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Note

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*m*CPBA-Mediated Intramolecular Oxidative Annulation of *ortho*-Crotyl or Cinnamyl Arylaldehydes. Synthesis of Benzofused Five-, Six- and Seven-Membered Oxacycles

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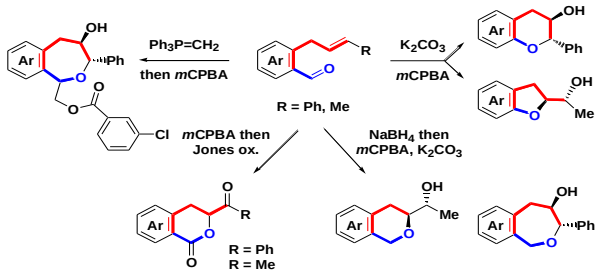
Supporting Information Placeholder

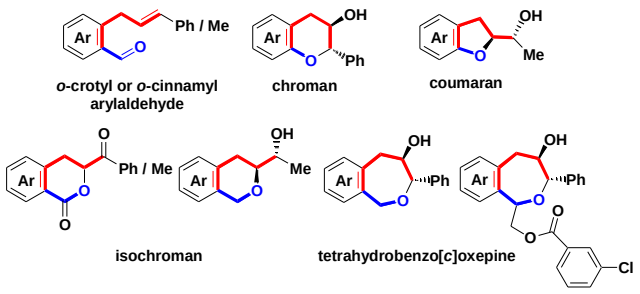


ABSTRACT: *m*CPBA-mediated intramolecular oxidative annulation of *ortho*-crotyl or cinnamyl arylaldehydes provides chroman, coumaran, isochroman, and tetrahydrobenzo[*c*]oxepine under different reaction conditions. This research investigates the reaction conditions for facile and efficient transformation.

ortho-Carbonyl allylarenes are the key synthetic intermediates for diversified structural transformations, and they are also used as building blocks to prepare many bioactive molecules.[1-2] For this core structure along with its related derivatives, many synthetic applications on the construction of different benzofused five-membered carbocycles (indene,[3] 1-indanol,[4] 1-indanone[5]), six-membered carbocycles (dialin,[6] 1-tetralone,[7] dihydroisoquinoline nitrone[8]), and heterocycles (dioxacycle,[9] isoquinoline[10]) have been reported via transition metal-catalyzed and base or acid-promoted intramolecular annulation. Intramolecular annulations of *ortho*-carbonyl vinylarenes are also popular approaches.[11]

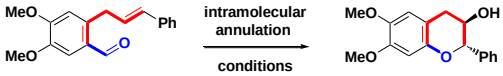
We recently explored synthetic applications of *ortho*-methylallyl (crotyl) and phenylallyl (cinnamyl) arylaldehydes for establishing some significant frameworks using facile condensation and cyclization strategies, including benzoazahomoisotwistane,[12a] tetrahydrocyclobuta[*a*]naphthalene,[12b] aryldihydronaphthalene,[12c] benzobicycle.[12d-f] and vinylindane.[12g] Although many synthetic protocols have been extensively investigated in the formation of multiple unique skeletons via functionalization of *ortho*-carbonyl allylarenes, few reports focus on the synthesis of oxygen-containing cyclic frameworks.[9,11a] Therefore, the development of an easy, one-pot route for the simultaneous carbon-oxygen (C-O) bond formation and ring-construction of diversified oxa-benzocycles from readily available starting *ortho*-carbonyl allylarenes is still a continuing need in the organic synthetic field. Among the present scaffolds in the benzofused oxacyclic family, the core structures of chroman, coumaran, isochroman, and tetrahydrobenzo[*c*]oxepine having five-, six-, or seven-membered ring systems are relatively well-studied, especially elegant synthetic methods[13] and biological activities (Scheme 1).[14] However, the involvement of a direct *m*CPBA (*m*-chloroperoxybenzoic acid)-mediated intramolecular annulation route into different ring-size oxacyclic skeletons has not been reported until recently. Based on the recent findings and studies, facile and efficient methods for their preparation are needed.

Scheme 1. Structures of *ortho*-Crotyl or Cinnamyl Arylaldehyde, Chroman, Coumaran, Isochroman, and Tetrahydrobenzo[*c*]oxepine



Continuing our research on the synthetic applications of *o*-cinnamyl arylaldehydes,[12] herein, we present the peroxide reagents-mediated preparation of chroman skeleton via one-pot synthetic sequence of epoxidation, Dakin reaction, deformylation and intramolecular annulation (Table 1). The initial study commenced with treatment of model substrate **1a** (1.0 mmol) with 2.2 equivalents of *m*CPBA in CH_2Cl_2 (10 mL) at 25 °C for 3 h. However, the complex mixture was isolated as major products and only trace **2a** (5% yield) were detected (entry 1). By the addition of K_2CO_3 (2.2 equiv), the yield of **2a** was increased to 57% along with 30% yield of the complex mixture (entry 2). Elongating the reaction time (3 → 15, 30 and 45 h), the yield increased to 70%, 90%, and 89%, respectively (entries 3-5). In entry 4, **2a** was isolated as a sole *trans*-isomer, and *cis*-form diastereomer was not detected. However, when the reaction temperature was elevated to reflux (~40 °C), the yield of **2a** decreased to 65% (entry 6). From the results, we envisioned that the elongated reaction time could increase the yield of **2a**. Subsequently, two peroxides were examined, such as *t*-butyl hydroperoxide (*t*BuO_2H) and H_2O_2. However, no isolation of the desired **2a** was observed (entries 7-8). After changing K_2CO_3 to Na_2CO_3 and Li_2CO_3, **2a** was produced at only 32% and 22% yields, respectively, due to weaker basicity inhibiting the intramolecular annulation (entries 9-10). By controlling *m*CPBA and K_2CO_3 (2.2 equiv) as the combination, other equivalents (1.1 and 3.3 equiv) were examined; however, 1.1 equivalents provided complex products and 3.3 equivalents afforded a similar yield (85%, entries 11-12). Solvent screening was performed next. It was found that the reaction had poorer yields (70% and 52%) obtained in DMF and MeCN, respectively (entries 13-14), while no desired product was detected in toluene (entry 15).

Table 1. Intramolecular Annulation Conditions[a]



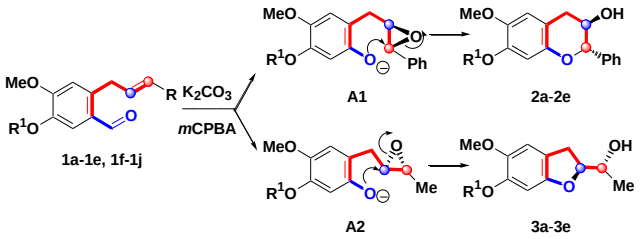
1a 2a

entry	peroxide	base	solvent	time (h)	**2a** (%)[b]
1	*m*CPBA	–	CH_2Cl_2	3	5[c]
2	*m*CPBA	K_2CO_3	CH_2Cl_2	3	57
3	*m*CPBA	K_2CO_3	CH_2Cl_2	15	70
4	*m*CPBA	K_2CO_3	CH_2Cl_2	30	90
5	*m*CPBA	K_2CO_3	CH_2Cl_2	45	89
6[d]	*m*CPBA	K_2CO_3	CH_2Cl_2	30	65
7	*t*BuO_2H	K_2CO_3	CH_2Cl_2	30	–[e]
8	H_2O_2	K_2CO_3	CH_2Cl_2	30	–[e]
9	*m*CPBA	Na_2CO_3	CH_2Cl_2	30	32[c]
10	*m*CPBA	Li_2CO_3	CH_2Cl_2	30	22[c]
11	*m*CPBA[f]	K_2CO_3[f]	CH_2Cl_2	30	–[e]
12	*m*CPBA[g]	K_2CO_3[g]	CH_2Cl_2	30	85
13	*m*CPBA	K_2CO_3	DMF	30	70
14	*m*CPBA	K_2CO_3	MeCN	30	52
15	*m*CPBA	K_2CO_3	toluene	30	–[e]

[a]The reactions were run on a 1.0 mmol scale with **1a**, peroxide (2.2 equiv), base (2.2 equiv), solvent (10 mL), 25 °C, time (h). [b]Isolated yields. [c]Complex products were isolated as major products. [d]Reflux. [e]No detection. [f]1.1 equivalents. [g]3.3 equivalents.

To study the scope of this route, *o*-cinnamyl arylaldehydes **1b**-**1e** (R^1 = benzyl, cyclopentyl, *n*-butyl and isopropyl) were reacted with the combination of *m*CPBA and K_2CO_3 to afford diversified **2b**-**2e** with the dihydrobenzopyran skeleton at 80%-84% based on the optimal conditions established (Table 1, entry 4), as shown in Table 2, entries-2-5. For treatment of *o*-crotyl arylaldehydes **1f**-**1j** (R^1 = methyl, benzyl, cyclopentyl, *n*-butyl and isopropyl), only coumaran **3a**-**3e** with dihydrobenzofuran skeleton were isolated at 76%-84% yields (entries 6-10). One possible reason could be the cinnamyl arm provided a more reactive epoxide center than the crotyl arm such that *in-situ* generated phenoxide (for intermediate **A1**) that could attack this benzylic center to form **2a**-**2e** with a six-membered ring via the intramolecular annulation. According to the efficiency of ring-formation, the five-membered ring was preferred to cyclize versus the six-membered ring by intramolecular annulation of *in-situ* generated phenoxide (for intermediate **A2**) and crotyl epoxide arm. On the basis of the results, we understood that the substituent of the cinnamyl (R = Ph) and crotyl (R = Me) could control the generation of two key benzofused oxacycles, chroman and coumaran, via the combination of *m*CPBA and K_2CO_3. The stereochemical structures of **2a** and **3b** were determined by single-crystal X-ray crystallography.[15]

Table 2. Synthesis of **2** and **3**[a]



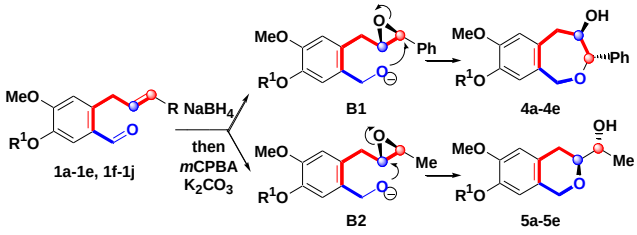
entry	**1**, R =, R^1 =	**2** / **3** (%)[b]
1	**1a**, Ph, Me	**2a**, 90
2	**1b**, Ph, Bn	**2b**, 82
3	**1c**, Ph, *c*-C_5H_9	**2c**, 80
4	**1d**, Ph, *n*-C_4H_9	**2d**, 81
5	**1e**, Ph, *i*-C_3H_7	**2e**, 84
6	**1f**, Me, Me	**3a**, 84
7	**1g**, Me, Bn	**3b**, 83
8	**1h**, Me, *c*-C_5H_9	**3c**, 78
9	**1i**, Me, *n*-C_4H_9	**3d**, 76
10	**1j**, Me, *i*-C_3H_7	**3e**, 78

[a]The reactions were run on a 1.0 mmol scale with **1a-1j**, K_2CO_3 (2.2 equiv), *m*CPBA (70%, 2.2 equiv), CH_2Cl_2 (10 mL), 25 °C, 30 h. [b]Isolated yields.

