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Synthesis of a Range of Polyhydroxy 8-Aryl Flavones

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Abstract: The 8-iodo flavones formed by cyclization of benzyl-protected chalcones with iodine in dimethyl sulfoxide have been transformed by a Suzuki coupling reaction into a variety of 8-aryl derivatives. Deprotection with boron tribromide has generated a family of new 8-aryl flavones containing four to eight hydroxyl groups.

Keywords: Chalcone cyclization, selective iodination, Suzuki coupling

Although biflavonoids incorporating a C-C connection to C-8 of a flavone are well known (278 structures in a recent SciFinder® search), the number of known compounds involving C-8 connection to a simple unfused benzene ring is relatively small (32 structures from SciFinder®). Few of the known structures have oxygenation in ring B. Simple 8-aryl flavones are rare in nature,[1] but some were identified in early structural investigations of biflavonoids involving degradative studies.[2] Initial attempts at synthesis employed Ullmann coupling of iodoaryl compounds, but yields were poor.[3] Photolysis of an 8-iodoflavone in benzene has been reported to yield an 8-phenyl derivative,[4] and some phenyl flavones have been prepared by cyclization of appropriately substituted chalcones.[5] More recently, Suzuki couplings have been used with considerable success.[6]

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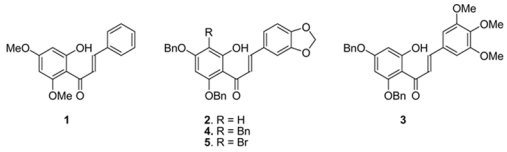
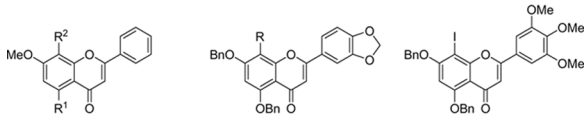
Polyhydroxyflavones have attracted considerable attention as potential antioxidants. One study[7] has identified a 2′3′4′-trihydroxylation pattern as being particularly effective in a radical scavenging role, and a more recent investigation has found variable effects on ultraviolet (UV)–induced apoptosis in keratinocytes with varying hydroxylation patterns.[8] In this study, we set out to use Suzuki coupling of iodo flavones for the introduction of a benzene ring in the 8-position, a locus for introduction of further hydroxylation. Thus, our goal was to produce flavones with new patterns of hydroxylation, functionalized in ring B, as found in the well-known natural products, but with additional phenolic centers in the newly introduced benzene ring. Exploration of the potential bioactivity of such compounds would be highly valuable. We have also achieved synthesis of 8-bromo and 8-benzyl tetrahydroxy flavones.

A selection of chalcones (**1–5**) (Scheme 1) was obtained from acetophenone derivatives by condensation with appropriately substituted benzaldehydes, using aqueous sodium hydroxide (NaOH) in dioxane.[9] Compounds **4** and **5** have not been reported previously. Cyclization of chalcones to form flavones has been achieved previously by heating with catalytic amounts of iodine in DMSO (dimethyl sulfoxide).[10] Although the original reference gave no indication of the amount of iodine used, a more recent study[11] employed a 1:9 ratio of iodine to chalcone. In our hands, reaction of compound **1** using this ratio of reactants yielded the expected flavone **6** in poor yield (16%) but gave a significant quantity (8%) of an 8-iodoflavone **7** that had been demethylated at C-5. Incorporation of iodine in the I_2/DMSO reaction has been noted previously, where the use of a 1:1 ratio of iodine to chalcone yielded diiodoflavones.[12] Mixtures containing monoiodo derivatives were obtained with a 1:2 ratio of iodine to substrate.[13] Compound **7** has been reported previously from iodination of a flavone.[14]

Such iodo compounds offered promise as substrates for the introduction of further C-8 functionality, and we found that increasing the amount of iodine used to a 1:1 ratio enabled the isolation of **7** in 85% yield. In similar fashion, reaction of the benzyl-protected chalcones **2** and **3** gave the new mono-iodoflavones **8** and **9** in 59 and 70% yields respectively. It is noteworthy that a C-5 benzyloxy grouping was



Scheme 1.



