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Synthesis of 7-hydroxy-6*H*-benzo[*c*]chromen-6-ones based on a '[3+3] cyclization/domino retro-Michael–aldol–lactonization' strategy

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Abstract—The $TiCl_4$-mediated [3+3] cyclization of 2,4-bis(trimethylsilyloxy)penta-1,3-diene with 3-silyloxyalk-2-en-1-ones afforded 2-acetylphenols, which were transformed into functionalized 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-6*H*-benzo[*c*]chromen-6-ones.

1. Introduction

Functionalized 6*H*-benzo[*c*]chromen-6-ones (dibenzo[*b*,*d*]-pyran-6-ones) are present in a number of pharmacologically relevant natural products. For example, autumnariol has been isolated from *Eucomis autumnalis* Greab. (Liliaceae).[1] The isolation of related 6*H*-benzo[*c*]chromen-6-ones, such as autumnariniol,[2] alternariol,[3] or altenuisol,[4] has been reported (Chart 1).[5] It has been demonstrated that 6*H*-benzo[*c*]-chromen-6-ones are specific inhibitors of the growth of endothelic cells[6] and represent estrogen receptors.[7] Ellagic and coruleoellagic acid, which have been isolated mainly from plant sources,[8] occur both as glycosides and aglycons. Dibenzo[*c*,*d*]chromen-6-ones occur in a number of natural antibiotics and antitumor agents, such as the gilvocarcins, chrysomycins, and ravidomycins.[9]

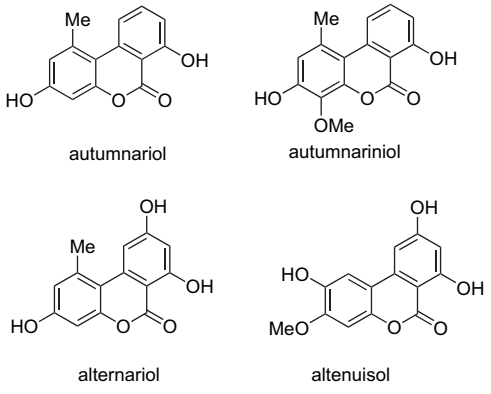

Chart 1. 7-Hydroxy-6*H*-benzo[*c*]chromen-6-ones in nature.

6*H*-Benzo[*c*]chromen-6-ones have been prepared by cyclizations of *o*-bromobenzoic acids with phenols,[10] intramolecular palladium(II) catalyzed coupling reactions of aryl benzoates,[11] and Suzuki reactions.[12–14] Harris et al. reported the synthesis of 9-*O*-methylalternariol by condensation of the dianion of acetylacetone with a protected salicylate.[15,16] We have recently reported[17] the synthesis of 7-hydroxy-6*H*-benzo[*c*]chromen-6-ones by condensation of 1,3-bis(silyl enol ethers)[18] with 4-silyloxybenzopyrylium triflates, in situ generated from chromones,[19] and subsequent base-mediated domino 'retro-Michael–aldol–lactonization' reaction. The preparative scope of this method severely depends on the availability of the chromones as starting materials. Chan and co-workers developed an elegant approach to arenes by [3+3] cyclization of 1,3-bis(silyl enol ethers) with 3-siloxyalk-2-en-1-ones.[20] Based on this work we herein report a new approach to functionalized chromones by [3+3] cyclization of 2,4-bis(trimethylsilyloxy)penta-1,3-diene with 3-silyloxyalk-2-en-1-ones. The combination of these reactions with the domino reaction of chromones with 1,3-bis(silyl enol ethers) provides a versatile strategy for the synthesis of 7-hydroxy-6*H*-benzo[*c*]chromen-6-ones. Notably, this strategy relies on the sequential use of 1,3-bis(silyl enol ethers)[18] at two stages of the synthesis.

Keywords: Chromones; Cyclizations; Domino reactions; Oxygen heterocycles; Silyl enol ethers.
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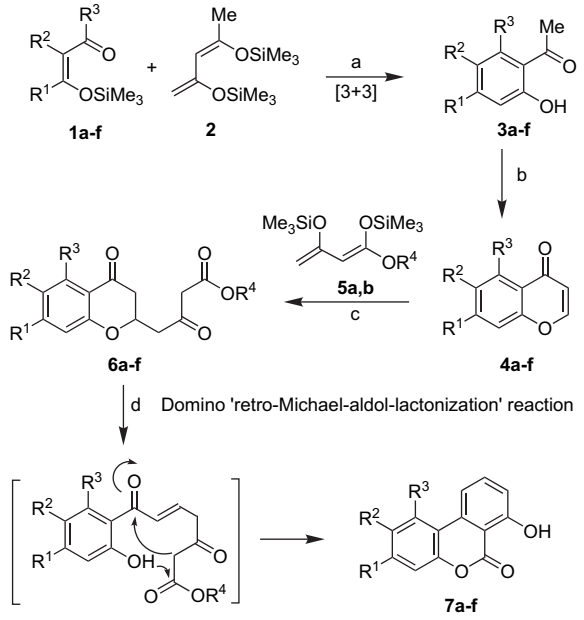
2. Results and discussion

The $TiCl_4$-mediated [3+3] cyclization of 2,4-bis(trimethylsilyloxy)penta-1,3-diene (**2**) with 3-silyloxyalk-2-en-1-ones, following the conditions reported by Chan[20] and us,[21] afforded the 2-acetylphenols **3a–f** (Scheme 1, Table 1). The synthesis of chloro-[21e] and acetoxy-substituted[21f] salicylates by [3+3] cyclizations of 1,3-bis(silyl enol ethers) with appropriate 3-silyloxyalk-2-en-1-ones has been previously reported. The cyclization of 1,3-bis(silyl enol ether) **2** with **1d** and **1e** proceeded with very good regioselectivity, which can be explained as previously reported.[20,21i] Treatment of the acetylphenols with $HC(OEt)_3$ and $HClO_4$ afforded the chromones **4a–f**. During the formation of **4f**, the acetoxy group was cleaved to give a hydroxyl group. The Me_3SiOTf-mediated condensation of **4a–f** with 1-ethoxy or 1-methoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene (**5a**,**b**) gave the 2,3-dihydrobenzopyrans **6a–f**. Treatment of the latter with NEt_3 in EtOH afforded the novel 7-hydroxy-6*H*-benzo[*c*]chromen-6-ones **7a–f**. The formation of the latter can be explained by a domino 'retro-Michael–aldol–lactonization' reaction.[17] The synthesis of compounds **3b**,[22] **3c**,[23] and **4c**[24] has been previously reported.



