Reactions of Carbanions with 1,3-Benzodioxin-4-ones: Facile Routes to Flavones, Aurones, and Acyl Phloroglucinols

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Abstract: Two 1,3-benzodioxin-4-ones react with enolates, acetylides and aryllithium reagents to afford adducts that were converted into flavones, aurones, and an acyl phloroglucinol.

Key words: carbanions, ketones, natural products, nucleophilic addition

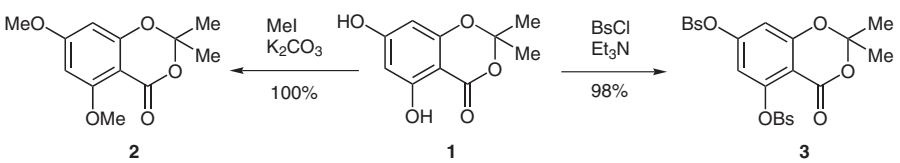
The carbanion addition chemistry of 1,3-benzodioxin-4-ones has been little studied. To the best of our knowledge, only two reactions of 1,3-benzodioxin-4-ones with a carbanion have been reported. In one case an organozinc reagent reacted with a 1,3-benzodioxin-4-one to afford a tertiary alcohol and in the other case a Grignard reagent reacted to provide a ketone.[1,2] The infrequent use of 1,3-benzodioxin-4-ones was in part due to the absence of a convenient general method of preparation.[3] Recently, Takahashi reported an improved synthesis of 1,3-benzodioxin-4-ones such as **1**.[4] Methylation of **1** using potassium carbonate and methyl iodide afforded **2** in 100% yield. Protection of **1** using benzenesulfonyl chloride and triethylamine gave **3** in 98% yield (Scheme 1).

Because of the ready availability of **2** and **3**, we evaluated their reactions against a panel of carbanions. These reactions are depicted below in Table 1. The reaction of the enolate of acetophenone [prepared by deprotonation of acetophenone with lithium diisopropylamide (LDA) in THF at –78 °C] with **2** did not take place and only the starting materials were recovered. However, the reaction of the enolate with the more electrophilic reagent **3** generated β-diketone **4** in 77% yield. Unexpectedly, no reaction of the enolate of 4-methoxyacetophenone with **3** took place and only the starting materials were recovered. Fortunately, the LDA-derived enolate of 4-benzenesulfonyloxyacetophenone reacted efficiently with **3** to produce the β-diketone **5** in 66% yield.

Treatment of **2** with the lithium anion of phenylacetylene at 0 °C (generated from phenylacetylene and *n*-butyllithium at –78 °C) afforded the acetylenic ketone **6** in 45% yield. Similarly, the anion of 3,4-dimethoxyphenylacetylene furnished the ketone **7** in 31% isolated yield. When 3,4-dimethoxybromobenzene was metalated with *n*-butyllithium in THF at –78 °C and reacted with **3**, adduct **8** was produced in 74% yield. When 4-benzyloxy-3-methoxybromobenzene was lithiated and reacted with **2**, benzophenone **9** was generated in 70% yield. The reaction of phenyllithium with **2** produced adduct **10** in 75% yield whose spectra matched the literature data.[5]

We next studied the conversion of adducts from Table 1 into natural products. Diketone **4** was readily cyclized using PTSA and then deprotected using potassium carbonate in methanol to afford the natural product chrysin (**11**) in 69% overall yield from acetophenone (Scheme 2). The ^{1}H and ^{13}C NMR spectra of our synthetic material were identical with the spectra obtained from an authentic sample of chrysin.[6] The β-diketone **5** could be cyclized using PTSA and deprotected to provide apigenin (**12**) in 42% overall yield from **5**. Again, ^{1}H and ^{13}C NMR spectra of our synthetic material matched the spectra of an authentic sample of apigenin.[6] Apigenin is a natural antioxidant that occurs in a number of species of *Hypericum*.[7] It has been shown to promote cell cycle arrest and apoptosis in various malignant cell lines and is also a potent inhibitor of glucosyltransferase activity.[8]

