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A Practical and Economical High-Yielding, Six-Step Sequence Synthesis of a Flavone: Application to the Multigram-Scale Synthesis of Ladanein

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Supporting Information

ABSTRACT: Herein we report a short and economic synthesis of the antiviral flavonoid lead ladanein (**1**). Ladanein is obtained from 2,6-dimethoxyquinone (**11**) in six steps with 51% overall yield. After a high-yielding reductive acetylation and Fries rearrangement, the flavone skeleton is built by means of a Baker−Venkataraman rearrangement. Throughout the synthetic pathway no chromatographic columns were used, and the reaction products were isolated and purified by optimized work-up and crystallization processes. This new process has been tested on a multigram-scale with an improved overall yield from 16 to 51% through six steps, and three chromatographic purifications used in the earlier synthesis were eliminated.

INTRODUCTION

Flavonoids are secondary metabolites that are broadly distributed in nature, in particular in the plant kingdom. As one of the most ubiquitous groups of natural products in plants these polyphenols are responsible for the major nutritional, healthy, and organoleptic properties of plant-derived foods and beverages.[1] Notably, many representatives were shown to exert anticarcinogenic,[2] antimicrobial,[3] antiprotozoan,[4] antipsoriasis,[5] antineurodegenerative,[6] antidiabetic,[7] or antiviral[8,9] properties. Besides the wide range of biological activities, they are well-known for their high antioxidant activity,[1,10] which contributes to proven health benefits or to reduce the risk of disease prevalence in populations consuming them every day and on long-term. In the last years, flavonoids have attracted a huge interest for developing future drug strategies as dietary supplements (functional food) to reduce the risk of pathologic disorders, at both the levels of treatment and prevention of diseases. These include natural, hemisynthetic and synthetic flavonoids, alone or in combination with other agents.

An antiviral flavone (ladanein, **1**), identified from *Lamiaceae* extracts,[11] was found to be active against enveloped viruses such as the human immunodeficiency virus (HIV) and hepatitis C virus (HCV). Ladanein displays an antiviral activity in the low micromolar range with an innovative mode of action.[12] With respect to HCV infection, it has been estimated that more than 150 million people live with this disease in the world, affecting particularly middle Asia countries. About 80% of the people living with HCV develop a chronic infection, which may lead to hepatocellular carcinoma and death.[13] Hepatitis C is the main cause of liver transplantation in the world, but HCV virus reinfection in liver transplant patients is the major cause of rapid progression of HCV-related liver diseases, like cirrhosis. There are seven major HCV genotypes and several subtypes that can be primarily cross-transmitted through percutaneous exposure to contaminated blood, especially in healthcare settings and among people who inject drugs.[14] They display varying antiviral drug responses and cross resistance. Also, there is an urgent need of safe anti-HCV drugs, like flavonoids, that can be administered prophylactically after liver transplantation to prevent or to delay HCV recurrence and spread in chronically infected liver transplant patients.[8,9,15,16] In this context a versatile and scalable synthesis of ladanein has been developed. A survey of the literature showed that the flavone core can be generally built via the cyclization of a chalcone precursor under iodine treatment[17] or via the Baker−Venkataraman rearrangement of a β-diketone.[18]

ORIGINAL SYNTHESIS

In this context, some of us previously developed a simple and robust synthesis (depicted in Scheme 1) in order to obtain the synthetic analogue of ladanein and other analogues bearing different R groups. The synthesis is quite short, but it has four major drawbacks for industrial process. First, it starts with an Elbs oxidation,[19] which is a low-yielding (35% yield on average) and long reaction (7 days) that needs an extremely laborious work-up and purification process to recover the unreacted starting acetophenone **2** and isolated product **3**. Also, the starting material is quite expensive. Second, the LiHMDS used for the Baker−Venkataraman rearrangement is commercially available, but its quality is inconsistent between different batches. This fact makes it unreliable for large-scale syntheses. Third, after the demethylation step using BBr_3, a Sephadex LH-20 is needed to obtain pure ladanein. Sephadex LH-20 is an extremely expensive chromatography gel, and a long time is needed to achieve a successful separation, sometimes even after several column separations. Finally, products **3** and **6** had to be purified by silica gel column chromatography, which is an expensive and time-consuming method compared to recrystallization. Due to these drawbacks, a new synthesis was developed to access a more efficient synthetic route for the

