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Trifluoroacetic Anhydride-Mediated One-Pot Synthesis of 1-Aryl Isochroman-3-ones *via* the Carboxy-Pictet-Spengler Reaction

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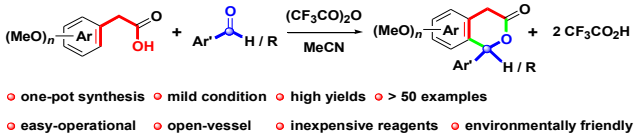
Supporting Information Placeholder

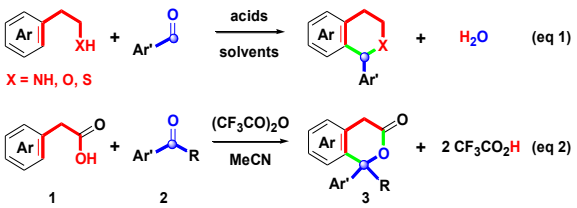


ABSTRACT: In this paper, a novel and open-vessel route for the facile-operational synthesis of 1-aryl isochroman-3-ones is described via $(CF_3CO)_2O$ (trifluoroacetic anhydride, TFAA)-mediated intermolecular (4+2) annulation of oxygenated arylacetic acids with arylaldehydes or ketones under mild reaction conditions. A plausible mechanism is proposed and discussed herein. Various reaction conditions are investigated for efficient transformation under an environmentally friendly one-pot carboxy-Pictet-Spengler reaction.

Introduction

The Pictet-Spengler reaction is an important tool for preparing isoquinoline and β-carboline derivatives via cyclocondensation of β-arylethylamines with carbonyl compounds.[1] On the basis of the Pictet-Spengler type reactions (Scheme 1, eq 1, X = NH), many review articles have documented synthetic applications for diversified natural products, bioactive molecules, functionalized materials and synthetic blocks.[2-4] After *ca.* ninety years, an oxa-Pictet-Spengler reaction (X = O) was developed by Wunsch and Zott to construct the core skeleton of substituted isochroman with modest to good yields by the combination of $ZnCl_2$, *p*TsOH and $HCl_{(g)}$ or Lewis acid (e.g., $TiCl_4$, $AlCl_3$, and $SnCl_2$)-mediated intermolecular annulation of 2-arylethanol with aldehydes or ketones.[5-12] In recent years, the evaluated scope has been extended to a thia-Pictet-Spengler reaction (X = S) in the formation of a thiaisochroman skeleton.[13-15] Overall, the facile intermolecular annulation of 2-arylethyl amines, alcohols and thiols with a variety of carbonyl synthons has seen growing interest with Brønsted acids or Lewis acids-promoted routes.

Scheme 1. Heteroatom-Pictet-Spengler Type Reactions



Among these synthetic variations towards heteroatom-Pictet-Spengler type reactions, to the best of our knowledge, only a few early examples on the generation of 1-substituted isochromans via the synthetic route have been reported.[16-18] On the basis of the above recorded observations for Pictet-Spengler type reactions and the ongoing effort to emphasize the synthesis of oxygen-containing benzocycles,[19-23] herein, we present an efficient, one-step synthetic route towards 1-aryl isochroman-3-ones **3** via a carboxy-Pictet-Spengler reaction of oxygenated arylacetic acids **1** with arylaldehydes or ketones **2** in the presence of inexpensive commercially available $(CF_3CO)_2O$ (trifluoroacetic anhydride, TFAA) via intermolecular (4+2) annulation. In equation 2, only 2 equivalents of trifluoroacetic acid (TFA, a byproduct) are generated from the hydrolysis of TFAA with the *in situ*-formed H_2O. This is important from a facile-operational point of view because a TFAA-mediated reaction possesses excellent selectivity and activity, and it produces high-yield products.[24-25]

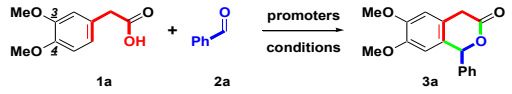
For preparation of the skeleton of 1-substituted isochroman, many efforts using synthetic routes have also been well-documented.[26-32] Regarding the installation of 1-substituent into a key core skeleton of 1-substituted isochroman, the synthetic route has long held a respected position in a number of reports in the synthetic and pharmaceutic fields due to its specific chemoselectivity and diversified bioactivity.[33-37] These major significant efforts focus on transition metal (e.g., Mn^{4+}, Cu^{2+}, and Fe^{3+})-catalysed or oxidant (e.g., DDQ, PIFA, and TBHP)-mediated $C(sp^3)$-H bond functionization of isochromans with activated carbon nucleophiles (e.g., ketones,

β-dicarbonyls, and oxygenated arenes) under a direct cross-dehydrogenative-coupling (CDC) procedure.

Results and discussion

The initial study commenced with the treatment of model substrate **1a** (Ar = 3,4-$(MeO)_2C_6H_3$; Ar' = Ph, 1.0 mmol) with benzaldehyde (**2a**, 1.0 equiv). First, by the addition of TFAA (1.0 equiv), **3a** was obtained in an 80% yield in MeCN (10 mL) at 25 °C for 5 h via intramolecular annulation (Table 1, entry 1). With these results in mind, the optimal annulation condition was examined next. Controlling TFAA as the promoter, we surveyed the factors of solvent, time and reaction temperature on the ring-closure process. However, a lower yield (63%) of **3a** was observed for $MeNO_2$ (entry 2), and THF provided a low yield (28%) along with other major complex mixtures (entry 3).

Table 1. Reaction Conditions[a]

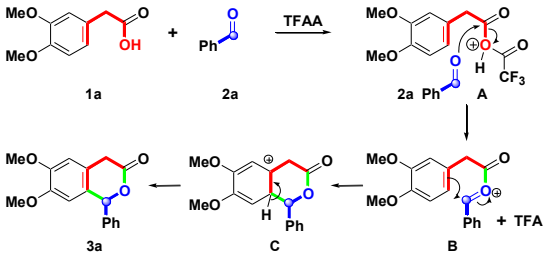


entry	promoters	solvent	time (h)	temp (°C)	**3a** (%)[b]
1	TFAA	MeCN	5	25	80
2	TFAA	$MeNO_2$	5	25	63
3	TFAA	THF	5	25	28[c]
4	TFAA	CH_2Cl_2	5	25	70
5	TFAA	MeCN	10	25	90
6	TFAA	MeCN	20	25	87
7	TFAA	MeCN	40	25	88
8	TFAA	MeCN	10	50	78
9	TFAA	MeCN	10	82	69
10	Ac_2O	MeCN	5	25	10[d]
11	Tf_2O	MeCN	5	25	25[c]
12	AcOH	MeCN	5	25	<5[e]
13	TFA	MeCN	5	25	72
14	TfOH	MeCN	5	25	18[c]
15	TFAA[f]	MeCN	5	25	52

[a]Reactions were run on a 1.0 mmol scale with **1a**, **2a** (106 mg, 1.0 equiv), solvent (10 mL), and promoter (1.0 equiv). [b]Isolated yields. [c]Major complex mixture was isolated. [d]**2a** (35%) was recovered. [e]Major **1a** was isolated. [f]0.5 equivalent.

By changing the solvent to CH_2Cl_2, a better yield of **3a** was obtained in 70% (entry 4). To increase the yield, elongated times (10, 20 and 40 h) were investigated. In entries 5-7, the three reaction times provided yields of nearly 90%, 87% and 88%, respectively, under TFAA/MeCN conditions. From the results, we found that longer reaction times (20 or 40 h) did not enhance the yield. Furthermore, reaction temperature screening (50 and 82 °C) was performed. By elevating the temperature to 50 °C, a 78% yield of **3a** was isolated (entry 8), but when the reaction was treated at a reflux temperature (82 °C), the yield of **3a** was decreased to 69% (entry 9). It is obvious that the reaction was highly temperature-dependent with higher yields obtained at 25 °C. On the basis of the abovementioned experimental data, different anhydrides were investigated next. After changing the promoters from TFAA to Ac_2O and Tf_2O, however, neither of them obtained higher yields of **3a**. In entry 10, only a 10% yield of **3a** was isolated along with the recovered amount (35%) of **1a** since the reactivity of Ac_2O was lower than TFAA. Tf_2O might possess a higher reactivity than TFAA such that a low yield (25%) of **3a** was obtained (entry 11). Subsequently, three Brønsted acids, AcOH, TFA, and TfOH, were studied. However, trace amounts (<5%) of **3a** were provided for AcOH (entry 12). For TFA and TfOH, no better yields of **3a** were observed than for TFAA (entries 13-14). These results from acid-mediated reactions were similar to those for anhydride. Finally, catalytic amounts of TFAA were tested. The amounts of TFAA were decreased to 0.5 equivalent, and a lower yield (52%) was provided (entry 15). From these observations, we concluded that entry 5 provided optimal conditions for the formation of **3a** (90%) via an intramolecular annulation of **1a** with **2a**. Generally, we found that conditions of TFAA (1.0 equiv), MeCN (10 mL), and reaction time of 10 h at room temperature (25 °C) efficiently obtained higher yields of **3a**.

Scheme 2. Plausible Mechanism

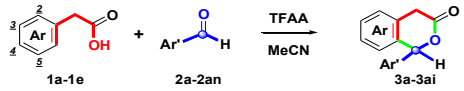


On the basis of our experimental results, a plausible mechanism for the formation of **3a** is illustrated in Scheme 2. Initially, coupling **1a** with TFAA yields **A** via intermolecular acylation. With the involvement of **2a**, carbonyl-mediated acylation of **A** leads to **B** and TFA. Following the Pictet-Spengler type annulation, an oxygenated group on the benzene ring promoted the intramolecular ring-closure of **B** generating **C**. Finally, after dehydrogenative aromatization, **3a** could be formed spontaneously.

To investigate the substrate scope and limitations of this one-pot approach, homoveratric acid **1a** and its derivatives of **1b-1e** were reacted with substituted arylbenzaldehydes **2a-2an** to afford diversified 1-aryl isochroman-3-ones **3a-3ai** in the presence of TFAA, as shown in Table 2. With optimal conditions established (Table 1, entry 5) and a plausible mechanism proposed (Scheme 2), we found that this route allowed a direct one-pot reduction under mild conditions in the range of moderate to good yields (52%-94%). Among entries 1-16, efficient formations of **3a-3p** showed that the Ar' group with monosubstituent halogen, oxygenated groups, nitro group, etc. did not affect the isolated yields. In entries 17-18, bicyclic 2-naphthyl and tricyclic 9-anthryl groups provided **3q** and **3r** in 87% and 72% yields, respectively. For the Ar' group with disubstituent halogen and oxygenated groups, entries 19-24 showed that yields of **3s-3x** were provided in a range of 72%-89%. The tri-substituted oxygenated Ar' group produced **3y** and **3z** at good yields (86% and 85%, entries 25 and 26, respectively). By changing **1a** to 2,3-dioxymethylenephenylacetic acid (**1b**), **3aa-3ad** were obtained in similar yields (83%-88%, entries 27-30). After elongating the carbon chain from methoxy to propoxy on the Ar' group

(for **1c**), however, the yield of **3ae** was decreased to 65% (entry 31), and 2,3-dimethoxyphenylacetic acid (**1d**) provided **3af** in an 80% yield (entry 32). For **1e** with the trimethoxy Ar' group, **3ag** was afforded in a 78% yield (entry 33). Furthermore, when the treatment of **1a** was reacted with 1,4-diformylbenzene (**2aa**), **3ah** with a 1,4-benzo conjugated bis-isochroman-3-one was isolated in a 72% yield. This was a facile route to obtain the dimeric isochroman-3-one skeleton.

