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Convenient Synthesis of 3-Cinnamoyl-2-styrylchromones: Reinvestigation of the Baker–Venkataraman Rearrangement

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An efficient and straightforward, one-pot sequence gives access to highly functionalized 3-cinnamoyl-2-styrylchromones in excellent yields. The low solubility of the target molecules allows convenient isolation. The formation of an α,α-dicinnamoylated acetophenone, as a consequence of a two-fold Baker–Venkataraman sequence, has to be anticipated.

Introduction

In recent years, the number of publications dealing with chromones, i.e., 4*H*-1-benzopyran-4-ones, has dramatically increased and syntheses have also been intensively reviewed.[1] This can be attributed to the flavones (2-phenylchromones), the most prominent class of naturally occurring chromones, which are found throughout the plant kingdom.[2] A wide variety of applications has been found for chromones, including, for example, anticoagulants,[3] antitumor agents,[4] and antiasthmatics.[5] In contrast to flavones, there are only two natural products that are known to contain the vinylogue 2-styrylchromone architecture: Hormothamnione (**1**) and desmethoxyhormothamnione (**2**) (Figure 1). Both compounds were isolated from the blue-green algae, *chrysophaeum taylori*.[6]

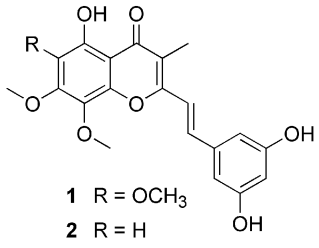

Figure 1. Naturally occurring products hormothamnione (**1**) and desmethoxyhormothamnione (**2**).

Additionally, many synthetic 2-styrylchromones have been produced that have revealed striking biological activity such as anti-inflammatory,[7] antiproliferative,[8] and antioxidant properties.[9]

Results and Discussion

In the course of a natural product synthesis, we required efficient access to 3-cinnamoyl-2-styrylchromones with a specific substitution pattern at the A-ring, i.e., 5-hydroxy-7-methyl-2-styrylchromone. Among the possible synthetic routes, the Baker–Venkataraman sequence involving the appropriate acetophenone and cinnamic acid seemed to be the most convenient.[10]

In this transformation, an *ortho*-acyloxy ketone is rearranged to a β-diketone by the catalytic action of base. Cyclization to the desired chromone may occur in situ or could require an extra step, which can either be performed oxidatively or be accomplished in strongly acidic media.[11,12] For the synthesis of 3-cinnamoyl-2-styrylchromones, a three-step procedure has been reported by Silva et al.;[12] however, because 3-cinnamoyl-2-styrylchromones were considered to be by-products, the yields were usually low (<10%, three steps). A two-step approach elaborated by the same group employed K_2CO_3 in anhydrous pyridine to mediate both the rearrangement and cyclization reaction. In this protocol, the 3-cinnamoyl-2-styrylchromones are afforded in moderate yields (Scheme 1).[13] Some results were, however, contradictory to earlier reports, wherein a one-pot synthesis of 2-styrylchromones was claimed.[14] Polyhydroxyphenones were treated with cinnamoyl chloride in K_2CO_3/acetone to yield the corresponding 2-styrylchromones. The hydroxy groups of the resulting chromone were anticipated to be acylated with cinnamoyl moieties and were subsequently saponified with 5% KOH in methanol.

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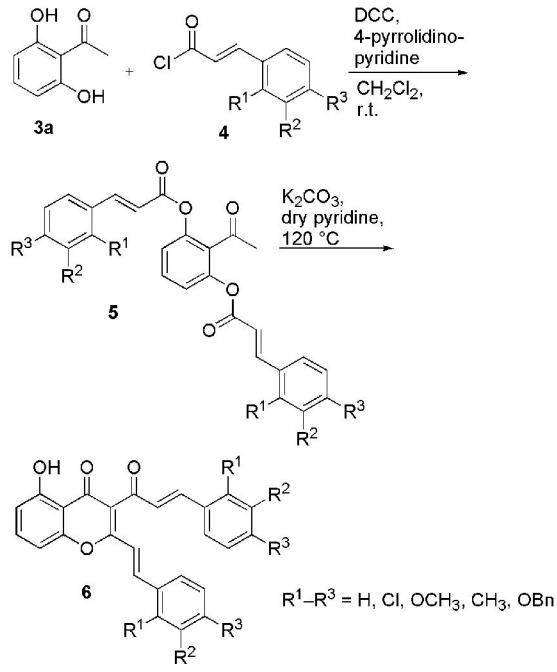
Several substrates decomposed and did not yield the desired chromones. Interestingly, a one-pot synthesis of 5-hydroxyflavones by using K_2CO_3/acetone has been published.[15] We were thus inspired to apply this protocol to our substrates.