Scheme 1. Synthesis of 7-hydroxy-6*H*-benzo[*c*]chromen-6-ones **7a–f**: (a) $TiCl_4$, CH_2Cl_2, −78 °C; (b) $HC(OEt)_3$, $HClO_4$ (70%), reflux, 12 h; (c) (1) Me_3SiOTf (1.3 equiv), 20 °C, 1 h; (2) **5a**,**b** (1.3 equiv), CH_2Cl_2, 0→20 °C, 12 h; (3) HCl (10%); (d) NEt_3 (2.0 equiv), EtOH, 20 °C, 12 h.

The combination of two different cyclization reactions of 1,3-bis(silyl enol ethers) allows a facile approach to a number of novel 7-hydroxy-6*H*-benzo[*c*]chromen-6-ones. The core structure of the products contains 13 carbon atoms out of which 9 carbons are derived from the two 1,3-bis(silyl enol ethers), 3 carbons from the 3-silyloxyalk-2-en-1-one and 1 carbon from the orthoformate.

In conclusion, we have reported the synthesis of 7-hydroxy-6*H*-benzo[*c*]chromen-6-ones based on sequential reactions of 1,3-bis(silyl enol ethers) with 3-silyloxyalk-2-en-1-ones and chromones.

3. Experimental

3.1. General comments

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For the ^1H and ^{13}C NMR spectra the deuterated solvents indicated were used. Chemical shifts δ are reported in parts per million relative to $CHCl_3$ (^1H, 7.26 ppm) and $CDCl_3$ (^{13}C, 77.0 ppm) as internal standards. ^{13}C NMR spectral assignments are supported by DEPT analyses. Mass spectral 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. Melting points are uncorrected.

3.2. General procedure for the synthesis of 2-acetylphenols 3a–f

To a stirred CH_2Cl_2 solution (2 mL/mmol) of 1,3-bis(silyl enol ether) **2** (1.0 mmol) and 3-siloxyalk-2-en-1-one **1** (1.0 mmol) was added $TiCl_4$ (1.0 mmol) at −78 °C under argon atmosphere. The temperature of the reaction mixture was allowed to rise to 20 °C during 20 h and a saturated aqueous solution of $NaHCO_3$ (10 mL) was added. The organic layer was separated and extracted with diethyl ether (3×30 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, EtOAc/heptane=1:4).

3.2.1. 1-(3-Chloro-2,4-diethyl-6-hydroxyphenyl)ethanone (3a). Starting with 4-chloro-5-(trimethylsilyloxy)hept-4-en-3-one (**1a**) (1.021 g, 4.3 mmol), 2,4-bis(trimethylsilyloxy)penta-1,3-diene (**2**) (1.041 g, 4.3 mmol), and $TiCl_4$ (0.812 g, 4.3 mmol), **3a** was obtained (0.490 g, 50%) as

Table 1. Products and yields

	R^1	R^2	R^3	R^4	**3** (%)[a]	**4** (%)[a]	**6** (%)[a]	**7** (%)[a]
a	Et	Cl	Et	Me	50	80	77	28 (48)
b	Me	Me	Me	Et	51	70	65	22 (42)
c	Me	H	Me	Et	40	84	68	24 (46)
d	Me	$-(CH_2)_4-$		Et	36	78	61	50
e	Me	$-(CH_2)_3-$		Me	20	69	73	35 (60)
f	Me	OAc	Me	Me	42	—	—	—
f	Me	OH	Me	Me	—	70	68	33 (40)

[a] Yields of isolated products; the synthesis of compounds **3b**,[22] **3c**,[23] and **4c**[24] has been previously reported; values in brackets: yields based on recovered starting material.

a yellow solid; mp 60 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 10.40 (s, 1H, OH), 6.74 (s, 1H, Ar-H), 3.00 (q, 2H, J=7.6 Hz, CH_2), 2.75 (q, 2H, J=7.3 Hz, CH_2), 2.67 (s, 3H, CH_3), 1.32–1.19 (m, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.8 (CO), 157.9 (C–OH), 148.7, 141.6 (C), 125.8 (C–Cl), 122.8 (C), 116.8 (CH), 32.8 (CH_3), 28.3, 26.0 (CH_2), 14.7, 13.7 (CH_3). IR (Nujol, cm^{-1}): $\tilde{\nu}$ 3229 (w), 1678 (m), 1225 (s), 1081 (s), 856 (w). MS (EI, 70 eV): *m*/*z* (%) 226 (M^+, 34), 211 (100), 193 (17), 173 (10). Anal. Calcd for $C_{12}H_{15}O_2Cl$ (226.0): C 63.57, H 6.62; found: C 63.97, H 6.57.

