A One-Pot Synthesis of Aurones from Substituted Acetophenones and Benzaldehydes: A Concise Synthesis of Aureusidin

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Abstract: A one-pot synthesis of aurones from substituted acetophenone and benzaldehyde has been developed on the basis of an improved Algar–Flynn–Oyamada reaction. By using this method, several aurones were prepared in three steps from commercial starting materials. The usefulness of this one-pot strategy was confirmed by a synthesis of aureusidin, an inhibitor of iodothyronine deiodinase, in 41% overall yield. In comparison with a two-step synthesis of this product from the same substrates, the one-pot strategy was more effective, giving a higher yield and requiring fewer and simpler operations.

Key words: heterocycles, natural products, total synthesis, cyclizations, furans, bicyclic compounds

Flavonoids have been considered as pharmacological agents since these natural products were shown to constitute the active ingredients of many folk medicines.[1] Aurones [2-benzylidenebenzofuran-3(2*H*)-ones], a sub-class of flavonoids that are isomeric with flavones, display analgesic and other activities.[2] For example, aureusidin (Figure 1) inhibits iodothyronine deiodinase,[3] hamiltron shows DNA strand-scission activity,[4] and sulfuretin shows antiradical activity.[5]

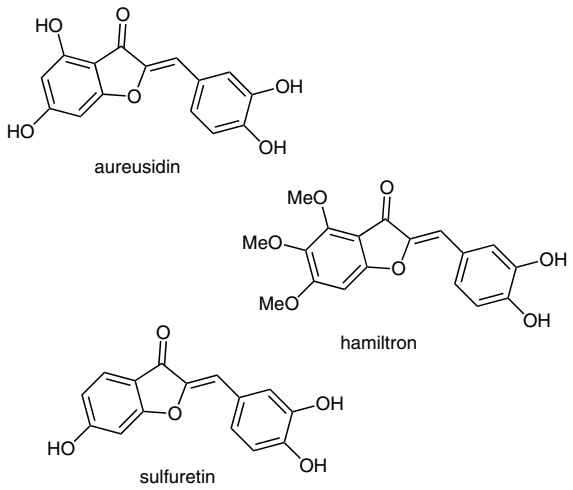

Figure 1 Selected members of the aurone family

The interesting biological activities and structural feature of the aurones have stimulated many studies on their synthesis.[2] The most popular method for the preparation of aurones[6] is based on the condensation of benzaldehydes with benzofuran-3(2*H*)-one derivatives obtained from the corresponding acetophenones or phenols. Other important methods for the synthesis of aurones include the oxidative cyclization of 2′-hydroxychalcones[7–10] and the ring closure of *o*-hydroxyaryl phenylethynyl ketones.[11] In addition, some other unusual methods have been reported, such as the Wheeler aurone synthesis from chalcone dihalides[12] and a gold(I) iodide-catalyzed cyclization.[13] Furthermore, aurones have been obtained as byproducts in the Algar–Flynn–Oyamada synthesis of flavonols.[14]

Our continued interest in the chemistry of naturally occurring flavonoid,[15] and the shortage of investigations on aurones[2] prompted us to develop a convenient and general method for the synthesis of these compounds. We report here a simple one-pot synthesis of aurones from substituted acetophenones and benzaldehydes. Although Britsch and Grisebach have reported a synthesis of aurones by the Algar–Flynn–Oyamada reaction,[16] to the best of our knowledge there is no precedent for a one-pot synthesis of aurones from substituted acetophenones and benzaldehydes.[2,17]

In our initial studies of the one-pot synthesis of aurones, we examined the reaction of 1-(2-hydroxy-4,6-dimethoxyphenyl)ethanone (**1a)** with 4-methoxybenzaldehyde (**2a**). In most cases, chalcones are prepared from the appropriate 1-(2-hydroxyphenyl)ethanones and benzaldehydes by condensation in the presence of sodium or potassium hydroxide in an alcoholic solvent. By following this procedure, we prepared the corresponding chalcone in a good yield. However, when the 30% or 50% of hydrogen peroxide was added to the mixture, most of the chalcone decomposed to the corresponding benzoic acid derivative, and only a trace of the desired product was detected (Table 1, entry 1). There have been several reports that chalcones can be decomposed by alkaline hydrogen peroxide.[8,18] To inhibit this decomposition, we added water (2.4 mL) to the reaction mixture and we obtained the desired aurone **3a** in 19% yield (entry 2). To improve this yield, we examined the effects of adding various amounts of alkali. The yield of aurone **3a** increased when the number of equivalents of sodium hydroxide was increased from 4 to 16, (entries 3 and 4). However, when the number of equivalents of sodium hydroxide was increased to 32,

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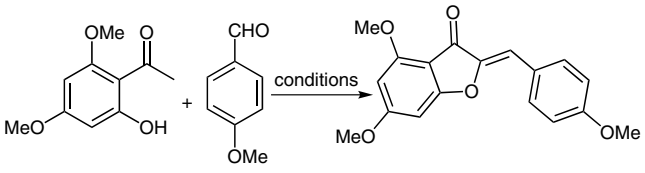
the yield of the aurone **3a** fell (entry 5). Because it is known that water plays an important role in the retro-Claisen–Schmidt condensation, we then attempted to optimize the amount of water in the system. Surprisingly, when the amount of water was increased from 1.2 to 9.6 mL, the yield of aurone **3a** increased slowly (entries 4 and 6–8). However, the yield decreased slowly on further increasing the amount of water (entries 9 and 10). Next, we examined the role of the amount of hydrogen peroxide, which has been shown to affect the outcome of the reactions. We found that excessive amounts of hydrogen peroxide reduced the yield of aurone **3a** (entries 12 and 13) and that two equivalents of hydrogen peroxide was the most appropriate amount for converting **1a** and **2a** into aurone **3a**.