As an extension of *m*CPBA-mediated intramolecular annulations *o*-cinnamyl and *o*-crotyl arylaldehydes, the synthetic application on the skeleton of tetrahydrobenzo[*c*]oxepine was investigated (Table 3). By reduction of substrates **1a**-**1j** with $NaBH_4$ in MeOH at 25 °C, the primary alcohols were generated in quantitative amounts. Without purification, reaction of the resulting products with the combination of *m*CPBA and K_2CO_3 at 25 °C for 30 h produced tetrahydrobenzo[*c*]oxepines **4a**-**4e** (for R = Ph) and isochromans **5a**-**5d** (for R = Me) at 80%-88% yields. Among entries 1-9, efficient formation of **4a**-**4e** and **5a**-**5d** showed that the R^1 substituent did not affect

the yield. However, when R^1 is an isopropyl group (entry 10), only de-isopropyl **5e** (R^1 = H) was obtained at a 67% yield. Attempts to afford isopropyl-**5e** failed. For the intramolecular ring-closure of *in-situ* formed benzyloxide (for intermediate **B1**), the reactive benzylic position on the cinnamyl epoxide arm of **1a-1e** could be attacked to yield **4a-4e** with a seven-membered ring specifically. In contrast to the generation of **4a-4e**, the situation for the formation of **5a-5e** was similar to **3a-3e**. The intramolecular ring-closure from benzyloxide to the crotyl epoxide arm (for intermediate **B2**) still obeyed the ring-formation principal to generate a six-membered ring rather than a seven-membered ring. The stereochemical structures of **4a**, **4d**, and **5b** were determined by single-crystal X-ray crystallography.[15]

Table 3. Synthesis of **4** and **5**[a]

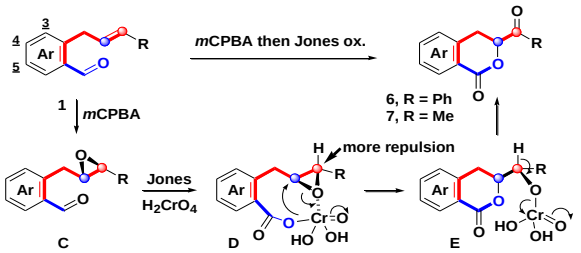


entry	**1**, R =, R^1 =	**4** / **5** (%)[b]
1	**1a**, Ph, Me	**4a**, 86
2	**1b**, Ph, Bn	**4b**, 88
3	**1c**, Ph, *c*-C_5H_9	**4c**, 83
4	**1d**, Ph, *n*-C_4H_9	**4d**, 84
5	**1e**, Ph, *i*-C_3H_7	**4e**, 80
6	**1f**, Me, Me	**5a**, 80
7	**1g**, Me, Bn	**5b**, 84
8	**1h**, Me, *c*-C_5H_9	**5c**, 80
9	**1i**, Me, *n*-C_4H_9	**5d**, 84
10	**1j**, Me, *i*-C_3H_7	**5e**,[c] 67

[a]The reactions were run on a 1.0 mmol scale with **1a-1j**, $NaBH_4$ (1.0 equiv), MeOH (10 mL), 25 °C, 30 min; *m*CPBA (70%, 1.1 equiv), then K_2CO_3 (1.1 equiv), CH_2Cl_2 (10 mL), 25 °C, 30 h. [b]Isolated yields. [c]R^1 = H.

After examining the phenoxide and benzyloxide-mediated intramolecular annulations, this study also explored how benzoate promoted ring-closure. Similarly, *o*-cinnamyl and *o*-crotyl arylaldehydes **1a-1e** and **1f-1j** (1.0 mmol) were reacted with 1.1 equivalents of *m*CPBA in the absence of K_2CO_3 in CH_2Cl_2 at 25 °C for 30 min to give an epoxide intermediate **C**. Subsequently, the resulting intermediate was oxidized by an excess Jones reagent (2 mL) at 25 °C for 3 h to afford isochroman-1-ones **6a-6e** (R = Ph) and **7a-7e** (R = Me) in good to excellent yields (89%-94% and 94%-96%) via intramolecular annulation of *in-situ* formed chromium benzoate intermediate **D** with cinnamyl epoxide chain followed by further oxidation of intermediate **E** with the resulting secondary alcohols (Table 4, entries 1-10). The structure of **6a** was determined by single-crystal X-ray crystallography.[15] Compared with the formation of **2a-2e** and **4a-4e**, the motif of carboxylate on the chromium-cheated complex favored to attack the less-reactive benzylic position of **1a-1e** to construct a six-membered ring system under the acidic conditions. According to our experimental results, one plausible reason is that the benzylic position with a bulkier steric hindrance provided more repulsion such that the carboxylate attacked another carbon. A similar phenomenon was observed in the formation of **7a-7e** (R = Me) via intramolecular annulation of chromium benzoate with a crotyl epoxide chain (for **1f-1j**). To demonstrate reproducibility, different aryl (Ar) groups were tested (Table 4, entries 11-18). For the electronic nature of the Ar group, the electron-neutral group (**1k**) and electron-withdrawing (**1m-1n**) and electron-donating groups (**1l**, **1o-1r**) were appropriate and well-tolerated.

Table 4. Synthesis of **6** and **7**[a]



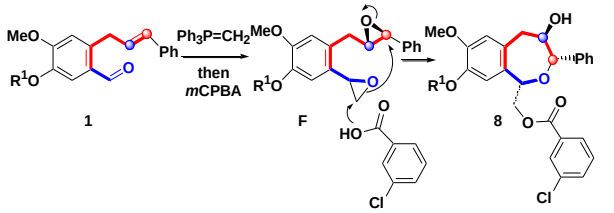
entry	**1**, R =, Ar =	**6** / **7** (%)[b]
1	**1a**, Ph, 4,5-$(MeO)_2C_6H_2$	**6a**, 93
2	**1b**, Ph, 4-MeO-5-$BnOC_6H_2$	**6b**, 94
3	**1c**, Ph, 4-MeO-5-*c*-$C_5H_9OC_6H_2$	**6c**, 90
4	**1d**, Ph, 4-MeO-5-*n*-$C_4H_9OC_6H_2$	**6d**, 91
5	**1e**, Ph, 4-MeO-5-*i*-$C_3H_7OC_6H_2$	**6e**, 89
6	**1f**, Me, 4,5-$(MeO)_2C_6H_2$	**7a**, 94
7	**1g**, Me, 4-MeO-5-$BnOC_6H_2$	**7b**, 96
8	**1h**, Me, 4-MeO-5-*c*-$C_5H_9OC_6H_2$	**7c**, 96
9	**1i**, Me, 4-MeO-5-*n*-$C_4H_9OC_6H_2$	**7d**, 95
10	**1j**, Me, 4-MeO-5-*i*-$C_3H_7OC_6H_2$	**7e**, 94
11	**1k**, Ph, Ph	**6f**, 93
12	**1l**, Ph, 4-MeO-5-allylOC_6H_2	**6g**, 93
13	**1m**, Ph, 4-FC_6H_3	**6h**, 94
14	**1n**, Ph, 5-FC_6H_3	**6i**, 93
15	**1o**, Ph, 5-$MeOC_6H_3$	**6j**, 90
16	**1p**, Ph, 3,5-$(MeO)_2C_6H_2$	**6k**, 89
17	**1q**, Ph, 3-MeO-5-$BnOC_6H_2$	**6l**, 84
18	**1r**, Ph, 3-MeO-5-*n*-$C_4H_9OC_6H_2$	**6m**, 88

[a]The reactions were run on a 1.0 mmol scale with **1a-1r**, *m*CPBA (70%, 1.1 equiv), CH_2Cl_2 (10 mL), 25 °C, 30 min; Jones reagent (2 mL), 25 °C, 3 h. [b]Isolated yields.

After investigating how the oxygen-atom (phenoxide, benzyloxide and benzoate) mediated the carbon-oxygen bond formation, this study then examined *m*CPBA-promoted carbon-carbon formation. First, Wittig olefination of the formyl group of **1a-1e** (R = Ph, 1.0 mmol) with *in-situ* generated excess $Ph_3P{=}CH_2$ (prepared from 2.0 equivalents of Ph_3CH_3I and 1.8 equivalents *t*BuOK) in THF (Table 5). Without further purification, the double expoxdation of the resulting olefin with 2.2 equivalents of *m*CPBA provided **8a-8e** as a mixture of two isomers (ratio ~ 1:1) in modest yields (60%-73%) via the release of *m*-chlorobenzoic acid mediating two epoxide ring-openings of intermediate **F** and a seven-membered ring formation (entries 1-5). However, after treatment of **1k** with the combination of $Ph_3P{=}CH_2$ and *m*CPBA, only di-epoxide product **9a** with a mixture of two isomers (ratio ~ 1:1) was

generated at a 78% yield, while no desired product conjugated *m*-chlorobenzoic acid was observed (Scheme 2). The possible reason should be that the oxygenated group on arene (Ar) played a key factor at promoting epoxide ring-opening such that *in-situ* generated alkoxy group could attack the benzylic position of another epoxide ring to produce polysubstituted oxygenated tetrahydrobenzo[*c*]oxepine skeleton via an intramolecular tandem process.

