$NbCl_5$-Promoted Synthesis of 4-Aryl-3,4-dihydrocoumarins by Multicomponent Reaction

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Abstract: Substituted 4-aryl-3,4-dihydrocoumarins are synthesized from multicomponent reactions between phenols, dimethyl malonate, and aryl aldehydes catalyzed by niobium pentachloride. This new method is simple, cost-effective, and high-yielding, and can be conducted in acceptable reaction times.

Key words: niobium pentachloride, multicomponent reaction, coumarin derivatives, Lewis acid, phenols

Coumarins are an important class of natural products that can be found in many plants and fruits. They were first isolated by Vogel in 1820 from the plant species *Coumarona odorata* and, currently, more than 1400 types of natural coumarins have been described.[1] They are found in several families of the plant kingdom, as in Papilonaceae (Fabaceae), Lamiaceae, Asteraceae, Solanaceae, Poaceae, Umbelliferae, Rutaceae, and Apiaceae.[2] Their concentration is higher in fruits, seeds, and roots.[2] The coumarins show anti-inflammatory, antioxidant, anticoagulant, antibiotic, immunomodulatory, antimicrobial, antiviral, and bronchodilator properties and thus, they are widely used in medicine.[3] They are also used in various sectors of the chemical industry, such as dyes, essences, perfumes, toothpastes, synthetic rubber, plastics, insecticides, detergents, paints, and sprays.[4]

Coumarins can be synthesized through several methods, including Knoevenagel, Perkin, Pechmann, and Wittig reactions, using different acid catalysts, such as $AlCl_3$, $ZrCl_4$, $TiCl_4$, $Sm(NO)_3$, $InCl_3$, H_2SO_4, HCl, P_2O_5, and others.[5]

Coumarin derivatives, which have the carbon structure of 4-aryl-3,4-dihydrocoumarin, belong to the class of the neoflavonoids[6] and are present in several classes of plants. Among them, we can mention the derivatives **1**, **2**, and **3** (Figure 1), isolated, respectively, from *Aloe vera*, *Gnetum cleistostachyum*, and *Vaccinum myrtillus L.*, showing anti-inflammatory and antioxidant activities.[7]

The most frequently used method for the synthesis of 4-aryl-3,4-dihydrocoumarin derivatives is through the hydroarylation of cinnamic acid derivatives with different types of phenols and catalytic hydrogenation of coumarins.[8]

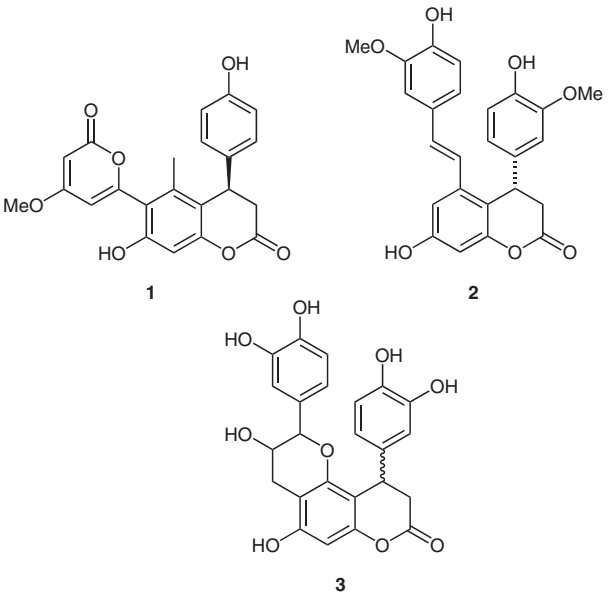

Figure 1 Examples of natural 4-aryl-3,4-dihydrocoumarins

In this work, a new method for the synthesis of derivatives of 4-aryl-3,4-dihydrocoumarins by multicomponent reaction (MCR) between 2,5-dimethoxyphenol, dimethyl malonate, and benzaldehyde derivatives promoted by niobium pentachloride is described. Niobium pentachloride, a stronger Lewis acid that is currently gaining increasing popularity as a reagent in organic synthesis, has been used by our group and other researchers as an effective catalyst in synthetic methodologies of a variety of organic reactions.[9,10]

A multicomponent reaction is usually defined as a process in which three or more reactants are combined in order to form a product that has structural characteristics of each reagent used, generating products with a good structural complexity in only one step.[11] MCRs also have the additional advantages of being selective and having atom economy, presenting a very important role in modern synthetic methodology.[12] The application of catalysts (metals, acids, or enzymes) in the development of MCRs has also been the subject of research in various research groups.[13]