Ketone **6** was rapidly cyclized to aurone **13** upon reaction with potassium carbonate in boiling acetone. The exclusive 5-*exo* reaction pathway has precedent in the work of Garcia.[9] The NMR spectrum of our material is identical to that of the natural product. The melting point of **13** compares closely with the literature value.[10] Similarly, adduct **7** was converted into aurone **14** in 80% yield (Scheme 3). The ^{1}H NMR spectrum of **14** matched the literature data.[11]



Scheme 1

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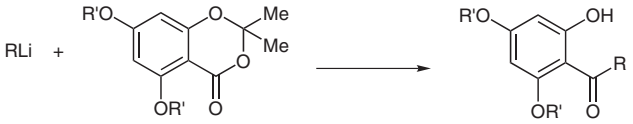
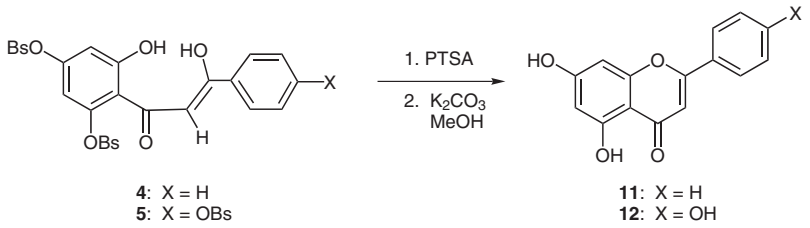
Table 1 The Reactions of Carbanions with 1,3-Benzodioxin-4-ones **2** and **3**



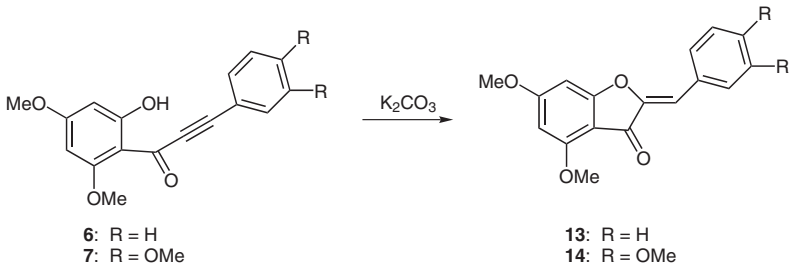
RLi	Conditions[a]	Acceptor	Yield (%)	
Acetophenone enolate	A	**2**	0	–
Acetophenone enolate	A	**3**	77	**4**
4-Methoxyacetophenone enolate	A	**3**	0	–
4-Benzenesulfonyloxyacetophenone enolate	A	**3**	60	**5**
Lithium phenylacetylide	B	**2**	45	**6**
Lithium 3,4-dimethoxyphenylacetylide	B	**2**	31	**7**
3,4-Dimethoxyphenyllithium[b]	B	**3**	74	**8**
4-Benzyloxy-3-methoxyphenyllithium[b]	B	**2**	70	**9**
Phenyllithium[b]		**2**	75	**10**

[a] Ketone, LDA, –78 °C.
[b] Aryl bromide, *n*-BuLi, –78 °C.



4: X = H
5: X = OBs
11: X = H
12: X = OH

Scheme 2

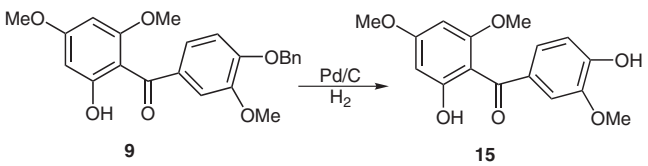


6: R = H
7: R = OMe
13: R = H
14: R = OMe

Scheme 3

Acyl phloroglucinols are a diverse class of natural products that exhibit antibacterial activity, anticancer activity and antitubercular activity.[12] Removal of the benzyl protecting group from ketone **9** using hydrogen and 10% palladium on carbon afforded the acyl phloroglucinol **15** in 73% yield (Scheme 4). The identity of synthetic benzophenone **15** was confirmed by comparison of our ^{1}H NMR, ^{13}C NMR, LRMS, and HRMS data with the published spectra for the natural product.[13] This is the first synthesis of benzophenone **15**.