Table 1 Optimization of the One-Pot Synthesis of Aurones



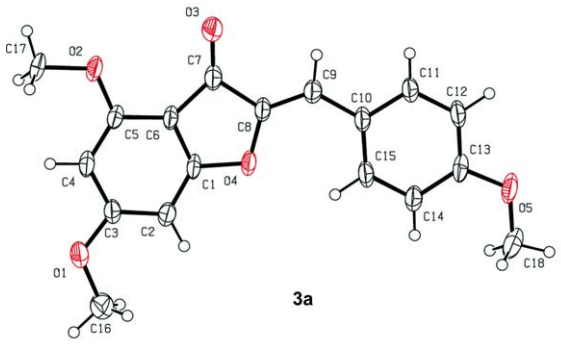
1a **2a** **3a**

Entry[a]	NaOH (equiv)	H_2O (mL)	H_2O_2 (equiv)	Yield[b] (%)
1	4	0	2	trace
2	4	2.4	2	19
3	8	2.4	2	28
4	16	2.4	2	62
5	32	2.4	2	21
6	16	1.2	2	61
7	16	4.8	2	65
8	16	9.6	2	70
9	16	12	2	69
10	16	14.4	2	58
11	16	9.6	1	59
12	16	9.6	4	31
13	16	9.6	8	28

[a] Reaction conditions: **1a** (1 mmol), **2a** (1.05 mmol), NaOH, EtOH (9.6 mL), r.t., 24 h; then H_2O, H_2O_2, r.t., 24 h.
[b] Yields of filtered product washed with H_2O with no further purification.

The structure of aurone **3a** was confirmed by means of X-ray crystallographic analysis (Figure 2).[19]

Having optimized the reaction conditions, we examined the scope of the reaction for various substrates (Table 2). Electron-donating substituents, such as methoxymethoxy, methoxy, alkyl, or pyrrolidinyl, on the aryl ring of the *o*-hydroxyacetophenone had no apparent effect on the reaction and the corresponding aurones were obtained by the one-pot strategy in yields of 50–72% (entries 2–4). However, the chloro derivative **1g** was the only *o*-hydroxyacetophenone with an electron-withdrawing substituent that gave the corresponding product in a significant yield (63%) (entry 10). Attempts to perform the reaction with *o*-hydroxyacetophenones containing other electron-withdrawing group, such as nitro or and amide groups resulted in complex products as a result of instability under the reaction conditions. Similarly, benzaldehydes substituted with chloro or fluoro electron-withdrawing groups gave the desired products in similar yields (entries 8 and 9). When both the reactants contained electron-withdrawing groups (for example, **1g** and **2d**), the reaction was unsuccessful. It is noteworthy that the presence of a substituent in the 6-position of the 2-hydroxyacetophenone reactant is vital for the Algar–Flynn–Oyamada reaction. However, despite this constraint on the choice of substrate, the method is suitable for the synthesis of polysubstituted aurones such as **3e** and **3f** (entries 5 and 6, respectively). Furthermore, the Algar–Flynn–Oyamada reaction showed a good regioselectivity and only small amounts of flavonols were detected in the filtrate as byproducts (entries 4–6).



3a

Figure 2 The X-ray crystal structure of aurone **3a**

To test the effectiveness and usefulness of our one-pot strategy, we examined the synthesis of aureusidin, the best-known aurone. Reactants **1d** and **2c** were prepared from commercially available 1-(2,4,6-trihydroxyphenyl)ethanone and 3,4-dihydroxybenzaldehyde in 78% and 84% yields, respectively. Aurone **3h** was then obtained from **1d** and **2c** in 66% yield by our one-pot method. Detsi[9] and Hu[10] have reported syntheses of **3h** from same substrates in two-step operations in yields of 53% and 58%, respectively. Those results confirm that our one-pot strategy is more effective than the two-step method in terms of the yield. Furthermore, our method has a significant advantage in requiring simpler operations. The aurone product can be collected as a solid merely by filtration of the reaction medium and it can then be washed with water and dried without the need for any additional purification. The methoxymethyl protecting groups of aurone **3h** were readily removed by treatment with 10% hydrochloric acid in methanol to give aureusidin (Scheme 1). The ^{1}H NMR, ^{13}C NMR, and high-resolution mass spectra of the product were identical with those previously reported for the natural product.[3]

Table 2 Scope of the One-Pot Synthesis of Aurones from Substituted Acetophenones and Benzaldehydes

