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Intramolecular Direct Arylation of 3-Halo-2-pyrones and 2-Coumarins

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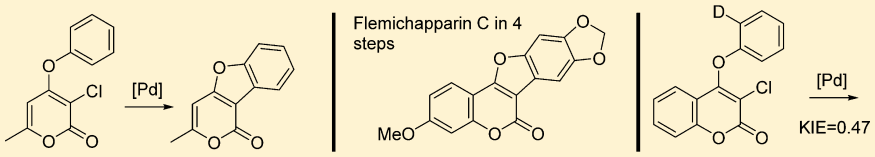
Supporting Information



ABSTRACT: Direct arylation represents a favorable alternative to traditional cross-coupling and has found widespread use with simple aryls and robust heterocycles. Herein a direct arylation protocol has been optimized and applied to 2-pyrones, which are delicate and privileged biological motifs. Regioselective halogenation at the 3-position allows intramolecular coupling by activation of a pyrone C−Br or C−Cl bond and a phenoxy C−H bond. Importantly, electron-poor phenoxy substrates also worked well. The methodology was extended to 2-coumarins and applied to the synthesis of flemichapparin C and a novel analogue. Deuterium isotope effects, typical of a concerted metalation−deprotonation (CMD) mechanism, were observed in the case of a bromopyrone, but a highly unusual, inverse kinetic isotope effect was evident using a chlorocoumarin, implying that a different mechanism is operating.

INTRODUCTION

The formation of aryl−heteroaryl (Ar−HetAr) bonds is an important transformation in organic synthesis[1] due to the abundance of the Ar−HetAr moiety in natural products and pharmaceuticals.[2] The most widely used methods for its formation involve Suzuki−Miyaura,[3] Stille,[4] Negishi,[5] and similar reactions.[6] More recently the development of direct arylation protocols which involve at least one C−H activation event has emerged and offers a number of advantages over traditional cross-coupling.[7] The 2-pyrone substrate, specifically 4-hydroxy-based 2-pyrones,[8] represents a privileged biological scaffold with broad spectrum biological activity,[8,9] spanning cytotoxic, antibiotic, and antifungal activity. For example, radicinin (Figure 1) demonstrates inhibitory activity toward the growth of some Gram-positive bacteria.[10] Other appropriate examples include *neo*-tanshinlactone analogues which display antibreast cancer activity.[11] Additionally, 2-pyrones are a promising class of biorenewable platform chemicals that provide access to an array of chemical products and intermediates.[12] Finally, the 2-pyrone moiety displays reactivity reminiscent of that of aromatic compounds,[13] dienes,[14] and enones,[15] and its framework can ring-open under some cross-coupling conditions,[16] thus bestowing 2-pyrones with challenging and rewarding properties. The related 2-coumarins (especially 4-hydroxy variants) display a similarly remarkable biological profile.[17,18] The coumestan subgroup exhibits impressive biological activities,[19] and thus a number of novel synthetic methods have been developed for constructing the coumestan and related ring systems.[19a,c,20]

The intramolecular direct arylation of 2-pyrones involving the formation of five-membered[21] (Scheme 1) and six-membered rings[22] (not shown) has been reported. In these cases coupling occurred between a C−H on the pyrone/coumarin and a C−X on the phenoxy/benzyloxy moiety, which presumably occurs via trouble-free oxidative addition to the phenyl halide followed by C−H activation of the pyrone. The

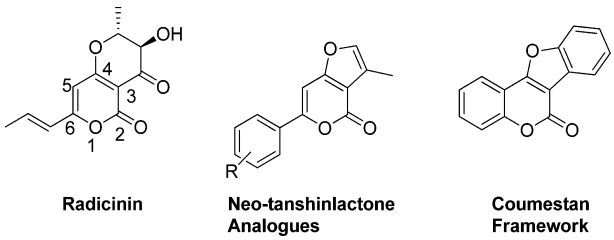


Figure 1. Biologically active examples of 4-alkoxy-2-pyrone and 2-coumarin.

Scheme 1. Previous Studies and This Work

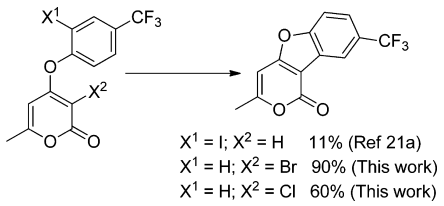


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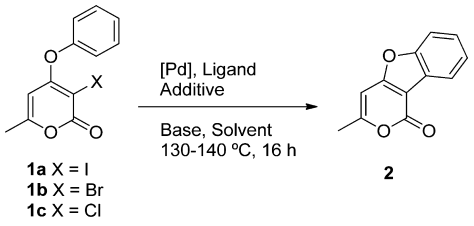
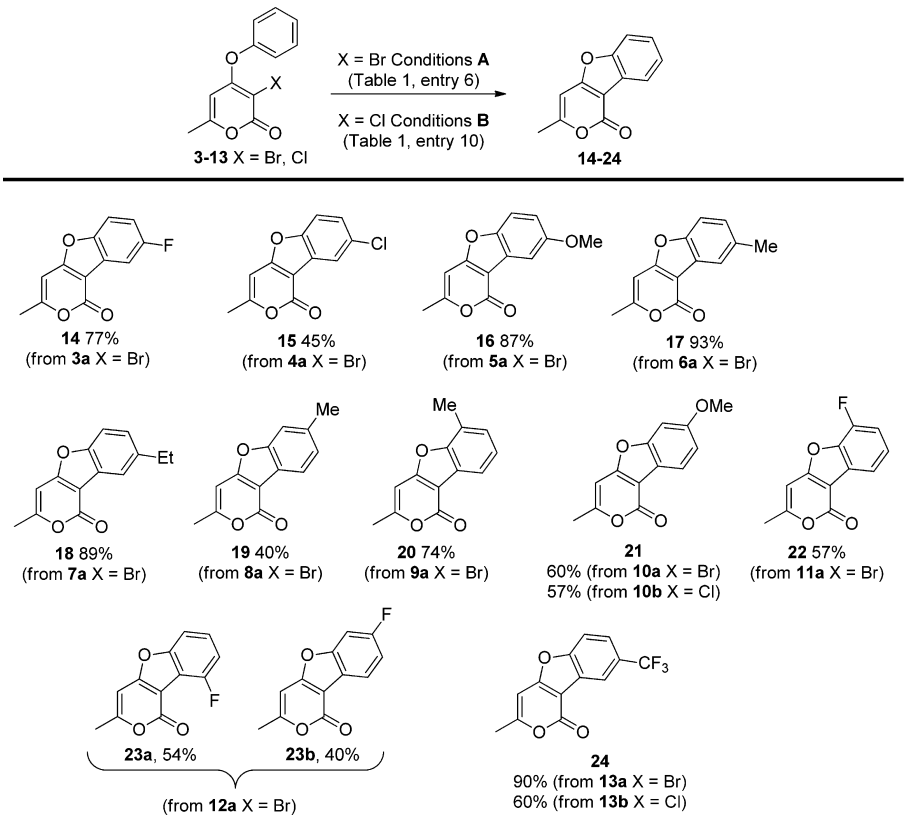
Table 1. General Procedure for Intramolecular Direct Arylation Reaction of Pyrone 1 to 2



entry	X	Pd (mol %)	ligand (mol %)	base (equiv)	solvent	additive (equiv)	conversn (%)	yield (%)
1	I	Pd_2dba_3 (5.0)	PPh_3 (10)	Na_2CO_3 (3.0)	NMP		0	
2	I	$Pd(OAc)_2$ (5.0)	$PCy_3{\cdot}HBF_4$ (10)	K_2CO_3 (2.0)	DMA		0	
3	Br	$Pd(OAc)_2$ (5.0)	$PCy_3{\cdot}HBF_4$ (10)	K_2CO_3 (2.0)	DMA		43	
4	Br	$Pd(OAc)_2$ (5.0)	PPh_3 (5.0)	K_2CO_3 (3.0)	DMA	PivOH (0.3)	53	
5	Br	$Pd(OAc)_2$ (2.0)	SPhos (4.0)	K_2CO_3 (2.0)	xylene		25	
6	**Br**	**$Pd(OAc)_2$ (5.0)**	**PPh_3 (15)**	**K_2CO_3 (2.0)**	**xylene**		**100**	**80**
7	**Br**	**$Pd(OAc)_2$ (5.0)**	**PPh_3 (15)**	**K_2CO_3 (3.0)**	**xylene**	**PivOH (0.3)**	**100**	**88**
8	Cl	$Pd(OAc)_2$ (5.0)	PPh_3 (15)	K_2CO_3 (3.0)	xylene		40	
9	Cl	$Pd(OAc)_2$ (5.0)	PPh_3 (15)	K_2CO_3 (3.0)	xylene	PivOH (0.3)	12	
10	Cl	$Pd(OAc)_2$ (5.0)	$PCy_3{\cdot}HBF_4$ (15)	Cs_2CO_3 (1.1)	xylene		100	63
11	**Cl**	**$Pd(OAc)_2$ (5.0)**	**$PCy_3{\cdot}HBF_4$ (15)**	**K_2CO_3 (3.0)**	**xylene**		**100**	**79**

Scheme 2. Effect of Substituents on Phenoxy Group



C3−H site of such compounds is known to be acidic,[21a] and thus base-assisted proton removal is probably facile.

A more challenging approach would be to locate the halide on the pyrone and develop a methodology to activate the C−H bond of the phenoxy-based coupling partner.[23] This should (1) facilitate complete regioselectivity (pyrone-C3 vs -C5 arylation),[24] (2) avoid the use of a halogenated site on the phenoxy coupling partner, thus providing easier access to di- and trisubstituted products via cheaper substituted phenols, and (3) improve yields when using electron-poor phenoxy coupling partners, by invoking a mechanism involving C−H cleavage of an electron-poor substrate.[25] The last point has proven to be a limitation of previous studies[21a] (see Scheme 1).

RESULTS AND DISCUSSION

We initially prepared the 4-phenoxy-3-iodopyrone **1a** via iodination of the phenoxy pyrone in a completely regioselective manner (only iodination at C-3).[26] A variety of conditions were tried, but disappointingly no cyclization was observed and only starting material and significant amounts of dehalogenated

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product were isolated (Table 1, entries 1 and 2). Surprised by these results, we then tested the corresponding bromides (entries 3–7). A direct comparison of the iodo and bromo substrates (entries 2 and 3) showed that only the latter afforded product. Optimized conditions involved $Pd(OAc)_2$, PPh_3, and K_2CO_3 in xylenes. The addition of pivalic acid[27] improved the yield from 80 (entry 6) to 88% (entry 7). However, the increase in yield was not considered sufficient to warrant inclusion of 30 mol % of PivOH going forward. We then challenged our optimized conditions by using chlorinated pyrone **1c** as a substrate, which was easily and regioselectively prepared by chlorination of the parent pyrone. The reaction proved sluggish (entries 8 and 9) using the previously optimized conditions. However, changing the ligand to a bulkier variant[28] facilitated complete conversion of starting material in both Cs_2CO_3 (entry 10) and K_2CO_3 (entry 11) in good isolated yields.

