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Synthesis of 2-Alkyl-Substituted Chromone Derivatives Using Microwave Irradiation

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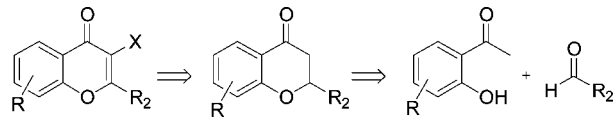

A base-promoted condensation between 2-hydroxyacetophenones and aliphatic aldehydes has been studied. The reaction has been optimized to afford 2-alkyl-substituted 4-chromanones in an efficient manner using microwave heating. Performing the reaction using diisopropylamine in EtOH at 170 °C for 1 h gave moderate to high yields (43−88%). The 4-chromanones could be further converted into highly functionalized 2,3,6,8-tetrasubstituted chromones in which a 3-substituent (acetate, amine, or bromine) was introduced via straightforward chemical transformations.

Introduction

The chromone structure is a common heterocyclic framework that can be found in numerous natural compounds exhibiting interesting biological activities such as antiviral,[1] anticancer,[2] anti-inflammatory,[3] and antioxidant[4] properties. They have also been shown to act as kinase inhibitors.[5] The vast range of biological effects associated with this scaffold has resulted in the chromone ring system being considered as a privileged structure.[6] Several different synthetic methodologies to prepare substituted chromone derivatives have been reported (e.g., methods based on Pd-mediated coupling reactions).[7] In an ongoing project focusing on the use of chromones as scaffolds for development of novel peptidomimetics,[8] we became interested in preparing derivatives with alkyl substituents in the 2-position. Such chromones can be synthesized via the corresponding 4-chromanones. Many synthetic methods are known to produce 4-chromanone derivatives carrying an aryl substituent in the 2-position, so-called flavanones. These compounds are commonly prepared by reacting an acetophenone with an appropriate aryl aldehyde and often involving strong basic[9] or acidic[8] conditions. These conditions are, however, not suitable for the preparation of 2-alkyl-substituted 4-chromanones due to extensive self-condensation of the aliphatic aldehyde. Our intention was therefore to develop a fast and efficient method for the preparation of such 4-chromanone derivatives, which can then be further converted to the corresponding chromones.

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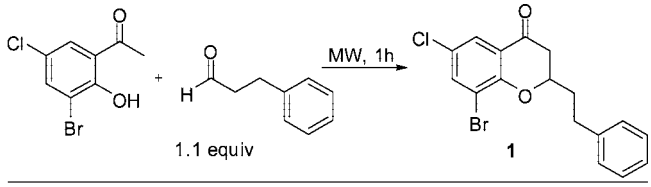
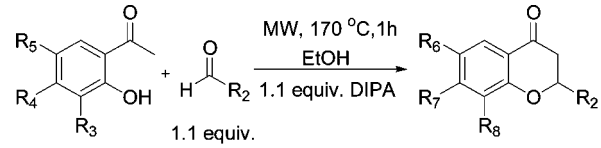
TABLE 1. Synthesis of 2-Substituted 4-Chromanone 1



		yields (%)[a]					
		EtOH		water		toluene	
entry	bases[b]	100 °C	170 °C	100 °C	170 °C	100 °C	170 °C
1	pyrrolidine	52	16	36	15	30[f]	nr[g]
2	morpholine	68	72	12	72	nr[g]	61
3	DIPA	71	88[c]	45	48	nr[g]	78
4	piperazine		61[d]				
5	piperidine		63[e]				
6	DIPEA		81				

[a] Isolated yields. [b] 1.1 equiv of the base was used. [c] 0.3 equiv of DIPA resulted in lower yield and condensation products. [d] Unreacted 3-bromo-5-chloro-2-hydroxyacetophenone was recovered. [e] 0.3 equiv of piperidine resulted in lower yield and condensation products. [f] The yield was estimated from ^{1}H NMR spectra on the crude reaction mixture due to purification problems. [g] No reaction.

TABLE 2. Synthesis of 2-Substituted 4-Chromanones Using Different Aldehydes



1-11: R_6 = Cl, R_8 = Br
12: R_7 = F
13: R_6 = NO_2
14: R_6 = Me

entry	R_2	product	yield[a] (%)
1	$PhCH_2CH_2$	**1**	88
2	1-naphthylCH_2CH_2	**2**	84
3	3-indolylCH_2CH_2	**3**	86
4	(*N*-Bn)indolylCH_2CH_2	**4**	84
5	(*N*-Ts)indolylCH_2CH_2	**5**	74
6	$CH_3(CH_2)_4$	**6**	80
7	$(CH_3)_2CH$	**7**	43
8	C_6H_{11}	**8**	46
9	Ph	**9**	24
10	4-OMePh	**10**	nr[b]
11	4-CF_3Ph	**11**	trace[c]
12	$PhCH_2CH_2$	**12**	70[c]
13	C_6H_{11}	**13**	50[c]
14	$PhCH_2CH_2$	**14**	17[c]

[a] Isolated yields. [b] 32% of the chalcone was isolated. [c] Estimated yield of product according to crude ^{1}H NMR spectra, but product could not be isolated due to purification problems.