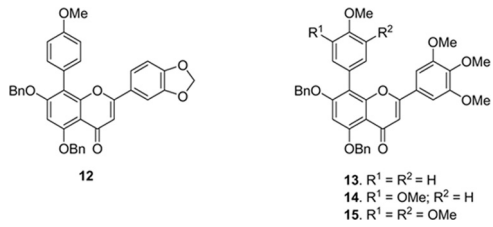
Scheme 2.

unaffected, unlike the C-5 methoxyl, which was removed in the conversion of **1** into **7** (Scheme 2). Flavones such as **6** characteristically show two doublets ($J \approx 2$ Hz) for H-6 and H-8 in the ^{1}H NMR spectrum. The ^{1}H NMR spectrum of the iodo derivatives showed one singlet that showed heteronuclear multiple bond correlation (HMBC) correlation to C-5, consistent with assignment of this peak to H-6 rather than H-8. The iodinated carbon signal in the ^{13}C NMR spectrum was characteristically upfield ($\delta_C = 66.4$ for **8** and 66.3 for **9**).

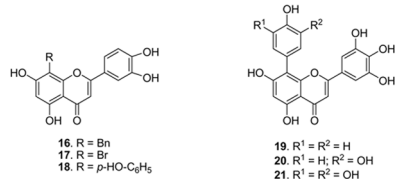
When the cyclization reaction was conducted using the 8-benzylchalcone **4** or the 8-bromo derivative **5**, the new iodine-free flavones **10** and **11** were obtained in 86 and 87% yields respectively (Scheme 2). In addition to the lack of iodination in this case, we found no significant levels of diiodination with any of the substrates used, even when the iodine-to-chalcone ratio was raised to 11:4. Unlike our substrates, the literature examples of compounds undergoing diiodination had no substitution at C-7.[12,13]

Suzuki arylation reactions on the two iodoflavones **8** and **9** with *p*-methoxyphenylboronic acid led to two new polyalkoxy flavones **12** and **13** in 80 and 96% yields, respectively. Reaction of **9** with 3,4-dimethoxy and 3,4,5-trimethoxyphenylboronic acids gave two more highly substituted derivatives, **14** and **15,** in 73 and 58% yields (Scheme 3). Each alkoxyflavone produced in this study was dealkylated with boron tribromide in good yield to generate a collection of six new polyhydroxy flavones **16**–**21** (Scheme 4).

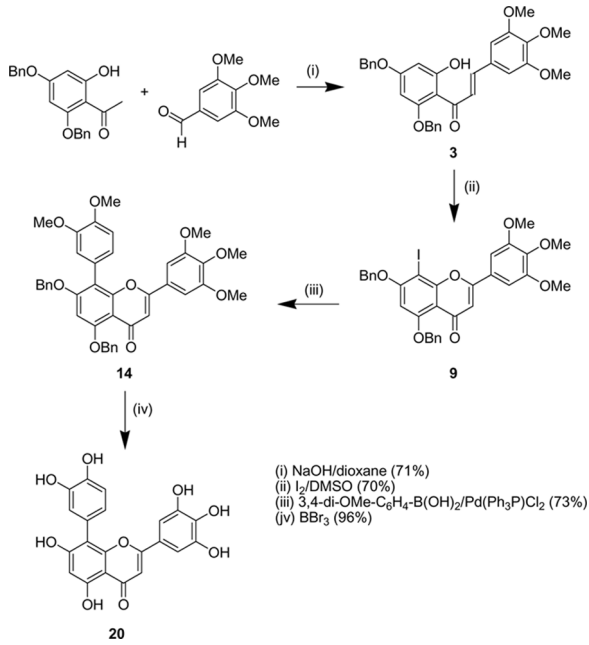
In summary, the overall scheme is illustrated in Scheme 5 for the production of the heptahydroxyflavone **20**. In the course of this



Scheme 3.



Scheme 4.