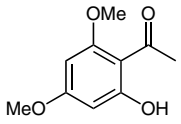
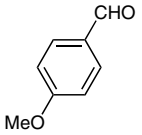
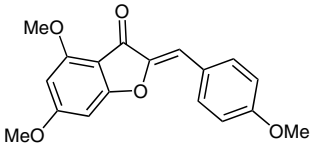
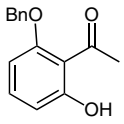
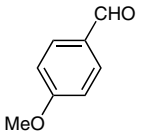
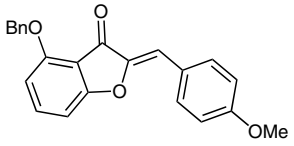
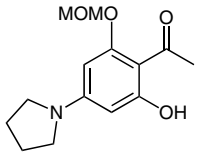
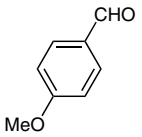
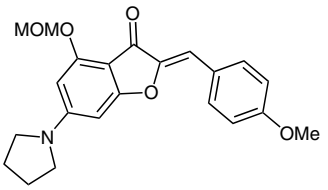
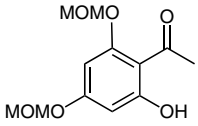
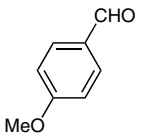
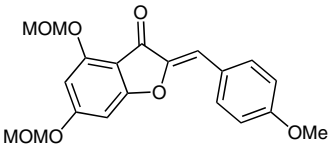
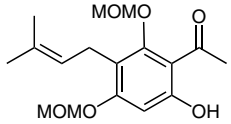
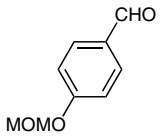
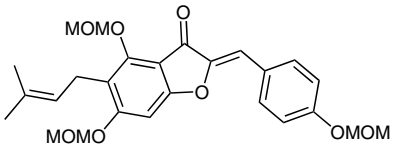
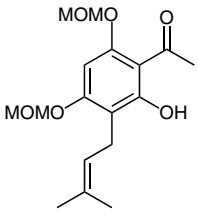
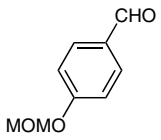
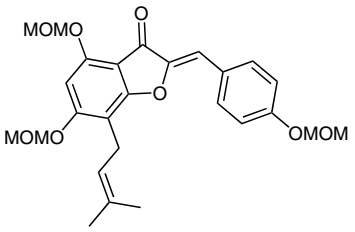
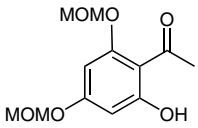
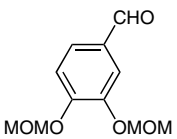
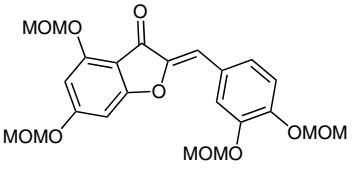
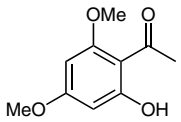
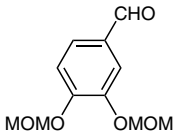
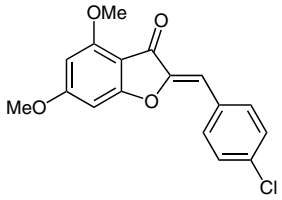
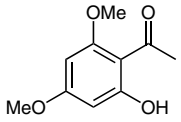
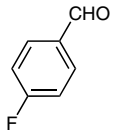
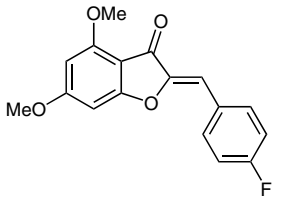
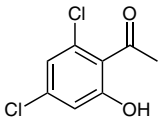
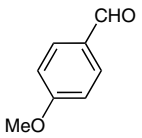
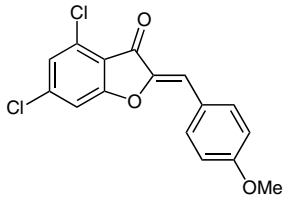
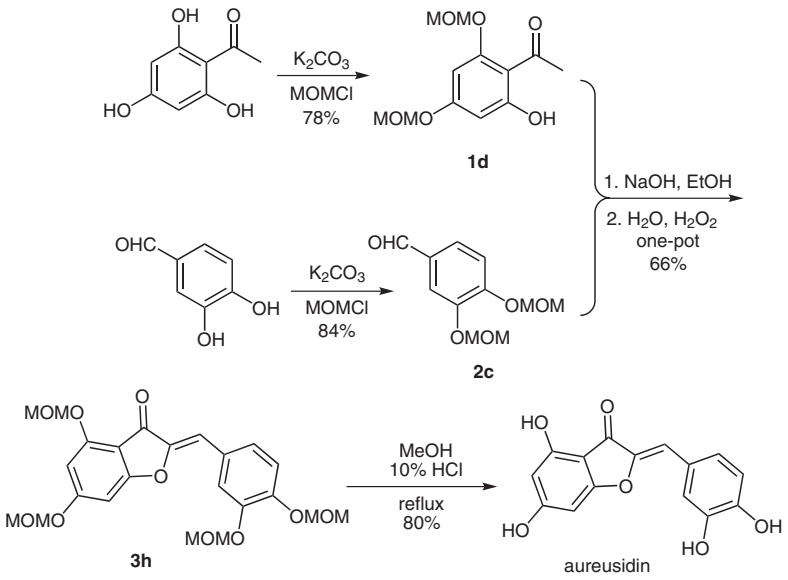
Entry[a]	Acetophenone	Benzaldehyde	Product	Yield (%)[b]
1	 **1a**	 **2a**	 **3a**	70
2	 **1b**	 **2a**	 **3b**	51
3	 **1c**	 **2a**	 **3c**	50
4	 **1d**	 **2a**	 **3d**	72
5	 **1e**	 **2b**	 **3e**	68
6	 **1f**	 **2b**	 **3f**	70
7	 **1d**	 **2c**	 **3h**	66

Table 2 Scope of the One-Pot Synthesis of Aurones from Substituted Acetophenones and Benzaldehydes (continued)

Entry[a]	Acetophenone	Benzaldehyde	Product	Yield (%)[b]
8	 **1a**	 **2d**	 **3i**	62
9	 **1a**	 **2e**	 **3j**	63
10	 **1g**	 **2a**	 **3g**	63[c]

[a] Reaction conditions: **1a** (1 mmol), **2a** (1.05 mmol), NaOH (16 equiv), EtOH (9.6 mL), r.t., 24 h, then H_2O (9.6 mL), H_2O_2 (2 equiv), r.t., 24 h.
[b] Isolated yield.
[c] Yield after column chromatography.

In conclusion, we have developed a simple and effective one-pot strategy for the synthesis of aurones from substituted acetophenones and benzaldehydes. By using this method, several aurones were prepared in three steps from commercial starting materials. The effectiveness and usefulness of the one-pot strategy were demonstrated by means of a synthesis of aureusidin, an inhibitor of iodothyroninedeiodinase, in 41% overall yield.



Scheme 1 Application of the one-pot procedure to the synthesis of aureusidin

Solvents were purified and dried by standard methods before use. Column chromatography was performed on silica gel (200–300 mesh). EtOH, H_2O_2, and other commercially available reagents were used without additional purification. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-400 MHz spectrometer, and chemical shifts are reported in ppm relative to TMS as internal standard. Mass spectra were recorded by direct inlet at 70 eV. High-resolution mass spectra were recorded on a Bruker Daltonics APEX II 47e FT-ICR spectrometer operating in the ESI mode.

1-(2-Hydroxy-4,6-dimethoxyphenyl)ethanone (1a)
A stirred soln of 1-(2,4,6-trihydroxyphenyl)ethanone (2.5 g, 15 mmol), Me_2SO_4 (2.7 mL, 28 mmol), and anhyd K_2CO_3 (4.1 g, 28 mmol) in acetone (40 mL) was refluxed for 5 h. The mixture was then filtered and concentrated in vacuo. Crystallization of the solid residue from PE–hexane (1:9) gave a white solid; yield: 2.6 g (90%).

^1H NMR (400 MHz, $CDCl_3$): δ = 14.05 (s, 1 H), 6.06 (d, *J* = 2.4 Hz, 1 H), 5.92 (d, *J* = 2.4 Hz, 1 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 2.61 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.1, 167.5, 166.0, 162.9, 105.9, 93.4, 90.7, 55.5, 32.9.

The spectra of the product matched those of the known compound.[20]

1-[2-(Benzyloxy)-6-hydroxyphenyl]ethanone (1b)
BnCl (1.15 mL, 10 mmol) was added to a mixture of 1-(2,6-dihydroxyphenyl)ethanone (1.52 g, 10 mmol) and anhyd K_2CO_3 (2.76 g, 20 mmol) in DMF (15 mL). The mixture was stirred for 24 h then poured into 1 M HCl (100 mL). The mixture was extracted with EtOAc (3 × 50 mL) and the organic layer was washed successively with H_2O (2 × 20 mL) and brine (3 × 20 mL), dried (Na_2SO_4), and concentrated. The resulting mixture was purified by flash column chromatography [PE–EtOAc (6:1)] to give a colorless oil; yield: 1.997 g (78.0%).