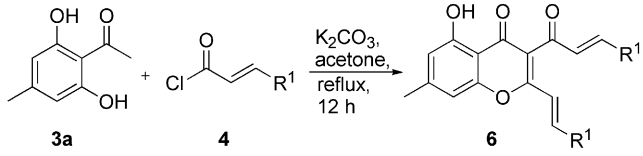


Scheme 1. Two-step synthesis of 3-cinnamoyl-2-styrylchromones.[13]

Here, we present a straightforward approach to the conversion of 2,6-dihydroxyacetophenone derivatives into the corresponding 3-cinnamoyl-2-styrylchromones in high yields (Table 1). The protocol exhibits significant advances, because it is simple to perform and employs very mild reaction conditions. The crude yields of 3-cinnamoyl-2-styrylchromones **6** are quantitative and the microanalyses of these crude materials showed only slight deviations from acceptable tolerance (^{1}H NMR spectroscopic analysis revealed only traces of solvent as impurities). The major reason for the outstanding yield of **6** arises from its poor solubility in the reaction media. In fact, attempts to purify the target compounds by column chromatography on silica resulted in tremendously reduced yields, because these compounds are prone to crystallization on the column during the chromatography process. Thus, the depressed yield upon chromatography is a direct consequence of the poor solubility of the individual derivative **6**.

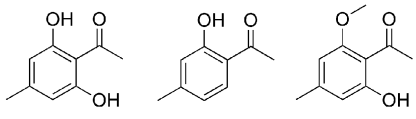
2,6-Dihydroxy-4-methylacetophenone (**3a**) can be converted with cinnamoyl chloride into the intensely yellow product **6a** (Table 1, Entry 1). Introduction of a *tert*-butyl moiety at the 4-position of the cinnamoyl fragment enhances the solubility of the target compound **6b** (Table 1, Entry 2). Both chromones **6a** and **6b** furnished suitable single crystals for X-ray crystallographic analysis (Figure 2). 3-Cinnamoyl-2-styryl-chromone (**6a**) shows dispersion interactions leading to a herringbone structure. This is due to the cinnamoyl moiety, which is tilted by 62.14° versus the chromone plane. The crystal structure of **6b** exhibits a tetrameric assembly with the bulky *tert*-butyl groups pointing to

Table 1. Substrates subjected to the one-pot Baker–Venkataraman rearrangement.[a]



Entry	Acetophenone	Acroyl chloride (R^1)		Product	Yield: crude (after chromatography) [%]
1	**3a**	Ph	**4a**	**6a**	99 (54)
2	**3a**	4-*t*BuC_6H_4	**4b**	**6b**	99 (79)[b]
3	**3a**	4-MeOC_6H_4	**4c**	**6c**	99 (86)[b]
4	**3a**	3,4-(MeO)$_2C_6H_4$	**4d**	**6d**	99 (94)[b]
5	**3a**	3-FC_6H_4	**4e**	**6e**	61 (61)
6	**3a**	3,4-(CH_2O_2)C_6H_3	**4f**	**6f**	97 (93)
7	**3a**	2-thienyl	**4g**	**6g**	99 (40)
8	**3a**	2-furyl	**4h**	**6h**	92 (45)
9	**3b**	4-*t*BuC_6H_4	**4b**	**6i**	–[c]
10	**3c**	$SiMe_3$	**4a**	**6j**	–[c]

[a] Reagents and conditions: acyl chloride (2.3 equiv.), K_2CO_3 (3.0 equiv.), acetone, reflux. [b] Recrystallized from ethanol. [c] Complete formation of β-diketone, originating from a single cinnamoyl transfer.



3a **3b** **3c**

the corners of a four-fold water wheel, which forms interlocked columns. The cinnamoyl moiety is twisted out of the chromone plane by 62.59°, which also prevents close π-stacking. The molecular structure of both derivatives **6a** and **6b** exhibits similar geometries in the solid state. Whereas the 2-styrylchromone forms an almost planar system, the cinnamoyl fragment is tilted out of plane, which results in a significantly longer C(sp2)–C(sp2) bond of 1.502(1) Å in comparison to 1.44–1.46 Å values for the C–C bonds within the conjugated fragments.