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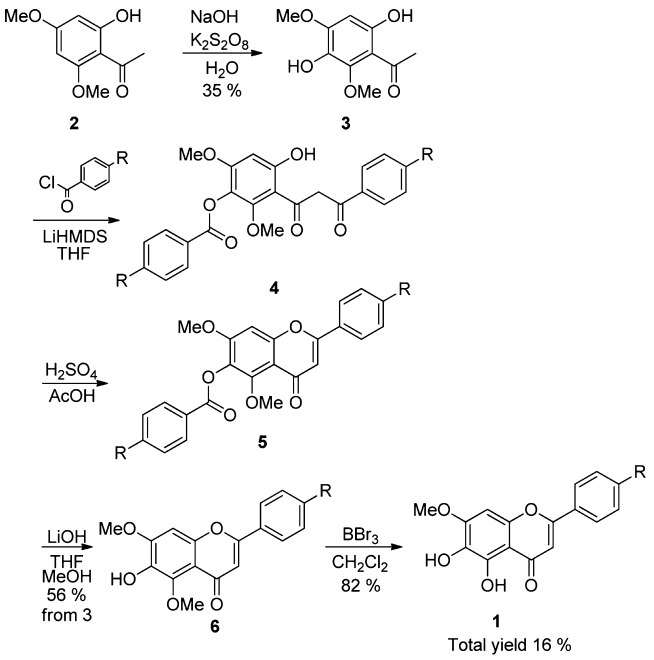
Scheme 1. Original synthesis



preparation of ladanein and other analogues, formulations, and biological testing.

IMPROVED SYNTHESIS

The first goal was to improve the synthesis of acetophenone **3**, the initial precursor of ladanein. A new synthetic scheme was proposed starting from cheap syringaldehyde (**7**), as shown in Scheme 2. It involved a Baeyer–Villiger reaction, followed by an acetylation and a Fries rearrangement.

However, reaction of product **8** did not yield dihydroquinone **9** but the corresponding oxidized quinone **11** and only in 29% yield after a two day-long reaction and a difficult separation through silica gel column chromatography. This setback was used as new starting point, because quinone **11** is a commercially available and cheap starting material. This allows shortening the overall time needed for ladanein synthesis by 3 days.

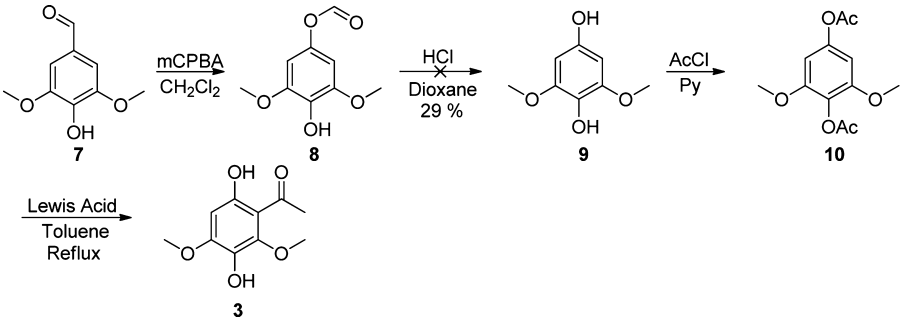
Initial precursor **3** is obtained from **11** after a high-yielding reductive acetylation using Zn powder and acetic anhydride and a Fries rearrangement as depicted in Scheme 3. Both reactions are performed on ∼10 g scale.