In summary, 1,3-benzodioxin-4-ones **2** and **3** react with a number of commonly used carbanions to provide adducts in good yields. The adducts could be converted into the flavones chrysin and apigenin, aurones, and an acyl phloroglucinol.



9 **15**

Scheme 4

Tetrahydrofuran was distilled from sodium benzophenone ketyl. Dichloromethane, toluene and HMPA were distilled over calcium hydride. All experiments were performed under argon atmosphere. Organic extracts were dreid over anhydrous sodium sulfate. Infrared spectra were obtained on a Perkin-Elmer model 1320 spectrophotometer. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or a Bruker 400 MHz instrument. High-resolution mass spectra were recorded on a Kratos model MS-50 spectrometer and low-resolution mass spectra were performed with a Finnegan 4023 mass spectrometer. Standard grade silica gel (60 Å) was used for flash column chromatography.

5,7-Dimethoxy-2,2-dimethylbenzo[1,3]dioxin-4-one (2)

To **1** (0.30 g, 1.4 mmol) and anhyd K_2CO_3 (1.18 g, 8.57 mmol) in acetone (40 mL) at 0 °C was slowly added MeI (1.22 g, 8.57 mmol). The mixture was warmed slowly to r.t., poured into H_2O (20 mL), and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (10 mL) and dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by flash chromatography (hexanes–EtOAc, 2:1) afforded compound **2** (0.34 g, ~100%) as a light yellow solid; mp 128–129 °C; R_f = 0.38 (EtOAc–hexanes, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.68 (s, 6 H), 3.83 (s, 3 H), 3.91 (s, 3 H), 6.06 (d, *J* = 3 Hz, 1 H), 6.13 (d, *J* = 3 Hz, 1 H).

5,7-Dibenzenesulfonyloxy-2,2-dimethylbenzo[1,3]dioxin-4-one (3)

To **1** (0.240 g, 1.14 mmol) in THF (20 mL) at 0 °C was added Et_3N (0.25 g, 2.5 mmol), followed by slow addition of benzenesulfonyl chloride (0.44 g, 2.5 mmol). The mixture was warmed slowly to r.t. and stirred overnight. The solution was neutralized with 0.5 M aq AcOH, diluted with H_2O (20 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (10 mL) and dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by flash chromatography (hexanes–EtOAc, 2:1) afforded compound **3** (0.55 g, 98%) as a white solid; mp 132–133 °C; R_f = 0.18 (EtOAc–hexanes, 1:2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.61 (s, 6 H), 6.68 (d, *J* = 2.4 Hz, 1 H), 6.75 (d, *J* = 2.4 Hz, 1 H), 7.52–7.63 (m, 4 H), 7.66–7.77 (m, 2 H), 7.87–7.90 (m, 2 H), 9.95–7.98 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.6, 106.8, 107.4, 110.6, 112.7, 128.6, 129.2, 129.4, 129.9, 134.8, 135.0, 135.3, 149.7, 154.4, 156.0, 158.1.

MS: *m*/*z* = 490, 489, 432, 431, 141, 140.

HRMS: *m*/*z* calcd for $C_{22}H_{18}O_9S_2$: 490.0392; found: 490.0398.

