CSIRO PUBLISHING

Aust. J. Chem. **2015**, *68*, 1102–1107
http://dx.doi.org/10.1071/CH14620

Full Paper

Phase Transfer Catalysis Extends The Scope of The Algar–Flynn–Oyamada Synthesis of 3-Hydroxyflavones

Duong Nhu,[A,B] *Bill C. Hawkins,*[A,B,D] *and Christopher J. Burns*[A,B,C,E]

[A]ACRF Chemical Biology Division, Walter and Eliza Hall Institute of Medical Research, 1G Royal Parade, Parkville, Vic. 3052, Australia.
[B]Department of Medical Biology, The University of Melbourne, Vic. 3010, Australia.
[C]School of Chemistry, The Bio21 Institute, The University of Melbourne, Vic. 3010, Australia.
[D]Current address: Department of Chemistry, University of Otago, PO Box 56, Dunedin, New Zealand.
[E]Corresponding author. Email: burns@wehi.edu.au

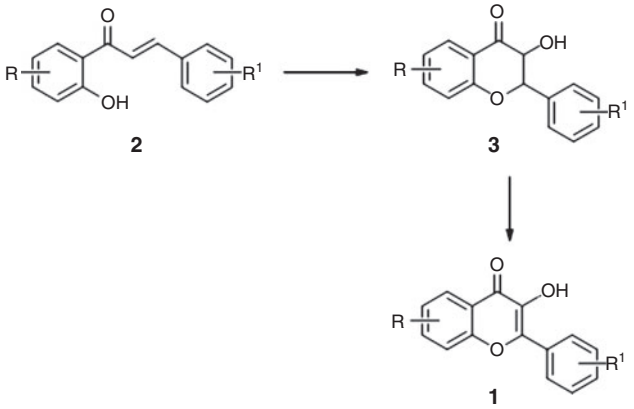
The Algar–Flynn–Oyamada reaction is the classical method to synthesize 3-hydroxyflavones from chalcones. Despite its relative simplicity, the reaction has several drawbacks including variable and often low product yields. We have found that phase transfer catalysis improves the yields and expands the scope of the Algar–Flynn–Oyamada reaction of a series of 4-benzyloxy-2-hydroxy chalcones.

Manuscript received: 16 October 2014.
Manuscript accepted: 21 November 2014.
Published online: 23 March 2015.

Introduction

Flavonoids are a class of polyphenolic compounds found extensively in nature and widely consumed in food and for medicinal purposes.[1] They have been shown to possess a variety of biological activities including anti-cancer,[2,3] anti-inflammatory,[4] anti-microbial,[5] and anti-viral properties[6] among others.[7,8] Of the flavanoids, 3-hydroxyflavones (flavanols, **1**) have received considerable attention, not only for their manifold biological activities,[9–17] but also due to their use as fluorescent sensors,[18–22] and more recently as synthetic intermediates for photochemical transformations.[23–27]

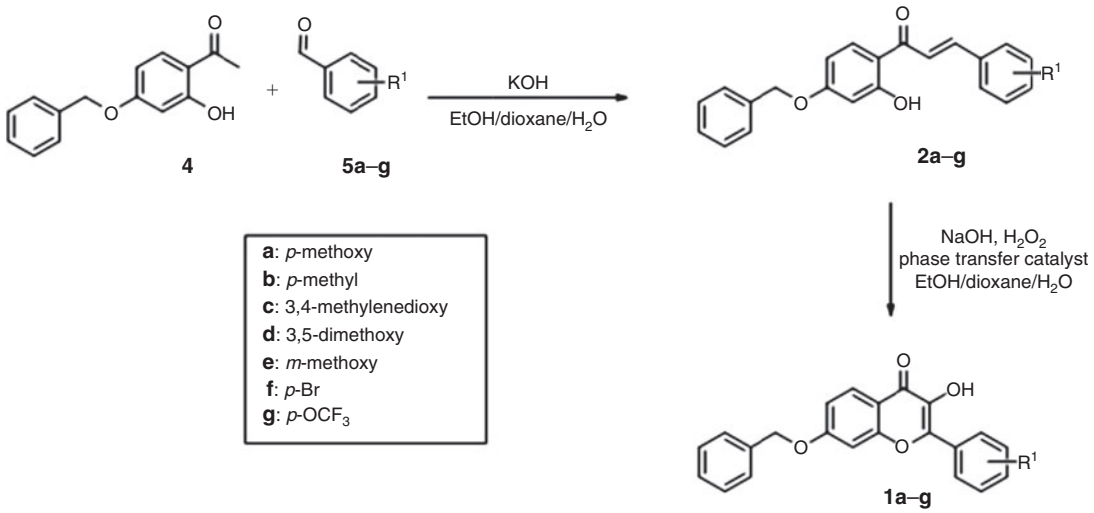
The classical route to the preparation of 3-hydroxyflavones is via the base-induced oxidative cyclization of chalcones (**2**) known as the Algar–Flynn–Oyamada (AFO) reaction (Scheme 1).[28,29] The reaction proceeds via formation of the dihydroflavanol (**3**), which is then further oxidized to the desired product (**1**), though the precise mechanism is a matter of continued debate.[30–33] Despite the apparent simplicity of this reaction, it is capricious and somewhat limited in scope: complex reaction mixtures are often formed making product isolation difficult, and product yields are generally poor-to-moderate.[34] As a consequence, several alternative routes to 3-hydroxyflavones have been devised including oxidation of the corresponding flavones directly[35] or via borylation of lithiated flavones and subsequent oxidation and hydrolysis of the intermediate boronate.[36,37] More recently Kraus et al. have reported a novel base-induced ring-closure/rearrangement reaction of α-cyanobenzyloxy hydroxyacetate derivatives,[38] while numerous groups have reported variations to the conventional AFO reaction conditions.[39–41] As part of our research program on the synthesis and biological evaluation of analogues of the cytotoxic natural product silvestrol,[42] prepared using a photocycloaddition reaction of 3-hydroxyflavones,[23,24] we required a robust route to a variety of 7-benzyloxy-3-hydroxyflavones with variable substitution patterns on the 2-phenyl ring. This paper describes our preliminary results from this endeavour.



Scheme 1. AFO reaction.