A thorough study was undertaken in order to find the best conditions for the Fries rearrangement. Several Lewis acids were tested as well as different temperatures. The best conditions were found to be boron trifluoride etherate in toluene (Table 1, entry 9). Although microwave irradiation (Table 1, entry 10) afforded the acetophenone with similar to slightly increased yield, it was discarded because it did not allow the scale-up of the reaction under the conditions found in our laboratory environment. Using 3 equiv of boron trifluoride etherate at 110 °C overnight, the desired acetophenone **3** was obtained with 70% yield. A byproduct was also obtained in 30% yield, which corresponded to the acetylated acetophenone **12**. Filtration through a silica gel pad afforded a mixture of **3** and **12**. Both products can be separated by means of a recrystallization or a silica gel column chromatography, but the separation is not essential because product **12** can be used as starting material to synthesize ladanein as well. A ∼8 g-scale Fries rearrangement of diacetate **10** gave a 63:37 mixture (from NMR) of acetophenone **3** and acetylated acetophenone **12**, which was then used in the next step without separation.

The synthesis continues with a Baker–Venkataraman rearrangement in the presence of LiHMDS, as depicted in Scheme 4. It was decided to synthesize LiHMDS *in situ* by reacting freshly distilled HMDS with *n*-BuLi.[20] This produced LiHMDS of superior quality and a lower price than those of the commercially available. Then, it was added to a solution of acetophenone **3**. Once all the acetophenone had been deprotonated, *p*-methoxybenzoyl chloride was added to the mixture to form diketone **4**. Without purification, the flavone cycle was built via a cyclization using AcOH and H_2SO_4, and the resulting product **5** was saponified using LiOH. At this point, with the previous synthesis a silica gel column chromatography was necessary to isolate flavone **6**. However, the separation had to be done very carefully in order to obtain the product with a satisfactory purity.

Different recrystallization systems were tested; however, none of them yielded the pure product. To solve the problem, a different work-up protocol was designed as shown in Figure 1. After saponification of **5**, alongside with flavone **6** and other impurities, carboxylic acid **13** is also present. Once the saponification is complete, the pH is acidified to 5 using AcOH, and the solution is extracted with DCM. At this point both the flavone and carboxylic acid are present in the organic phase. Then, the organic phase is thoroughly washed with NaOH, to make sure that both the flavone and the acid are deprotonated and present in the aqueous phase. This way, some impurities remained in the organic phase. Next, the basic aqueous phase is acidified to pH 7 and extracted again with DCM. Adjusting the pH to 7 allows the flavone to be protonated and be transferred to the organic phase while the carboxylic acid remains still soluble in the aqueous phase.

Scheme 2. Proposed synthesis of 3



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Scheme 3. Improved synthesis of 3

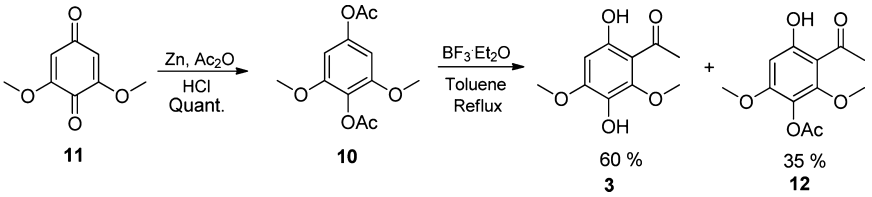


Table 1. Reaction conditions screen[a] for Fries rearrangement to produce the acetophenone 3

entry	Lewis Acid	temp °C	reaction time h	equiv	solvent	yield (3) %
1	$BF_3{\cdot}Et_2O$	120	3	20	toluene	50
2	BCl_3	110	24	3	toluene	0
3	BBr_3	110	4	3	toluene	0
4	$B(OH)_3$	70	4	6	THF	0
5	$AlCl_3$	110	2	3	toluene	0
6	$TiCl_4$	110	72	3	toluene	30
7	$ZrCl_4$	110	1.5	3	toluene	0
8	$SnCl_4$	110	2	3	toluene	0
9	$BF_3{\cdot}Et_2O$	110	18	3	toluene	70
10	$BF_3{\cdot}Et_2O$	130 (MW)	1	3	toluene	85

[a]All optimization test reactions were performed with similar scale of starting diacetate **10** (200 mg). MW = microwave.