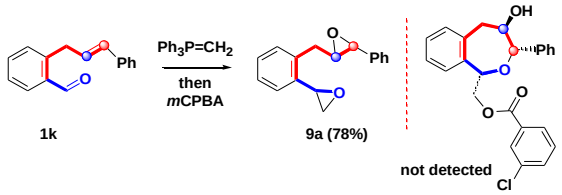
Table 5. Synthesis of **8**[a]



entry	**1**, R =, R^1 =	**8** (%)[b]
1	**1a**, Ph, Me	**8a**, 73
2	**1b**, Ph, Bn	**8b**, 70
3	**1c**, Ph, *c*-C_5H_9	**8c**, 66
4	**1d**, Ph, *n*-C_4H_9	**8d**, 60
5	**1e**, Ph, *i*-C_3H_7	**8e**, 67

[a]The reactions were run on a 1.0 mmol scale with **1a-1e**, Ph_3P=CHI (excess, *in-situ* formed from 2.0 equiv of PPh_3-CH_3I and 1.8 equiv of *t*BuOK), THF (10 mL), 25 °C, 30 min; *m*CPBA (70%, 1.1 equiv), CH_2Cl_2 (10 mL), 25 °C, 30 h. [b]Isolated yields.

Scheme 2. Synthesis of **9a**



In summary, we have herein developed *m*CPBA promoted facile and the efficient synthesis of benzofused oxacycles, including chroman, coumaran, isochroman, and tetrahydrobenzo[*c*]oxepine via intramolecular oxidative annulation of *o*-crotyl or *o*-cinnamyl arylaldehydes under different reaction combinations (e.g. K_2CO_3, $NaBH_4$, Jones reagent, and Ph_3P=CH_2) at 25 °C in moderate to good yields. The protocol provided products **2-3** and **4-5** as sole *trans*-isomers diastereoselectively. As far as we know, there have been no reports on the use of *o*-crotyl or *o*-cinnamyl arylaldehydes serving as the starting materials in the formation of benzofused oxacycles by the *m*CPBA-mediated one-pot synthetic route. The process provides a cascade pathway of carbon-oxygen and then carbon-carbon bond formations. We have also discussed the related plausible reaction mechanisms. The structures of the key products were confirmed by X-ray crystallography. Further investigations regarding the synthetic application of *o*-crotyl or *o*-cinnamyl arylaldehydes will be conducted and published in due course.

Experimental Section

General. All reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Products in organic solvents were dried with anhydrous magnesium sulfate before concentration in vacuo. Melting points were determined with a SMP3 melting apparatus. ^1H and ^{13}C NMR spectra were recorded on a Varian INOVA-400 spectrometer operating at 400 and at 100 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (*J*) are given in Hertz. High resolution mass spectra (HRMS) were measured with a mass spectrometer Finnigan/Thermo Quest MAT 95XL by electrospray ionization (ESI-TOF) method. X-ray crystal structures were obtained with an Enraf-Nonius FR-590 diffractometer (CAD4, Kappa CCD).

*Representative synthetic procedure of compounds **1a-1j**, **1l** and **1p-1r** is as follows:* K_2CO_3 (2.7 g, 20.0 mmol) was added to a stirred solution of isovanillin (1.52 g, 10.0 mmol) or 3-hydroxy-5-methoxy-benzaldehyde (1.52 g, 10.0 mmol) in MeCN (100 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 10 min. *Trans*-cinnamyl bromide (2.1 g, 11.0 mmol) or crotyl bromide (1.5 g, 11.0 mmol) was added to the reaction mixture at 25 °C. The reaction mixture was stirred at reflux for 8 h. The reaction was traced by TLC until isovanillin was consumed. The reaction mixture was cooled to 25 °C, concentrated, and extracted with EtOAc (3 x 60 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Without further purification, decalin (15 mL) was added to a solution of the resulting products. The reaction mixture was stirred at reflux for 8 h. The reaction was traced by TLC until the resulting product was consumed. The reaction mixture was cooled to 25 °C. Decalin was evaporated to afford crude product under reduced pressure. Without further purification, K_2CO_3 (2.7 g, 20.0 mmol) was added to a solution of the resulting product in THF (100 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 10 min. Methyl iodide (1.6 g, 11.0 mmol, for **1a**, **1f 1p**), benzyl bromide (1.9 g, 11.0 mmol, for **1b**, **1g**, **1q**), cyclopentyl bromide (1.6 g, 11.0 mmol for **1c**, **1h**), *n*-butyl bromide (1.5 g, 11.0 mmol for **1d**, **1i**, **1r**), isopropyl bromide (1.36 g, 11.0 mmol for **1e**, **1j**) or allyl bromide (1.3 g, 11.0 mmol, for **1l**) was added to the reaction mixture at 25 °C. The reaction mixture was stirred at reflux for 8 h (the reaction was traced by TLC). The reaction mixture was cooled to 25 °C, concentrated, and extracted with EtOAc (3 x 60 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 10/1~2/1) afforded **1a-1j**, **1l** and **1p-1r**. Compounds **1a-1j**, **1l** and **1p-1r** are known compounds and the analytical data are consistent with those in the references 12a-12g.

*Representative synthetic procedure of compounds **1k** and **1m-1o** is as follows:* $Pd(OAc)_2$ (5.6 mg, 2.5 mol %) and PPh_3 (13 mg, 5.0 mol %) were added to a solution of cinnamyl bromide (200 mg, 1.0 mmol) in a cosolvent of DME and EtOH (v/v = 9/1, 10 mL) at 25 °C. Then, Na_2CO_3 (159 mg, 1.5 mmol) and arylboronic acid (1.1 mmol) were added to the solution directly. The reaction mixture was stirred at reflux for 18 h. The reaction mixture was cooled to 25 °C, and the solvent was concentrated, and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 10/1~6/1)

afforded compounds **1k** and **1m-1o**. Compounds **1k** and **1m-1o** are known compounds and the analytical data are consistent with those in the reference 12g.

*Representative synthetic procedure of compounds **2a-2e** and **3a-3e** is as follows: m*CPBA (70%, 550 mg, 2.2 mmol) was added to a solution of **1a-1j** (1.0 mmol) in CH_2Cl_2 (10 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 30 min. Then, K_2CO_3 (300 mg, 2.2 mmol) was added to reaction mixture at 25 °C. The reaction mixture was stirred at 25 °C for 30 h. The reaction mixture was diluted with water (10 mL) and the mixture was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with saturated $NaHCO_{3(aq)}$ (3 x 20 mL), dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 8/1~4/1) afforded compounds **2a-2e** and **3a-3e**.

*3-Hydroxy-6,7-dimethoxy-2-phenylchroman (**2a**)*. Yield = 90% (257 mg); Colorless solid; mp = 128-130 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{17}H_{19}O_4$ 287.1283, found 287.1286; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.31 (m, 5H), 6.56 (s, 1H), 6.50 (s, 1H), 4.73 (d, *J* = 8.4 Hz, 1H), 4.11-4.06 (m, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 2.96 (dd, *J* = 5.6, 16.0 Hz, 1H), 2.81 (dd, *J* = 8.8, 16.0 Hz, 1H), 2.01 (br s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 148.4, 147.7, 143.5, 138.1, 128.6 (2C), 128.5, 127.0 (2C), 112.2, 110.2, 100.5, 81.7, 68.1, 56.3, 55.7, 32.3. Single-crystal X-Ray diagram: crystal of compound **2a** was grown by slow diffusion of EtOAc into a solution of compound **2a** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the triclinic crystal system, space group P - 1, *a* = 8.0587(6) Å , *b* = 8.8690(7) Å , *c* = 10.2746(8) Å , *V* = 705.26(9) Å^3, *Z* = 2, d_{calcd} = 1.348 g/cm^3, *F*(000) = 304, 2θ range 2.063~26.410°, R indices (all data) R1 = 0.0405, wR2 = 0.0928.

*7-Benzyloxy-6-methoxy-2-phenylchroman-3-ol (**2b**)*. Yield = 82% (297 mg); Colorless oil; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{23}H_{23}O_4$ 363.1596, found 363.1599; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.28 (m, 10H), 6.61 (s, 1H), 6.54 (s, 1H), 5.12 (d, *J* = 12.8 Hz, 1H), 5.09 (d, *J* = 12.8 Hz, 1H), 4.73 (d, *J* = 8.0 Hz, 1H), 4.13-4.08 (m, 1H), 3.85 (s, 3H), 2.99 (dd, *J* = 5.6, 16.0 Hz, 1H), 2.84 (dd, *J* = 8.8, 16.0 Hz, 1H), 1.80 (br s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 147.8, 147.7, 144.2, 138.1, 136.9, 128.8 (2C), 128.6, 128.5 (2C), 127.8, 127.2 (2C), 127.1 (2C), 113.1, 111.1, 102.8, 81.7, 70.8, 68.3, 56.7, 32.4.

*7-Cyclopentyloxy-6-methoxy-2-phenylchroman-3-ol (**2c**)*. Yield = 80% (272 mg); Colorless oil; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{21}H_{25}O_4$ 341.1753, found 341.1753; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.34 (m, 5H), 6.58 (s, 1H), 6.51 (s, 1H), 4.75 (d, *J* = 7.6 Hz, 1H), 4.71-4.67 (m, 1H), 4.15-4.09 (m, 1H), 3.80 (s, 3H), 3.00 (dd, *J* = 5.6, 15.6 Hz, 1H), 2.84 (dd, *J* = 8.8, 15.6 Hz, 1H), 1.94-1.76 (m, 7H), 1.63-1.55 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 147.8, 147.4, 144.6, 138.1, 128.8 (2C), 128.6, 127.2 (2C), 113.3, 110.3, 103.5, 81.8, 80.3, 68.4, 56.8, 32.8, 32.7, 32.4, 24.0 (2C).

*7-n-Butoxy-6-methoxy-2-phenyl-chroman-3-ol (**2d**)*. Yield = 81% (266 mg); Colorless oil; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{20}H_{25}O_4$ 329.1753, found 329.1756; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.35 (m, 5H), 6.58 (s, 1H), 6.52 (s, 1H), 4.74 (d, *J* = 7.6 Hz, 1H), 4.13-4.08 (m, 1H), 3.96 (t, *J* = 6.8 Hz, 2H), 3.82 (s, 3H), 2.99 (dd, *J* = 5.2, 16.0 Hz, 1H), 2.83 (dd, *J* = 8.4, 16.0 Hz, 1H), 1.88 (br s, 1H), 1.85-1.76 (m, 2H), 1.52-1.43 (m, 2H), 0.96 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 148.2, 147.8, 144.0, 138.1, 128.7 (2C), 128.6, 127.1 (2C), 112.9, 110.3, 101.8, 81.7, 68.6, 68.3, 56.7, 32.4, 31.0, 19.1, 13.8.