Results and Discussion

Our structure–activity exploration of analogues of the natural product silvestrol required access to a variety of 3-hydroxyflavones **1a**–**g**.[42] Given the extensive literature on the AFO reaction and the reported preparation of close analogues to those we required,[43] our initial attempts to prepare this



Scheme 2. Synthesis of 7-benzyloxy-3-hydroxyflavones.

Table 1. Yields of isolated 3-hydroxyflavones under conventional and modified AFO conditions

Entry	Chalcone	Yield [%] under conventional conditions[A]	Additive[B]	Yield [%] under modified conditions
1	**2a**	38	$BnPPh_3Cl$	70
2	**2b**	45	–[C]	–[C]
3	**2c**	28	$BnPPh_3Cl$	55
4	**2d**	19	$BnPPh_3Cl$	49
5	**2e**	0	$BnPPh_3Cl$	32 (14)[D]
6	**2f**	0	$BnPPh_3Cl$	16
7	**2g**	0	$BnPPh_3Cl$	19
8	**2g**	–	$EtPPh_3I$	0
9	**2d**	19	$(n\text{-}Bu)_4NBr$	67
10	**2d**	–	$(n\text{-}Bu)_4NI$	67
11	**2d**	–	$(n\text{-}Bu)_4NHSO_4$	62
12	**2d**	–	$i\text{-}PrPPh_3I$	63
13	**2d**	–	$n\text{-}PrPPh_3Br$	71
14	**2d**	–	$EtPPh_3I$	82

[A] 5 % aqueous NaOH (12 equiv.), 30 % aqueous H_2O_2 (12 equiv.), ethanol/dioxane (1 : 1), room temperature, 48 h.
[B] 5 % aqueous NaOH (12 equiv.), 30 % aqueous H_2O_2 (12 equiv.), PTC (0.1 equiv.), ethanol/dioxane (1 : 1), room temperature, 24–48 h.
[C] Reaction was not undertaken.
[D] 5 % aqueous NaOH (6 equiv.), 30 % aqueous H_2O_2 (6 equiv.), ethanol/dioxane (1 : 1), room temperature, 48 h.

series of compounds employed the conventional two-step approach: generation of the requisite chalcones **2a**–**g** via the Claisen–Schmidt reaction, and subsequent oxidative cyclization with basic peroxide (Scheme 2). In the event, the chalcones **2a**–**g** were obtained from the acetophenone **4** and aldehydes **5a**–**g** in moderate-to-good yields using potassium hydroxide in a mixed solvent system of water/ethanol/dioxane over 3 days at room temperature. The resultant chalcones were then subjected to conventional AFO conditions (hydrogen peroxide and sodium hydroxide) in the same solvent mixture of ethanol, dioxane, and water for 48 h at room temperature. A complex reaction mixture was obtained and only the desired 3-hydroxyflavones **3a**–**d** were obtained in pure form after acidification of the reaction mixture, filtration, and recrystallization of the resultant solid (Table 1, entries 1–4).

While the *p*-methyl and *p*-methoxy hydroxyflavones (**1a** and **1b**, respectively) were obtained in acceptable yields, only low yields of the 3,4-methylenedioxy and 3,5-dimethoxy compounds (**1c** and **1d**, respectively) could be isolated. Furthermore, the 3-hydroxyflavones derived from the *m*-methoxy-substituted chalcone **2e** or from chalcones bearing electron withdrawing groups (**2f** and **2g**) could not be isolated under these conditions. We hypothesized that key reaction intermediates, and in particular the dihydroflavanols **3**, were precipitating from solution in reactions that were low yielding or that had failed, therefore negatively impacting the reaction outcome. Increasing the reaction temperature, extending the reaction time, or changing the solvent mixture to DMF/water did not improve the reaction outcome (data not shown). Given the heterogeneous nature of the reaction mixture, we wondered whether the addition of a phase transfer catalyst may provide an alternative approach to addressing substrate and intermediate solubility.[44] Preliminary studies compared the effects of representative ammonium and phosphonium phase transfer catalysts (tetrabutylammonium

bromide and benzyltriphenylphosphonium chloride) on the AFO reaction of **2e**, and though the former resulted in a complex mixture of products as assessed by proton NMR, we found that addition of benzyltriphenylphosphonium chloride led to smooth conversion to the product **1e**. Indeed, this catalyst significantly improved the product yields in all cases explored (Table 1, entries 1, 3–7), particularly when a large excess of peroxide and base were employed (see entry 5). To further explore the effect of phase transfer catalysis on the reaction, we surveyed the effects of a range of commercially available phase transfer catalysts (both ammonium and phosphonium salts) on the reaction of the 3,5-dimethoxy chalcone (**2d**) (entries 9–14). All catalysts trialled gave improved yields of the desired product **1d**, with ethyltriphenylphosphonium iodide affording the product in 82 % yield. Surprisingly, however, the use of ethyltriphenylphosphonium iodide as the catalyst for the AFO reaction of **2g** did not lead to any isolable quantities of the 3-hydroxyflavone **1g** (entry 8).

The phase transfer catalysts employed presumably improve the solubility of key reaction intermediates (such as the dihydroflavanols **3**) allowing the reaction to proceed to completion. Thus, though both ammonium and phosphonium salts smoothly affect the formation of **1d**, TLC and NMR analysis of the crude reaction mixture of **2e** and **2f** under the conventional AFO conditions indicated the presence of a complex mixture, of which only a trace amount of the product was detectable (Table 1, entries 5 and 6) along with unreacted starting material and dihydroflavanols **3e** and **3f** (respectively). Similarly, when **2f** was subjected to recently reported modified AFO conditions,[41] minimal product could be observed. However, analysis of the crude reaction mixture of these substrates in the presence of benzyltriphenylphosphonium chloride showed complete consumption of the chalcones, a small amount of the corresponding intermediate **3** (removed during purification), and the desired products **1e** and **1f**, isolated by recrystallization in 32 % and 16 % yields, respectively.

We are not aware of any reports on the use of phase transfer catalysis for the AFO reaction despite the operational simplicity of this modification. Phase transfer catalysis has been previously employed with aqueous hydrogen peroxide in the oxidation of alcohols though in these cases the reaction is performed in the presence of metal catalysts such as tungsten polyoxometallates.[45]

These modified conditions described, however, do not overcome some known shortcomings of the AFO reaction. Thus, for example, chalcones derived from aliphatic aldehydes do not generate the corresponding 3-hydroxyflavones, and 2-hydroxy-6-methoxy-substituted chalcones also fail to react. Moreover, the use of the ethyltriphenylphosphonium iodide did not lead to formation of the 3-hydroxyflavone **1g** despite this being the best catalyst for the conversion of the chalcone **2d**, whereas benzyltriphenylphosphonium chloride led to formation of flavone **1g**, albeit in modest 16 % yield. This outcome may reflect a level of substrate dependence on the reaction.