^1H NMR (400 MHz, $CDCl_3$): δ = 13.26 (s, 1 H), 7.41 (m, 5 H), 7.30 (t, *J* = 8.4 Hz, 1 H), 6.57 (d, *J* = 8.4 Hz, 1 H), 6.44 (d, *J* = 8.4 Hz, 1 H), 5.10 (s, 2 H), 2.59 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.0, 164.7, 160.6, 136.0, 135.7, 128.7, 128.4, 127.9, 110.9, 102.2, 71.1, 33.9.

The spectra of the product matched those of the known compound.[21]

1-[2-Hydroxy-6-(methoxymethoxy)-4-pyrrolidin-1-ylphenyl]ethanone (1c)
MOMCl (0.83 mL, 11 mmol) was added dropwise to a mixture of 1-(2,6-dihydroxy-4-pyrrolidin-1-ylphenyl)ethanone (2.21 g, 10 mmol) and anhyd K_2CO_3 (2.025 g, 15 mmol) in anhyd acetone (30 mL). The mixture was refluxed for 2 h, cooled to r.t. and filtered. The filtrate was washed with acetone and concentrated to give a yellowish oil that was purified by flash column chromatography [PE–EtOAc (8:1)] to give a yellowish solid; yield: 1.64 g, (62.0%); mp 81 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 14.15 (s, 1 H), 5.78 (s, 1 H), 5.70 (s, 1 H), 5.25 (s, 2 H), 3.51 (s, 3 H), 3.34 (m, 4 H), 2.60 (s, 3 H), 2.00 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.8, 166.6, 160.5, 152.9, 102.8, 94.3, 92.4, 89.3, 56.5, 47.5, 32.3, 25.3.

HRMS-FAB: *m/z* $[M + H]^+$ calcd for $C_{14}H_{20}NO_4$: 266.1387; found: 266.1386.

Compounds 1d, 1f, and 2c; General Procedure
MOMCl (1.64 mL, 22 mmol) was added dropwise to a mixture of the appropriate *o*-hydroxyacetophenone (10 mmol) and anhyd K_2CO_3 (3.375 g, 25 mmol) in anhyd acetone (50 mL). The mixture was refluxed for 2 h, cooled to r.t., and filtered. The filtrate was washed with acetone and concentrated to give an oil that was purified by flash column chromatography (PE–EtOAc) to give the corresponding protected acetophenone.

1-[2-Hydroxy-4,6-bis(methoxymethoxy)phenyl]ethanone (1d)
Prepared by the general procedure from 1-(2,4,6-trihydroxyphenyl)ethanone as a colorless oil; yield: 1.997 g (78.0%).

^1H NMR (400 MHz, $CDCl_3$): δ = 13.66 (s, 1 H), 6.18 (d, *J* = 4.4 Hz, 2 H), 5.19 (s, 2 H), 5.10 (s, 2 H), 3.46 (s, 3 H), 3.41 (s, 3 H), 2.59 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.9, 166.6, 163.2, 160.2, 106.6, 96.8, 94.3, 93.7, 56.4, 56.1, 32.7.

The spectra of this product matched those of the known compound.[22]

1-[2-Hydroxy-4,6-bis(methoxymethoxy)-3-(3-methylbut-2-en-1-yl)phenyl]ethanone (1f)
Prepared by the general procedure and purified by flash column chromatography [PE–EtOAc, (8:1)] as a colorless oil; yield: 2.50 g (77.0%).

^1H NMR (400 MHz, $CDCl_3$): δ = 13.82 (s, 1 H), 6.40 (s, 1 H), 5.26 (s, 2 H), 5.24 (s, 2 H), 5.20 (m, 1 H), 3.51 (s, 3 H), 3.48 (s, 3 H), 3.31 (d, *J* = 7.2 Hz, 2 H), 2.66 (s, 3 H), 1.78 (s, 3 H), 1.67 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.5, 163.4, 160.7, 158.7, 131.3, 122.5, 111.6, 106.9, 94.5, 93.9, 91.2, 56.6, 56.3, 33.1, 25.8, 21.5, 17.7.

The spectra of this product matched those of the known compound.[23]

3,4-Bis(methoxymethoxy)benzaldehyde (2c)
Prepared by the general procedure and purified by flash column chromatography [PE–EtOAc (16:1)] as a colorless oil; yield: 1.89 g (83.6%).

^1H NMR (400 MHz, $CDCl_3$): δ = 9.86 (s, 1 H), 7.68 (s, 1 H), 7.51 (d, *J* = 8.4 Hz, 1 H), 7.29 (d, *J* = 8.4 Hz, 1 H), 5.33 (s, 2 H), 5.30 (s, 2 H), 3.53 (d, *J* = 1.2 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.5, 152.4, 147.2, 130.9, 126.1, 115.7, 115.2, 95.1, 94.7, 56.2, 56.1.

1-{2,4-Bis(methoxymethoxy)-6-[(3-methylbut-2-en-1-yl)oxy]phenyl}ethanone
60% NaH (0.56 g, 14 mmol) was added to a stirred soln of hydroxy ketone **1d** (3.582 g, 14 mmol) in anhyd DMF (40 mL) under argon, and the mixture was stirred for 10 min. $Me_2C{=}CHCH_2Br$ (1.696 mL, 14.5 mmol) was added dropwise and the mixture was stirred overnight at r.t. The reaction was quenched with H_2O and the mixture was extracted with Et_2O (3 × 30 mL). The organic phases were combined, washed with H_2O (3 × 30 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated under vacuum. The residue was purified by flash column chromatography [PE–EtOAc (8:1)] to give a colorless oil; yield: 4.5 g (99%).

^1H NMR (400 MHz, $CDCl_3$): δ = 6.44 (d, *J* = 1.9 Hz, 1 H), 6.32 (d, *J* = 1.9 Hz, 1 H), 5.45 –5.36 (m, 1 H), 5.15 (s, 2 H), 5.13 (s, 2 H), 4.50 (d, *J* = 6.6 Hz, 2 H), 3.48 (s, 3 H), 3.46 (s, 3 H), 2.47 (s, 3 H), 1.76 (s, 3 H), 1.71 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.62, 159.44, 157.14, 155.14, 137.81, 119.27, 116.25, 95.94, 94.99, 94.71, 94.37, 65.55, 56.21, 56.05, 32.43, 25.63, 18.14.