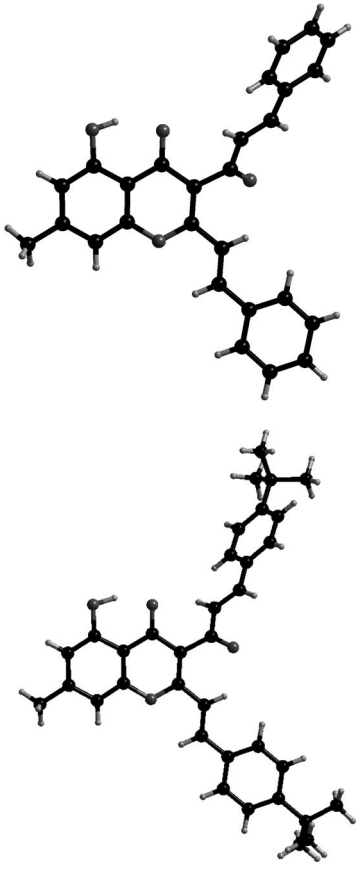
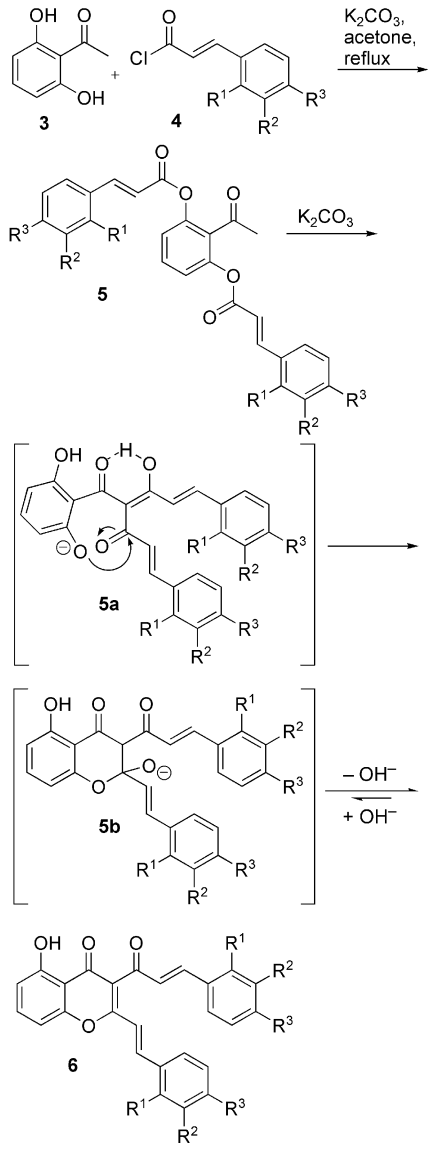


Figure 2. Molecular structure of chromones **6a** (top) and **6b** (bottom) obtained by X-ray crystallographic analysis.

The procedure is applicable to electron-rich cinnamoyl chlorides (Table 1, Entries 3 and 4). However, the adjacent methoxy groups on the 3,4-dimethoxyphenyl moiety cause steric demand and slightly enhances the solubility. Compound **6d** was efficiently recrystallized from ethanol, providing the analytically pure compound in excellent yield. When using electron-poor cinnamoyl chlorides, for example, the 3-fluoro derivative, an extremely low solubility of **6e** was observed. This might be attributed to effective π-stacking in the solid state, which stabilizes the lattice. The lower yield for **6e** might be caused by the high reactivity of **4e**.

Heterocyclic analogues of cinnamoyl chloride can also be subjected to this protocol. However, the electron-rich thiophene and furan moieties led to better solubility of the products **6g** and **6h**, respectively (Table 1, Entries 7 and 8). Consequently, the thiophene congener **6g** follows the opposite trend leading to lower solubility and higher yields (Table 1, Entry 7). All substances were stable to air and moisture, but were sensitive to good nucleophiles such as hydroxide. This is made clear with 3-cinnamoylchromone, which forms a double Michael acceptor that is prone to 1,4-addition reactions. As a result of our work, the reported 5-cinnamoyloxy-2-styrylchromones[14] should be structurally reassigned because they most likely represent 3-cinnamoyl-2-styrylchromones **6**. From these observations, a plausible mechanism can be deduced (Scheme 2). Concerning the acetophenone substrate **3**, two hydroxy groups in positions 2 and 6 are essential. If a single hydroxy group is protected or if there is only one group present in the acetophenone component **3**, the reaction with cinnamoyl chloride will always afford the corresponding β-diketone (Table 1, Entries 9 and 10).



Scheme 2. Proposed mechanism of 3-cinnamoyl-2-styrylchromone formation.