Conclusion

We have identified an operationally simple modification to the AFO reaction providing access to a variety of 3-hydroxyflavones in significantly higher yields than those obtained from the conventional reaction conditions. The phase transfer catalysis presumably improves the solubility of key reaction intermediates allowing the reaction to proceed to completion.

Experimental

Reagents were purchased from commercial suppliers and were used without further purification. Infrared (IR) spectra were obtained on a Bruker Tensor27 FT-IR spectrometer and the frequencies were quoted in wavenumbers (cm^{-1}). NMR spectra were recorded on a Bruker Advance DRX 300 (^1H NMR at 300 MHz; ^{13}C NMR at 75 MHz) and a Varian INOVA 600 (^1H NMR at 600 MHz; ^{13}C at 150 MHz). Melting points were determined on the MPA100 Optimelt automated melting point system and are uncorrected. Electrospray ionization (ESI) was employed in mass spectrometry in tandem with reversed phase liquid chromatography (LCMS) which was performed using two methods. *Method A*: Finnigan LCQ Advantage MAX (column: Gemini 3 µm C18 20 × 4.0 mm 110A column); solvent A: water 0.1 % formic acid; solvent B: acetonitrile 0.1 % formic acid; gradient: 10–100 % B over 10 min; and detection: 100–600 nm and ESI in positive mode with source temperature 300°C. *Method B*: Waters ZQ 3100 (Column: XBridge™ C18 5 µm 4.6 × 100 mm); solvent A: water 0.1 % formic acid; solvent B: acetonitrile 0.1 % formic acid; gradient: 10–100 % B over 10 min; and detection: 100–600 nm and ESI positive ion mode, single-quadrupole at 150°C. The purity of the compounds was determined to be ≥98 % by HPLC at $\lambda = 254$ nm. High-resolution mass spectrometry (HRMS) patterns were recorded on a Bruker microTOFQ (University of Otago, New Zealand) or on Agilent Q-TOF 6200 (Monash Institute of Pharmaceutical Sciences, Melbourne, Australia) using an ESI source in either the positive or negative modes.

*1-(4-(Benzyloxy)-2-hydroxyphenyl)ethanone (**4**)*

To a solution of 1-(2,4-dihydroxyphenyl)ethanone (6 g, 39.4 mmol, 1 equiv.) in toluene (78.8 mL) were added potassium acetate (6.97 g, 70.9 mmol, 1.8 equiv.), tetra-*n*-butylammonium iodide [$(n\text{-Bu})_4NI$] (1.45 g, 3.94 mmol, 0.1 equiv.), and benzyl bromide (4.65 mL, 47.3 mmol, 1.2 equiv.), and the reaction mixture was heated to 60–80°C for 6 h. Ice-cold water (200 mL) was added to the cooled reaction mixture and acidified with 1 M HCl to pH 1. The mixture was diluted with diethyl ether (Et_2O; 200 mL) and the organic layer was collected. The aqueous layer was extracted again with Et_2O (100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The solid residue was purified by recrystallization from a mixture of cyclohexane/ethyl acetate (EtOAc)/Et_2O to furnish the desired product as an off-white solid (6.7 g, 70 %), mp 110–115°C. ν_{max} (film)/cm^{-1} 3032, 1619, 1325. δ_H ($CDCl_3$, 300 MHz) 7.6 (1H, d, *J* 9.3, ArH), 7.44 – 7.32 (5H, m, ArH), 6.52 (2H, dd, *J* 8.2, 2.0, ArH), 6.51 (1H, s, ArH), 5.10 (2H, s, OCH_2Ph), 2.56 (3H, s, $(CO)CH_3$). δ_C ($CDCl_3$, 75 MHz) 202.6, 165.2, 135.9, 132.4, 128.7, 128.3, 127.5, 114.1, 108.1, 101.9, 70.2, 26.2. Method A: t_R 5.74. *m*/*z* (ESI^+) 243 ($[M+H]^+$). *m*/*z* 243.1002. HRMS Anal. Calc. for ($C_{15}H_{15}O_3$) 243.1021.

General Procedure for the Synthesis of Chalcones (Modified from Ref. 14)

To a suspension of 1-(4-(benzyloxy)-2-hydroxyphenyl)ethanone (**4**) and aldehyde **5** (1 equiv.) in ethanol (EtOH)/dioxane (1 : 1) (0.25 M) was added dropwise 40 % KOH aqueous solution (6 equiv.) while cooling on ice. The resulting blue–green reaction mixture was then warmed to room temperature, and stirring continued for 3 days. After this time, the solution was cooled to 0°C and acidified with 2 M acetic acid to pH 6. The solid thus formed was collected by filtration or centrifugation

(2 min at 1000*g*; repeated once after removal of the mother liquor and addition of cold EtOH), washed with cold EtOH, and recrystallized from a mixture of dichloromethane/cyclohexane. The mother liquor was extracted with dichloromethane and concentrated, and the resultant yellow solid was recrystallized from the same solvent mixture or triturated with Et_2O to give the corresponding chalcones.

(E)-1-(4-(Benzyloxy)-2-hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**2a**)

The title compound[46] was obtained as yellow needles (981 mg, 35 %), mp: 132–135°C. ν_{max} (film)/cm^{-1} 3001, 2936, 1636, 1574, 1505, 1455, 1275, 1251, 1152, 1131, 836, 802, 737, 697. δ_H ($CDCl_3$, 300 MHz) 7.89 (1H, d, *J* 18.0, –C*H*=CH–), 7.87 (1H, d, *J* 9.0, ArH), 7.64 (2H, d, *J* 8.8, ArH), 7.52–7.33 (6H, m, ArH, –CH=C*H*–, overlap), 6.97 (2H, d, *J* 8.8, ArH), 6.62–6.56 (2H, m, ArH), 5.14 (1H, s, OCH_2Ph), 3.89 (2H, s, OCH_3). δ_C ($CDCl_3$, 75 MHz) 191.9, 166.5, 165.1, 161.8, 144.3, 135.9, 131.2, 130.4, 128.7, 128.3, 127.5, 117.9, 114.5, 114.4, 108.1, 102.1, 70.3, 55.4. Method A: t_R 6.32. *m/z* (ESI^+) 361.3 ($[M+H]^+$). *m/z* 383.1254. HRMS Anal. Calc. for ($C_{23}H_{20}O_4Na$) 383.1259.