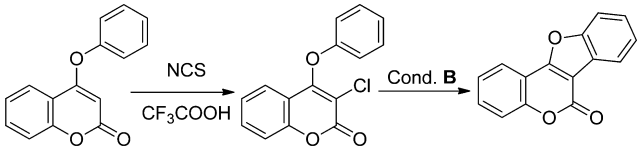
The reaction worked well with a number of electron-rich substrates (Scheme 2, **5**–**10** to **16**–**21**). It also displayed some regioselectivity (**10a** was converted to **21** in 60% yield) and substrate tolerance (see chloro analogue **15**).

To our delight, electron-poor phenoxy substrates worked very well (Scheme 2, forming **14**, **15**, and **22**–**24**). Cyclized product **24** was isolated in excellent yields of 90% and 60% using the bromide and chloride substrates **13a,b**, respectively, in sharp contrast to previous studies[21a] (Scheme 1).

We then turned our attention to the important coumarin class. Surprisingly, bromination of coumarin **25** failed under the conditions which had previously worked for the 2-pyrones. A diverse set of bromination conditions such as Br_2, NBS, NBS/TBAB, and NBS/CF_3COOH also failed to give any bromination. Bromination of the parent 4-*hydroxy*-coumarin did occur using Br_2/TBAB (72%, Supporting Information), but the subsequent conditions tested to install the phenyl group (e.g., $PhB(OH)_2$, $Cu(OAc)_2$, Et_3N)[29] failed.

We then attempted to chlorinate the 3-position. Using NCS and CF_3COOH, this reaction proceeded smoothly, giving the chlorocoumarin **26** in 67% yield (Scheme 3). Subsequent intramolecular direct arylation proceeded very well in 90% yield.

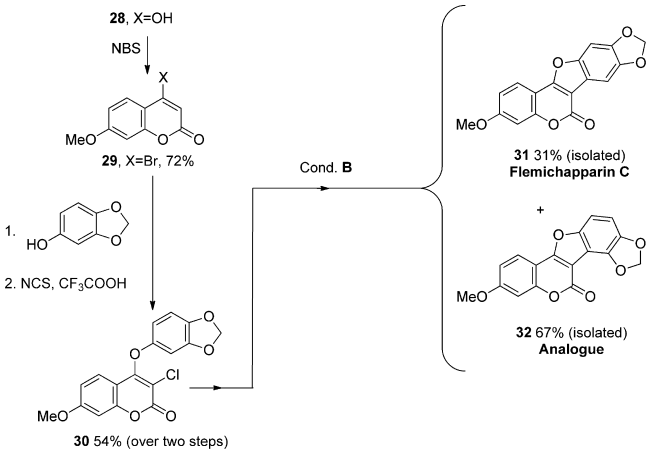
Scheme 3. Cyclization of the Coumarin Variant



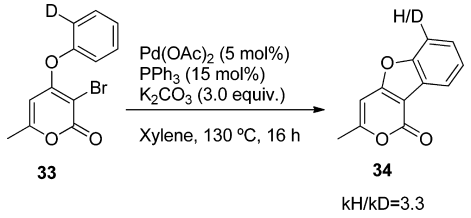
This good yield prompted us to attempt to access the coumestan group of natural products.[19] Commercially available 4-hydroxy-2-coumarin **28** (Scheme 4) was brominated at the 4-position in good yield (**29**; 72%), coupled with sesamol and chlorinated (**30**; 54% over two steps). Intramolecular arylation occurred to form flemichapparin C (**31**) and its regioisomer (**32**) (in 98% overall yield), which were easily separated using silica gel chromatography. This represents a rapid four-step route to these compounds, in comparison to more complex chemical[30] or enzyme-mediated routes.[31]

We then turned our attention to the mechanism. An intramolecular kinetic isotope effect (KIE) experiment was undertaken with pyrone **33** (Scheme 5). A KIE of 3.3 (average

Scheme 4. Synthesis of Flemichapparin C (31) and 32



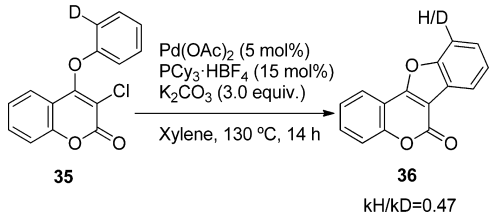
Scheme 5. Intramolecular Deuterium Isotope Studies in the Pyrone System



of two runs) was observed, which represents a kinetically significant C–H activation event (although not necessarily a rate-determining C–H activation step[32]), typical of a CMD/AMLA mechanism, as reported in the literature.[33]

Next we applied the same protocol to chlorocoumarin **35**. An intramolecular KIE experiment revealed a remarkable KIE value of 0.47 (average of two runs) (Scheme 6), indicating that an entirely different mechanism is at play with chlorocoumarin **35** in comparison to that for bromopyrone **33**, at least under the conditions used.

Scheme 6. Intramolecular Deuterium Isotope Studies in the Coumarin System



The absence of a large, positive KIE in this experiment rules out a CMD/AMLA mechanism. At this stage we considered a number of mechanistic scenarios which would result in a significant inverse KIE. The most likely scenario involves reversible Pd insertion into the C–H bond followed by a kinetically significant subsequent step: e.g., slow oxidative addition into the coumarin–Cl bond (possibly invoking Pd(II)/Pd(IV))[34] (Scheme 7). Alternatively oxidative addition into the coumarin–Cl bond occurs first. In either case, a reversible C–H activation will result in the buildup of the more stable Pd–D species (in comparison to Pd–H).[35] A slow subsequent step would then result in more product arising from

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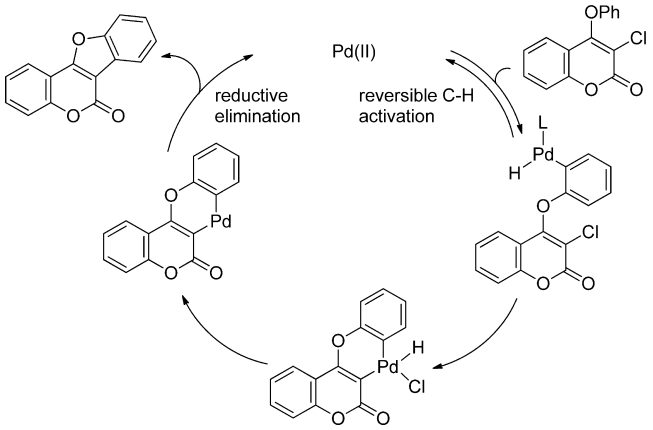
Scheme 7. Plausible Mechanistic Cycle for the Chlorocoumarin System



the greater amount of Pd−D intermediate. Other mechanistic routes involving an electrophilic aromatic process[36] were considered less likely, as inverse KIEs associated with this mechanism are secondary and thus of lower magnitude. Finally, observation of an inverse KIE arising from a faster reductive elimination or β-elimination[37] is also considered unlikely. First, the presence of only one D atom[37] would not affect the electron density on palladium sufficiently, and in any case we consider it unlikely that either reductive elimination or β-elimination would be the rate-determining step.

CONCLUSION

In conclusion, we report intramolecular direct arylation of brominated and chlorinated pyrones. Yields are very good, and importantly, electron-withdrawing substituents on the phenoxy ring are tolerated. The analogous 2-coumarin works well, facilitating access to flemichapparin C and an analogue in four steps. Deuterium isotope experiments show a large, positive KIE for a bromopyrone typical of a CMD/AMLA mechanism, whereas an unusually large inverse kinetic isotope effect is observed for a chlorocoumarin, indicating that a different mechanism is at play.

EXPERIMENTAL SECTION

Melting point determinations were performed by the open capillary method and are reported uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 25 °C in $CDCl_3$ at 300 and 75.5 MHz with a spectrometer unless otherwise specified, with TMS as the internal standard. Chemical shifts (δ_H, δ_C, and δ_F) were expressed as parts per million (ppm), positive shifts being downfield from TMS; coupling constants (J) are expressed in hertz (Hz). High-resolution mass spectra (HRMS) were obtained on a TOF MS instrument with an ESI source. High-resolution mass spectra were recorded only for new compounds. Literature citations are provided for known compounds, along with representative characterization data. IR spectra were recorded on an FT-IR spectrometer as a thin film (liquid samples) or applied as a solution in chloroform, and the chloroform was allowed to evaporate (solid samples). Column chromatography was carried out using 60 Å (35−70 μm) silica.

4-Bromo-6-methyl-2-pyrone.[38] A solution of 4-hydroxy-6-methyl-2-pyrone (5.00 g, 39.7 mmol), TBAB (14.80 g, 46.0 mmol), and P_2O_5 (13.5 g, 95.2 mmol) in toluene (4.0 mL/mmol starting material) was stirred at 94 °C for 1.5 h. Upon cooling, the reaction mixture was washed with toluene (2 × 30 mL). The combined organic extracts were then washed with saturated aqueous $NaHCO_3$ (2 × 20 mL) and H_2O (2 × 20 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product, 4-bromo-6-methyl-2-pyrone, was isolated as an orange solid (6.40 g, 85%): mp 72−74 °C (lit. mp 73−74 °C); δ_H ($CDCl_3$, 300 MHz) 2.25 (d, J = 0.5, 3H), 6.19 (t, J = 0.8, 1H), 6.46 (t, J = 0.7, 1H); δ_C ($CDCl_3$, 75.5 MHz) 19.7, 108.4, 114.8, 141.1, 160.6, 162.1; m/z (ES+) 188 (98).

General Procedure for Preparation of 4-Phenoxy-6-methyl-2-pyrones. A solution of 4-bromo-6-methyl-2-pyrone (1.0 equiv), phenol (1.5 equiv), and K_2CO_3 (1.8 equiv) in acetone (4.0 mL/mmol starting material) was heated to 65 °C and stirred for 16 h. Upon cooling, the reaction mixture was diluted with water (10 mL) and EtOAc (20 mL). The mixture was extracted with EtOAc (2 × 20 mL), and the combined organic layers were washed with aqueous NaOH (10% w/v, 2 × 20 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residues were purified by recrystallization from EtOH.

4-Phenoxy-6-methyl-2-pyrone.[39] yellow solid (1.69 g, 71%), mp 86 °C (lit. 89−91 °C); δ_H ($CDCl_3$, 300 MHz) 2.26 (s, 3H), 5.21 (d, J = 2.1, 1H), 5.96−5.97 (m, 1H), 7.07 (d, J = 8.0, 2H), 7.29 (t, J = 7.3, 1H), 7.43 (t, J = 7.8, 2H); δ_C ($CDCl_3$, 75.5 MHz) 20.0, 91.0, 99.9, 121.1, 126.5, 130.2, 152.4, 163.3, 164.6, 170.8; m/z (ES+) 203 (100).