Results and Discussion

According to Kabbe et al.,[10] 2-substituted 4-chromanones can be obtained via an enamine-catalyzed reaction using pyrrolidine in refluxing toluene. An alternative route is to perform Mukayiama aldol condensations.[11] However, this latter method requires the use of $TiCl_4$. Such harsh conditions are not suitable if (acid) sensitive groups such as esters or nitriles are present on the acetophenone or the aldehyde.

In addition, it has been shown that condensation reactions to form flavanones can be performed under rather mild conditions using L-proline in DMF at 80 °C.[12] Therefore, we initially attempted to synthesize compound **1** (Table 1) by reacting 3-bromo-5-chloro-2-hydroxyacetophenone with 3-phenylpropanal using these conditions. Unfortunately, the highest yield of the desired product **1** (obtained as a racemate) was a disappointing 38%. It was therefore decided to screen other bases, solvents, and temperatures in an effort to improve the yield of this reaction.

A set of different amine bases was thus tested in reactions run at 170 °C using microwave (MW) heating (Table 1). By using pyrrolidine (1.1 equiv) in EtOH, the desired chromanone **1** was obtained in only 16% yield (Table 1, entry 1). At lower temperatures using conventional heating, no product was formed. These poor results were probably due to a slow formation of the intermediate enamine, and the major product was therefore the self-condensation product of 3-phenylpropanal. The secondary amines morpholine, piperazine, or piperidine (Table 1, entries 2, 4, and 5) gave much better results, and compound **1** was isolated in moderate to good yields (61−72%). Morpholine is expected to form enamines much slower than pyrrolidine;[13] however, a considerably higher yield of **1** was obtained with morpholine when the reaction was performed at 170 °C (Table 1, entry 2). This might indicate a change from an enamine to an aldol mechanism. Using diisopropylamine (DIPA) as the base gave the best result, 88% yield of **1** (Table 1, entry 3).

These results are in contrast to those of Kabbe et al.,[10] who reported low yields in enamine reactions using 3-phenylpropanal. They also observed a slow formation of the chromanones when using tertiary amines or other secondary amines than pyrrolidine. In our hands, the tertiary amine diisopropylethylamine (DIPEA) also gave high yields (81%) of **1**, which implies that the reaction proceeds via an aldol condensation rather than an enamine mechanism.

Further experiments to investigate the outcome of the microwave-heated reactions by using different temperatures and solvents were then performed (Table 1). Water is known to be efficient in microwave-heated reactions[14] and was selected together with EtOH and toluene as solvents. Three different bases (pyrrolidine, morpholine, and DIPA) were also chosen, and the temperature was set to 100 or 170 °C for 1 h. In contrast to previously reported results,[10] a difference in yields between EtOH and toluene was observed when using pyrrolidine as the base. Pyrrolidine gave highest yields of product in EtOH and water at 100 °C (52 and 36%, respectively). Trace of product or no product was isolated at 170 °C in the different solvents (Table 1, entry 1). The yields were not improved when using morpholine or DIPA in water or toluene compared to the results obtained in EtOH (Table 1, entries 2 and 3). To further evaluate the scope of the reaction, different aldehydes were investigated (Table 2).

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The aliphatic aldehydes gave good to high yields of the desired chromanones (entries 1−6), even for more complicated substrates carrying indoles, both without protective group (entry 3) or with benzyl or tosyl protecting groups (entries 4 and 5). The branched isopropyl and cyclohexyl aldehydes (entries 7 and 8) gave somewhat lower yields (43 and 46%, respectively). This is probably due to sterical hindrance in the aldol reaction.