(E)-1-(4-(Benzyloxy)-2-hydroxyphenyl)-3-p-tolylprop-2-en-1-one (**2b**)

The *title compound* was obtained as a yellow solid (225 mg, 45 %), mp 117–120°C. ν_{max} (film)/cm^{-1} 2938, 2837, 1685, 1598, 1556, 1515, 1252, 1135, 1112, 1031, 1006, 898, 830. δ_H ($CDCl_3$, 600 MHz) 13.48 (1H, s, br, O*H*), 7.87 (1H, -d, *J* 15.4, C*H*=CH–), 7.84 (1H, d, *J* 9.3, ArH), 7.54 (d, *J* 7.8, ArH, overlap), 7.53 (1H, d, *J* 15.0, –CH=C*H*–, overlap), 7.41 (5H, dt, *J* 12.9, 7.4, ArH), 7.37–7.32 (1H, m, ArH), 7.23 (2H, d, *J* 8.0, ArH), 6.61–6.37 (2H, m, ArH), 5.10 (2H, s, OCH_2Ph), 2.39 (3H, s, PhCH_3). δ_C ($CDCl_3$, 151 MHz) 191.9, 166.6, 165.2, 144.6, 141.3, 135.9, 132.0, 131.3, 129.7, 128.7, 128.6, 128.3, 127.6, 119.2, 114.3, 108.2, 102.1, 70.2, 21.6. Method A: t_R 6.55. *m/z* (ESI^+) 345.4 ($[M+H]^+$). *m/z* (HRMS ESI^+) 367.1221; $[M+Na]^+$ requires 367.1310.

(E)-3-(Benzo[d][1,3]dioxol-5-yl)-1-(4-(benzyloxy)-2-hydroxyphenyl)prop-2-en-1-one (**2c**)

The *title compound* was obtained from the general procedure as a yellow solid (1.05 g, 56 %), mp 175–178°C. ν_{max} (film)/cm^{-1} 2914, 1635, 1603, 1560, 1505, 1478, 1371, 1241, 1212, 1032, 1005, 840, 808, 790, 670. δ_H ($CDCl_3$, 300 MHz) 7.83 (1H, d, *J* 15.9, –C*H*=CH–), 7.82 (1H, d, *J* 6.7, ArH), 7.48–7.34 (6H, m, ArH, –CH=C*H*–, overlap), 7.20–7.14 (2H, m, ArH), 6.88 (1H, d, *J* 8.0, ArH), 6.61–6.55 (2H, m, ArH), 6.06 (2H, s, OCH_2O), 5.14 (2H, s, OCH_2Ph). δ_C ($CDCl_3$, 75 MHz) 191.8, 166.6, 165.2, 150.1, 148.5, 144.3, 135.9, 131.2, 129.3, 128.7, 128.3, 127.6, 125.4, 118.3, 114.3, 108.7, 108.2, 106.7, 102.1, 101.7, 70.3. Method B: t_R 9.05. *m/z* (ESI^+) 375.1 ($[M+H]^+$). *m/z* 397.1030, 375.1220. HRMS Anal. Calc. for ($C_{23}H_{18}O_5Na$) 397.1052, ($C_{23}H_{19}O_5$) 375.1232.

(E)-1-(4-(Benzyloxy)-2-hydroxyphenyl)-3-(3,5-dimethoxyphenyl)prop-2-en-1-one (**2d**)

The *title compound* was obtained as a yellow solid after workup (4.23 g, 43 %), mp 133–137°C. ν_{max} (film)/cm^{-1} 3001, 2836, 2939, 1636, 1574, 1505, 1455, 1205, 1152, 1131, 1017, 991, 935, 926, 836, 802. δ_H ($CDCl_3$, 600 MHz) 13.39 (1H, s, O*H*), 7.82 (1H, d, *J* 8.6, ArH), 7.79 (1H, d, *J* 15.4 Hz, –C*H*=CH–), 7.51 (1H, d, *J* 15.4, –CH=C*H*–), 7.41 (5H, dt, *J* 12.7, 7.4, ArH), 7.34 (1H, t, *J* 7.0, ArH), 5.11 (2H, s, OCH_2Ph), 3.84 (6H, s, 2(OCH_3)). δ_C ($CDCl_3$, 150 MHz) 191.8, 166.6, 165.3, 161.1, 144.5, 136.6, 135.8, 131.3, 128.7, 128.3, 127.6, 120.8, 114.2, 108.3, 106.4, 102.8, 102.1, 70.3, 55.5, 55.5. Method A: t_R 6.41. *m/z* (ESI^+) 391.2 ($[M+H]^+$). *m/z* (HRMS ESI^+) 413.1370, 391.1516 ($[M+H]^+$); $[M+Na]^+$ requires 413.1365.

(E)-1-(4-(Benzyloxy)-2-hydroxyphenyl)-3-(3-methoxyphenyl)prop-2-en-1-one (**2e**)

The title compound[47] was obtained as yellow solid (713 mg, 39 %), mp 137–139°C. ν_{max} (film)/cm^{-1} 3060, 3037, 2940, 1640, 1574, 1495, 1456, 1362, 1304, 1258, 1213, 1190, 1156, 978, 956, 853, 738, 698. δ_H ($CDCl_3$, 300 MHz) 13.39 (1H, s, OH), 7.86 (1H, d, *J* 15, –C*H*=CH–), 7.84 (1H, d, *J* 9.4, ArH), 7.56 (1H, d, *J* 15.5, –CH=C*H*–), 7.45–7.36 (5H, m, ArH), 7.34 (1H, d, *J* 9, ArH), 7.24 (1H, m, ArH), 7.16 (1H, m, ArH), 6.98 (1H, ddd, *J* 8.1, 2.6, 1.0, ArH), 6.59–6.55 (2H, m, ArH), 5.12 (2H, s, OCH_2Ph), 3.87 (3H, s, OCH_3). δ_C ($CDCl_3$, 75 MHz) 191.8, 166.6, 165.4, 160.0, 144.4, 136.2, 135.9, 131.3, 130.0, 128.7, 128.3, 127.6, 121.2, 120.6, 116.4, 114.3, 113.6, 108.3, 102.1, 70.3, 55.4. Method A: t_R 6.34. *m/z* (ESI^+) 361.1 ($[M+H]^+$). *m/z* 383.1228. HRMS Anal. Calc. for ($C_{23}H_{20}O_4Na$) 383.1259.