*7-Isopropoxy-6-methoxy-2-phenylchroman-3-ol (**2e**)*. Yield = 84% (264 mg); Colorless oil; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{19}H_{23}O_4$ 315.1596, found 315.1598; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.37 (m, 5H), 6.59 (s, 1H), 6.53 (s, 1H), 4.74 (d, *J* = 8.0 Hz, 1H), 4.49-4.43 (m, 1H), 4.13-4.09 (m, 1H), 3.81 (s, 3H), 3.00 (dd, *J* = 5.2, 16.0 Hz, 1H), 2.84 (dd, *J* = 8.8, 16.0 Hz, 1H), 1.85 (br s, 1H), 1.37 (d, *J* = 5.6 Hz, 3H), 1.36 (d, *J* = 5.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 147.7, 146.9, 144.8, 138.1, 128.8 (2C), 128.6, 127.1 (2C), 113.0, 110.7, 103.9, 81.8, 71.1, 68.3, 56.6, 32.5, 22.0, 21.9.

*1-(5,6-Dimethoxy-2,3-dihydrobenzofuran-2-yl)ethanol (**3a**)*. Yield = 84% (188 mg); Colorless oil; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{12}H_{17}O_4$ 225.1127, found 225.1125; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.60 (s, 1H), 6.26 (s, 1H), 4.51 (dt, *J* = 4.0, 12.4 Hz, 1H), 3.95-3.89 (m, 1H), 3.66 (s, 3H), 3.65 (s, 3H), 3.52 (dd, *J* = 8.0, 15.2 Hz, 1H), 2.97 (br s, 1H), 2.92 (dd, *J* = 9.6, 15.2 Hz, 1H), 1.08 (d, *J* = 6.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 153.3, 148.7, 142.8, 116.2, 109.0, 94.3, 86.7, 67.8, 56.5, 55.5, 29.5, 17.5.

*1-(6-Benzyloxy-5-methoxy-2,3-dihydrobenzofuran-2-yl)ethanol (**3b**)*. Yield = 83% (249 mg); Colorless solid; mp = 88-90 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{18}H_{21}O_4$ 301.1440, found 301.1442; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.26 (m, 5H), 6.76 (s, 1H), 6.42 (s, 1H), 5.06 (s, 2H), 4.62 (dt, *J* = 4.0, 12.4 Hz, 1H), 4.06-4.03 (m, 1H), 3.80 (s, 3H), 3.14 (dd, *J* = 8.4, 15.2 Hz, 1H), 3.01 (dd, *J* = 9.6, 15.2 Hz, 1H), 2.38 (br s, 1H), 1.17 (d, *J* = 6.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 153.4, 148.2, 143.9, 136.9, 128.3 (2C), 127.6, 127.1 (2C), 117.4, 110.1, 97.1, 87.0, 71.1, 68.0, 57.1, 29.5, 17.6. Single-crystal X-Ray diagram: crystal of compound **3b** was grown by slow diffusion of EtOAc into a solution of compound **3b** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the monoclinic crystal system, space group C 2/c, *a* = 22.457(3) Å , *b* = 5.2177(7) Å , *c* = 25.976(3) Å , *V* = 3028.0(7) Å^3, *Z* = 8, d_{calcd} = 1.318 g/cm^3, *F*(000) = 1280, 2θ range 1.576~26.616°, R indices (all data) R1 = 0.0983, wR2 = 0.1661.

*1-(6-Cyclopentyloxy-5-methoxy-2,3-dihydrobenzofuran-2-yl)ethanol (**3c**)*. Yield = 78% (217 mg); Colorless oil; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{16}H_{23}O_4$ 279.1596, found 279.1598; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.68 (s, 1H), 6.35 (s, 1H), 4.63-4.56 (m, 2H), 4.04-3.98 (m, 1H), 3.71 (s, 3H), 3.09 (dd, *J* = 8.4, 15.2 Hz, 1H), 2.97 (dd, *J* = 9.2, 15.2 Hz, 1H), 2.66 (br s, 1H), 1.84-1.71 (m, 6H), 1.56-1.49 (m, 2H), 1.15 (d, *J* = 6.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 153.5, 147.7, 144.1, 116.6, 110.5, 97.6, 86.9, 80.3, 68.0, 57.2, 32.50, 32.47, 29.6, 23.7 (2C), 17.7.

*1-(6-n-Butoxy-5-methoxy-2,3-dihydrobenzofuran-2-yl)ethanol (**3d**)*. Yield = 76% (202 mg); Colorless solid; mp = 56-58 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{15}H_{23}O_4$ 267.1596, found 267.1596; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.65 (s, 1H), 6.32 (s,

1H), 4.54 (dt, *J* = 4.0, 12.4 Hz, 1H), 3.98-3.94 (m, 1H), 3.83 (t, *J* = 6.8 Hz, 2H), 3.69 (s, 3H), 3.05 (dd, *J* = 8.4, 15.2 Hz, 1H), 2.94 (dd, *J* = 9.6, 15.2 Hz, 1H), 2.84 (br s, 1H), 1.74-1.66 (m, 2H), 1.44-1.35 (m, 2H), 1.12 (d, *J* = 6.4 Hz, 3H), 0.88 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 153.5, 148.5, 143.4, 116.4, 110.1, 95.9, 86.8, 68.5, 67.9, 57.0, 30.8, 29.6, 18.8, 17.6, 13.5.

*1-(6-Isopropoxy-5-methoxy-2,3-dihydrobenzofuran-2-yl)ethanol (**3e**)*. Yield = 78% (197 mg); Colorless oil; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{14}H_{21}O_4$ 253.1440, found 253.1441; ^1H NMR (400 MHz, $CDCl_3$): δ 6.69 (s, 1H), 6.36 (s, 1H), 4.58 (dt, *J* = 4.0, 8.8 Hz, 1H), 4.38-4.32 (m, 1H), 4.04-3.98 (m, 1H), 3.71 (s, 3H), 3.09 (dd, *J* = 8.4, 15.2 Hz, 1H), 2.98 (dd, *J* = 9.2, 15.2 Hz, 1H), 2.58 (br s, 1H), 1.28 (d, *J* = 6.0 Hz, 6H), 1.15 (d, *J* = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 153.5, 147.2, 144.6, 117.4, 110.2, 98.6, 86.9, 71.5, 68.0, 57.0, 29.6, 21.84, 21.80, 17.7.

*A representative synthetic procedure of compounds **4a**-**4e** and **5a**-**5e** is as follows:* $NaBH_4$ (38 mg, 1.0 mmol) was added to a solution of **1a**-**1j** (1.0 mmol) in MeOH (10 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 30 min. Then, water (1 mL) was added to the reaction mixture at 25 °C and the reaction mixture was concentrated. Then, the residue was diluted with water (10 mL) and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Without further purification, *m*CPBA (70%, 270 mg, 1.1 mmol) was added to a solution of the resulting crude product in CH_2Cl_2 (10 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 30 min. Then, K_2CO_3 (150 mg, 1.1 mmol) was added to the reaction mixture at 25 °C. The reaction mixture was stirred at 25 °C for 30 h. The reaction mixture was diluted with water (10 mL) and the mixture was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with saturated $NaHCO_{3(aq)}$ (3 x 20 mL), dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 8/1~4/1) afforded compounds **4a**-**4e** and **5a**-**5e**.

*7,8-Dimethoxy-3-phenyl-1,3,4,5-tetrahydrobenzo[c]oxepin-4-ol (**4a**)*. Yield = 86% (258 mg); Colorless solid; mp = 145-147 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{21}O_4$ 301.1440, found 301.1442; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41-7.31 (m, 5H), 6.83 (s, 1H), 6.75 (s, 1H), 4.73 (s, 2H), 4.42 (d, *J* = 8.8 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.71 (dt, *J* = 2.4, 8.8 Hz, 1H), 3.29 (dd, *J* = 10.4, 14.4 Hz, 1H), 3.11 (dd, *J* = 2.4, 14.4 Hz, 1H), 2.00 (br s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 148.3, 147.1, 140.0, 132.4, 129.3, 128.7 (2C), 128.5, 127.6 (2C), 113.9, 112.2, 91.6, 73.7, 72.2, 56.02, 56.00, 42.1. Single-crystal X-Ray diagram: crystal of compound **4a** was grown by slow diffusion of EtOAc into a solution of compound **4a** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the monoclinic crystal system, space group P 21/n, a = 6.8432(2) Å, b = 18.7402(7) Å, c = 11.7029(4) Å, V = 1500.39(9) Å^3, Z = 4, d_{calcd} = 1.330 g/cm^3, F(000) = 640, 2θ range 2.052~26.409°, R indices (all data) R1 = 0.0542, wR2 = 0.1116.

*8-Benzyloxy-7-methoxy-3-phenyl-1,3,4,5-tetrahydrobenzo[c]oxepin-4-ol (**4b**)*. Yield = 88% (331 mg); Colorless solid; mp = 78-80 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{24}H_{25}O_4$ 377.1753, found 377.1754; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46-7.29 (m, 10H), 6.86 (s, 1H), 6.78 (s, 1H), 5.14 (s, 2H), 4.68 (d, *J* = 12.8 Hz, 1H), 4.66 (d, *J* = 12.8 Hz, 1H), 4.41 (d, *J* = 8.4 Hz, 1H), 3.91 (s, 3H), 3.71 (dt, *J* = 2.4, 8.8 Hz, 1H), 3.28 (dd, *J* = 10.4, 14.4 Hz, 1H), 3.12 (dd, *J* = 2.4, 14.4 Hz, 1H), 1.95 (br s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 149.1, 146.4, 140.0, 137.1, 133.6, 132.4, 128.8 (2C), 128.6 (2C), 128.5 (2C), 127.8, 127.6 (2C), 127.3, 115.0, 114.5, 91.6, 73.7, 72.2, 71.3, 56.2, 42.1.

*8-Cyclopentyloxy-7-methoxy-3-phenyl-1,3,4,5-tetrahydrobenzo[c]oxepin-4-ol (**4c**)*. Yield = 83% (294 mg); Colorless solid; mp = 115-117 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{22}H_{27}O_4$ 355.1909, found 355.1912; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41-7.29 (m, 5H), 6.82 (s, 1H), 6.74 (s, 1H), 4.79-4.74 (m, 1H), 4.70 (s, 2H), 4.40 (d, *J* = 8.8 Hz, 1H), 3.86 (s, 3H), 3.69 (dt, *J* = 2.0, 8.4 Hz, 1H), 3.26 (dd, *J* = 10.0, 14.0 Hz, 1H), 3.08 (dd, *J* = 2.4, 14.4 Hz, 1H), 2.20 (br s, 1H), 1.95-1.79 (m, 6H), 1.64-1.57 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 149.3, 145.7, 140.1, 132.3, 129.2, 128.6 (2C), 128.4, 127.5 (2C), 115.8, 114.6, 91.5, 80.6, 73.7, 72.1, 56.2, 42.1, 32.8, 32.7, 23.9 (2C).