Finally, recrystallization from water/EtOAc yielded 72% of flavone **6**.

Finally, the demethylation was performed using $MgBr_2$ etherate. The inexpensive Lewis acid was easily synthesized in the laboratory from magnesium turnings and 1,2-dibromoethane.[22] The demethylation step yielded 75% of pure and stable ladanein **1** after recrystallization from DCM. The time-consuming and expensive Sephadex LH-20 column is not required to purify the product.

CONCLUSION

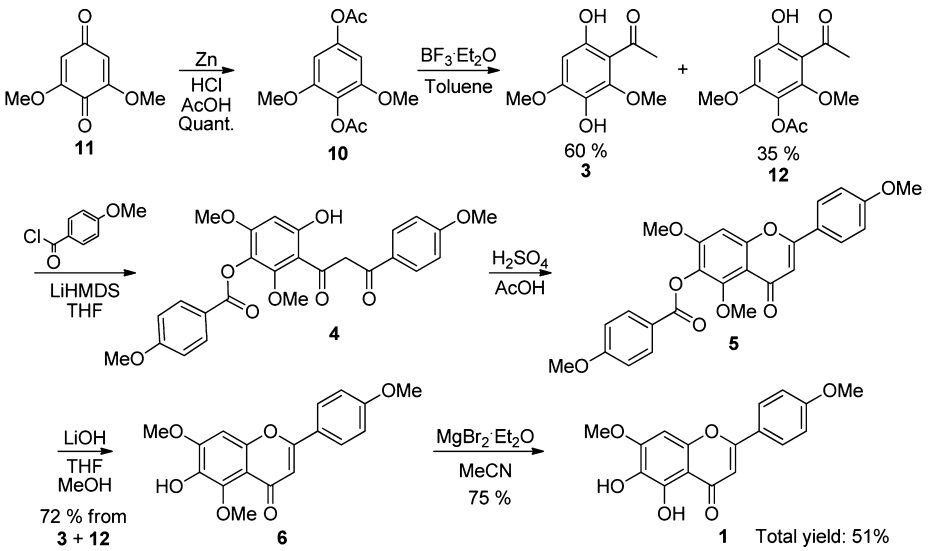
In conclusion, a short, inexpensive and scalable synthesis of ladanein (**1**) was developed in bulk. The initial precursor **3** was synthesized via a high-yielding reductive acetylation and Fries rearrangement. The flavone core was built via a Baker–Venkataraman reaction and an acidic cyclization. The final demethylation step was achieved using $MgBr_2$ etherate. All chromatographic columns were avoided during the synthetic pathway as well as the extremely costly and time-consuming Sephadex LH-20 column. Overall, the new synthesis is much faster and cheaper than the previously established one.

EXPERIMENTAL SECTION

General. Commercially available starting materials were purchased from Sigma-Aldrich, ABCR GmbH & Co. KG, Alfa Aesar, and Apollo Scientific and were used without further purification. Solvents were obtained from Sigma-Aldrich and Carlo Erba; unless noted, reagent grade was used for reactions and column chromatography, and analytical grade was used for recrystallization. When specified, anhydrous solvents were required; dichloromethane (DCM) was distilled over CaH_2 under argon. Tetrahydrofuran (THF) was dried by passage through an activated alumina column under argon. ^1H NMR spectra were recorded on a Bruker AC 300 (300 MHz) with solvent peaks as reference. Chemical shifts (δ) are reported in ppm. Multiplicities are given as: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), m (multiplet), br s (broad singlet).^{13}C NMR spectra were recorded on a Bruker AC 300 (75 MHz). Infrared (IR) spectra (cm^{-1}) were recorded neat on a Perkin Elmer Spectrum One spectrophotometer. ESI-HRMS mass spectra were carried out on a Bruker MicroTOF spectrometer. Melting points were measured on a Stuart Melting Point 10 apparatus and are given uncorrected (dec = decomposition).