The multicomponent reaction between 3,5-dimethoxyphenol (**4**; 1.0 equiv), dimethyl malonate (**5**; 1.1 equiv), and benzaldehyde derivatives **6a**–**k** (1.1 equiv) in the presence of niobium pentachloride (1.0 equiv) was per-

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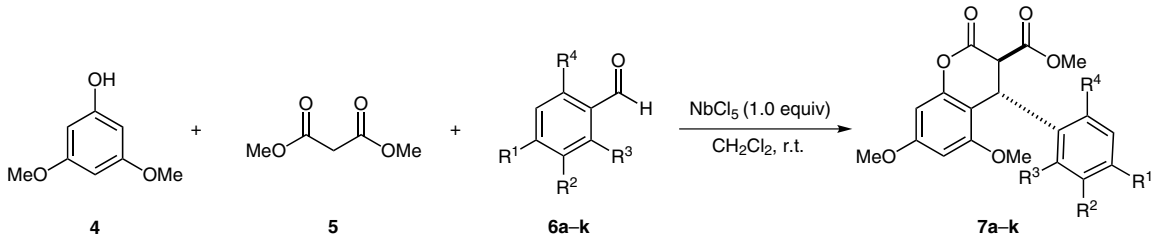
formed under N_2 atmosphere in dichloromethane at room temperature for 48 hours, to give the corresponding 4-alkyl-3,4-dihydrocoumarins **7a**–**k**, in high yields. The results are summarized in Scheme 1 and Table 1.

All products were isolated and their structures confirmed by ^{1}H NMR, ^{13}C NMR, and IR spectra. The *trans*-stereochemistry of adducts obtained are in accordance with the results described by Tunge and co-workers,[8b] who obtained similar derivatives of 4-alkyl-3,4-dihydrocoumarins by hydroarylation of benzylidene malonates with phenols catalyzed by $TiCl_4$, followed by lactonization reaction. In all reactions carried out, the formation of the *cis*-isomer was not observed.

In general, the results in Table 1 show that high yields of 4-alkyl-3,4-dihydrocoumarins were obtained with 1.0 equivalent of $NbCl_5$ at room temperature in dichloromethane for 48 hours. An increase of reaction yield was observed by conducting the reaction for a longer reaction time (48 h), but a reaction time of 24 hours gives only a yield of 64% (Table 1, entry 1). The low yield observed for compound **7e** (entry 6) can be explained by the high steric impediment caused by methyl groups present in positions R^3 and R^4 in the mesitylaldehyde (**6e**).

Probably, the multicomponent reaction proceeds initially due to the occurrence of Knoevenagel condensation between the aldehyde **6** and dimethyl malonate (**5**), followed by the reaction of hydroarylation of the benzylidene malonate formed in situ with phenol, with subsequent intramolecular lactonization (Scheme 2). This statement is justified, because in the reaction between benzaldehyde (**6a**), dimethyl malonate (**5**), and 3,5-dimethoxylphenol (**4**), with a reaction duration of 24 hours (entry 1), benzylidene malonate **8** was isolated as one of the products of the reaction.

In conclusion, a concise new three-component reaction was described for the synthesis of coumarin derivatives catalyzed by niobium pentachloride. The method reported here is simple and efficient, providing the products in high yields in acceptable reaction times.

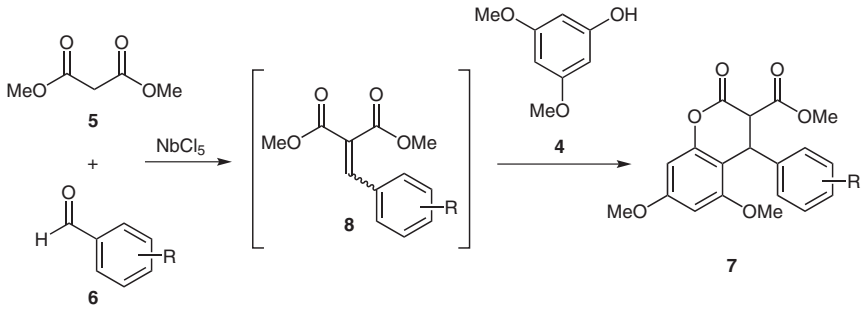


Scheme 1 $NbCl_5$-Promoted multicomponent reaction between 3,5-dimethoxyphenol (**4**), dimethyl malonate (**5**), and several aryl aldehydes **6a**–**k**