This finding can easily be explained by the involvement of intermediate **5a**, which can arise from rearrangement of both cinnamoyl groups through a Baker–Venkataraman reaction from diester **5** into the key derivative **5a**. One of the cinnamoyl ketones will predominantly exist as its enol tautomer. This is supported by previous reports wherein 2-styrylchromones have been isolated in the enol form.[16] Consequently, the second cinnamoyl carbonyl group exists as ketone moiety, which can be attacked by a phenolate nucleophile. Elimination of water takes place during workup as a result of rearomatization. Concerning the α,β-unsaturated acyl chloride, the absence of protons in the γ-position is crucial. In the course of reaction, deprotonation at the γ-position of ester **5** will proceed faster than the Baker–Venkataraman rearrangement and lead exclusively to the formation of 3-alkenyl-5-hydroxycoumarins.[17]

Conclusions

A very versatile and reliable protocol for the synthesis of 3-cinnamoyl-2-styrylchromones has been established that yields highly functionalized building blocks. The acetophenone component requires two hydroxy moieties in both the 2 and 6 positions. The study indicated that an α,α-dicinnamoylated acetophenone (**5a**) is most likely the key intermediate. Synthetic operations such as olefin metathesis or stereoselective transformations should readily enhance product diversity and enable natural product synthesis.[18] The class of compound is closely related to the 2-styrylchromones; however, in contrast to the latter, the biological properties are as yet unexplored.

Experimental Section

General Comments: All reagents were analytical grade. Solvents were dried, if necessary, by standard methods. Melting points were determined with a B-545 Melting Point Apparatus (Büchi Labortechnik AG, 9320 Flawil 1, Schweiz). Microanalyses were performed with a Vario EL cube (Elementar-Analysensysteme, Hanau, Germany) instrument. NMR spectra were recorded with a Bruker ARX 300, DPX 300 and DPX 400 (Analytische Messtechnik, Karlsruhe, Germany) spectrometer calibrated against $CHCl_3$ [δ = 7.26 ppm (^{1}H) and δ = 77.0 ppm (^{13}C)] or [D$_6$]DMSO [δ = 2.50 ppm (^{1}H) and δ = 39.51 ppm (^{13}C)]; chemical shifts are expressed in ppm. Full assignments of chemical shifts are reported in the Supporting Information. Mass spectra were obtained with a MAT8200 (Finnigan, Bremen, Germany) instrument by employing EI or with MS50 (Kratos, Manchester, England) or MAT95XL (Finnigan, Bremen, Germany) instruments for HRMS. All reactions were monitored by thin layer chromatography (TLC); visualization was effected by UV irradiation and by heating with a 1% aqueous solution of $Ce(SO_4)_2{\cdot}4H_2O$ containing 2.5% of molybdatophosphoric acid and 6% sulfuric acid. Column chromatography was performed on silica gel (particle size 63–200 μm, Merck, Darmstadt, Germany) by using mixtures of cyclohexane with ethyl acetate as eluents.

General Procedure: Acetophenone derivative **3** (6.0 mmol, 1.0 equiv.) was dissolved at r.t. in acetone (80 mL), and potassium carbonate (2.49 g, 18.0 mmol, 3.0 equiv.) and α,β-unsaturated acyl chloride (14.0 mmol, 2.3 equiv.) were added. The reaction mixture was stirred at reflux temperature overnight (the transformation was monitored by TLC). When the reaction was complete, the solvent was evaporated, and the residue was fractionated between water (80 mL) and dichloromethane (80 mL). The mixture was acidified to pH = 4 with citric acid, and the aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (80 mL), water (80 mL), and brine (80 mL), dried with anhydrous calcium chloride and concentrated under reduced pressure. Purification of the crude chromone **6** was typically performed by column chromatography with cyclohexane/ethyl acetate as eluent. Details are mentioned with the individual procedures.

(*E*,*E*)-3-Cinnamoyl-5-hydroxy-7-methyl-2-styrylchromone (6a): Obtained after column chromatography on silica (cyclohexane/EtOAc, 9:1) as yellow solid in 54% yield. R_f = 0.39 (cyclohexane/EtOAc, 9:1); m.p. 217 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.45 (s, 3 H), 6.66 (d, $^4J_{H,H}$ = 0.6 Hz, 1 H), 6.85 (d, $^4J_{H,H}$ = 0.6 Hz, 1 H), 7.16 (d, $^3J_{H,H}$ = 15.9 Hz, 1 H), 7.24 (d, $^3J_{H,H}$ = 16.0 Hz, 1 H), 7.38–7.40 (m, 6 H), 7.56–7.63 (m, 4 H), 7.69 (d, $^3J_{H,H}$ = 16.0 Hz, 1 H), 7.76 (d, $^3J_{H,H}$ = 15.9 Hz, 1 H), 12.29 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 22.5, 107.3, 108.4, 112.7, 117.6, 120.7, 127.3, 128.3, 128.8, 128.9, 129.0, 130.5, 130.8, 134.5, 134.7, 140.5, 144.6, 148.0, 155.2, 160.6, 162.3, 181.3, 190.9 ppm. HRMS (EI): calcd. for $C_{27}H_{20}O_4$ $[M]^{\cdot+}$ 408.1362; found 408.1360.

