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Cp*Ir(III)-Catalyzed C−H/O−H Functionalization of Salicylaldehydes for the Synthesis of Chromones at Room Temperature

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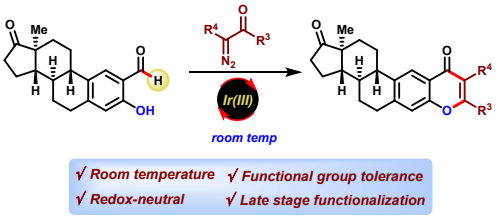


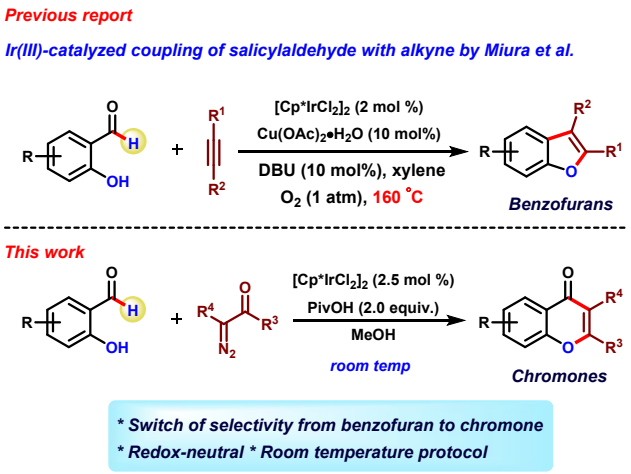
ABSTRACT: Herein we report Cp*Ir(III)-catalyzed C−H/O−H bond functionalization of salicylaldehydes with α-diazocarbonyl compounds for the synthesis of chromones under redox-neutral conditions. The reactions proceeds at room temperature and displays excellent functional group tolerance along with high yields of the corresponding products. The developed reaction protocol was successfully applied for the late stage functionalization of estrone derivative.

INTRODUCTION

In recent years, the area of mild C–H activation has gained significant importance; as it allows to carry out the reactions at or below room temperature and in the absence of any oxidant or reductant.[1] This results into the enhancement of the functional group tolerance of the reactions and ultimately it leads to the application in the late stage functionalization of complex biomolecules. Salicylaldehydes constitutes an important class of organic molecules wide range of applicability. They serve as an important precursor for the synthesis of salen ligands of Jacobsen's catalyst.[2] In recent years, aldehydic C(sp^2)−H bond functionalization has gained considerable attention.[3,4] The synthesis of various important organic scaffolds such as chromones, benzofurans, 3-coumaranones, chroman-4-

ones, homoisoflavonoids, and flavones have been reported starting from salicylaldehydes through hydroxy-directed aldehydic C–H functionalization.[5] Although, there are several reports on transition metal catalyzed C–H functionalization/annulation reactions of salicylaldehydes, there is only one report in the literature by Miura et al. using iridium catalytic system wherein, they have reported iridium(III)/copper(III) catalyzed decarbonylative coupling of salicylaldehydes with alkynes for the synthesis of benzofurans (Scheme 1).[5h] The major limitations of this protocol are the requirements of co-catalytic amounts of copper salt, oxygen as a external oxidant and very high temperature (165 °C) to perform the reaction. Therefore, we became interested to develop an Ir(III)-catalyzed C–H functionalization/annulation of salicylaldehydes under mild conditions, which can suppress the decarbonylation and switch the product selectivity from benzofurans to chromones. Chromones are oxygen containing heterocycles often encounters in biologically important natural products such flavones and isoflavones.[6] In order to achieve this goal, initially we envisioned that the coupling of salicylaldehydes with diazo compounds would be an ideal route.[7] However, very recently Huang et al. reported Rh(III)-catalyzed coupling between salicylaldehydes with α-diazomalonates for the synthesis of 4-hydroxycoumarins, wherein during optimization studies they have reported that, the Ir(III) catalytic system failed to produced the required product.[8]

Scheme 1. Ir(III)-Catalyzed C–H Functionalization/Annulation of Salicylaldehydes



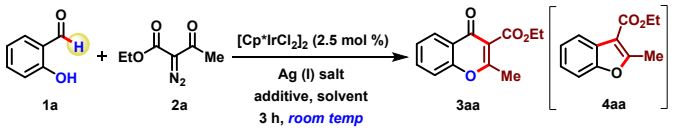
Therefore, the choice of the diazo compound would be crucial to in order to synthesize the chromones from salicylaldehydes under Ir(III) catalytic system. In continuation of our interest in the area of mild

C–H bond functionalization,[9] herein we report Cp*Ir(III)-catalyzed C–H/O–H functionalization of salicylaldehydes with α-diazocarbonyl compounds for the synthesis of chromones at room temperature.[10]

RESULTS AND DISCUSSION

Recently, we have successfully developed an iridium-catalyzed synthesis of 1,2-benzothaizines via C−H/N−H bond functionalization of sulfoximines with α-diazocarbonyl compounds,[9b] wherein during the optimization studies, ethyl diazoacetoacetate (**2a**) has been used as a coupling partner. Therefore, we have decided to use salicylaldehyde (**1a**) and ethyl diazoacetoacetate (**2a**) as a model substrates for optimization of the reaction parameters (Table 1).