4-(Acetyloxy)-3,5-dimethoxyphenyl Acetate (10). A cold (0 °C) solution of concentrated HCl (40 mL, excess)

Scheme 4. Improved general synthetic pathway



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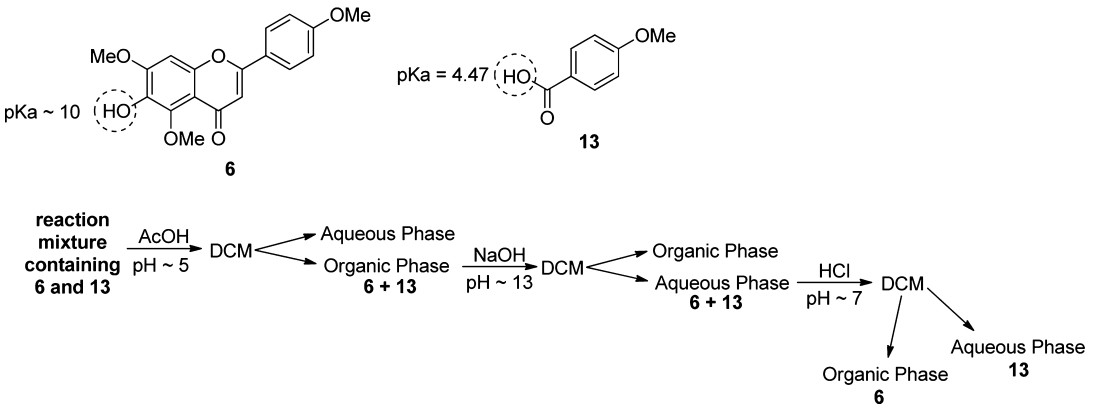

Figure 1. Protonation constants (pK_a) of the flavone and the carboxylic acid and work-up strategy to purify **6**. The pK_a of **6** has been estimated on the basis of the values determined for ladanein (not shown) and that of *p*-anisic acid (**13**) is taken from the literature.[21]

and Ac_2O (225 mL, excess) was added to a mixture of 2,6-dimethoxy-1,4-benzoquinone (**11**) (9.90 g, 59 mmol, 1 equiv) and activated Zn powder (29.03 g, 444 mmol, 7.5 equiv). The mixture was stirred at 0 °C for 5 min. Et_2O (300 mL) was added, and the solid was filtrated. The organic phase was washed with water and brine, dried over magnesium sulfate, and concentrated under reduced pressure, adding toluene to coevaporate the acetic acid, to yield a white solid (14.62 g, 58 mmol, quantitative yield). mp 126 °C; ^{1}H NMR ($CDCl_3$; 300 MHz): δ 6.40 (s, 2 H), 3.81 (s, 6 H), 2.34 (s, 3 H), 2.31 (s, 3 H); ^{13}C NMR ($CDCl_3$; 75 MHz): δ 169.4, 168.8, 152.6, 149.1, 126.6, 99.1, 56.4, 21.3, 20.6; IR (neat): 1754, 1615, 1504, 1423, 1179, 1129, 1018, 983, 909, 831, 567.

1-(3,6-Dihydroxy-2,4-dimethoxyphenyl)ethan-1-one (3) and 3-Acetyl-4-hydroxy-2,6-dimethoxyphenyl Acetate (12). $BF_3{\cdot}Et_2O$ (12 mL, 94.7 mmol, 3.05 equiv) was added dropwise to a solution of 4-(acetyloxy)-3,5-dimethoxyphenyl acetate **10** (7.88 g, 30.9 mmol, 1 equiv) in toluene (150 mL), and the mixture was heated to 110 °C for 18 h. Then, water (100 mL) and a saturated solution of NH_4Cl (100 mL) were added, and the aqueous phase was extracted three times with EtOAc. The separated organic layer was washed with water and brine, dried over magnesium sulfate, and concentrated under reduced pressure to yield a brown solid. The solid was diluted in CH_2Cl_2, filtered through silica gel, and solvent evaporated under reduced pressure to yield a mixture of **3** and **12** (yellow solid, 6.73 g of a 63:37 mixture of **3** (60% corrected yield) and **12** (35% corrected yield)). The solid was used without further purification.