X-ray Crystal Data for 6a: Formula $C_{27}H_{20}O_4$; M = 408.43; a = 13.797(1), b = 4.045(1), c = 17.765(1) Å, β = 92.38(1)°; V = 990.6(3) Å^3; $\rho_{calcd.}$ = 1.369 g cm^{-3}; μ = 0.738 mm^{-1}; empirical absorption correction ($0.757 \leq T \leq 0.978$); Z = 2; monoclinic; space group *Pn* (No. 7); T = 223 K; ω and ϕ scans, 6527 reflections collected ($\pm h$, $\pm k$, $\pm l$), [(sinθ)/λ] = 0.60 Å^{-1}, 2456 independent (R_{int} = 0.035) and 2393 observed reflections [$I \geq 2\sigma(I)$], 285 refined parameters, R = 0.035, wR^2 = 0.097, max./min. residual electron density 0.14/–0.17 e Å^{-3}. Hydrogen atoms were calculated and refined as riding atoms, except for the hydroxy hydrogen atom, which was revealed from the difference Fourier map and refined isotropically. The data set for **6a** was collected with a Nonius KappaCCD diffractometer. Programs used: data collection COLLECT (Nonius B.V., 1998), data reduction Denzo-SMN,[19] absorption correction Denzo,[20] structure solution SHELXS-97;[21] structure refinement by full-matrix least-squares against F^2 using SHELXL-97 (G. M. Sheldrick, University of Göttingen, 1997). CCDC-781934 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(*E*,*E*)-3-[4-(1,1-Dimethylethyl)cinnamoyl]-2-{2-[4-(1,1-dimethylethyl)phenyl]ethenyl}-5-hydroxy-7-methylchromone (6b): For the synthesis of **6b** the general procedure was altered: The crude product, containing 20% 5-cinnamoyloxychromone was liberated by stirring at r.t. with potassium carbonate (10.0 equiv.) in methanol/dichloromethane (1:2) for 1 h. Workup was performed according to the general procedure. The crude product was recrystallized from ethanol at r.t. to afford **6b** as a yellow solid in 79% yield. R_f = 0.45 (cyclohexane/EtOAc, 9:1); m.p. 196.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.33 (s, 9 H), 1.33 (s, 9 H), 2.45 (s, 3 H), 6.66 (s, 1 H), 6.86 (s, 1 H), 7.09 (d, $^3J_{H,H}$ = 15.9 Hz, 1 H), 7.19 (d, $^3J_{H,H}$ = 16.0 Hz, 1 H), 7.41 (d, $^3J_{H,H}$ = 8.4 Hz, 4 H), 7.51 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H), 7.54 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H), 7.65 (d, $^3J_{H,H}$ = 16.0 Hz, 1 H), 7.74 (d, $^3J_{H,H}$ = 15.9 Hz, 1 H), 12.34 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 22.5, 29.7, 31.1, 34.9, 107.3, 108.5, 112.6, 116.8, 120.5, 125.9, 126.0, 126.68, 128.1, 128.7,

131.7, 132.1, 140.2, 144.9, 147.9, 154.2, 154.5, 155.3, 160.7, 162.2, 181.2, 191.1 ppm. HRMS (EI): calcd. for $C_{35}H_{36}O_4$ $[M]^{+}$ 520.2614; found 520.2612. $C_{35}H_{36}O_4$ (520.66): calcd. C 80.74, H 6.97; found C 80.48, H 7.39.