Reaction of Ketones with 3 General Procedure

To *i*-Pr_2NH (1 equiv) in THF (0.2 M) at –78 °C was added *n*-BuLi (1 equiv) slowly. After 5 min, the temperature was raised to 0 °C for 15 min. After the solution was cooled to –78 °C, the respective ketone (1 equiv) in THF (5 mL/mmol) was added slowly. After stirring at –78 °C for 1 h, compound **3** (0.5 equiv) in THF (2 mL/mmol) was added slowly. The mixture was warmed slowly to r.t. and stirred for 2 h. The mixture was neutralized with 0.5 M aq AcOH, diluted with H_2O (20 mL), and extracted with EtOAc (2 × 20 mL). The organic layers were washed with brine (20 mL) and dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by flash chromatography (hexanes–EtOAc, 2:1) afforded the purified product (Table 1).

1-(2,4-Dibenzenesulfonyloxy-6-hydroxyphenyl)-3-phenylpropane-1,3-dione (4)

R_f = 0.38 (EtOAc–hexanes, 1:2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.50 (d, *J* = 2.4 Hz, 1 H), 6.55 (d, *J* = 2.4 Hz, 1 H), 6.95 (s, 1 H), 7.39–7.51 (m, 4 H), 7.55–7.72 (m, 6 H), 7.87–7.91 (m, 4 H), 11.82 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 98.7, 109.2, 111.0, 114.1, 127.4, 128.7, 128.9, 129.2, 129.5, 129.7, 133.2, 133.3, 134.3, 135.0, 135.1, 135.2, 149.0, 153.0, 163.3, 179.5, 191.8.

MS: *m*/*z* = 552, 470, 419, 394, 393, 103, 77.

HRMS: *m*/*z* calcd for $C_{27}H_{20}O_9S_2$: 552.0549; found: 552.0555.

1-(2,4-Dibenzenesulfonyloxy-6-hydroxyphenyl)-3-(4-benzenesulfonyloxyphenyl)propane-1,3-dione (5)

Compound **5** was taken on directly to **12** without purification.

1-(2,4-Dimethoxy-6-hydroxyphenyl)-3-phenylprop-2-ynone (6)

To phenylacetylene (20 mg, 0.2 mmol) in THF (5 mL) at 0 °C was added *n*-BuLi (2.5 M, 80 μL, 0.2 mmol) slowly. After 1 h at 0 °C, the lithium reagent was cooled to –78 °C, and compound **2** (43 mg, 0.18 mmol) in THF (2 mL) of was added slowly. The mixture was warmed slowly to r.t. and stirred for 2 h. The mixture was neutralized with 0.5 M aq AcOH, diluted with H_2O (20 mL) and extracted with EtOAc (2 × 20 mL). The organic layers were washed with brine (10 mL) and dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by flash chromatography twice (hexanes–EtOAc, 2:1 and hexanes–CH_2Cl_2, 1:2) afforded the starting material **2** (19 mg) and product (23 mg, 45% yield, 82% conversion); R_f = 0.24 (CH_2Cl_2–hexanes, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.85 (s, 3 H), 3.93 (s, 3 H), 5.94 (d, *J* = 2.4 Hz, 1 H), 6.07 (d, *J* = 2.4 Hz, 1 H), 7.42 (m, 3 H), 7.63 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.9, 56.0, 89.9, 91.3, 93.7, 95.1, 107.3, 121.4, 128.8, 130.7, 133.2, 162.9, 167.6, 168.5, 177.8.

1-(2,4-Dimethoxy-6-hydroxyphenyl)-3-(3,4-dimethoxyphenyl)prop-2-ynone (7)