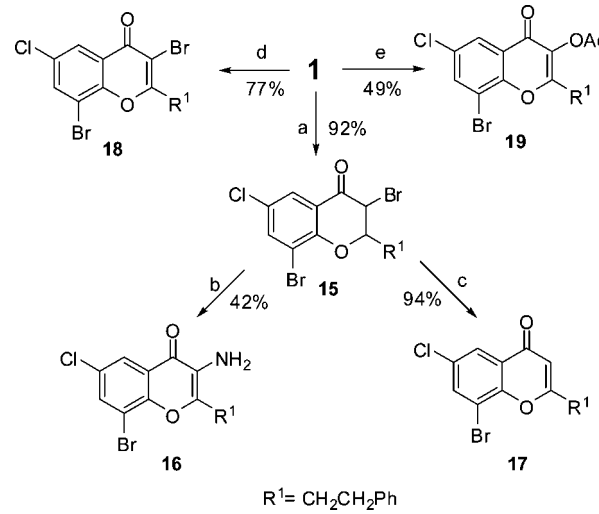
Delighted over the good results obtained with aliphatic aldehydes, we also decided to further evaluate the generality of the method by using aryl aldehydes (entries 9−11). This resulted in low yields when using benzaldehyde (entry 9) and gave no or only traces of product with 4′-substituted benzaldehydes (entries 10 and 11), instead chalcone intermediates were isolated. Thus, the developed method seems to be general for aliphatic aldehydes but results in lower yields when bulky aldehydes are used. To investigate whether the method is general also regarding the substitution in the acetophenone, we used 5′-methyl-, 5′-nitro-, and 4′-fluoroacetophenone as starting materials (entries 12−14). The desired products were formed in low to good yields (17−70%) as estimated from ^{1}H NMR spectra of the crude reaction mixtures. The only side product formed was the self-condensation product from the aldehyde.[15] Thus the reaction is efficient for electron-poor acetophenones.

In an ongoing project, we are interested in using Pd-mediated chemistry for the introduction of different substituents in the 3-position of the chromanone. In addition to Pd-catalyzed cross-coupling reactions, acylation and alkylation reactions could also be useful to introduce diverse and flexible substituents in this position. Potentially useful functionalities could therefore be halogen, hydroxyl, or amine. The 2-phenethyl chromanone **1** was chosen to be further explored for structural modifications in the 3-position and in subsequent oxidation reactions to obtain the corresponding chromone derivatives.

Initial attempts to oxidize chromanone **1** to the corresponding chromone using different oxidation methods such as DDQ in dioxane,[16] I_2 in pyridine,[17] and NBS and AIBN in CCl_4[18] were unsuccessful. Instead, compound **1** was brominated to form **15** in 86% yield using $CuBr_2$ under reflux in a 1:1 (v/v) mixture of $CHCl_3$ and EtOAc (Scheme 1).[19]

The reaction gave the thermodynamically more stable *cis*-isomer as the major product in a diastereomeric ratio of 80:20 according to ^{1}H NMR spectroscopy. To further corroborate this result, computational calculations were performed. After a conformational search using molecular mechanics (MacroModel v. 8.0, MM3* force field), one low energy conformation of each isomer was reevaluated using density functional theory (DFT) (B3LYP/LACVP*).[20] The results were in full agreement with the ^{1}H NMR spectral interpretation and showed that the *cis*-isomer was more stable than the *trans*-isomer.[21]

SCHEME 1. Introduction of Different Functional Groups in the 3-Position of 2-Phenethyl-Substituted 4-Chromanone[a]



[a] Reagents and conditions: (a) Py·Br_3, CH_2Cl_2, rt, 30 min; (b) NaN_3, DMSO, rt; (c) $CaCO_3$, DMF, 100 °C, 10 min; (d) (i) Py·Br_3, CH_2Cl_2, 80 °C, 70 min, MW, (ii) $CaCO_3$, DMF, 100 °C, 10 min, MW; (e) (i) isoamyl nitrite, HCl, THF, 60 °C, 7 h, MW, (ii) AcCl, TEA, CH_2Cl_2, 2 h, rt.

This diastereomeric mixture was then reacted with NaN_3 in DMF in an effort to prepare amine **16** (Scheme 1).[22] Unfortunately, **16** was only obtained in 39% yield; instead, the major product was chromone **17**, which was formed in 49% yield. To overcome this problem, attempts to increase the yield of the *trans*-isomer over the *cis*-isomer of the monobrominated **15** were made. Therefore, other bromination methods were evaluated such as Br_2 in HOAc and pyridinium tribromide (Py·Br_3)[23] in AcOH or THF. The latter increased the formation of *trans*-product, but still the *cis*-isomer was the major product. By changing solvent, Py·Br_3 in dichloromethane at room temperature gave **15** in 92% yield with a *cis*:*trans* ratio of 40:60 according to ^{1}H NMR spectroscopy. The result may be explained by pyridine preventing enolization of the *trans*-isomer and thereby avoiding the epimerization to the *cis*-isomer. However, an epimerization occurred instead during the purification by column chromatography on silica resulting in a *cis*:*trans* ratio of 60:40.