3.2.2. 1-(6-Hydroxy-2,3,4-trimethylphenyl)ethanone (3b). The synthesis of **3b** has been previously reported.[22] Starting with 3-methyl-4-(trimethylsilyloxy)pent-3-en-2-one (**1b**) (0.500 g, 2.68 mmol), **2** (0.653 g, 2.68 mmol), and $TiCl_4$ (0.506 g, 2.68 mmol), **3b** (0.241 g, 51%) was obtained as a slight yellow solid; mp 62 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 10.87 (s, 1H, OH), 6.66 (s, 1H, Ar-H), 2.58 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.12 (s, 3H, CH_3). ^{13}C NMR (62 MHz, $CDCl_3$): δ 206.3 (CO), 157.7, 144.2, 136.4, 128.1, 122.3 (C), 116.6 (CH), 32.7, 21.5, 20.2, 15.0 (CH_3). IR (Nujol, cm^{-1}): $\tilde{\nu}$ 3191 (m), 2975 (s), 1661 (m), 1450 (s), 1304 (m), 845 (s). MS (EI, 70 eV): *m*/*z* (%) 178 (M^+, 30), 163 (100), 135 (8), 91 (12), 44 (14). Anal. Calcd for $C_{11}H_{14}O_2$ (178.1): C 74.15, H 7.86; found: C 74.00, H 7.96.

3.2.3. 1-(6-Hydroxy-2,4-dimethylphenyl)ethanone (3c). The synthesis of **3c** has been previously reported.[23] Starting with 4-trimethylsilyloxy-pent-3-en-2-one (**1b**) (1.000 g, 5.81 mmol), **2** (1.417 g, 5.81 mmol), and $TiCl_4$ (1.098 g, 5.81 mmol), **3b** (0.380 g, 40%) was obtained as a slight yellow solid; mp 42 °C.

3.2.4. 1-(2-Hydroxy-4-methyl-5,6,7,8-tetrahydronaphthalen-1-yl)ethanone (3d). Starting with 1-(2-trimethylsilyloxycyclohex-1-enyl)ethanone (**1d**) (0.500 g, 2.35 mmol), **2** (0.573 g, 2.35 mmol), and $TiCl_4$ (0.444 g, 2.35 mmol), **3d** (0.172 g, 36%) was obtained as a brownish solid; mp 55 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 11.49 (s, 1H, OH), 6.67 (s, 1H, Ar-H), 2.93 (t, 2H, J=6.4 Hz, CH_2), 2.64 (s, 3H, CH_3), 2.57 (t, 2H, J=6.7 Hz, CH_2), 2.19 (s, 3H, CH_3), 1.87–1.68 (m, 4H, CH_2). ^{13}C NMR (62 MHz, $CDCl_3$): δ 206.1 (CO), 158.9, 145.1, 137.6, 127.3, 121.0 (C), 117.2 (CH), 33.4 (CH_3), 31.3, 26.6, 22.9, 22.6 (CH_2), 20.4 (CH_3). IR (Nujol, cm^{-1}): $\tilde{\nu}$ 3410 (w), 2950 (s), 1629 (m), 1460 (s), 1340 (s), 1298 (m). MS (EI, 70 eV): *m*/*z* (%) 204 (M^+, 64), 189 (100), 161 (43), 146 (15), 44 (39). HRMS (EI) calcd for $C_{13}H_{16}O_2$ $[M]^+$: 204.1145; found: 204.1141.

3.2.5. 1-(5-Hydroxy-7-methylindan-4-yl)ethanone (3e). Starting with 2-(1-trimethylsilyloxy-ethylidene)cyclopentanone (**1a**) (1.000 g, 5.04 mmol), **2** (1.230 g, 5.04 mmol), and $TiCl_4$ (0.952 g, 5.04 mmol), **3e** (0.200 g, 20%) was obtained as a yellow solid; mp 58 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 12.18 (s, 1H, OH), 6.74 (s, 1H, Ar-H), 2.92 (t, 2H, J=7.3 Hz, CH_2), 2.83 (t, 2H, J=7.6 Hz, CH_2), 2.66 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 2.07 (quint, 2H, J=7.6 Hz, CH_2). ^{13}C NMR (62 MHz, $CDCl_3$): δ 205.8 (CO), 161.8. 152.0, 135.4, 134.1, 120.3 (C), 111.6 (CH), 33.8 (CH_2), 33.0 (CH_3), 31.5, 24.3 (CH_2), 20.5 (CH_3). IR (Nujol, cm^{-1}): $\tilde{\nu}$ 2952 (s), 1622 (w), 1470 (s), 1353 (s), 1234 (w), 841 (w). MS (EI, 70 eV): *m*/*z* (%) 190 (M^+, 40), 175 (100), 115 (12), 91 (16), 43.0 (24). HRMS (EI) calcd for $C_{12}H_{14}O_2$ $[M]^+$: 190.0988; found: 190.0985.

3.2.6. 1-[3-(Acetoxy)-6-hydroxy-2,4-dimethylphenyl]-ethanone (3f). Starting with **1f** (1.005 g, 4.37 mmol), **2** (1.066 g, 4.37 mmol), and $TiCl_4$ (0.825 g, 4.37 mmol), **3f** (0.410 g, 42%) was obtained as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 11.80 (s, 1H, OH), 6.71 (s, 1H, Ar-H), 2.61 (s, 3H, CH_3COO), 2.34 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.21 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.5, 169.1(CO), 159.5, 141.0, 138.6, 130.4, 121.2 (C), 118.3 (CH), 33.3, 20.7, 17.5, 16.5 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ 3407 (br), 2929 (w), 1760 (s), 1198 (s), 908 (w). MS (EI, 70 eV): *m*/*z* (%) 222 (M^+, 9), 180 (84), 165 (100), 43 (23). HRMS (EI) calcd for $C_{12}H_{14}O_4$ $[M]^+$: 222.0887; found: 222.0881.

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

To ethanone **3** (1.0 equiv) were slowly added triethyl orthoformate (20 equiv) and perchloric acid (70%, 1.3 equiv) and the reaction mixture was refluxed for 20 h at 80 °C. After cooling to 20 °C, the reaction mixture was filtered and washed with cold water. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×30 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).

