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Access to 2-alkyl chromanones via a conjugate addition approach

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ABSTRACT

The introduction of alkyl substituents at C-2 of chromanones via conjugate addition of silyl enol ethers to a variety of chromenones is reported. In most cases racemic 2-alkyl chromanones were obtained in good yield in the presence of TMSOTf. The copper(II)-promoted conjugate addition of silyl enol ethers to chromenones was also carried out, albeit in low yields and no selectivity. Reliable syntheses of the chromenones via acylation of the corresponding β-diketo-compounds are also described.

1. Introduction

The chromanone scaffold **1** is represented in a large number of natural products, exhibiting a wide variety of biological activities.[1–3] The synthesis of flavanones (e.g., pinostrobin **2**) that possess aromatic substituents at C-2 is well represented in the literature.[4] The corresponding chromanones bearing aliphatic substituents at C-2 are less well described, though naturally occurring examples such as gonytolide A **3** and microdiplodiasone **4** exhibit interesting immunogenic and antimicrobial activity.[5,6] In addition, methods for the enantioselective synthesis of these chromanones are rare (Fig. 1).

Two main strategies for the enantioselective synthesis of 2-substituted chromanones of type **5** are well documented, namely the intramolecular oxa-Michael cyclisation of an appropriately substituted phenol **6**, and the conjugate addition of varying nucleophiles to chromenones **7** (Fig. 2).[4] The former strategy has been employed by several research groups,[7–12] while asymmetric conjugate addition of aromatic nucleophiles for flavanone synthesis has been reported.[13–15]

Somewhat surprisingly, only two examples of enantioselective methods for the introduction of simple aliphatic substituents at C-2 have been described.[16,17]

Our group has developed a number of approaches for the asymmetric synthesis of pyronaphthoquinone natural products[18] and we became interested in investigating the related chromanone natural products such as **3** and **4**. We envisaged it should be possible to introduce alkyl substituents at C-2 of chromanones via an asymmetric conjugate addition to a chromenone (Fig. 3).[19]

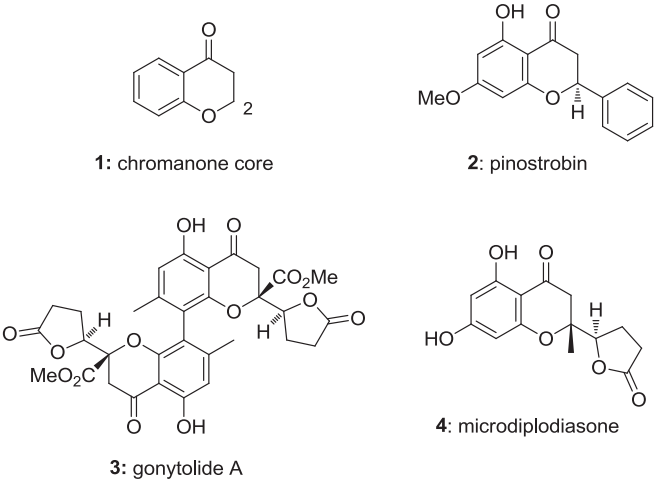

Fig. 1. Chromanone-based natural products.

Towards this end, an efficient method for the introduction of an alkyl group onto the chromenone scaffold using silyl enol ether nucleophiles was initially undertaken, albeit racemically. Furthermore, we decided to investigate the asymmetric addition of silyl enol ethers to a range of chromenones **7** using Cu(II)–box or Cu(II)–pybox catalysts. In order to pursue this aim we also required practical and scalable methodology to access the necessary chromenone substrates to study the proposed conjugate addition chemistry.

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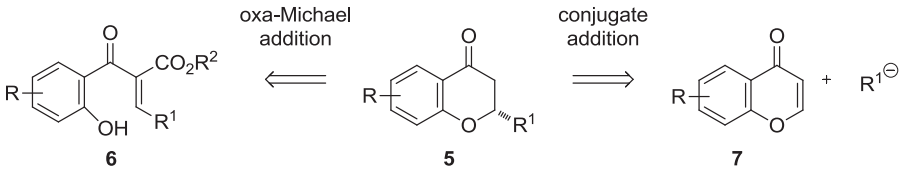


Fig. 2. Reported asymmetric approaches to 2-substituted chromanones.

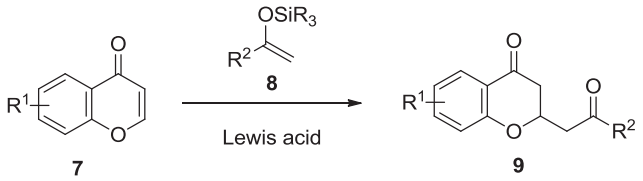


Fig. 3. Proposed conjugate addition of silyl enol ethers to chromenones.

2. Results and discussion

2.1. Synthesis of chromenones

Initial attention focused on the synthesis of the required chromenones **7a**–**h**. Despite the number of publications involving chromenone synthesis in the literature,[20] we were disappointed to find that many reported methods performed poorly in our hands and characterisation in many cases was cursory or absent altogether.[21,22]

The desired 3-substituted chromanones **7e**–**h** could be accessed via Kostanecki–Robinson acylation of the corresponding phenols **11**. These, in turn, were synthesised in high yield from the corresponding 2′-hydroxyacetophenones **10a** and **10b**.

Although several methods for the synthesis of diketone **11a** are reported in the literature, in our hands attempts to obtain **11a** via Baker–Venkataraman rearrangement of 2-acetylphenyl acetate were low yielding.[23–25] The only procedure that provided **11a** in satisfactory yield was that reported recently by Patonay et al.[26] Thus, Claisen condensation of **10a** with ethyl acetate using sodium hydride as base afforded **11a** in high yield.

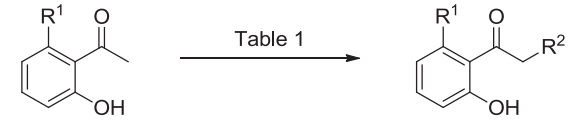
Reports by Wallace et al.[27] and later Scheidt et al.[7] have demonstrated that 3-ester substituents on chromanones can be removed by simple decarboxylation under mildly acidic conditions. It was hoped that an ester substituent at the 3-position would increase the reactivity of the chromenone electrophile in conjugate additions, and importantly, it would be readily removed or derivatised in subsequent steps. The 3-*tert*-butyl ester substituted chromenone **7g** was derived from the corresponding β-keto ester **11c**. In turn, **11c** was synthesised in 79% yield from **10a** using lithium bis(trimethylsilyl)amide and di-*tert*-butyl dicarbonate (Table 1).

Treatment of the dicarbonyl compounds **11a** and **11c** with acetic formic anhydride[28] and sodium formate in THF then afforded the desired chromenones **7e** and **7g** as crystalline solids in moderate yield (Table 2).[29] Alternatively, the 2-methyl derivatives **7f** and **7h** could be synthesised in an analogous manner from the same dicarbonyl compounds **11a** and **11c** using acetic anhydride and sodium acetate, providing the chromenones in moderate yield. 5-Methoxy-substituted chromenones **7b** and **7d** were also synthesised in good yields from **10b** and **11b**, respectively. [3,30] Known chromenones **7a** and **7c**[31] were also prepared from phenols **10a** and **11a** for the purpose of comparison with their C-3 and C-5 substituted counterparts.