Table 1. Optimization Study[a]



Entry	Ag(I) salt (10 mol %)	Additive (equiv.)	Solvent	Yield (%)[b] of **3aa**
1	$AgSbF_6$	-	MeOH	n.d.[c]
2	$AgSbF_6$	PivOH (1.0)	MeOH	n.d.[d]
3	-	PivOH (1.0)	MeOH	73
4	**-**	**PivOH (2.0)**	**MeOH**	**97**
5	-	AcOH (2.0)	MeOH	62
6	-	$AdCO_2H$ (2.0)	MeOH	77
7	-	$PhCO_2H$ (2.0)	MeOH	86
8	-	NaOAc (2.0)	MeOH	60
9	-	KOAc (2.0)	MeOH	62
10	-	PivOH (2.0)	1,4-Dioxane	80
11	-	PivOH (2.0)	1,2-DCE	62
12	-	PivOH (2.0)	THF	44
13	-	PivOH (2.0)	MeCN	71
14[e]	-	PivOH (2.0)	MeOH	70
15[f]	-	PivOH (2.0)	MeOH	n.d.
16[g]	-	PivOH (2.0)	MeOH	13
17[h]	-	PivOH (2.0)	MeOH	n.d.
18[i]	-	PivOH (2.0)	MeOH	n.d.

[a]Reaction conditions: **1a** (0.10 mmol), **2a** (0.12 mmol), $[Cp^*IrCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %) and additives in solvent (0.6 mL) at room temperature for 3 h. [b]Yields are based on crude ^1H NMR (internal

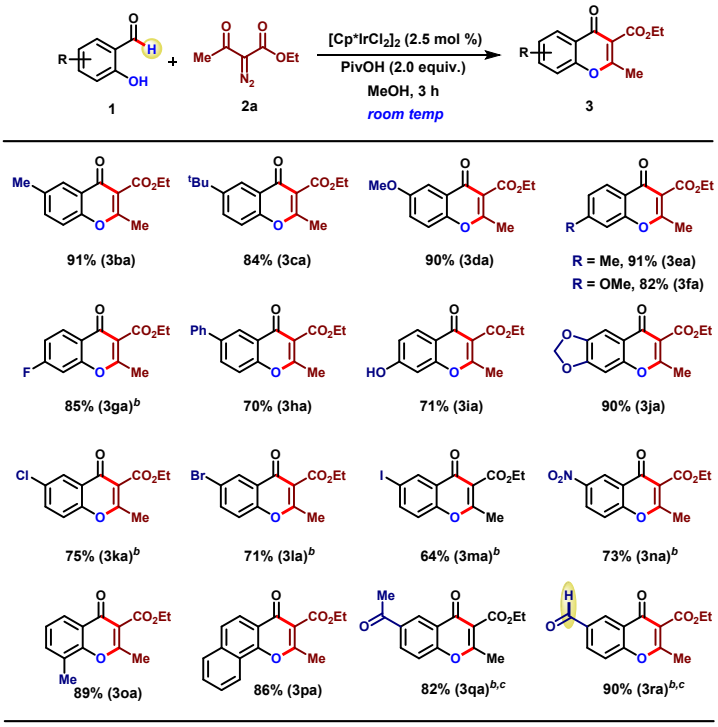
standard: 1,1,2,2 tetrachloroethane). [c]Formation of **4aa** was observed in 22% yield. [d]Formation of **4aa** was observed in 27% yield. [e]$[Cp^*IrCl_2]_2$ (1.0 mol %). [f]Without $[Cp^*IrCl_2]_2$. [g]Using $[Cp^*RhCl_2]_2$ (2.5 mol %). [h]Using $[Ru(p\text{-Cymene})Cl_2]_2$ (2.5 mol %). [i]Using $[Cp^*Co(CO)I_2]$ (5.0 mol %). n.d. = not detected. Room temperature refers to 25 °C.

At first, when salicylaldehyde **1a** was reacted with ethyl diazoacetoacetate (**2a**) in presence of $[Cp^*IrCl_2]_2/AgSbF_6$ in MeOH at room temperature, it resulted in the formation of benzofuran **4aa** in lower yield (entry 1). The addition of PivOH (1.0 equiv.) also did not change the outcome of the reaction (entry 2). To our surprise, when the reaction was performed using 1.0 equiv of PivOH in the absence of $AgSbF_6$, it resulted in the complete switch in the product selectivity from benzofuran (**4aa**) to chromone (**3aa**), wherein **3aa** was formed exclusively in 73% yield (entry 3). After screening the effect of different additives (entries 4-9), it was observed that the 2.0 equiv. of pivalic acid furnished the superior results giving quantitative yield of the product (entry 4). The use of other solvents such as 1,2-DCE, CH_3CN, 1,4-dioxane, and THF was not beneficial to further improve the yield of the reaction (entries 10-13). The yield of the product was dropped to 70% when catalyst loading was reduced to 1 mol% (entry 14). It is worth to mention that, although Lin and Yao et al. reported a similar reaction using $[Cp^*RhCl_2]_2$ catalyst,[5d] when we used Rh(III) catalytic system under the present condition at *room temperature*, it resulted in the sluggish reaction with the lower yield (13% yield) of required chromone **3aa** (entry 16). The use of other catalysts such as $[(p\text{-cymene})RuCl_2]_2$ and $[Cp^*Co(CO)I_2]$ did not furnish the required product (entries 17-18).