(E)-1-(4-(Benzyloxy)-2-hydroxyphenyl)-3-(4-bromophenyl)prop-2-en-1-one (**2f**)

The *title compound* was prepared according to the general procedure as an off-white solid (480 mg, 29 %), mp 148–151°C. ν_{max} (film)/cm^{-1} 3031, 1648, 1575, 1514, 1489, 828, 790, 670, 635. δ_H ($CDCl_3$, 300 MHz) 7.83 (1H, d, *J* 15.0, –C*H*=CH–, overlap), 7.83 (1H, d, *J* 6.0, ArH, overlap), 7.61–7.52 (5H, m, ArH), 7.52–7.37 (5H, m, ArH, –CH=C*H*–), 6.61–6.57 (2H, m, ArH), 5.14 (2H, s, OCH_2Ph). δ_C ($CDCl_3$, 75 MHz) 191.5, 166.7, 165.5, 143.0, 135.8, 133.7, 132.3, 131.3, 129.9, 128.7, 128.4, 127.6, 125.0, 120.9, 114.2, 108.4, 102.1, 70.3. Method A: t_R 6.59. *m/z* (ESI^+) 407.2, 409.2 ($[M+H]^+$). *m/z* (HRMS ESI^+) 431.0253 and 433.0234; $[M+Na]^+$ requires 431.0259 and 433.0238.

(E)-1-(4-(Benzyloxy)-2-hydroxyphenyl)-3-(4-(trifluoromethoxy)phenyl)prop-2-en-1-one (**2g**)

The title compound[46] was prepared according to the general procedure as a yellow solid (640 mg, 22 %), mp 120–125°C. ν_{max} (film)/cm^{-1} 3040, 1643, 1608, 1573, 1508, 1261, 1212, 1179, 1154, 1020, 976, 731, 692, 659. δ_H ($CDCl_3$, 300 MHz) 13.35 (1H, s), 7.86 (1H, d, *J* 15.0, –C*H*=CH–), 7.4 (1H, d, *J* 9.0, ArH), 7.69 (1H, d, *J* 8.3, ArH), 7.56 (1H, d, *J* 15.5, –CH=C*H*–), 7.47–7.33 (5H, m, ArH), 7.29 (2H, d, *J* 7.9, ArH), 6.63–6.56 (2H, m, ArH), 5.13 (1H, s, OCH_2Ph). δ_C ($CDCl_3$, 75 MHz) 191.5, 166.7, 165.5, 150.7, 142.6, 135.8, 133.4, 131.3, 129.9, 128.7, 128.4, 127.6, 122.1, 121.2, 118.7, 114.2, 108.4, 102.2, 70.3. Method A: t_R 6.55. *m/z* (ESI^-) 413.2 ($[M-H]^-$). *m/z* 415.1185. HRMS Anal. Calc. for ($C_{23}H_{18}F_3O_4$) 415.1157.

General Procedure for the Synthesis of 3-Hydroxyflavones

To a solution of 1-(4-(benzyloxy)-2-hydroxyphenyl)ethanone (**4**) and the appropriate aldehyde **5** (1 equiv.) in a mixture of

EtOH/dioxane (1 : 1) (0.25 M) at 0°C was added aqueous KOH (40 %). The reaction mixture was stirred at room temperature for 2 days. The reaction was cooled to 0°C, followed by dropwise addition of 2 M acetic acid (AcOH) until the mixture became slightly acidic (pH 4–5). The aqueous layer was extracted thrice with dichloromethane. The combined organic layers were washed with brine, concentrated, and dried (Na_2SO_4) to afford the corresponding chalcone **2** as a yellow solid. The crude residue was resuspended in the solvent mixture of EtOH/dioxane (0.07 M) and cooled to 0°C. An aqueous solution of NaOH (5 %) (12 equiv.) was added to afford an orange solution. To this was added dropwise an aqueous solution of H_2O_2 (30 %) (12 equiv.). The appropriate phase transfer catalyst (benzyltriphenylphosphonium chloride or as described in Table 1) (0.1 equiv.) was added to the resultant yellow suspension and the reaction mixture was allowed to warm to room temperature overnight to 48 h and monitored by TLC. The reaction mixture was then acidified with 1 M HCl while cooling on ice. The yellow solid was collected by filtration or centrifugation (2 min at 1000*g*; repeated once after removal of the mother liquor and addition of cold EtOH) and recrystallized with dichloromethane/EtOH to afford the 3-hydroxyflavone.

*7-(Benzyloxy)-3-hydroxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (**1a**)*

The title compound[48] was obtained as a yellow solid (70 %), mp 247–258°C. ν_{max} (film)/cm^{-1} 1650, 1451, 1404, 1255, 1180, 832, 747. δ_H (DMSO, 300 MHz) 8.43 (2H, d, *J* 7.6, ArH), 7.96 (1H, d, *J* 8.9, ArH), 7.56–7.23 (6H, m, ArH), 7.02 (3H, s, ArH), 5.26 (2H, s, OCH_2Ph), 3.82 (3H, s, OCH_3). δ_C (DMSO, 75 MHz) 161.9, 159.0, 155.9, 144.5, 140.8, 136.9, 129.09, 128.5, 128.3, 127.9, 126.6, 118.4, 116.2, 115.0, 114.3, 114.0, 101.4, 70.3, 55.6. Method A: t_R 6.06. *m*/*z* (ESI$^+$) 375.3 ([M+H]$^+$). *m*/*z* 397.1017. HRMS Anal. Calc. for ($C_{23}H_{18}O_5Na$) 397.1052.