Table 1 Results Obtained from MCRs Catalyzed by $NbCl_5$

Entry	Aldehyde	R^1	R^2	R^3	R^4	Time (h)	Product, yield (%)[a]
1	**6a**	H	H	H	H	24	**7a**, 64[8b]
2	**6a**	H	H	H	H	48	**7a**, 88[8b]
3	**6b**	Me	H	H	H	48	**7b**, 93[8b]
4	**6c**	H	Me	H	H	48	**7c**, 87
5	**6d**	H	H	Me	H	48	**7d**, 98
6	**6e**	Me	H	Me	Me	48	**7e**, 56
7	**6f**	*t*-Bu	H	H	H	48	**7f**, 78
8	**6g**	H	OMe	H	H	48	**7g**, 80[8b]
9	**6h**	H	H	OMe	H	48	**7h**, 93[8b]
9	**6i**	F	H	H	H	48	**7i**, 92
11	**6j**	Cl	H	H	H	48	**7j**, 80
12	**6k**	Br	H	H	H	48	**7k**, 85[8b]

[a] Isolated yield.



Scheme 2 Proposed reaction mechanism of the multicomponent reaction for the synthesis of 4-alkyl-3,4-dihydrocoumarins catalyzed by $NbCl_5$

All reactions were carried out under an atmosphere of N_2, unless otherwise specified. CH_2Cl_2 was distilled from CaH_2. All commercially available reagents were used without further purification. TLC was performed on 0.2 mm Merck $60F_{254}$ silica gel aluminum sheets, which were visualized with a vanillin/MeOH–H_2O–H_2SO_4 mixture. ACROS 80–230 silica gel 60 was employed for column chromatography. A Perkin–Elmer RX-FTIR System was used to record IR spectra (neat or film). Bruker DPX 300 and DRX 500 spectrometers were employed for the NMR spectra ($CDCl_3$ solutions) using TMS as internal reference for ^1H and $CDCl_3$ as an internal reference for ^{13}C NMR spectra.

Multicomponent Reaction of Dimethyl Malonate, 3,5-Dimethoxyphenol, and Benzaldehyde Derivatives with $NbCl_5$; General Procedure

To a solution of $NbCl_5$ (270 mg, 1 mmol) in anhyd CH_2Cl_2 (2 mL), maintained at r.t. under N_2 atmosphere, were added a solution of the dimethyl malonate (132 mg, 1.0 mmol), 3,5-dimethoxyphenol (154 mg, 1.0 mmol), and the respective aldehyde **6a**–**k** (1 mmol) in anhyd CH_2Cl_2 (5 mL). After completion of the addition, stirring was continued at the same temperature for 48 h. The reaction mixture was quenched by the addition of H_2O (3 mL). The mixture was extracted with CH_2Cl_2 (10 mL). The organic layer was separated and washed with sat. aq $NaHCO_3$ (3 × 10 mL), brine (2 × 10 mL), and dried ($MgSO_4$). The solvent was removed under vacuum and the products **7a**–**k** were purified by column chromatography through silica gel using mainly a mixture of hexane and EtOAc (7:3) as eluent.

Methyl 5,7-Dimethoxy-4-phenyl-2-oxochroman-3-carboxylate (7a)

Yield: 273 mg (88%); white solid; mp 110–112 °C.

IR (neat): 1778, 1737, 1627, 1595, 1502, 1454, 1437, 1423, 1319, 1255, 1215, 1157, 1134, 1097 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.22 (m, 3 H), 7.11 (d, *J* = 7.3 Hz, 2 H), 6.35 (d, *J* = 2.2 Hz, 1 H), 6.27 (d, *J* = 2.2 Hz, 1 H), 4.97 (s, 1 H), 3.95 (d, *J* = 1.4 Hz, 1 H), 3.81 (s, 3 H), 3.72 (s, 3 H), 3.69 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.7, 164.1, 161.4, 158.2, 153.0, 140.2, 129.4, 127.9, 127.3, 104.1, 95.9, 94.3, 56.3, 55.9, 54.8, 53.6, 39.2.

ESI-HRMS: *m*/*z* calcd for $C_{19}H_{19}O_6$ $[M + H]^+$: 343.11816; found: 343.1145.