After optimizing the reaction parameters, next we investigated the scope and generality of the developed protocol using different salicylaldehydes with ethyl diazoacetoacetate (**2a**) as a representative coupling partner (Scheme 2). To our delight, salicylaldehydes having electron-donating substituents such as Me, ^{t}Bu, and OMe at C5 position and C4 position gave the corresponding products in high yields (**3ba**−**3fa**).The substrate with C5 phenyl group also furnish the chromone **3ha** in 70% yield. The substrate bearing electron-withdrawing fluoro substituent (**1g**) at C4 position furnished the corresponding product (**3ga**) in quantitative yield. The salicylaldehyde bearing free hydroxy group also well tolerated furnishing the chromone **3ia** in 71% yield. Ethyl 6-methyl-8-oxo-

8*H*-[1,3]dioxolo[4,5-g]chromene-7-carboxylate (**3ja**) was obtained starting from 6-hydroxybenzo[*d*][1,3]dioxole-5-carbaldehyde (**1j**) in 90% yield. The substrates having halogen functionality such as Cl, Br and I gave the corresponding products in high yield (**3ka**–**3ma**).

Scheme 2. Scope of Salicylaldehydes[a]



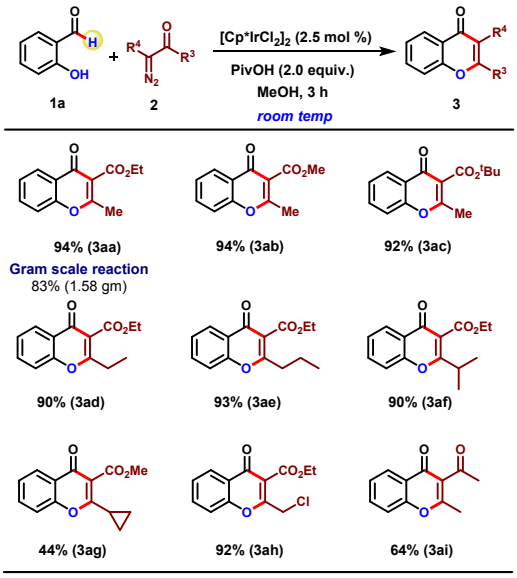
[a]Reaction conditions: **1** (0.40 mmol), **2a** (1.5 equiv.), $[Cp^*IrCl_2]_2$ (2.5 mol %) and PivOH (2.0 equiv.) in MeOH (2.5 mL) at room temperature for 3 h. [b]*t*-AmOH was used as a solvent. [c]Reaction carried out on 0.3 mmol scale. Isolated yields are given.

The salicylaldehyde containing electron-withdrawing NO_2 group at C5 position also participated in the reaction to furnish **3na** in 73% yield. The reaction was further employed to the substrate having *ortho*-methyl group which resulted in the 89% yield of **3oa**.Furthermore, when the reaction was performed on 1-hydroxy-2-naphthaldehyde (**1p**), it resulted in formation of required product (**3pa**) in good yield. The functional group tolerance of the current protocol was further demonstrated by using salicylaldehydes possessing keto and aldehyde functionalities which furnished the required chromones in excellent yields (**3qa**–**3ra**). It is quite interesting to note that, in case of 5-formyl salicylaldehyde (**1r**) the reaction selectively occurs at aldehydic C–H bond next to the hydroxy group,

and thus keep other formyl group intact and provides an opportunity for further manipulation of C5 formyl group.

Next, the scope and reactivity pattern of α-diazocarbonyl compounds was investigated using salicylaldehyde **1a** as a representative coupling partner (Scheme 3). The reaction worked well with diazo compounds having ethyl ester (**2a**), methyl ester (**2b**), and *tert*-butyl ester (**2c**) to give the chromones in excellent yields (**3aa**−**3ac**). The reaction worked well with α-diazocarbonyls having various substituents such as ethyl (**2d**), propyl (**2e**), isopropyl (**2f**), cyclopropyl (**2g**), and chloromethyl (**2h**), to furnish corresponding chromones in excellent yields (**3ad**−**3ah**). Diazo precursor obtained from pentane-2,4-dione also underwent coupling with salicylaldehyde to furnish the required product in moderate yield (**3ai**). The practicality of the current protocol was demonstrated by gram scale synthesis of the chromone **3aa;** wherein when 1.0 gm of **1a** was reacted under standard conditions, it furnished **3aa** in 83% yield (1.58 gm).

Scheme 3. Scope of α-diazocarbonyl compounds[a]

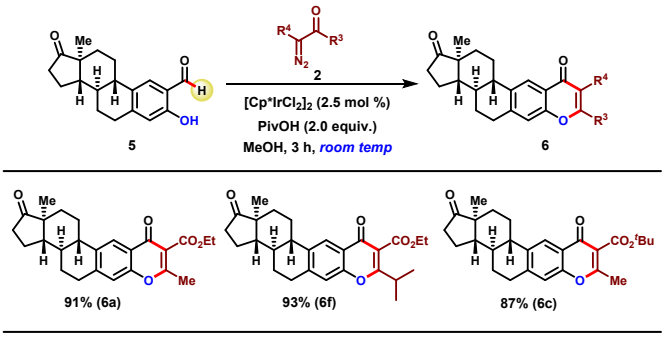


[a]Reaction conditions: **1a** (0.40 mmol), **2** (1.5 equiv.), $[Cp^*IrCl_2]_2$ (2.5 mol %) and PivOH (2.0 equiv.) in MeOH (2.5 mL) at room temperature for 3 h. Isolated yields are given.