Independent assay yield of **3** and **12** for this step was 8.84 g (quantitative). For the isolated **3**: mp 162 °C; ^{1}H NMR ($CDCl_3$; 300 MHz): δ 13.20 (s, 1 H), 6.28 (s, 1 H), 5.10 (s, 1 H), 3.98 (s, 3 H), 3.94 (s, 3 H), 2.69 (s, 3 H); ^{13}C NMR ($CDCl_3$; 75 MHz): δ 203.6, 159.1, 154.3, 147.6, 131.5, 108.7, 95.7, 60.9, 56.5, 31.8; IR (neat): 3261, 1630, 1594, 1499, 1433, 1230, 1078, 959, 892, 820, 593. For the isolated **12**: mp 103 °C; ^{1}H NMR ($CDCl_3$; 300 MHz): δ 13.52 (s, 1 H), 6.31 (s, 1 H), 3.91 (s, 3 H), 3.86 (s, 3 H), 2.67 (s, 3 H), 2.36 (s, 3 H); ^{13}C NMR ($CDCl_3$; 75 MHz): δ 203.3, 168.9, 163.9, 158.5, 154.6, 125.8, 108.6, 96.7, 61.6, 56.5, 31.8, 20.6; IR (neat): 1762, 1594, 1444, 1360, 1261, 1202, 1156, 1103, 1080, 926, 817, 503.

4-Hydroxy-2,6-dimethoxy-3-(3-(4-methoxyphenyl)-3-oxopropanoyl)phenyl-4-methoxybenzoate (4). A solution of LiHMDS was prepared by adding 103 mL of *n*-BuLi (1.6 M in hexane, 164.8 mmol, 7.5 equiv) to a solution of freshly distilled HMDS (36 mL, 172 mmol, 7.9 equiv) in dry THF (100 mL) at 0 °C. The mixture was stirred at that temperature for 30 min and then was added dropwise to a mixture of 1-(3,6-dihydroxy-2,4-dimethoxyphenyl)ethan-1-one (**3**) and 3-acetyl-4-hydroxy-2,6-dimethoxyphenyl acetate (**12**) (4.94 g) in dry THF (200 mL) under Ar atmosphere and at −78 °C. The mixture was left to stir for 1 h at −78 °C, 2 h at −10 °C, and then it was cooled down to −78 °C again. A solution of 4-methoxybenzoyl chloride (6.4 mL, 47.6 mmol, 2.2 equiv) in dry THF (50 mL) was added, and the reaction was stirred for 1 h at −78 °C and at room temperature overnight. The solution was poured into a mixture of crushed ice and concentrated HCl, extracted three times with DCM, dried over magnesium sulfate, and concentrated under reduced pressure to yield a brown solid. The solid was used without further purification. For the isolated **4**: mp 240−242 °C; ^{1}H NMR ($CDCl_3$; 300 MHz): δ 8.08 (d, J = 8.71 Hz, 2 H), 7.78 (d, J = 8.71 Hz, 2 H), 6.89 (dd, J = 4.51, 8.59 Hz, 4 H), 6.62 (s, 1 H), 6.47 (s, 1H), 5.60 (br s, 1 H), 3.93 (s, 3 H), 3.92 (s, 3 H), 3.85 (s, 6 H); ^{13}C NMR ($CDCl_3$; 75 MHz): δ 165.3, 163.9, 163.1, 148.8, 141.4, 136.7, 132.4, 129.2, 128.2, 127.5, 121.4, 118.0, 113.9, 104.0, 102.6, 98.9, 62.0, 56.4, 55.5; FAB$^+$ MS: 481.6 [M + H]$^+$.