2.2. Conjugate addition of silyl enol ethers to chromenones

Acetophenone-derived silyl enol ether **8a** was first selected to probe the conjugate addition to chromenone **7a** (Table 3). After some experimentation, the optimal reaction conditions (TMSOTf 1 equiv, CH_2Cl_2, rt) provided the desired chromanone **9a** in only 20% yield. Other Lewis acids ($BF_3{\cdot}OEt_2$, $TiCl_4$, $SnCl_2$) failed to promote the addition. Hoping that the acetyl group in **7e** would confer greater reactivity to the chromenone, we applied the same reaction conditions to chromenone **7e** (entry 2), but the yield of **9b** was still unsatisfactory (21%). In addition, the keto–enol tautomerism of **9b** afforded complex spectra making identification and separation via HPLC of the possible diastereomers difficult.

Table 1
Preparation of β-dicarbonyl-phenols **11**



Entry	R^1	R^2	Method[a]	Product	Yield (%)
1	H	Ac	A	**11a**	87
2	OMe	Ac	A	**11b**	77
3	H	CO_2^tBu	B	**11c**	79

[a] Method A: NaH (4 equiv), EtOAc (2.5 equiv), THF, rt, 15 min; method B: LiHMDS (3 equiv), Boc_2O (1.1 equiv), THF, −78 °C to rt, 18 h.

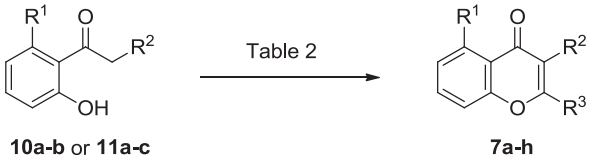
Chromenone **7g** appeared to be a good candidate to improve the conjugate addition, hoping that its enhanced reactivity due to the presence of the electron-withdrawing CO_2^tBu group at C-3 would facilitate the conjugate addition. The C-3 group could then be removed under mild conditions to afford chromanone **9a**. With this in mind, the same reaction conditions used for **7e** were applied to **7g** (entry 3).

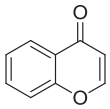
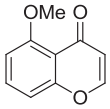
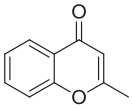
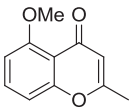
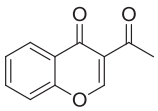
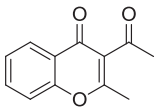
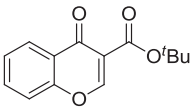
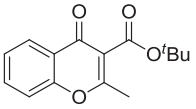
Reaction of **7g** with **8a** afforded an inseparable mixture of unreacted chromenone **7g** and chromanone **9a** rather than the expected chromanone. Compound **9a** could arise either from TMSOTf-promoted in situ decarboxylation of the expected product, or in situ decarboxylation of chromenone **7a** with subsequent addition of the silyl enol ether. Treatment of a solution of **7g** with TMSOTf, however, did not provide **7a**, suggesting that the first possibility is most likely.

The presence of the electron-withdrawing CO_2^tBu substituent at C-3 in **7g** afforded no increase in reactivity of the chromenone. Hoping to improve the efficiency of the conjugate addition process before attempting an asymmetric variant, we next turned to the use of the more reactive silyl ketene acetal **8b**. The improved reactivity of **8b** was immediately apparent, with the known chromanone **9c** isolated in high yield upon reaction with **7a** using TMSOTf as catalyst in CH_2Cl_2 for 4 h. The reaction of **8b** with an array of chromenones **7b**–**f** was then examined to investigate the effect of substituents at both C-2 and C-3 on the conjugate addition reaction.

As expected, substitution at C-2 using **7c**, **7d**, and **7f** led to decreased efficiency of the reaction (entries 6, 7, and 9), an important consideration for the future synthesis of more complex natural product frameworks using this approach. Furthermore, the presence of increased electron density in the benzene ring (methoxy-group at C-5) and C-2 substitution in **7d** resulted in reduced yields

Table 2
Summary of practical methods for preparation of chromenones **7a**–**h**



Entry	Phenol	Method[a]	Product		Yield (%)
1	**10a**	A		**7a**	92
2	**10b**	A		**7b**	81
3	**11a**	B		**7c**	92
4	**11b**	B		**7d**	93
5	**11a**	C		**7e**	73
6	**11a**	D		**7f**	48
7	**11c**	C		**7g**	55
8	**11c**	D		**7h**	22

[a] Method A: NaH, ethyl formate, then HCl; method B: HCl, MeOH; method C: HCO_2Na, acetic formic anhydride, THF; method D: NaOAc, Ac_2O, reflux.

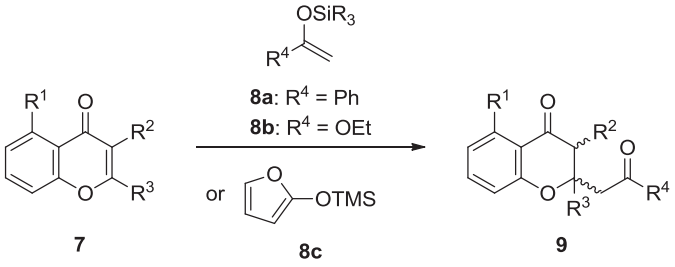
of chromanone (entry 7). Unfortunately, reactions with chromenones **7g** and **7h** were unsuccessful and did not provide the expected chromanones.

Use of 2-(trimethylsilyloxy)furan **8c** as the nucleophile in the conjugate addition was also examined. Porco et al.[32] had earlier reported a similar addition of **8c** to a related chromenone, utilising stoichiometric benzopyrylium ion methodology. In the present work, employing a 2-fold excess of **8c** in the reaction afforded good yields of adducts **9i**–**k**, which were obtained as diastereomeric mixtures (entries 10–12). Again, C-2 substitution resulted in lower reactivity in the conjugate addition (entry 13).

2.3. Asymmetric conjugate addition study

Cu(II)–box catalysts have been successfully used to effect a variety of asymmetric reactions, including the Mukaiyama–Michael addition of 2-(trimethylsilyloxy)furan to (*E*)-3-crotonoyl-1,3-oxazolidin-2-one.[33,34]

Table 3
Conjugate addition of silyl enol ethers **8a**–**c** to chromenones **7a**–**f**



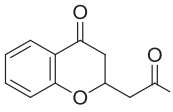
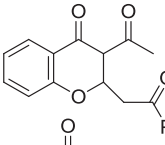
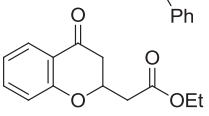
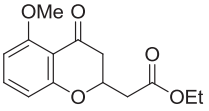
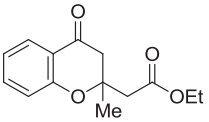
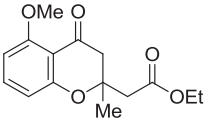
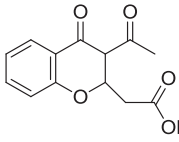
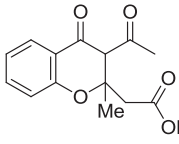
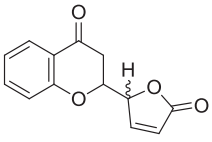
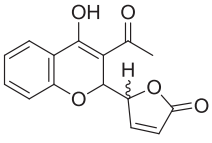
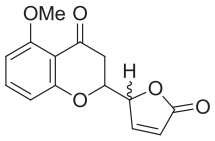
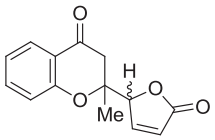
Entry	Chromenone	Silyl enol ether	Method[a]	Product		Yield (%)
1	**7a**	**8a**	A		**9a**	26
2	**7e**	**8a**	A		**9b**	21[b] dr, n.d.
3	**7g**	**8a**	A		**9a**	20
4	**7a**	**8b**	B		**9c**	80
5	**7b**	**8b**	B		**9d**	>99
6	**7c**	**8b**	B		**9e**	71
7	**7d**	**8b**	B		**9f**	18
8	**7e**	**8b**	B		**9g**	10[b] dr, n.d.
9	**7f**	**8b**	B		**9h**	16[b] dr, n.d.
10	**7a**	**8c**	C		**9i**	77 dr, 3:2
11	**7e**	**8c**	C		**9j**	77 dr, 77:23