Table 2. Synthesis of **3a-3ai**[a]

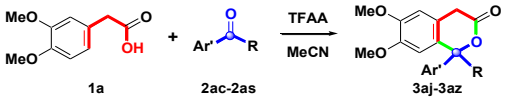


entry	**1a**, Ar =	**2**, Ar' =, R =	**3** (%)[b]
1	**1a**, 3,4-$(MeO)_2C_6H_3$	**2a**, Ph, H	**3a**, 90
2	**1a**, 3,4-$(MeO)_2C_6H_3$	**2b**, 2-FC_6H_4, H	**3b**, 94
3	**1a**, 3,4-$(MeO)_2C_6H_3$	**2c**, 4-BrC_6H_4, H	**3c**, 83
4	**1a**, 3,4-$(MeO)_2C_6H_3$	**2d**, 2-HOC_6H_4, H	**3d**, 82
5	**1a**, 3,4-$(MeO)_2C_6H_3$	**2e**, 2-$NO_2C_6H_4$, H	**3e**, 60
6	**1a**, 3,4-$(MeO)_2C_6H_3$	**2f**, 3-$MeOC_6H_4$, H	**3f**, 83
7	**1a**, 3,4-$(MeO)_2C_6H_3$	**2g**, 3-$NO_2C_6H_4$, H	**3g**, 82
8	**1a**, 3,4-$(MeO)_2C_6H_3$	**2h**, 4-MeC_6H_4, H	**3h**, 93
9	**1a**, 3,4-$(MeO)_2C_6H_3$	**2i**, 4-ClC_6H_4, H	**3i**, 87
10	**1a**, 3,4-$(MeO)_2C_6H_3$	**2j**, 4-FC_6H_4, H	**3j**, 90
11	**1a**, 3,4-$(MeO)_2C_6H_3$	**2k**, 4-$CF_3C_6H_4$, H	**3k**, 84
12	**1a**, 3,4-$(MeO)_2C_6H_3$	**2l**, 4-$MeOC_6H_4$, H	**3l**, 90
13	**1a**, 3,4-$(MeO)_2C_6H_3$	**2m**, 4-$MeSC_6H_4$, H	**3m**, 90
14	**1a**, 3,4-$(MeO)_2C_6H_3$	**2n**, 4-NCC_6H_4, H	**3n**, 84
15	**1a**, 3,4-$(MeO)_2C_6H_3$	**2o**, 4-$NO_2C_6H_4$, H	**3o**, 52
16	**1a**, 3,4-$(MeO)_2C_6H_3$	**2p**, 4-PhC_6H_4, H	**3p**, 87
17	**1a**, 3,4-$(MeO)_2C_6H_3$	**2q**, 2-naphthyl, H	**3q**, 87
18	**1a**, 3,4-$(MeO)_2C_6H_3$	**2r**, 9-anthryl, H	**3r**, 72
19	**1a**, 3,4-$(MeO)_2C_6H_3$	**2s**, 3,4-$Cl_2C_6H_3$, H	**3s**, 80
20	**1a**, 3,4-$(MeO)_2C_6H_3$	**2t**, 3,4-$CH_2O_2C_6H_3$, H	**3t**, 80
21	**1a**, 3,4-$(MeO)_2C_6H_3$	**2u**, 2-F-6-ClC_6H_3, H	**3u**, 78
22	**1a**, 3,4-$(MeO)_2C_6H_3$	**2v**, 3,4-$F_2C_6H_3$, H	**3v**, 73
23	**1a**, 3,4-$(MeO)_2C_6H_3$	**2w**, 3,4-$(MeO)_2C_6H_3$, H	**3w**, 89
24	**1a**, 3,4-$(MeO)_2C_6H_3$	**2x**, 3-HO-4-$MeOC_6H_3$, H	**3x**, 74
25	**1a**, 3,4-$(MeO)_2C_6H_3$	**2y**, 3,4,5-$(MeO)_3C_6H_2$, H	**3y**, 86
26	**1a**, 3,4-$(MeO)_2C_6H_3$	**2z**, 2,3,4-$(MeO)_3C_6H_2$, H	**3z**, 85
27	**1b**, 3,4-$CH_2O_2C_6H_3$	**2t**, 3,4-$CH_2O_2C_6H_3$, H	**3aa**, 83
28	**1b**, 3,4-$CH_2O_2C_6H_3$	**2w**, 3,4-$(MeO)_2C_6H_3$, H	**3ab**, 85
29	**1b**, 3,4-$CH_2O_2C_6H_3$	**2y**, 3,4,5-$(MeO)_3C_6H_2$, H	**3ac**, 88
30	**1b**, 3,4-$CH_2O_2C_6H_3$	**2z**, 2,3,4-$(MeO)_3C_6H_2$, H	**3ad**, 84
31	**1c**, 3,4-*n*$BuO_2C_6H_3$	**2w**, 3,4-$(MeO)_2C_6H_3$, H	**3ae**, 65
32	**1d**, 2,3-$(MeO)_2C_6H_3$	**2f**, 3-$MeOC_6H_4$, H	**3af**, 80
33	**1e**, 3,4,5-$(MeO)_3C_6H_2$	**2w**, 3,4-$(MeO)_2C_6H_3$, H	**3ag**, 78
34	**1a**, 3,4-$(MeO)_2C_6H_3$	**2aa**, 1,4-$(CHO)_2C_6H_4$, H	**3ah**, 72
35	**1a**, 3,4-$(MeO)_2C_6H_3$	**2ab**, 2-thienyl, H	**3ai**, 60

[a]Reactions were run on a 1.0 mmol scale with **1a-1e**, **2a-2ab** (1.0 equiv), TFAA (210 mg, 1.0 equiv), MeCN (10 mL), 10 h, 25 °C. [b]Isolated yields.

Then, **2ab** with a heterocyclic 2-thienyl group provided **3ai** in a fairly low yield (60%). However, for treatment of **1a** with furfural, no desired product was isolated, and only a complex unknown mixture was detected due to the low aromaticity of the furan ring. For the treatment of **1a** with 3- or 4-picolinaldehydes, no reactions were observed. A possible reason could be that the lone-pair of nitrogen atoms trapped the TFAA such that the reaction could not be initiated. To obtain the desired 1-pyridyl isochroman-3-one, excess amounts of TFAA (2.0 or 3.0 equivs) were added to compensate for the potential nitrogen-trapped intermediate. However, attempts to increase additional equivalents of TFAA failed, and only **1a** was recovered. From these results, we understood that the electronic nature of aryl substituent (Ar') of **2** was appropriate for different electron-neutral, electron-donating and electron-withdrawing groups. The molecular structures of **3j**, **3p**, **3s**, **3z**, **3af** and **3ag** were determined by single-crystal X-ray crystallography.[38]

Table 3. Synthesis of **3aj-3az**[a]



entry	**2**, Ar =	**3** (%)[b]
1	**2ac**, Ph, Me	**3aj**, 74
2	**2ad**, 3-$MeOC_6H_4$, Me	**3ak**, 73
3	**2ae**, 3-FC_6H_4, Me	**3al**, 72
4	**2af**, 4-ClC_6H_4, Me	**3am**, 72
5	**2ag**, 4-FC_6H_4, Me	**3an**, 80
6	**2ah**, 4-MeC_6H_4, Me	**3ao**, 73
7	**2ai**, 4-$MeOC_6H_4$, Me	**3ap**, 74
8	**2aj**, 4-FC_6H_4, Me	**3aq**, 70
9	**2ak**, 4-$NO_2C_6H_4$, Me	**3ar**, 62
10	**2al**, 2-naphthyl, Me	**3as**, 70
11	**2am**, 4-PhC_6H_4, Me	**3at**, 67
12	**2an**, 3,4-$Cl_2C_6H_4$, Me	**3au**, 70
13	**2ao**, 5-F-2,4-$Cl_2C_6H_2$, Me	**3av**, 80
14	**2ap**, 3,4,5-$(MeO)_3C_6H_2$, Me	**3aw**, 66
15	**2aq**, Ph, *n*Pr	**3ax**, 67
16	**2ar**, 4-FC_6H_4, Bn	**3ay**, 63
17	**2as**, Ph, Ph	**3az**, 47

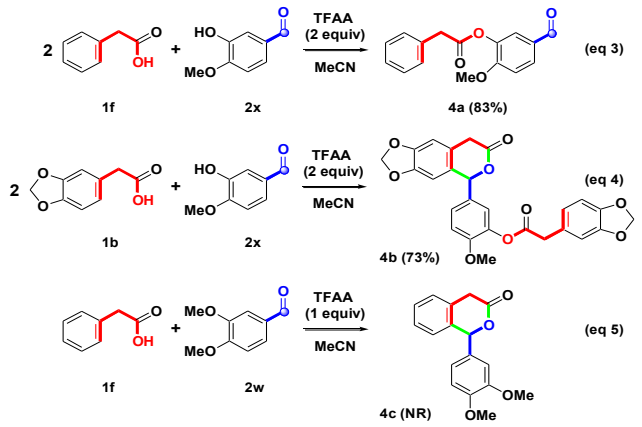
[a]Reactions were run on a 1.0 mmol scale with **1a**, **2ac-2as** (1.0 equiv), TFAA (210 mg, 1.0 equiv), MeCN (10 mL), 10 h, 25 °C. [b]Isolated yields.

By using **1a** as the carboxy source, different arylketones **2ac-2as** were screened next (Table 3). However, controlling the R as a methyl group (for **2ac-2ap**) diversified the Ar' substituent, so that the electron-neutral, electron-donating and electron-withdrawing groups were tolerated, and the isolated yields of **3aj-3aw** were distributed in a range of 62%-80%. When R was adjusted to the propyl and benzyl groups, **3ax** and **3ay** were produced in 67% and 63% yields, respectively. However, after choosing benzophenone (**2as**) as the carbonyl synthon, only a 47% yield of **3az** was obtained. Compared with the isolated yields for **3a-3ai** and **3aj-3az** overall, we

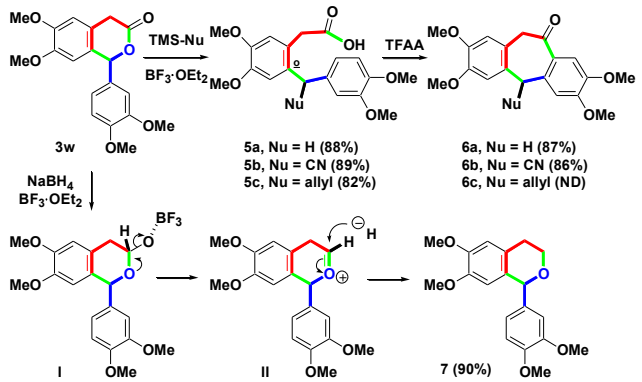
found that arylaldehydes provided better results than arylketones due to the slightly higher reactivities of the carbonyl group's intermolecular (4+2) annulation. The structures of **3aj** and **3at** were determined by single-crystal X-ray analysis.[38]

In addition to the carboxy-Pictet-Spengler reaction, TFAA was also a good promoter for *O*-acylation of carboxylic acids with phenols. To compare the reactivity, the competitive results between *O*-acylation and the carboxy-Pictet-Spengler reaction were examined (Scheme 3). Using 2 equivalents of TFAA, the treatment of isovanillin (**2x**) with 2 equivalents of phenylacetic acid (**1f**) afforded **4a** in an 83% yield via the *O*-acylation process, and no desired 1-aryl isochroman-3-one skeleton was detected (eq 3). The results showed that TFAA was a more specific protomer for *O*-acylation. To understand the electronic influences of substituents on the aromatic (Ar) ring, the electron-rich Ar group was examined for the *O*-acylation and the carboxy-Pictet-Spengler reaction. When **1f** was displaced as **1b**, the reaction of **1b** (2 equiv) with **2x** produced **4b** in a 73% yield via the intermolecular annulation and then the *O*-acylation procedure. From this phenomenon, we envisioned that the oxygenated group could enrich the electron density of the Ar ring such that a carboxy-Pictet-Spengler reaction would be triggered (eq 4). By the removal of the phenol moiety (Ar') and oxygenated group of Ar, no reaction was observed, and the desired product could not be isolated via the treatment of **1f** with **2w** (eq 5). Although substrate **1** was limited to the oxygenated aryl group, it still provided a novel and efficient synthesis of the 1-aryl isochroman-3-one skeleton.