X-ray Crystal Data for 6b: Formula $C_{35}H_{36}O_4$; M = 520.64; $a = b$ = 29.5935(4), c = 13.7585(3) Å; V = 12049.4(3) Å^3; $\rho_{calcd.}$ = 1.148 g cm^{-3}; μ = 0.074 mm^{-1}; no absorption correction; Z = 16; tetragonal; space group $I4_1/a$ (No. 88); T = 123 K; ω and ϕ scans, 75707 reflections collected, 7267 unique (R_{int} = 0.0696), 418 parameters, 67 restraints, R = 0.0617, wR^2 = 0.1258 (both for all data), max./min. residual electron density 0.255/–0.218 e·Å^{-3}. The hydrogen atoms were calculated and refined as riding atoms, except for the hydroxy hydrogen atom, which was revealed from the difference Fourier map and refined isotropically. The data set for **6b** was collected with a Nonius KappaCCD diffractometer. Programs used: data collection COLLECT (Nonius B. V., 1998), data reduction Denzo-SMN,[19] absorption correction Denzo,[20] structure solution SHELXS-97;[21] structure refinement by full-matrix least-squares against F^2 using SHELXL-97 (G. M. Sheldrick, University of Göttingen, 1997). CCDC-779410 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(*E*,*E*)-5-Hydroxy-3-(4-methoxycinnamoyl)-2-[2-(4-methoxyphenyl)-ethenyl]-7-methylchromone (6c): For purification, the crude product was stirred at 78 °C in ethanol for 1 h. Filtration at r.t. afforded **6c** as a yellow solid in 86% yield; m.p. 186 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.44 (s, 3 H), 3.84 (s, 6 H), 6.64 (s, 1 H), 6.82 (s, 1 H), 6.90 (d, $^3J_{H,H}$ = 8.8 Hz, 4 H), 6.91 (d, $^3J_{H,H}$ = 8.7 Hz, 2 H), 7.00 (d, $^3J_{H,H}$ = 15.8 Hz, 1 H), 7.11 (d, $^3J_{H,H}$ = 15.9 Hz, 1 H), 7.51 (d, $^3J_{H,H}$ = 8.7 Hz, 2 H), 7.56 (d, $^3J_{H,H}$ = 8.8 Hz, 2 H), 7.63 (d, $^3J_{H,H}$ = 15.9 Hz, 1 H), 7.70 (d, $^3J_{H,H}$ = 15.8 Hz, 1 H), 12.38 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 22.5, 55.4, 55.4, 107.2, 108.4, 112.5, 114.4, 114.4, 115.2, 120.2, 125.3, 127.2, 127.6, 130.0, 130.6, 140.0, 144.7, 147.7, 155.3, 160.6, 161.6, 161.9, 162.4, 181.2, 191.0 ppm. HRMS (EI): calcd. for $C_{29}H_{24}O_6$ $[M]^{+}$ 468.1573; found 468.1572.

(*E*,*E*)-3-(3,4-Dimethoxycinnamoyl)-2-[2-(3,4-dimethoxyphenyl)-ethenyl]-5-hydroxy-7-methylchromone (6d): Obtained as a yellow solid after recrystallization from ethanol (10 mL) at r.t. in 94% yield. R_f = 0.41 (cyclohexane/EtOAc, 6:4); m.p. 211.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.43 (s, 3 H), 3.91 (s, 12 H), 6.63 (d, $^4J_{H,H}$ = 0.5 Hz, 1 H), 6.82 (d, $^4J_{H,H}$ = 0.5 Hz, 1 H), 6.86 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H), 6.97 (d, $^3J_{H,H}$ = 15.9 Hz, 1 H), 7.04 (d, $^4J_{H,H}$ = 1.9 Hz, 1 H), 7.09 (d, $^3J_{H,H}$ = 15.8 Hz, 1 H), 7.12 (d, $^4J_{H,H}$ = 1.9 Hz, 1 H), 7.15 (dd, $^3J_{H,H}$ = 8.4, $^4J_{H,H}$ = 1.9 Hz, 1 H), 7.18 (dd, $^3J_{H,H}$ = 8.4, $^4J_{H,H}$ = 1.9 Hz, 1 H), 7.61 (d, $^3J_{H,H}$ = 15.9 Hz, 1 H), 7.69 (d, $^3J_{H,H}$ = 15.8 Hz, 1 H), 12.37 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 22.4, 55.9, 56.0, 56.0, 56.0, 107.2, 108.4, 109.4, 110.13, 111.0, 111.1, 112.5, 115.2, 120.2, 122.9, 123.7, 125.47, 127.4, 127.8, 140.3, 145.0, 147.8, 149.2, 149.3, 151.4, 151.7, 155.2, 160.6, 162.3, 181.1, 191.0 ppm. HRMS (EI): calcd. for $C_{31}H_{28}O_8$ $[M]^{+}$ 528.1784; found 528.1785.