Interestingly, when repeating the NaN_3 experiment in DMF on the *cis*:*trans* (40:60) mixture, it was shown that the diastereomeric ratio of the monobrominated product **15** did not affect the ratio of compounds **16** and **17**, and chromone **17** was still the major product. The azide reaction was therefore evaluated further in attempts to favor the formation of **16** over **17**. In this effort, different azide sources (NaN_3, $TMSN_3$ or $TMGN_3$), solvents (DMF, DMSO, THF, acetone, or MeCN), and temperatures were tested. Unfortunately, this did not substantially improve the yield of **16**; the best result was obtained by using 10 equiv of NaN_3 in DMSO, which provided **16** in 42% and **17** in 43% yields. The outcome of the reaction was probably due to an epimerization of the *trans*-isomer to the *cis*-isomer when using NaN_3, which then promotes an E2-

(15) Unfortunately, the side product was impossible to separate from the chromanone by chromatography due to identical retention times, independently of elution system used. To isolate the pure product, repeating purification by preparative HPLC is probably required.

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(20) For a description of the methods employed, see http://www.schrodinger.com.

(21) For the *cis*-isomer, the conformation with the bromine in an axial position and the phenethyl substituent in the equatorial position was favored. The two *trans* conformations were virtually isoenergetic. For atomic coordinates from B3LYP/LACVP* calculations of the global minimum conformations, see Supporting Information.

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reaction. Alternatively, an azide ion attacks the *trans*-isomer, forming the *cis*-2-phenethyl-3-azido derivative, which then eliminates HN_3 to form **17**.

Dibromination of **1** was then performed using Py·Br_3 in dichloromethane. Running the reaction at room temperature gave very slow conversion and a lot of monobrominated material, but raising the temperature to 80 °C using microwave heating gave a smooth conversion to the dibrominated intermediate. An HBr elimination yielded the brominated chromone **18** in 77% (over two steps) using $CaCO_3$ in DMF.[24] Other bases such as DBU or TEA in dichloromethane or Cs_2CO_3 in DMF also gave product **18** but were always accompanied with other impurities. $CaCO_3$ in DMF was then also used to prepare chromone **17** in 94% yield from the monobrominated compound **15**.

Finally, 3-hydroxychromone was synthesized with isoamyl nitrite and HCl in EtOH.[25] The reaction was performed at different temperatures (60, 70, 100, and 120 °C) using microwave as well as conventional heating sources and by using different solvents (EtOH, iPrOH, or THF). For most of the experiments, the desired alcohol was obtained in significant amounts although together with several byproducts which complicated the purification. The best result was obtained at 60 °C in EtOH using conventional heating. To facilitate the purification, the alcohol was acetylated using acetyl chloride and triethylamine, which gave the 3-acetoxy chromone **19** in 49% yield over two steps.

Conclusion

An efficient method to synthesize a diverse set of 2-alkyl-substituted 4-chromanones from 2-hydroxyacetophenones and aliphatic aldehydes has been developed. Incorporation of heterofunctional groups in the chromone 3-position provides opportunities for further substitution. Compounds **16**, **17**, **18**, and deacetylated **19** could be applicable in Pd-mediated chemistry to introduce appropriate substituents in the 3-, 6-, and 8-positions.[7b,c] The 3-amine and the 3-hydroxy analogues (**16** and deacetylated **19**) could also be useful in acylation and alkylation reactions. This work is ongoing in our laboratory.

Experimental Section

General Procedure for Preparation of Chromanones 1−9: DIPA (1.1 mmol) and the appropriate aldehyde (1.1 mmol) were added to a solution of 3-bromo-5-chloro-2-hydroxyacetophenone (1 mmol) in EtOH (2.5 mL). The reaction mixture was heated in a microwave cavity at 170 °C for 1 h (fixed hold time, normal absorption) and then cooled to rt. The resulting solution was diluted with CH_2Cl_2. For chromanones **1**−**4**, the organic phase was washed twice with aqueous NaOH (1%). For all chromanones, the organic phase was washed twice with aqueous HCl (10%) and then with water and brine. The organic phase was dried with $MgSO_4$, filtered, and concentrated. Purification by column chromatography gave chromanones **1**−**9**.