Scheme 3. Synthesis of **4a-4c**

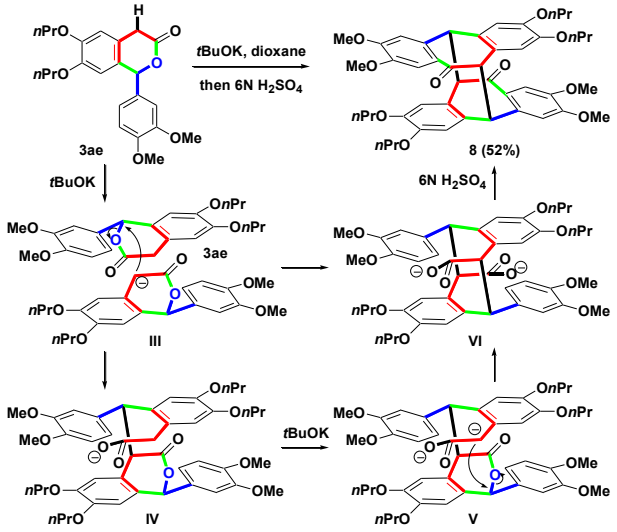


Scheme 4. Synthesis of **5a-5c**, **6a-6b** and **7**



Encouraged by the above experimental results, synthesis of the skeletons of dibenzosuberanone and isochroman were studied next (Scheme 4). By involvement of $Me_3SiH/BF_3{\cdot}OEt_2$, **3w** was converted into **5a** with an *o*-benzylphenylacetic acid skeleton in an 88% yield. By intramolecular Friedel-Crafts annulation, treatment of **5a** with TFAA produced tricyclic **6a** in an 87% yield. Changing Nu from a hydride to cyano group, **5b** and **6b** were obtained in 89% and 86% yields, respectively, by similar annulation conditions. After adjusting Nu to an allyl group, **5c** was isolated in an 82% yield. However, attempts to annulate **5c** failed. Only complex unknown products were detected. The reason could be the competition among the olefinic moiety, carboxylic acid and the two oxygenated aryl rings in the presence of TFAA. Herein, we developed a novel, concise two-step synthetic transformation from a 1-aryl isochroman-3-one to a dibenzosuberanone skeleton via one carbon-oxygen bond cleavage and one carbon-carbon bond formation. By the combination of $NaBH_4$ and $BF_3{\cdot}OEt_2$, a one-pot conversion from isochroman-3-one to isochroman was examined. The first reduction of **3w** provided BF_3-chelated lactol intermediate **I**. After the lone-pair of oxygen atoms promoted the removal of OBF_3, $NaBH_4$ mediated a second reduction of the resulting intermediate **II** with the oxocarbenium ion produced **7** in a 90% yield. This was an efficient transformation for the preparation of an isochroman. For the combination of $BF_3{\cdot}OEt_2$ and nucleophile (Nu)-mediated ring opening and addition/reduction, this strategy was reported by Kishi *et al.* in the 1980s,[39] investigated by Woerpel,[40] and expanded in the area of natural product total synthesis by Jennings.[41]

Scheme 5. Synthesis of **8**

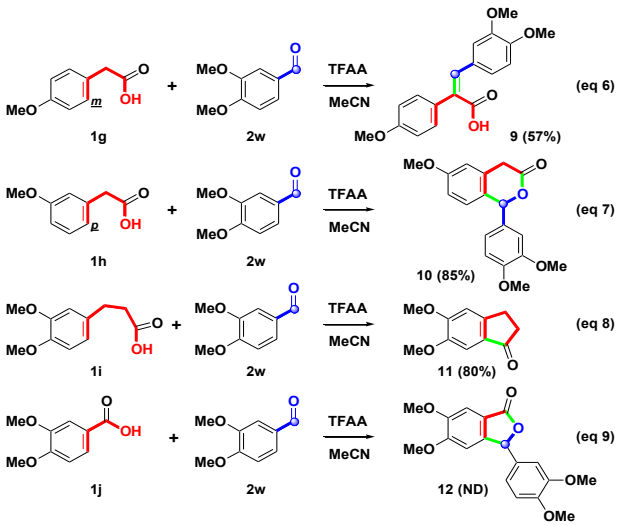


After changing the Lewis acid ($BF_3{\cdot}OEt_2$)-mediated conditions to a bulky base, treatment of **3ae** with excess amounts (3 equiv) of *t*BuOK was examined, as shown in Scheme 5. In particular, dimeric dibenzosuberanone **8** was obtained in a 52% yield. After deprotonation of **3ae**, intermediate **III** with a α-carbanion ion was formed. Then, an intermolecular self-dimerization of **3ae** and *in situ*-formed **III** provided **IV**. By another equivalent of *t*BuOK, deprotonation of **IV**, **V** was generated. The intramolecular annulation of **V** provided **VI**. Following the acidic process (6N H_2SO_4), the carboxylate ion on **VI** was protonated and then cyclized to

afford **8** under a one-pot process. The transformation was a facile and efficient route to establish the novel tricyclic dimer molecule with a head-to-tail conjugation. The structural characterization of **8** were supported by 2D NMR experiments (gCOSY and gHSQC) as well (see Supporting Information). In addition to 2D-NMR techniques, the stereochemical structure of **8** was determined by single-crystal X-ray analysis.[38]

By adjusting the Ar group on arylacetic acid from a di- or tri- to a mono-oxygenated group, 4-methoxyphenylacetic acid (**1g**) and 3-methoxyphenylacetic acid (**1h**) were involved in the above TFAA-mediated condition (Scheme 6). When **1g** was reacted with veratraldehyde (**2w**), however, only **9** was isolated in a 57% yield under the dehydration process (eq 6). One possible reason could be that the C4-methoxy group on the Ar group of **1g** could not promote the electron density efficiently to the *meta*-position such that dehydration occurred more easily than a ring-closure. As expected, reaction of **1h** with a C3-methoxy group provided **10** in an 85% yield under the TFAA-mediated condition (eq 7). On the basis of the electronic influences of substituents on aromatic ring, 3-methoxy group (for **1h**) showed better reactivity than 4-methoxy group (for **1g**) because aromatic ring position *para* to a 3-methoxy substituent would be involved in nucleophilic attack on aldehydic carbon of **2w** (also see Scheme 2). By changing arylacetic acid to arylpropionic acid (one-carbon elongation), **11**, with an indenone skeleton, was generated in an 80% yield via an intramolecular annulation (eq 8). Under the TFAA-mediated conditions, no desired benzo-fused oxepinone skeleton was detected. On the basis of the ring-formation efficacy, a five-membered ring was preferred to cyclize rather than the seven-membered ring. By changing arylacetic acid to benzoic acid (one-carbon diminishing), no reaction was observed. The desired product, **12**, with an isobenzofuranone skeleton could not be yielded, and only two starting materials were recovered (eq 9). Compared with the reactivity of the carboxylic group between **1i** and **1j**, benzoic acid with a stable conjugated system possessed a low reactivity such that the formyl group of **3w** could not react with the *in situ*-formed anhydride moiety (Scheme 3, intermediate **A**).

Scheme 6. Synthesis of **9-12**



In summary, we have developed a facile, environmentally friendly, one-step carboxy-Pictet-Spengler route for the synthesis of 1-aryl isochroman-3-ones via TFAA-mediated intermolecular (4+2) annulation of oxygenated arylacetic acids with arylaldehydes or ketones. Related plausible mechanisms have been proposed. The structures of the key products were confirmed by X-ray crystallography. The uses of various reaction conditions were investigated for efficient transformation. Further investigations regarding the TFAA-mediated synthetic application 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 air 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. ^{1}H 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. X-ray crystal structures were obtained with an Enraf-Nonius FR-590 diffractometer (CAD4, Kappa CCD).

For the starting substrates **1** and **2**, these materials were purchased commercially and were used without further purification.

*General Procedure for Synthesis of Compounds **3a-3az***: A 100 mL dry two-necked round-shaped flask equipped with a magnetic stirrer was charged with arylacetic acids **1a-1e** (1.0 mmol) and MeCN (8 mL) at 25 °C. Trifluoroacetic anhydride (TFAA, 210 mg, 1.0 mmol) was added in one portion to the solution at 25 °C. The reaction mixture was stirred at 25 °C for 10 min. Then, aldehydes **2a-2ab** or ketones **2ac-2as** (1.0 mmol) in MeCN (2 mL) was added to the reaction mixture at 25 °C. The reaction mixture was stirred at 25 °C for 10 h. The crude solution was evaporated by rotavapor, diluted with water (10 mL), and extracted with CH_2Cl_2 (3 × 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 = 15/1~1/1) afforded compounds **3a-3az**.

*6,7-Dimethoxy-1-phenylisochroman-3-one (**3a**).* Yield = 90% (256 mg); Colorless liquid; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{17}H_{17}O_4$ 285.1127, found 285.1130; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.32 (m, 3H), 7.26-7.24 (m, 2H), 6.71 (s, 1H), 6.46 (s, 1H), 6.32 (s, 1H), 3.86 (s, 3H), 3.72 (s, 3H), 3.64 (d, *J* = 18.4 Hz, 1H), 3.51 (d, *J* = 18.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.5, 149.3, 148.0, 137.2, 128.7, 128.6 (2C), 127.3 (2C), 126.1, 122.9, 110.1, 109.2, 81.9, 55.94, 55.90, 35.6.

*1-(2-Fluorophenyl)-6,7-dimethoxyisochroman-3-one (**3b**).* Yield = 94% (284 mg); Colorless liquid; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{17}H_{16}FO_4$ 303.1033, found 303.1035; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.31 (m, 1H), 7.19-7.07 (m, 3H), 6.72 (s, 1H), 6.61 (s, 1H), 6.34 (s, 1H), 3.84 (s, 3H), 3.71 (d, *J* = 18.0 Hz, 1H), 3.69 (d, *J* = 18.0 Hz, 1H), 3.66 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.0, 160.3 (d, *J* =

247.1 Hz), 149.4, 148.1, 130.7 (d, J = 7.6 Hz), 128.8 (d, J = 3.1 Hz), 125.0, 124.4 (d, J = 3.8 Hz), 124.3, 122.9, 115.6 (d, J = 21.2 Hz), 109.9, 108.5, 76.1 (d, J = 3.8 Hz), 55.9, 55.8, 35.4.

1-(2-Bromophenyl)-6,7-dimethoxyisochroman-3-one ***(3c)***. Yield = 83% (300 mg); Colorless liquid; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{16}BrO_4$ 363.0232, found 363.0236; ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (dd, J = 1.2, 8.0 Hz, 1H), 7.38-7.24 (m, 3H), 6.76 (s, 1H), 6.70 (s, 1H), 6.20 (s, 1H), 3.88 (s, 3H), 3.81 (d, J = 18.4 Hz, 1H), 3.73 (d, J = 18.4 Hz, 1H), 3.65 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.1, 149.6, 148.2, 136.2, 132.9, 130.4, 129.6, 128.0, 125.4, 123.4, 123.2, 110.0, 109.0, 80.5, 56.03, 55.96, 35.9.

1-(2-Hydroxyphenyl)-6,7-dimethoxyisochroman-3-one ***(3d)***. Yield = 82% (246 mg); Colorless liquid; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{17}O_5$ 301.1076, found 301.1077; ^1H NMR (400 MHz, $CDCl_3$): δ 7.28-7.24 (m, 1H), 6.95 (d, J = 8.0 Hz, 1H), 6.90-6.85 (m, 2H), 6.75 (s, 1H), 6.65 (s, 1H), 6.52 (s, 1H), 6.30 (br s, 1H), 3.91 (s, 3H), 3.75 (s, 3H), 3.70 (d, J = 18.8 Hz, 1H), 3.66 (d, J = 18.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.7, 154.7, 149.6, 148.4, 130.7, 128.4, 124.9, 123.2, 123.0, 120.7, 117.0, 110.2, 109.1, 79.4, 56.12, 56.07, 35.6.

6,7-Dimethoxy-1-(2-nitrophenyl)isochroman-3-one ***(3e)***. Yield = 60% (197 mg); Colorless liquid; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{16}NO_6$ 330.0978, found 330.0979; ^1H NMR (400 MHz, $CDCl_3$): δ 8.08 (dd, J = 1.2, 8.4 Hz, 1H), 7.70 (dt, J = 1.2, 7.6 Hz, 1H), 7.60 (dt, J = 1.6, 8.0 Hz, 1H), 7.57 (dd, J = 1.2, 7.6 Hz, 1H), 6.99 (s, 1H), 6.77 (s, 1H), 6.18 (s, 1H), 3.90 (s, 3H), 3.81 (d, J = 18.4 Hz, 1H), 3.70 (d, J = 18.4 Hz, 1H), 3.64 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.8, 149.9, 148.7, 148.3, 133.9, 132.1, 130.0, 129.9, 125.7, 124.5, 123.4, 110.1, 109.2, 76.8, 56.1 (2C), 36.1.

6,7-Dimethoxy-1-(3-methoxyphenyl)isochroman-3-one ***(3f)***. Yield = 83% (261 mg); Colorless liquid; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{19}O_5$ 315.1233, found 315.1235; ^1H NMR (400 MHz, $CDCl_3$): δ 7.23 (dt, J = 1.6, 8.8 Hz, 1H), 6.84 (dd, J = 2.4, 8.0 Hz, 1H), 6.80-6.78 (m, 2H), 6.69 (s, 1H), 6.47 (s, 1H), 6.26 (s, 1H), 3.84 (s, 3H), 3.72 (s, 3H), 3.71 (s, 3H), 3.61 (d, J = 18.8 Hz, 1H), 3.50 (d, J = 18.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.5, 159.6, 149.3, 147.9, 138.7, 129.5, 125.9, 122.8, 119.5, 114.1, 112.9, 110.1, 109.2, 81.6, 55.9 (2C), 55.0, 35.5.