*8-Butoxy-7-methoxy-3-phenyl-1,3,4,5-tetrahydrobenzo[c]oxepin-4-ol (**4d**)*. Yield = 84% (287 mg); Colorless solid; mp = 70-72 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{27}O_4$ 343.1909, found 343.1912; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40-7.34 (m, 5H), 6.83 (s, 1H), 6.75 (s, 1H), 4.71 (s, 2H), 4.41 (d, *J* = 8.4 Hz, 1H), 4.02 (dt, *J* = 2.4, 5.2 Hz, 2H), 3.88 (s, 3H), 3.70 (dt, *J* = 2.4, 8.8 Hz, 1H), 3.28 (dd, *J* = 10.4, 14.4 Hz, 1H), 3.10 (dd, *J* = 2.4, 14.4 Hz, 1H), 1.86-1.79 (m, 2H), 1.54-1.45 (m, 2H), 1.60 (br s, 1H), 0.98 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 148.7, 146.7, 140.1, 132.4, 129.2, 128.7 (2C), 128.5, 127.6 (2C), 114.4, 113.9, 91.6, 73.8, 72.2, 68.9, 56.2, 42.1, 31.3, 19.2, 13.8. Single-crystal X-Ray diagram: crystal of compound **4d** was grown by slow diffusion of EtOAc into a solution of compound **4d** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the monoclinic crystal system, space group P 21/n, a = 12.0101(14) Å, b = 10.6094(13) Å, c = 15.9081(19) Å, V = 1883.8(4) Å^3, Z = 4, d_{calcd} = 1.207 g/cm^3, F(000) = 736, 2θ range 2.363~26.438°, R indices (all data) R1 = 0.0542, wR2 = 0.1079.

*8-Isopropoxy-7-methoxy-3-phenyl-1,3,4,5-tetrahydrobenzo[c]oxepin-4-ol (**4e**)*. Yield = 80% (262 mg); Colorless oil; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{25}O_4$ 329.1753, found 329.1754; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40-7.31 (m, 5H), 6.83 (s, 1H), 6.76 (s, 1H), 4.69 (s, 2H), 4.54-4.48 (m, 1H), 4.40 (d, *J* = 8.8 Hz, 1H), 3.87 (s, 3H), 3.70 (dt, *J* = 2.4, 8.8 Hz, 1H), 3.27 (dd, *J* = 10.4, 14.4 Hz, 1H), 3.09 (dd, *J* = 2.4, 14.4 Hz, 1H), 1.98 (br s, 1H), 1.38 (d, *J* = 5.6 Hz, 3H), 1.36 (d, *J* = 6.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 149.7, 145.3, 140.1, 132.4, 129.8, 128.6 (2C), 128.4, 127.5 (2C), 116.8, 114.6, 91.5, 73.7, 72.1, 71.7, 56.1, 42.2, 22.13, 22.08.

*1-(6,7-Dimethoxyisochroman-3-yl)ethanol (**5a**)*. Yield = 80% (190 mg); Colorless oil; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{13}H_{19}O_4$ 239.1283, found 239.1282; ^1H NMR

(400 MHz, $CDCl_3$): δ 6.63 (s, 1H), 6.48 (s, 1H), 4.78 (s, 2H), 4.06-4.01 (m, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.61 (dt, *J* = 3.2, 11.2 Hz, 1H), 2.90 (dd, *J* = 11.2, 16.0 Hz, 1H), 2.55 (dd, *J* = 3.2, 16.0 Hz, 1H), 2.17 (br s, 1H), 1.24 (d, *J* = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 147.8, 147.5, 126.2, 124.8, 111.9, 107.0, 77.9, 69.2, 68.1, 55.9 (2C), 26.7, 17.7.

1-(7-Benzyloxy-6-methoxyisochroman-3-yl)ethanol ***(5b)***. Yield = 84% (264 mg); Colorless solid; mp = 113-115 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{23}O_4$ 315.1596, found 315.1598; ^1H NMR (400 MHz, $CDCl_3$): δ 7.44-7.42 (m, 2H), 7.37-7.27 (m, 3H), 6.65 (s, 1H), 6.51 (s, 1H), 5.09 (s, 2H), 4.78 (s, 2H), 4.04-3.99 (m, 1H), 3.85 (s, 3H), 3.56 (dt, *J* = 3.2, 11.2 Hz, 1H), 2.89 (dd, *J* = 11.2, 16.0 Hz, 1H), 2.55 (dd, *J* = 3.2, 16.0 Hz, 1H), 2.50 (br s, 1H), 1.23 (d, *J* = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 148.4, 146.5, 137.0, 128.4 (2C), 127.7, 127.2 (2C), 126.1, 125.9, 112.4, 109.9, 77.9, 71.1, 69.1, 67.9, 56.0, 26.7, 17.6. Single-crystal X-Ray diagram: crystal of compound **5b** was grown by slow diffusion of EtOAc into a solution of compound **5b** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the monoclinic crystal system, space group C 2/c, *a* = 35.856(6) Å , *b* = 5.1944(10) Å , *c* = 19.808(3) Å , *V* = 3252.1(10) Å ^{3}, *Z* = 8, d_{calcd} = 1.321 g/cm^3, *F*(000) = 1384, 2*θ* range 1.288~25.3316°, R indices (all data) R1 = 0.1516, wR2 = 0.2804.

1-(7-Cyclopentyloxy-6-methoxyisochroman-3-yl)ethanol ***(5c)***. Yield = 80% (234 mg); Colorless oil; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{25}O_4$ 293.1753, found 293.1752; ^1H NMR (400 MHz, $CDCl_3$): δ 6.61 (s, 1H), 6.47 (s, 1H), 4.74 (s, 2H), 4.71-4.66 (m, 1H), 4.03-3.97 (m, 1H), 3.79 (s, 3H), 3.57 (dt, *J* = 3.2, 11.2 Hz, 1H), 2.87 (dd, *J* = 11.2, 16.0 Hz, 1H), 2.64 (br s, 1H), 2.60 (dd, *J* = 3.2, 16.0 Hz, 1H), 1.92-1.76 (m, 6H), 1.62-1.53 (m, 2H), 1.22 (d, *J* = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 148.8, 146.0, 126.1, 124.8, 112.5, 110.8, 80.5, 78.0, 69.1, 68.0, 56.0, 32.6 (2C), 26.7, 23.9 (2C), 17.6.

1-(7-n-Butoxy-6-methoxyisochroman-3-yl)ethanol ***(5d)***. Yield = 84% (235 mg); Colorless oil; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{25}O_4$ 281.1753, found 281.1756; ^1H NMR (400 MHz, $CDCl_3$): δ 6.62 (s, 1H), 6.49 (s, 1H), 4.76 (s, 2H), 4.05-3.99 (m, 1H), 3.95 (dt, *J* = 1.6, 6.8 Hz, 2H), 3.82 (s, 3H), 3.58 (dt, *J* = 3.6, 11.2 Hz, 1H), 2.89 (dd, *J* = 11.2, 15.6 Hz, 1H), 2.54 (dd, *J* = 3.2, 16.0 Hz, 1H), 2.50 (br s, 1H), 1.83-1.76 (m, 2H), 1.52-1.43 (m, 2H), 1.23 (d, *J* = 6.4 Hz, 3H), 0.96 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 148.2, 147.0, 126.1, 126.8, 112.3, 108.7, 78.0, 69.1, 68.8, 68.1, 56.0, 31.2, 26.7, 19.1, 17.7, 13.8.

3-(1-Hydroxyethyl)-6-methoxyisochroman-7-ol ***(5e)***. Yield = 67% (150 mg); Colorless solid; mp = 135-137 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{12}H_{17}O_4$ 225.1127, found 225.1123; ^1H NMR (400 MHz, $CDCl_3$): δ 6.61 (s, 1H), 6.55 (s, 1H), 5.53 (br s, 1H), 4.75 (s, 2H), 4.06-4.00 (m, 1H), 3.86 (s, 3H), 3.58 (dt, *J* = 3.6, 11.2 Hz, 1H), 2.89 (dd, *J* = 11.2, 16.0 Hz, 1H), 2.54 (dd, *J* = 3.2, 16.0 Hz, 1H), 2.18 (br s, 1H), 1.24 (d, *J* = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 145.4, 144.0, 127.0, 124.2, 111.2, 109.8, 77.9, 69.2, 68.0, 56.0, 26.8, 17.7.

A representative synthetic procedure of compounds ***6a-6m*** *and* ***7a-7e*** *is as follows:* *m*CPBA (70%, 270 mg, 1.1 mmol) was added to a solution of **1a-1r** (1.0 mmol) in CH_2Cl_2 (10 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 30 min. Excess Jones reagent (1 mL) was added to the reaction mixture at 25 °C. The reaction mixture was stirred at 25 °C for 3 h. Then, isopropanol (1 mL) was added to the reaction mixture at 25 °C and the reaction mixture was concentrated. Then, the residue was diluted with water (10 mL) and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 8/1~2/1) afforded compounds **6a-6m** and **7a-7e**.

3-Benzoyl-6,7-dimethoxyisochroman-1-one ***(6a)***. Yield = 93% (290 mg); Colorless solid; mp = 132-134 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{17}O_5$ 313.1076, found 313.1077; ^1H NMR (400 MHz, $CDCl_3$): δ 7.99-7.97 (m, 2H), 7.64-7.60 (m, 1H), 7.55 (s, 1H), 7.52-7.47 (m, 2H), 6.63 (s, 1H), 5.92 (dd, *J* = 5.6, 6.8 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.40 (dd, *J* = 5.6, 16.8 Hz, 1H), 3.33 (dd, *J* = 6.8, 16.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 194.1, 163.9, 153.9, 148.7, 134.0, 133.8, 130.9, 129.0 (2C), 128.9 (2C), 117.0, 111.6, 109.4, 78.0, 56.2, 56.1, 29.3. Single-crystal X-Ray diagram: crystal of compound **6a** was grown by slow diffusion of EtOAc into a solution of compound **6a** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the triclinic crystal system, space group P-1, *a* = 27.5282(6) Å , *b* = 8.2601(7) Å , *c* = 13.8286(12) Å , *V* = 731.54(11) Å ^{3}, *Z* = 2, d_{calcd} = 1.418 g/cm^3, *F*(000) = 328, 2*θ* range 2.810~26.406°, R indices (all data) R1 = 0.04273, wR2 = 0.1079.