8-Bromo-6-chloro-2-phenethylchroman-4-one (1): Purification by column chromatography EtOAc/heptane (2.5%) gave **1** as an orange oil (0.31 g, 88%). The yellow oil was converted to a yellow solid over time: mp 58−60 °C; ^{1}H NMR δ 7.78 (d, J = 2.6 Hz, 1H), 7.71 (d, J = 2.6 Hz, 1H), 7.34−7.07 (m, 5H), 4.50−4.35 (m, 1H), 3.03−2.80 (m, 2H), 2.74−2.58 (m, 2H), 2.35−2.20 (m, 1H), 2.05−1.88 (m, 1H); ^{13}C NMR δ 190.1, 156.3, 140.4, 138.2, 128.5, 128.4, 126.8, 126.1, 125.6, 122.2, 112.6, 77.4, 42.2, 36.1, 30.8; HRMS (FT-ICR-MS) [M + H]$^+$ calcd for $C_{17}H_{15}BrClO_2$ 366.9919, found 366.9933.

8-Bromo-6-chloro-2-(2-(1-naphthyl)ethyl)chroman-4-one (2): Purification by trituration with MeOH, followed by column chromatography toluene/heptane (8:2) gave **2** as a light yellow solid (4.1 g, 84%): mp 36−37 °C; ^{1}H NMR δ 8.14 (d, J = 8.1 Hz, 1H), 7.87 (d, J = 7.7 Hz, 1H), 7.81 (d, J = 2.6 Hz, 1H), 7.77 (d, J = 2.6 Hz, 1H), 7.75 (d, J = 7.3 Hz, 1H), 7.57−7.47 (m, 2H), 7.45−7.37 (m, 2H), 4.61−4.47 (m, 1H), 3.61−3.47 (m, 1H), 3.39−3.26 (m, 1H), 2.83−2.67 (m, 2H), 2.47−2.32 (m, 1H), 2.22−2.07 (m, 1H); ^{13}C NMR δ 190.2, 156.5, 138.4, 136.6, 133.9, 131.6, 128.9, 127.1, 127.0, 126.4, 126.1, 125.8, 125.61, 125.55, 123.6, 122.4, 112.7, 77.8, 42.3, 35.7, 28.1; HRMS (FT-ICR-MS) [2M + Na]$^+$ calcd for $[C_{21}H_{16}BrClO_2]_2Na$ 850.9938, found 850.9906.

8-Bromo-6-chloro-2-(2-(1*H*-indol-3-yl)ethyl)chroman-4-one (3): Purification by column chromatography EtOAc/heptane (20%) gave **3** as a yellow solid (0.28 g, 86%): mp 134−136 °C; ^{1}H NMR δ 8.01 (s, 1H), 7.79 (d, J = 2.6 Hz, 1H), 7.74 (d, J = 2.6 Hz, 1H), 7.66 (d, J = 8.1 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.24−7.19 (m, 1H), 7.17−7.11 (m, 1H), 7.06 (d, J = 1.8 Hz, 1H), 4.58−4.43 (m, 1H), 3.18−3.02 (m, 2H), 2.79−2.63 (m, 2H), 2.40−2.27 (m, 1H), 2.15−2.01 (m, 1H); ^{13}C NMR δ 190.5, 156.5, 138.3, 136.3, 127.2, 126.8, 125.7, 122.4, 122.1, 121.8, 119.3, 118.7, 114.5, 112.7, 111.2, 77.8, 42.3, 34.9, 20.4; HRMS (FT-ICR-MS) [2M + Na]$^+$ calcd for $[C_{19}H_{15}BrClNO_2]_2Na$ 830.9823, found 830.9860.

2-(2-(1-Benzyl-1*H*-indol-3-yl)ethyl)-8-bromo-6-chlorochroman-4-one (4): Purification by column chromatography EtOAc/hexane (5→20%) gave **4** as a yellow solid (0.33 g, 84%): mp 150 °C; ^{1}H NMR δ 7.77 (d, J = 2.6 Hz, 1H), 7.69 (d, J = 2.6 Hz, 1H), 7.63 (d, J = 8.1 Hz, 1H), 7.31−7.01 (m, 8H), 6.98 (s, 1H), 5.24 (s, 2H), 4.56−4.39 (m, 1H), 3.17−3.01 (m, 2H), 2.78−2.62 (m, 2H), 2.38−2.24 (m, 1H), 2.14−2.00 (m, 1H); ^{13}C NMR δ 190.4, 156.6, 138.4, 137.5, 136.8, 128.7, 127.8, 127.6, 126.9, 126.7, 125.9, 125.8, 122.4, 121.9, 119.1, 118.9, 113.8, 112.7, 109.7, 77.9, 49.8, 42.4, 35.1, 20.4; HRMS (FT-ICR-MS) [M + Na]$^+$ calcd for $C_{26}H_{21}BrClNNaO_2$ 516.0337, found 516.0317.