Scheme 5. Synthesis of heptahydroxyflavone **20**.

investigation, we have synthesized two new chalcone derivatives and 14 new substituted flavones. Most notably this work has led to the production of six new highly phenolic flavones. Antioxidant properties of the compounds produced in this study are currently under investigation.

EXPERIMENTAL

NMR spectra were recorded at 500 MHz (^{1}H) and 125 MHz (^{13}C) on a Varian Inova-500 spectrometer. Spectra were recorded in $CDCl_3$, methanol-d_4, or DMSO-d_6. ^{1}H spectra were referenced to residual

^{1}H-bearing solvent ($\delta_H = 7.26$, 3.30, and 2.50), and ^{13}C spectra were referenced to the central line of the solvent resonance ($\delta_C = 77.1$, 49.0, and 39.5). Infrared (IR) spectra were recorded as KBr disks on a Perkin-Elmer Spectrum BX Fourier transform (FT)-IR system spectrometer. High-resolution mass spectra (HRMS) were recorded on a Bruker Microtof-Q spectrometer.

Column fractionation was performed using Merck 60 silica (200–400 mesh, 40–63 μm) as adsorbent. Columns were pre-equilibrated with the starting solvent before use. All solvents were distilled before use. Known compounds are referenced by their *Chemical Abstracts* reference number in square brackets.

Chalcone Formation

Aqueous NaOH (50% w/w, 10 ml) was added to a stirred solution of the substituted acetophenone and the aldehyde in dioxane (10 ml). After vigorous stirring for 24 h at room temperature, the reaction mixture was neutralized with HCl (1 mol L^{-1}, 20 ml) and extracted into ethyl acetate (EtOAc) (3 × 20 mL). Removal of the EtOAc *in vacuo* and recrystallization from ethanol (EtOH) gave the chalcone. Experiments are summarized as follows: acetophenone (mass, amount), aldehyde (mass, amount), product (mass yield, % yield), data.

(*E*)-1-(2,4-Bis(benzyloxy)-6-hydroxyphenyl)-3-(benzo[d][1,3]dioxol-5-yl)prop-2-en-1-one (**2**)

1-(2,4-Bis(benzyloxy)-6-hydroxyphenyl)ethanone [18065–05-9][15] (0.500 g, 1.44 mmol), piperonal [120–57-0] (0.250 g, 1.67 mmol), and **2** [120980-03-2][16] (0.450 g, 65%). ^{1}H NMR ($CDCl_3$) δ 7.71 (d, $J = 16$ Hz, 1H), 7.67 (d, $J = 16$ Hz, 1H), 7.35–7.45 (10H, m, 10H), 6.68 (d, $J = 6$ Hz, 1H), 6.70 (dd, $J = 1.5$, 6 Hz, 1H), 6.50 (d, $J = 1.5$ Hz, 1H), 6.22 (d, $J = 2.4$ Hz, 1H), 6.16 (d, $J = 2.4$ Hz, 1H), 5.99 (s, 2H), 5.10 (s, 2H), 5.05 (s, 2H).

(*E*)-1-(2,4-Bis(benzyloxy)-6-hydroxyphenyl)-3-(3,4,5-trimethoxyphenyl) prop-2-en-1-one (**3**)

1-(2,4-Bis(benzyloxy)-6-hydroxyphenyl)ethanone [18065-05-9][15] (0.500 g, 1.44 mmol), 3,4,5-trimethoxybenzaldehyde [86-81-7] (0.250 g, 1.36 mmol), and **3** [120980-02-1] (0.51 g, 71%). ^{1}H NMR data as reported.[17]

(*E*)-1-(3-Benzyl-4,6-bis(benzyloxy)-2-hydroxyphenyl)-3-(benzo[d][1,3] dioxol-5-yl) prop-2-en-1-one (**4**)