The spectra of this product matched those of the known compound.[24]

1-[6-Hydroxy-2,4-bis(methoxymethoxy)-3-(3-methylbut-2-en-1-yl)phenyl]ethanone (1e)
1-{2,4-Bis(methoxymethoxy)-6-[(3-methylbut-2-en-1-yl)oxy]phenyl}ethanone (0.324 g, 1 mmol) was dissolved in $PhNEt_2$ (10 mL) and the mixture was heated at 200 °C for 35 min. EtOAc (50 mL) was added and the mixture washed with 1 M aq HCl (2 × 50 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography [silica gel, PE–EtOAc

(20:1 gradient to 5:1)]. Evaporation of the organic fractions gave a yellowish oil; yield: 0.226 g (70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.95 (s, 1 H), 6.47 (s, 1 H), 5.22 (s, 2 H), 5.14–5.16 (m, 1 H), 4.96 (s, 2 H), 3.52 (s, 3 H), 3.46 (s, 3 H), 3.31 (d, *J* = 6.4 Hz, 2 H), 2.70 (s, 3 H), 1.76 (s, 3 H), 1.69 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.9, 163.5, 161.6, 157.1, 131.6, 123.0, 116.2, 111.0, 101.4, 98.8, 93.9, 58.4, 56.3, 31.4, 25.7, 23.1, 17.9.

The spectra of this product matched those of the known compound.[22]

1-(2,4-Dichloro-6-hydroxyphenyl)ethanone (1g)

3,5-Dichlorophenol (5g, 30.7 mmol) was dissolved in anhyd CH_2Cl_2 (150 mL) under argon at 0 °C. DIPEA (15.2 mL, 92.1 mmol) was added and the mixture was stirred for 10 min. MOMCl (4.66 mL, 61.4 mmol) was slowly added and the resulting mixture was stirred for 10 h. Anhyd CH_2Cl_2 (200 mL) was then added and the resulting mixture was washed successively with 1 M aq HCl (130 mL), H_2O (100 mL), and brine (100 mL), dried (Na_2SO_4), and concentrated to give crude 1,3-dichloro-5-(methoxymethoxy)benzene as a yellowish oil.

This oil was dissolved in THF (50 mL) and a 1.3 M soln of *sec*-BuLi in hexane (23.1 mL, 30 mmol) was added at –78 °C. The mixture was stirred for 30 min then added to a soln of distilled Ac_2O (3.12 mL, 33 mmol) in THF (20 mL) at –78 °C. The resulting mixture was stirred for another 2 h at –78 °C, diluted with sat. aq NH_4Cl (50 mL), and extracted with EtOAc (3 × 100 mL). The organic layer was separated and washed successively with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure to give a yellowish oil. This oil was dissolved in MeOH (40 mL) and 10% HCl (5 mL) was added. The mixture was refluxed for 1 h, the MeOH was evaporated, and the concentrated mixture was extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with H_2O (2 × 50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography (petroleum ether) to give a white solid; yield: 5.38 g (86.0%); R_f = 0.6 (EtOAc–PE, 16:1); mp 40 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.75 (s, 1 H), 6.95 (d, *J* = 2.0 Hz, 1 H), 6.91 (d, *J* = 2.0 Hz, 1 H), 2.82 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.3, 164.3, 140.5, 135.9, 122.3, 118.1, 117.7, 33.5.

HRMS-FAB: *m/z* $[M - H]^+$ calcd for $C_8H_5Cl_2O_2$: 202.9627; found: 202.9674.

One-Pot Synthesis of Aurones; General Procedure

The appropriate *o*-hydroxyacetophenone (1 mmol) was added to a soln of NaOH (0.64 g) in EtOH (9.6 mL) at r.t. and the mixture was stirred for 5 min. The benzaldehyde component (1.05 mmol) was added and the mixture was stirred for 24 h. H_2O (9.6 mL) was added and then 30% H_2O_2 (0.272 mL) was added dropwise over 5 min. The mixture was stirred for another 24 h then filtered. The resulting yellowish solid was washed with H_2O (5 × 2 mL) and dried to give the desired aurone without any further purification.

(2*Z*)-4,6-Dimethoxy-2-(4-methoxybenzylidene)-1-benzofuran-3(2*H*)-one (3a)

Prepared by the general procedure from **1a** and 4-methoxybenzaldehyde (**2a**) as a yellowish solid; yield: 219 mg (70%); mp 172–174 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.8 Hz, 2 H), 6.96 (d, *J* = 8.8 Hz, 2 H), 6.74 (s, 1 H), 6.37 (d, *J* = 1.6 Hz, 1 H), 6.11 (d, *J* = 1.6 Hz, 1 H), 3.94 (s, 3 H), 3.90 (s, 3 H), 3.85 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.6, 168.8, 168.7, 160.5, 159.3, 146.8, 132.8, 125.3, 114.3, 110.9, 105.4, 93.9, 89.1, 56.2, 56.0, 55.3.

The spectra of this product matched those of the known compound.[20]

(2*Z*)-4-(Benzyloxy)-2-(4-methoxybenzylidene)-1-benzofuran-3(2*H*)-one (3b)

Prepared by the general procedure from **1b** and 4-methoxybenzaldehyde (**2a**) as a yellowish solid; yield: 183 mg (51%); mp 177–179 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 8.0 Hz, 2 H), 7.50–7.30 (m, 6 H), 6.96 (d, *J* = 8.0 Hz, 2 H), 6.84 (d, *J* = 8.0 Hz, 2 H), 6.59 (d, *J* = 8.0 Hz, 1 H), 5.32 (s, 2 H), 3.84 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 182.0, 166.8, 160.7, 157.4, 145.7, 137.8, 136.2, 133.1, 128.6, 127.9, 126.7, 125.2, 114.4, 112.0, 111.6, 106.9, 104.9, 70.6, 55.3.

HRMS-FAB: *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}O_4$: 359.1278; found: 359.1271.