To a solution of 3,4-dimethoxyphenylacetylene (200 mg, 1.24 mmol) in THF (10 mL) at 0 °C was added *n*-BuLi (2.5 M solution in hexanes, 0.5 mL, 1.24 mmol). After 1 h at 0 °C, the solution was cooled further to –78 °C and **2** (150 mg, 0.62 mmol) in THF (5 mL) was added dropwise. The mixture was gradually warmed to r.t. and stirred overnight upon which it was quenched with aq 4.3 N AcOH. The resulting solution was diluted with EtOAc and the EtOAc layer was washed with H_2O (20 mL) and brine (10 mL) successively. The organic layer was dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was purified twice by flash column chromatography on silica gel (hexanes–EtOAc, 6:1 and CH_2Cl_2–EtOAc, 19:1) to afford the acetylenic ketone **7** (66 mg, 31%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.27 (m, 1 H), 7.14 (s, 1 H), 6.89 (d, *J* = 8.4 Hz, 1 H), 6.09 (d, *J* = 2.4 Hz, 1 H), 5.96 (d, *J* = 2.0 Hz, 1 H), 3.95 (s, 3 H), 3.94 (s, 3 H), 3.92 (s, 3 H), 3.86 (s, 3 H).

Reaction of Aryllithium Reagents with 2 or 3; General Procedure

To aryl bromide (1.0 equiv) in THF (5 mL/mmol) at –78 °C was added *n*-BuLi (0.95 equiv) dropwise. After 30 min at –78 °C, the temperature was increased to 0 °C for 1 h and the mixture was cooled to –78 °C. Compound **2** or **3** (0.3 equiv, see Table 1) in 5 mL/mmol of THF was added slowly at –78 °C. The mixture was warmed slowly to r.t. and stirred overnight. The solution was neutralized by 0.5 M aq HCl, diluted with H_2O (20 mL) and EtOAc (2 × 20 mL). The combined organic layers were washed with brine (10 mL) and dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by flash chromatography (hexanes–EtOAc, 2:1) afforded the purified product.

(2,4-Dibenzenesulfonyloxy-6-hydroxyphenyl)(3,4-dimethoxyphenyl)methanone (8)

R_f = 0.14 (EtOAc–hexanes, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.88 (s, 3 H), 3.91 (s, 3 H), 6.50 (d, *J* = 2.4 Hz, 1 H), 6.67 (d, *J* = 2.4 Hz, 1 H), 6.74 (d, *J* = 8.4 Hz, 1 H), 7.11–7.17 (m, 2 H), 7.40–7.42 (m, 4 H), 7.56–7.64 (m, 3 H), 7.69–7.73 (m, 1 H), 7.88–7.91 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.27, 56.32, 109.4, 109.9, 110.7, 111.7, 115.8, 125.7, 128.4, 128.6, 129.3, 129.7, 130.7, 134.6, 134.8, 135.0, 135.2, 147.8, 148.9, 152.7, 154.1, 161.4, 194.5.

MS: *m*/*z* = 570, 429, 287, 259, 164, 137.

HRMS: *m*/*z* calcd for $C_{27}H_{22}O_{10}S_2$: 570.0654; found: 570.0663.

(2,4-Dimethoxy-6-hydroxyphenyl)(3-methoxy-4-benzyloxyphenyl)methanone (9)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.75 (s, 1 H), 7.46–7.30 (m, 5 H), 7.23 (d, *J* = 1.6 Hz, 1 H), 7.15 (dd, *J* = 8.4, 1.6 Hz, 1 H), 6.87 (d, *J* = 8.4 Hz, 1 H), 6.18 (d, *J* = 2.4 Hz, 1 H), 5.96 (d, *J* = 2.4 Hz, 1 H), 5.23 (s, 2 H), 3.91 (s, 3 H), 3.85 (s, 3 H), 3.50 (s, 3 H).

2,4-Dimethoxy-6-hydroxybenzophenone (10)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.46 (s, 3 H), 3.86 (s, 3 H), 5.93 (d, *J* = 2.4 Hz, 1 H), 6.17 (d, *J* = 2.4 Hz, 1 H), 7.34–7.43 (m, 2 H), 7.44–7.49 (m, 1 H), 7.50–7.57 (m, 2 H), 12.27 (s, 1 H).