Late stage functionalization has gain considerable attention in recent years, as it utilizes C–H bond of drug-like molecules for further diversification in order to generate new functionalized analogues.[11] Hence, we were interested check the applicability of the current protocol for the late stage

functionalization (Scheme 4). To our delight, estrone derivative **5** underwent C–H/O–H functionalization to furnish the required chromones in good yields (**6a, 6f and 6c**).

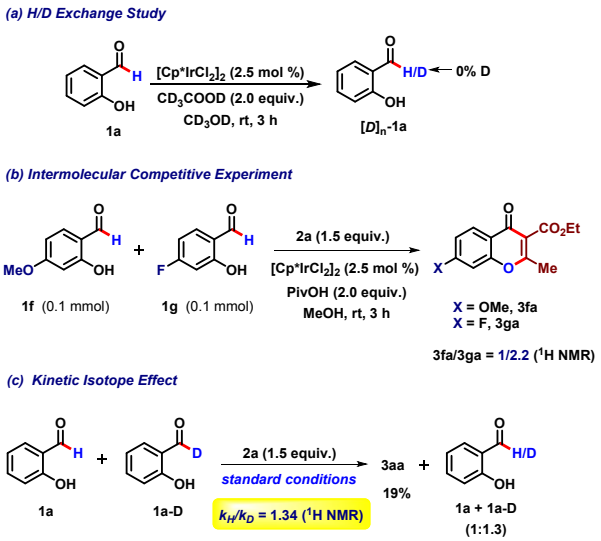
Scheme 4. Late Stage Functionalization of Estrone Derivative[a]



[a]Reaction conditions: **5** (0.20 mmol), **2** (1.5 equiv.), $[Cp^*IrCl_2]_2$ (2.5 mol %) and PivOH (2.0 equiv.) in MeOH (1.2 mL) at room temperature for 3 h. Isolated yields are given.

In order to elucidate the reaction mechanism, some preliminary experiments were conducted (Scheme 5).[12] At first, H/D exchange experiments of salicylaldehyde **1a** was carried out to check the reversibility of the C−H activation step. When **1a** was treated with 2.5 mol% of $[Cp^*IrCl_2]_2$ along with CD_3COOD (2.0 equiv.) in the absence of ethyl diazoacetoacetate (**2a**) in CD_3OD, it did not show any D incorporation at the aldehydic C–H bond (Scheme 5a), which indicates the irreversible nature of the C−H activation step.

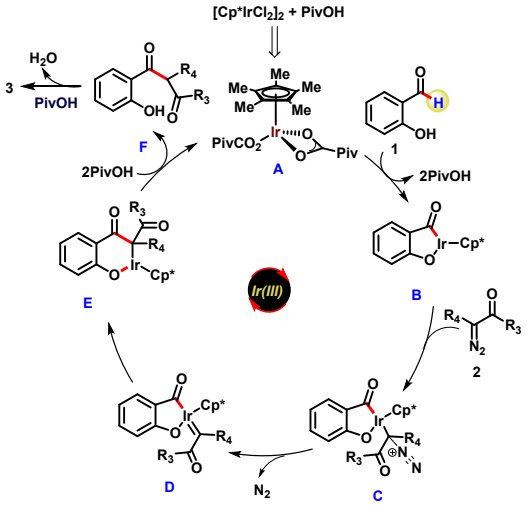
Scheme 5. Mechanistic Findings



The intermolecular competition experiment between salicylaldehydes having OMe and F substituents at C4 position revealed that substrate having F functionality reacts preferentially (Scheme 5b). In order to determine the kinetic isotope effect (KIE), the intermolecular competition experiment was carried out between equimolar quantities of **1a** and **1a-D**. The ^{1}H NMR analysis of the mixture of unreacted **1a** and **1a-D** gave k_H/k_D = 1.34 (Scheme 5c). Furthermore, parallel experiments were conducted using **1a** and **1a-D** which resulted in KIE of value k_H/k_D = 1.5 (see supporting information for details). These moderate values of KIE indicates that the C−H bond cleavage may be the turnover-determining step.

Based on our preliminary mechanistic studies and precedent literature,[10] the plausible mechanistic cycle is proposed in Scheme 6. At first $[Cp^*IrCl_2]_2$ reacts with PivOH to form catalytically active Ir(III) species **A**, which undergoes irreversible cyclometallation with **1** through hydroxy-directed aldehydic C–H bond activation to generate five-membered iridacycle **B**. Later on, diazo precursor **2** coordinates with **B** in order to generate diazonium species **C**,[7c] which undergoes loss of nitrogen to generates Ir(III)-carbene species **D**. Migratory insertion of the Ir-carbene **D** into the iridium−carbon bond provides the six membered iridacyclic intermediate **E** which on protonolysis with pivalic acid leads to the formation **F** and regenerates Ir(III) species **A**. Finally, the alkylated product **F** undergoes acid promoted cyclization followed by dehydration to generate required chromone **3**.