Table 3 (*continued*)

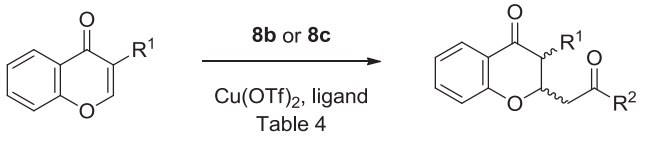
Entry	Chromenone	Silyl enol ether	Method[a]	Product	Yield (%)
12	**7b**	**8c**	C	 **9k**	76 dr, 73:27
13	**7c**	**8c**	C	 **9l**	9 dr, n.d.

[a] Method A: **8a** (1.5 equiv), TMSOTf (1 equiv), CH_2Cl_2, −78 °C to rt, 4 h; method B: **8b** (1.2 equiv), TMSOTf (1 equiv), CH_2Cl_2, rt, 4 h; method C: **8c** (2.2 equiv), TMSOTf (1.1 equiv), CH_2Cl_2, −78 °C, 2 h. n.d.=not determined.

[b] Diastereomeric ratios for these compounds were unable to be determined due to overlapping of signals in the ^1H NMR spectra.

Given that silyl enol ethers **8b** and **8c** and chromenones **7a** and **7e** gave the highest yields in the racemic conjugate addition reactions, these compounds were selected to investigate an asymmetric variant of this reaction (Table 4).

Table 4
Cu(II)–box and Cu(II)–pybox promoted conjugate addition of silyl enol ethers **8b** and **8c** to chromenones **7a** and **7e**



Entry	Chromenone	Silyl enol ether	Ligand	Method[a]	Product	Yield[b] (%)
1	**7a**	**8b**	**12**	A	**9c**	20
2	**7a**	**8b**	**14**	A	**9c**	<10
3	**7a**	**8b**	**15**	A	**9c**	23
4	**7a**	**8b**	**13**	A	**9c**	20
5	**7e**	**8b**	**12**	A	**9g**	11
6	**7e**	**8b**	**12**	B	**9g**	16
7	**7e**	**8b**	**12**	C	**9g**	22
8	**7e**	**8c**	**12**	D	**9i**	<10
9	**7a**	**8c**	**12**	D	**9i**	48

[a] Method A: 20 mol % ligand **12**–**15**, 20 mol % $Cu(OTf)_2$, CH_2Cl_2, rt, 4 h; method B: 20 mol % **12**, 20 mol % $CuCl_2$, 20 mol % $AgSbF_6$, CH_2Cl_2, rt, 4 h; method C: 20 mol % **12**, 20 mol % $Cu(OTf)_2$, 1 equiv TMSCl, CH_2Cl_2, rt, 4 h; method D: 20 mol % **12**, 20 mol % $Cu(OTf)_2$, CH_2Cl_2, −78 °C to rt, 1 h.

[b] Diastereomeric ratio of products identical to material prepared in the TMSOTf-promoted conjugate additions (Table 3).

The chiral complexes were generated in situ, followed by addition of the chromenone **7a** or **7e**, then silyl enol ether **8b** or **8c**. Several ligands were screened for this transformation, including diPhBOX **12**, PyBOX **14**, IndaBOX **13**, and IndaPyBOX **15** (Fig. 4).[35]

The yields of chromanones **9c**, **9g**, and **9i** obtained using these chiral catalysts were significantly lower than those promoted by TMSOTf. This is likely due to the reaction taking place via a Lewis acid-catalysed mechanism, rather than through a benzopyrylium ion as in the case of TMSOTf-promoted additions. To date, most reported examples of conjugate addition to chromenones have required stoichiometric generation of benzopyrylium salts.

Again, attempts to improve the yield through addition of an electron-withdrawing group at C-3 proved futile, providing the adduct **9g** in lower yield than its unsubstituted counterpart **9c** (entries 5–7). Changing the counterion to the less coordinating SbF_6^- (entry 6) had little effect, resulting in a small increase in yield only. Reasoning that the low yields were a result of irreversible binding of the Lewis acid complex to the substrate, we attempted to increase turnover of the metal centre by adding TMSCl to the mixture (entry 7).[36] This did improve the yield slightly, but not to a synthetically useful extent.

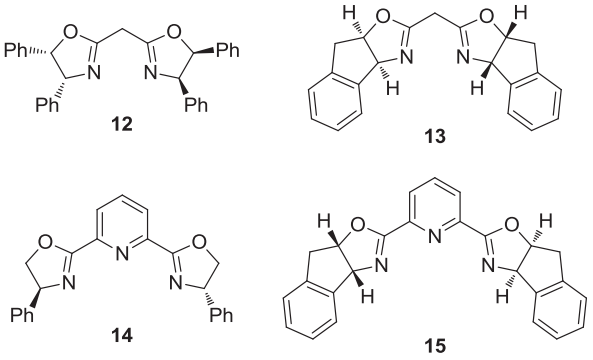


Fig. 4. Chiral catalysts screened in the Mukaiyama–Michael reaction.

Unfortunately, in each case the products **9c**–**i** obtained were racemic. The lack of stereocontrol may be due to several factors, and further work is underway to identify ligand classes that will successfully effect enantioselective conjugate addition to these heterocyclic systems.

3. Conclusion

In summary, we herein report the conjugate addition of silyl enol ethers to a variety of substituted chromenones. In most cases the 2-alkyl chromanones were obtained in good yield in the presence of TMSOTf. The presence of electron-withdrawing substituents at C-3 did not increase the reactivity of the chromenones towards conjugate addition, and C-2 substitution reduced the yield of products obtained. The copper(II)-promoted conjugate addition of silyl enol ethers to chromenones was also carried out, albeit in low yield. Investigations into an asymmetric variant of this reaction have not been successful to date and further work to achieve this goal is currently underway.

Furthermore, a number of the chromenone substrates, though previously reported, were not supported by detailed experimental procedures or characterisation data. Reliable syntheses of these compounds via acylation of the corresponding β-diketo-compounds have been carried out, and these detailed experimental procedures have been provided together with full spectroscopic characterisation data.

4. Experimental

4.1. General information and materials

Reagents purchased from commercial sources were used as received. All reactions were carried out under an inert atmosphere of N_2. THF was distilled from sodium/benzophenone immediately prior to use. Dichloromethane was distilled from CaH_2. Melting points were recorded on a hot-stage apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance-300 or DRX-400 at the frequencies stated, and are referenced to tetramethylsilane at 0.00 ppm for ^1H in $CDCl_3$ and residual solvent signals at 77.0 ppm for ^{13}C in $CDCl_3$. IR spectra were obtained using a PerkinElmer Spectrum100 UATR FT-IR spectrometer, using either

a solid or thin film of the compound to be analysed. High-resolution mass spectra were obtained by electron spray ionisation (ESI) using a microTOF-Q mass spectrometer. HPLC was performed on a Daicel Chiralpak™ IC column using Dionex Ultimate 3000™ HPLC kit with Chromeleon software.