Methyl 5,7-Dimethoxy-4-(*p*-tolyl)-2-oxochroman-3-carboxylate (7b)

Yield: 331 mg (93%); white solid; mp 75–76 °C.

IR (neat): 1774, 1734, 1623, 1593, 1502, 1454, 1432, 1423, 1328, 1261, 1213, 1157, 1135, 1097 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.11 (d, *J* = 8.0 Hz, 2 H), 7.03 (d, *J* = 8.0 Hz, 2 H), 6.36 (d, *J* = 2.3 Hz, 1 H), 6.28 (d, *J* = 2.3 Hz, 1 H), 4.96 (s, 1 H), 3.95 (d, *J* = 1.5 Hz, 1 H), 3.83 (s, 3 H), 3.75 (s, 3 H), 3.71 (s, 3 H), 2.31 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.4, 163.8, 160.9, 157.8, 152.6, 137.2, 136.7, 129.7, 126.7, 103.8, 95.4, 93.8, 55.9, 54.5, 53.2, 38.5, 20.9.

ESI-HRMS: *m*/*z* calcd for $C_{20}H_{21}O_6$ $[M + H]^+$: 357.13382; found: 357.1332.

Methyl 5,7-Dimethoxy-4-(*m*-tolyl)-2-oxochroman-3-carboxylate (7c)

Yield: 310 mg (87%); white solid; mp 90–92 °C.

IR (neat): 1776, 1735, 1621, 1593, 1506, 1469, 1434, 1423, 1332, 1280, 1267, 1226, 1193, 1130, 1099 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.16 (t, *J* = 7.5 Hz, 1 H), 7.03 (d, *J* = 7.5 Hz, 1 H), 6.90 (m, 2 H), 6.35 (d, *J* = 2.2 Hz, 1 H), 6.27 (d, *J* = 2.2 Hz, 1 H), 4.94 (s, 1 H), 3.94 (d, *J* = 1.5 Hz, 1 H), 3.82 (s, 3 H), 3.73 (s, 3 H), 3.69 (s, 3 H), 2.28 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.4, 163.8, 160.9, 157.8, 152.6, 139.6, 138.7, 128.9, 128.3, 127.5, 123.9, 103.6, 95.4, 93.8, 55.9, 55.4, 54.5, 53.2, 38.8, 21.4.

ESI-HRMS: *m*/*z* calcd for $C_{20}H_{21}O_6$ $[M + H]^+$: 357.13382; found: 357.1333.

Methyl 5,7-Dimethoxy-4-(*o*-tolyl)-2-oxochroman-3-carboxylate (7d)

Yield: 349 mg (98%); white solid; mp 155–159 °C.

IR (neat): 1774, 1739, 1622, 1593, 1506, 1452, 1434, 1330, 1280, 1263, 1222, 1195, 1135, 1097 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.20 (d, *J* = 7.5 Hz, 1 H), 7.16 (t, *J* = 7.5 Hz, 1 H), 7.02 (t, *J* = 7.5 Hz, 1 H), 6.71 (d, *J* = 7.5 Hz, 1 H), 6.38 (d, *J* = 2.2 Hz, 1 H), 6.26 (d, *J* = 2.2 Hz, 1 H), 5.16 (s, 1 H), 3.83 (s, 3 H), 3.77 (d, *J* = 1.1 Hz, 1 H), 3.71 (s, 3 H), 3,69 (s, 3 H), 2.54 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.5, 163.6, 161.0, 157.6, 153.1, 137.6, 135.2, 131.0, 127.5, 126.7, 126.1, 103.6, 95.4, 93.6, 55.9, 55.5, 53.2, 53.1, 35.6, 19.2.

ESI-HRMS: *m*/*z* calcd for $C_{20}H_{21}O_6$ $[M + H]^+$: 357.13382; found: 357.1307.

Methyl 5,7-Dimethoxy-4-(2,4,6-trimethylphenyl)-2-oxochroman-3-carboxylate (7e)

Yield: 215 mg (56%); white solid; mp 96–98 °C.