Chrysin (11)

To compound **4** (0.30 g, 0.54 mmol) in toluene (20 mL) was added PTSA monohydrate (0.30 g, 1.6 mmol). The solution was heated overnight to 114 °C. After the mixture was cooled to r.t., toluene was removed by evaporation under vacuum. The residue was treated with H_2O and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (10 mL) and dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by flash chromatography (hexanes–EtOAc, 4:1) afforded the intermediate cyclized compound with one benzenesulfonyloxy-protected group (0.20 g, 90%); R_f = 0.42 (EtOAc–hexanes, 1:2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.34 (d, *J* = 2.1 Hz, 1 H), 6.74 (d, *J* = 1.5 Hz, 1 H), 6.90 (d, *J* = 2.1 Hz, 1 H), 7.53–7.61 (m, 5 H), 7.69–7.73 (m, 1 H), 7.86–7.93 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 101.9, 105.9, 106.4, 109.8, 126.7, 128.6, 129.5, 129.7, 130.8, 132.6, 135.0, 135.3, 154.4, 156.8, 162.2, 165.2, 183.0.

MS: *m*/*z* = 394, 393, 331,329, 301, 288, 151, 141, 123, 122, 121, 101, 77, 76, 75.

HRMS: *m*/*z* calcd for $C_{21}H_{14}O_6S$: 394.0511; found: 394.0516.

To the above cyclized compound (60 mg, 0.15 mmol) and anhyd K_2CO_3 (0.50 g) was added MeOH (20 mL). The mixture was heated to 65 °C for 2 h. After the mixture had cooled to r.t., concd HCl was added to neutralize the solution. The KCl salts were removed by filtration. The filtrate was evaporated under vacuum. The residue was dissolved in EtOAc (20 mL), washed with aq sat. $NaHCO_3$ (20 mL), brine (10 mL), and dried ($MgSO_4$). Evaporation of the solvent and purification by flash chromatography (hexanes–EtOAc, 4:1) afforded chrysin (**11**) (38 mg, ~100%); R_f = 0.25 (EtOAc–hexanes, 1:2).

^{1}H NMR (300 MHz, acetone-d_6): δ = 6.28 (d, *J* = 2.1 Hz, 1 H), 6.58 (d, *J* = 2.1 Hz, 1 H), 6.80 (s, 1 H), 7.61 (m, 3 H), 8.07 (m, 2 H), 12.9 (s, 1 H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 94.2, 99.2, 104.9, 105.5, 126.6, 129.3, 131.6, 132.1, 158.2, 162.7, 164.0, 164.4, 182.5.

Apigenin (12)

To compound **5** (0.25 g) in toluene (10 mL) was added PTSA monohydrate (0.15 g). The solution was heated overnight to 114 °C. After the mixture had cooled to r.t., the toluene was removed by evaporation. The residue was treated with H_2O and extracted with EtOAc (2 × 20 mL). The organic layers were washed with brine (10 mL) and dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by flash chromatography (hexanes–EtOAc, 2:1) afforded the intermediate cyclized compound (0.16 g).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.35 (d, *J* = 2.1 Hz, 1 H), 6.67 (s, 1 H), 6.88 (d, *J* = 2.1 Hz, 1 H), 7.18 (m, 2 H), 7.51–7.61 (m, 5 H), 7.68–7.74 (m, 2 H), 7.81–7.92 (m, 5 H), 12.63 (s, 1 H).

To the above cyclized compound (50 mg, 0.090 mmol) and anhyd K_2CO_3 (0.50 g) was added MeOH (20 mL). The mixture was heated to 65 °C for 5 h. After the mixture had cooled to r.t., concd HCl was added to neutralize the solution. The KCl salts were removed by filtration. The filtrate was evaporated under vacuum. The residue was recrystallized from MeOH (5 mL) and H_2O (2 mL) to afford apigenin (**12**; 16 mg, 66%); R_f = 0.20 (EtOAc–hexanes, 1:1).