4.2. General procedure A: preparation of chromanones 9a–l via TMSOTf-catalysed conjugate addition of 8a, 8b, or 8c

TMSOTf (1 equiv) was added to a solution of the chromenone (1 equiv) in dichloromethane (1 mL/0.1 mmol chromenone) at room temperature, and the mixture allowed to stir for 15 min. A solution of silyl enol ether **8a** (1.5 equiv), silyl ketene acetal **8b** (1.2 equiv), or **8c** (2.2 equiv) in dichloromethane (1 mL/0.1 mmol) was then added dropwise, and the resulting mixture allowed to stir for an additional 4–6 h. Satd aq $NaHCO_3$ was added, and the mixture extracted with dichloromethane three times. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford the crude adducts.

4.3. General procedure B: asymmetric Lewis acid-catalysed conjugate addition of silyl enol ether 8b or 8c to chromenones 7a and 7e

$Cu(OTf)_2$ (0.2 equiv) was added to a solution of the ligand (0.2 equiv) in dichloromethane (5 mL) and the resulting brightly coloured solution allowed to stir at room temperature for 10 min. A solution of the chromenone (1 equiv) in dichloromethane (0.5 mL/0.1 mmol) was then added dropwise, and the mixture allowed to stir for 30 min. A solution of silyl ketene acetal **8b** (1.2 equiv) or silyl enol ether **8c** (3 equiv) in dichloromethane (1 mL/0.1 mmol) was then added dropwise, and the mixture allowed to stir for a further 4–6 h. Water (10 mL) was added, and the mixture extracted with dichloromethane three times. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford the crude adducts.

4.4. Procedure for counterion exchange to SbF_6^- (method B, Table 4)

A mixture of $CuCl_2$ (4 mg, 0.03 mmol), $AgSbF_6$ (22 mg, 0.06 mmol), and ligand **12** (15 mg, 0.03 mmol) was diluted with dichloromethane (5 mL) and the mixture allowed to stir at room temperature for 1 h, becoming yellow-green in colour. A solution of **7e** (30 mg, 0.16 mmol) in dichloromethane (1.5 mL) was then added and the resulting pale blue mixture allowed to stir for 0.5 h. A solution of **8b** (39 mg, 0.19 mmol) in dichloromethane (1.5 mL) was then added dropwise and the resulting green-yellow mixture allowed to stir for an additional 3.5 h. Water (10 mL) was added, and the organic layer removed. The aqueous layer was extracted with dichloromethane (2×10 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated under reduced pressure to afford a yellow-brown solid. The crude product was purified via flash column chromatography (silica gel, ethyl acetate/hexanes 1:9 as eluent) to give **9g** (7 mg, 16%) as a colourless oil. Spectral data were identical with material prepared according to general procedure A.

4.5. 1-Phenyl-1-(trimethylsilyloxy)ethene (8a)

Prepared according to the procedure reported by Watts et al.[37] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62–7.59 (m, 2H), 7.32–7.29 (m, 3H), 5.04 (d, J=2.2 Hz, 1H), 4.78 (d, J=2.2 Hz, 1H), 0.16 (s, 9H). Spectral data are in agreement with literature values.[38]

4.6. 1-Ethoxy-1-(*tert*-butyldimethylsilyloxy)ethene (8b)

Prepared according to the procedure reported by Jacobsen and Wenzel.[39] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.74 (q, J=7.0 Hz, 2H), 3.21 (d, J=2.3 Hz, 1H), 3.05 (d, J=2.3 Hz, 1H), 1.29 (t, J=7.0 Hz, 3H), 0.92 (s, 9H), 0.17 (s, 6H). Spectral data are in agreement with literature values.[39]

4.7. 1-(2-Hydroxyphenyl)butane-1,3-dione (11a)

Prepared according to the procedure reported by Patonay et al.[26] Sodium hydride (60% dispersion in mineral oil, 3.53 g, 88.2 mmol) was rinsed three times with hexanes, then suspended in THF (9 mL). A mixture of 2′-hydroxyacetophenone **10a** (2.65 mL, 22.0 mmol) and EtOAc (5.42 mL, 55.1 mmol) in THF (2.5 mL) was added dropwise to the above suspension at room temperature. A vigorous reaction was observed, and the temperature rose to reflux. After complete addition, the reaction mixture was stirred for a further 5 min, then quenched by pouring onto ice, then acidified to pH 6 with 6 M aq HCl. The resulting precipitate was collected via filtration, washed with water, and dried under high vacuum to afford the title compound **11a** (3.41 g, 87%) as a crystalline white solid as a 1:4 mixture of keto/enol tautomers: mp 90–92 °C (lit.[26] 93–96 °C). R_f (hexanes/EtOAc 7:3): 0.47. IR: 3361, 2920, 1674, 1608, 1327, 1115, 1087, 891, 775 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.97 (s, 1H), 12.06 (s, 1H), 11.93* (s, 0.25H), 7.90* (dd, J=1.7, 7.8 Hz, 0.25H), 7.63 (dd, J=1.5, 8.2 Hz, 1H), 7.53–7.47* (m, 0.25H), 7.44 (ddd, J=1.5, 7.0, 8.5 Hz, 1H), 7.06–6.98* (m, 0.25H), 6.97 (dd, J=1.0, 8.5 Hz, 1H), 6.94–6.90* (m, 0.25H), 6.88 (ddd, J=1.0, 7.0, 8.2 Hz, 1H), 6.18 (s, 1H), 4.10* (s, 0.5H), 2.32* (s, 0.75H), 2.15 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6, 190.9*, 186.2*, 183.1, 162.7, 160.4*, 137.4*, 135.9, 128.6, 126.8*, 119.5*, 119.2*, 119.1, 118.8, 118.6*, 118.3, 95.6, 47.9*, 30.7*, 22.9. HRMS (ESI) calcd for $C_{10}H_{11}O_3$ $[MH]^+$ 179.0703; found 179.0699. *=keto (minor) tautomer. Spectral data are in agreement with literature values.[25]

4.8. 1-(2-Hydroxy-6-methoxyphenyl)-1,3-butanedione (11b)

Prepared as for **11a**, from 2′-hydroxy-6′-methoxyacetophenone **10b** (1.25 g, 7.52 mmol), as a yellow powder (1.20 g, 77%) and as a 2:1 mixture of keto/enol tautomers: mp 99–100 °C (lit.[40] 96–97 °C). R_f (hexanes/EtOAc 7:3): 0.36. ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.30* (s, 0.5H), 12.95 (s, 1H), 12.48* (s, 0.5H), 7.38 (t, J=8.5 Hz, 1H), 7.30* (t, J=8.5 Hz, 0.5H), 6.61 (dd, J=1.0, 8.5 Hz, 1H), 6.57* (dd, J=1.6, 8.5 Hz, 0.5H), 6.40–6.38 (m, 1.5H), 4.07 (s, 2H), 3.89* (s, 1.5H), 3.86 (s, 3H), 2.25 (s, 3H), 2.13* (s, 1.5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 200.4*, 194.5, 183.5*, 165.2, 164.0*, 160.9, 160.4*, 137.1, 135.1*, 111.3, 111.2*, 111.1, 110.0*, 101.9*, 101.8*, 101.3, 60.2, 55.9*, 55.8, 30.3, 23.1*. HRMS (ESI) calcd for $C_{11}H_{13}O_4$ $[MH]^+$ 209.0808; found 209.0806. *=enol (minor) tautomer.

