}Cl, 15), 366 (M^+, ^{35}Cl, 46), 239 (13), 212 (100), 155 (17). HRMS (EI, 70 eV): calcd for $C_{20}H_{11}CO_5$ (M^+): 366.02895; found: 366.02788.

3.4.3. 7-Hydroxy-2-(2-hydroxy-5-methylbenzoyl)benzo-[*c*]chromen-6-one (7c). Starting with **4c** (130 mg, 0.46 mmol), Me_3SiOTf (133 mg, 0.60 mmol), **5b** (156 mg, 0.60 mmol) in CH_2Cl_2 (8 mL) (first step), and triethylamine (218 mg, 2.15 mmol) in ethanol (5 mL) (second step), **7c** was isolated (80 mg, 51%) as a colourless solid, mp 213–214 °C; R_f 0.70 (*n*-heptane/EtOAc=1:1). ^{1}H NMR ($CDCl_3$, 250 MHz): δ=11.67 (s, 1H, OH), 11.25 (s, 1H, OH), 8.39 (d, ^4J=2.1 Hz, 1H, Ar), 7.83–7.79 (m, 1H, Ar), 7.75 (d, ^3J=8.5 Hz, 1H, Ar), 7.63 (d, ^3J=8.9 Hz, 1H, Ar), 7.51 (d, ^3J=8.9 Hz, 1H, Ar), 7.40–7.34 (m, 2H, Ar), 7.15 (dd, ^4J=2.1 Hz, ^3J=8.5 Hz, 1H, Ar), 7.03 (d, ^3J=8.5 Hz, 1H, Ar), 2.27 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ= 199.6 (C=O), 164.8, 162.6, 161.2, 152.5 (C_{Ar}–O), 137.8, 137.7 (CH_{Ar}), 135.0, 134.3, 133.2 (C_{Ar}), 132.7, 131.3 (CH_{Ar}), 128.2 (C_{Ar}), 124.9, 118.6, 118.5, 117.7 (CH_{Ar}), 117.4 (C_{Ar}), 112.5 (CH_{Ar}), 106.1 (C_{Ar}), 20.5 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3441 (s, br), 3079 (w), 3058 (w), 2925 (m), 2855 (m), 1691 (s), 1629 (s), 1592 (s). MS (EI, 70 eV): *m*/*z* (%)=346.0 (M^+, 15), 311.0 (10), 265.0 (37), 251.0 (24), 221.0 (27), 178.0 (25), 134.0 (21). HRMS (EI, 70 eV): calcd for $C_{21}H_{14}O_5$ (M^+): 346.0836; found: 346.0842.

3.4.4. 7-Hydroxy-2-(2-hydroxybenzoyl)-8-(methyl)benzo-[*c*]chromen-6-one (7d). Starting with **4a** (360 mg, 1.35 mmol), Me_3SiOTf (391 mg, 1.76 mmol) and **5c** (385 mg, 1.76 mmol) in CH_2Cl_2 (7 mL) (first step), and triethylamine (545 mg, 5.4 mmol) in ethanol (20 mL) (second step), **7d** was isolated (192 mg, 41%) as a slightly yellow solid, mp 190–191 °C; R_f 0.51 (*n*-heptane/EtOAc=1:1). ^{1}H NMR ($CDCl_3$, 250 MHz): δ=11.87 (s, 1H, OH), 11.47 (s, 1H, OH), 8.38 (d, ^4J=2.1 Hz, 1H, Ar), 7.79 (dd, ^3J=8.5 Hz, ^4J=2.1 Hz, 1H, Ar), 7.65–7.46 (m, 5H, Ar), 7.13 (d, ^3J=8.5 Hz, 1H, Ar), 6.93 (t, ^3J=8.5 Hz, 1H, Ar), 2.38 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=199.8 (C=O), 165.2, 163.3, 160.6, 152.4 (C_{Ar}–O), 138.6, 136.7 (CH_{Ar}), 134.7, 134.1 (C_{Ar}), 133.1 (CH_{Ar}), 131.7 (C_{Ar}), 130.7 (CH_{Ar}), 127.2 (C_{Ar}), 124.7 (CH_{Ar}), 118.9 (C_{Ar}), 118.9 (CH_{Ar}), 118.7, 117.7, 111.9 (CH_{Ar}), 105.3 (C_{Ar}), 15.8 (CH_3). IR (Nujol, cm^{-1}): $\tilde{\nu}$ = 1685 (s), 1623 (s), 1603 (s). MS (EI, 70 eV): *m*/*z* (%)=346 (M^+, 100), 345 (35), 266 (27), 265 (25), 226 (82), 121 (44). HRMS (EI, 70 eV): calcd for $C_{21}H_{14}O_5$ (M^+): 346.08358; found: 346.08421.

3.4.5. 8-Ethyl-7-hydroxy-2-(2-hydroxybenzoyl)benzo[*c*]-chromen-6-one (7e). Starting with **4a** (267 mg, 0.5 mmol), Me_3SiOTf (145 mg, 0.65 mmol) and **5d** (144 mg, 0.5 mmol) in CH_2Cl_2 (2.5 mL) (first step), and triethylamine (202 mg, 2.0 mmol) and ethanol (5 mL) (second step), **7e** was isolated (40 mg, 23%) as a colourless solid, mp 160–161 °C; R_f 0.28 (*n*-heptane/EtOAc=9:1). ^{1}H NMR ($CDCl_3$, 250 MHz): δ=11.86 (s, 1H, OH), 11.47 (s, 1H, OH), 8.34 (s, 1H, Ar), 8.36 (d, ^4J=2.1 Hz, 1H, Ar), 7.78 (dd, ^3J=8.5 Hz, ^4J=2.1 Hz, 1H, Ar), 7.65–7.48 (m, 4H, Ar), 7.12 (d, ^3J=8.5 Hz, 1H, Ar), 6.92 (m, 1H, Ar), 2.78 (q, ^3J=7.3 Hz, 2H, CH_2CH_3), 1.28 (t, ^3J=7.3 Hz, 3H, CH_2CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=199.8 (C=O), 165.2, 163.3, 160.3, 152.4 (C_{Ar}–O), 137.0, 136.7 (CH_{Ar}), 134.7 (C_{Ar}), 133.1 (CH_{Ar}), 133.0 (C_{Ar}), 131.6 (C_{Ar}), 130.8, 124.7 (CH_{Ar}), 118.9 (C_{Ar}), 118.9, 118.7, 117.7, 112.1 (CH_{Ar}), 105.4 (C_{Ar}), 2.9 (CH_2CH_3), 13.5 (CH_2CH_3). MS (EI, 70 eV): *m*/*z* (%)=360 (M^+, 100), 345 (98), 240 (49), 225 (56), 121 (38). HRMS (EI, 70 eV): calcd for $C_{22}H_{16}O_5$ (M^+): 360.0980; found: 360.0992.

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