4-(4-Fluorophenoxy)-6-methyl-2-pyrone. yellow solid (0.39 g, 84%), mp 75−76 °C; ν_{max}/cm^{-1} (NaCl) 3079, 1732, 1649, 1596, 1406, 1322, 1242, 1091; δ_H ($CDCl_3$, 300 MHz) 2.26 (s, 3H), 5.17 (d, J = 2.2, 1H), 5.96 (d, J = 1.5, 1H), 7.01−7.16 (m, 4H); δ_C ($CDCl_3$, 75.5 MHz) 20.0, 91.0, 100.0, 117.0 (d, J = 24), 122.7 (d, J = 9), 148.2 (d, J = 3), 160.6 (d, J = 247), 163.5, 164.4, 170.8; δ_F ($CDCl_3$, 282 MHz) −115.3; m/z (ES+) 220 (15); HRMS (ESI) exact mass calculated for $C_{12}H_{10}O_3F$ [M + H$^+$] 221.0614, found 221.0618.

4-(4-Chlorophenoxy)-6-methyl-2-pyrone. pale yellow solid (0.41 g, 82%), mp 76−77 °C; ν_{max}/cm^{-1} (NaCl) 3055, 1731, 1646, 1609, 1485, 1448, 1405, 1341; δ_H ($CDCl_3$, 300 MHz) 2.26 (s, 3H), 5.20 (d, J = 2.2. 1H), 5.9 (t, J = 1.4, 1H), 6.99−7.05 (m, 2H), 7.36−7.43 (m, 2H); δ_C ($CDCl_3$, 75.5 MHz) 20.1, 91.2, 99.2, 122.5, 130.4, 132.0, 150.8, 163.6, 164.3, 170.4; HRMS (ESI) exact mass calculated for $C_{12}H_{10}O_3Cl$ [M + H$^+$] 237.0318, found 237.0310.

4-(4-Methoxyphenoxy)-6-methyl-2-pyrone. white solid (0.38 g, 78%), mp 105−106 °C; ν_{max}/cm^{-1} (NaCl) 2838, 1731, 1646, 1568, 1446, 1405, 1322, 1299; δ_H ($CDCl_3$, 300 MHz) 2.25 (t, J = 0.7, 3H), 3.82 (s, 3H), 5.19 (dd, J = 2.2, 0.4, 1H), 5.95 (overlapping dd, J = 2.2, 1.0, 1H), 6.89−6.94 (m, 2H), 6.96−7.03 (m, 2H); δ_C ($CDCl_3$, 75.5 MHz) 20.0, 55.7, 90.7, 99.9, 115.2, 122.0, 145.8, 157.8, 163.2, 164.1, 171.3; Exact mass calculated for $C_{13}H_{13}O_4$ [M + H$^+$] 233.0814, found 233.0810.

4-(4-Methylphenoxy)-6-methyl-2-pyrone. cream solid (0.45 g, 79%), mp 53 °C; ν_{max}/cm^{-1} (NaCl) 3056, 1736, 1644, 1569, 1452, 1324, 1271; δ_H ($CDCl_3$, 300 MHz) 2.25 (s, 3H), 2.37 (s, 3H), 5.20 (d, J = 2.1, 1H), 5.95 (t, J = 1.0, 1H), 6.94 (d, J = 8.5, 2H), 7.21 (d, J = 8.2, 2H); δ_C ($CDCl_3$, 75.5 MHz) 20.0, 20.9, 90.8, 99.9, 120.8, 130.7, 136.3, 150.1, 163.2, 164.7, 171.0; m/z (ES-): 216 (16); HRMS (ESI) exact mass calculated for $C_{13}H_{13}O_3$ [M + H$^+$] 217.0865, found 217.0869.

4-(4-Ethylphenoxy)-6-methyl-2-pyrone. cream solid (0.57 g, 88%), mp 54−55 °C; ν_{max}/cm^{-1} (NaCl) 2966, 2932, 2873, 1732, 1651, 1603, 1447, 1321, 1231; δ_H ($CDCl_3$, 300 MHz) 1.25 (t, J = 7.6, 3H), 2.25 (s, 3H), 2.66 (dd, J = 15.2, 7.62, 2H), 5.20 (d, J = 2.2, 1H), 5.96 (overlapping dd, J = 2.2, 0.9, 1H), 6.94−6.99 (m, 2H), 7.21−7.26 (m, 2H); δ_C ($CDCl_3$, 75.5 MHz) 15.6, 20.0, 28.3, 90.9, 100.0, 120.9, 129.5, 142.7, 150.3, 163.7, 164.7, 171.0; m/z (ES+) 230 (100); HRMS (ESI) exact mass calculated for $C_{14}H_{15}O_3$ [M + H$^+$] 231.1021, found 231.1021.

4-(3-Methylphenoxy)-6-methyl-2-pyrone. cream solid (0.46 g, 81%), mp 59−60 °C; ν_{max}/cm^{-1} (NaCl) 3099, 1731, 1646, 1612, 1586, 1487, 1321, 1249; δ_H ($CDCl_3$, 300 MHz) 2.26 (m, 3H), 2.37 (s, 3H), 5.21 (dd, J = 2.2, 0.4, 1H), 5.96 (dd, J = 2.2, 0.9, 1H, $_{app}$), 6.84−6.89 (m, 2H), 7.08−7.11 (m, 1H), 7.29 (td, J = 7.6, 1.0, 1H); δ_C ($CDCl_3$, 75.5 MHz) 20.0, 21.3, 91.0, 100.0, 118.0, 121.6, 127.3, 129.9, 140.6, 152.3, 163.2, 164.7, 170.8; m/z (ES+) 216 (14); HRMS (ESI) exact mass calculated for $C_{13}H_{13}O_3$ [M + H$^+$] 217.0865, found 217.0868.

4-(2-Methylphenoxy)-6-methyl-2-pyrone. cream solid (0.38 g, 66%), mp 59−60 °C; ν_{max}/cm^{-1} (NaCl) 1731, 1643, 1567, 1447,

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1404, 1232; δ_H ($CDCl_3$, 300 MHz) 2.15 (s, 3H), 2.24 (s, 3H), 5.06 (d, J = 2.2, 1H), 6.00 (dd, J = 2.2, 0.9, 1H), 6.97 (dd, J = 7.5, 1.7, 1H), 7.14−7.21 (m, 2H), 7.22−7.28 (m, 1H); δ_C ($CDCl_3$, 75.5 MHz) 20.0, 21.3, 91.0, 100.0, 118.0, 121.6, 127.3, 129.9, 140.6, 152.3, 163.2, 164.7, 170.8; m/z (ES+) 216 (100); HRMS (ESI) exact mass calculated for $C_{13}H_{13}O_3$ [M + H^+] 217.0865, found 217.0863.

4-(3-Methoxyphenoxy)-6-methyl-2-pyrone. off-white solid (0.53 g, 86%), mp 100 °C; ν_{max}/cm^{-1} (NaCl) 3097, 1732, 1647, 1608, 1489, 1446, 1404, 1321, 1285; δ_H ($CDCl_3$, 300 MHz) 2.26 (s, 3H), 3.81 (s, 3H), 5.26 (d, J = 2.1, 1H), 5.96 (dd, J = 2.1, 0.9, 1H), 6.61 (t, J = 2.3, 1H), 6.66 (dd, J = 8.0, 2.2, 1H), 6.83 (dt, J = 8.4, 2.0, 1H), 7.32 (t, J = 8.2, 1H); δ_C ($CDCl_3$, 75.5 MHz) 20.0, 55.7, 90.7, 99.9, 115.2, 122.0, 145.8, 157.8, 163.2, 164.1, 171.3; m/z (ES+) 232 (100); HRMS (ESI) exact mass calculated for $C_{13}H_{13}O_4$ [M + H^+] 233.0814, found 233.0813.

4-(2-Fluorophenoxy)-6-methyl-2-pyrone. yellow solid (0.40 g, 70%), mp 52−53 °C; ν_{max}/cm^{-1} (NaCl) 1732, 1648, 1609, 1448, 1322, 1264, 1192; δ_H ($CDCl_3$, 300 MHz) 2.25 (s, 3H), 5.18 (s, 1H), 6.03 (s, 1H), 7.13−7.31 (m, 4H); δ_C ($CDCl_3$, 75.5 MHz) 19.9, 90.5, 99.4, 117.4 (d, J_{C-F} = 18), 123.4, 125.2 (d, J_{C-F} = 4), 127.9 (d, J_{C-F} = 7), 139.3 (d, J_{C-F} = 12), 153.9 (d, J_{C-F} = 251), 163.5, 164.3, 170.0; δ_F ($CDCl_3$, 282 MHz) −129.1; m/z (ES+) 220 (100); HRMS (ESI) exact mass calculated for $C_{12}H_{10}O_3F$ [M + H^+] 221.0614, found 221.0611.

4-(3-Fluorophenoxy)-6-methyl-2-pyrone. yellow solid (0.39 g, 83%), mp 77−80 °C; ν_{max}/cm^{-1} (NaCl) 1732, 1646, 1605, 1447, 1404, 1322, 1228; δ_H ($CDCl_3$, 300 MHz) 2.27 (s, 3H), 5.25 (d, J = 2.3, 1H), 5.96−5.97 (m, 1H), 6.83 (dt, J = 9.1, 2.3, 1H), 6.89 (dd, J = 8.2, 2.1, 1H), 7.02 (m, 1H), 7.36−7.44 (m, 1H); δ_C ($CDCl_3$, 75.5 MHz) 20.1, 91.4, 99.7, 109.3 (d, J_{C-F} = 24), 113.7 (d, J_{C-F} = 21), 116.9 (d, J_{C-F} = 4), 131.2 (d, J_{C-F} = 9), 153.2 (d, J_{C-F} = 11), 163.3 (d, J_{C-F} = 249), 163.6, 164.3, 170.2; δ_F ($CDCl_3$, 282 MHz) −109.2; m/z (ES+) 220 (100); HRMS (ESI) exact mass calculated for $C_{12}H_{10}O_3F$ [M + H^+] 221.0614, found 221.0614.

4-(4-Trifluoromethylphenoxy)-6-methyl-2-pyrone. brown oil (0.22 g, 76%); ν_{max}/cm^{-1} (NaCl) 1732, 1646, 1612, 1448, 1407, 1323, 1233; δ_H ($CDCl_3$, 300 MHz) 2.28 (s, 3H), 5.23 (d, J = 2.3, 1H), 5.98 (dd, J = 2.2, 0.9, 1H), 7.21 (d, J = 8.4, 2H), 7.72 (d, J = 8.4, 2H); δ_C ($CDCl_3$, 75.5 MHz) 20.1, 91.7, 99.6, 121.6, 127.6, 127.7, 127.8, 163.8, 164.1, 169.8; δ_F ($CDCl_3$, 282 MHz) −62.3; m/z (ES+) 270 (100); HRMS (ESI) exact mass calculated for $C_{13}H_{10}O_3F_3$ [M + H^+] 271.0582, found 271.0587.