3.3.1. 6-Chloro-5,7-diethylchromen-4-one (4a). Starting with **3a** (0.302 g, 1.33 mmol), triethyl orthoformate (3.936 g, 26.60 mmol, 20 equiv), and perchloric acid (70%) (0.172 g, 1.72 mmol), **4a** (0.251 g, 80%) was obtained as a colorless solid; mp 80 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.68 (d, 1H, J=6.1 Hz, CH), 7.18 (s, 1H, Ar-H), 6.23 (d, 1H, J=5.8 Hz, CH), 3.55 (q, 2H, J=7.3 Hz, CH_2), 2.85 (q, 2H, J=7.6 Hz, CH_2), 1.32–1.19 (m, 6H, CH_3). ^{13}C NMR (62 MHz, $CDCl_3$): δ 178.4 (CO), 156.5 (C), 153.1 (CH), 148.0, 144.2, 131.7, 121.0 (C), 116.3, 114.4 (CH), 28.0, 24.3 (CH_2), 13.7, 13.3 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ 3436 (br), 2970 (w), 1648 (s), 1436 (s), 1254 (s), 843 (s). MS (EI, 70 eV): *m*/*z* (%) 236 (M^+, 89), 219 (100), 193 (20), 115 (11). Anal. Calcd for $C_{13}H_{13}O_2Cl$ (236.0): C 66.10, H 5.55; found: C 65.97, H 5.63.

3.3.2. 5,6,7-Trimethylchromen-4-one (4b). Starting with **3b** (0.202 g, 1.15 mmol), triethyl orthoformate (3.400 g, 23.00 mmol), and perchloric acid (70%) (0.152 g, 1.50 mmol), **4b** (0.151 g, 70%) was obtained as a white solid; mp 124 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.64 (d, 1H, J=5.8 Hz, CH), 7.07 (s, 1H, Ar-H), 6.20 (d, 1H, J=5.7 Hz, CH), 2.83 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.23 (s, 3H, CH_3). ^{13}C NMR (62 MHz, $CDCl_3$): δ 180.0 (CO), 156.0 (C), 153.0 (CH), 143.0, 138.5, 133.2, 121.3 (C), 116.2, 114.1 (CH), 21.6, 17.3, 15.2 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ 3438 (br), 2925 (w), 1647 (s), 1428 (s), 1236 (s), 1001 (s), 848 (s). MS (EI, 70 eV): *m*/*z* (%) 188 (M^+, 100), 173 (57), 145 (9), 91 (7). Anal. Calcd for $C_{12}H_{12}O_2$ (188.0): C 76.60, H 6.38; found: C 76.20, H 6.31.

3.3.3. 5,7-Dimethylchromen-4-one (4c). The synthesis of **4c** has been previously reported.[24] Starting with **3c**

(0.175 g, 1.07 mmol), triethyl orthoformate (3.502 g, 21.34 mmol), and perchloric acid (70%) (0.140 g, 1.40 mmol), **4c** (0.156 g, 84%) was obtained as a brownish solid; mp 58 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.66 (d, 2H, J=5.8 Hz, CH), 7.04 (s, 1H, Ar-H), 6.92 (s, 1H, Ar-H), 6.20 (d, 2H, J=6.1 Hz, CH), 2.80 (s, 3H, CH_3), 2.38 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.6 (CO), 158.1 (C), 153.5 (CH), 143.7, 140.7 (C), 129.2 (CH), 121.0 (C), 116.3, 114.5 (CH), 22.7, 21.5 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ 3432 (br), 2925 (m), 1648 (s), 1350 (s), 1239 (s), 827 (s). MS (EI, 70 eV): *m*/*z* (%) 174 (M^+, 100), 159 (12), 145 (30), 91 (36), 39 (21). Anal. Calcd for $C_{11}H_{10}O_2$ (174.1): C 75.58, H 5.74; found: C 75.23, H 5.80.

3.3.4. 6-Methyl-7,8,9,10-benzo[*f*]chromen-1-one (4d). Starting with **3d** (0.150 g, 0.73 mmol), triethyl orthoformate (2.161 g, 14.60 mmol), and perchloric acid (0.095 g, 0.95 mmol), **4d** (0.122 g, 78%) was obtained as a white solid; mp 70 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.66 (d, 1H, J=5.7 Hz, CH), 7.07 (s, 1H, Ar-H), 6.23 (d, 1H, J=6.1 Hz, CH), 3.45 (t, 2H, J=6.4 Hz, CH_2), 2.64 (t, 2H, J=5.4 Hz, CH_2), 2.31 (s, 3H, CH_3), 1.80–1.77 (m, 4H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.9 (CO), 156.2 (C), 153.3 (CH), 143.6, 139.7, 133.3, 120.9 (C), 116.5, 114.7 (CH), 30.1, 27.8, 23.1, 22.5 (CH_2), 20.8 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ 3437 (br), 2925 (s), 1620 (s), 1605 (s), 1455 (s), 1232 (s), 850 (m). MS (EI, 70 eV): *m*/*z* (%) 214 (M^+, 100), 199 (80), 181 (29), 131 (33), 69 (51). Anal. Calcd for $C_{14}H_{14}O_2$ (214.1): C 78.85, H 6.94; found: C 78.70, H 6.30.

3.3.5. 4-Methyl-2,3-dihydro-1*H*-6-oxacyclopenta[*a*]-naphthalen-9-one (4e). Starting with **3e** (0.240 g, 1.30 mmol), triethyl orthoformate (3.863 g, 26.10 mmol), and perchloric acid (0.170 g, 1.70 mmol), **4e** (0.180 g, 69%) was obtained as a colorless solid; mp 130 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.70 (d, 1H, J=6.1 Hz, CH), 7.03 (s, 1H, Ar-H), 6.21 (d, 1H, J=5.8 Hz, CH), 3.50 (t, 2H, J=7.6 Hz, CH_2), 2.81 (t, 2H, J=7.6 Hz, CH_2), 2.33 (s, 3H, CH_3), 2.15 (p, 2H, J=7.6 Hz, CH_2). ^{13}C NMR (62 MHz, $CDCl_3$): δ 179.4 (CO), 157.0 (C), 154.6 (CH), 144.6, 141.3, 140.7, 133.9 (C), 116.4, 113.9 (CH), 34.0, 29.3, 24.0 (CH_2), 20.3 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ 3438 (br), 2914 (w), 1662 (s), 1603 (s), 1230 (m), 849 (m). MS (EI, 70 eV) *m*/*z* (%) 199 (M^+, 100), 184 (5), 128 (12), 115 (7). HRMS (EI, 70 eV) calcd for $C_{13}H_{11}O_2$ $[M]^+$: 199.0754; found: 199.0747.