8-Bromo-6-chloro-2-(2-(1-tosyl-1*H*-indol-3-yl)ethyl)chroman-4-one (5): Purification by column chromatography toluene/heptane (50%) gave **5** as a yellow solid (2.28 g, 74%): mp 57−60 °C; ^{1}H NMR δ 8.01 (d, J = 8.1 Hz, 1H), 7.81 (d, J = 2.2 Hz, 1H), 7.76 (d, J = 2.6 Hz, 1H), 7.68 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.1 Hz, 1H), 7.42 (s, 1H), 7.36−7.30 (m, 1H), 7.29−7.21 (m, 1H), 7.19−7.13 (m, 1H), 7.09 (d, J = 8.1 Hz, 1H), 4.39−4.29 (m, 1H), 3.09−2.94 (m, 2H), 2.79−2.62 (m, 2H), 2.36 (s, 1H), 2.30 (s, 3H), 2.11−1.99 (m, 1H); ^{13}C NMR δ 190.0, 156.4, 144.8, 138.5, 135.5, 135.1, 130.6, 129.7, 129.0, 128.2, 127.1, 126.6, 125.8, 124.6, 123.3, 123.1, 122.4, 121.3, 119.2, 113.9, 112.7, 77.5, 42.3, 33.9, 21.5, 20.3; HRMS (FT-ICR-MS) [M + H]$^+$ calcd for $C_{26}H_{22}BrClNO_4S$ 558.0136, found 558.0137.

8-Bromo-6-chloro-2-pentylchroman-4-one (6): Purification by column chromatography EtOAc/heptane (5%) gave **6** as a white solid (0.26 g, 80%): mp 67−68 °C; ^{1}H NMR δ 7.79 (d, J = 2.6 Hz, 1H), 7.69 (d, J = 2.6 Hz, 1H), 4.57−4.46 (m, 1H), 2.78−2.65 (m, 2H), 2.02−1.88 (m, 1H), 1.80−1.67 (m, 1H), 1.67−1.56 (m, 1H), 1.56−1.42 (m, 1H), 1.42−1.27 (m, 4H), 1.00−0.79 (m, 3H); ^{13}C NMR δ 190.7, 156.7, 138.4, 126.8, 125.7, 122.3, 112.7, 79.0, 42.4, 34.6, 31.4, 24.6, 22.5, 14.0; HRMS (FT-ICR-MS) [M + H]$^+$ calcd for $C_{14}H_{17}BrClO_2$ 331.0095, found 331.0099.

8-Bromo-6-chloro-2-isopropylchroman-4-one (7): Purification by column chromatography EtOAc/heptane (10%) gave **7** as a white solid (0.13 g, 43%): mp 58−60 °C; ^{1}H NMR δ 7.78 (d, J = 2.6 Hz, 1H), 7.69 (d, J = 2.6 Hz, 1H), 4.27−4.15 (m, 1H), 2.76−2.68 (m, 2H), 2.16−2.02 (m, 1H), 1.14 (d, J = 7.0 Hz, 3H), 1.07 (d, J = 7.0 Hz, 3H); ^{13}C NMR δ 191.0, 156.9, 138.3, 126.7, 125.7, 122.2, 112.8, 83.7, 39.8, 32.3, 18.0, 17.9; HRMS (FT-ICR-MS) [M + H]$^+$ calcd for $C_{12}H_{13}BrClO_2$ 304.9753, found 304.9766.

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8-Bromo-6-chloro-2-cyclohexylchroman-4-one (8): Purification by column chromatography EtOAc/heptane (5→15%) gave **8** as a white solid (0.16 g, 46%): mp 86−87 °C; ^{1}H NMR δ 7.78 (d, J = 2.6 Hz, 1H), 7.68 (d, J = 2.6 Hz, 1H), 4.29−4.17 (m, 1H), 2.78−2.67 (m, 2H), 2.10 (d, J = 12.5 Hz, 1H), 1.88−1.67 (m, 5H), 1.37−1.10 (m, 5H); ^{13}C NMR δ 191.1, 156.8, 138.3, 126.7, 125.7, 122.3, 112.8, 83.1, 41.6, 39.9, 28.32, 28.29, 26.2, 25.8, 25.7; HRMS (FT-ICR-MS) $[M + H]^+$ calcd for $C_{15}H_{17}BrClO_2$ 345.0076, found 345.0083.