6,7-Dimethoxy-1-(3-nitrophenyl)isochroman-3-one ***(3g)***. Yield = 82% (270 mg); Colorless liquid; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{16}NO_6$ 330.0978, found 330.0979; ^1H NMR (400 MHz, $CDCl_3$): δ 8.23 (ddd, J = 1.2, 2.4, 8.0 Hz, 1H), 8.12 (t, J = 2.0 Hz, 1H), 7.67 (dt, J = 1.2, 8.0 Hz, 1H), 7.60 (t, J = 8.0 Hz, 1H), 6.76 (s, 1H), 6.42 (s, 2H), 3.90 (s, 3H), 3.74 (s, 3H), 3.70 (d, J = 18.4 Hz, 1H), 3.54 (d, J = 18.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.7, 149.9, 148.4, 139.6, 133.5, 129.9, 124.7, 123.9, 122.9, 122.5, 122.3, 110.5, 109.0, 80.7, 56.12, 56.09, 35.6.

6,7-Dimethoxy-1-p-tolylisochroman-3-one ***(3h)***. Yield = 93% (277 mg); Colorless liquid; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{19}O_4$ 299.1283, found 299.1286; ^1H NMR (400 MHz, $CDCl_3$): δ 7.11-7.10 (br s, 4H), 6.69 (s, 1H), 6.44 (s, 1H), 6.26 (s, 1H), 3.83 (s, 3H), 3.69 (s, 3H), 3.60 (d, J = 18.4 Hz, 1H), 3.49 (d, J = 18.4 Hz, 1H), 2.29 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.5, 149.1, 147.8, 138.4, 134.1, 129.1 (2C), 127.2 (2C), 126.1, 122.8, 109.9, 109.1, 81.7, 55.78, 55.76, 35.5, 20.9.

1-(4-Chlorophenyl)-6,7-dimethoxyisochroman-3-one ***(3i)***. Yield = 87% (277 mg); Colorless solid; mp = 127-129 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{16}ClO_4$ 319.0737, found 319.0742; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38-7.35 (m, 2H), 7.24-7.21 (m, 2H), 6.74 (s, 1H), 6.45 (s, 1H), 6.31 (s, 1H), 3.90 (s, 3H), 3.76 (s, 3H), 3.67 (d, J = 18.4 Hz, 1H), 3.53 (d, J = 18.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.3, 149.7, 148.3, 135.9, 134.9, 129.99 (2C), 128.96 (2C), 125.7, 123.0, 110.3, 109.2, 81.3, 56.1 (2C), 35.7; Anal. Calcd for $C_{17}H_{15}ClO_4$: C, 64.06; H, 4.74. Found: C, 64.28; H, 4.55.

1-(4-Fluorphenyl)-6,7-dimethoxyisochroman-3-one ***(3j)***. Yield = 90% (272 mg); Colorless solid; mp = 125-127 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{16}FO_4$ 303.1033, found 303.1038; ^1H NMR (400 MHz, $CDCl_3$): δ 7.27-7.23 (m, 2H), 7.08-7.03 (m, 2H), 6.73 (s, 1H), 6.42 (s, 1H), 6.31 (s, 1H), 3.88 (s, 3H), 3.73 (s, 3H), 3.66 (d, J = 18.8 Hz, 1H), 3.53 (d, J = 18.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.4, 162.8 (d, J = 247.1 Hz), 149.5, 148.2, 133.2 (d, J = 3.8 Hz), 129.5 (d, J = 8.4 Hz, 2C), 125.9, 122.9, 115.7 (d, J = 21.2 Hz, 2C), 110.2, 109.1, 81.3, 56.03, 56.00, 35.7; Anal. Calcd for $C_{17}H_{15}FO_4$: C, 67.54; H, 5.00. Found: C, 67.78; H, 5.27. Single-crystal X-Ray diagram: crystal of compound **3j** was grown by slow diffusion of EtOAc into a solution of compound **3j** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the monoclinic crystal system, space group P 21/n, a = 10.6600(12) Å, b = 8.2642(9) Å, c = 16.2137(17) Å, V = 1420.5(3) Å^3, Z = 4, d_{calcd} = 1.414 g/cm^3, F(000) = 632, 2θ range 2.185~26.592°, R indices (all data) R1 = 0.0460, wR2 = 0.1030.

6,7-Dimethoxy-1-(4-trifluoromethylphenyl)isochroman-3-one ***(3k)***. Yield = 84% (296 mg); Colorless solid; mp = 124-126 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{16}F_3O_4$ 353.1001, found 353.1002; ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 6.75 (s, 1H), 6.46 (s, 1H), 6.38 (s, 1H), 3.90 (s, 3H), 3.77 (s, 3H), 3.68 (d, J = 18.8 Hz, 1H), 3.52 (d, J = 18.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.0, 149.8, 148.4, 141.3, 131.1 (q, J = 32.6 Hz), 127.8 (2C), 125.8 (q, J = 3.8 Hz, 2C), 125.3, 123.0, 122.9 (q, J = 89.4 Hz), 110.4, 109.2, 81.1, 56.15, 56.12, 35.7; Anal. Calcd for $C_{18}H_{15}F_3O_4$: C, 61.37; H, 4.29. Found: C, 61.59; H, 4.01.

6,7-Dimethoxy-1-(4-methoxyphenyl)isochroman-3-one ***(3l)***. Yield = 90% (283 mg); Colorless liquid; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{19}O_5$ 315.1233, found 315.1234; ^1H NMR (400 MHz, $CDCl_3$): δ 7.18 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.72 (s, 1H), 6.46 (s, 1H), 6.29 (s, 1H), 3.88 (s, 3H), 3.80 (s, 3H), 3.74 (s, 3H), 3.64 (d, J = 18.4 Hz, 1H), 3.54 (d, J = 18.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.7, 159.9, 149.3, 148.1, 129.3, 129.0 (2C), 126.4, 123.0, 114.0 (2C), 110.1, 109.3, 81.9, 56.03, 56.00, 55.2, 35.7.

6,7-Dimethoxy-1-(4-methylsulfanylphenyl)isochroman-3-one ***(3m)***. Yield = 90% (297 mg); Colorless liquid; HRMS (ESI, M^++1) calcd for $C_{18}H_{19}O_4S$ 331.1004, found 331.1005; ^1H NMR (400 MHz, $CDCl_3$): δ 7.18 (d, J = 8.8 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 6.70 (s, 1H), 6.44 (s, 1H), 6.26 (s, 1H), 3.84 (s, 3H), 3.71 (s, 3H), 3.61 (d, J = 18.8 Hz, 1H), 3.49 (d, J

= 18.4 Hz, 1H), 2.42 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.4, 149.3, 147.9, 139.5, 133.7, 127.8 (2C), 126.0 (2C), 125.8, 122.8, 110.0, 109.1, 81.5, 55.9 (2C), 35.5, 15.1.

*4-(6,7-Dimethoxy-3-oxoisochroman-1-yl)benzonitrile (**3n**).* Yield = 84% (260 mg); Colorless solid; mp = 172-174 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{16}NO_4$ 310.1079, found 310.1077; ^1H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 6.74 (s, 1H), 6.42 (s, 1H), 6.37 (s, 1H), 3.90 (s, 3H), 3.76 (s, 3H), 3.68 (d, *J* = 18.8 Hz, 1H), 3.50 (d, *J* = 18.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.8, 149.9, 148.4, 142.4, 132.6 (2C), 128.1 (3C), 124.8, 122.9, 118.2, 112.8, 110.4, 109.0, 80.9, 56.1, 35.6; Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.72; H, 4.78; N, 4.28.

*6,7-Dimethoxy-1-(4-nitrophenyl)isochroman-3-one (**3o**).* Yield = 52% (171 mg); Colorless liquid; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{16}NO_6$ 330.0978, found 330.0982; ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.8 Hz, 2H), 6.70 (s, 1H), 6.38 (s, 1H), 6.37 (s, 1H), 3.81 (s, 3H), 3.67 (s, 3H), 3.63 (d, *J* = 18.8 Hz, 1H), 3.47 (d, *J* = 18.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.7, 149.6, 148.1, 147.7, 144.1, 128.1 (2C), 124.6, 123.6 (2C), 122.6, 110.2, 108.7, 80.4, 55.83, 55.81, 35.3.

*1-Biphenyl-4-yl-6,7-dimethoxyisochroman-3-one (**3p**).* Yield = 87% (313 mg); Colorless solid; mp = 132-134 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{21}O_4$ 361.1440, found 361.1442; ^1H NMR (400 MHz, $CDCl_3$): δ 7.63-7.58 (m, 4H), 7.47-7.43 (m, 2H), 7.39-7.34 (m, 3H), 6.76 (s, 1H), 6.57 (s, 1H), 6.40 (s, 1H), 3.91 (s, 3H), 3.79 (s, 3H), 3.69 (d, *J* = 18.4 Hz, 1H), 3.58 (d, *J* = 18.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.6, 149.5, 148.2, 141.7, 140.2, 136.3, 128.8 (2C), 127.9 (2C), 127.6, 127.4 (2C), 127.0 (2C), 126.0, 123.0, 110.2, 109.3, 81.9, 56.1 (2C), 35.8; Anal. Calcd for $C_{23}H_{20}O_4$: C, 76.65; H, 5.59. Found: C, 76.90; H, 5.38. Single-crystal X-Ray diagram: crystal of compound **3p** was grown by slow diffusion of EtOAc into a solution of compound **3p** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the monoclinic crystal system, space group P 21/c, *a* = 8.203(2) Å, *b* = 21.807(7) Å, *c* = 10.328(3) Å, *V* = 1779.9(9) Å^3, *Z* = 4, d_{calcd} = 1.345 g/cm^3, *F*(000) = 760, 2*θ* range 1.868~26.786°, R indices (all data) R1 = 0.1267, wR2 = 0.1826.

*6,7-Dimethoxy-1-naphthalen-2-ylisochroman-3-one (**3q**).* Yield = 87% (291 mg); Colorless liquid; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{19}O_4$ 335.1283, found 335.1287; ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.8 Hz, 1H), 7.86-7.84 (m, 1H), 7.80-7.79 (m, 1H), 7.65 (s, 1H), 7.54-7.47 (m, 2H), 7.46 (dd, *J* = 2.0, 8.8 Hz, 1H), 6.76 (s, 1H), 6.52 (s, 1H), 6.51 (s, 1H), 3.92 (s, 3H), 3.73 (s, 3H), 3.70 (d, *J* = 18.8 Hz, 1H), 3.58 (d, *J* = 18.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.6, 149.5, 148.2, 134.6, 133.3, 132.9, 128.8, 128.2, 127.7, 126.70, 126.65, 126.5, 126.1, 125.0, 123.1, 110.2, 109.4, 82.2, 56.1 (2C), 35.8.

*1-Anthracen-9-yl-6,7-dimethoxyisochroman-3-one (**3r**).* Yield = 72% (276 mg); Colorless solid; mp = 172-174 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{21}O_4$ 385.1440, found 385.1438; ^1H NMR (400 MHz, $CDCl_3$): δ 8.59 (s, 1H), 8.06 (d, *J* = 8.4 Hz, 2H), 7.99 (br s, 2H), 7.81 (s, 1H), 7.48-7.40 (m, 4H), 6.88 (s, 1H), 5.91 (s, 1H), 4.04 (d, *J* = 18.0 Hz, 1H), 3.98 (d, *J* = 18.0 Hz, 1H), 3.91 (s, 3H), 3.23 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.6, 149.7, 148.4, 130.5, 130.2 (4C), 129.3 (2C), 127.6, 126.4 (2C), 125.5, 125.0 (4C), 122.9, 110.1, 109.4, 77.3, 56.1, 55.9, 36.7; Anal. Calcd for $C_{25}H_{20}O_4$: C, 78.11; H, 5.24. Found: C, 78.38; H, 5.40.

*1-(3,4-Dichlorophenyl)-6,7-dimethoxyisochroman-3-one (**3s**).* Yield = 80% (282 mg); Colorless solid; mp = 129-131 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{15}Cl_2O_4$ 353.0347, found 353.0345; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.8 Hz, 1H), 7.32 (d, *J* = 2.0 Hz, 1H), 7.10 (ddd, *J* = 0.8, 2.0, 8.4 Hz, 1H), 6.71 (s, 1H), 6.43 (s, 1H), 6.25 (s, 1H), 3.86 (s, 3H), 3.74 (s, 3H), 3.63 (d, *J* = 18.8 Hz, 1H), 3.48 (d, *J* = 18.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.8, 149.6, 148.2, 137.6, 132.9, 132.8, 130.6, 129.3, 126.7, 124.8, 122.8, 110.3, 109.0, 80.4, 56.03, 56.96, 35.5; Anal. Calcd for $C_{17}H_{14}Cl_2O_4$: C, 57.81; H, 4.00. Found: C, 57.68; H, 4.18. Single-crystal X-Ray diagram: crystal of compound **3s** was grown by slow diffusion of EtOAc into a solution of compound **3s** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the monoclinic crystal system, space group C 2/c, *a* = 20.246(2) Å, *b* = 4.8365(5) Å, *c* = 31.055(3) Å, *V* = 3040.7(6) Å^3, *Z* = 8, d_{calcd} = 1.543 g/cm^3, *F*(000) = 1456, 2*θ* range 2.012~26.462°, R indices (all data) R1 = 0.0348, wR2 = 0.0738.