3.3.6. 6-Hydroxy-5,6-dimethylchromen-4-one (4f). Starting with **3f** (0.205 g, 0.90 mmol), triethyl orthoformate (2.666 g, 18.01 mmol), and perchloric acid (70%) (0.117 g, 1.17 mmol), **4f** (0.120 g, 70%) was obtained as a colorless solid; mp 140 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.67 (d, 1H, J=5.8 Hz, CH), 7.10 (s, 1H, Ar-H), 6.20 (d, 1H, J=7.1 Hz, CH), 2.81 (s, 3H, CH_3), 2.36 (s, 3H, CH_3). ^{13}C NMR (62 MHz, $CDCl_3$): δ 177.0 (CO), 154.8 (CH), 149.5, 148.5, 131.6, 121.7, 119.4 (C), 117.0, 113.0 (CH), 17.7, 13.9 (CH_3). IR (Nujol, cm^{-1}): $\tilde{\nu}$ 3410 (br), 2950 (s), 1642 (w), 1634 (w), 1294 (w), 1280 (w). MS (EI, 70 eV): *m*/*z* (%) 190 (M^+, 94), 161 (56), 147 (54), 43 (100). HRMS (EI, 70 eV) calcd for $C_{11}H_{10}O_3$ $[M]^+$: 190.0624; found: 190.0621.

3.4. General procedure for the synthesis of 4-(chroman-2-yl)-3-oxobutyrates 6a–f

To chromone **4** (1.0 equiv) was added Me_3SiOTf (1.3 equiv) at 20 °C. After stirring for 1 h, CH_2Cl_2 (8 mL) and the 1,3-bis(silyl enol ether) **5** (1.3 equiv) were added at 0 °C. The mixture was stirred for 12 h at 20 °C and was subsequently poured into an aqueous solution of hydrochloric acid (10%). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (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 from polar side-products by column flash chromatography (silica gel, *n*-hexane/EtOAc=1:1) to give **6a–f**. Products **6a–f** were isolated and characterized and subsequently transformed into **7a–f**.

3.4.1. 4-(6-Chloro-5,7-diethyl-4-oxochroman-2-yl)-3-oxobutyric acid methyl ester (6a). Starting with **4a** (0.212 g, 0.89 mmol), TMSOTf (0.256 g, 1.15 mmol), and 1-methoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene (**5a**) (0.300 g, 1.15 mmol), **6a** (0.240 g, 77%) was obtained as a brownish solid; mp 72 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.73 (s, 1H, Ar-H), 4.95–4.84 (m, 1H, CH chain), 3.76 (s, 3H, OCH_3), 3.56 (s, 2H, CH_2), 3.32–3.27 (m, 2H, CH_2), 3.14 (dd, 1H, ^2J=17.0 Hz, ^3J=7.3 Hz, CH_2), 2.90 (dd, 1H, ^2J=17.0 Hz, ^3J=7.1 Hz, CH_2), 2.79–2.70 (m, 4H, CH_2), 1.22 (t, 3H, J=7.6 Hz, CH_3), 1.16 (t, 3H, J=7.3 Hz, CH_3). ^{13}C NMR (62 MHz, $CDCl_3$): δ 199.0, 191.4, 160.9 (CO), 150.3, 148.1, 148.5, 145.5, 145.4 (C), 115.9, 73.0 (CH), 53.0 (OCH_3), 50.0, 47.7, 44.4, 28.5, 24.7 (CH_2), 14.0 (2C, CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ 3437 (br), 2977 (m), 1746 (s), 1677 (s), 1417 (s), 1194 (s), 867 (m). MS (EI, 70 eV): *m*/*z* (%) 352 (M^+, 78), 320 (14), 237 (100), 167 (40), 115 (9). Anal. Calcd for $C_{18}H_{21}O_5Cl$ (352.0): C 61.27, H 5.95; found: C 61.19, H 6.10.

3.4.2. 3-Oxo-4-(5,6,7-trimethyl-4-oxochroman-2-yl)-butyric acid ethyl ester (6b). Starting with **4b** (0.13 g, 0.70 mmol), TMSOTf (0.20 g, 0.91 mmol), and 1-ethoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene (**5b**) (0.25 g, 0.91 mmol), **6b** (0.145 g, 65%) was obtained as a yellow solid; mp 56 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.63 (s, 1H, Ar-H), 4.90–4.79 (m, 1H, CH), 4.20 (q, 2H, J=7.0 Hz, CH_2), 3.53 (s, 2H, CH_2), 3.15 (dd, 1H, ^2J=16.7 Hz, ^3J=7.3 Hz, CH_2), 2.85 (dd, 1H, ^2J=16.7 Hz, ^3J=7.3 Hz, CH_2), 2.72–2.70 (m, 2H, CH_2), 2.67 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 1.28 (t, 3H, J=7.3 Hz, CH_3). ^{13}C NMR (62 MHz, $CDCl_3$): δ 199.4, 193.2, 166.8 (CO), 159.9, 145.0, 139.7, 129.6, 118.0 (C), 116.2, 72.4 (CH), 61.6, 50.0, 47.5, 44.4 (CH_2), 21.7, 17.5, 14.9, 14.0 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ 3435 (br), 2982 (w), 1741 (s), 1677 (s), 1271 (s), 1100 (m), 857 (w). MS (EI, 70 eV): *m*/*z* (%) 318 (M^+, 60), 272 (20), 203 (9), 189 (42), 162 (100), 91 (16). HRMS (EI, 70 eV) calcd for $C_{18}H_{22}O_5$ $[M]^+$: 318.1462; found: 318.1458. Anal. Calcd for $C_{18}H_{22}O_5$ (318.0): C 67.92, H 6.91; found: C 68.44, H 6.75.