(*E*,*E*)-3-(3-Fluorocinnamoyl)-2-[2-(3-fluorophenyl)ethenyl]-5-hydroxy-7-methylchromone (6e): Prepared according to the general procedure by using 2,6-dihydroxy-4-methylacetophenone (685 mg, 4.13 mmol, 1.0 equiv.), 3-fluorocinnamoyl chloride (1.93 g, 9.62 mmol, 2.33 equiv.) and potassium carbonate (1.71 g, 14.2 mmol, 3.0 equiv.) in acetone (55 mL). When the reaction was complete, the solvent was evaporated, and the residue was suspended in distilled water (50 mL). The mixture was acidified with citric acid (pH = 3) and filtered. The residue was dried under vacuum (10^{-3} mbar), and the crude product was stirred at 100 °C in 1,4-dioxane (25 mL) for 1 h, cooled to r.t. and filtered off to afford **6e** as a bright-yellow solid, which was dried in high vacuum. Yield: 1.123 g, 61%. R_f = 0.46 (cyclohexane/EtOAc, 8:2); m.p. 237.6 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO, 25 °C): δ = 2.44 (s, 1 H), 6.73 (s, 1 H), 7.01 (d, $^3J_{H,H}$ = 15.9 Hz, 1 H), 7.08 (s, 1 H), 7.24–7.31 (m, 2 H), 7.28 (d, $^3J_{H,H}$ = 16.4 Hz, 1 H), 7.45–7.52 (m, 2 H), 7.54 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H), 7.60 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H), 7.63–7.83 (m, 2 H), 7.72 (d, $^3J_{H,H}$ = 16.4 Hz, 1 H), 7.89 (d, $^3J_{H,H}$ = 15.9 Hz, 1 H), 12.1 (s, 1 H) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO, 25 °C): δ = 22.1, 107.2, 107.8, 112.1, 114.5 ($^2J_{C,F}$ = 22.2 Hz), 115.0 ($^2J_{C,F}$ = 22.2 Hz), 117.3 ($^2J_{C,F}$ = 21.4 Hz), 117.7 ($^2J_{C,F}$ = 21.4 Hz), 118.75, 121.0, 124.8 ($^4J_{C,F}$ = 2.3 Hz), 125.3 ($^4J_{C,F}$ = 2.3 Hz), 129.3, 131.0 ($^3J_{C,F}$ = 8.4 Hz), 131.1 ($^3J_{C,F}$ = 8.4 Hz), 136.9 ($^3J_{C,F}$ = 8.0 Hz), 137.0 ($^3J_{C,F}$ = 8.0 Hz), 138.7, 144.4, 148.3, 155.1, 159.6, 160.2, 162.4 ($^1J_{C,F}$ = 244.4 Hz), 162.5 ($^1J_{C,F}$ = 244.4 Hz), 180.8, 191.3 ppm. ^{19}F NMR (75.5 MHz, [D$_6$]DMSO): δ = –112.4, –112.5 ppm. HRMS (EI): calcd. for $C_{27}H_{18}F_2O_4$ $[M - H]^{\cdot+}$ 443.1089; found 443.1097.

(*E*,*E*)-3-[3-(Benzo[1,3]dioxol-5-yl)acroyl]-2-[2-(benzo[1,3]dioxol-5-yl)ethenyl]-5-hydroxy-7-methylchromone (6f): Prepared according to the general procedure by using 2,6-dihydroxy-4-methylacetophenone (593 mg, 3.58 mmol, 1.0 equiv.), 3-(benzo[1,3]dioxol-5-yl)-acroyl chloride (1.75 g, 8.33 mmol, 2.33 equiv.) and potassium carbonate (1.48 g, 10.74 mmol, 3.0 equiv.) in acetone (45 mL). When the reaction was complete, the solvent was evaporated, and the residue was suspended in distilled water (50 mL). The mixture was acidified with citric acid (pH = 3) and filtered. The residue was treated with saturated $NaHCO_3$ (30 mL) at 50 °C for 1 h to remove the remaining 3,4-methylenedioxycinnamic acid, cooled to r.t. and filtered. After drying under vacuum (10^{-3} mbar), the crude product was stirred at 100 °C in 1,4-dioxane (30 mL) for 1 h, cooled to r.t. and filtered to afford **6f** as a yellow solid. Yield: 1.651 g, 93%. R_f = 0.24 (cyclohexane/EtOAc, 8:0); m.p. 234.2 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO, 25 °C): δ = 2.42 (s, 3 H), 6.08 (s, 4 H), 6.70 (s, 1 H), 6.75 (d, $^3J_{H,H}$ = 15.7 Hz, 1 H), 6.96 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H), 6.99 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H), 7.05 (s, 1 H), 7.06 (d, $^3J_{H,H}$ = 16.1 Hz, 1 H), 7.20 (dd, $^3J_{H,H}$ = 8.1, $^4J_{H,H}$ = 1.6 Hz, 1 H), 7.24 (dd, $^3J_{H,H}$ = 8.1, $^4J_{H,H}$ = 1.6 Hz, 1 H), 7.33 (d, $^4J_{H,H}$ = 1.6 Hz, 1 H), 7.42 (d, $^4J_{H,H}$ = 1.6 Hz, 1 H), 7.60 (d, $^3J_{H,H}$ = 16.1 Hz, 1 H), 7.77 (d, $^3J_{H,H}$ = 15.7 Hz, 1 H), 12.26 (s, 1 H) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO, 25 °C): δ = 21.9, 101.7, 101.8, 106.6, 107.0, 107.6, 107.9, 108.6, 108.8, 111.9, 115.1, 120.2, 125.1, 125.9, 126.3, 128.8, 129.0, 139.8, 146.1, 147.9, 148.1, 148.3, 149.6, 149.9, 155.1, 159.6, 160.6, 180.6, 191.2 ppm. HRMS (EI): calcd. for $C_{29}H_{20}O_8$ $[M]^{+}$ 496.1158; found 496.1160.