*1-Benzo[1,3]dioxol-5-yl-6,7-dimethoxyisochroman-3-one (**3t**).* Yield = 80% (262 mg); Colorless liquid; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{17}O_6$ 329.1025, found 329.1028; ^1H NMR (400 MHz, $CDCl_3$): δ 6.77 (d, *J* = 8.0 Hz, 1H), 6.75 (d, *J* = 2.0 Hz, 1H), 6.72 (s, 1H), 6.71-6.69 (m, 1H), 6.49 (s, 1H), 6.24 (s, 1H), 5.97 (d, *J* = 1.2 Hz, 1H), 5.96 (d, *J* = 1.6 Hz, 1H), 3.89 (s, 3H), 3.77 (s, 3H), 3.64 (d, *J* = 18.8 Hz, 1H), 3.54 (d, *J* = 18.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.5, 159.5, 148.2, 148.1, 148.0, 131.2, 126.1, 123.0, 121.4, 110.2, 109.3, 108.11, 108.07, 101.3, 82.0, 56.09, 56.06, 36.7.

*1-(2-Chloro-6-fluorophenyl)-6,7-dimethoxyisochroman-3-one (**3u**).* Yield = 78% (262 mg); Colorless solid; mp = 116-118 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{15}ClFO_4$ 337.0643, found 337.0649; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 2H), 7.04 (dt, *J* = 1.2, 8.0 Hz, 1H), 7.01 (s, 1H), 6.69 (s, 1H), 6.29 (s, 1H), 3.88 (s, 3H), 3.82 (d, *J* = 18.8 Hz, 1H), 3.80 (d, *J* = 18.4 Hz, 1H), 3.68 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.1, 161.5 (d, *J* = 252.4 Hz), 149.5, 148.4, 134.8 (d, *J* = 5.3 Hz), 131.2 (d, *J* = 9.9 Hz), 126.0 (d, *J* = 3.8 Hz), 123.6 (d, *J* = 22.7 Hz), 123.5, 121.9, 115.2 (d, *J* = 21.9 Hz), 109.9, 107.3, 76.1, 56.02, 55.99, 34.4 (d, *J* = 2.3 Hz); Anal. Calcd for $C_{17}H_{14}ClFO_4$: C, 60.63; H, 4.19. Found: C, 60.48; H, 4.40.

*1-(3,4-Difluorophenyl)-6,7-dimethoxyisochroman-3-one (**3v**).* Yield = 73% (234 mg); Colorless solid; mp = 127-129 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{15}F_2O_4$ 321.0939, found 321.0945; ^1H NMR (400 MHz, $CDCl_3$): δ 7.11-6.93 (m, 3H), 6.68 (s, 1H), 6.39 (s, 1H), 6.22 (s, 1H), 3.80 (s, 3H), 3.67 (s, 3H), 3.58 (d, *J* = 18.4 Hz, 1H), 3.44 (d, *J* = 18.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.8, 150.1 (ddd, *J* = 8.3, 12.1, 248.6 Hz), 149.9 (ddd, *J* = 7.6, 12.2, 247.9 Hz), 149.4, 148.0, 134.4 (t, *J* = 5.4 Hz), 125.0, 123.6 (dd, *J* = 3.8, 6.8 Hz), 122.7, 117.3 (d, *J* =

17.4 Hz), 116.5 (d, J = 17.4 Hz), 110.1, 108.8, 80.4, 55.8, 55.7, 35.2; Anal. Calcd for $C_{17}H_{14}F_2O_4$: C, 63.75; H, 4.41. Found: C, 63.50; H, 4.26.

*1-(3,4-Dimethoxyphenyl)-6,7-dimethoxyisochroman-3-one (**3w**)*. Yield = 89% (306 mg); Colorless solid; mp = 118-120 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{21}O_6$ 345.1338, found 345.1336; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.77 (d, J = 2.0 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 6.65 (s, 1H), 6.63 (dd, J = 2.0, 8.4 Hz, 1H), 6.36 (s, 1H), 6.18 (s, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.71 (s, 3H), 3.62 (s, 3H), 3.56 (d, J = 18.8 Hz, 1H), 3.46 (d, J = 18.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.4, 149.1, 149.0, 148.9, 147.7, 129.3, 126.1, 122.8, 119.9, 110.4 (2C), 109.8, 109.0, 81.6, 55.7 (2C), 55.5, 55.4, 35.4; Anal. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C, 66.52; H, 6.07.

*1-(3-Hydroxy-4-methoxyphenyl)-6,7-dimethoxyisochroman-3-one (**3x**)*. Yield = 74% (244 mg); Colorless liquid; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{19}O_6$ 331.1182, found 331.1184; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.82 (d, J = 8.4 Hz, 1H), 6.79-6.74 (m, 2H), 6.70 (s, 1H), 6.51 (s, 1H), 6.25 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.76 (s, 3H), 3.62 (d, J = 18.4 Hz, 1H), 3.53 (d, J = 18.8 Hz, 1H), 2.53 (br s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.8, 149.3, 148.1, 146.9, 145.7, 130.5, 126.1, 122.9, 119.5, 113.9, 110.5, 110.1, 109.3, 81.9, 56.0 (2C), 55.9, 35.6.

*6,7-Dimethoxy-1-(3,4,5-trimethoxyphenyl)isochroman-3-one (**3y**)*. Yield = 86% (322 mg); Colorless liquid; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{23}O_7$ 375.1444, found 375.1443; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.68 (s, 1H), 6.433 (s, 2H), 6.426 (s, 1H), 6.20 (s, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 3.73 (s, 6H), 3.68 (s, 3H), 3.59 (d, J = 18.0 Hz, 1H), 3.51 (d, J = 18.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.3, 153.1 (2C), 149.3, 147.9, 138.0, 132.5, 125.9, 122.9, 109.9, 109.2, 104.6 (2C), 81.8, 60.5, 55.90, 55.87 (2C), 55.8, 35.5.

*6,7-Dimethoxy-1-(2,3,4-trimethoxyphenyl)isochroman-3-one (**3z**)*. Yield = 85% (318 mg); Colorless solid; mp = 136-138 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{23}O_7$ 375.1444, found 375.1443; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.72 (d, J = 9.2 Hz, 1H), 6.70 (s, 1H), 6.61 (d, J = 8.8 Hz, 1H), 6.60 (s, 1H), 6.37 (s, 1H), 3.89 (s, 3H), 3.86 (s, 6H), 3.83 (s, 3H), 3.69 (s, 3H), 3.68 (br s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.5, 154.4, 152.2, 149.2, 148.1, 142.1, 126.1, 123.2, 123.1, 122.9, 109.8, 108.8, 107.1, 77.6, 61.4, 60.6, 56.0, 55.9, 55.8, 35.4; Anal. Calcd for $C_{20}H_{22}O_7$: C, 64.16; H, 5.92. Found: C, 64.37; H, 6.22. Single-crystal X-Ray diagram: crystal of compound **3z** was grown by slow diffusion of EtOAc into a solution of compound **3z** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the monoclinic crystal system, space group $P2_1/c$, a = 11.8572(4) Å, b = 21.4415(7) Å, c = 7.3083(3) Å, V = 1768.69(11) Å^3, Z = 4, d_{calcd} = 1.406 g/cm^3, $F(000)$ = 792, 2θ range 1.804~26.437°, R indices (all data) R1 = 0.0457, wR2 = 0.0916.

*5-Benzo[1,3]dioxol-5-yl-5,8-dihydro[1,3]dioxolo[4,5-g]isochromen-7-one (**3aa**)*. Yield = 83% (259 mg); Colorless liquid; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{13}O_6$ 313.0712, found 313.0718; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.77 (d, J = 8.0 Hz, 1H), 6.76 (d, J = 2.0 Hz, 1H), 6.75-6.70 (m, 1H), 6.67 (s, 1H), 6.39 (s, 1H), 6.17 (s, 1H), 5.961 (d, J = 1.6 Hz, 1H), 5.957 (d, J = 1.6 Hz, 1H), 5.951 (d, J = 2.0 Hz, 1H), 5.948 (d, J = 2.0 Hz, 1H), 3.62 (d, J = 18.0 Hz, 1H), 3.53 (dd, J = 2.0, 18.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.7, 148.1, 148.04, 147.99, 146.9, 130.6, 127.8, 124.3, 121.3, 108.1, 107.9, 107.5, 106.6, 101.4, 101.3, 81.7, 36.1.

*5-(3,4-Dimethoxyphenyl)-5,8-dihydro[1,3]dioxolo[4,5-g]isochromen-7-one (**3ab**)*. Yield = 85% (279 mg); Colorless solid; mp = 156-158 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{17}O_6$ 329.1025, found 329.1028; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87 (d, J = 1.6 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.75 (dd, J = 2.4, 8.4 Hz, 1H), 6.70 (s, 1H), 6.38 (s, 1H), 6.21 (s, 1H), 5.97 (d, J = 1.6 Hz, 1H), 5.96 (d, J = 1.2 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.64 (d, J = 18.4 Hz, 1H), 3.55 (d, J = 18.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.6, 149.5, 149.3, 148.0, 146.9, 129.2, 128.2, 124.5, 120.1, 110.7, 110.5, 107.5, 106.8, 101.4, 81.8, 55.91, 55.87, 36.4; Anal. Calcd for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91. Found: C, 66.08; H, 5.23.

*5-(3,4,5-Trimethoxyphenyl)-5,8-dihydro[1,3]dioxolo[4,5-g]isochromen-7-one (**3ac**)*. Yield = 88% (315 mg); Colorless liquid; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{19}O_7$ 359.1131, found 359.1135; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.70 (s, 1H), 6.51 (s, 2H), 6.38 (s, 1H), 6.18 (s, 1H), 5.97 (d, J = 1.2 Hz, 1H), 5.96 (d, J = 1.2 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 6H), 3.65 (d, J = 18.4 Hz, 1H), 3.57 (d, J = 18.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.5, 143.4 (2C), 148.1, 146.9, 138.3, 132.2, 128.1, 124.5, 107.5, 106.7, 104.6 (2C), 101.5, 81.7, 60.8, 56.1 (2C), 36.4.

*5-(2,3,4-Trimethoxyphenyl)-5,8-dihydro[1,3]dioxolo[4,5-g]isochromen-7-one (**3ad**)*. Yield = 84% (301 mg); Colorless solid; mp = 149-150 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{19}O_7$ 359.1131, found 359.1125; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.72 (d, J = 8.4 Hz, 1H), 6.57 (d, J = 8.8 Hz, 1H), 6.52 (s, 1H), 6.44 (s, 1H), 6.18 (s, 1H), 5.79 (d, J = 1.2 Hz, 2H), 3.78 (s, 3H), 3.77 (s, 3H), 3.74 (s, 3H), 3.61 (d, J = 18.4 Hz, 1H), 3.54 (d, J = 18.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.1, 154.0, 151.6, 147.4, 146.5, 141.6, 127.6, 124.1, 122.8, 122.4, 107.0, 106.8, 105.7, 101.0, 76.8, 61.0, 60.3, 55.5, 35.6; Anal. Calcd for $C_{19}H_{18}O_7$: C, 63.68; H, 5.06. Found: C, 63.57; H, 5.33.

*1-(3,4-Dimethoxyphenyl)-6,7-dipropoxyisochroman-3-one (**3ae**)*. Yield = 65% (260 mg); Colorless solid; mp = 127-129 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{29}O_6$ 401.1964, found 401.1963; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.86 (d, J = 2.0 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.74-6.71 (m, 2H), 6.47 (s, 1H), 6.26 (s, 1H), 3.96 (t, J = 6.4 Hz, 2H), 3.88 (s, 3H), 3.83 (s, 3H), 3.80-3.78 (m, 2H), 3.63 (d, J = 18.4 Hz, 1H), 3.53 (d, J = 18.4 Hz, 1H), 1.87-1.81 (m, 2H), 1.78-1.73 (m, 2H), 1.04 (t, J = 7.2 Hz, 3H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.9, 149.7, 149.4, 149.2, 148.1, 129.7, 126.5, 123.3, 120.2, 112.4, 112.1, 110.7, 110.6, 82.0, 71.0, 70.8, 55.9, 55.8, 55.9, 22.5, 22.4, 10.4, 10.3; Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 68.67; H, 7.32.