*7-(Benzyloxy)-3-hydroxy-2-*p*-tolyl-4*H*-chromen-4-one (**1b**)*

The *title compound* was obtained as yellow needles (conventional method, no PTC, 233 mg, 45 %), mp 216–220°C. ν_{max} (film)/cm^{-1} 3255, 2916, 1610, 1567, 1455, 1404, 1254, 1206, 1185. δ_H ($CDCl_3$, 300 MHz) 8.18 (1H, d, *J* 9.0, ArH), 8.15 (2H, d, *J* 8.4, ArH), 7.53–7.39 (5H, m, ArH), 7.36 (2H, d, *J* 8.2, ArH), 7.12–7.04 (2H, m, ArH), 5.21 (2H, s, OCH_2Ph), 2.46 (3H, s, PhCH_3). δ_C ($CDCl_3$, 150 MHz) 172.7, 163.0, 156.8, 145.2, 140.0, 138.9, 136.6, 129.5, 129.0, 128.9, 128.4, 127.8, 115.8, 115.7, 101.7, 101.6, 70.5, 21.5. Method B: t_R 9.05. *m*/*z* (ESI$^+$) 359.1 ([M+H]$^+$). *m*/*z* (HRMS ESI$^-$) 357.1137; [M−H]$^-$ requires 357.1127.

*2-(Benzo[*d*][1,3]dioxol-5-yl)-7-(benzyloxy)-3-hydroxy-4*H*-chromen-4-one (**1d**)*

The *title compound* was obtained as a yellow solid (55 %), mp 226–229°C. ν_{max} (film)/cm^{-1} 3259, 1599, 1563, 1500, 1470, 1252, 1208, 1182, 1122, 1015, 997, 857, 818. δ_H ($CDCl_3$, 300 MHz) 8.16 (1H, d, *J* 8.9, ArH), 7.84 (1H, dd, *J* 8.4, 1.8, ArH), 7.76 (1H, d, *J* 1.7, ArH), 7.52–7.36 (5H, m, ArH), 7.10 (1H, dd, *J* 8.9, 2.4, ArH), 7.04 (1H, d, *J* 2.3, ArH), 6.99 (1H, d, *J* 8.4, ArH), 6.08 (2H, s, –CH_2O–), 5.21 (2H, s, OCH_2Ph). δ_C ($CDCl_3$, 75 MHz) 172.5, 163.3, 157.1, 137.5, 135.7, 128.8, 128.5, 127.5, 126.8, 125.2, 122.6, 115.2, 114.8, 108.7, 107.9, 101.7, 101.0, 70.6. Method A t_R 5.98. *m*/*z* (ESI$^+$) 389.0 ([M+H]$^+$). *m*/*z* (HRMS ESI$^-$) 387.0860; [M–H]$^-$ requires 387.0869.

*7-(Benzyloxy)-2-(3,5-dimethoxyphenyl)-3-hydroxy-4*H*-chromen-4-one (**1c**)*

The *title compound* was obtained as a white solid (49 %), mp 235–254°C. ν_{max} (film)/cm^{-1} 3255, 2916, 1610, 1568, 1455, 1404, 1254, 1206, 1185, 702, 746. δ_H ($CDCl_3$, 300 MHz) 8.17 (1H, d, *J* 8.9, ArH), 7.53–7.35 (7H, m, ArH), 7.10 (1H, dd, *J* 8.9, 2.4, ArH), 7.06 (1H, d, *J* 2.3, ArH), 6.60 (1H, t, *J* 2.3, ArH), 5.21 (2H, s, –OCH_2Ph), 3.91 (6H, s, OCH_3). δ_C ($CDCl_3$, 75 MHz) 172.8, 163.4, 160.8, 157.3, 138.2, 135.7, 132.8, 128.8, 128.5, 127.6, 126.9, 115.39, 114.7, 105.8, 102.2, 101.0, 77.4, 77.0, 76.6, 70.6, 55.5. Method A: t_R 8.67. *m*/*z* (ESI$^+$) 405.3 ([M+H]$^+$). *m*/*z* (HRMS ESI$^-$) 403.1136; [M−H]$^-$ requires 403.1182.

*7-(Benzyloxy)-3-hydroxy-2-(3-methoxyphenyl)-4*H*-chromen-4-one (**1e**)*

The *title compound* was obtained as a yellow solid (32 %), mp 249–260°C. ν_{max} (film)/cm^{-1} 3256, 2916, 1611, 1568, 1504, 1455, 1254, 1206, 1185, 1046, 966, 765, 746. δ_H ($CDCl_3$, 600 MHz) 8.14 (1H, d, *J* 8.9, ArH), 7.81 (1H, d, *J* 8.1, ArH), 7.79 (1H, s, br, ArH), 7.45 (3H, t, *J* 7.1, ArH), 7.42 (3H, t, *J* 8.0, ArH), 7.37 (1H, t, *J* 7.2, ArH), 7.07 (1H, dd, *J* 8.9, 2.1, ArH), 7.04 (1H, d, *J* 2.0, ArH), 7.00 (1H, dd, *J* 8.3, 2.2, ArH), 5.18 (2H, s, OCH_2Ph), 3.88 (3H, d, *J* 15.8, OCH_3). δ_C (DMSO, 75 MHz) 172.4, 162.7, 160.4, 156.3, 144.0, 139.1, 136.1, 133.0, 128.5, 128.1, 127.9, 126.2, 115.2, 115.1, 105.8, 101.4, 101.3, 70.1, 55.4. Method B: t_R 6.07. *m*/*z* (ESI$^+$) 375.3 ([M+H]$^+$). *m*/*z* (HRMS ESI$^+$) 397.1052; [M+Na]$^+$ requires 397.1052.

*7-(Benzyloxy)-2-(4-bromophenyl)-3-hydroxy-4*H*-chromen-4-one (**1f**)*

The *title compound* was obtained as an off-white solid (16 %), mp 202–204°C. ν_{max} (film)/cm^{-1} 3216, 1602, 1567, 1453, 1413, 1254, 1214, 832, 699, 750, 633. δ_H (DMSO, 300 MHz) 9.74 (1H, s, OH), 8.17 (2H, d, *J* 8.8, ArH), 8.02 (1H, d, *J* 8.9, ArH), 7.78 (2H, d, *J* 8.8, ArH), 7.53–7.48 (2H, m, ArH), 7.47–7.33 (4H, m, ArH), 7.13 (1H, dd, *J* 8.9, 2.3, ArH), 5.28 (2H, s, OCH_2Ph). δ_C (DMSO, 75 MHz) 172.8, 163.3, 156.8, 143.9, 139.6, 136.7, 132.1, 131.1, 129.7, 129.0, 128.6, 128.3, 126.8, 123.5, 115.8, 115.7, 101.8, 70.5. Method B: t_R 9.35. *m*/*z* (ESI$^+$) 421.1, 423.1 ([M+H]$^+$). *m*/*z* (HRMS ESI$^-$) 421.0081 and 423.0062; [M−H]$^-$ requires 421.0075 and 423.0055.