Scheme 6. Plausible Mechanism



CONCLUSION

In conclusion, we have developed Ir(III)-catalyzed C–H/O–H functionalization of salicylaldehyde with α-diazocarbonyl compounds for the synthesis of chromones. The salient features of the present protocol includes mild reaction conditions (room temperature), high yields of the products with excellent functional group tolerance. The reaction works under air atmosphere and doesn't require any special precaution to maintain the inert atmosphere, thus makes it very operationally simple and practical method. The mechanistic studies revealed that C−H activation step is irreversible and may be the rate-determining step. The synthetic utility of this protocol was demonstrated via late stage functionalization.

EXPERIMENTAL SECTION

General Remarks

Unless otherwise stated, all commercial reagents and solvents were used without additional purification. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F_{254} plates. Visualization on TLC was achieved by the use of UV light (254 nm). Column chromatography was undertaken on silica gel (100–200 mesh) using a proper eluent system. NMR spectra were recorded in chloroform-d at 300 or 400 MHz for ^{1}H NMR spectra and 75 MHz or 100 MHz for ^{13}C NMR spectra. Chemical shifts were quoted in parts per million (ppm) referenced to the appropriate solvent peak or 0.0 ppm for tetramethylsilane. The following abbreviations were used to describe peak splitting patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, td = triplet of doublet, m = multiplet. Coupling constants, *J*, were reported in hertz unit (Hz). For ^{13}C NMR chemical shifts were reported in ppm referenced to the center of a triplet at 77.0 ppm of chloroform-*d*. HRMS were recorded using ESI-TOF techniques. The substituted salicylaldehyde derivatives were prepared according to literature procedure.[13] The α-diazocarbonyl compounds were prepared according to the procedure described in the literature.[14]

General Procedure for Ir-Catalyzed C–H/O–H Functionalization of Salicylaldehydes for the Synthesis of Chromones.

To a screw capped seal tube vial with a Teflon stirbar were added salicylaldehyde **1** (0.40 mmol), diazo compound **2** (0.60 mmol, 1.2 equiv), $[Cp^*IrCl_2]_2$ (8.0 mg, 2.5 mol %), PivOH (81.6 mg, 2.0 equiv.), and MeOH (2.5 mL) under air atmosphere. The reaction mixture was stirred at room temperature for 3 h. Then the reaction mixture was diluted with CH_2Cl_2 (10 mL). The solvents were removed under reduced pressure and the residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc) to give the desired chromone derivatives.

Ethyl 2-methyl-4-oxo-4*H*-chromene-3-carboxylate (3aa).[10] White solid (87.0 mg, 94%); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.20 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.69 – 7.64 (m, 1H), 7.45 – 7.36 (m, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 2.52 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 174.3, 166.6, 165.1, 155.5, 133.9, 126.1, 125.5, 123.3, 118.1, 117.7, 61.7, 19.5, 14.2.

Gram Scale Synthesis of 3aa: To a screw capped seal tube vial with a Teflon stirbar were added salicylaldehyde **1a** (1.0 gm, 8.20 mmol), ethyl diazoacetoacetate **2a** (1.92 gm, 12.3 mmol, 1.5 equiv), $[Cp^*IrCl_2]_2$ (163 mg, 2.5 mol %), PivOH (1.67 gm, 2.0 equiv.), and MeOH (50 mL) under air atmosphere. The reaction mixture was stirred at room temperature for 3 h. Then solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc) to give the desired chromone **3aa** (1.58 gm, 83%).

Ethyl 2,6-dimethyl-4-oxo-4*H*-chromene-3-carboxylate (3ba).[5d] White solid (90.0 mg, 91%); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.97 (d, *J* = 0.9 Hz, 1H), 7.46 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 4.46 – 4.37 (m, 2H), 2.50 (s, 3H), 2.44 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 174.4, 166.4, 165.2, 153.8, 135.5, 135.1, 125.4, 123.0, 118.0, 117.4, 61.7, 20.9, 19.5, 14.2.

Ethyl 6-(*tert*-butyl)-2-methyl-4-oxo-4*H*-chromene-3-carboxylate (3ca).[10] Pale yellow solid (97.0 mg, 84%); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.19 (d, *J* = 2.4 Hz, 1H), 7.71 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.35 (d, *J* = 8.8 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 2.50 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.36 (s, 9H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 174.6, 166.4, 165.3, 153.7, 148.8, 131.7, 122.6, 121.8, 117.9, 117.2, 61.6, 34.8, 31.2, 19.4, 14.2.

Ethyl 6-methoxy-2-methyl-4-oxo-4*H*-chromene-3-carboxylate (3da).[10] White solid (94.0 mg, 90%); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.56 (d, *J* = 3.1 Hz, 1H), 7.35 (d, *J* = 9.1 Hz, 1H), 7.24 (dd, *J* = 9.1, 3.1 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 2.51 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 174.2, 166.3, 165.3, 157.1, 150.3, 123.9, 123.8, 119.1, 105.2, 61.6, 55.9, 19.4, 14.2.

Ethyl 2,7-dimethyl-4-oxo-4*H*-chromene-3-carboxylate (3ea).[5d] White solid (90.0 mg, 91%); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.07 (d, *J* = 8.4 Hz, 1H), 7.24 – 7.12 (m, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 2.49 (s, 3H), 2.47 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 174.3, 166.3, 165.23, 155.7, 145.3, 126.9, 125.8, 121.1, 118.0, 117.4, 61.7, 21.8, 19.4, 14.2.