4.9. *tert*-Butyl 3-(2-hydroxyphenyl)-3-oxopropanoate (11c)

A solution of 2′-hydroxyacetophenone **10a** (1.77 mL, 14.7 mmol) in THF (40 mL) was added dropwise via addition funnel to a solution of LiHMDS (1.0 M in THF, 44.1 mL, 44.1 mmol) at −78 °C. The mixture was allowed to stir at this temperature for 2 h, then a solution of di-*tert*-butyl dicarbonate (3.60 mL, 15.9 mmol) in THF (15 mL) was added quickly. The mixture was allowed to slowly warm to room temperature and stirred overnight. The mixture was then poured onto a mixture of ice (100 mL) and concd HCl (10 mL). The resulting solution was extracted with dichloromethane (3×150 mL) and the combined organic extracts were washed with water (2×100 mL), dried over Na_2SO_4, and concentrated under reduced pressure to afford an orange oil. The crude product was purified via flash column chromatography (silica gel, ethyl acetate/

hexanes 1:9 as eluent) to give the title compound **11c** (2.74 g, 79%) as a bright yellow oil: R_f (hexanes/EtOAc 7:3): 0.71. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.91 (s, 1H), 7.67 (dd, J=1.6, 8.1 Hz, 1H), 7.52–7.47 (m, 1H), 7.01–6.99 (m, 1H), 6.94–6.90 (m, 1H), 3.91 (s, 2H), 1.46 (s, 9H). Spectral data are in agreement with literature values.[7]

4.10. Chromone (1-benzopyran-4-one, 7a)

Prepared according to the procedure reported by Li et al.[30] Sodium hydride (60% dispersion in mineral oil, 1.06 g, 44.1 mmol, washed three times with hexanes) was added portion-wise to a solution of 2′-hydroxyacetophenone **10a** (0.88 mL, 7.34 mmol) in ethyl formate (60 mL) at 0 °C over a period of 2 h. The mixture was allowed to stir for a further 1.5 h, then quenched with methanol (3.5 mL). Concd HCl (11.5 mL) was added, and the mixture allowed to warm to room temperature and stirred for another 16 h. Water (50 mL) was added, and the mixture extracted with dichloromethane (3×50 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure to afford a yellow oil. The crude product was purified via flash column chromatography (silica gel, ethyl acetate/hexanes 1:9 as eluent) to give the title compound **7a** (0.990 g, 92%) as pale yellow crystals: mp 52–54 °C (lit.[41] 55–57 °C). R_f (hexanes/EtOAc 1:1): 0.46. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, J=1.8, 8.0 Hz, 1H), 7.85 (d, J=6.0 Hz, 1H), 7.70–7.66 (m, 1H), 7.46 (br d, J=7.8 Hz, 1H), 7.41 (br t, J=7.8 Hz, 1H), 6.35 (d, J=6.0 Hz, 1H). Spectral data are in agreement with literature values.[22]

4.11. 5-Methoxy-4*H*-chromen-4-one (7b)

Prepared as for **7a**, from 2′-hydroxy-6′-methoxyacetophenone **10b** (0.500 g, 3.01 mmol) as white crystals (0.430 g, 81%): mp 81–84 °C (lit.[42] 83–84 °C). R_f (hexanes/EtOAc 1:9): 0.40. IR: 3074, 1921, 1637, 1600, 1432, 1083, 741, 686 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J=5.9 Hz, 1H), 7.54 (t, J=8.4 Hz, 1H), 7.00 (dd, J=0.7, 8.4 Hz, 1H), 6.82–6.80 (m, 1H), 6.24 (d, J=5.9 Hz, 1H), 3.98 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 159.8, 158.5, 153.0, 133.7, 115.6, 114.6, 110.2, 106.4, 56.4. HRMS (ESI) calcd for $C_{10}H_9O_3$ $[MH]^+$ 177.0546; found 177.0548.

4.12. 2-Methyl-4*H*-chromen-4-one (7c)

Prepared according to the procedure reported by Shaw et al.[3] Concd HCl (1 mL) was added to a solution of **11a** (2.50 g, 14.0 mmol) in methanol (30 mL), and the mixture allowed to stir at room temperature for 14 h. The mixture was concentrated under reduced pressure and the residue diluted with EtOAc (50 mL), then washed successively with solutions of satd aq $NaHCO_3$ (3×30 mL), water (30 mL), and brine (30 mL). The organic layer was then dried over $MgSO_4$ and concentrated under reduced pressure to afford an orange solid. The crude product was purified via flash column chromatography (silica gel, ethyl acetate/hexanes 1:4 as eluent) to give the title compound **7c** (2.07 g, 92%) as a yellow solid: mp 67–70 °C (lit.[43] 69–70 °C). R_f (hexanes/EtOAc 7:3): 0.33. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (dd, J=1.6, 8.0 Hz, 1H), 7.63 (ddd, J=1.6, 7.2, 8.6 Hz, 1H), 7.41–7.35 (m, 2H), 6.17 (d, J=0.8 Hz, 1H), 2.38 (s, 3H). Spectral data are in agreement with literature values.[3]

4.13. 5-Methoxy-2-methyl-4*H*-chromen-4-one (7d)

Prepared as for **7c** from **11b** (1.20 g, 5.76 mmol). Purified via flash column chromatography (silica gel, ethyl acetate/hexanes 1:1 as eluent) to give the title compound **7d** (1.02 g, 93%) as a pale yellow solid: mp 95–97 °C (lit.[3] 97–98 °C). R_f (hexanes/EtOAc 1:1): 0.11. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (t, J=8.3 Hz, 1H), 6.97 (dd, J=0.8, 8.3 Hz, 1H), 6.78 (d, J=8.3 Hz, 1H), 6.07 (d, J=0.8 Hz, 1H), 3.97 (s, 3H), 2.30 (s, 3H). Spectral data are in agreement with literature values.[3]

4.14. 3-Acetyl-4*H*-chromen-4-one (7e)

Acetic formic anhydride[28] (14.0 mL, 103 mmol) was added to a solution of **11a** (1.50 g, 8.42 mmol) and sodium formate (0.740 g, 10.9 mmol) in THF (15 mL) at room temperature and the mixture allowed to stir for 24 h. Water (30 mL) was added and the mixture extracted with ethyl acetate (3×30 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ (50 mL), water, (50 mL), and brine (50 mL) then dried over $MgSO_4$, and concentrated under reduced pressure to afford a peach solid. The crude product was recrystallised from ethanol to afford the title compound **7e** (1.15 g, 73%) as fluffy white needles: mp 125–128 °C (lit.[29] 129 °C). R_f (hexanes/EtOAc 7:3): 0.37. IR: 1992, 1611, 1312, 1080, 745, 627 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.29 (dd, J=1.6, 8.0 Hz, 1H), 7.73 (ddd, J=1.6, 7.0, 8.6 Hz, 1H), 7.53–7.47 (m, 2H), 2.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7, 175.3, 161.7, 155.8, 134.3, 126.4, 126.3, 125.3, 122.8, 118.2, 31.5. HRMS (ESI) calcd for $C_{11}H_9O_3$ $[MH]^+$ 189.0546; found 189.0547.