3-Benzoyl-7-benzyloxy-6-methoxyisochroman-1-one ***(6b)***. Yield = 94% (365 mg); Colorless solid; mp = 143-145 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{24}H_{21}O_5$ 389.1389, found 389.1385; ^1H NMR (400 MHz, $CDCl_3$): δ 7.98-7.96 (m, 2H), 7.64-7.58 (m, 1H), 7.62 (s, 1H), 7.50-7.44 (m, 4H), 7.39-7.29 (m, 3H), 6.64 (s, 1H), 5.90 (dd, *J* = 6.0, 6.8 Hz, 1H), 5.15 (d, *J* = 12.0 Hz, 1H), 5.11 (d, *J* = 12.0 Hz, 1H), 3.88 (s, 3H), 3.37 (dd, *J* = 6.0, 16.8 Hz, 1H), 3.31 (dd, *J* = 6.8, 16.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 194.0, 163.8, 154.4, 147.8, 136.5, 134.0, 133.7, 131.3, 128.9 (2C), 128.8 (2C), 128.5 (2C), 128.0, 127.5 (2C), 116.8, 113.6, 109.7, 77.9, 70.9, 56.1, 29.3.

3-Benzoyl-7-cyclopentyloxy-6-methoxyisochroman-1-one ***(6c)***. Yield = 90% (329 mg); Colorless solid; mp = 108-110 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{22}H_{23}O_5$ 367.1546, found 367.1546; ^1H NMR (400 MHz, $CDCl_3$): δ 8.01-7.98 (m, 2H), 7.64-7.60 (m, 1H), 7.55 (s, 1H), 7.52-7.48 (m, 2H), 6.62 (s, 1H), 5.89 (t, *J* = 6.0 Hz, 1H), 4.84-4.80 (m, 1H), 3.87 (s, 3H), 3.34 (br d, *J* = 6.4 Hz, 2H), 2.04-1.93 (m, 2H), 1.90-1.76 (m, 4H), 1.67-1.57 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 194.1, 163.9, 154.9, 147.4, 134.0, 133.9, 130.6, 129.1 (2C), 128.9 (2C), 116.8, 114.5, 109.7, 80.6, 78.0, 56.2, 32.7, 32.6, 29.3, 24.04, 24.02.

3-Benzoyl-7-n-butoxy-6-methoxyisochroman-1-one ***(6d)***. Yield = 91% (322 mg); Colorless solid; mp = 131-133 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{23}O_5$ 355.1546, found 355.1545; ^1H NMR (400 MHz, $CDCl_3$): δ 7.98-7.96 (m, 2H), 7.63-7.59 (m, 1H), 7.53 (br d, *J* = 1.2 Hz, 1H), 7.51-7.47 (m, 2H), 6.61 (s,

1H), 5.91 (dd, *J* = 5.6, 7.2 Hz, 1H), 4.04 (dt, *J* = 1.2, 6.8 Hz, 2H), 3.88 (br d, *J* = 1.6 Hz, 3H), 3.38 (dd, *J* = 5.6, 16.4 Hz, 1H), 3.32 (dd, *J* = 6.8, 16.4 Hz, 1H), 1.86-1.79 (m, 2H), 1.53-1.43 (m, 2H), 0.97 (dt, *J* = 1.2, 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 194.1, 163.9, 154.2, 148.2, 134.0, 133.8, 130.6, 129.0 (2C), 128.9 (2C), 116.9, 112.7, 109.5, 78.0, 68.8, 56.1, 31.0, 29.3, 19.1, 13.8.

3-Benzoyl-7-isopropoxy-6-methoxyisochroman-1-one ***(6e)***. Yield = 89% (303 mg); Colorless oil; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{21}O_5$ 341.1389, found 341.1388; ^1H NMR (400 MHz, $CDCl_3$): δ 8.00-7.98 (m, 2H), 7.64-7.60 (m, 1H), 7.57 (s, 1H), 7.52-7.48 (m, 2H), 6.64 (s, 1H), 5.89 (t, *J* = 6.4 Hz, 1H), 4.64-4.58 (m, 1H), 3.88 (s, 3H), 3.35 (d, *J* = 6.4 Hz, 2H), 1.38 (d, *J* = 6.0 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 194.1, 163.9, 155.1, 147.0, 134.0, 133.9, 130.9, 129.0 (2C), 128.9 (2C), 116.9, 115.0, 109.8, 78.0, 71.4, 56.1, 29.3, 22.0, 21.8.

3-Benzoylisochroman-1-one ***(6f)***. Yield = 93% (234 mg); Colorless solid; mp = 128-130 ºC (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{13}O_3$ 253.0865, found 253.0866; ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, *J* = 0.8, 7.6 Hz, 1H), 7.97-7.95 (m, 2H), 7.64-7.60 (m, 1H), 7.54-7.47 (m, 3H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 5.97 (dd, *J* = 5.6, 6.8 Hz, 1H), 3.49 (dd, *J* = 5.6, 16.8 Hz, 1H), 3.38 (dd, *J* = 6.8, 16.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 193.8, 163.9, 136.3, 134.1, 134.0, 133.6, 130.2, 128.93 (2C), 128.91 (2C), 128.0, 127.5, 124.9, 77.8, 29.8.

7-Allyloxy-3-benzoyl-6-methoxyisochroman-1-one ***(6g)***. Yield = 93% (314 mg); Colorless solid; mp = 141-143 ºC (re-crystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{19}O_5$ 339.1233, found 339.1235; ^1H NMR (400 MHz, $CDCl_3$): δ 7.98-7.95 (m, 2H), 7.62-7.58 (m, 1H), 7.53 (s, 1H), 7.50-7.46 (m, 2H), 6.63 (s, 1H), 6.11-6.01 (m, 1H), 5.90 (dd, *J* = 5.6, 6.8 Hz, 1H), 5.42 (dq, *J* = 1.2, 17.2 Hz, 1H), 5.30 (dq, *J* = 1.2, 10.4 Hz, 1H), 4.61 (dt, *J* = 1.2, 6.4 Hz, 2H), 3.88 (s, 3H), 3.37 (dd, *J* = 5.6, 16.8 Hz, 1H), 3.31 (dd, *J* = 6.8, 16.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 194.0, 163.8, 154.2, 147.5, 134.0, 133.7, 132.4, 131.1, 128.9 (2C), 128.8 (2C), 118.6, 116.8, 113.2, 109.6, 77.9, 69.7, 56.1, 29.3.

3-Benzoyl-6-fluoroisochroman-1-one ***(6h)***. Yield = 94% (254 mg); Colorless solid; mp = 117-119 ºC (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{12}FO_3$ 271.0771, found 271.0771; ^1H NMR (400 MHz, $CDCl_3$): δ 8.14 (dd, *J* = 5.6, 8.8 Hz, 1H), 7.98-7.95 (m, 2H), 7.66-7.61 (m, 1H), 7.53-7.49 (m, 2H), 7.08 (dt, *J* = 2.4, 8.4 Hz, 1H), 6.91 (dd, *J* = 2.4, 8.4 Hz, 1H), 5.97 (t, *J* = 6.4 Hz, 1H), 3.49 (dd, *J* = 5.6, 16.8 Hz, 1H), 3.39 (dd, *J* = 6.4, 16.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 193.5, 165.9 (d, *J* = 254.7 Hz), 163.0, 139.4 (d, *J* = 9.8 Hz), 134.3, 133.5, 133.3 (d, *J* = 9.8 Hz), 129.00 (2C), 128.97 (2C), 121.3 (d, *J* = 3.1 Hz), 115.7 (d, *J* = 22.0 Hz), 114.5 (d, *J* = 22.7 Hz), 77.5, 29.8 (d, *J* = 1.5 Hz).

3-Benzoyl-7-fluoroisochroman-1-one ***(6i)***. Yield = 93% (251 mg); Colorless solid; mp = 110-112 ºC (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{12}FO_3$ 271.0771, found 271.0775; ^1H NMR (400 MHz, $CDCl_3$): δ 8.15 (dd, *J* = 5.6, 8.8 Hz, 1H), 7.98-7.96 (m, 2H), 7.66-7.62 (m, 1H), 7.53-7.49 (m, 2H), 7.09 (dt, *J* = 2.4, 8.4 Hz, 1H), 6.91 (dd, *J* = 2.4, 8.4 Hz, 1H), 5.97 (dd, *J* = 5.6, 6.4 Hz, 1H), 3.49 (dd, *J* = 5.6, 16.8 Hz, 1H), 3.39 (dd, *J* = 6.4, 16.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 193.5, 165.9 (d, *J* = 255.5 Hz), 163.0, 139.4 (d, *J* = 9.8 Hz), 134.3, 133.5, 133.3 (d, *J* = 9.9 Hz), 129.01 (2C), 128.98 (2C), 121.3 (d, *J* = 3.1 Hz), 115.7 (d, *J* = 21.9 Hz), 114.5 (d, *J* = 21.9 Hz), 77.5, 29.8.

3-Benzoyl-7-methoxyisochroman-1-one ***(6j)***. Yield = 90% (254 mg); Colorless oil; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{15}O_4$ 283.0970, found 283.0970; ^1H NMR (400 MHz, $CDCl_3$): δ 7.97-7.94 (m, 2H), 7.63-7.61 (m, 2H), 7.53-7.48 (m, 2H), 7.11-7.06 (m, 2H), 5.96 (dd, *J* = 5.6, 6.4 Hz, 1H), 3.85 (s, 3H), 3.46 (dd, *J* = 5.6, 16.4 Hz, 1H), 3.32 (dd, *J* = 6.4, 16.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 194.0, 164.1, 159.2, 134.1, 133.6, 129.5, 129.0 (2C), 128.9 (2C), 128.7, 128.3, 121.9, 112.8, 78.1, 56.6, 29.2.

3-Benzoyl-5,7-dimethoxyisochroman-1-one ***(6k)***. Yield = 89% (278 mg); Colorless oil; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{17}O_5$ 313.1076, found 313.1078; ^1H NMR (400 MHz, $CDCl_3$): δ 7.97-7.95 (m, 2H), 7.64-7.60 (m, 1H), 7.52-7.48 (m, 2H), 7.23 (d, *J* = 2.0 Hz, 1H), 6.61 (d, *J* = 2.4 Hz, 1H), 5.97 (t, *J* = 6.0 Hz, 1H), 3.85 (s, 3H), 3.76 (s, 3H), 3.37 (dd, *J* = 6.0, 17.2 Hz, 1H), 3.27 (dd, *J* = 6.0, 17.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 194.1, 164.1, 159.8, 156.8, 134.0, 133.5, 128.93 (2C), 128.88 (2C), 126.2, 117.9, 104.4, 103.4, 77.8, 55.70, 55.68, 23.5.