Ethyl 7-methoxy-2-methyl-4-oxo-4*H*-chromene-3-carboxylate (3fa).[10] White solid (86.0 mg, 82%); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.10 (d, *J* = 8.9 Hz, 1H), 6.96 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.81 (d, *J* = 2.4 Hz, 1H), 4.41 (d, *J* = 7.1 Hz, 2H), 3.90 (s, 3H), 2.48 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 173.7, 166.0, 165.2, 164.2, 157.3, 127.5, 118.0, 117.1, 114.5, 100.1, 61.7, 55.8, 19.3, 14.2.

Ethyl 7-fluoro-2-methyl-4-oxo-4H-chromene-3-carboxylate (3ga). White solid (64.0 mg, 85%); m.p. 89– 91 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.21 (dd, *J* = 8.7, 6.3 Hz, 1H), 7.19 – 7.06 (m, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 2.51 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 173.3, 166.8, 165.62 (d, *J* = 255.7 Hz), 164.7, 156.38 (d, *J* = 13.3 Hz), 128.55 (d, *J* = 10.7 Hz), 120.1, 118.2, 114.19 (d, *J* = 22.7 Hz), 104.44 (d, *J* = 25.5 Hz), 61.8, 19.3, 14.1; **HRMS (ESI)** m/z calcd. for $C_{13}H_{11}FO_4Na$ $[M+H]^+$: 273.0539, found: 273.0542.

Ethyl 2-methyl-4-oxo-6-phenyl-4*H*-chromene-3-carboxylate (3ha).[5d] White solid (86.0 mg, 70%); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.40 (d, *J* = 2.2 Hz, 1H), 7.89 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.63 (d, *J* = 7.2 Hz, 2H), 7.54 – 7.42 (m, 3H), 7.41 – 7.31 (m, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 2.52 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 174.3, 166.6, 165.0, 154.9, 139.0, 138.6, 132.7, 128.9, 127.9, 127.1, 123.8, 123.4, 118.2, 118.1, 61.7, 19.5, 14.2.

Ethyl 7-hydroxy-2-methyl-4-oxo-4*H*-chromene-3-carboxylate (3ia). Light brown solid (70.0 mg, 71%); m.p. 184– 186 °C; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.47 (brs, 1H), 8.04 (d, *J* = 8.8 Hz, 1H), 7.01 (dd, *J* = 8.8, 2.2 Hz, 1H), 6.89 (d, *J* = 2.2 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 2.50 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H); **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 174.7, 167.1, 165.3, 162.6, 157.5, 127.7, 117.5, 116.3, 115.8, 102.9, 61.9, 19.5, 14.1; **HRMS (ESI)** m/z calcd. for $C_{13}H_{13}O_5$ $[M+H]^+$: 249.0763, found: 249.0759.

Ethyl 6-methyl-8-oxo-8*H*-[1,3]dioxolo[4,5-*g*]chromene-7-carboxylate (3ja).[5d] White solid (99.0 mg, 90%); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.49 (s, 1H), 6.81 (s, 1H), 6.10 (s, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 2.47 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 173.3, 165.6, 165.2, 152.9, 152.8, 146.3, 118.3, 117.5, 102.6, 102.5, 97.7, 61.7, 19.2, 14.2.

Ethyl 6-chloro-2-methyl-4-oxo-4*H*-chromene-3-carboxylate (3ka).[10] Light yellow solid (77.0 mg, 75%); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.15 (d, *J* = 2.6 Hz, 1H), 7.61 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.39 (d, *J* = 8.9 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 2.52 (s, 3H), 1.39 (d, *J* = 7.1 Hz, 3H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 173.1, 166.9, 164.7, 153.8, 134.2, 131.5, 125.5, 124.3, 119.5, 118.1, 61.9, 19.5, 14.2.

Ethyl 6-bromo-2-methyl-4-oxo-4*H*-chromene-3-carboxylate (3la).[5d] White solid (88.0 mg, 71%); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.31 (d, *J* = 2.4 Hz, 1H), 7.75 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.32 (d, *J* = 8.9 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 2.51 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 173.0, 166.9, 164.7, 154.3, 136.9, 128.7, 124.7, 119.7, 119.0, 118.2, 61.9, 19.5, 14.2.

Ethyl 6-iodo-2-methyl-4-oxo-4*H*-chromene-3-carboxylate (3ma).[10] White solid (92.0 mg, 64%); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.50 (d, *J* = 2.1 Hz, 1H), 7.92 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.19 (d, *J* = 8.8 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 2.51 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H); **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 172.8, 166.9, 164.6, 155.0, 142.5, 134.9, 124.9, 119.8, 118.3, 89.4, 61.9, 19.5, 14.2.

Ethyl 2-methyl-6-nitro-4-oxo-4*H*-chromene-3-carboxylate (3na).[5d] White solid (81.0 mg, 73%); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.04 (d, *J* = 2.8 Hz, 1H), 8.51 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.61 (d, *J* = 9.2 Hz, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 2.57 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$,)** 172.7, 167.4, 164.0, 158.2, 144.9, 128.3, 123.5, 122.7, 119.6, 118.6, 62.1, 19.4, 14.1.

Ethyl 2,8-dimethyl-4-oxo-4*H*-chromene-3-carboxylate (3oa).[5d] White solid (88.0 mg, 89%); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.03 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 7.3 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 2.54 (s, 3H), 2.46 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H); **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 174.6, 166.2, 165.2, 154.0, 134.8, 127.0, 124.9, 123.6, 123.2, 117.9, 61.6, 19.4, 15.4, 14.2.