5,6-Dimethoxy-1-(4-methoxyphenyl)-isochroman-3-one (**3af**). Yield = 80% (251 mg); Colorless solid; mp = 138-140 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-

TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{19}O_5$ 315.1233, found 315.1239; ^{1}H NMR (400 MHz): δ 7.22-7.19 (m, 2H), 6.92-6.89 (m, 2H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 6.29 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 3.72 (s, 2H); ^{13}C NMR (100 MHz): δ170.7, 159.9, 152.6, 145.6, 129.4, 129.0 (2C), 127.7, 124.7, 121.6, 114.0 (2C), 110.7, 81.6, 60.9, 55.9, 55.3, 30.6; Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 69.05; H, 6.06. Single-crystal X-Ray diagram: crystal of compound **3af** was grown by slow diffusion of EtOAc into a solution of compound **3af** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the monoclinic crystal system, space group P 1 21/c 1, *a* = 12.6139(9) Å, *b* = 14.2691(10) Å, *c* = 9.0436(7) Å, *V* = 1579.1(2) Å^3, *Z* = 4, d_{calcd} = 1.322 g/cm^3, *F*(000) = 664, 2*θ* range 1.66~26.39°, R indices (all data) R1 = 0.1402, wR2 = 0.1211.

*1-(3,4-Dimethoxyphenyl)-6,7,8-trimethoxyisochroman-3-one (**3ag**)*. Yield = 78% (292 mg); Colorless solid; mp = 131-133 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{23}O_7$ 375.1444, found 375.1446; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.90 (d, *J* = 2.4 Hz, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 6.67 (s, 1H), 6.52 (dd, *J* = 1.2, 8.4 Hz, 1H), 6.51 (d, *J* = 2.4 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.52 (d, *J* = 19.2 Hz, 1H), 3.37 (dd, *J* = 0.8, 18.8 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.8, 154.2, 149.8, 149.21, 149.17, 140.7, 130.5, 126.3, 119.1, 118.5, 110.6, 110.5, 106.0, 77.6, 61.1, 60.9, 56.1, 55.83, 55.79, 35.6; Anal. Calcd for $C_{20}H_{22}O_7$: C, 64.16; H, 5.92. Found: C, 64.47; H, 6.24. Single-crystal X-Ray diagram: crystal of compound **3ag** was grown by slow diffusion of EtOAc into a solution of compound **3ag** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the monoclinic crystal system, space group P 21/n, *a* = 8.2452(3) Å, *b* = 7.9051(3) Å, *c* = 27.3274(10) Å, *V* = 1781.17(11) Å^3, *Z* = 4, d_{calcd} = 1.396 g/cm^3, *F*(000) = 792, 2*θ* range 1.490~26.414°, R indices (all data) R1 = 0.0444, wR2 = 0.0928.

*1,1'-(1,4-phenylene)bis(6,7-dimethoxyisochroman-3-one) (**3ah**)*. Rotamer; Ratio = 2:1; Yield = 72% (353 mg); Colorless solid; mp = 174-176 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{28}H_{27}O_8$ 491.1706, found 491.1708; For major comformation; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (s, 4H), 6.73 (s, 2H), 6.48 (s, 2H), 6.36 (s, 2H), 3.90 (s, 6H), 3.77 (s, 6H), 3.68 (d, *J* = 18.8 Hz, 2H), 3.54 (d, *J* = 18.4 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.4 (2C), 149.7 (2C), 148.3 (2C), 138.24, 138.19, 128.0 (4C), 125.6 (2C), 123.0 (2C), 110.3 (2C), 109.3 (2C), 81.6 (2C), 56.2 (2C), 56.1 (2C), 35.73, 35.70.

*6,7-Dimethoxy-1-thiophen-2-ylisochroman-3-one (**3ai**)*. Yield = 60% (174 mg); Colorless liquid; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{15}O_4S$ 291.0691, found 291.0696; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (dd, *J* = 1.2, 4.8 Hz, 1H), 6.97 (dd, *J* = 3.6, 4.8 Hz, 1H), 6.87 (dd, *J* = 1.2, 3.6 Hz, 1H), 6.71 (s, 2H), 6.56 (s, 1H), 3.91 (s, 3H), 3.84 (s, 3H), 3.63 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.1, 149.7, 148.3, 141.4, 127.3, 127.1, 126.8, 125.5, 122.6, 110.2, 108.8, 78.1, 56.12, 56.09, 35.3.

*6,7-Dimethoxy-1-methyl-1-phenylisochroman-3-one (**3aj**)*. Yield = 74% (221 mg); Colorless solid; mp = 159-161 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{19}O_4$ 299.1283, found 299.1288; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.19 (m, 3H), 7.15-7.13 (m, 2H), 6.98 (s, 1H), 6.65 (s, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 3.44 (d, *J* = 18.4 Hz, 1H), 3.07 (dd, *J* = 0.8, 18.4 Hz, 1H), 2.00 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 171.0, 149.2, 147.9, 143.3, 130.1, 128.3 (2C), 127.8, 125.2 (2C), 123.0, 110.4, 108.5, 85.9, 56.2, 55.9, 36.2, 29.0; Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.75; H, 6.30. Single-crystal X-Ray diagram: crystal of compound **3aj** was grown by slow diffusion of EtOAc into a solution of compound **3aj** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the monoclinic crystal system, space group $P2_1/c$, *a* = 9.7914(3) Å, *b* = 11.0553(4) Å, *c* = 14.4153(5) Å, *V* = 1506.22(9) Å^3, *Z* = 4, d_{calcd} = 1.316 g/cm^3, *F*(000) = 632, 2*θ* range 2.155~26.402°, R indices (all data) R1 = 0.0386, wR2 = 0.0900.

*6,7-Dimethoxy-1-(3-methoxyphenyl)-1-methylisochroman-3-one (**3ak**)*. Yield = 73% (239 mg); Colorless liquid; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{21}O_5$ 329.1389, found 329.1383; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (t, *J* = 8.0 Hz, 1H), 6.98 (s, 1H), 6.79-6.71 (m, 3H), 6.66 (s, 1H), 3.94 (s, 3H), 3.88 (s, 3H), 3.73 (s, 3H), 3.47 (d, *J* = 18.4 Hz, 1H), 3.14 (dd, *J* = 0.8, 18.4 Hz, 1H), 2.01 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 171.2, 159.5, 149.3, 148.0, 145.2, 130.2, 129.5, 123.2, 117.7, 112.8, 111.6, 110.5, 108.6, 85.9, 56.3, 56.0, 55.2, 36.4, 29.0.

*1-(3-Fluorophenyl)-6,7-dimethoxy-1-methylisochroman-3-one (**3al**)*. Yield = 72% (228 mg); Colorless liquid; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{18}FO_4$ 317.1189, found 317.1193; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.23 (m, 1H), 7.01-6.93 (m, 2H), 6.97 (s, 1H), 6.87-6.84 (m, 1H), 6.67 (s, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 3.50 (d, *J* = 18.4 Hz, 1H), 3.13 (dd, *J* = 1.2, 18.4 Hz, 1H), 2.02 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.8, 162.7 (d, *J* = 245.6 Hz), 149.6, 148.2, 146.3 (d, *J* = 6.1 Hz), 130.2 (d, *J* = 8.4 Hz), 129.6, 123.2, 121.1 (d, *J* = 3.1 Hz), 115.0 (d, *J* = 21.2 Hz), 112.8 (d, *J* = 22.8 Hz), 110.6, 108.6, 85.4, 56.3, 56.1, 36.3, 29.0.

*1-(4-Chlorophenyl)-6,7-dimethoxy-1-methylisochroman-3-one (**3am**)*. Yield = 72% (239 mg); Colorless liquid; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{18}ClO_4$ 333.0894, found 333.0896; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 2H), 6.95 (s, 1H), 6.66 (s, 1H), 3.93 (s, 3H), 3.88 (s, 3H), 3.49 (d, *J* = 18.4 Hz, 1H), 3.10 (dd, *J* = 0.8, 18.4 Hz, 1H), 2.00 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.7, 149.5, 148.1, 142.1, 133.9, 129.6, 128.6 (2C), 126.8 (2C), 123.0, 110.5, 108.5, 85.5, 56.3, 56.0, 36.2, 29.0.

*1-(4-Fluorophenyl)-6,7-dimethoxy-1-methylisochroman-3-one (**3an**)*. Yield = 80% (253 mg); Colorless liquid; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{18}FO_4$ 317.1189, found 317.1184; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16-7.13 (m, 2H), 6.97-6.93 (m, 2H), 6.95 (s, 1H), 6.67 (s, 1H), 3.94 (s, 3H), 3.90 (s, 3H), 3.50 (d, *J* = 18.4 Hz, 1H), 3.11 (dd, *J* = 0.8, 18.4 Hz, 1H), 2.01 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.9, 162.2 (d, *J* = 245.6 Hz), 149.5, 148.2, 139.4 (d, *J* = 3.0 Hz), 129.9, 127.3 (d, *J* = 8.4 Hz, 2C), 123.1, 115.4 (d, *J* = 21.2 Hz, 2C), 110.6, 108.5, 85.6, 56.3, 56.1, 36.3, 29.2.

*6,7-Dimethoxy-1-(4-methylphenyl)-1-methylisochroman-3-one (**3ao**)*. Yield = 73% (228 mg); Colorless liquid; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{21}O_4$ 313.1440, found 313.1442; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09-7.03 (m, 4H), 6.98 (s, 1H), 6.66 (s, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 3.47 (d, *J*

= 18.4 Hz, 1H), 3.13 (dd, *J* = 0.8, 18.4 Hz, 1H), 2.30 (s, 3H), 2.02 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.3, 149.3, 148.0, 140.5, 137.8, 130.4, 129.1 (2C), 125.3 (2C), 123.3, 110.5, 108.6, 86.1, 56.3, 56.1, 36.4, 29.2, 20.9.

*6,7-Dimethoxy-1-(4-methoxyphenyl)-1-methylisochroman-3-one (**3ap**).* Yield = 74% (243 mg); Colorless liquid; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{21}O_5$ 329.1389, found 329.1386; ^1H NMR (400 MHz, $CDCl_3$): δ 7.08 (d, *J* = 8.8 Hz, 2H), 6.96 (s, 1H), 6.80 (d, *J* = 9.2 Hz, 2H), 6.67 (s, 1H), 3.94 (s, 3H), 3.90 (s, 3H), 3.77 (s, 3H), 3.48 (d, *J* = 18.0 Hz, 1H), 3.15 (dd, *J* = 0.8, 18.0 Hz, 1H), 2.02 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.3, 159.2, 149.3, 148.1, 135.6, 130.4, 126.8 (2C), 123.3, 113.7 (2C), 110.5, 108.6, 86.0, 56.3, 56.1, 55.3, 36.4, 29.2.

*6,7-Dimethoxy-1-methyl-1-(4-trifluoromethylphenyl)isochroman-3-one (**3aq**).* Yield = 70% (256 mg); Colorless solid; mp = 125-127 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{18}F_3O_4$ 367.1157, found 367.1152; ^1H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.99 (s, 1H), 6.67 (s, 1H), 3.94 (s, 3H), 3.88 (s, 3H), 3.50 (d, *J* = 18.4 Hz, 1H), 3.06 (dd, *J* = 0.8, 18.4 Hz, 1H), 2.02 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.5, 149.7, 148.2, 147.5, 130.2 (q, *J* = 32.6 Hz), 129.3, 125.8 (2C), 125.5 (q, *J* = 3.8 Hz, 2C), 123.7 (q, *J* = 270.6 Hz), 123.0, 110.6, 108.5, 85.4, 56.3, 56.0, 36.2, 29.0; Anal. Calcd for $C_{19}H_{17}F_3O_4$: C, 62.29; H, 4.68. Found: C, 62.44; H, 4.93.

*6,7-Dimethoxy-1-methyl-1-(4-nitrophenyl)isochroman-3-one (**3ar**).* Yield = 62% (213 mg); Colorless solid; mp = 159-161 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{18}NO_6$ 344.1134, found 344.1138; ^1H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 9.2 Hz, 2H), 7.40 (d, *J* = 8.8 Hz, 2H), 6.98 (s, 1H), 6.69 (s, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 3.54 (d, *J* = 18.8 Hz, 1H), 3.07 (dd, *J* = 0.8, 18.4 Hz, 1H), 2.05 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.2, 150.6, 149.9, 148.5, 147.5, 128.9, 126.5 (2C), 123.8 (2C), 123.0, 110.7, 108.5, 85.2, 56.4, 56.1, 36.2, 29.0; Anal. Calcd for $C_{18}H_{17}NO_6$: C, 62.97; H, 4.99; N, 4.08. Found: C, 63.30; H, 5.30; N, 4.32.