(2*Z*)-2-(4-Methoxybenzylidene)-4-(methoxymethoxy)-6-pyrrolidin-1-yl-1-benzofuran-3(2*H*)-one (3c)

Prepared by the general procedure from **1c** and 4-methoxybenzaldehyde (**2a**) as a yellowish solid; yield: 191 mg (50%); mp 182–183 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.4 Hz, 2 H), 6.94 (d, *J* = 8.4 Hz, 2 H), 6.63 (s, 1 H), 6.01 (d, *J* = 4.4 Hz, 2 H), 5.39 (s, 2 H), 3.85 (s, 3 H), 3.54 (s, 3 H), 3.41 (s, 4 H), 2.05 (s, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.2, 168.5, 160.0, 157.0, 155.2, 147.8, 132.4, 126.0, 114.2, 108.6, 101.8, 95.2, 93.8, 87.9, 56.6, 55.3, 48.2, 25.3.

HRMS-FAB: *m/z* $[M + H]^+$ calcd for $C_{22}H_{24}NO_5$: 382.1649; found: 382.1654.

(2*Z*)-2-(4-Methoxybenzylidene)-4,6-bis(methoxymethoxy)-1-benzofuran-3(2*H*)-one (3d)

Prepared by the general procedure from **1d** and 4-methoxybenzaldehyde (**2a**) as a yellowish solid; yield: 268 mg (72%); mp 90–93 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.8 Hz, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 6.75 (s, 1 H), 6.63 (d, *J* = 1.6 Hz, 1 H), 6.51 (d, *J* = 1.6 Hz, 1 H), 5.37 (s, 2 H), 5.25 (s, 2 H), 3.86 (s, 3 H), 3.54 (s, 3 H), 3.52 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.7, 168.2, 165.8, 160.6, 156.7, 146.6, 132.9, 125.2, 114.3, 111.3, 106.7, 98.7, 95.0, 94.5, 92.8, 56.6, 56.5, 55.3.

HRMS-FAB: *m/z* $[M + H]^+$ calcd for $C_{20}H_{21}O_7$: 373.1282; found: 373.1289.

(2*Z*)-4,6-Bis(methoxymethoxy)-2-[4-(methoxymethoxy)benzylidene]-5-(3-methylbut-2-en-1-yl)-1-benzofuran-3(2*H*)-one (3e)

Prepared by the general procedure from **1e** and 4-(methoxymethoxy)benzaldehyde (**2b**) as a yellowish solid; yield: 320 mg (68%); mp 113–115 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.8 Hz, 2 H), 7.09 (d, *J* = 8.8 Hz, 2 H), 6.77 (s, 1 H), 6.73 (s, 1 H), 5.54 (s, 2 H), 5.31 (s, 2 H), 5.23 (s, 2 H), 5.17 (m, 1 H), 3.57 (s, 3 H), 3.50 (s, 3 H), 3.50 (s, 3 H), 3.41 (m, 2 H), 1.79 (s, 3 H), 1.67 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.7, 166.7, 163.4, 158.2, 153.6, 146.7, 132.9, 131.6, 126.3, 122.5, 118.2, 116.4, 111.3, 107.5, 100.3, 94.2, 94.1, 93.2, 57.6, 56.4, 56.2, 25.7, 22.7, 17.8.

HRMS-FAB: *m/z* $[M + H]^+$ calcd for $C_{26}H_{31}O_8$: 471.2013; found: 471.2005.

(2*Z*)-4,6-Bis(methoxymethoxy)-2-[4-(methoxymethoxy)benzylidene]-7-(3-methylbut-2-en-1-yl)-1-benzofuran-3(2*H*)-one (3f)

Prepared by the general procedure from **1f** and 4-(methoxymethoxy)benzaldehyde (**2b**) as a yellowish solid; yield: 329 mg (70%); mp 117–119 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 8.8 Hz, 2 H), 7.10 (d, *J* = 8.8 Hz, 2 H), 6.75 (s, 1 H), 6.64 (s, 1 H), 5.38 (s, 2 H), 5.32–5.29 (m, 3 H), 5.24 (s, 2 H), 3.54 (s, 3 H), 3.52 (s, 3 H), 3.51 (s, 3 H), 3.47 (d, *J* = 7.2 Hz, 2 H), 1.87 (s, 3 H), 1.71 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.3, 165.1, 162.9, 158.0, 155.0, 147.0, 132.8, 132.2, 126.5, 121.6, 116.4, 110.6, 108.3, 106.4, 96.3, 95.3, 94.5, 94.2, 56.7, 56.5, 56.2, 25.8, 21.9, 17.9.

HRMS-FAB: *m/z* $[M + H]^+$ calcd for $C_{26}H_{31}O_8$: 471.2013; found: 471.2023.

(2*Z*)-2-[3,4-Bis(methoxymethoxy)benzylidene]-4,6-bis(methoxymethoxy)-1-benzofuran-3(2*H*)-one (3h)
Prepared by the general procedure from **1d** and **2c** as a yellowish solid; yield: 305 mg (66%); mp 86–88 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (s, 1 H), 7.54 (d, *J* = 8.8 Hz, 1 H), 7.21 (d, *J* = 8.8 Hz, 1 H), 6.72 (s, 1 H), 6.60 (s, 1 H), 6.52 (s, 1 H), 5.37 (s, 2 H), 5.29 (s, 4 H), 5.26 (s, 2 H), 3.56 (s, 3 H), 3.54 (s, 3 H), 3.53 (s, 3 H), 3.52 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.6, 168.3, 166.0, 156.8, 148.6, 147.1, 147.0, 126.9, 126.4, 119.6, 116.3, 111.0, 106.6, 98.7, 95.7, 95.1, 95.0, 94.5, 92.9, 56.7, 56.5, 56.3, 56.3.

HRMS-FAB: *m/z* $[M + H]^+$ calcd for $C_{23}H_{27}O_{10}$: 463.1599; found: 463.1590.

(2*Z*)-2-(4-Chlorobenzylidene)-4,6-dimethoxy-1-benzofuran-3(2*H*)-one (3i)
Prepared by the general procedure from **1a** and **2d** as a yellowish solid; yield: 196 mg (62%); mp 169–171 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.4 Hz, 2 H), 7.54 (d, *J* = 8.4 Hz, 2 H), 6.67 (d, *J* = 7.2 Hz, 1 H), 6.36 (d, *J* = 3.6 Hz, 1 H), 6.11 (d, *J* = 3.6 Hz, 1 H), 3.93 (s, 3 H), 3.90 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.3, 169.0, 168.9, 159.3, 147.9, 135.0, 132.1, 131.0, 128.9, 109.1, 104.9, 94.0, 89.2, 56.1, 56.0.