Ethyl 2-methyl-4-oxo-4*H*-benzo[*h*]chromene-3-carboxylate (3pa).[10] White solid (97.0 mg, 86%); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.38 (d, *J* = 8.1 Hz, 1H), 8.08 (d, *J* = 8.7 Hz, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.73 – 7.60 (m, 3H), 4.45 (q, *J* = 7.1 Hz, 2H), 2.62 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 174.1, 165.5, 165.0, 152.8, 135.8, 129.3, 128.0, 127.1, 125.4, 123.3, 121.9, 120.7, 119.6, 119.7, 61.71, 19.3, 14.2.

Ethyl 6-acetyl-2-methyl-4-oxo-4*H*-chromene-3-carboxylate (3qa). White solid (68.0 mg, 82%); m.p. 134– 136 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.73 (d, *J* = 2.2 Hz, 1H), 8.30 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 2.69 (s, 3H), 2.55 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 196.2, 173.8, 167.0, 164.5, 158.0, 134.2, 133.0, 127.4, 122.8, 118.5, 61.9, 26.6, 19.4, 14.1 (one carbon is missing because of overlap); **HRMS (ESI)** m/z calcd. for $C_{15}H_{15}O_5$ $[M+H]^+$: 275.0919, found 275.0919.

Ethyl 6-formyl-2-methyl-4-oxo-4*H*-chromene-3-carboxylate (**3ra).** White solid (70.0 mg, 90%); m.p. 126– 128 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 10.10 (s, 1H), 8.67 (d, *J* = 2.0 Hz, 1H), 8.22 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 2.56 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 190.2, 173.4, 167.1, 164.3, 158.7, 133.5, 132.2, 130.7, 123.5, 119.2, 118.7, 62.0, 19.4, 14.1; **HRMS (ESI)** m/z calcd. for $C_{14}H_{14}O_5$ $[M+H]^+$: 261.0763, found: 261.0765.

Methyl 2-methyl-4-oxo-4*H*-chromene-3-carboxylate (3ab).[10] Yellow solid (82.0 mg, 94%); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.19 (d, *J* = 7.9 Hz, 1H), 7.67 (t, *J* = 7.8 Hz, 1H), 7.46 – 7.37 (m, 2H), 3.94 (s, 3H), 2.52 (s, 3H); **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 174.2, 167.2, 165.5, 155.4, 133.9, 126.0, 125.5, 123.2, 117.6, 52.6, 19.6.

***tert*-Butyl 2-methyl-4-oxo-4*H*-chromene-3-carboxylate (3ac).**[5d] White solid (96.0 mg, 92%); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.18 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.68 – 7.60 (m, 1H), 7.43 – 7.33 (m, 2H), 2.48 (s, 3H), 1.61 (s, 9H); **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 174.4, 165.1, 164.2, 155.6, 133.7, 125.9, 125.2, 123.4, 119.6, 117.6, 82.7, 28.1, 19.1.

Ethyl 2-ethyl-4-oxo-4*H*-chromene-3-carboxylate (3ad).[5d] Yellow gummy solid; (88.0 mg, 90%); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.20 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.67 (ddd, *J* = 8.6, 7.2, 1.6 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.42 – 7.36 (m, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 2.78 (q, *J* = 7.6 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.37 (t, *J* = 7.6 Hz, 3H); **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 174.6, 170.2, 165.0, 155.6, 133.9, 126.0, 125.4, 123.3, 117.9, 117.5, 61.67, 26.63, 14.1, 11.6.

Ethyl 4-oxo-2-propyl-4*H*-chromene-3-carboxylate (3ae).[5d] White solid (97.0 mg, 93%); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.20 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.67 (ddd, *J* = 8.6, 7.2, 1.6 Hz, 1H), 7.49 – 7.34 (m, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 2.73 (t, *J* = 7.5 Hz, 2H), 1.96 – 1.72 (m, 2H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.04 (t, *J* = 7.4 Hz, 3H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 174.5, 169.1, 165.0, 155.6, 133.9, 125.9, 125.3, 123.2, 118.2, 117.7, 61.6, 34.8, 20.8, 14.1, 13.6.

Ethyl 2-isopropyl-4-oxo-4*H*-chromene-3-carboxylate (3af). Pale yellow solid (94.0 mg, 90%); m.p.58– 60 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.20 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.71 – 7.63 (m, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.43 – 7.36 (m, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 3.14 (hept, *J* = 6.8 Hz, 1H), 1.42 – 1.35 (m, 9H); **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 174.8, 172.0, 165.0, 155.6, 133.8, 125.9, 125.3, 123.3, 117.7, 116.9, 61.7, 32.2, 19.8, 14.1; **HRMS (ESI)** m/z calcd. for $C_{15}H_{17}O_4$ $[M+H]^+$: 261.1127, found: 261.1124.