Preparation of 3-Iodo-4-phenoxy-6-methyl-2-pyrone (1a).[26] A solution of 4-phenoxy-6-methyl-2-pyrone (1.00 g, 4.9 mmol), iodine (0.63 g, 4.9 mmol), and $[Bu_4N]_2[S_2O_8]$ (3.35 g, 4.9 mmol) in acetonitrile (10 mL/mmol) was stirred in darkness at room temperature (ca. 17 °C) for 120 h. The reaction mixture was diluted with 10% aqueous $Na_2S_2O_3$ (25 mL) and EtOAc (25 mL). The mixture was extracted with EtOAc (2 × 25 mL), and the combined organic extracts were washed with H_2O (3 × 25 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residues were purified by silica gel chromatography using 5% EtOAc in hexane as eluent. The product, 3-iodo-4-phenoxy-6-methyl-2-pyrone, was isolated as a white solid (0.38 g, 23%): mp 151−153 °C (lit. mp 142 °C); δ_H ($CDCl_3$, 300 MHz) 2.17 (d, J = 0.8, 3H), 5.55 (d, J = 0.8, 1H), 7.06−7.11 (m, 2H), 7.29−7.35 (m, 1H), 7.42−7.49 (m, 2H); δ_C ($CDCl_3$, 75.5 MHz) 19.9, 64.9, 97.3, 120.9, 126.5, 130.4, 153.1, 161.8, 163.6, 169.4; m/z (ES+) 327 (<10); HRMS (ESI) exact mass calculated for $C_{12}H_{10}O_3I$ [M + H^+] 328.9675, found 328.9674.

General Procedure for Preparation of 3-Bromo-4-phenoxy-6-methyl-2-pyrones via Br_2 (1b, 3−13a). A solution of 4-phenoxy-6-methyl-2-pyrone (1.0 equiv) and bromine (1.1 equiv) in DCM (5.0 mL/mmol starting material) was stirred in darkness at room temperature (ca. 17 °C) for 2 h. The reaction mixture was concentrated under reduced pressure. The residues were purified by recrystallization from EtOH to afford the title products.

*3-Bromo-4-phenoxy-6-methyl-2-pyrone (**1b**):* white solid (0.75 g, 83%), mp 94−95 °C; ν_{max}/cm^{-1} (NaCl) 3102, 1728, 1646, 1590, 1443, 1314, 1230; δ_H ($CDCl_3$, 300 MHz) 2.17 (s, 3H), 5.62 (s, 1H), 7.09 (d, J = 7.9, 2H), 7.32 (t, J = 7.4, 1H), 7.42−7.49 (m, 2H); δ_C ($CDCl_3$, 75.5 MHz) 20.0, 91.0, 97.6, 120.9, 126.5, 130.4, 152.9, 160.9, 162.3, 165.5; m/z (ES+) 281 (100); HRMS (ESI) exact mass calculated for $C_{12}H_{10}O_3Br$ [M + H^+] 280.9813, found 280.9816.

*3-Bromo-4-(4-fluorophenoxy)-6-methyl-2-pyrone (**3a**):* white solid (0.11 g, 81%), mp 119−120 °C; ν_{max}/cm^{-1} (NaCl) 1725, 1644, 1501, 1498, 1311, 1267, 1083; δ_H ($CDCl_3$, 300 MHz) 2.19 (s, 3H), 5.60 (s, 1H), 7.06−7.18 (m, 4H); δ_C ($CDCl_3$, 75.5 MHz) 20.4, 91.1, 97.5, 117.2 (d, J_{C-F} = 24), 122.6 (d, J_{C-F} = 9), 148.8 (d, J_{C-F} = 3), 160.6 (d, J_{C-F} = 246), 160.8, 162.6, 165.5; δ_F ($CDCl_3$, 282 MHz) −115.1; HRMS (ESI) exact mass calculated for $C_{12}H_9O_3FBr$ [M + H^+] 298.9716, found 298.9717.

*3-Bromo-4-(4-chlorophenoxy)-6-methyl-2-pyrone (**4a**):* white solid (0.09 g, 83%), mp 127−128 °C; ν_{max}/cm^{-1} (NaCl) 1728, 1644, 1592, 1443, 1382, 1315; δ_H ($CDCl_3$, 300 MHz) 2.18 (s, 3H), 5.61 (s, 1H), 7.02−7.07 (m, 2H), 7.39−7.45 (m, 2H); δ_C ($CDCl_3$, 75.5 MHz) 20.0, 91.4, 97.4, 122.2, 130.4, 132.0, 151.4, 160.7, 162.5, 165.1; m/z (ES+) 315 (100); HRMS (ESI) exact mass calculated for $C_{12}H_9O_3ClBr$ [M + H^+] 314.9424, found 314.9426.

*3-Bromo-4-(4-methoyphenoxy)-6-methyl-2-pyrone (**5a**):* white solid (0.10 g, 78%), mp 143−145 °C; ν_{max}/cm^{-1} (NaCl) 2838, 1723, 1643, 1442, 1385, 1316; δ_H ($CDCl_3$, 300 MHz) 2.16 (d, J = 0.7, 3H), 3.84 (s, 3H), 5.61 (d, J = 0.7, 1H), 6.95 (d, J = 9.0, 2H), 7.03 (d, J = 9.0, 2H); δ_C ($CDCl_3$, 75.5 MHz) 20.0, 55.7, 90.1, 97.3, 115.2, 122.0, 146.3, 157.9, 160.9, 162.2, 166.0; m/z (ES+) 311 (100); HRMS (ESI) exact mass calculated for $C_{13}H_{12}O_4Br$ [M + H^+] 310.9919, found 310.9926.

*3-Bromo-6-methyl-4-(4-methylphenoxy)-2-pyrone (**6a**):* white solid (0.20 g, 73%), mp 147−148 °C; ν_{max}/cm^{-1} (NaCl) 1727, 1639, 1441, 1382, 1315; δ_H ($CDCl_3$, 300 MHz) 2.15 (s, 3H), 2.39 (s, 3H) 5.62 (d, J = 0.6, 1H), 6.95−6.99 (m, 2H, m), 7.24 (d, J = 8.3, 2H); δ_C ($CDCl_3$, 75.5 MHz) 20.0, 20.9, 90.5, 97.5, 120.7, 130.8, 136.4, 150.7, 160.9, 162.2, 165.8; m/z (ES+) 295 (100); HRMS (ESI) exact mass calculated for $C_{13}H_{12}O_3Br$ [M + H^+] 294.9970, found 294.9972.

*3-Bromo-4-(4-ethylphenoxy)-6-methyl-2-pyrone (**7a**):* white solid (0.19 g, 71%), mp 109−110 °C; ν_{max}/cm^{-1} (NaCl) 3060, 3044, 1728, 1669, 1646, 1443, 1386, 1380; δ_H ($CDCl_3$, 300 MHz) 1.27 (t, J = 7.6, 3H), 2.16 (d, J = 0.8, 3H), 2.69 (q, J = 7.6, 2H), 5.63 (d, J = 0.8, 1H), 6.97−7.02 (m, 2H), 7.26 (d, J = 8.6, 2H); δ_C ($CDCl_3$, 75.5 MHz) 15.5, 20.0, 28.3, 90.5, 97.6, 120.7, 129.6, 142.7, 150.8, 160.9, 162.2, 165.8; m/z (ES+) 309 (100); HRMS (ESI) exact mass calculated for $C_{14}H_{14}O_3Br$ [M + H^+] 309.0126, found 309.0135.

*3-Bromo-4-(3-methylphenoxy)-6-methyl-2-pyrone (**8a**):* white solid (0.22 g, 80%), mp 147−148 °C; ν_{max}/cm^{-1} (NaCl) 3055, 1724, 1648, 1609, 1436, 1422, 1386; δ_H ($CDCl_3$, 300 MHz) 2.17 (s, 3H), 2.39 (s, 3H), 5.63 (s, 1H), 6.87−6.90 (m, 2H), 7.12 (d, J = 7.6, 1H), 7.32 (t, J = 7.7, 1H); δ_C ($CDCl_3$, 75.5 MHz) 20.0, 21.3, 90.8, 97.7, 117.8, 121.4, 127.8, 130.0, 140.9, 152.9, 160.9, 162.2, 165.6; m/z (ES+) 295 (100); HRMS (ESI) exact mass calculated for $C_{13}H_{12}O_3Br$ [M + H^+] 294.9970, found 294.9960.

*3-Bromo-4-(2-methylphenoxy)-6-methyl-2-pyrone (**9a**):* white solid (0.13 g, 76%), mp 82−83 °C; ν_{max}/cm^{-1} (NaCl) 3102, 1723, 1646, 1584, 1384, 1237; δ_H ($CDCl_3$, 300 MHz) 2.15 (d, J = 0.6, 3H), 2.20 (s, 3H), 5.51 (d, J = 0.6, 1H,), 7.01 (dd, J = 7.4, 1.8, 1H), 7.20−7.33 (m, 3H); δ_C ($CDCl_3$, 75.5 MHz) 15.9, 20.1, 90.0, 97.0, 121.3, 126.8, 127.7, 130.4, 132.0, 151.2, 160.9, 162.4, 165.6; m/z (ES+) 295 (100); HRMS (ESI) exact mass calculated for $C_{13}H_{12}O_3Br$ [M + H^+] 294.9970, found 294.9978.

*Preparation of 3-bromo-4-(3-methoxyphenoxy)-6-methyl-2-pyrone via NBS (**10a**).* A solution of 4-(3-methoxyphenoxy)-6-methyl-2-pyrone (0.21 g, 0.9 mmol) and *N*-bromosuccinimide (0.20 g, 1.1 mmol) in $CHCl_3$ (5.0 mL/mmol starting material) was stirred in darkness at 50 °C for 18 h. Upon cooling, the reaction mixture was washed with aqueous saturated $NaHCO_3$ (2 × 20 mL), and H_2O (2 × 20 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residues were purified by recrystallization from acetic acid. The product, 3-bromo-4-(3-methoxyphenoxy)-6-methyl-2-pyrone, was isolated as a white solid (0.17 g, 62%): mp 179−180 °C; ν_{max}/cm^{-1} (NaCl) 3070, 1720, 1642, 1605, 1440, 1314, 1266; δ_H ($CDCl_3$, 300 MHz) 2.17 (s, 3H), 3.83 (s,

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3H), 5.67 (s, 1H), 6.64−6.69 (m, 2H), 6.86 (dd, J = 8.4, 2.2, 1H), 7.34 (t, J = 8.1, 1H); δ_C ($CDCl_3$, 75.5 MHz) 20.0, 55.6, 91.0, 97.7, 106.9, 112.2, 112.8, 130.7, 153.9, 160.9, 161.2, 162.2, 165.4; m/z (ES+) 311 (100); HRMS (ESI) exact mass calculated for $C_{13}H_{12}O_4Br$ [M + H^+] 310.9919, found 310.9904.