3.4.3. 4-(5,7-Dimethyl-4-oxochroman-2-yl)-3-oxobutyric acid ethyl ester (6c). Starting with **4c** (0.228 g, 1.30 mmol), TMSOTf (0.375 g, 1.70 mmol), and 1-ethoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene (**5b**) (0.465 g, 1.70 mmol), **6c** (0.265 g, 68%) was obtained as a yellow

oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.61 (s, 2H, Ar-H), 4.93–4.82 (m, 1H, CH), 4.21 (q, 2H, J=7.3 Hz, CH_2), 3.53 (s, 2H, CH_2), 3.14 (dd, 1H, ^2J=16.7 Hz, ^3J=7.3 Hz, CH_2), 2.85 (dd, 1H, ^2J=16.7 Hz, ^3J=7.3 Hz, CH_2), 2.71–2.67 (m, 2H, CH_2), 2.58 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 1.28 (t, 3H, J=7.3 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.3, 192.2, 166.5 (CO), 162.07, 146.0, 141.9 (C), 126.2 (CH), 117.2 (C), 116.3, 73.1 (CH), 61.9, 50.3, 47.8, 44.2 (CH_2), 23.0, 22.0, 14.5 (CH_3). IR (Nujol, cm^{-1}): $\tilde{\nu}$ 3436 (br), 2979 (m), 1744 (s), 1614 (s), 1326 (s), 1029 (s), 846 (w). MS (EI, 70 eV): m/z (%) 304 (M^+, 71), 189 (34), 175 (100), 148 (96), 91 (40). Anal. Calcd for $C_{17}H_{20}O_5$ (304.1): C 67.67, H 6.57; found: C 67.84, H 6.61.

3.4.4. 4-(6-Methyl-1-oxo-2,3,7,8,9,10-hexahydro-1*H*-benzo[*f*]chromen-3-yl)-3-oxobutyric acid ethyl ester (6d). Starting with **4d** (0.092 g, 0.43 mmol), TMSOTf (0.124 g, 0.56 mmol), and 1-ethoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene (**5b**) (0.153 g, 0.56 mmol), **6d** (0.091 g, 61%) was obtained as a yellow oil. ^{1}H NMR (keto/enol=10:1, 250 MHz, $CDCl_3$, only keto tautomer was listed): δ 6.63 (s, 1H, Ar-H), 4.91–4.80 (m, 1H, CH), 4.21 (q, 2H, J=7.3 Hz, CH_2), 3.53 (s, 2H, CH_2), 3.17–3.0 (m, 1H, CH_2), 2.85 (dd, 1H, ^2J=16.3 Hz, ^3J=7.1 Hz, CH_2), 2.70–2.67 (m, 2H, CH_2), 2.31 (s, 3H, CH_3), 1.19–1.17 (m, 2H, CH_2), 1.73–1.66 (m, 6H, CH_2), 1.28 (t, 3H, J=7.0 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.3, 192.7, 166.7 (CO), 159.9, 145.6, 140.7, 130.0, 117.1 (C), 116.3, 72.4 (CH), 61.3, 49.9, 47.3, 44.3, 30.9, 26.8, 23.3, 22.6 (CH_2), 20.41, 14.03 (CH_3). IR (Nujol, cm^{-1}): $\tilde{\nu}$ 3437 (br), 2925 (s), 1620 (s), 1605 (s), 1455 (s), 1232 (s), 850 (m). MS (EI, 70 eV): m/z (%) 344 (M^+, 73), 298 (15), 272 (17), 214 (100), 188 (85), 91 (11). Anal. Calcd for $C_{20}H_{24}O_5$ (344.2): C 69.73, H 6.97; found: C 69.72, H 7.16.

3.4.5. 4-(9-Methyl-8-oxo-1,2,3,6,7,8-hexahydro-5-oxacyclopenta[*b*]naphthalen-6-yl)-3-oxabutyric acid methyl ester (6e). Starting with **4e** (0.100 g, 0.54 mmol), TMSOTf (0.155 g, 0.70 mmol), and 1-methoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene (**5a**) (0.182 g, 0.70 mmol), **6e** (0.125 g, 73%) was obtained as a yellow solid; mp 68 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.59 (s, 1H, Ar-H), 4.93–4.82 (m, 1H, CH), 3.76 (s, 3H, OCH_3), 3.57 (s, 2H, CH_2), 3.28 (t, 2H, J=7.9 Hz, CH_2), 3.18 (dd, 1H, ^2J=16.7 Hz, ^3J=7.3 Hz, CH_2), 2.88 (dd, 1H, ^2J=16.5 Hz, ^3J=7.3 Hz, CH_2), 2.72–2.66 (m, 4H, CH_2), 2.24 (s, 3H, CH_3), 2.15–2.06 (m, 2H, CH_2). ^{13}C NMR (62 MHz, $CDCl_3$): δ 199.4, 192.4, 167.2 (CO), 160.8, 148.6, 146.4, 142.8, 138.0 (C), 116.6, 73.5 (CH), 53.0 (OCH_3), 50.0, 47.8, 43.8, 34.7, 30.5, 25.2 (CH_2), 21.0 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ 3435 (br), 2982 (w), 1741 (s), 1677 (s), 1271 (s), 1100 (m), 857 (w). MS (EI, 70 eV): m/z (%) 316 (M^+, 59), 284 (15), 200 (100), 174 (50), 115 (12). HRMS (EI, 70 eV) calcd for $C_{18}H_{20}O_5$ $[M]^+$: 316.1305; found: 316.1303.