Methyl 2-cyclopropyl-4-oxo-4*H*-chromene-3-carboxylate (3ag). White solid (43.0 mg, 44%); m.p. 151– 153 °C; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.19 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.63 (ddd, *J* = 8.7, 7.2, 1.7 Hz, 1H), 7.41 – 7.35 (m, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 3.97 (s, 3H), 2.35 – 2.26 (m, 1H), 1.39 – 1.33 (m, 2H), 1.21 – 1.13 (m, 2H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 173.9, 170.0, 166.0, 154.9, 133.8, 126.2, 125.4, 123.4, 117.3, 117.0, 52.7, 13.1, 9.7; **HRMS (ESI)** m/z calcd. for $C_{14}H_{13}O_4$ $[M+H]^+$: 245.0814, found: 245.0813.

Ethyl 2-(chloromethyl)-4-oxo-4*H*-chromene-3-carboxylate (3ah).[5d] Yellow solid (98.0 mg, 92%); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.20 (d, *J* = 8.0 Hz, 1H), 7.77 – 7.67 (m, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 4.63 (s, 2H), 4.45 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 174.2, 163.8, 162.5, 155.4, 134.6, 126.1, 126.0, 123.4, 118.5, 118.0, 62.2, 39.8, 14.1.

3-Acetyl-2-methyl-4*H*-chromen-4-one (3ai).[10] White solid (52.0 mg, 64%); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.21 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.73 – 7.61 (m, 1H), 7.47 – 7.38 (m, 2H), 2.65 (s, 3H), 2.53 (s, 3H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 200.5, 175.9, 168.7, 155.4, 134.1, 125.9, 125.6, 123.8, 123.7, 117.7, 32.2, 19.9.

Ethyl (3a*S*,3b*R*,11b*S*,13aS)-8,13a-dimethyl-1,10-dioxo-1,2,3,3a,3b,4,5,10,11b,12,13,13a-dodecahydrocyclopenta[5,6]naphtho[1,2-*g*]chromene-9-carboxylate (6a).[5d] White solid (74.0 mg, 91%); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.06 (s, 1H), 7.14 (s, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 3.18 – 2.93 (m, 2H), 2.60 – 2.49 (m, 2H), 2.48 (s, 3H), 2.39 – 2.26 (m, 1H), 2.23 – 1.95 (m, 4H), 1.71 – 1.45 (m, 6H),

1.40 (t, *J* = 7.1 Hz, 3H), 0.92 (s, 3H); **$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$)** δ 220.3, 174.3, 166.2, 165.3, 153.7, 144.4, 138.2, 122.2, 120.9, 117.7, 116.8, 61.6, 50.4, 47.8, 43.9, 37.7, 35.7, 31.3, 29.6, 25.9, 25.6, 21.5, 19.4, 14.1, 13.7.

Ethyl (3a*S*,3b*R*,11b*S*,13a*S*)-8-isopropyl-13a-methyl-1,10-dioxo-1,2,3,3a,3b,4,5,10,11b,12,13, 13a-dodecahydrocyclopenta[5,6]naphtho[1,2-*g*]chromene-9-carboxylate (6f). White solid (81.0 mg, 93%); m.p. 176– 178 °C; **^1H NMR (400 MHz, $CDCl_3$)** δ 8.07 (s, 1H), 7.19 (s, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 3.24 – 2.95 (m, 3H), 2.63 – 2.43 (m, 2H), 2.40 – 2.26 (m, 1H), 2.22 – 1.93 (m, 4H), 1.74 – 1.43 (m, 6H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.35 (d, *J* = 3.2 Hz, 3H), 1.33 (d, *J* = 3.2 Hz, 3H); **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$)** δ 220.3, 174.8, 171.6, 165.3, 153.9, 144.3, 138.1, 122.1, 121.0, 116.9, 116.6, 61.6, 50.4, 47.8, 44.0, 37.8, 35.7, 32.1, 31.3, 29.6, 25.9, 25.6, 21.5, 19.8, 14.1, 13.7; **HRMS (ESI)** m/z calcd. for $C_{27}H_{33}O_5$ $[M+H]^+$: 437.2328, found: 437.2335.

***tert*-Butyl (3a*S*,3b*R*,11b*S*,13a*S*)-8,13a-dimethyl-1,10-dioxo-1,2,3,3a,3b,4,5,10,11b,12,13,13a-dodecahydrocyclopenta[5,6]naphtho[1,2-*g*]chromene-9-carboxylate (6c).** White solid (76.0 mg, 87%); m.p. 163– 165 °C; **^1H NMR (400 MHz, $CDCl_3$)** δ 8.05 (s, 1H), 7.12 (s, 1H), 3.11 – 2.91 (m, 2H), 2.61 – 2.47 (m, 2H), 2.45 (s, 3H), 2.37 – 2.26 (m, 1H), 2.23 – 1.95 (m, 4H), 1.69 – 1.43 (m, 6H),1.62 (s, 9H) 0.91 (s, 3H); **$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$)** δ 220.3, 174.4, 164.8, 164.5, 153.8, 144.1, 138.0, 122.1, 121.1, 119.2, 116.8, 82.5, 50.4, 47.8, 43.9, 37.7, 35.7, 31.3, 29.6, 28.1, 26.0, 25.6, 21.5, 19.1, 13.7; **HRMS (ESI)** m/z calcd. for $C_{27}H_{32}O_5Na$ $[M+Na]^+$: 459.2147, found: 459.2158.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at http://pubs.acs.org.

Details of mechanistic studies including the isotope labeling experiments (H/D exchange and KIE), competitive experiment and characterization data for all synthesized chromone derivatives including ^1H and ^{13}C NMR spectra

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NOTES

The authors declare no competing financial interest.

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