HRMS-FAB: *m/z* $[M + H]^+$ calcd for $C_{17}H_{14}ClO_4$: 317.0575; found: 317.0568.

(2*Z*)-2-(4-Fluorobenzylidene)-4,6-dimethoxy-1-benzofuran-3(2*H*)-one (3j)
Prepared by the general procedure from **1a** and **2e** as a yellowish solid; yield: 189 mg (63%); mp 174 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (m, 2 H), 7.10 (m, 2 H), 6.70 (s, 1 H), 6.36 (s, 1 H), 6.11 (s, 1 H), 3.94 (s, 3 H), 3.90 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.5, 169.0, 168.9, 164.3, 161.8, 159.4, 147.5, 147.4, 133.0, 132.9, 128.8, 128.7, 116.0, 115.7, 109.5, 105.1, 94.0, 89.2, 56.1, 56.0.

HRMS-FAB: *m/z* $[M + H]^+$ calcd for $C_{17}H_{14}FO_4$: 301.0871; found: 301.0874.

(2*Z*)-4,6-Dichloro-2-(4-methoxybenzylidene)-1-benzofuran-3(2*H*)-one (3g)
Dichloro ketone **1g** (204 mg, 1 mmol) was added to a soln of NaOH (0.64 g) in EtOH (9.6 mL) at r.t. and the mixture was stirred for 5 min. Aldehyde **2a** (143 mg, 1.05 mmol) was then added and the mixture was stirred for 24 h. H_2O (9.6 mL) was added, followed by 30% H_2O_2 (0.272 mL) added dropwise over 5 min. The mixture was stirred for another 24 h then extracted with EtOAc (3 × 20 mL). The organic layer was washed successively with 1 M HCl (20 mL), H_2O (20 mL), and brine (20 mL) then dried (Na_2SO_4) and concentrated. The resulting mixture was purified by flash column chromatography (petroleum ether) to give a yellowish solid; yield: 202 mg (63.0%); mp 167–169 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.8 Hz, 2 H), 6.96 (d, *J* = 1.6 Hz, 1 H), 6.88 (d, *J* = 8.8 Hz, 2 H), 6.77 (d, *J* = 1.6 Hz, 1 H), 6.24 (s, 1 H), 3.80 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.9, 160.5, 155.5, 146.4, 136.7, 132.8, 132.7, 132.3, 126.5, 122.2, 121.5, 121.2, 115.4, 114.1, 113.7, 55.3.

MS (EI): *m/z* (%) = 320 (100) $[M^+]$, 322 (73), 324 (15).

Aureusidin [(2*Z*)-2-(3,4-dihydroxybenzylidene)-4,6-dihydroxy-1-benzofuran-3(2*H*)-one]
10% aq HCl (5 mL) was added dropwise to a mixture of benzofuranone **3h** (463 mg, 1 mmol) and MeOH (20 mL) and the resulting mixture was refluxed for 30 min. Evaporation of the solvent gave a yellow precipitate that was filtered off and washed successively with H_2O and CH_2Cl_2; yield: 80% (230 mg).

^{1}H NMR (400 MHz, CD_3OD): δ = 7.47 (d, *J* = 2.0 Hz, 1 H), 7.18 (dd, *J* = 8.4, 2.0 Hz, 1 H), 6.82 (d, *J* = 8.4 Hz, 1 H), 6.56 (s, 1 H), 6.20 (d, *J* = 1.6 Hz, 1 H), 6.02 (d, *J* = 1.6 Hz, 1 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 183.0, 169.7, 169.5, 160.0, 149.0, 148.0, 146.7, 126.1, 125.9, 118.8, 116.7, 113.0, 104.8, 98.7, 91.8.

HRMS-FAB: *m/z* $[M + H]^+$ calcd for $C_{15}H_{11}O_6$: 287.0550; found: 287.0544.

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

References

(1) (a) *Plant Flavonoids in Biology and Medicine: Biochemical, Pharmacological and Structure–Activity Relationships: Proceedings of a Symposium Held in Buffalo / New York, July 22–26, 1985*; Cody, V.; Middleton, E. Jr.; Harborne, J. B., Eds.; Allan R. Liss: New York, **1986**. (b) Iwashina, T. *J. Plant Res.* **2000**, *113*, 287. (c) *Flavonoids: Chemistry, Biochemistry and Applications*; Andersen, O. M.; Markham, K. R., Eds.; CRC Press: Boca Raton, **2006**.
(2) Boumendjel, A. *Curr. Med. Chem.* **2003**, *10*, 2621.
(3) Auf'mkolk, M.; Koerhle, J.; Hesch, R. D.; Cody, V. *J. Biol. Chem.* **1986**, *261*, 11623.
(4) Huang, L.; Wall, M. E.; Wani, M. C.; Navarro, H.; Santisuk, T.; Reutrakul, V.; Seo, E.-K.; Farnsworth, N. R.; Kinghorn, A. D. *J. Nat. Prod.* **1998**, *61*, 446.
(5) Júnior, G. M. V.; Sousa, C. M. M.; Cavalheiro, A. J.; Lago, J. H. G.; Chaves, M. H. *Helv. Chim. Acta* **2008**, *91*, 2159.
(6) (a) Varma, R. S.; Varma, M. *Tetrahedron Lett.* **1992**, *33*, 5937. (b) Schoepfer, J.; Fretz, H.; Chaudhuri, B.; Muller, L.; Seeber, E.; Meijer, L.; Lozach, O.; Vangrevelinghe, E.; Furet, P. *J. Med. Chem.* **2002**, *45*, 1741. (c) Lawrence, N. J.; Rennison, D.; McGown, A. T.; Hadfield, J. A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3759. (d) Venkateswarlu, S.; Panchagnula, G. K.; Subbaraju, G. V. *Biosci., Biotechnol., Biochem.* **2004**, *68*, 2183. (e) Okombi, S.; Rival, D.; Bonnet, S.; Mariotte, A.-M.; Perrier, E.; Boumendjel, A. *J. Med. Chem.* **2006**, *49*, 329. (f) Morimoto, M.; Fukumoto, H.; Nozoe, T.; Hagiwara, A.; Komai, K. *J. Agric. Food Chem.* **2007**, *55*, 700. (g) Lee, C-Y.; Chew, E-H.; Go, M-L. *Eur. J. Med. Chem.* **2010**, *45*, 2957. (h) Cheng, H. M.; Zhang, L. W.; Liu, Y. X.; Chen, S. P.; Cheng, H.; Lu, X.; Zheng, Z. X.; Zhou, G.-C. *Eur. J. Med. Chem.* **2010**, *45*, 5950.
(i) Haudecoeur, R.; Ahmed-Belkacem, A.; Yi, W.; Fortuné,