IR (neat): 1766, 1737, 1621, 1594, 1504, 1469, 1450, 1434, 1421, 1324, 1261, 1242, 1222, 1201, 1164, 1145, 1097 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.88 (s, 1 H), 6.67 (s, 1 H), 6.29 (d, *J* = 2.2 Hz, 1 H), 6.21 (d, *J* = 2.3 Hz, 1 H), 5.28 (d, *J* = 2.2 Hz, 1 H), 3.80 (s, 3 H), 3.76 (d, *J* = 2.2 Hz, 1 H), 3.73 (s, 3 H), 3.61 (s, 3 H), 2.51 (s, 3 H), 2.22 (s, 3 H), 1.86 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.3, 164.4, 160.7, 158.4, 152.6, 136.4, 134.8, 131.4, 129.7, 103.5, 95.4, 93.6, 55.9, 55.5, 53.3, 52.0, 35.6, 21.1, 20.6, 19.6.

ESI-HRMS: *m*/*z* calcd for $C_{22}H_{25}O_6$ $[M + H]^+$: 385.16512; found: 385.1628.

Methyl 5,7-Dimethoxy-4-(4-*tert*-butylphenyl)-2-oxochroman-3-carboxylate (7f)
Yield: 310 mg (78%); white solid; mp 115–118 °C.

IR (neat): 1774, 1743, 1625, 1591, 1500, 1461, 1434, 1421, 1369, 1359, 1319, 1215, 1159, 1141, 1095 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.1 Hz, 2 H), 6.98 (d, *J* = 8.1 Hz, 2 H), 6.29 (d, *J* = 2.3 Hz, 1 H), 6.22 (d, *J* = 2.3 Hz, 1 H), 4.90 (d, *J* = 1.5 Hz, 1 H), 3.91 (d, *J* = 1.5 Hz, 1 H), 3.76 (s, 3 H), 3.69 (s, 3 H), 3.64 (s, 3 H), 1.21 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.4, 164.0, 160.9, 157.8, 152.5, 150.3, 136.5, 126.5, 125.9, 104.0, 95.4, 93.8, 55.9, 55.5, 54.4, 53.2, 38.3, 34.4, 31.2.

ESI-HRMS: *m*/*z* calcd for $C_{23}H_{27}O_6$ $[M + H]^+$: 399.18077; found: 399.1797.

Methyl 5,7-Dimethoxy-4-(3-methoxyphenyl)-2-oxochroman-3-carboxylate (7g)
Yield: 297 mg (80%); white solid; mp 133–135 °C.

IR (neat): 2956, 1776, 1735, 1623, 1593, 1500, 1456, 1434, 1423, 1324, 1286, 1213, 1159, 1134, 1097 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19 (t, *J* = 7.9 Hz, 1 H), 6.77–6.65 (m, 3 H), 6.34 (d, *J* = 2.3 Hz, 1 H), 6.27 (d, *J* = 2.3 Hz, 1 H), 4.94 (s, 1 H), 3.95 (d, *J* = 1.5 Hz, 1 H), 3.82 (s, 3 H), 3.75 (s, 3 H), 3.74 (s, 3 H), 3.69 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3, 161.0, 160.0, 157.8, 152.6, 141.3, 130.1, 119.1, 113.1, 112.6, 103.5, 95.5, 93.8, 55.9, 55.5, 55.1, 54.4, 53.2, 38.8.

ESI-HRMS: *m*/*z* calcd for $C_{20}H_{21}O_7$ $[M + H]^+$: 373.12873; found: 373.1283.

Methyl 5,7-Dimethoxy-4-(2-methoxyphenyl)-2-oxochroman-3-carboxylate (7h)
Yield: 346 mg (93%); white solid; mp 140–144 °C.

IR (neat): 2921, 1772, 1735, 1627, 1593, 1504, 1456, 1434, 1423, 1282, 1263, 1220, 1159, 1137, 1110, 1095 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22 (ddd, *J* = 8.2, 7.5, 1.8 Hz, 1 H), 6.88 (d, *J* = 8.2 Hz, 1 H), 6.81 (dt, *J* = 7.5, 1.0 Hz, 1 H) 6.74 (dd, *J* = 7.5, 1.8 Hz, 1 H), 6.34 (d, *J* = 2.3 Hz, 1 H), 6.26 (d, *J* = 2.3 Hz, 1 H), 5.17 (s, 1 H), 4.08 (d, *J* = 1.5 Hz, 1 H), 3.88 (s, 3 H), 3.82 (s, 3 H), 3.70 (s, 3 H), 3.69 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.8, 164.1, 160.8, 157.9, 156.8, 153.2, 128.8, 128.2, 127.2, 120.6, 110.5, 103.1, 95.3, 93.7, 55.8, 55.5, 55.1, 53.1, 51.9, 34.5.