*3-Bromo-4-(2-fluorophenoxy)-6-methyl-2-pyrone (**11a**; via Br_2 procedure):* white solid (0.44 g, 83%), mp 118−119 °C; ν_{max}/cm^{-1} (NaCl) 3055, 1728, 1644, 1444, 1422, 1383, 1348, 1266; δ_H ($CDCl_3$, 300 MHz) 2.18 (s, 3H), 5.59 (s, 1H), 7.18−7.36 8 (m, 4H); δ_C ($CDCl_3$, 75.5 MHz) 20.0, 90.6, 96.7, 117.6 (d, J_{C-F} = 18), 123.3, 125.3 (d, J_{C-F} = 4), 128.0 (d, J_{C-F} = 7), 140.1 (d, J_{C-F} = 12), 154.0 (d, J_{C-F} = 251), 160.8, 162.5, 165.2; δ_F ($CDCl_3$, 282 MHz) −129.3; m/z (ES+) 299 (100); HRMS (ESI) exact mass calculated for $C_{12}H_9O_3FBr$ [M + H^+], 298.9719, found 298.9722.

*3-Bromo-4-(3-fluorophenoxy)-6-methyl-2-pyrone (**12a**; via Br_2 procedure):* white solid (0.10 g, 75%), mp 173−174 °C; ν_{max}/cm^{-1} (NaCl) 1725, 1639, 1604, 1484, 1383, 1371, 1198; δ_H ($CDCl_3$, 300 MHz) 2.19 (s, 3H), 5.66 (s, 1H), 6.83−6.92 (m, 2H), 7.04 (td, J = 8.3, 2.2, 1H), 7.39−7.46 (m, 1H); δ_C ($CDCl_3$, 75.5 MHz) 20.1, 91.8, 97.6, 108.8 (d, J_{C-F} = 24), 113.6 (d, J_{C-F} = 21), 116.4 (d, J_{C-F} = 3), 131.3 (d, J_{C-F} = 10), 153.8 (d, J_{C-F} = 11), 160.7, 162.5, 163.3 (d, J_{C-F} = 251), 165.5; δ_F ($CDCl_3$, 282 MHz) −108.9; HRMS (ESI) exact mass calculated for $C_{12}H_9O_3FBr$ [M + H^+] 298.9719, found 298.9712.

*3-Bromo-4-(4-trifluoromethylphenoxy)-6-methyl-2-pyrone (**13a**; via Br_2 procedure):* white solid (0.10 g, 40%), mp 148−150 °C; ν_{max}/cm^{-1} (NaCl) 1732, 1645, 1609, 1543, 1323; δ_H ($CDCl_3$, 300 MHz) 2.20 (d, J = 0.8, 3H), 5.64 (d, J = 0.9, 1H), 7.21 (d, J = 8.3, 2H), 7.73 (d, J = 8.3, 2H); δ_C ($CDCl_3$, 75.5 MHz) 20.0, 92.7, 97.8, 120.8, 121.8, 127.7, 127.8 (q, J_{C-F} = 3.8), 155.5, 160.5, 162.7, 164.4; δ_F ($CDCl_3$, 282 MHz) −62.3; m/z (ES+) 349 (100); HRMS (ESI) exact mass calculated for $C_{13}H_9O_3F_3Br$ [M + H^+] 348.9687, found 348.9693.

General Procedure for Preparation of 3-Chloro-4-phenoxy-6-methyl-2-pyrones (1c, 10b, 13b). A solution of 4-phenoxy-6-methyl-2-pyrone (1.0 equiv), *N*-chlorosuccinimide (1.2 equiv), and TFA (1.2 equiv) in $CHCl_3$ (5.0 mL/mmol starting material) was stirred at 55 °C for 23 h. The reaction mixture was then washed with aqueous saturated $NaHCO_3$ (2 × 20 mL) and H_2O (2 × 20 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residues were purified by recrystallization from EtOH to afford the title products.

*3-Chloro-4-phenoxy-6-methyl-2-pyrone (**1c**):* pale cream solid (1.73 g, 67%), mp 96−97 °C; ν_{max}/cm^{-1} (NaCl) 1730, 1590, 1444, 1232, 1153; δ_H ($CDCl_3$, 300 MHz) 2.18 (s, 3H), 5.67 (s, 1H), 7.07−7.11 (m, 2H), 7.32 (t, J = 7.4, 1H), 7.42−7.49 (m, 2H); δ_C ($CDCl_3$, 75.5 MHz) 20.0, 97.6, 101.9, 120.8, 126.5, 130.4, 152.9, 160.9, 161.3, 163.6; m/z (ES+) 236 (100); HRMS (ESI) exact mass calculated for $C_{12}H_{10}O_3Cl$ [M + H^+] 237.0318, found 237.0314.

*3-Chloro-4-(3-methoxyphenoxy)-6-methyl-2-pyrone (**10b**):* white solid (0.11 g, 50%), mp 155−158 °C; ν_{max}/cm^{-1} (NaCl) 1714, 1546, 1319; δ_H ($CDCl_3$, 300 MHz) 2.18 (dd, J = 5.0, 0.9, 3H), 3.83 (s, 3H), 5.69 (d, J = 0.9, 1H), 6.6−6.69 (m, 2H), 6.82−6.89 (m, 1H), 7.30−7.38 (m, 1H); δ_C ($CDCl_3$, 75.5 MHz) 20.0, 55.6, 97.7, 101.9, 106.8, 112.2, 112.8, 130.7, 153.9, 160.8, 161.2, 161.3, 163.5; m/z (ES+) 266 (10); HRMS (ESI) exact mass calculated for $C_{13}H_{12}O_4Cl$ [M + H^+] 267.0424, found 267.0415.

*3-Chloro-4-(4-trifluoromethylphenoxy)-6-methyl-2-pyrone (**13b**):* white powder (0.053 g, 57%), mp 134−136 °C; ν_{max}/cm^{-1} (NaCl) 1735, 1551, 1322, 1242; δ_H ($CDCl_3$, 300 MHz) 2.22 (d, J = 0.9, 3H), 5.68 (d, J = 0.9, 1H), 7.20 (d, J = 8.3, 2H), 7.73 (d, J = 8.3, 2H); δ_C ($CDCl_3$, 75.5 MHz) 20.0, 97.9, 103.6, 120.6, 123.6 (d, J_{C-F} = 272), 125.4, 127.8 (d, J_{C-F} = 3.7), 128.5 (d, J_{C-F} = 33), 155.6, 160.5, 161.7, 162.4; δ_F ($CDCl_3$, 282 MHz) −62.3; m/z (ES+) 304 (80); HRMS (ESI) exact mass calculated for $C_{13}H_9O_3ClF_3$ [M + H^+] 305.0192, found 305.0202.

General Procedure for Phenoxy Intramolecular Coupling of Pyrones 1 and 3−13: Synthesis of Compounds 2 and 14−24. *Conditions A: Coupling of 3-Bromo-4-phenoxypyrones **1b** and **1−13a**.* K_2CO_3 (3 equiv) was placed in a Schlenk tube. The Schlenk tube was then heated under vacuum using a heat gun and refilled with N_2. This procedure was repeated twice more, and the Schlenk tube was cooled. Pyrone (1 equiv), $Pd(OAc)_2$ (5 mol %), and PPh_3 (15 mol %) were then added. The reagents were then stirred under vacuum, and the Schlenk tube was refilled with N_2. This procedure was repeated twice more. Xylenes (1 mL/0.25 mmol) was then added. The reaction mixture was heated to 130 °C and stirred for 16 h. Upon cooling, the reaction mixture was diluted with water (15 mL) and EtOAc (15 mL). The mixture was extracted with EtOAc (2 × 15 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residues were purified by silica gel chromatography using 6% EtOAc in hexane as eluent to afford the title products.

*Conditions B: Coupling of 3-Chloro-4-phenoxypyrones **1c**, **10b**, and **13b**.* K_2CO_3 (3.0 equiv) was placed in a Schlenk tube. The Schlenk tube was then heated under vacuum using a heat gun and refilled with N_2. This procedure was repeated twice more, and the Schlenk tube was cooled. Pyrone (1.0 equiv), $Pd(OAc)_2$ (5 mol %), and $PCy_3{\cdot}HBF_4$ (15 mol %) were then added. The reagents were then stirred under vacuum, and the Schlenk tube was refilled with N_2. This procedure was repeated twice more. Xylenes (1 mL/0.25 mmol) was then added. The reaction mixture was heated to 130 °C and stirred for 14 h. Upon cooling, the reaction mixture was diluted with water (15 mL) and EtOAc (15 mL). The mixture was extracted with EtOAc (2 × 15 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residues were purified by silica gel chromatography using 3% EtOAc in hexane as eluent to afford the title products.

*3-Methyl-1H-pyrano[4,3-b]benzofuran-1-one (**2**):*[21a] white solid (from **1b**, conditions A, 0.03 g, 80%; from **1c**, conditions **B**, 0.07 g, 79%), mp 187−188 °C (lit. 188−190 °C); ν_{max}/cm^{-1} (NaCl) 2922, 1727, 1626, 1446, 1284, 1104; δ_H ($CDCl_3$, 300 MHz) 2.42 (s, 3H), 6.53 (s, 1H), 7.34−7.37 (m, 2H), 7.51−7.59 (m, 1H), 8.02−8.06 (m, 1H); δ_C ($CDCl_3$, 75.5 MHz) 20.6, 95.9, 103.7, 111.5, 121.3, 122.9, 124.9, 126.1, 154.9, 159.5, 162.9, 164.5; m/z (ES+) 200 (99); HRMS (ESI) exact mass calculated for $C_{12}H_9O_3$ [M + H^+], 201.0552, found 201.0554.

*8-Fluoro-3-methyl-1H-pyrano[4,3-b]benzofuran-1-one (**14**):* (conditions A) white solid (0.06 g, 77%), mp 124−125 °C; ν_{max}/cm^{-1} (NaCl) 3055, 2923, 2850, 1741, 1634, 1574, 1502, 1453, 1265; δ_H ($CDCl_3$, 300 MHz) 2.43 (s, 3H), 6.52 (s, 1H), 7.11 (dd, J = 9.0, 2.7, 1H), 7.48 (dd, J = 9.0, 3.9, 1H), 7.69 (dd, J = 8.0, 2.7, 1H); δ_C ($CDCl_3$, 75.5 MHz) 20.7, 95.8, 103.2, 107.5 (d, J_{C-F} = 26), 112.3 (d, J_{C-F} = 10), 113.6 (d, J_{C-F} = 26), 124.1 (d, J_{C-F} = 12), 150.9 (d, J_{C-F} = 1), 159.1, 160.3 (d, J_{C-F} = 242), 163.6, 165.7; δ_F ($CDCl_3$, 282 MHz) −117.1; HRMS (ESI) exact mass calculated for $C_{12}H_8O_3F$ [M + H^+] 219.0457, found 219.0448.