A.; Brillet, R.; Belle, C.; Nicolle, E.; Pallier, C.; Pawlotsky, J-M.; Boumendjel, A. *J. Med. Chem.* **2011**, *54*, 5395.
(7) (a) Donnelly, D. J.; Donnelley, J. A.; Keegan, J. R. *Tetrahedron* **1977**, *33*, 3285. (b) Lèvai, A.; Tökès, A. L. *Synth. Commun.* **1982**, *12*, 701. (c) Imafuku, K.; Honda, M.; McOmie, J. F. W. *Synthesis* **1987**, 199. (d) Sekizaki, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1407. (e) Varma, R. S.; Varma, M. *Tetrahedron Lett.* **1992**, *33*, 5937. (f) Thakkar, K.; Cushman, M. *Tetrahedron Lett.* **1994**, *35*, 6441. (g) Thakkar, K.; Cushman, M. *J. Org. Chem.* **1995**, *60*, 6499. (h) Botta, B.; Delle Monache, G.; Cristina De Rosa, M.; Scurria, R.; Vitali, A.; Vinciguerra, V.; Menendez, P.; Misiti, D. *Heterocycles* **1996**, *43*, 1415. (i) Bose, G.; Modal, E.; Khan, A. T.; Bordoloi, M. J. *Tetrahedron Lett.* **2001**, *42*, 8907.
(8) Saxena, S.; Makrandi, J. K.; Grover, S. K. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1986**, *25*, 473.
(9) (a) Detsi, A.; Majdalani, M.; Kontogiorgis, C. A.; Dimitra, H.-L.; Kefalas, P. *Bioorg. Med. Chem.* **2009**, *17*, 8073. (b) Venkateswarlu, S.; Panchagnula, G. K.; Gottumukkala, A. L.; Subbaraju, G. V. *Tetrahedron* **2007**, *63*, 6909.
(10) Hu, K.; Liu, X.; Ren, J. *Hecheng Huaxue* **2011**, *19*, 115; *Chem. Abstr.* **2011**, *155*, 67721.
(11) (a) Garcia, H.; Iborra, S.; Primo, J.; Miranda, M. A. *J. Org. Chem.* **1986**, *51*, 4432. (b) Brennan, C. M.; Johnson, C. D.; McDonnell, P. D. *J. Chem. Soc., Perkin Trans. 2* **1989**, 957. (c) An, Z.-W.; Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1990**, *397*, 371. (d) Jong, T.-T.; Leu, S.-J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 423.
(12) (a) Donnelly, J. A.; Fox, M. J.; Sharma, T. C. *Tetrahedron* **1979**, *35*, 875. (b) Bose, G.; Mondal, E.; Khan, A. T.; Bordoloi, M. J. *Tetrahedron Lett.* **2001**, *42*, 8907.
(13) Harkat, H.; Blanc, A.; Weibel, J.-M.; Pale, P. *J. Org. Chem.* **2008**, *73*, 1620.
(14) Dean, F. M.; Podimuang, V. *J. Chem. Soc.* **1965**, 3978.
(15) (a) Huang, C.-S.; Li, X.-Y.; Li, Y.; Li, Y.-L. *Gaodeng Xuexiao Huaxue Xuebao* **1997**, *18*, 1804; *Chem. Abstr.* **1997**, *128*, 48379. (b) Li, Y.; Hou, L.; Huang, C.; Li, W.; Li, Y. *Lanzhou Daxue Xuebao, Ziran Kexueban* **1996**, *32*, 101; *Chem. Abstr.* **1997**, *127*, 135608. (c) Zhang, Y.-P.; Li, Y.; Xue, J.-J.; Niu, Y.-H.; Wu, J. *Gaodeng Xuexiao Huaxue Xuebao* **2004**, *25*, 292; *Chem. Abstr.* **2004**, *140*, 406653. (d) Xue, J.-J.; Zhang, Y.-P.; Chen, X.-S.; Li, Y. *Lanzhou Daxue Xuebao, Ziran Kexueban* **2003**, *39*, 43; *Chem. Abstr.* **2004**, *142*, 240207. (e) Huang, C. S.; Li, X. Y.; Li, Y.; Li, Y. L. *Chin. Chem. Lett.* **1996**, *7*, 701.
(16) Britsch, L.; Grisebach, H. *Eur. J. Biochem.* **1986**, *156*, 569.
(17) Sousa, C. M.; Berthet, J.; Delbaere, S.; Coelho, P. J. *Dyes Pigm.* **2011**, *92*, 537.
(18) (a) Takahashi, H.; Kubota, Y.; Fang, L.; Onda, M. *Heterocycles* **1986**, *24*, 1099. (b) Geissman, T. A.; Fukushima, D. K. *J. Am. Chem. Soc.* **1948**, *70*, 1686.
(19) Crystallographic data for compound **3a** have been deposited with the accession number CCDC 854238 and can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk; Web site: www.ccdc.cam.ac.uk/conts/retrieving.html.
(20) Shawa, A. Y.; Chang, C.-Y.; Liau, H.-H.; Lu, P.-J.; Chen, H.-L.; Yang, C.-N.; Li, H.-Y. *Eur. J. Med. Chem.* **2009**, *44*, 2552.
(21) Brunskole, M.; Štefane, B.; Zorko, K.; Anderluh, M.; Stojan, J.; Rižner, T. L.; Gobec, S. *Bioorg. Med. Chem.* **2008**, *16*, 5881.
(22) Khupse, R. S.; Erhardt, P. W. *J. Nat. Prod.* **2007**, *70*, 1507.
(23) Dong, X.; Fan, Y.; Yu, L.; Hu, Y. *Arch. Pharm. (Weinheim, Ger.)* **2007**, *340*, 372.
(24) Yang, L.-X.; Huang, K.-X.; Li, H.-B.; Gong, J.-X.; Wang, F.; Feng, Y.-B.; Tao, Q.-F.; Wu, Y.-H.; Li, X.-K.; Wu, X.-M.; Zeng, S.; Spencer, S.; Zhao, Y.; Qu, J. *J. Med. Chem.* **2009**, *52*, 7732.