*6,7-Dimethoxy-1-methyl-1-naphthalen-2-ylisochroman-3-one (**3as**).* Yield = 70% (244 mg); Colorless liquid; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{21}O_4$ 349.1440, found 349.1437; ^1H NMR (400 MHz, $CDCl_3$): δ 7.82-7.78 (m, 2H), 7.74-7.71 (m, 1H), 7.50-7.46 (m, 3H), 7.42 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.07 (s, 1H), 6.69 (s, 1H), 3.99 (s, 3H), 3.92 (s, 3H), 3.50 (d, *J* = 18.0 Hz, 1H), 3.16 (dd, *J* = 0.8, 18.4 Hz, 1H), 2.12 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.2, 149.5, 148.1, 140.8, 132.8, 132.7, 130.2, 128.6, 128.2, 127.5, 126.6, 126.5, 124.1, 123.5, 123.4, 110.6, 108.8, 86.2, 56.4, 56.1, 36.4, 29.1.

*1-Biphenyl-4-yl-6,7-dimethoxy-1-methylisochroman-3-one (**3at**).* Yield = 67% (251 mg); Colorless solid; mp = 172-174 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{23}O_4$ 375.1596, found 375.1599; ^1H NMR (400 MHz, $CDCl_3$): δ 7.55-7.48 (m, 4H), 7.44-7.40 (m, 2H), 7.36-7.32 (m, 1H), 7.27-7.23 (m, 2H), 7.03 (s, 1H), 6.69 (s, 1H), 3.97 (s, 3H), 3.91 (s, 3H), 3.52 (d, *J* = 18.8 Hz, 1H), 3.20 (dd, *J* = 0.8, 18.4 Hz, 1H), 2.08 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.1, 149.4, 148.1, 142.4, 140.9, 140.1, 130.2, 128.8 (2C), 127.5, 127.1 (2C), 127.0 (2C), 125.8 (2C), 123.3, 110.6, 108.6, 85.9, 56.3, 56.1, 36.4, 29.1; Anal. Calcd for $C_{24}H_{22}O_4$: C, 76.99; H, 5.92. Found: C, 77.28; H, 6.20. Single-crystal X-Ray diagram: crystal of compound **3at** was grown by slow diffusion of EtOAc into a solution of compound **3at** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the monoclinic crystal system, space group P 21/c, *a* = 16.0440(14) Å, *b* = 11.1195(9) Å, *c* = 10.6719(8) Å, *V* = 1900.2(3) Å^3, *Z* = 4, d_{calcd} = 1.309 g/cm^3, *F*(000) = 792, 2*θ* range 2.230~26.434°, R indices (all data) R1 = 0.0585, wR2 = 0.1043.

*1-(3,4-Dichlorophenyl)-6,7-dimethoxy-1-methylisochroman-3-one (**3au**).* Yield = 70% (256 mg); Colorless liquid; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{17}Cl_2O_4$ 367.0504, found 367.0506; ^1H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, *J* = 8.4 Hz, 1H), 7.20 (d, *J* = 2.4 Hz, 1H), 7.02 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.92 (s, 1H), 6.67 (s, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 3.47 (d, *J* = 18.8 Hz, 1H), 3.11 (d, *J* = 18.4 Hz, 1H), 1.97 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.3, 149.6, 148.2, 143.9, 132.7, 132.2, 130.4, 128.9, 127.5, 124.8, 122.9, 110.6, 108.4, 84.9, 56.3, 56.0, 36.1, 28.9.

*1-(2,4-Dichloro-5-fluorophenyl)-6,7-dimethoxy-1-methylisochroman-3-one (**3av**).* Yield = 80% (307 mg); Colorless liquid; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{16}Cl_2FO_4$ 385.0410, found 385.0418; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 6.8 Hz, 1H), 7.04 (d, *J* = 10.0 Hz, 1H), 6.66 (s, 1H), 6.54 (s, 1H), 3.90 (s, 3H), 3.80 (s, 3H), 3.68 (d, *J* = 19.6 Hz, 1H), 3.47 (d, *J* = 19.6 Hz, 1H), 2.11 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.3, 156.2 (d, *J* = 247.9 Hz), 149.6, 148.4, 139.6 (d, *J* = 5.3 Hz), 133.7, 129.2 (d, *J* = 3.8 Hz), 128.6, 122.1, 121.9 (d, *J* = 18.2 Hz), 116.3 (d, *J* = 24.3 Hz), 110.4, 108.4, 85.3, 56.3, 56.1, 35.0, 27.1.

*6,7-Dimethoxy-1-methyl-1-(3,4,5-trimethoxyphenyl)isochroman-3-one (**3aw**).* Yield = 66% (256 mg); Colorless solid; mp = 153-155 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{25}O_7$ 389.1600, found 389.1602; ^1H NMR (400 MHz, $CDCl_3$): δ 6.98 (s, 1H), 6.67 (s, 1H), 6.35 (s, 2H), 3.93 (s, 3H), 3.89 (s, 3H), 3.79 (s, 3H), 3.71 (s, 6H), 3.49 (d, *J* = 18.0 Hz, 1H), 3.19 (dd, *J* = 0.8, 18.4 Hz, 1H), 2.01 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.2, 153.0 (2C), 149.4, 148.0, 139.3, 137.6, 130.1, 123.5, 110.5, 108.6, 102.9 (2C), 86.0, 60.7, 56.4, 56.1 (2C), 56.0, 36.4, 29.1; Anal. Calcd for $C_{21}H_{24}O_7$: C, 64.94; H, 6.23. Found: C, 65.28; H, 6.00.

*6,7-Dimethoxy-1-phenyl-1-propylisochroman-3-one (**3ax**).* Yield = 67% (218 mg); Colorless solid; mp = 109-111 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{23}O_4$ 327.1596, found 327.1598; ^1H NMR (400 MHz, $CDCl_3$): δ 7.27-7.21 (m, 3H), 7.16-7.14 (m, 2H), 6.97 (s, 1H), 6.63 (s, 1H), 3.95 (s, 3H), 3.86 (s, 3H), 3.46 (d, *J* = 18.8 Hz, 1H), 3.09 (d, *J* = 18.8 Hz, 1H), 2.23 (t, *J* = 7.6 Hz, 2H), 1.56-1.42 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.2, 149.2, 147.9, 142.9, 128.7, 128.3 (2C), 127.6, 125.5 (2C), 123.6, 110.6, 109.0, 88.5, 56.3, 55.9, 43.5, 36.0, 17.1, 14.1; Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.81; H, 6.90.

*1-Benzyl-1-(4-fluorophenyl)-6,7-dimethoxyisochroman-3-one (**3ay**).* Yield = 63% (247 mg); Colorless liquid; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{22}FO_4$ 393.1502,

found 393.1508; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21-7.11 (m, 5H), 7.01-6.91 (m, 4H), 6.86 (s, 1H), 6.50 (s, 1H), 3.851 (s, 3H), 3.846 (s, 3H), 3.66 (d, *J* = 14.0 Hz, 1H), 3.57 (d, *J* = 14.0 Hz, 1H), 3.08 (d, *J* = 19.6 Hz, 1H), 2.92 (d, *J* = 19.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.0, 162.2 (d, *J* = 246.3 Hz), 149.2, 147.8, 138.3 (d, *J* = 3.0 Hz), 134.6, 131.1 (2C), 128.2 (d, *J* = 8.4 Hz, 2C), 128.1, 127.9 (2C), 126.9, 123.3, 115.0 (d, *J* = 21.2 Hz, 2C), 110.0, 109.1, 87.9, 56.2, 55.9, 47.1, 34.9.

*6,7-Dimethoxy-1,1-diphenylisochroman-3-one (**3az**).* Yield = 47% (169 mg); Colorless liquid; HRMS (ESI, M^++1) calcd for $C_{23}H_{21}O_4$ 361.1440, found 361.1445; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.30 (m, 6H), 7.16-7.12 (m, 4H), 6.71 (s, 1H), 6.19 (s, 1H), 3.90 (s, 3H), 3.60 (s, 3H), 3.38 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 171.0, 149.4, 147.6, 141.7 (2C), 130.8, 128.4 (2C), 128.1 (8C), 123.4, 111.4, 110.2, 90.8, 56.1, 55.9, 36.6.

*General Procedure for Synthesis of Compounds **4a-4b***: A 100 mL dry two-necked round-shaped flask equipped with a magnetic stirrer was charged with arylacetic acids **1f** or **1b** (2.0 mmol) in MeCN (8 mL) at 25 °C. Trifluoroacetic anhydride (TFAA, 420 mg, 2.0 mmol) was added in one portion to the solution at 25 °C. The reaction mixture was stirred at 25 °C for 10 min. Then, isovanillin (**2x**, 152 mg, 1.0 mmol) in MeCN (2 mL) was added to the reaction mixture at 25 °C. The reaction mixture was stirred at 25 °C for 10 h. The crude solution was evaporated by rotavapor, diluted with water (10 mL), and extracted with CH_2Cl_2 (3 × 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 = 15/1~1/1) afforded compounds **4a**-**4b**.

*Phenylacetic acid 5-formyl-2-methoxyphenyl ester (**4a**).* Yield = 83% (224 mg); Colorless liquid; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{16}H_{15}O_4$ 271.0970, found 271.0974; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.82 (s, 1H), 7.71 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.55 (d, *J* = 2.0 Hz, 1H), 7.42-7.29 (m, 5H), 7.01 (d, *J* = 8.4 Hz, 1H), 3.90 (s, 2H), 3.80 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 189.9, 169.1, 156.1, 140.1, 133.1, 130.1, 129.7, 129.2 (2C), 128.5 (2C), 127.2, 123.0, 111.9, 55.9, 40.7.

*Benzo[1,3]dioxol-5-ylacetic acid 2-methoxy-5-(7-oxo-7,8-dihydro-5H-[1,3]dioxolo[4,5-g]isochromen-5-yl)phenyl ester (**4b**).* Yield = 73% (348 mg); Colorless liquid; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{26}H_{21}O_9$ 477.1186, found 477.1194; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 6.93 (d, *J* = 2.4 Hz, 1H), 6.88 (d, *J* = 1.2 Hz, 1H), 6.81 (dd, *J* = 2.0, 8.4 Hz, 1H), 6.78 (d, *J* = 7.6 Hz, 1H), 6.69 (s, 1H), 6.45 (s, 1H), 6.21 (s, 1H), 6.98 (d, *J* = 1.2 Hz, 1H), 6.97 (d, *J* = 1.2 Hz, 1H), 5.95 (s, 2H), 3.80 (s, 3H), 3.78 (s, 2H), 3.60 (d, *J* = 18.4 Hz, 1H), 3.50 (d, *J* = 18.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.4, 169.4, 151.5, 148.2, 147.8, 147.0, 146.8, 140.0, 129.5, 127.6, 126.9, 126.1, 124.4, 122.6, 122.1, 112.4, 109.8, 108.3, 107.7, 106.8, 101.5, 101.0, 81.1, 55.9, 40.5, 36.3.

*General Procedure for Synthesis of Compounds **5a-5c***: A 100 mL dry two-necked round-shaped flask equipped with a magnetic stirrer was charged with **3w** (344 mg, 1.0 mmol) in CH_2Cl_2 (20 mL) at 25 °C. TMSNu (Me_3SiH, Me_3SiCN, Me_3Si-allyl, 2.0 mmol) was added in one portion to the solution at 25 °C. The reaction mixture was stirred at 25 °C for 10 min. Then, $BF_3{\cdot}OEt_2$ (210 mg, 1.5 mmol) was added to the reaction mixture at 25 °C. The reaction mixture was stirred at 25 °C for 10 h. The crude solution was evaporated by rotavapor, diluted with water (10 mL), 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 = 15/1~1/1) afforded compounds **5a-5c**.