*8-Chloro-3-methyl-1H-pyrano[4,3-b]benzofuran-1-one (**15**):* (conditions A) white solid (0.05 g, 45%), mp 181−182 °C; ν_{max}/cm^{-1} (NaCl) 1743, 1631, 1573, 1439, 1258; δ_H ($CDCl_3$, 300 MHz) 2.43 (s, 3H), 6.53 (s, 1H), 7.36 (dd, J = 8.8, 2.1, 1H), 7.46 (d, J = 8.8, 1H), 8.00 (d, J = 2.0, 1H); δ_C ($CDCl_3$, 75.5 MHz) 20.7, 95.8, 103.2, 112.4, 121.1, 124.4, 126.3, 130.8, 153.3, 158.9, 163.8, 165.4; m/z (ES+) 234 (34); HRMS (ESI) exact mass calculated for $C_{12}H_8O_3Cl$ [M + H^+] 235.0155, found 235.0162.

*8-Methoxy-3-methyl-1H-pyrano[4,3-b]benzofuran-1-one (**16**):* (conditions A) white solid (0.06 g, 87%), mp 152−154 °C; ν_{max}/cm^{-1} (NaCl) 1635, 1571, 1459, 1429, 1274, 1227; δ_H ($CDCl_3$, 300 MHz) 2.42 (d, J = 0.7, 3H), 3.89 (s, 3H), 6.97 (d, J = 0.8, 1H), 6.97 (dd, J = 9.0, 2.7, 1H), 7.42 (d, J = 9.0, 1H), 7.48 (d, J = 2.6, 1H); δ_C ($CDCl_3$, 75.5 MHz) 20.6, 56.0, 96.0, 103.3, 103.9, 112.0, 115.1, 123.7, 149.6, 157.5, 159.6, 162.6, 165.0; m/z (ES+) 230 (99); HRMS (ESI) exact mass calculated for $C_{13}H_{11}O_4$ [M + H^+] 231.0657, found 231.0661.

*3,8-Dimethyl-1H-pyrano[4,3-b]benzofuran-1-one (**17**):* (conditions A) white solid (0.07 g, 93%), mp 159−160 °C; ν_{max}/cm^{-1} (NaCl) 3089, 1715, 1615, 1572, 1448, 1422, 1265; δ_H ($CDCl_3$, 300 MHz) 2.41 (d, J = 0.6, 3H), 2.48 (s, 3H), 6.49 (d, J = 0.8, 1H), 7.19 (dd, J = 8.4, 1.4, 1H), 7.39 (d, J = 8.5, 1H), 7.82 (s, 1H); δ_C ($CDCl_3$, 75.5 MHz) 20.6, 21.3, 95.9, 103.5, 110.9, 121.2, 122.9, 127.2, 134.8, 153.3, 159.6, 162.6, 164.6; m/z (ES+) 214 (99); HRMS (ESI) exact mass calculated for $C_{13}H_{11}O_3$ [M + H^+] 215.0708, found 215.0698.

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*8-Ethyl-3-methyl-1H-pyrano[4,3-b]benzofuran-1-one, (**18**):* (conditions A) white solid (0.07 g, 89%), mp 72−73 °C; ν_{max}/cm^{-1} (NaCl) 2963, 1734, 1625, 1449, 1344, 1265; δ_H ($CDCl_3$, 300 MHz) 1.29 (t, *J* = 7.9, 3H), 2.41 (d, *J* 0 0.7, 3H), 2.78 (q, *J* = 7.6, 2H), 6.51 (d, *J* = 0.8, 1H), 7.23 (dd, *J* = 8.5, 1.8, 1H), 7.43 (d, *J* = 8.5, 1H), 7.85 (d, *J* = 1.2, 1H); δ_C ($CDCl_3$, 75.5 MHz) 16.1, 20.6, 28.9, 96.0, 103.6, 111.0, 120.1, 122.9, 126.2, 141.4, 153.5, 159.7, 162.6, 164.6; *m*/*z* (ES+) 228 (100); HRMS (ESI) exact mass calculated for $C_{14}H_{13}O_3$ [M + H$^+$] 229.0865, found 229.0871.

*7-Methyl-3-methyl-1H-pyrano[4,3-b]benzofuran-1-one (**19**):* (conditions A) white solid (0.03 g, 40%), mp 139−141 °C; ν_{max}/cm^{-1} (NaCl) 2921, 1734, 1620, 1576, 1447, 1380, 1317; δ_H ($CDCl_3$, 300 MHz) 2.41 (s, 3H), 2.49 (s, 3H), 6.50 (s, 1H), 7.22 (d, *J* = 7.9, 1H), 7.33 (s, 1H), 7.88 (d, *J* = 7.9, 1H); δ_C ($CDCl_3$, 75.5 MHz) 20.6, 21.8, 95.9, 103.7, 111.7, 120.3, 120.8, 126.2, 136.7, 155.4, 159.6, 162.4, 164.2; *m*/*z* (ES+) 214 (100); HRMS (ESI) exact mass calculated for $C_{13}H_{11}O_3$ [M + H$^+$] 215.0708, found 215.0702.

*3,6-Dimethyl-1H-pyrano[4,3-b]benzofuran-1-one (**20**):* (conditions A) white solid (0.05 g, 74%), mp 169−170 °C; ν_{max}/cm^{-1} (NaCl) 1725, 1642, 1571, 1434, 1263, 1204; δ_H ($CDCl_3$, 300 MHz) 2.41 (d, *J* = 0.8, 3H), 2.54 (s, 3H), 6.52 (d, *J* = 0.8, 1H), 7.19 (d, *J* = 7.4, 1H), 7.29 (t, *J* = 7.6, 1H), 7.89 (d, *J* = 7.8, 1H); δ_C ($CDCl_3$, 75.5 MHz) 14.9, 20.6, 95.9, 103.9, 118.7, 121.7, 122.4, 124.9, 127.2, 153.9, 159.6, 162.6, 164.2; *m*/*z* (ES+) 214 (99); HRMS (ESI) exact mass calculated for $C_{13}H_{11}O_3$ [M + H$^+$] 215.0708, found 215.0702.

*7-Methoxy-3-methyl-1H-pyrano[4,3-b]benzofuran-1-one (**21**):* white solid (from **10a**, conditions A, 0.04 g, 60%; from **10b**, conditions B, 0.02 g, 57%), mp 158−159 °C; ν_{max}/cm^{-1} (NaCl) 1716, 1642, 1618, 1427, 1376, 1327; δ_H ($CDCl_3$, 300 MHz) 2.41 (s, 3H), 3.88 (s, 3H), 6.50 (d, *J* = 0.6, 1H), 7.02 (dd, *J* = 8.5, 2.2, 1H), 7.07 (d, *J* = 2.1, 1H), 7.88 (d, *J* = 8.6, 1H); δ_C ($CDCl_3$, 75.5 MHz) 20.5, 55.8, 95.9, 96.8, 103.9, 113.0, 115.9, 121.5, 156.1, 159.2, 159.6, 161.7, 164.0; *m*/*z* (ES+) 230 (100); HRMS (ESI) exact mass calculated for $C_{13}H_{11}O_4$ [M + H$^+$] 231.0657, found 231.0659.

*6-Fluoro-3-methyl-1H-pyrano[4,3-b]benzofuran-1-one (**22**):* (conditions A) white solid (0.06 g, 57%), mp 221−223 °C; ν_{max}/cm^{-1} (NaCl) 3096, 1734, 1616, 1572, 1435, 1272, 1260; δ_H ($CDCl_3$, 300 MHz) 2.44 (s, 3H), 6.57 (s, 1H), 7.13−7.19 (m, 1H), 7.31−7.38 (t, *J* = 8.0, 1H), 7.79 (d, *J* = 7.8, 1H); δ_C ($CDCl_3$, 75.5 MHz) 20.7, 95.8, 103.8, 112.8 (d, J_{C-F} = 16), 116.9 (d, J_{C-F} = 4), 125.9 (d, J_{C-F} = 6), 126.3 (d, J_{C-F} = 3), 141.6 (d, J_{C-F} = 12), 147.7 (d, J_{C-F} = 251), 159.0, 163.8, 164.9; δ_F ($CDCl_3$, 282 MHz) −136.3; *m*/*z* (ES+) 218 (16); HRMS (ESI) exact mass calculated for $C_{12}H_8O_3F$ [M + H$^+$] 219.0457, found 219.0452.

*9-Fluoro-3-methyl-1H-pyrano[4,3-b]benzofuran-1-one (**23a**):* (conditions A) white solid (0.06 g, 54%), mp 183−185 °C; ν_{max}/cm^{-1} (NaCl) 3055, 1741, 1647, 1623, 1436, 1373, 1266; δ_H ($CDCl_3$, 300 MHz) 2.43 (d, *J* = 0.89, 3H), 6.51 (d, *J* = 0.8, 1H), 7.06−7.17 (m, 1H), 7.32−7.39 (m, 2H); δ_C ($CDCl_3$, 75.5 MHz) 20.6, 95.4, 102.2 (d, J_{C-F} = 4), 107.7 (d, J_{C-F} = 4), 111.6 (d, J_{C-F} = 20), 112.0 (d, J_{C-F} = 22), 127.0 (d, J_{C-F} = 7), 156.0 (J_{C-F} = 255), 156.4 (d, J_{C-F} = 9), 158.1, 164.0, 164.6 (d, J_{C-F} = 1); δ_F ($CDCl_3$, 282 MHz) −113.7; *m*/*z* (ES+) 218 (100); HRMS (ESI) exact mass calculated for $C_{12}H_8O_3F$ [M + H$^+$] 219.0457, found 219.0453.

*7-Fluoro-3-methyl-1H-pyrano[4,3-b]benzofuran-1-one (**23b**):* (conditions A) white solid (0.04 g, 40%), mp 201−202 °C; ν_{max}/cm^{-1} (NaCl) 1731, 1643, 1575, 1498, 1416, 1324, 1279; δ_H ($CDCl_3$, 300 MHz) 2.42 (s, 3H), 6.53 (s, 1H), 7.17 (td, *J* = 9.0, 2.2, 1H), 7.27 (d, *J* = 2.2, 1H), 7.95 (d, *J* = 8.6, 1H); δ_C ($CDCl_3$, 75.5 MHz) 20.6, 95.8, 99.8 (d, J_{C-F} = 27), 103.5, 113.1 (d, J_{C-F} = 24), 119.2 (d, J_{C-F} = 2), 121.8 (d, J_{C-F} = 10), 155.0 (d, J_{C-F} = 13), 159.2, 162.5 (d, J_{C-F} = 246), 162.8, 165.1; δ_F ($CDCl_3$, 282 MHz) −112.2; *m*/*z* (ES+) 218 (100); HRMS (ESI) exact mass calculated for $C_{12}H_8O_3F$ [M + H$^+$] 219.0457, found 219.0449.