4.15. 3-Acetyl-2-methyl-4*H*-chromen-4-one (7f)

Acetic anhydride (6.00 mL) was added to a mixture of **11a** (0.700 g, 3.93 mmol) and sodium acetate (0.338 g, 4.13 mmol) and the mixture heated at reflux for 3 h. The mixture was allowed to cool to room temperature, whereupon it solidified to an orange mass. The mixture was diluted with toluene (30 mL) and filtered to remove undissolved salts. The filtrate was stirred with water (30 mL) for 1.5 h. The organic layer was then removed, dried over $MgSO_4$, and concentrated under reduced pressure to afford orange crystals. The crude product was purified via flash column chromatography (silica gel, ethyl acetate/hexanes 1:4 as eluent) to give the title compound **7f** (0.382 g, 48%) as white crystals: mp: 84–88 °C (lit.[44] 89–90 °C). R_f (hexanes/EtOAc 7:3): 0.40. IR: 2923, 1688, 1635, 1614, 1561, 1463, 1387, 1216, 1124, 1060, 952, 757 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, J=1.5, 8.0 Hz, 1H), 7.67 (ddd, J=1.5, 7.4, 8.8 Hz, 1H), 7.41–7.37 (m, 2H), 2.63 (s, 3H), 2.51 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.1, 175.5, 168.2, 155.0, 133.8, 125.4, 125.2, 123.34, 123.26, 117.4, 31.8, 19.5. HRMS (ESI) calcd for $C_{12}H_{10}NaO_3$ $[MNa]^+$ 225.0522; found 225.0529.

4.16. 3-*tert*-Butoxycarbonyl-4*H*-chromen-4-one (7g)

Prepared as for **7e**, from **11c** (1.50 g, 6.35 mmol) to afford a yellow solid. The crude product was purified via flash column chromatography (silica gel, ethyl acetate/hexanes 3:17 as eluent) to give the title compound **7g** (0.857 g, 55%) as white crystalline flakes: mp 101–105 °C. R_f (hexanes/EtOAc 7:3): 0.71. IR: 2969, 1728, 1648, 1615, 1570, 1562, 1463, 1392, 1289, 1089, 752 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.28 (dd, J=1.6, 8.0 Hz, 1H), 7.69 (ddd, J=1.6, 7.2, 8.7 Hz, 1H), 7.48–7.42 (m, 2H), 1.60 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 162.2, 161.2, 155.6, 134.0, 126.6, 126.0, 125.3, 118.1, 117.5, 82.3, 28.2. HRMS (ESI) calcd for $C_{14}H_{14}NaO_4$ $[MNa]^+$ 269.0784; found 269.0778.

4.17. 3-*tert*-Butoxycarbonyl-2-methyl-4*H*-chromen-4-one (7h)

Sodium acetate (anhydrous, 182 mg, 2.22 mmol) was added to a solution of **11c** (500 mg, 2.11 mmol) in acetic anhydride (2.80 mL) and the mixture heated at 100–110 °C for 3 h. The mixture was allowed to cool and diluted with toluene (5 mL). The mixture was filtered through cotton wool to remove the salt and the filtrate

stirred with water (30 mL) for 3 h. The organic layer was removed, dried over $MgSO_4$, and concentrated under reduced pressure to afford an orange oil. The crude product was purified via flash column chromatography (silica gel, ethyl acetate/hexanes 1:9 as eluent) to give the title compound **7h** (122 mg, 22%) as white needles: mp 70–76 °C. R_f (hexanes/EtOAc 7:3): 0.59. IR: 2978, 1769, 1723, 1647, 1575, 1464, 1400, 1366, 1254, 1222, 1129, 1073, 762 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, J=1.6, 7.8 Hz, 1H), 7.64 (ddd, 1.6, 7.2, 8.8 Hz, 1H), 7.41–7.36 (m, 2H), 2.48 (s, 3H), 1.61 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 165.2, 164.3, 155.7, 133.7, 126.0, 125.3, 123.5, 119.7, 117.7, 82.7, 28.1, 19.1. HRMS (ESI) calcd for $C_{15}H_{16}NaO_4$ $[MNa]^+$ 283.0941; found 283.0938.

4.18. 2-(2-Oxo-2-phenylethyl)chroman-4-one (9a)

Prepared according to general procedure A from chromenone **7a** (50 mg, 0.34 mmol) and silyl enol ether **8a** (99 mg, 0.51 mmol) to afford an orange oil. The crude product was purified via flash column chromatography (silica gel, ethyl acetate/hexanes 1:9 as eluent) to give the title compound **9a** (24 mg, 26%) as yellow crystals: mp: 85–92 °C (lit.[45] 99–102 °C). R_f (hexanes/EtOAc 7:3): 0.56. ^1H NMR (400 MHz, $CDCl_3$) δ 8.00–7.98 (m, 2H), 7.90 (dd, J=1.7, 7.9 Hz, 1H), 7.63–7.59 (m, 1H), 7.52–7.44 (m, 3H), 7.03 (td, J=0.7, 7.9 Hz, 1H), 6.93 (d, J=8.3 Hz, 1H), 5.21–5.14 (m, 1H), 3.70 (dd, J=6.4, 17.0 Hz, 1H), 3.29 (dd, J=6.0, 17.0 Hz, 1H), 2.92 (dd, J=3.3, 16.8 Hz, 1H), 2.80 (dd, J=12.2, 16.8 Hz, 1H). Spectral data are in agreement with literature values.[45]

4.19. 3-Acetyl-2-(2-oxo-2-phenylethyl)chroman-4-one (9b)

Prepared according to general procedure A from chromenone **7e** (50 mg, 0.27 mmol) and silyl enol ether **8a** (77 mg, 0.40 mmol) to afford an orange oil. The crude product was purified via flash column chromatography (silica gel, ethyl acetate/hexanes 1:9 as eluent) to give the title compound **9b** (8 mg, 10%) as a pale yellow oil as an approximately 1:8 mixture of keto/enol tautomers: R_f (hexanes/EtOAc 7:3): 0.59. IR: 3065, 2923, 1718, 1682, 1604, 1463, 1448, 1359, 1302, 1216, 1149, 974, 755, 690 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J=1.6, 7.9 Hz, 1H), 7.85–7.82 (m, 2H), 7.58–7.54 (m, 1H), 7.44–7.36 (m, 3H), 7.06 (td, J=0.7, 7.9 Hz, 1H), 6.93–6.91* (m, 0.13H), 6.76 (dd, J=0.7, 8.4 Hz, 1H), 5.99 (dd, J=4.0, 8.8 Hz, 1H), 5.49–5.44* (m, 0.13H), 4.11* (d, J=9.9 Hz, 0.13H), 3.79 (dd, J=8.8, 16.3 Hz, 1H), 3.48–3.37* (m, 0.26H), 2.93 (dd, J=4.0, 16.3 Hz, 1H), 2.45* (s, 0.39H), 2.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.3*, 202.7*, 196.7, 189.5*, 188.0, 176.1, 156.7, 156.6*, 136.7*, 136.6, 135.1, 135.1*, 133.6*, 133.6, 128.7, 128.7*, 128.3, 128.3*, 126.2, 126.2*, 121.9, 121.8*, 119.3, 119.3*, 118.1, 118.1*, 105.5, 74.5*, 72.3, 62.9*, 43.6, 41.0*, 31.3*, 22.1. HRMS (ESI) calcd for $C_{19}H_{16}NaO_4$ $[MNa]^+$ 331.0941; found 331.0937. *=keto (minor) tautomer.