1-(3-Benzyl-4,6-bis(benzyloxy)-2-hydroxyphenyl)ethanone [18065-06-0][15] (0.500 g, 1.14 mmol), piperonal [120-57-0] (0.250 g, 1.67 mmol), and **4** (0.57 g, 88%). ^{1}H NMR ($CDCl_3$) δ 7.68 (d, $J = 15.5$ Hz, 1H), 7.65 (d, $J = 15.5$ Hz, 1H), 7.13–7.45 (m, 15H), 6.71 (dd, $J = 2.5$, 10 Hz, 1H), 6.68 (d, $J = 10$ Hz, 1H), 6.15 (s, 1H), 6.52 (d, $J = 2.5$ Hz, 1H), 5.98 (s, 2H), 5.15 (s, 2H), 5.03 (s, 2H), 4.03 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 192.9, 164.9, 162.5, 160.7, 149.4, 148.1, 142.6, 141.7, 136.3, 135.5, 129.9, 129.0 (2C), 128.9 (2C), 128.8 (2C), 128.7 (2C), 128.5 (2C), 128.2, 128.1 (2C), 127.3, 125.9, 125.5, 124.8, 110.6, 108.5, 107.1, 106.6, 101.4, 88.8, 71.5, 70.3, 28.2. IR (KBr): 3061, 3028, 2881, 1615, 1556, 1501, 1488, 1421, 1418, 1248, 1143, 1105, 1038, 755, 736, 698 cm^{-1}. HRMS (ESI) calcd for $C_{37}H_{30}O_6Na/C_{37}H_{30}O_6K$ 593.1935/609.1679, found 593.1921/609.1661 $[M^+ + Na]$ / $[M^+ + K]$.

(*E*)-1-(4,6-Bis(benzyloxy)-3-bromo-2-hydroxyphenyl)-3-(benzo[d][1,3] dioxol-6-yl)prop-2-en-1-one (**5**)

1-(4,6-Bis(benzyloxy)-3-bromo-2-hydroxyphenyl)ethanone [141238-45-1][18] (0.500 g, 1.25 mmol), piperonal [120-57-0] (0.250 g, 1.67 mmol), and **5** (0.480 g, 72%). ^{1}H NMR ($CDCl_3$) δ 7.68 (d, $J = 15.5$ Hz, 1H), 7.67 (d, $J = 15.5$ Hz, 1H), 7.13–7.45 (m, 10H), 6.72 (dd, $J = 2$ Hz, $J = 8$ Hz, 1H), 6.69 (d, $J = 8$ Hz, 1H), 6.49 (d, $J = 2$ Hz, 1H), 6.20 (s, 1H), 5.99 (s, CH_2, 2H), 5.27 (s, CH_2, 2H), 5.04 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 192.7, 165.7, 163.8, 161.2, 161.0, 148.2, 144.0, 135.7, 135.0, 129.6, 129.2 (2C), 129.2, 128.9 (2C), 128.7, 128.6 (2C), 128.4, 126.9 (2C), 125.2, 124.9, 108.5, 107.0, 101.5, 89.9, 71.8, 71.0. This compound was characterized fully as the cyclized flavone **11**.

Chalcone Cyclizations

A solution of the chalcone and iodine in dry DMSO (volume) was heated at 150°C under reflux in a nitrogen atmosphere for the specified time. After cooling, the mixture was diluted with aqueous Na_2SO_3 (2 × volume), then extracted three times with dichloromethane (DCM, volume). The solution was dried (Na_2SO_4), and the solvent was removed in vacuo. The resulting material was purified (method) to give the flavone. Experiments are summarized as follows: chalcone (mass, amount), iodine (mass, amount), DMSO (volume), time, purification method, product (mass yield, % yield).

5-Hydroxy-8-iodo-7-methoxyflavone (**7**)

a. 2′-Hydroxy-4′,6′-dimethoxychalcone [1775-97-9] (**1**) (0.250 g, 0.88 mmol), iodine (0.020 g, 0.079 mmol), and DMSO (10 ml), 4 h, chromatography on silica [DCM/ether (Et_2O) gradient] gave 5,7-dimethoxyflavone [21392-57-4] (**6**) (0.040 g, 16%) (^{1}H NMR data as reported[19]) and **7** [26505-96-4][14] (0.028 g, 8%). ^{1}H NMR ($CDCl_3$) δ 8.05 (m, 2H), 7.47 (m, 3H), 6.74 (s, 1H), 6.42 (s, 1H), 4.04 (s, 3H).
b. 2′-Hydroxy-4′,6′-dimethoxychalcone (**1**) (0.250 g, 0.88 mmol), iodine (0.200 g, 0.79 mmol), and DMSO (10 ml), 4 h, chromatography on silica (DCM/Et_2O gradient) gave **7** (0.170 g, 85%).