*[2-(3,4-Dimethoxybenzyl)-4,5-dimethoxyphenyl]acetic acid (**5a**).* Yield = 88% (304 mg); Colorless solid; mp = 111-113 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{19}H_{23}O_6$ 347.1495, found 347.1496; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.14 (br s, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 6.75 (s, 1H), 6.65 (s, 1H), 6.63 (d, *J* = 2.0 Hz, 1H), 6.61 (dd, *J* = 2.0, 8.4 Hz, 1H), 3.92 (s, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.56 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 177.4, 148.9, 148.2, 147.4, 147.3, 132.8, 131.8, 124.1, 120.5, 113.9, 113.7, 111.9, 111.2, 55.9, 55.84, 55.82, 55.7, 38.1, 37.9; Anal. Calcd for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40. Found: C, 65.62; H, 6.68. Single-crystal X-Ray diagram: crystal of compound **5a** was grown by slow diffusion of EtOAc into a solution of compound **5a** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the triclinic crystal system, space group P -1, *a* = 11.4341(7) Å, *b* = 12.3823(8) Å, *c* = 13.3138(7) Å, *V* = 1839.91(19) Å^3, *Z* = 4, d_{calcd} = 1.315 g/cm^3, *F*(000) = 776, 2θ range 1.566~26.422°, R indices (all data) R1 = 0.0641, wR2 = 0.1691.

*{2-[Cyano-(3,4-dimethoxyphenyl)methyl]-4,5-dimethoxyphenyl}acetic acid (**5b**).* Yield = 89% (330 mg); Colorless solid; mp = 87-89 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{20}H_{22}NO_6$ 372.1447, found 372.1443; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.08 (br s, 1H), 6.91 (br s, 1H), 6.81 (d, *J* = 0.8 Hz, 2H), 6.75 (s, 2H), 5.39 (s, 1H), 3.88 (s, 3H), 3.844 (s, 3H), 3.841 (s, 3H), 3.79 (s, 3H), 3.59 (d, *J* = 16.0 Hz, 1H), 3.54 (d, *J* = 16.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 176.5, 149.4, 148.93, 148.92, 148.8, 127.3, 126.4, 123.8, 120.0, 119.7, 114.4, 112.0, 111.3, 110.8, 56.04, 55.98, 55.9 (2C), 38.6, 37.8; Anal. Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.90; H, 5.98; N, 4.01.

*{2-[1-(3,4-Dimethoxyphenyl)but-3-enyl]-4,5-dimethoxyphenyl}acetic acid (**5c**).* Yield = 82% (317 mg); Colorless liquid; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{22}H_{27}O_6$ 387.1808, found 387.1809; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.50 (br s, 1H), 6.80 (s, 1H), 6.77-6.73 (m, 3H), 6.70 (s, 2H), 5.77-5.66 (m, 1H), 5.04 (dq, *J* = 1.6, 16.8 Hz, 1H), 4.96 (dq, *J* = 1.6, 10.0 Hz, 1H), 4.16 (t, *J* = 7.6 Hz, 1H), 3.84 (s, 2H), 3.822 (s, 3H), 3.819 (s, 3H), 3.76 (s, 3H), 3.62 (d, *J* = 16.4 Hz, 1H), 3.58 (d, *J* = 16.4 Hz, 1H), 2.79-2.66 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 178.0, 148.7, 148.2, 147.3, 147.1, 136.52, 136.49, 135.2, 123.8, 119.5, 116.4, 113.9, 111.6, 111.1, 110.9, 55.9, 55.74, 55.71, 55.6, 45.6, 40.5, 37.9.

*General Procedure for Synthesis of Compounds **6a-6b***: A 100 mL dry two-necked round-shaped flask equipped with a magnetic stirrer was charged with **5a** or **5b** (1.0 mmol) in MeCN (10 mL) at 25 °C. Trifluoroacetic anhydride (TFAA, 420 mg, 2.0 mmol) was added in one portion to the solution at 25 °C. The reaction mixture was stirred at 25 °C for 10 h. The

crude solution was evaporated by rotavapor, diluted with water (10 mL), and extracted with CH_2Cl_2 (3 × 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 = 15/1~1/1) afforded compounds **6a-6b**.

*2,3,7,8-Tetramethoxy-5,11-dihydrodibenzo[a,d]cyclohepten-10-one (**6a**)*. Yield = 87% (285 mg); Colorless solid; mp = 191-193 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{21}O_5$ 329.1389, found 329.1393; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (s, 1H), 6.79 (s, 1H), 6.78 (s, 1H), 6.74 (s, 1H), 4.07 (s, 2H), 4.00 (s, 2H), 3.92 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 193.2, 152.4, 147.6, 147.5, 147.4, 137.6, 132.1, 127.1, 124.7, 112.5, 112.1, 111.7, 111.4, 55.89, 55.86 (2C), 55.8, 50.1, 41.6; Anal. Calcd for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found: C, 69.83; H, 6.45.

*2,3,7,8-Tetramethoxy-10-oxo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-carbonitrile (**6b**)*. Yield = 86% (304 mg); Colorless solid; mp = 215-217 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{20}NO_5$ 354.1342, found 354.1344; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (s, 1H), 7.17 (s, 1H), 7.09 (s, 1H), 6.82 (s, 1H), 5.57 (s, 1H), 4.23 (d, *J* = 18.0 Hz, 1H), 4.13 (d, *J* = 18.0 Hz, 1H), 4.03 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 191.7, 152.9, 149.1, 148.9, 148.2, 130.5, 126.5, 126.4, 124.0, 117.9, 113.3, 113.2, 109.8, 109.5, 56.3 (2C), 56.2, 56.1, 49.6, 40.9; Anal. Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 68.25; H, 5.67; N, 4.23.

*1-(3,4-Dimethoxyphenyl)-6,7-dimethoxyisochroman (**7**)*. A 100 mL dry two-necked round-shaped flask equipped with a magnetic stirrer was charged with **3w** (344 mg, 1.0 mmol) in MeOH (10 mL) at 25 °C. $NaBH_4$ (70 mg, 2.0 mmol) was added in one portion to the solution at 25 °C. The reaction mixture was stirred at 25 °C for 10 min. Then, $BF_3{\cdot}OEt_2$ (210 mg, 1.5 mmol) was added to the reaction mixture at 25 °C. The reaction mixture was stirred at 25 °C for 10 h. The crude solution was evaporated by rotavapor, diluted with water (10 mL), 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 = 15/1~1/1) afforded compound **7**. Yield = 90% (297 mg); Colorless liquid; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{23}O_5$ 331.1546, found 331.1548; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.82 (br s, 3H), 6.64 (s, 1H), 6.25 (s, 1H), 5.61 (s, 1H), 4.13 (dt, *J* = 4.4, 11.6 Hz, 1H), 3.90-3.84 (m, 1H), 3.867 (s, 3H), 3.865 (s, 3H), 3.82 (s, 3H), 3.66 (s, 3H), 3.02 (ddd, *J* = 5.6, 8.8, 15.2 Hz, 1H), 2.71 (dt, *J* = 4.0, 16.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 149.0, 148.8, 147.8, 147.1, 134.7, 129.0, 126.0, 121.4, 111.7, 111.1, 110.6, 109.7, 79.0, 63.5, 55.84, 55.81, 55.78 (2C), 28.3.

*2,3,9,10-Tetramethoxy-18,19,24,25-tetra-n-propoxy-5,6,12,13-tetrahydro-5,13:6,12-bis([1,2]benzeno)dibenzo[a,f][10]annulene-7,14-dione (**8**)*. A 100 mL dry two-necked round-shaped flask equipped with a magnetic stirrer was charged with **3ae** (400 mg, 1.0 mmol) in dioxane (10 mL) at 25 °C. *t*BuOK (330 mg, 3.0 mmol) was added in one portion to the solution at 25 °C. The reaction mixture was stirred at reflux for 10 h. The reaction mixture was cooled to 25 °C. Aqueous H_2SO_4 solution (6N, 10 mL) was added to the reaction mixture, and the mixture was stirred at reflux for 10 h. The solvent of reaction mixture was cooled to 25 °C, evaporated by rotavapor, diluted with water (10 mL), 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 = 15/1~1/1) afforded compound **8**. Yield = 52% (200 mg); Colorless solid; mp > 250 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{46}H_{53}O_{10}$ 765.3639, found 765.3645; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (s, 2H), 6.66 (s, 2H), 6.61 (s, 2H), 6.14 (s, 2H), 4.75 (d, *J* = 11.2 Hz, 2H), 4.50 (d, *J* = 11.2 Hz, 2H), 3.96-3.79 (m, 4H), 3.94 (s, 6H), 3.79 (s, 6H), 3.75-3.63 (m, 4H), 1.80-1.71 (m, 4H), 1.62-1.52 (m, 4H), 0.98 (t, *J* = 7.2 Hz, 6H), 0.89 (t, *J* = 7.2 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 195.7 (2C), 152.5 (2C), 147.8 (2C), 147.71 (2C), 147.68 (2C), 136.8 (2C), 131.8 (2C), 127.8 (2C), 127.3 (2C), 118.4 (2C), 117.0 (2C), 112.9 (2C), 112.2 (2C), 71.0 (2C), 70.8 (2C), 66.3 (2C), 56.8 (2C), 56.1 (2C), 55.8 (2C), 22.4 (2C), 22.2 (2C), 10.4 (2C), 10.2 (2C); Anal. Calcd for $C_{46}H_{52}O_{10}$: C, 72.23; H, 6.85. Found: C, 72.50; H, 6.67. Single-crystal X-Ray diagram: crystal of compound **8** was grown by slow diffusion of EtOAc into a solution of compound **8** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the monoclinic crystal system, space group P 21/n, *a* = 16.1741(16) Å, *b* = 8.5137(8) Å, *c* = 28.773(3) Å, *V* = 3930.5(7) Å^3, *Z* = 4, d_{calcd} = 1.293 g/cm^3, *F*(000) = 1632, 2θ range 1.375~26.776°, R indices (all data) R1 = 0.1227, wR2 = 0.1502.

*General Procedure for Synthesis of Compounds **9-11***: A 100 mL dry two-necked round-shaped flask equipped with a magnetic stirrer was charged with arylacetic acids **1g-1i** (1.0 mmol) in MeCN (8 mL) at 25 °C. Trifluoroacetic anhydride (TFAA, 210 mg, 1.0 mmol) was added in one portion to the solution at 25 °C. The reaction mixture was stirred at 25 °C for 10 min. Then, veratraldehyde (**2w**, 166 mg, 1.0 mmol) in MeCN (2 mL) was added to the reaction mixture at 25 °C. The reaction mixture was stirred at 25 °C for 10 h. The crude solution was evaporated by rotavapor, diluted with water (10 mL), and extracted with CH_2Cl_2 (3 × 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 = 15/1~1/1) afforded compounds **9-11**.

*3-(3,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)acrylic acid (**9**)*. Yield = 57% (179 mg); Colorless solid; mp = 208-210 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{19}O_5$ 315.1233, found 315.1239; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.90 (brs, 1H), 7.86 (s, 1H), 7.21 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.86 (dd, *J* = 2.0, 8.4 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 1H), 6.52 (d, *J* = 2.0 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.46 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.9, 159.3, 150.3, 148.2, 142.2, 131.2 (2C), 128.7, 128.0, 127.3, 125.8, 114.4 (2C), 112.5, 110.5, 55.8, 55.3, 55.2; Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.93; H, 5.52.

*1-(3,4-Dimethoxyphenyl)-6-methoxyisochroman-3-one (**10**)*. Yield = 85% (267 mg); Colorless liquid; HRMS (ESI-TOF)

m/z: $[M + H]^+$ calcd for $C_{18}H_{19}O_5$ 315.1233, found 315.1241; ^1H NMR (400 MHz, $CDCl_3$): δ 6.85 (d, *J* = 2.0 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 6.80 (s, 1H), 6.75 (s, 1H), 6.75-6.72 (m, 2H), 6.26 (s, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.69 (d, *J* = 18.0 Hz, 1H), 3.60 (d, *J* = 18.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.5, 159.9, 149.3, 149.2, 132.5, 129.5, 127.1, 126.9, 120.0, 112.5, 112.4, 110.60, 110.55, 81.7, 55.78, 55.77, 55.3, 36.7.

*5,6-dimethoxy-2,3-dihydro-1H-inden-1-one (**11**).* Yield = 80% (154 mg); Colorless solid; mp = 119-121 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{11}H_{13}O_3$ 193.0865, found 193.0863; ^1H NMR (400 MHz, $CDCl_3$): δ 7.08 (s, 1H), 6.81 (s, 1H), 3.89 (s, 3H), 3.82 (s, 3H), 2.98-2.95 (m, 2H), 2.59-2.57 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 205.5, 155.2, 150.2, 149.2, 129.7, 107.3, 103.9, 56.0, 55.9, 36.3, 25.4; Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.90; H, 6.47.

ASSOCIATED CONTENT

Supporting Information

Scanned photocopies of NMR spectral data for all compounds and X-ray analysis data of **3j**, **3p**, **3s**, **3z**, **3af**, **3ag**, **3aj**, **3at**, **5a** and **8**. 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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