4.20. Ethyl 2-(4-oxochroman-2-yl)acetate (9c)

Prepared according to general procedure A from chromenone **7a** (50 mg, 0.34 mmol) and silyl ketene acetal **8b** (83 mg, 0.41 mmol) to afford an orange oil. The crude product was purified via flash column chromatography (silica gel, ethyl acetate/hexanes 1:9 as eluent) to give the title compound **9c** (66 mg, 80%) as a colourless oil: R_f (hexanes/EtOAc 7:3): 0.53. ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J=1.7, 7.9 Hz, 1H), 7.49–7.45 (m, 1H), 7.04–7.00 (m, 1H), 6.97 (dd, J=0.7, 8.5 Hz, 1H), 4.95–4.88 (m, 1H), 4.21 (q, J=7.2 Hz, 2H), 2.92 (dd, J=7.3, 15.8 Hz, 1H), 2.80–2.78 (m, 2H), 2.72 (dd, J=5.6, 15.8 Hz, 1H), 1.29 (t, J=7.2 Hz, 3H). Spectral data are in agreement with literature values.[45]

4.21. Ethyl 2-(5-methoxy-4-oxochroman-2-yl)acetate (9d)

Prepared according to general procedure A from chromenone **7b** (50 mg, 0.28 mmol) and silyl ketene acetal **8b** (69 mg, 0.34 mmol) to afford an orange oil. The crude product was purified via flash column chromatography (silica gel, ethyl acetate/hexanes 3:7 as eluent) to give the title compound **9d** (75 mg, >99%) as a yellow oil: R_f (hexanes/EtOAc 7:3): 0.10. ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (t, J=8.4 Hz, 1H), 6.57–6.51 (m, 2H), 4.90–4.83 (m, 1H), 4.21 (q, J=7.0 Hz, 2H), 3.91 (s, 3H), 2.87 (dd, J=7.4, 15.8 Hz, 1H), 2.74 (d, J=7.6 Hz, 2H), 2.69 (dd, J=5.6, 15.8 Hz, 1H), 1.29 (t, J=7.0 Hz, 3H). Spectral data are in agreement with literature values.[45]

4.22. Ethyl 2-(2-methyl-4-oxochroman-2-yl)acetate (9e)

Prepared according to general procedure A from chromenone **7c** (50 mg, 0.31 mmol) and silyl ketene acetal **8b** (76 mg, 0.37 mmol) to afford an orange oil. The crude product was purified via flash column chromatography (silica gel, ethyl acetate/hexanes 1:9 as eluent) to give the title compound **9e** (55 mg, 71%) as a colourless oil: R_f (hexanes/EtOAc 7:3): 0.42. IR: 2940, 1733, 1693, 1609, 1581, 1464, 1375, 1309, 1115, 1030, 765 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, J=1.8, 7.8 Hz, 1H), 7.50–7.45 (m, 1H), 7.02–6.98 (m, 1H), 6.94–6.92 (m, 1H), 4.15 (q, J=7.3 Hz, 2H), 3.08 (d, J=16.7 Hz, 1H), 2.82–2.72 (m, 3H), 1.56 (s, 3H), 1.26 (t, J=7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 169.2, 159.1, 136.2, 126.4, 121.1, 120.1, 118.3, 79.1, 60.7, 46.8, 43.9, 24.5, 14.1. HRMS (ESI) calcd for $C_{14}H_{16}NaO_4$ $[MNa]^+$ 271.0941; found 271.0941.

4.23. Ethyl 2-(5-methoxy-2-methyl-4-oxochroman-2-yl) acetate (9f)

Prepared according to general procedure A from chromenone **7d** (50 mg, 0.26 mmol) and silyl ketene acetal **8b** (64 mg, 0.32 mmol) to afford an orange oil. The crude product was purified via flash column chromatography (silica gel, ethyl acetate/hexanes 3:7 as eluent) to give the title compound **9f** (13 mg, 18%) as a brown oil: R_f (hexanes/EtOAc 7:3): 0.16. IR: 2920, 1732, 1686, 1601, 1576, 1473, 1338, 1256, 1087, 1034, 790 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (t, J=8.4 Hz, 1H), 6.54–6.49 (m, 2H), 4.15 (q, J=7.2 Hz, 2H), 3.91 (s, 3H), 3.02 (d, J=16.1 Hz, 1H), 2.77–2.73 (m, 3H), 1.54 (s, 3H), 1.26 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3, 169.3, 160.8, 160.3, 136.0, 110.6, 110.5, 103.6, 78.6, 60.7, 56.1, 48.4, 44.0, 24.3, 14.1. HRMS (ESI) calcd for $C_{15}H_{18}NaO_5$ $[MNa]^+$ 301.1046; found 301.1023.

4.24. Ethyl 2-(3-acetyl-4-oxochroman-2-yl)acetate (9g)

Prepared according to general procedure A from chromenone **7e** (50 mg, 0.27 mmol) and silyl ketene acetal **8b** (65 mg, 0.32 mmol) to afford an orange oil. The crude product was purified via flash column chromatography (silica gel, ethyl acetate/hexanes 7:93 as eluent) to give the title compound **9g** (7 mg, 10%) as a pale yellow oil as a 1:9 mixture of keto/enol tautomers: R_f (hexanes/EtOAc 7:3): 0.54. IR: 2980, 1731, 1684, 1606, 1461, 1369, 1302, 1164, 1034, 759 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.88–7.86* (m, 0.1H), 7.84 (dd, J=1.7, 7.8 Hz, 1H), 7.53–7.48* (m, 0.1H), 7.46–7.41 (m, 1H), 7.08–7.02 (m, 1H), 6.98* (br d, J=8.6 Hz, 0.1H), 6.89 (dd, J=0.8, 8.4 Hz, 1H), 5.72 (dd, J=4.2, 9.6 Hz, 1H), 5.20–5.15* (m, 0.1H), 4.24–4.12 (m, 2H), 2.91 (dd, J=9.6, 15.2 Hz, 1H), 2.47 (dd, J=4.2, 15.2 Hz, 1H), 2.43* (s, 0.3H), 2.21 (s, 3H), 1.27 (t, J=7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.8*, 203.1*, 187.9, 176.1, 169.8*, 169.8, 156.6, 141.2*, 135.2, 135.2*, 127.2*, 126.1, 122.0, 121.9*, 119.2, 118.1*, 118.0, 104.9, 74.8*, 72.5, 62.1*, 61.0*, 60.9, 40.7, 37.7*, 32.3*, 30.9*, 29.7*, 22.0, 14.2. HRMS (ESI) calcd for $C_{15}H_{16}NaO_5$ $[MNa]^+$ 299.0890; found 299.0877. *=keto (minor) tautomer.

4.25. Ethyl 2-(3-acetyl-2-methyl-4-oxochroman-2-yl)acetate (9h)

Prepared according to general procedure A from chromenone **9f** (50 mg, 0.25 mmol) and silyl ketene acetal **8b** (60 mg, 0.30 mmol) to afford an orange oil. The crude product was purified via flash column chromatography (silica gel, ethyl acetate/hexanes 1:9 as eluent) to give the title compound **9h** (12 mg, 16%) as a yellow oil, as a 3:2 mixture of keto/enol tautomers: R_f (hexanes/EtOAc 7:3): 0.42. IR: 2931, 1723, 1685, 1607, 1584, 1463, 1375, 1357, 1320, 1303, 1234, 1187, 1128, 1084, 917, 762 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (dt, J=2.1, 7.9 Hz, 1.4H), 7.53–7.45 (m, 3H), 7.04–6.98 (m, 1.4H), 6.95 (br d, J=8.6 Hz, 1.4H), 4.79 (s, 1H), 4.20–4.11 (m, 2.8H), 3.29* (d, J=15.3 Hz, 0.4H), 2.86* (d, J=15.3 Hz, 0.4H), 2.82 (d, J=3.4 Hz, 2H), 2.40 (s, 3H), 2.32* (s, 1.2H), 1.60 (s, 3H), 1.54* (s, 1.2H), 1.30–1.24 (m, 4.2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.4, 201.8*, 189.8, 187.9*, 169.8, 169.5*, 158.8*, 158.7, 137.0*, 136.6, 126.9*, 126.5, 121.3*, 121.3, 120.6, 118.9*, 118.5, 118.5*, 98.8*, 81.0, 79.8*, 64.1, 60.8, 60.8*, 43.2, 41.2*, 33.1, 31.9*, 23.9*, 21.2, 14.2, 14.1*. HRMS (ESI) calcd for $C_{16}H_{18}NaO_5$ $[MNa]^+$ 313.1046; found 313.1044. *=enol (minor) tautomer.