ESI-HRMS: *m*/*z* calcd for $C_{20}H_{21}O_7$ $[M + H]^+$: 373.12873; found 373.1283.

Methyl 5,7-Dimethoxy-4-(4-fluorophenyl)-2-oxochroman-3-carboxylate (7i)
Yield: 331 mg (92%); white solid; mp 75–76 °C.

IR (neat): 1778, 1739, 1631, 1591, 1502, 1463, 1454, 1436, 1425, 1321, 1297, 1261, 1213, 1184, 1153, 1128, 1091 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.09 (m, 2 H), 6.97 (m, 2 H), 6.34 (d, *J* = 2.1 Hz, 1 H), 6.27 (d, *J* = 2.1 Hz, 1 H), 4.95 (s, 1 H), 3.91 (d, *J* = 1.3 Hz, 1 H), 3.81 (s, 3 H), 3.74 (s, 3 H), 3.69 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.5, 163.9, 162.5 ($J_{C,F}$ = 245.7 Hz), 161.6, 158.2, 152.9, 135.9, 130.0, 129.0, 128.9, 116.4, 116.2, 103.9, 95.9, 94.3, 56.3, 55.9, 54.8, 53.7, 38.6.

ESI-HRMS: *m*/*z* calcd for $C_{19}H_{18}FO_6$ $[M + H]^+$: 361.10874; found: 361.1080.

Methyl 5,7-Dimethoxy-4-(4-chlorophenyl)-2-oxochroman-3-carboxylate (7j)
Yield: 301 mg (80%); white solid; mp 110–114 °C.

IR (neat): 2848, 2925, 1772, 1737, 1627, 1591, 1502, 1488, 1461, 1432, 1423, 1321, 1292, 1259, 1216, 1205, 1186, 1159, 1137, 1095 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 9.6 Hz, 2 H), 7.02 (d, *J* = 9.6 Hz, 2 H), 6.32 (d, *J* = 2.3 Hz, 1 H), 6.24 (d, *J* = 2.3 Hz, 1 H), 4.92 (d, *J* = 1.4 Hz, 1 H), 3.88 (d, *J* = 1.7 Hz, 1 H), 3.79 (s, 3 H), 3.71 (s, 3 H), 3.67 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 165.3, 161.2, 157.7, 152.5, 139.6, 138.7, 133.4, 129.2, 128.3, 103.1, 95.5, 93.8, 55.9, 55.6, 54.2, 38.2.

ESI-HRMS: *m*/*z* calcd for $C_{19}H_{18}ClO_6$ $[M + H]^+$: 377.07919; found: 377.0794.

Methyl 5,7-Dimethoxy-4-(4-bromophenyl)-2-oxochroman-3-carboxylate (7k)
Yield: 358 mg (85%); white solid; mp 107–110 °C.

IR (neat): 1776, 1735, 1625, 1591, 1504, 1485, 1461, 1434, 1423, 1400, 1369, 1324, 1292, 1261, 1242, 1218, 1184, 1159, 1137, 1095 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.4 Hz, 2 H), 6.69 (d, *J* = 8.4 Hz, 2 H), 6.34 (d, *J* = 2.2 Hz, 1 H), 6.27 (d, *J* = 2.2 Hz, 1 H), 4.93 (s, 1 H), 3.90 (d, *J* = 1.4 Hz, 1 H), 3.82 (s, 3 H), 3.73 (s, 3 H), 3.70 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 163.4, 161.2, 152.5, 138.8, 132.1, 128.7, 121.5, 103.4, 95.5, 93.8, 55.9, 55.5, 54.1, 53.3, 38.3.

ESI-HRMS: *m*/*z* calcd for $C_{19}H_{18}BrO_6$ $[M + H]^+$: 421.02868; found: 421.0280.

Dimethyl Benzylidenepropanedioate (8)
Isolated as a side product from the reaction of benzaldehyde (**6a**), 3,5-dimethoxyphenol (**4**), and dimethyl malonate (**5**), following the general procedure with a reaction time of 24 h; yield: 32 mg (14 %); viscous yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 (s, 1 H), 7.42 (m, 5 H), 3.86 (s, 3 H), 3.85 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1, 164.5, 142.9, 132.8, 130.7, 129.4, 128.9, 125.5, 52.7.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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