2-(Benzo[d][1,3]dioxol-5-yl)-5,7-bis(benzyloxy)-8-iodo-4 H-chromen-4-one (**8**)

Chalcone **2** (0.500 g, 1.04 mmol), iodine (0.550 g, 2.17 mmol), and DMSO (30 ml), 5 h, recrystallization from EtOH gave **8** (0.37 g, 59%). ^{1}H NMR ($CDCl_3$) δ 7.56 (dd, $J = 5$, 8.5 Hz, 1H), 7.30–7.52 (m, 10H), 7.44 (d, $J = 5$ Hz, 1H), 6.92 (d, $J = 8.5$ Hz, 1H), 6.58 (s, 1H), 6.49 (s, 1H), 6.07 (s, 2H), 5.21 (s, 2H), 5.17 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 177.1, 161.5, 160.9, 160.5, 157.7, 150.5, 148.5, 136.2, 135.5, 128.8 (2C), 128.8 (2C), 128.4, 128.0, 127.1 (2C), 126.8 (2C), 125.3, 108.9, 108.7, 107.5, 106.7, 106.2, 102.1, 96.1, 71.4, 71.4, 66.4. IR (KBr): 3050, 3030, 3004, 2900, 1642, 1589, 1503, 1488, 1450, 1380, 1322, 1254, 1123, 1037, 751 cm^{-1}. HRMS (ESI) calcd. for $C_{30}H_{22}O_6I$ 605.0456, found 605.0467 [$M^+ + H$].

5,7-Bis(benzyloxy)-8-iodo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-4-one (**9**)

Chalcone **3** (0.500 g, 0.95 mmol), iodine (0.550 g, 2.17 mmol), and DMSO (30 ml), 5 h, recrystallization from EtOH gave **9** (0.43 g, 70%). ^{1}H NMR ($CDCl_3$) δ 7.54 (d, $J = 8$ Hz, 2H), 7.30–7.43 (m, 6H), 7.39 (d, $J = 7$ Hz, 2H), 7.33 (s, 2H), 6.67 (s, 1H), 6.46 (s, 1H), 5.25 (s, 2H), 5.18 (s, 2H), 3.97 (s, 6H), 3.93 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 177.2, 161.6, 160.8, 160.6, 153.6 (2C), 141.0, 136.1, 135.5, 128.8 (2C), 128.8 (2C), 128.4, 128.0, 127.0 (2C), 126.8 (2C), 126.3, 110.7, 107.9, 104.2 (2C), 103.9, 96.2, 71.4 (2C), 66.3, 61.1, 56.4 (2C). IR (KBr): 3050, 3030, 3004, 2939, 1640, 1593, 1505, 1456, 1419, 1394, 1342, 1246, 1128, 1058, 836, 734 cm^{-1}. HRMS (ESI) calcd. for $C_{32}H_{27}INaO_7$ 673.0694; found 673.0693 [$M^+ + Na$].

2-(Benzo[d][1,3]dioxol-5-yl)-8-benzyl-5,7-bis(benzyloxy)-4H-chromen-4-one (**10**)