3.4.6. Methyl 4-(3,4-dihydroxy-5,7-dimethyl-4-oxo-2*H*-chromen-2-yl)-3-oxobutanoate (6f). Starting with **4f** (0.082 g, 0.45 mmol), TMSOTf (0.129 g, 0.58 mmol), and 1-methoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene (**5a**) (0.150 g, 0.58 mmol), **6f** (0.093 g, 68%) was obtained as a yellow oil. ^{1}H NMR (keto/enol=10:3, 250 MHz, $CDCl_3$, only keto tautomer was listed): δ 6.69 (s, 1H, Ar-H), 4.95–4.77 (m, 1H, ring CH), 3.75 (s, 3H, OCH_3), 3.56 (s, 2H, chain CH_2), 3.19–3.07 (m, 1H, ring CH_2), 2.91–2.80 (m, 1H, ring CH_2), 2.72–2.66 (m, 2H, chain CH_2), 2.55 (s, 3H, CH_3), 2.42 (s, 3H, CH_3). ^{13}C NMR (62 MHz, $CDCl_3$): δ 199.2, 192.7, 169.0 (CO), 159.5 (C–OH), 147.1, 138.9, 133.4, 133.1 (C), 117.7, 73.1 (CH), 53.0 (OCH_3), 50.0, 47.8, 44.6 (CH_2), 17.6, 14.6 (CH_3). IR (Nujol, cm^{-1}): $\tilde{\nu}$ 3476 (br), 2955 (w), 1748 (s), 1614 (s), 1196 (s), 1073 (m), 862 (w). MS (EI, 70 eV): m/z (%) 306 (M^+, 97), 274 (18), 191 (51), 164 (100), 135 (10). HRMS (EI, 70 eV) calcd for $C_{16}H_{18}O_6$ $[M]^+$: 306.1098; found: 306.1097.

3.5. General procedure for the synthesis of 7-hydroxy-6*H*-benzo[*c*]chromen-6-ones 7a–f

To an EtOH solution (10 mL) of **6** was added NEt_3 (2.0 equiv) and the mixture was refluxed for 12 h at 80 °C. After cooling down to 20 °C, an aqueous solution of hydrochloric acid (1 M) and Et_2O (50 mL) was added. The organic layer was separated and the aqueous layer was extracted with Et_2O (3×100 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, *n*-hexane/EtOAc=20:1→3:1) to give product **7**.

3.5.1. 3-Chloro-2,4-diethyl-8-hydroxy-10*H*-phenanthren-9-one (7a). Starting with **6a** (0.170 g, 0.48 mmol) and NEt_3 (0.097 g, 0.96 mmol), **7a** (0.041 g, 28%; 48% based on recovered starting material) was obtained as a colorless solid; mp 140 °C. Starting material **6a** (0.070 g) was recovered. ^{1}H NMR (250 MHz, $CDCl_3$): δ 11.70 (s, 1H, OH), 8.14–8.06 (m, 2H, Ar-H), 7.55 (s, 1H, Ar-H), 7.47 (dd, 1H, J=6.4 Hz, J=2.7 Hz, Ar-H), 3.30 (q, 2H, J=7.3 Hz, CH_2), 2.82 (q, 2H, J=7.6 Hz, CH_2), 1.50 (t, 3H, J=7.3 Hz, CH_3), 1.28 (t, 3H, J=7.3 Hz, CH_3). ^{13}C NMR (62 MHz, $CDCl_3$): δ 165.7, 163.2, 150.0, 145.0, 140.2 (C), 137.0 (CH), 135.8, 133.0, 117.3 (C), 116.7, 116.5, 116.0 (CH), 107.0 (C), 27.6, 26.2 (CH_2), 13.3, 12.7 (CH_3). IR (Nujol, cm^{-1}): $\tilde{\nu}$ 3430 (br), 2910 (s), 1678 (s), 1224 (m), 1081 (w), 856 (w). MS (EI, 70 eV): m/z (%) 302 (M^+, 100), 287 (44), 267 (20), 152 (15), 57 (20). HRMS (EI, 70 eV) calcd for $C_{17}H_{15}O_3Cl$ $[M]^+$: 302.0704; found: 302.0704.

3.5.2. 7-Hydroxy-1,2,3-trimethylbenzo[*c*]chromen-6-one (7b). Starting with **6b** (0.120 g, 0.37 mmol) and NEt_3 (0.076 g, 0.75 mmol), **7b** (0.021 g, 22%; 42% based on recovered starting material) was obtained as a white solid; mp 182 °C. Starting material (**6b**) (0.040 g) was recovered. ^{1}H NMR (250 MHz, $CDCl_3$): δ 11.68 (s, 1H, OH), 7.68 (d, 1H, J=7.9 Hz, Ar-H), 7.66 (s, 1H, Ar-H), 7.06–7.03 (m, 2H, Ar-H), 2.71 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.29 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.2, 162.8, 152.2, 149.9, 139.9 (C), 136.9 (CH), 135.0, 134.0, 117.9 (C), 116.6, 116.4, 115.9 (CH), 107.3 (C), 21.6, 21.5, 16.7 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ 2952 (s), 1671 (w), 1477 (s), 1371 (s), 1238 (w), 817 (w). MS (EI, 70 eV): m/z (%) 254 (M^+, 100), 239 (32), 211 (47), 149 (19), 91 (5). HRMS (EI, 70 eV) calcd for $C_{16}H_{14}O_3$ $[M]^+$: 254.0937; found: 254.0940.