*3-Methyl-8-trifluoromethyl-1H-pyrano[4,3-b]benzofuran-1-one (**24**):*[21a] yellow solid (from **13a**, conditions A, 0.03 g, 90%; from **13b**, conditions B, 0.03 g, 60%), mp 139−142 °C; ν_{max}/cm^{-1} (NaCl) 1747, 1321, 1116; δ_H ($CDCl_3$, 300 MHz) 2.46 (d, *J* = 0.8, 3H), 6.58 (d, *J* = 0.9, 1H), 7.43−7.82 (m, 2H), 8.17−8.45 (m, 1H); δ_C ($CDCl_3$, 75.5 MHz) 20.7, 95.7, 103.4, 111.9, 119.0 (d, *J* 4.0), 123.3, 123.5, 125.9, 127.8 (q, *J* = 33), 156.2, 158.8, 164.3, 165.7; δ_F ($CDCl_3$, 282 MHz) −61.2; *m*/*z* (ES+) 268 (100); HRMS (ESI) exact mass calculated for $C_{13}H_8O_3F_3$ [M + H$^+$], 269.0426, found 269.0428.

4-Bromo-2-coumarin.[21a] A solution of 4-hydroxy-2-coumarin (1.0 equiv), TBAB (1.16 equiv), and P_2O_5 (2.4 equiv) in toluene (4.0 mL/mmol starting material) was stirred at 94 °C for 1.5 h. Upon cooling, the reaction mixture was washed with toluene (2 × 30 mL). The combined organic extracts were then washed with saturated aqueous $NaHCO_3$ (2 × 20 mL) and H_2O (2 × 20 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product, 4-bromo-2-coumarin, was isolated as a brown solid (3.00 g, 72%): mp 88−89 °C (lit. mp 92−93 °C); δ_H ($CDCl_3$, 300 MHz) 6.87 (s, 1H), 7.23−7.39 (m, 2H), 7.57−7.63 (m, 1H), 7.85 (dd, *J* = 7.9, 1.5, 1H); δ_C ($CDCl_3$, 75.5 MHz) 117.0, 119.0, 119.6, 125.0, 128.1, 133.2, 141.5, 152.5, 158.7; *m*/*z* (ES+) 225 (76).

4-Phenoxy-2-coumarin (25).[40] A solution of 4-bromo-2-coumarin (1.0 equiv), substituted phenol (1.5 equiv), and K_2CO_3 (1.8 equiv) in acetone (4.0 mL/mmol starting material) was heated to 65 °C and stirred for 16 h. Upon cooling, the reaction mixture was diluted with water (10 mL) and EtOAc (20 mL). The mixture was extracted with EtOAc (2 × 20 mL), and the combined organic layers were washed with aqueous NaOH (10% w/v, 2 × 20 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residues were purified by recrystallization from EtOH. The product 4-phenoxy-2-coumarin was isolated as a yellow solid (1.40 g, 68%): mp 131−132 °C (lit. mp 133−134 °C); δ_H ($CDCl_3$, 300 MHz) 5.42 (s, 1H), 7.16−7.20 (m, 2H), 7.32−7.38 (m, 3H), 7.46−7.52 (m, 2H), 7.59−7.65 (dd, *J* = 8.7, 1.6, 1H), 8.03 (dd, *J* = 8.0, 1.5, 1H); δ_C ($CDCl_3$, 75.5 MHz) 93.5, 115.4, 116.9, 121.3, 123.1, 124.2, 126.0, 130.5, 132.9, 152.4, 153.7, 162.6, 166.4; *m*/*z* (ES+) 239 (100).

3-Chloro-4-phenoxy-2-coumarin (26).[41] A solution of 4-phenoxy-2-coumarin (0.10 g, 0.42 mmol), *N*-chlorosuccinimide (0.07 g, 0.50 mmol), and TFA (0.06 g, 0.50 mmol) in $CHCl_3$ (5.0 mL/mmol starting material) was stirred in darkness at 55 °C for 72 h. The reaction mixture was then washed with aqueous saturated $NaHCO_3$ (2 × 5 mL) and H_2O (2 × 5 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residues were purified by silica gel chromatography using 2% EtOAc in hexane as eluent. The product, 3-chloro-4-phenoxy-2-coumarin, was isolated as a brown solid (0.08 g, 67%): mp 74−75 °C (lit. mp 88.8−90.4 °C); ν_{max}/cm^{-1} (NaCl) 3057, 1735, 1611, 1563, 1451, 1351, 1266; δ_H ($CDCl_3$, 300 MHz) 6.97−7.01 (m, 2H), 7.15 (tt, *J* = 7.4, 1.1, 1H), 7.26−7.39 (m, 3H), 7.43 (dd, *J* = 8.4, 0.7, 1H), 7.57−7.60 (m, 1H), 7.66 (dd, *J* = 8.0, 1.7, 1H); δ_C ($CDCl_3$, 75.5 MHz) 112.0, 116.1, 116.8, 117.0, 123.8, 124.1, 124.9, 130.1, 132.7, 151.7, 155.6, 158.3, 158.8; *m*/*z* (ES+) 272 (100); HRMS (ESI) exact mass calculated for $C_{15}H_{10}O_3Cl$ [M + H$^+$] 273.0318, found 273.0311.

6*H*-Benzofuro[3,2-*c*]chromen-6-one (27).[21a] K_2CO_3 (0.06 g, 0.44 mmol) was placed in a Schlenk tube. The Schlenk tube was then heated under vacuum using a heat gun and refilled with N_2. This procedure was repeated twice more, and the Schlenk tube was cooled. 3-Chloro-4-phenoxy-2-coumarin (**26**; 0.04 g, 0.15 mmol), $Pd(OAc)_2$ (0.18 g, 0.007 mmol), and $PCy_3{\cdot}HBF_4$ (0.008 g, 0.022 mmol) were then added. The reagents were then stirred under vacuum, and the Schlenk tube was refilled with N_2. This procedure was repeated twice more. Xylenes (1 mL/0.25 mmol) was then added. The reaction mixture was heated to 130 °C and stirred for 14 h. Upon cooling, the reaction mixture was diluted with water (15 mL) and EtOAc (15 mL). The mixture was extracted with EtOAc (2 × 15 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residues were purified by silica gel chromatography using 3% EtOAc in hexane as eluent. The product, 6*H*-benzofuro[3,2-*c*]chromen-6-one, was isolated as a white solid (0.03 g, 90%): mp 177−180 °C (lit. mp 179−180 °C); ν_{max}/cm^{-1} (NaCl) 1742, 1736, 1675, 1486, 1373; δ_H ($CDCl_3$, 300 MHz) 7.39−7.52 (m, 4H), 7.59−7.70 (m, 2H), 8.03 (dd, *J* = 7.8, 1.3, 1H), 8.13−8.18 (m, 1H); δ_C ($CDCl_3$, 75.5 MHz) 105.9, 111.8, 112.6, 117.5, 121.9, 123.4, 124.7, 125.2, 126.8, 132.0, 153.7, 155.5, 158.1, 160.0; *m*/*z*

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(ES+) 236 (48); HRMS (ESI) exact mass calculated for $C_{15}H_9O_3$ [M + H$^+$] 237.0552, found 237.0547.

4-Bromo-7-methoxy-2-coumarin (29). A solution of 4-hydroxy-7-methoxy-2-coumarin (3.00 g, 15.6 mmol), TBAB (7.50 g, 23.4 mmol), and P_2O_5 (5.32 g. 37.5 mmol) in toluene (4.0 mL/mmol starting material) was stirred at 94 °C for 1.5 h. Upon cooling, the reaction mixture was washed with toluene (2 × 30 mL). The combined organic extracts were then washed with saturated aqueous $NaHCO_3$ (2 × 20 mL) and H_2O (2 × 20 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product, 4-bromo-7-methoxy-2-coumarin, was isolated as a brown solid (2.70 g, 72%): mp 114−117 °C; ν_{max}/cm^{-1} (NaCl) 1732, 1719, 1609, 1592; δ_H ($CDCl_3$, 300 MHz) 3.90 (s, 3H), 6.67 (s, 1H), 6.79 (d, J = 2.5, 1H), 6.90 (dd, J = 8.9, 2.5, 1H), 7.71 (d, J = 8.9, 1H); δ_C ($CDCl_3$, 75.5 MHz) 56.0, 100.6, 112.6, 113.1, 116.0, 129.1, 141.5, 154.3, 159.2, 163.8; m/z (ES+) 255 (20); HRMS (ESI) exact mass calculated for $C_{10}H_8O_3Br$ [M + H$^+$] 254.9657, found 254.9653.

4-(Benzo[*d*][1,3]dioxol-5-yloxy)-7-methoxy-2*H*-chromen-2-one. A solution of 4-bromo-7-methoxy-2-coumarin (1 equiv), substituted phenol (1.5 equiv), and K_2CO_3 (1.8 equiv) in acetone (4.0 mL/mmol starting material) was heated to 65 °C and stirred for 16 h. Upon cooling, the reaction mixture was diluted with water (10 mL) and EtOAc (20 mL). The mixture was extracted with EtOAc (2 × 20 mL), and the combined organic layers were washed with aqueous NaOH (10% w/v, 2 × 20 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residues were purified by recrystallization from EtOH. The product was isolated as a pale yellow solid (3.20 g, 96%): mp 174−177 °C; ν_{max}/cm^{-1} (NaCl) 1717, 1617, 1389; δ_H ($CDCl_3$, 300 MHz) 3.90 (s, 3H), 5.33 (s, 1H), 6.02 (s, 2H), 6.64 (dd, J = 9.0, 5.2, 2H), 6.74−7.06 (m, 3H), 7.87 (d, J = 9.0, 1H); δ_C ($CDCl_3$, 75.5 MHz) 55.8, 90.9, 100.6, 102.1, 103.3, 108.6, 112.4, 113.8, 124.1, 146.0, 146.7, 148.7, 155.5, 163.1, 163.6, 167.0; m/z (ES+) 312 (79); HRMS (ESI) exact mass calculated for $C_{17}H_{13}O_6$ [M + H$^+$], 313.0712, found 313.0707.

4-(Benzo[*d*][1,3]dioxol-5-yloxy)-3-chloro-7-methoxy-2*H*-chromen-2-one (30). A solution of 4-phenoxy-2-coumarin (0.15 g, 0.48 mmol), *N*-chlorosuccinimide (0.06 g, 0.48 mmol), and TFA (0.033 mL, 0.4 mmol) in $CHCl_3$ (5.0 mL/mmol starting material) was stirred in darkness at 55 °C for 72 h. The reaction mixture was then washed with aqueous saturated $NaHCO_3$ (2 × 5 mL), and H_2O (2 × 5 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residues were purified by silica gel chromatography using DCM as eluent. The product was isolated as a pale white solid (0.09 g, 56%): mp 129−132 °C; ν_{max}/cm^{-1} (NaCl) 1732, 1616, 1482, 1365, 1172; δ_H ($CDCl_3$, 300 MHz) 3.89 (s, 3H), 5.98 (s, 2H), 6.38 (dd, J = 8.5, 2.5, 1H), 6.58 (d, J = 2.5, 1H), 6.71 (d, J = 8.5, 1H), 6.86 (dt, J = 8.6, 2.2, 2H), 7.55 (dd, J = 8.6, 0.5, 1H); δ_C ($CDCl_3$, 75.5 MHz) 55.9, 99.3, 100.8, 101.8, 108.2, 108.5, 110.0, 113.2, 124.9, 144.1, 148.7, 150.7, 153.6, 159.0, 159.3, 163.5; m/z (ES+) 346 (60); HRMS (ESI) exact mass calculated for $C_{17}H_{12}O_6Cl$ [M + H$^+$] 347.0322, found 347.0320.