Chalcone **4** (0.500 g, 0.88 mmol), iodine (0.550 g, 2.17 mmol), and DMSO (30 ml), 5 h, recrystallization from EtOH gave **10** (0.43 g, 86 %) as yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.58 (2H, d, $J = 7$ Hz, 2H), 7.33 (ddm, $J = 7$, 7 Hz, 2H), 7.32 (ddm, $J = 7$, 7 Hz, 2H), 7.30 (m, 1H), 7.29 (dd, $J = 2$, 8 Hz, 1H), 7.24 (m, 1H), 7.23 (d, $J = 8$ Hz, 2H), 7.21 (d, $J = 7$ Hz, 2H), 7.17 (ddm, $J = 7$, 7 Hz, 1H), 7.13 (d, $J = 2$ Hz, 1H), 6.85 (d, $J = 8$ Hz, 1H), 6.52 (s, 1H), 6.52 (s, 1H), 6.03 (s, 2H), 5.23 (s, 2H), 5.08 (s, CH_2, 2H), 4.25 (s, CH_2, 2H). ^{13}C NMR ($CDCl_3$) δ 177.9, 167.8, 160.7, 160.4, 158.4, 156.7, 150.2, 148.4, 140.5, 136.7, 136.0, 128.7 (2C), 128.7 (2C), 128.4 (2C), 128.3 (3C), 127.8, 127.4 (2C), 126.8 (2C), 126.0, 125.9, 121.1, 110.2, 109.8, 108.7, 107.8, 106.2, 101.8, 95.9, 71.4, 70.7. IR (KBr): 3050, 3031, 2882, 1621, 1582, 1557, 1501, 1489, 1446, 1423, 1247, 1215, 1167, 1105, 1038, 980, 932, 817 cm^{-1}. HRMS (ESI) calcd. for $C_{37}H_{28}O_6Na$ 591.1778; found 591.1775 [$M^+ + Na$].

2-(Benzo[d][1,3]dioxol-5-yl)-5,7-bis(benzyloxy)-8-bromo-4H-chromen-4-one (**11**)

Chalcone **5** (0.500 g, 0.89 mmol), iodine (0.550 g, 2.17 mmol), and DMSO (30 ml), 5 h, recrystallization from EtOH gave **11** (0.43 g, 87 %) as yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.64 (dd, $J = 2$, 7.5 Hz, 1H), 7.52 (d, $J = 2$ Hz, 1H), 7.30–7.52 (m, 10H), 6.95 (d, $J = 7.5$ Hz, 1H), 6.59 (s, 1H), 6.47 (s, 1H), 6.07 (s, 2H), 5.24 (s, 2H), 5.18 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 177.2, 160.7, 159.2, 158.9, 155.3, 150.6, 148.5, 136.2, 135.5, 128.8 (2C), 128.7 (2C), 128.4, 128.0, 127.1 (2C), 126.8 (2C), 125.2 (C1′), 121.5, 110.6 (C4a), 108.9, 107.4, 106.4, 101.9, 96.5, 92.3 (C8), 71.4, 71.3. IR (KBr): 3050, 3030, 3004, 2902, 1641, 1592, 1503, 1488, 1450, 1380, 1324, 1254, 1127, 1036, 732 cm^{-1}. HRMS (ESI) calcd. for $C_{30}H_{22}O_6{}^{79}Br/C_{30}H_{22}O_6{}^{81}Br$ 557.0594/559.0574; found 557.0581/559.0565 [$M^+ + H$].

Suzuki Arylation of 8-Iodoflavones

Tetrakis(triphenylphosphine)palladium (0) [14221-01-3] was added to a solution of the 8-iodoflavone in dimethoxyethane (DME) (volume). The solution was degassed under vacuum and stirred at room temperature for 20 min, then saturated Na_2CO_3 solution (0.5 × volume)

was added. The resulting mixture was degassed again and then stirred in an atmosphere of nitrogen for 1 h. The substituted phenylboronic acid was added, and the mixture was heated at 80°C under nitrogen for 4 h. After cooling to room temperature, the mixture was diluted with dichloromethane (2 × volume); and water (2 × volume); the organic phase was separated, washed with water, and dried ($MgSO_4$). The solvent was evaporated in vacuo, and the product was purified (method) to give the 8-aryl flavone. Experiments are summarized as follows: 8-iodoflavone (mass, amount), $(Ph_3P)_4P$ (mass, amount), DME (volume), substituted phenylboronic acid (mass, amount), purification method, product (mass yield, % yield).