*7-(Benzyloxy)-3-hydroxy-2-(4-(trifluoromethoxy) phenyl)-4*H*-chromen-4-one (**1g**)*

The *title compound* was obtained as a bright yellow solid (19 %), mp 196–200°C. ν_{max} (film)/cm^{-1} 2922, 1618, 1501, 1451, 1260, 1212, 1180, 847, 747. δ_H (DMSO, 300 MHz) 8.56 (2H, d, *J* 8.4, ArH), 7.97 (1H, d, *J* 8.9, ArH), 7.53–7.48 (2H, m, ArH), 7.47–7.32 (5H, m, ArH), 7.29 (1H, d, *J* 2.2, ArH), 7.02 (1H, dd, *J* 8.9, 2.3, ArH), 5.26 (1H, s, OCH_2Ph). δ_C (DMSO, 75 MHz) 170.3, 162.3, 156.3, 147.3, 142.6, 136.8, 129.0, 128.6, 128.3, 127.8, 126.8, 121.0, 116.1, 114.5, 101.4, 70.3. Method B: t_R 9.28. *m*/*z* (ESI$^+$) 429.2 ([M+H]$^+$). *m*/*z* (HRMS ESI$^+$) 429.0953; [M+H]$^+$ requires 429.0950.

Supplementary Material

^{1}H NMR, ^{13}C NMR and LCMS spectra of all compounds are available on the Journal's website.

Acknowledgements

This work was supported by scholarships, fellowships, and grants from the following: Victorian State Government Operational Infrastructure Support (OIS) Grant, Australian Cancer Research Foundation, Cancer Therapeutics CRC (DN), Dyson Bequest funding (CJB), and an Independent Research Institutes Infrastructure Support Scheme Grant (361646) from the Australian National Health and Medical Research Council. Prof. David Huang and Assoc. Prof. Spencer Williams are thanked for useful discussions. Ms Dana Buczek is acknowledged for analytical support.