Coupling of 3-Chlorocoumarin (30): Synthesis of Compounds 31 and 32. K_2CO_3 (3.0 equiv) was placed in a Schlenk tube. The Schlenk tube was then heated under vacuum using a heat gun and refilled with N_2. This procedure was repeated twice more, and the Schlenk tube was cooled. Pyrone (1.0 equiv), $Pd(OAc)_2$ (5 mol %), and $PCy_3{\cdot}HBF_4$ (15 mol %) were then added. The reagents were then stirred under vacuum, and the Schlenk tube was refilled with N_2. This procedure was repeated twice more. Xylenes (1 mL/0.25 mmol) was then added. The reaction mixture was heated to 130 °C and stirred for 14 h. Upon cooling, the reaction mixture was diluted with water (15 mL) and EtOAc (15 mL). The mixture was extracted with EtOAc (2 × 15 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residues were purified by silica gel chromatography using 3% EtOAc in hexane as eluent to afford the title products.

*3-Methoxy-6H-[1,3]dioxolo[4′,5′:5,6]benzofuro[3,2-c]chromen-6-one (flemichapparin C, **31**):*[42] white solid (0.08 g, 31%), mp >230 °C (lit. mp 270−273 °C); ν_{max}/cm^{-1} (NaCl) 1739, 1628, 1472, 1362; δ_H ($CDCl_3$, 300 MHz) 3.91 (s, 3H), 6.08 (s, 2H), 6.96 (dd, J = 9.2, 2.5, 1H), 6.99 (d, J = 2.5, 1H), 7.12 (s, 1H), 7.47 (s, 1H), 7.85 (d, J = 9.2, 1H); δ_C ($CDCl_3$, 150 MHz) 55.8, 94.0, 100.2, 101.5, 102.0, 104.0, 106.2, 113.0, 117.1, 122.3, 146.1, 147.4, 150.6, 154.9, 158.5, 160.0, 162.5; m/z (ES+) 310 (20); HRMS (ESI) exact mass calculated for $C_{17}H_{11}O_6$ [M + H$^+$] 311.0556, found 311.0551.

*9-Methoxy-12H-[1,3]dioxolo[4′,5′:4,5]benzofuro[3,2-c]chromen-12-one (**32**).* white solid (0.18 g, 67%), mp >230 °C; ν_{max}/cm^{-1} (NaCl) 1732, 1639, 1449, 1254; δ_H ($CDCl_3$, 300 MHz) 3.91 (s, 3H), 6.19 (s, 2H), 6.83−7.03 (m, 3H), 7.10 (d, J = 8.6, 1H,), 7.87 (dd, J = 8.6, 1.6, 1H); δ_C ($CDCl_3$, 150 MHz) 55.9, 101.4, 101.7, 102.5, 103.5, 105.5, 106.4, 108.1, 113.3, 123.0, 139.8, 145.1, 152.0, 155.9, 157.8, 161.7, 163.3; m/z (ES+) 310 (10); HRMS (ESI) exact mass calculated for $C_{17}H_{11}O_6$ [M + H$^+$] 311.0556, found 311.0550.

***o*-Deuteriophenol.**[43] A solution of *o*-bromophenol (0.50 g, 2.89 mmol) in THF (14.0 mL/mmol of starting material) at 0 °C was stirred for 30 min. *n*-BuLi (2.5 M in hexanes, 3.3 mL, 6.36 mmol) was then added dropwise to the solution at 0 °C over 15 min. The reaction mixture was stirred at 0 °C for 3 h and quenched with D_2O. The reaction mixture was then concentrated under reduced pressure. The residue was then dissolved in ether (10 mL) and washed with saturated aqueous NH_4Cl (2 × 5 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product, *o*-deuteriophenol, synthesized twice (80% deuterium incorporated), was obtained as a yellow oil and used without further purification (0.33 g): δ_H ($CDCl_3$, 300 MHz) 6.83 (d, J = 8.3, 1.2H), 6.92 (td, J = 7.4, 1.0, 1H), 7.16−7.31 (m, 2H); m/z (ES−) mass calculated for $C_6H_4D_2O$ 95 (<10).

4-(2-Deuteriophenoxy)-6-methyl-2-pyrone. A solution of 4-bromo-6-methyl-2-pyrone (0.53 g, 2.8 mmol), *o*-deuteriophenol (0.40 g, 4.21 mmol), and K_2CO_3 (0.69 g, 5.05 mmol) in acetone (4.0 mL/mmol starting material) was heated to 65 °C and stirred for 16 h. Upon cooling, the reaction mixture was diluted with water (10 mL) and EtOAc (20 mL). The mixture was extracted with EtOAc (2 × 20 mL), and the combined organic layers were washed with aqueous NaOH (10% w/v, 2 × 20 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residues were purified by recrystallization from EtOH. The product, 4-(2-deuterio)phenoxy-6-methyl-2-pyrone, was isolated as a cream solid (0.35 g, 62%): mp 72−73 °C; ν_{max}/cm^{-1} (NaCl) 3091, 1732, 1645, 1570, 1445, 1320, 1261; δ_H ($CDCl_3$, 300 MHz) 2.26 (s, 3H), 5.21 (d, J = 2.1, 1H), 5.97 (dd, J = 2.1, 0.9, 1H), 6.94−7.18 (m, 1.2H), 7.18−7.35 (m, 1H), 7.43 (ddd, J = 7.1, 6.6, 2.0, 2H); δ_C ($CDCl_3$, 75.5 MHz) 20.0, 91.0, 99.9, 120.2 (t, $J_{C\text{-}D}$ = 25), 121.1, 126.5, 130.1, 130.2, 152.3, 163.3, 164.6, 170.7; HRMS (ESI) exact mass calculated for $C_{12}H_{10}DO_3$ [M + H$^+$] 204.0771, found 204.0770.

3-Bromo-4-(2-deuteriophenoxy)-6-methyl-2-pyrone (33). A solution of 4-(2-deuterio)phenoxy-6-methyl-2-pyrone (0.20, 0.99 mmol) and bromine (0.17 g, 1.08 mmol) in DCM (5.0 mL/mmol starting material) was stirred in darkness at room temperature (ca. 17 °C) for 2 h. The reaction mixture was concentrated under reduced pressure. The residues were purified by recrystallization from EtOH. The product, 3-bromo-4-(2-deuterio)phenoxy-6-methyl-2-pyrone, was isolated as a pale orange solid (0.21 g, 78%): mp 113−114 °C; ν_{max}/cm^{-1} (NaCl) 1727, 1643, 1544, 1442, 1313, 1262; δ_H ($CDCl_3$, 300 MHz) 2.17 (s, 3H), 5.62 (d, J = 0.7, 1H), 7.10 (dd, J = 8.5, 1.0, 1.2H), 7.28−7.36 (m, 1H), 7.44−7.49 (m, 2H); δ_C ($CDCl_3$, 75.5 MHz) 20.1, 90.8, 97.7, 120.4 (t, $J_{C\text{-}D}$ = 25), 120.9, 126.6, 130.3, 130.4, 152.9, 161.0, 162.4, 165.7; m/z (ES+) 282 (8); HRMS (ESI) exact mass calculated for $C_{12}H_9DO_3Br$ [M + H$^+$] 281.9876, found 281.9879.

4-(2-Deuteriophenoxy)-2-coumarin. A solution of 4-bromo-2-coumarin (0.87 g, 3.85 mmol), *o*-deuteriophenol (0.44 g, 4.63 mmol), and K_2CO_3 (0.96 g, 6.93 mmol) in acetone (4.0 mL/mmol of starting material) was heated to 65 °C and stirred for 16 h. Upon cooling, the reaction mixture was diluted with water (10 mL) and EtOAc (20 mL). The mixture was extracted with EtOAc (2 × 20 mL), and the combined organic layers were washed with aqueous NaOH (10% w/v, 2 × 20 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residues were purified by recrystallization from EtOH. The product, 4-(2-deuteriophenoxy)-2-coumarin, was isolated as a cream solid (0.35 g, 38%): mp 128−130

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°C; ν_{max}/cm^{-1} (NaCl) 1713, 1625, 1389, 1225; δ_H ($CDCl_3$, 300 MHz) 5.42 (s, 1H), 7.18 (dd, J = 8.5, 1.1, 1.2H), 7.29−7.43 (m, 3H), 7.43−7.56 (m, 2H), 7.62 (ddd, J = 8.5, 7.2, 1.2, 1H), 8.04 (dd, J = 7.9, 1.2, 1H); δ_C ($CDCl_3$, 75.5 MHz) 93.6, 115.4, 116.9, 121.3, 123.1, 124.1, 126.8, 130.3, 130.4, 132.8, 152.4, 153.7, 162.6, 166.4; m/z (ES+) 203 (12); HRMS (ESI) exact mass calculated for $C_{12}H_{10}DO_3$ [M + H$^+$], 204.0771, found 204.0769.

3-Chloro-4-(2-deuteriophenoxy)-2-coumarin (35). A solution of 4-(2-deuteriophenoxy)-2-coumarin (0.20 g, 0.84 mmol), *N*-chlorosuccinimide (0.13 g, 1.0 mmol), and TFA (0.08 mL, 1.0 mmol) in $CHCl_3$ (5.0 mL/mmol starting material) was stirred in darkness at 55 °C for 72 h. The reaction mixture was then washed with aqueous saturated $NaHCO_3$ (2 × 5 mL) and H_2O (2 × 5 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residues were purified by recrystallization from EtOH. The product was isolated as a yellow solid (0.12 g, 52%): mp 80−85 °C; ν_{max}/cm^{-1} (NaCl) 1737, 1609, 1468, 1350, 1175; δ_H ($CDCl_3$, 300 MHz) 6.94−7.06 (m, 1.2H), 7.15 (td, J = 7.6, 1.0, 1H), 7.22−7.49 (m, 4H), 7.52−7.75 (m, 2H); δ_C ($CDCl_3$, 75.5 MHz) 112.0, 116.1, 116.7, 117.0, 123.8, 124.1, 124.9, 130.0, 130.1, 132.7, 151.7, 155.6, 158.3, 158.8; m/z (ES+) 273 (30); HRMS (ESI) exact mass calculated for $C_{15}H_9DO_3Cl$ [M + H$^+$] 274.0381, found 274.0379.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02027.

Experimental procedure and data for mechanistic experiments and ^{1}H, ^{13}C, and ^{19}F NMR spectra for all novel compounds, key intermediates, and final products. (PDF)

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Notes

The authors declare no competing financial interest.

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