3-Benzoyl-7-benzyloxy-5-methoxyisochroman-1-one ***(6l)***. Yield = 84% (326 mg); Colorless oil; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{24}H_{21}O_5$ 389.1389, found 389.1388; ^1H NMR (400 MHz, $CDCl_3$): δ 7.98-7.96 (m, 2H), 7.64-7.61 (m, 1H), 7.52-7.34 (m, 8H), 6.70 (d, *J* = 2.4 Hz, 1H), 5.97 (t, *J* = 6.0 Hz, 1H), 5.09 (s, 2H), 3.75 (s, 3H), 3.38 (dd, *J* = 6.0, 17.2 Hz, 1H), 3.28 (dd, *J* = 6.8, 17.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 194.0, 164.1, 159.0, 156.9, 136.2, 134.1, 133.5, 128.93 (2C), 128.89 (2C), 128.7 (2C), 128.2, 127.8 (2C), 126.2, 118.2, 104.9, 104.3, 77.8, 70.4, 55.7, 23.5.

3-Benzoyl-7-n-butoxy-5-methoxyisochroman-1-one ***(6m)***. Yield = 88% (312 mg); Colorless solid; mp = 96-98 ºC (re-crystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{23}O_5$ 355.1546, found 355.1545; ^1H NMR (400 MHz, $CDCl_3$): δ 7.97-7.95 (m, 2H), 7.64-7.60 (m, 1H), 7.52-7.47 (m, 2H), 7.22 (d, *J* = 2.4 Hz, 1H), 6.62 (d, *J* = 2.4 Hz, 1H), 5.97 (t, *J* = 6.4 Hz, 1H), 4.01 (t, *J* = 6.8 Hz, 2H), 3.76 (s, 3H), 3.37 (dd, *J* = 6.0, 17.2 Hz, 1H), 3.26 (dd, *J* = 6.0, 17.2 Hz, 1H), 1.81-1.74 (m, 2H), 1.54-1.46 (m, 2H), 0.98 (t, *J* = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 194.1, 164.2, 159.4, 156.8, 134.0, 130.1, 128.92 (2C), 128.90 (2C), 126.1, 117.7, 104.7, 104.1, 77.8, 68.1, 55.7, 31.2, 23.5, 19.2, 13.8.

3-Acetyl-6,7-dimethoxyisochroman-1-one ***(7a)***. Yield = 94% (235 mg); Colorless solid; mp = 136-138 ºC (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{13}H_{15}O_5$ 251.0920, found 251.0922; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (s, 1H), 6.67 (s, 1H), 4.87 (dd, *J* = 4.8, 8.8 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.19 (dd, *J* = 5.2, 16.4 Hz, 1H), 3.11 (dd, *J* = 8.8, 16.4 Hz, 1H), 2.35 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 205.6, 163.8, 154.1, 148.7, 131.8, 116.6, 111.6, 109.3, 81.5, 56.2, 56.1, 28.6, 26.6.

3-Acetyl-7-benzyloxy-6-methoxyisochroman-1-one ***(7b)***. Yield = 96% (313 mg); Colorless solid; mp = 160-162 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{19}O_5$ 327.1233, found 327.1235; ^1H NMR (400 MHz, $CDCl_3$): δ 7.59 (s, 1H), 7.43-7.29 (m, 5H), 6.69 (s, 1H), 5.16 (d, *J* = 12.0 Hz, 1H), 5.13 (d, *J* = 12.0 Hz, 1H), 4.86 (dd, *J* = 5.2, 8.8 Hz, 1H), 3.93 (s, 3H), 3.18 (dd, *J* = 5.2, 16.8 Hz, 1H), 3.12 (dd, *J* = 8.8, 16.4 Hz, 1H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 205.7, 163.7, 154.7, 147.9, 136.1, 132.1, 128.6 (2C), 128.1, 127.5 (2C), 116.5, 113.8, 109.7, 81.5, 70.9, 56.2, 28.7, 26.7.

3-Acetyl-7-cyclopentyloxy-6-methoxyisochroman-1-one ***(7c)***. Yield = 96% (292 mg); Colorless solid; mp = 152-154 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{21}O_5$ 305.1389, found 305.1387; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (s, 1H), 6.66 (s, 1H), 4.87 (dd, *J* = 5.2, 8.8 Hz, 1H), 4.83-4.79 (m, 1H), 3.90 (s, 3H), 3.17 (dd, *J* = 5.2, 16.4 Hz, 1H), 3.11 (dd, *J* = 8.8, 16.4 Hz, 1H), 2.38 (s, 3H), 2.03-1.96 (m, 2H), 1.95-1.76 (m, 4H), 1.67-1.58 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 205.8, 163.9, 155.1, 147.5, 131.4, 116.5, 114.6, 109.7, 81.6, 80.6, 56.2, 32.7, 32.6, 28.7, 26.7, 24.0 (2C).

3-Acetyl-7-butoxy-6-methoxyisochroman-1-one ***(7d)***. Yield = 95% (277 mg); Colorless solid; mp = 142-144 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{21}O_5$ 293.1389, found 293.1390; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (s, 1H), 6.66 (s, 1H), 4.87 (dd, *J* = 4.8, 8.8 Hz, 1H), 4.04 (dt, *J* = 2.8, 6.8 Hz, 2H), 3.91 (s, 3H), 3.18 (dd, *J* = 5.2, 16.4 Hz, 1H), 3.12 (dd, *J* = 8.8, 16.4 Hz, 1H), 2.37 (s, 3H), 1.86-1.79 (m, 2H), 1.53-1.43 (m, 2H), 0.97 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 205.7, 163.9, 154.5, 148.3, 131.5, 116.5, 112.9, 109.5, 81.6, 68.9, 56.2, 31.0, 28.2, 26.7, 19.1, 13.8.

3-Acetyl-7-isopropoxy-6-methoxyisochroman-1-one ***(7e)***. Yield = 94% (261 mg); Colorless solid; mp = 146-148 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{19}O_5$ 279.1233, found 279.1235; ^1H NMR (400 MHz, $CDCl_3$): δ 7.53 (s, 1H), 6.67 (s, 1H), 4.87 (dd, *J* = 5.2, 8.8 Hz, 1H), 4.62-4.56 (m, 1H), 3.90 (s, 3H), 3.18 (dd, *J* = 5.2, 16.4 Hz, 1H), 3.11 (dd, *J* = 8.8, 16.4 Hz, 1H), 2.37 (s, 3H), 1.37 (d, *J* = 6.0 Hz, 3H), 1.36 (d, *J* = 6.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 205.7, 163.8, 155.3, 147.0, 131.6, 116.5, 115.1, 109.8, 81.5, 71.5, 56.2, 28.7, 26.7, 21.9, 21.8.

A representative synthetic procedure of compounds ***8a-8e*** *and* ***9a*** *is as follows:* *t*BuOK (200 mg, 1.8 mmol) was added to a solution of Ph_3PCH_3I (810 mg, 2.0 mmol) in anhydrous THF (8 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 10 min. Then, **1a**-**1e** and **1k** (1.0 mmol) in anhydrous THF (2 mL) was added to the reaction mixture at 25 °C. The reaction mixture was stirred at 25 °C for 30 min. Then, water (1 mL) was added to the reaction mixture at 25 °C and the reaction mixture was concentrated. Then, the residue was diluted with water (10 mL) and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Without further purification, *m*CPBA (70%, 550 mg, 2.2 mmol) was added to a solution of the resulting crude product in CH_2Cl_2 (10 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 30 h. The reaction mixture was diluted with saturated $NaHCO_{3(aq)}$ (10 mL) and the mixture was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with saturated $NaHCO_{3(aq)}$ (3 x 20 mL), dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 10/1~3/1) afforded compounds **8a**-**8e** and **9a**.

3-Chlorobenzoic acid 4-hydroxy-7,8-dimethoxy-3-phenyl-1,3,4,5-tetrahydrobenzo[c]oxepin-1-ylmethyl ester ***(8a)***. Two isomers (ratio = 1:1); Yield = 73% (342 mg); Colorless gum; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{26}ClO_6$ 469.1418, found 469.1419; ^1H NMR (400 MHz, $CDCl_3$): δ 8.03-8.02 (m, 1H), 7.95-7.92 (m, 1H), 7.54-7.51 (m, 1H), 7.39-7.22 (m, 6H), 6.97 (s, 1/2H), 6.95 (s, 1/2H), 6.792 (s, 1/2H), 6.788 (s, 1/2H), 6.31-6.26 (m, 1H), 4.14-4.08 (m, 1H), 4.02-3.81 (m, 2H), 3.873 (s, 3H), 3.868 (s, 3/2H), 3.86 (s, 3/2H), 3.61 (d, *J* = 2.4 Hz, 1/2H), 3.50 (dd, *J* = 4.4, 15.2 Hz, 1/2H), 3.31-3.22 (m, 1H), 3.17-3.12 (m, 1H), 2.40 (br s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.91 (1/2C), 164.87 (1/2C), 149.14 (1/2C), 149.09 (1/2C), 148.27 (1/2C), 148.23 (1/2C), 136.92 (1/2C), 136.85 (1/2C), 134.53 (1/2C), 134.51 (1/2C), 133.16 (1/2C), 133.12 (1/2C), 131.76 (1/2C), 131.70 (1/2C), 129.7 (1C), 129.6 (1C), 128.59 (1/2C), 128.52 (1/2C), 128.44 (2C), 128.21 (1/2C), 128.18 (1/2C), 127.81 (1/2C), 127.78 (1/2C), 127.74 (1/2C), 127.28 (1/2C), 125.6 (2C), 113.6 (1/2C), 113.0 (1/2C), 109.8 (1/2C), 109.7 (1/2C), 74.6 (1C), 65.7 (1/2C), 65.4 (1/2C), 63.3 (1/2C), 62.6 (1/2C), 59.1 (1/2C), 57.7 (1/2C), 56.1 (1/2C), 56.0 (1/2C), 55.90 (1/2C), 55.86 (1/2C), 35.4 (1/2C), 34.1 (1/2C).