References

[1] Ø. M. Andersen, K. R. Markham, *Flavonoids: Chemistry, Biochemistry and Applications* **2006** (CRC Press: Boca Raton, FL).
[2] W. Ren, Z. Qiao, H. Wang, L. Zhu, L. Zhang, *Med. Res. Rev.* **2003**, *23*, 519. doi:10.1002/MED.10033
[3] C. Kanadaswami, L.-T. Lee, P.-P. H. Lee, J.-J. Hwang, F.-C. Ke, Y.-T. Huang, M.-T. Lee, *In Vivo* **2005**, *19*, 895.
[4] E. Middleton, in *Flavonoids in the Living System* (Eds J. A. Manthey, B. S. Buslig) **1998**, Vol. 439, Ch. 13, pp. 175–182 (Springer: New York, NY).
[5] T. P. T. Cushnie, A. J. Lamb, *Int. J. Antimicrob. Agents* **2005**, *26*, 343. doi:10.1016/J.IJANTIMICAG.2005.09.002
[6] D. D. Orhan, B. Özçelik, S. Özgen, F. Ergun, *Microbiol. Res.* **2010**, *165*, 496. doi:10.1016/J.MICRES.2009.09.002
[7] E. Middleton, C. Kandaswami, T. C. Theoharides, *Pharmacol. Rev.* **2000**, *52*, 673.
[8] O. Benavente-García, J. Castillo, *J. Agric. Food Chem.* **2008**, *56*, 6185.
[9] C. J. Bennett, S. T. Caldwell, D. B. McPhail, P. C. Morrice, G. G. Duthie, R. C. Hartley, *Bioorg. Med. Chem.* **2004**, *12*, 2079. doi:10.1016/J.BMC.2004.02.031
[10] M. F. García-Saura, M. Galisteo, I. N. Villar, A. Bermejo, A. Zarzuelo, F. L. Vargas, J. Duarte, *Mol. Cell. Biochem.* **2005**, *270*, 147. doi:10.1007/S11010-005-4503-0
[11] L. Chen, J. Li, C. Luo, H. Liu, W. Xu, G. Chen, O. W. Liew, W. Zhu, C. M. Puah, X. Shen, H. Jiang, *Bioorg. Med. Chem.* **2006**, *14*, 8295. doi:10.1016/J.BMC.2006.09.014
[12] J. A. Smith, D. J. Maloney, S. M. Hecht, D. A. Lannigan, *Bioorg. Med. Chem.* **2007**, *15*, 5018. doi:10.1016/J.BMC.2007.03.087
[13] M. Rode, R. C. Gupta, B. K. Karale, S. S. Rindhe, *J. Heterocycl. Chem.* **2008**, *45*, 1597. doi:10.1002/JHET.5570450607
[14] C. X. Qin, X. Chen, R. A. Hughes, S. J. Williams, O. L. Woodman, *J. Med. Chem.* **2008**, *51*, 1874. doi:10.1021/JM070352H
[15] N. G. Amado, B. F. Fonseca, D. M. Cerqueira, V. M. Neto, J. G. Abreu, *Life Sci.* **2011**, *89*, 545. doi:10.1016/J.LFS.2011.05.003
[16] T. A. Dias, C. L. Duarte, C. F. Lima, M. F. Proença, C. Pereira-Wilson, *Eur. J. Med. Chem.* **2013**, *65*, 500. doi:10.1016/J.EJMECH.2013.04.064
[17] A. Kralj, M.-T. Nguyen, N. Tschammer, N. Ocampo, Q. Gesiotto, M. R. Heinrich, O. Phanstiel, *J. Med. Chem.* **2013**, *56*, 5019. doi:10.1021/JM4003457
[18] T. Ozturk, A. S. Klymchenko, A. Capan, S. Oncul, S. Cikrikci, S. Taskiran, B. Tasan, F. B. Kaynak, S. Ozbey, A. P. Demchenko, *Tetrahedron* **2007**, *63*, 10290. doi:10.1016/J.TET.2007.07.074
[19] V. V. Shynkar, A. S. Klymchenko, C. Kunzelmann, G. Duportail, C. D. Muller, A. P. Demchenko, J.-M. Freyssinet, Y. Mély, *J. Am. Chem. Soc.* **2007**, *129*, 2187. doi:10.1021/JA068008H
[20] Y. Kimura, M. Fukuda, K. Suda, M. Terazima, *J. Phys. Chem. B* **2010**, *114*, 11847. doi:10.1021/JP105033Q
[21] O. M. Zamotaiev, V. Y. Postupalenko, V. V. Shvadchak, V. G. Pivovarenko, A. S. Klymchenko, Y. Mély, *Bioconjugate Chem.* **2011**, *22*, 101. doi:10.1021/BC100434D
[22] Z. Darwich, O. A. Kucherak, R. Kreder, L. Richert, R. Vauchelles, Y. Mély, A. S. Klymchenko, *Methods Appl. Fluoresc.* **2013**, *1*, 025002. doi:10.1088/2050-6120/1/2/025002
[23] B. Gerard, G. Jones, J. A. Porco, *J. Am. Chem. Soc.* **2004**, *126*, 13620. doi:10.1021/JA044798O
[24] B. Gerard, R. Cencic, J. Pelletier, J. A. Porco, *Angew. Chem., Int. Ed.* **2007**, *46*, 7831. doi:10.1002/ANIE.200702707
[25] S. P. Roche, R. Cencic, J. Pelletier, J. A. Porco, *Angew. Chem., Int. Ed.* **2010**, *49*, 6533. doi:10.1002/ANIE.201003212
[26] C. M. Rodrigo, R. Cencic, S. P. Roche, J. Pelletier, J. A. Porco, *J. Med. Chem.* **2012**, *55*, 558. doi:10.1021/JM201263K
[27] N. J. Lajkiewicz, S. P. Roche, B. Gerard, J. A. Porco, *J. Am. Chem. Soc.* **2012**, *134*, 13108. doi:10.1021/JA305342F
[28] J. Algar, J. P. Flynn, *Proc. R. Ir. Acad., Sect. B* **1934**, *B42*, 1.
[29] T. Oyamada, *Bull. Chem. Soc. Jpn.* **1935**, *10*, 182. doi:10.1246/BCSJ.10.182
[30] M. Bennett, A. J. Burke, W. I. O'Sullivan, *Tetrahedron* **1996**, *52*, 7163. doi:10.1016/0040-4020(96)00334-1
[31] F. Gao, K. F. Johnson, J. B. Schlenoff, *J. Chem. Soc., Perkin Trans. 1* **1996**, 269. doi:10.1039/P29960000269
[32] S. Bhattacharyya, K. Hatua, *RSC Adv.* **2014**, *4*, 18702. doi:10.1039/C3RA46623J
[33] I. E. Serdiuk, A. D. Roshal, J. Blażejowski, *Chem. Heterocycl. Compd. (N. Y., NY, U. S.)* **2014**, *50*, 396. doi:10.1007/S10593-014-1487-2
[34] C. Limberakis, in *Name Reactions in Heterocyclic Chemistry* (Ed. J. J. Li) **2005**, Ch. 10, pp. 496–503 (Wiley: Hoboken, NJ).
[35] W. Adam, D. Golsch, L. Hadjiarapoglou, T. Patonay, *J. Org. Chem.* **1991**, *56*, 7292. doi:10.1021/JO00026A020
[36] A. M. B. S. R. C. S. Costa, F. M. Dean, M. A. Jones, R. S. Varma, *J. Chem. Soc., Perkin Trans. 1* **1985**, 799. doi:10.1039/P19850000799
[37] M. El Sous, M. L. Khoo, G. Holloway, D. Owen, P. J. Scammells, M. A. Rizzacasa, *Angew. Chem., Int. Ed. Engl.* **2007**, *46*, 7835. doi:10.1002/ANIE.200702700
[38] G. A. Kraus, V. Gupta, A. Kempema, *Synlett* **2012**, 385. doi:10.1055/S-0031-1290207
[39] A. C. Jain, S. M. Gupta, A. Sharma, *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1267. doi:10.1246/BCSJ.56.1267
[40] J. R. Dharia, K. F. Johnson, J. B. Schlenoff, *Macromolecules* **1994**, *27*, 5167. doi:10.1021/MA00096A046
[41] S. Gunduz, A. C. Goren, T. Ozturk, *Org. Lett.* **2012**, *14*, 1576. doi:10.1021/OL300310E
[42] B. C. Hawkins, L. M. Lindqvist, D. Nhu, P. P. Sharp, D. Segal, A. K. Powell, M. Campbell, E. Ryan, J. M. Chambers, J. M. White, M. A. Rizzacasa, G. Lessene, D. C. Huang, C. J. Burns, *ChemMedChem* **2014**, *9*, 1556. doi:10.1002/CMDC.201400024
[43] Z. Li, G. Ngojeh, P. DeWitt, Z. Zheng, M. Chen, B. Lainhart, V. Li, P. Felpo, *Tetrahedron Lett.* **2008**, *49*, 7243. doi:10.1016/J.TETLET.2008.10.032
[44] T. Werner, *Adv. Synth. Catal.* **2009**, *351*, 1469. doi:10.1002/ADSC.200900211
[45] K. Sato, M. Aoki, J. Takagi, R. Noyori, *J. Am. Chem. Soc.* **1997**, *119*, 12386. doi:10.1021/JA973412P
[46] K. N. Mewett, S. P. Fernandez, A. K. Pasricha, A. Pong, S. O. Devenish, D. E. Hibbs, M. Chebib, G. A. R. Johnston, J. R. Hanrahan, *Bioorg. Med. Chem.* **2009**, *17*, 7156. doi:10.1016/J.BMC.2009.08.062
[47] J. Alvim, R. P. Severino, E. F. Marques, A. M. Martinelli, P. C. Vieira, J. B. Fernandes, M. F. G. F. da Silva, A. G. Corrêa, *J. Comb. Chem.* **2010**, *12*, 687. doi:10.1021/CC100076K
[48] Z. Li, G. Ngojeh, P. DeWitt, Z. Zheng, M. Chen, B. Lainhart, V. Li, P. Felpo, *Tetrahedron Lett.* **2008**, *49*, 7243. doi:10.1016/J.TETLET.2008.10.032