8-Bromo-6-chloro-2-phenylchroman-4-one (9): Purification by column chromatography EtOAc/hexane (2.5%) gave **9** as a yellow solid (0.082 g, 24%). ^{1}H and ^{13}C NMR ($CDCl_3$) spectra were in agreement with data reported in the literature.[8]

3,8-Dibromo-6-chloro-2-phenethylchroman-4-one (15). Method 1: Bromination Using $CuBr_2$. Chromanone **1** (0.66 g, 0.18 mmol) in $CHCl_3$ (4 mL) was added to a solution of $CuBr_2$ (0.8 g, 0.36 mmol) in EtOAc (4 mL). The mixture was stirred for 2 h at reflux and then cooled to rt and filtered through Celite. Purification by column chromatography EtOAc/heptane (5%) gave **15** as a brown oil (0.68 g, 85%) in a *cis*:*trans* ratio of 80:20: ^{1}H NMR δ 7.86 (d, J = 2.4 Hz, *trans* 0.2H), 7.85 (d, J = 2.6 Hz, *cis* 0.8H), 7.80 (d, J = 2.6 Hz, *trans* 0.2H), 7.78 (d, J = 2.6 Hz, *cis* 0.8H), 7.37−7.19 (m, 5H, Ar), 4.62 (dd, J = 7.0, 6.6 Hz, *trans* 0.2H), 4.49 (d, J = 6.6 Hz, *trans* 0.2H), 4.35 (d, J = 1.5 Hz, *cis* 0.8H), 4.13 (ddd, J = 6.0, 4.0, 1.8 Hz, *cis* 0.8H), 3.06−2.78 (m, 2H), 2.67−2.49 (m, *cis* 0.8H), 2.21−2.09 (m, *trans* 0.4H), 2.08−1.94 (m, *cis* 0.8H); ^{13}C NMR δ 184.0, 183.7, 155.5, 154.1, 140.0, 139.7, 139.3, 139.0, 128.70, 128.67, 128.54, 128.48, 127.9, 127.8, 126.9, 126.6, 126.5, 120.1, 119.7, 112.8, 112.6, 81.2, 77.2, 49.5, 48.6, 34.3, 33.4, 31.1, 30.4; HRMS (FT-ICR-MS) $[M + Na]^+$ calcd for $C_{17}H_{13}Br_2ClNaO_2$ 464.8864, found 464.8837.

Method 2: Bromination Using Pyridinium Tribromide (Py·Br_3). Chromanone **1** (0.2 g, 0.55 mmol) was added to a solution of Py·Br_3 (0.17 g, 0.52 mmol) in CH_2Cl_2 (10 mL), and the mixture was allowed to stir at rt for 1 h. The mixture was diluted with CH_2Cl_2 and washed with brine and water. The organic phase was dried with $MgSO_4$, filtered, and concentrated under vacuum. Purification by column chromatography EtOAc/heptane (10%) gave **15** as a light brown oil (0.22 g, 92%) in a *cis*:*trans* ratio of 60:40.

3-Amino-8-bromo-6-chloro-2-phenethylchromone (16). NaN_3 (0.95 g, 14.5 mmol) was added to **15** (0.65 g, 1.45 mmol) in DMSO (7 mL). The mixture was run at rt for 3 h. The solution was diluted with water and EtOAc. The organic phase was washed with water and brine, dried with $MgSO_4$, filtered, and concentrated under vacuum. Purification by column chromatography using EtOAc/heptane (20%) gave **16** as a yellow solid (0.23 g, 42%) and **17** (0.23 g, 43%).

16: Mp 108−110 °C; ^{1}H NMR δ 8.15−8.11 (m, 1H), 7.83−7.79 (m, 1H), 7.33−7.16 (m, 5H), 3.45−2.88 (m, 6H); ^{13}C NMR δ 171.2, 150.3, 140.0, 135.5, 129.9, 128.7, 128.4, 128.2, 126.7, 124.4, 122.7, 112.5, 32.3; HRMS (FT-ICR-MS) $[M + H]^+$ calcd for $C_{17}H_{14}BrClNO_2$ 377.9891, found 377.9893.