3-Chlorobenzoic acid 8-benzyloxy-4-hydroxy-7-methoxy-3-phenyl-1,3,4,5-tetrahydrobenzo[c]oxepin-1-ylmethyl ester ***(8b)***. Yield = 70% (381 mg); Colorless gum; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{32}H_{30}ClO_6$ 545.1731, found 545.1733; ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (br s, 1H), 7.84-7.82 (m, 1H), 7.54-7.51 (m, 1H), 7.41-7.18 (m, 11H), 6.96 (s, 1/2H), 6.93 (s, 1/2H), 6.824 (s, 1/2H), 6.818 (s, 1/2H), 6.24-6.20 (m, 1H), 5.20-5.12 (m, 2H), 4.01-3.81 (m, 2H), 3.89 (s, 3/2H), 3.88 (s, 3/2H), 3.66-3.63 (m, 1H), 3.44 (dd, *J* = 4.4, 14.8 Hz, 1/2H), 3.30-3.24 (m, 3/2H), 3.16-3.08 (m, 1H), 2.60 (br s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.70 (1/2C), 164.65 (1/2C), 149.64 (1/2C), 149.60 (1/2C), 147.0 (1/2C), 146.9 (1/2C), 136.9 (1/2C), 136.79 (1/2C), 136.75 (1/2C), 136.72 (1/2C), 134.3 (1/2C), 133.00 (1/2C), 132.96 (1/2C), 131.5 (1/2C), 129.6 (1/2C), 129.5 (1C), 128.9 (1/2C), 128.4 (4C), 128.12 (1C), 128.10 (1C), 127.74 (1/2C), 127.72 (2C), 128.68 (1/2C), 127.6 (1C), 127.08 (1C), 127.07 (1C), 125.5 (2C), 113.9 (1/2C), 113.3 (1/2C), 112.9 (1/2C), 112.8 (1/2C), 74.31 (1/2C), 74.28 (1/2C), 71.1 (1C), 65.5 (1/2C), 65.3 (1/2C), 63.2 (1/2C), 62.5 (1/2C), 59.0 (1/2C), 57.7 (1/2C), 55.9 (1/2C), 55.8 (1/2C), 35.3 (1/2C), 34.1 (1/2C).

3-Chlorobenzoic acid 8-cyclopentyloxy-4-hydroxy-7-methoxy-3-phenyl-1,3,4,5-tetrahydrobenzo[c]oxepin-1-ylmethyl ester ***(8c)***. Yield = 66% (345 mg); Colorless gum; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{30}H_{32}ClO_6$ 523.1888, found 523.1886; ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 (t, *J* = 1.2 Hz, 1H), 7.95-7.92 (m, 1H), 7.55-7.52 (m, 1H), 7.40-7.24 (m, 5H), 6.99 (s, 1/2H), 6.97 (s, 1/2H), 6.78 (s, 1/2H), 6.77 (s, 1/2H), 6.31-6.26 (m, 1H), 4.78-4.75 (m, 2H), 4.12-3.91 (m, 2H), 3.84 (s, 3/2H), 3.83 (s, 3/2H), 3.63-3.62 (m, 1H), 3.45 (dd, *J* = 4.4, 14.8 Hz, 1/2H), 3.30-3.22 (m, 3/2H), 3.16-3.09 (m, 1H), 2.20 (br s, 1H), 1.95-1.76 (m, 8H); $^{13}C\{^1H\}$

NMR (100 MHz, $CDCl_3$): δ 164.92 (1C), 150.2 (1/2C), 150.1 (1/2C), 146.9 (1C), 137.0 (1/2C), 136.9 (1/2C), 134.6 (1C), 133.2 (1/2C), 133.1 (1/2C), 131.9 (1/2C), 131.8 (1/2C), 129.8 (1C), 129.7 (1C), 128.5 (2C), 128.3 (1/2C), 128.24 (1/2C), 128.21, (1/2C), 127.8 (1/2C), 127.7 (1/2C), 128.6 (1/2C), 127.1 (1C), 125.6 (2C), 114.2 (1/2C), 113.6 (1C), 113.4 (1/2C), 80.6 (1C), 74.5 (1C), 65.9 (1/2C), 65.6 (1/2C), 63.4 (1/2C), 62.7 (1/2C), 59.1 (1/2C), 57.8 (1/2C), 56.1 (1/2C), 56.0 (1/2C), 35.5 (1/2C), 34.2 (1/2C), 32.8 (1C), 32.6 (1C), 24.0 (2C).

*3-Chlorobenzoic acid 8-butoxy-4-hydroxy-7-methoxy-3-phenyl-1,3,4,5-tetrahydrobenzo[c]oxepin-1-yl methyl ester (**8d**).* Yield = 60% (306 mg); Colorless gum; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{29}H_{32}ClO_6$ 511.1888, found 511.1885; ^1H NMR (400 MHz, $CDCl_3$): δ 8.04-8.02 (m, 1H), 7.95-7.92 (m, 1H), 7.54-7.52 (m, 1H), 7.41-7.23 (m, 6H), 6.98 (s, 1/2H), 6.96 (s, 1/2H), 6.79 (s, 1/2H), 6.78 (s, 1/2H), 6.30-6.25 (m, 1H), 4.14-3.91 (m, 4H), 3.88-3.85 (m, 1H), 3.86 (s, 3/2H), 3.85 (s, 3/2H), 3.61 (d, *J* = 2.0 Hz, 1/2H), 3.49 (dd, *J* = 4.4, 15.2 Hz, 1/2H), 3.31-3.22 (m, 1H), 3.16-3.11 (m, 1H), 2.30 (br s, 1H), 1.82-1.75 (m, 2H), 1.52-1.43 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.92 (1/2C), 164.89 (1/2C), 149.62 (1/2C), 149.57 (1/2C), 147.79 (1/2C), 147.75 (1/2C), 136.98 (1/2C), 136.90 (1/2C), 134.5 (1C), 133.16 (1/2C), 133.13 (1/2C), 131.80 (1/2C), 131.74 (1/2C), 129.74 (1C), 129.65 (1C), 128.45 (2C), 128.21 (1/2C), 128.19 (1/2C), 127.8 (1C), 127.77 (1/2C), 128.72 (1/2C), 127.21 (1C), 125.6 (2C), 114.1 (1/2C), 113.4 (1/2C), 111.6 (1/2C), 111.5 (1/2C), 74.6 (1C), 69.0 (1/2C), 68.9 (1/2C), 65.7 (1/2C), 65.5 (1/2C), 63.3 (1/2C), 62.7 (1/2C), 59.1 (1/2C), 57.7 (1/2C), 56.01 (1/2C), 55.97 (1/2C), 35.4 (1/2C), 34.1 (1/2C), 31.1 (1C), 19.1 (1C), 13.8 (1C).

*3-Chlorobenzoic acid 4-hydroxy-8-isopropoxy-7-methoxy-3-phenyl-1,3,4,5-tetrahydrobenzo[c]oxepin-1-ylmethyl ester (**8e**).* Yield = 67% (332 mg); Colorless gum; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{28}H_{30}ClO_6$ 497.1731, found 497.1732; ^1H NMR (400 MHz, $CDCl_3$): δ 8.05-8.02 (m, 1H), 7.96-7.91 (m, 1H), 7.52-7.48 (m, 1H), 7.41-7.23 (m, 6H), 7.02 (s, 1/2H), 7.00 (s, 1/2H), 6.794 (s, 1/2H), 6.788 (s, 1/2H), 6.31-6.26 (m, 1H), 4.55-4.47 (m, 1H), 4.11-3.88 (m, 1H), 3.84 (s, 3H), 3.83 (s, 3/2H), 3.82 (s, 3/2H), 3.64 (d, *J* = 2.0 Hz, 1/2H), 3.43 (dd, *J* = 4.4, 15.2 Hz, 1/2H), 3.29-3.23 (m, 1H), 3.16-3.09 (m, 1H), 1.35 (d, *J* = 6.8 Hz, 3H), 1.31 (d, *J* = 6.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.84 (1/2C), 164.81 (1/2C), 150.4 (1/2C), 150.3 (1/2C), 146.23 (1/2C), 146.19 (1/2C), 136.9 (1/2C), 136.8 (1/2C), 134.4 (1C), 133.01 (1/2C), 132.99 (1/2C), 131.72 (1/2C), 131.67 (1/2C), 129.6 (1C), 129.5 (1C), 128.3 (2C), 128.10 (1/2C), 128.08 (1/2C), 127.74 (1/2C), 127.67 (1C), 127.6 (1/2C), 125.5 (2C), 119.6 (1/2C), 114.6 (1/2C), 114.5 (1/2C), 114.1 (1/2C), 113.5 (1/2C), 111.8 (1/2C), 74.47 (1/2C), 74.45 (1/2C), 71.56 (1/2C), 71.52 (1/2C), 65.6 (1/2C), 65.4 (1/2C), 63.2 (1/2C), 62.6 (1/2C), 59.0 (1/2C), 57.8 (1/2C), 55.83 (1/2C), 55.80 (1/2C), 32.3 (1/2C), 34.1 (1/2C), 22.00 (1/2C), 21.97 (1/2C), 21.9 (1/2C), 21.7 (1/2C).

*2-[2-(3-Phenyl-2,3-oxiranyl)phenyl]oxirane (**9a**).* Yield = 78% (197 mg); Two isomers, ratio = 1 : 1; Colorless gum; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{17}O_2$ 253.1229, found 253.1233; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39-7.28 (m, 9H), 4.16-4.13 (m, 1H), 3.74 (d, *J* = 1.6 Hz, 1/2H), 3.71 (d, *J* = 1.2 Hz, 1/2H), 3.29-3.18 (m, 4H), 2.79 (dd, *J* = 2.8, 6.0 Hz, 1/2H), 2.74 (dd, *J* = 2.8, 5.6 Hz, 1/2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 137.5 (1C), 136.13 (1/2C), 136.08 (1/2C), 135.4 (1/2C), 135.0 (1/2C), 129.7 (1/2C), 129.6 (1/2C), 128.4 (2C), 128.0 (1C), 127.9 (1/2C), 127.8 (1/2C), 127.2 (1/2C), 127.1 (1/2C), 125.4 (2C), 124.7 (1/2C), 124.6 (1/2C), 62.3 (1/2C), 62.2 (1/2C), 58.3 (1/2C), 58.2 (1/2C), 50.3 (1/2C), 50.20 (1/2C), 50.15 (1/2C), 50.1 (1/2C), 35.1 (1/2C), 34.9 (1/2C).

ASSOCIATED CONTENT

Supporting Information

Scanned photocopies of NMR spectral data for all compounds and X-ray analysis data of **2a**, **3b**, **4a**, **4d**, **5b** and **6a**. This information is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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