^{1}H NMR (300 MHz, acetone-d_6): δ = 6.25 (d, *J* = 2.1 Hz, 1 H), 6.54 (d, *J* = 2.1 Hz, 1 H), 6.64 (s, 1 H), 7.02 (m, 2 H), 7.96 (m, 2 H), 13.03 (s, 1 H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 94.1, 99.0, 103.4, 104.7, 116.2, 122.6, 128.6, 158.1, 161.2, 162.7, 164.2, 164.4, 182.4.

4,6-Dimethoxyaurone (13)

To compound **6** (10 mg) and K_2CO_3 (10 mg) in a sealed tube was added acetone (2 mL) and the mixture heated to 56 °C for 6 h. After the solution had cooled to r.t., it was neutralized with 0.5 M aq AcOH, diluted with H_2O (20 mL) and extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (10 mL) and dried ($MgSO_4$). Evaporation of solvent and purification by flash chromatography twice (hexanes–EtOAc, 2:1) afforded aurone **13** (9.5 mg, 95%) as a yellow solid; mp 148–151 °C (Lit.[10b] mp 152–153 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.93 (s, 1 H), 3.97 (s, 1 H), 6.15 (d, *J* = 1.8 Hz, 1 H), 6.41 (d, *J* = 1.8 Hz, 1 H), 6.79 (s, 1 H), 7.44 (m, 3 H), 7.88 (m, 2 H).

3′,4,4′,6-Tetramethoxyaurone (14)

To a solution of **13** (25 mg, 0.073 mmol) in acetone (5 mL), taken in a sealable tube, was added K_2CO_3 (31 mg, 0.22 mmol) at r.t. The tube was sealed and the mixture heated for 6 h at 56 °C. The mixture was cooled to r.t., passed through a pad of Celite, and then evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes–EtOAc, 1:4) to afford aurone **14** (20 mg, 80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.44 (m, 2 H), 6.93 (d, *J* = 8.4 Hz, 1 Hz), 6.75 (s, 1 H), 6.36 (d, *J* = 1.6 Hz, 1 H), 6.14 (d, *J* = 1.6 Hz, 1 H), 3.97 (s, 3 H), 3.96 (s, 3 H), 3.94 (s, 3 H), 3.92 (s, 3 H).

LRMS (EI): *m*/*z* = 342 (M^+, 100%), 311, 180.

HRMS (EI): *m*/*z* calcd for $C_{19}H_{18}O_6$: 342.1103; found: 342.1108.

(2,4-Dimethoxy-6-hydroxyphenyl)-3′-methoxy-4′-hydroxyphenylmethanone (15)

To a solution of benzophenone **9** (50 mg, 0.13 mmol) in a mixture of MeOH–EtOAc (10:7, 17 mL) was added 10% Pd/C (30 mg). After 18 h at r.t. under H_2 atmosphere (H_2 balloon), the mixture was passed through a pad of Celite and then evaporated in vacuo. The residue was purified by preparative TLC on silica gel (hexanes–EtOAc, 2:1) to afford the natural product **15**[13] (28 mg, 73%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.64 (s, 1 H), 7.25 (d, *J* = 2.0 Hz, 1 H), 7.16 (dd, *J* = 8.4, 2.0 Hz, 1 H), 6.89 (d, *J* = 8.4 Hz, 1 H), 6.18

(d, J = 2.4 Hz, 1 H), 6.04 (s, 1 H), 5.97 (d, J = 2.0 Hz, 1 H), 3.93 (s, 3 H), 3.86 (s, 3 H), 3.54 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.4, 166.0, 165.1, 161.6, 149.2, 146.1, 133.5, 124.3, 113.4, 111.0, 106.0, 93.9, 91.6, 56.3, 55.8, 55.4.

LRMS (EI): m/z = 304 (M^+), 303 (100%), 287, 181.

HRMS (EI): m/z calcd for $C_{16}H_{16}O_6$: 304.0947; found: 304.0952.

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