5,7-Dimethoxy-2-(4-methoxyphenyl)-4-oxo-4*H*-chromen-6-yl-4-methoxybenzoate (5). Product **4** was dissolved in acetic acid (120 mL), H_2SO_4 (3 mL) was added, and the reaction was heated at 95 °C for 3.5 h. Then, the solvent was evaporated under reduced pressure, water was added, and the aqueous phase was extracted three times with DCM. The organic phase was dried over magnesium sulfate, and the solvent was evaporated under reduced pressure to yield a dark-brown solid. The product was used without further purification.

6-Hydroxy-5,7-dimethoxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (6). Product **5** was dissolved in THF (150 mL), and a solution of LiOH (3.57 g, 149 mmol, excess) in MeOH (50 mL) was added. The reaction was stirred at room temperature for 2 h. The solution was poured into water, and AcOH was added until the pH was around 5. The aqueous phase was extracted three times with DCM, and the organic phase was thoroughly washed with a 0.5 M solution of NaOH. The aqueous phase was then acidified to neutral pH with a 1 M solution of HCl, and the aqueous phase was extracted three times with DCM. After concentration under reduced pressure and a recrystallization from water/EtOAc, a light-brown solid was obtained (5.15 g, 15.7 mmol, 72% yield from **3** and **12** in 63:37 ratio). mp 222−223 °C; ^{1}H NMR ($CDCl_3$; 300 MHz): δ

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7.84 (d, J = 8.9 Hz, 2 H), 7.02 (d, J = 8.9 Hz, 2 H), 6.84 (s, 1 H), 6.61 (s, 1 H), 5.93 (s, 1 H), 4.04 (s, 3 H), 4.03 (s, 3 H), 3.90 (s, 3 H); ^{13}C NMR ($CDCl_3$; 75 MHz): δ 177.0, 162.1, 161.4, 152.1, 151.9, 144.0, 136.6, 127.6, 124.0, 114.4, 112.3, 106.9, 96.2, 62.6, 56.4, 55.5; IR (neat): 3281, 1602, 1498, 1358, 1249, 1182, 1111, 838, 827, 555.

5,6-Dihydroxy-7-methoxy-2-(4-methoxyphenyl)-chromen-4-one (1). To a solution of 6-hydroxy-5,7-dimethoxy-2-(4-methoxyphenyl)-4H-chromen-4-one (3.91 g, 11.92 mmol, 1 equiv) in MeCN (250 mL) was added $MgBr_2$ etherate (7.69 g, 29.8 mmol, 2.5 equiv). The reaction mixture was stirred for 3 h at 80 °C. Then a solution of HCl 0.5 M was added, and the aqueous phase was extracted with EtOAc. The organic phase was washed three times with HCl 0.5 M, water, and brine. The separated organic layer was dried over magnesium sulfate and concentrated under reduced pressure. Recrystallization from DCM yielded a bright-yellow solid (2.86 g, 9.1 mmol, 76% yield). mp 215 °C dec; ^{1}H NMR (DMSO-d_6; 300 MHz): δ 12.62 (s, 1 H), 8.73 (s, 1 H), 8.07 (d, J = 8.8 Hz, 2 H), 7.13 (d, J = 8.8 Hz, 2 H), 6.96 (s, 1 H), 6.91 (s, 1 H), 3.94 (s, 3 H), 3.88 (s, 3 H); ^{13}C NMR (DMSO-d_6; 75 MHz): δ 182.2, 163.3, 162.2, 154.4, 149.6, 146.2, 129.9, 128.2, 123.0, 114.5, 105.1, 103.1, 91.2, 56.3, 55.5; IR (neat): 3518, 1482, 1464, 1359, 1248, 1179, 1108, 1035, 830, 803, 558; HRMS (ESI$^+$): 315.09 $[M + H]^+$

■ ASSOCIATED CONTENT

Supporting Information

Purification protocol for acetylated acetophenone **12** and acetophenone **3** applied in the screen of reaction conditions (Table 1), ^{1}H and ^{13}C NMR spectra for compounds **1**, **3**, **4**, **6**, **10**, and **12**. This material 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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