(*E*,*E*)-5-Hydroxy-7-methyl-3-[3-(2-thienyl)acroyl]-2-[2-(2-thienyl)-ethenyl]chromone (6g): Obtained after column chromatography on silica (cyclohexane/EtOAc, 9:1) as an orange solid in 40% yield. R_f = 0.23 (cyclohexane/EtOAc, 9:1); m.p. 177.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.44 (s, 3 H), 6.65 (d, $^4J_{H,H}$ = 0.6 Hz, 1 H), 6.81 (d, $^4J_{H,H}$ = 0.6 Hz, 1 H), 6.95 (d, $^3J_{H,H}$ = 15.6 Hz, 1 H), 7.03 (d, $^3J_{H,H}$ = 15.6 Hz, 1 H), 7.07 (dd, $^3J_{H,H}$ = 5.2, $^3J_{H,H}$ = 3.2 Hz, 1 H), 7.08 (dd, $^3J_{H,H}$ = 5.2, $^3J_{H,H}$ = 3.2 Hz, 1 H), 7.33 (d, $^3J_{H,H}$ = 3.2 Hz, 1 H), 7.35 (d, $^3J_{H,H}$ = 3.2 Hz, 1 H), 7.43 (d, $^3J_{H,H}$ = 5.2 Hz, 2 H), 7.80 (d, $^3J_{H,H}$ = 15.6 Hz, 1 H), 7.86 (d, $^3J_{H,H}$ = 15.6 Hz, 1 H), 12.32 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 22.5, 107.2, 108.4, 112.6, 116.4, 120.6, 126.2, 128.4, 129.4, 129.6, 131.0, 132.3, 133.0, 136.9, 140.0, 140.4, 148.0, 155.2, 160.7, 162.1, 181.1, 190.1 ppm. HRMS (ESI): calcd. for $C_{23}H_{16}O_4S_2$ $[M + H]^{+}$ 421.0568; found 421.0564. $C_{23}H_{16}O_4S_2$ (420.50): calcd. C 65.69, H 3.84; found C 65.13, H 4.28.

(*E*,*E*)-3-[3-(2-Furyl)acroyl]-2-[2-(2-furyl)ethenyl]-5-hydroxy-7-methylchromone (6h): Obtained as a yellow solid after column chromatography on silica [cyclohexane/EtOAc, 9:1 (2 L), then 8:2 (2 L), then 6:4 (1 L)] in 45% yield. R_f = 0.42 (cyclohexane/EtOAc, 8:2); m.p. 236 °C (dec). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.42 (s, 3 H), 6.48–6.49 (m, 2 H), 6.62 (d, $^4J_{H,H}$ = 0.4 Hz, 1 H), 6.68 (d, $^3J_{H,H}$ = 3.4 Hz, 1 H), 6.72 (d, $^3J_{H,H}$ = 3.4 Hz, 1 H), 6.77 (d, $^4J_{H,H}$ = 0.4 Hz, 1 H), 7.01 (d, $^3J_{H,H}$ = 15.6 Hz, 1 H), 7.09 (d, $^3J_{H,H}$ = 15.6 Hz, 1 H), 7.44 (d, $^3J_{H,H}$ = 15.6 Hz, 1 H), 7.48 (d, $^3J_{H,H}$ = 15.6 Hz, 1 H), 7.49 (d, $^3J_{H,H}$ = 1.5 Hz, 1 H), 7.52 (d, $^3J_{H,H}$ = 1.5 Hz, 1 H), 12.31 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4, 107.2, 108.3, 112.5, 112.7, 112.7, 115.3, 115.4, 116.7, 120.5, 124.7, 126.5, 130.3, 145.3, 145.4, 147.9, 151.2, 151.4, 155.1, 160.6, 162.1, 181.0, 190.2 ppm. HRMS (EI): calcd. for $C_{23}H_{16}O_6$ $[M]^{+\cdot}$ 388.0947; found 388.0951.

Supporting Information (see footnote on the first page of this article): Experimental details and full spectroscopic data for all new compounds.

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