3.5.3. 7-Hydroxy-1,3-dimethylbenzo[*c*]-6-one (7c). Starting with **6c** (0.091 g, 0.30 mmol) and NEt_3 (0.060 g,

0.60 mmol), **7c** (0.017 g, 24%; 46% based on recovered starting material) was obtained as a white solid; mp 180 °C. Starting material (**6c**) (0.042 g) was recovered. ^{1}H NMR (250 MHz, $CDCl_3$): δ 11.79 (s, 1H, OH), 7.80 (d, 1H, J=7.6 Hz, Ar-H), 7.70 (t, 1H, J=8.2 Hz, Ar-H), 7.08 (s, 1H, Ar-H), 7.31 (d, 1H, J=7.0 Hz, Ar-H), 7.30 (s, 1H, Ar-H), 7.25 (s, 1H, Ar-H), 2.82 (s, 3H, CH_3), 2.40 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.2, 162.8, 152.2, 149.4, 140.1, 136.8, 136.7 (C), 136.6, 130.6, 116.6, 116.2, 115.7 (CH), 115.2, 106.3 (C), 25.4, 20.9, 16.7 (CH_3). IR (Nujol, cm^{-1}): $\tilde{\nu}$ 3410 (br), 2930 (s), 1675 (m), 1460 (s), 1225 (w), 814 (w). MS (EI, 70 eV): *m/z* (%) 240 (M^+, 100), 197 (15), 165 (10), 111 (21), 97 (30). HRMS (EI, 70 eV) calcd for $C_{15}H_{12}O_3$ $[M]^+$: 240.0781; found: 240.0781.

3.5.4. 4-Hydroxy-8-methyl-9,10,11,12-tetrahydro-6-oxabenzo[*c*]phenanthren-5-one (7d). Starting with **6d** (0.072 g, 0.20 mmol) and NEt_3 (0.041 g, 0.40 mmol), **7d** (0.028 g, 50%) was obtained as a slight yellow solid; mp 115 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 11.82 (s, 1H, OH), 7.78–7.66 (m, 2H, Ar-H), 7.08–7.03 (m, 2H, Ar-H), 3.45 (t, 2H, J=6.1 Hz, CH_2), 2.84 (t, 2H, J=5.4 Hz, CH_2), 2.31 (s, 3H, CH_3), 1.89–1.77 (m, 4H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6, 163.0, 149.4, 139.0, 137.4 (C), 136.6 (CH), 123.9, 118.5, 118.2 (C), 116.8, 115.9 (CH), 107.2 (C), 33.3, 30.9, 23.8, 22.7 (CH_2), 20.5 (CH_3). IR (Nujol, cm^{-1}): $\tilde{\nu}$ 3130 (br), 1719 (w), 1663 (w), 1098 (w), 700 (w). MS (EI, 70 eV): *m/z* (%) 280 (M^+, 100), 265 (25), 214 (15), 149 (13), 57 (18). HRMS (EI, 70 eV) calcd for $C_{18}H_{16}O_3$ $[M]^+$: 280.1094; found: 280.1090.

3.5.5. 8-Hydroxy-4-methyl-2,3-dihydro-1*H*-6-oxacyclopenta[*c*]phenanthren-7-one (7e). Starting with **6e** (0.100 g, 0.31 mmol) and NEt_3 (0.063 g, 0.63 mmol), **7e** was obtained (0.030 g, 35%; 60% based on recovered starting material) as a colorless solid; mp 202 °C. Starting material (**6e**) (0.041 g) was recovered. ^{1}H NMR (250 MHz, $CDCl_3$): δ 11.74 (s, 1H, OH), 7.68 (t, 1H, J=7.0 Hz, Ar-H), 7.63 (s, 1H, Ar-H), 7.06–7.03 (m, 2H, Ar-H), 3.42 (t, 2H, J=7.3 Hz, CH_2), 2.90 (t, 2H, J=7.9 Hz, CH_2), 2.34 (s, 3H, CH_3), 2.30–2.18 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.6, 165.9, 162.6, 150.0, 141.4, 140.6, 136.8 (C), 135.8, 115.3, 114.6, 114.6 (CH), 106.2 (C), 35.1, 29.5, 23.8 (CH_2), 18.5 (CH_3). IR (Nujol, cm^{-1}): $\tilde{\nu}$ 3420 (br), 2910 (s), 1653 (w), 1320 (w), 1229 (w), 846 (w). MS (EI, 70 eV): *m/z* (%) 266 (M^+, 100), 251 (24), 207 (10), 165 (8), 57 (10). HRMS (EI, 70 eV) calcd for $C_{17}H_{14}O_3$ $[M]^+$: 266.0937; found: 266.0930.

3.5.6. 2,7-Dihydroxy-1,3-dimethyl-6*H*-benzo[*c*]chromen-6-one (7f). Starting with **6f** (0.120 g, 0.41 mmol) and NEt_3 (0.083 g, 0.82 mmol), **7f** (0.035 g, 33%; 40% based on recovered starting material) was obtained as a slight brownish solid mp 190 °C. Starting material (**6f**) (0.020 g) was recovered. ^{1}H NMR (250 MHz, DMSO-d_6): δ 11.69 (s, 1H, OH), 8.65 (s, 1H, OH), 7.87–7.77 (m, 2H, Ar-H), 7.12 (s, 1H, Ar-H), 7.09 (dd, 1H, J=8.2, 7.3 Hz, Ar-H), 2.64 (s, 3H, CH_3), 2.29 (s, 3H, CH_3). ^{13}C NMR (62 MHz, DMSO-d_6): δ 165.3, 161.8, 151.0, 144.5 (C), 137.2 (CH), 136.6, 129.2, 122.8 (C), 117.6, 117.5, 116.3, 115.6 (CH), 106.3 (C), 17.3, 17.0 (CH_3). IR (Nujol, cm^{-1}): $\tilde{\nu}$ 3415 (br), 2940 (s), 1635 (m), 1240 (s), 1120 (m), 810 (w). MS (EI, 70 eV): *m/z* (%) 256 (M^+, 100), 213 (5), 207 (10), 165 (8), 57 (10). HRMS (ESI) calcd for $C_{15}H_{13}O_4$ $[M+H]^+$: 257.08084; found: 257.08069.

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