4.26. 2-(5-Oxo-2,5-dihydrofuran-2-yl)chroman-4-one (9i)

Prepared according to general procedure A from chromenone **7a** (100 mg, 0.68 mmol) and silyl enol ether **8c** (345 μL, 2.04 mmol) to afford a brown solid. The crude product was purified via flash column chromatography (silica gel, ethyl acetate/hexanes 3:7 as eluent) to give the title compound **9i** (121 mg, 77%) as a pale orange solid as a 3:2 mixture of diastereomers: mp 118 °C (dec). R_f (hexanes/EtOAc 1:1): 0.34. IR: 3085, 1751, 1606, 1464, 1305, 1092, 818, 767 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.86–7.83 (m, 1H), 7.71* (d, J=5.8 Hz, 0.4H), 7.61 (d, J=5.8 Hz, 1H), 7.53–7.47 (m, 1H), 7.08–6.93 (m, 2H), 6.32–6.29 (m, 1H), 5.31 (br s, 1H), 4.79 (dt, J=3.4, 13.4 Hz, 1H), 4.61* (dt, J=4.7, 12.4 Hz, 0.4H), 3.02–2.72 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.2, 189.9*, 171.83, 171.77*, 160.2, 160.1*, 152.1*, 152.0, 136.3*, 136.2, 126.83*, 126.77, 123.3, 123.1*, 122.0*, 121.9, 120.7*, 120.6, 117.68, 117.66*, 82.7*, 82.6, 76.7*, 75.4, 38.6, 38.4*. HRMS (ESI) calcd for $C_{13}H_{11}O_4$ $[MH]^+$ 231.0652; found 231.0653. *=minor diastereomer.

4.27. 5-(3-Acetyl-4-hydroxy-2*H*-chromen-2-yl)furan-2(5*H*)-one (9j)

Prepared according to general procedure A from chromenone **7e** (50 mg, 0.27 mmol) and silyl enol ether **8c** (435 μL, 0.81 mmol) to afford a brown solid. The crude product was purified via flash column chromatography (silica gel, ethyl acetate/hexanes 3:7 as eluent) to give the title compound **9j** (57 mg, 77%) as a dark yellow solid as a 77:23 mixture of diastereomers: mp 175–178 °C. R_f (hexanes/EtOAc 3:2): 0.23. IR: 3231, 1802, 1789, 1640, 1619, 1465, 1402, 949, 758 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.89–7.85 (m, 1H), 7.54–7.45 (m, 1H), 7.12–7.08 (m, 1H), 7.03–6.99 (m, 2H), 6.12–6.09 (m, 1H), 5.54 (d, J=6.1 Hz, 1H), 5.29 (d, J=5.9 Hz, 0.23H), 5.28–5.26 (m, 1H), 4.92–4.91* (m, 0.23H), 2.24 (s, 0.69H), 2.21 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3*, 189.1, 177.6, 175.9*, 171.7*, 171.4, 157.1*, 156.9, 152.3*, 151.0, 135.8, 135.7*, 126.4, 126.3*, 123.4, 123.4*, 123.0, 122.6*, 122.6, 121.7*, 117.2, 117.1*, 101.2*, 99.3, 84.0*, 83.8, 75.3, 72.1*, 22.5*, 22.1. HRMS (ESI) calcd for $C_{15}H_{12}NaO_5$ $[MNa]^+$ 295.0577; found 295.0575. *=minor diastereomer.

4.28. 5-Methoxy-2-(5-oxo-2,5-dihydrofuran-2-yl)chroman-4-one (9k)

Prepared according to general procedure A from chromenone **7b** (100 mg, 0.57 mmol) and silyl enol ether **8c** (290 μL, 1.71 mmol) to afford a brown solid. The crude product was purified via flash column chromatography (silica gel, ethyl acetate/hexanes 3:2 as eluent) to give the title compound **9k** (113 mg, 76%) as a pale orange solid as a 73:27 mixture of diastereomers: mp 134 °C (dec). R_f (hexanes/EtOAc 1:9): 0.54. IR: 3081, 2940, 1742, 1470, 1103, 1086, 827 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.66–7.56 (m, 1H), 7.42–7.36 (m, 1H), 6.60–6.53 (m, 2H), 6.32–6.30 (m, 1H), 5.27 (br s, 1H), 4.71 (dt, J=3.3, 13.3 Hz, 1H), 4.55* (dt, J=4.2, 12.9 Hz, 0.27H), 3.90 (s, 3H), 2.99–2.66 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9, 188.6*, 171.9, 171.8*, 161.8, 161.7*, 160.6, 160.6*, 152.0*, 151.8, 136.2*, 136.2, 123.6, 123.3*, 111.1*, 111.0, 109.8, 109.7*, 104.7*, 104.5, 82.7*, 82.5, 76.2*, 75.2, 56.1, 56.1*, 40.0, 39.9*. HRMS (ESI) calcd for $C_{14}H_{13}O_5$ $[MH]^+$ 261.0757; found 261.0758. *=minor diastereomer.

4.29. 2-Methyl-2-(5-oxo-2,5-dihydrofuran-2-yl)chroman-4-one (9l)

Prepared according to general procedure A from chromenone **7c** (100 mg, 0.62 mmol) and silyl enol ether **8c** (315 μL, 1.86 mmol) to afford a brown solid. The crude product was purified via flash column chromatography (silica gel, ethyl acetate/hexanes 2:3 as eluent) to give the title compound **9l** (14 mg, 9%) as an orange solid: mp 99–100 °C. R_f (hexanes/EtOAc 3:2): 0.36. IR: 3118, 2919, 1749, 1674, 1463, 1099, 891, 771 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J=1.7, 7.8 Hz, 1H), 7.61 (dd, J=1.5, 6.0 Hz, 1H), 7.54–7.50 (m, 1H), 7.07–7.03 (m, 1H), 6.98–6.96 (m, 1H), 6.31 (dd, J=2.0, 6.0 Hz, 1H), 5.21 (t, J=1.7 Hz, 1H), 3.03 (d, J=16.5 Hz, 1H), 2.80 (d, J=16.8 Hz, 1H), 1.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 171.8, 158.5, 152.3, 136.6, 126.7, 123.8, 121.8, 120.2, 118.0, 85.3, 80.8, 44.7, 19.1. HRMS (ESI) calcd for $C_{14}H_{12}NaO_4$ $[MNa]^+$ 267.0628; found 267.0616.

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Supplementary data

Copies of ^1H NMR and ^{13}C NMR spectra for **7a**–**h**, **9a**–**i**, and **11a**–**c** are provided. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.05.115.

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