8-Bromo-6-chloro-2-phenethylchromone (17). $CaCO_3$ (0.10 g, 0.98 mmol) was added to a solution of 3,8-dibromo-6-chloro-2-phenethylchroman-4-one **15** (0.14 g, 0.33 mmol) in DMF (3 mL). The mixture was heated in a microwave cavity at 100 °C for 10 min. The resulting mixture was then diluted with EtOAc, and the organic phase was decanted off and washed with water and brine. The organic phase was dried with $MgSO_4$, filtered, and concentrated. Purification by column chromatography EtOAc/heptane (0→20%) gave **17** as a white solid (0.11 g, 94%): mp 106−107 °C; ^{1}H NMR 8.08 (d, J = 2.6 Hz, 1H), 7.85 (d, J = 2.6 Hz, 1H), 7.34−7.17 (m, 5H), 6.14 (s, 1H), 3.15−2.96 (m, 4H); ^{13}C NMR δ 176.3, 168.8, 151.6, 139.3, 136.6, 131.0, 128.7, 128.2, 126.6, 125.3, 124.6, 112.5, 110.3, 35.9, 32.6; HRMS (FT-ICR-MS) $[M + H]^+$ calcd for $C_{17}H_{13}BrClO_2$ 362.9782, found 362.9762.

3,8-Dibromo-6-chloro-2-phenethylchromone (18). Py·Br_3 (0.4 g, 1.26 mmol) was added to a solution of chromanone **1** (0.14 g, 0.38 mmol) in CH_2Cl_2 (4 mL). The reaction mixture was heated in a microwave cavity at 80 °C for 70 min. The resulting mixture was diluted with CH_2Cl_2, and the organic phase was washed with saturated aqueous $Na_2S_2O_3$, water, and brine. The organic phase was dried with $MgSO_4$, filtered, and concentrated to give the 3,3-dibrominated intermediate. The crude mixture was dissolved in DMF (4 mL), and $CaCO_3$ (0.12 g, 1.2 mmol) was added. The reaction was heated in a microwave cavity at 100 °C for 10 min. The mixture was diluted with EtOAc, and the organic phase was decanted off and then washed with water and brine. The organic phase was dried with $MgSO_4$, filtered, and concentrated. Purification by column chromatography EtOAc/heptane (5%) gave **18** as a white solid (0.13 g, 77%): mp 96.7−98 °C; ^{1}H NMR δ 8.12 (d, J = 8.1 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.33−7.18 (m, 5H), 3.37−3.29 (m, 2H), 3.20−3.12 (m, 2H); ^{13}C NMR δ 170.9, 166.4, 150.7, 139.3, 137.1, 131.7, 128.8, 128.4, 126.7, 125.2, 123.5, 112.4, 110.1, 36.6, 32.4; HRMS (FT-ICR-MS) $[M + H]^+$ calcd for $C_{17}H_{12}Br_2ClO_2$ 440.8888, found 440.8895.

3-Acetoxy-8-bromo-6-chloro-2-phenethylchromone (19). Isoamyl nitrite (0.24 mL, 1.81 mmol) and HCl (0.75 mL, 12 M) were added dropwise to a solution of chromanone **1** (0.22 g, 0.6 mmol) in EtOH (2.7 mL, 90%) at 60 °C. After 5 h at 60 °C, another portion of isoamyl nitrite (0.24 mL, 1.81 mmol) was added. After 2 h, the mixture was diluted with EtOAc, washed with water and brine, and extracted with CH_2Cl_2 (3×). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under vacuum. The crude product 8-bromo-6-chloro-3-hydroxy-2-phenethylchromone was dissolved in CH_2Cl_2 (5 mL), and acetyl chloride (60 μL, 0.084 mmol) and Et_3N (0.115 mL, 0.82 mmol) were added. The mixture was stirred for 2 h at rt. The solution was diluted with CH_2Cl_2 and washed with water. The organic phase was dried with $MgSO_4$, filtered, and concentrated under vacuum. Purification by column chromatography EtOAc/heptane (0→30%) gave **19** as a light yellow oil (0.13 g, 49% over two steps): ^{1}H NMR δ 8.11 (d, J = 2.6 Hz, 1H), 7.86 (d, J = 2.6 Hz, 1H), 7.33−7.18 (m, 5H), 3.14−3.00 (m, 4H), 2.35 (s, 3H); ^{13}C NMR δ 169.7, 167.7, 161.6, 150.7, 139.4, 136.7, 134.1, 131.2, 128.7, 128.2, 126.7, 125.4, 124.9, 112.6, 32.2, 31.1, 20.3; HRMS (FT-ICR-MS) $[M + H]^+$ calcd for $C_{19}H_{15}BrClO_4$ 420.9837, found 420.9834.

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Supporting Information Available: Compound characterization (^{1}H NMR and ^{13}C NMR spectra) of 3-(1-benzyl-1*H*-indol-3-yl)propanal, ethyl 3-(1-tosyl-1*H*-indol-3-yl)propanoate, 3-(1-tosyl-1*H*-indol-3-yl)propanal, and compounds **1**−**8** and **15**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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