2-(Benzo[d][1,3]dioxol-5-yl)-5,7-bis(benzyloxy)-8-(4-methoxyphenyl)-4H-chromen-4-one (**12**)

8-Iodoflavone **8** (0.100 g, 0.17 mmol), $(Ph_3P)_4Pd$ (0.010 g, 0.009 mmol), DME (10 ml), and *p*-methoxyphenylboronic acid [5720-07-0] (0.070 g, 0.46 mmol), recrystallization from EtOH gave **12** (0.085 g, 80%). ^{1}H NMR ($CDCl_3$) δ 7.58 (d, $J = 7$ Hz, 2H), 7.39 (m, 4H), 7.38 (d, $J = 8$ Hz, 2H), 7.29 (ddm, $J = 7$, 8 Hz, 2H), 7.21 (d, $J = 8$ Hz, 2H), 7.13 (dd, $J = 1.5$, 8 Hz, 1H), 7.03 (d, $J = 8$ Hz, 2H), 6.99 (d, $J = 1.5$ Hz, 1H), 6.79 (d, $J = 8$ Hz, 1H), 6.54 (s, 1H), 6.54 (s, 1H), 6.00 (s, 2H), 5.24 (s, 2H), 5.07 (s, 2H), 3.90 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 177.9, 160.4, 159.6, 159.0, 158.7, 156.1, 150.2, 148.3, 136.6, 136.3, 132.3 (2C), 128.7 (2C), 128.7 (2C), 128.0, 127.8, 126.8 (2C), 126.7 (2C), 125.5, 124.4, 121.0, 113.5 (2C), 112.7, 109.9, 108.6, 107.1, 106.2, 101.8, 96.6, 71.3, 70.7, 55.4. IR (KBr): 3050, 3030, 3005, 2936, 2836, 1645, 1591, 1500, 1489, 1451, 1384, 1321, 1251, 1178, 1120, 1035, 834, 813, 733, 696 cm^{-1}. HRMS (ESI) calcd. for $C_{37}H_{39}O_7/C_{37}H_{38}NaO_7$ 585.1908/607.1727; found 585.1931/607.1745 $[M^+ + H]$ / $[M^+ + Na]$.

5,7-Bis(benzyloxy)-2-(3,4,5-trimethoxyphenyl)-8-(4-methoxyphenyl)-4H-chromen-4-one (**13**)

8-Iodoflavone **9** (0.100 g, 0.15 mmol), $(Ph_3P)_4Pd$ (0.010 g, 0.009 mmol), DME (10 ml), and *p*-methoxyphenylboronic acid [5720-07-0] (0.070 g, 0.46 mmol), recrystallization from EtOH gave **13** (0.091 g, 96%). ^{1}H NMR ($CDCl_3$) δ 7.57 (d, $J = 8$ Hz, 2H), 7.40 (dd, $J = 7$, 7 Hz, 2H), 7.36 (dd, $J = 2$, 7 Hz, 2H), 7.32 (ddm, $J = 7$, 8 Hz, 2H), 7.29 (m, 1H), 7.28 (m, 1H), 7.19 (d, $J = 8$ Hz, 2H), 7.00 (dd, $J = 2$, 7 Hz, 2H), 6.75 (s, 2H), 6.63 (s, 1H), 6.54(s, 1H), 5.26 (s, 2H), 5.07 (s, 2H), 3.852 (s, 3H), 3.848 (s, 3H), 3.72

(s, 6H). ^{13}C NMR ($CDCl_3$) δ 177.9, 160.1, 159.7, 158.9, 158.8, 156.2, 153.4, 140.6, 136.6, 136.2, 132.2 (2C), 128.7 (2C), 128.7 (2C), 128.1, 127.9, 126.8 (2C), 126.7 (2C), 126.5, 124.8, 113.6 (2C), 112.7, 109.8, 107.5, 102.9 (2C), 96.5, 71.3, 70.6, 61.0, 56.2 (2C), 55.2. IR (KBr): 3050, 3030, 3005, 2934, 1642, 1594, 1506, 1456, 1419, 1340, 1244, 1189, 1128, 1056, 1029,837, 735 cm^{-1}. HRMS (ESI) calcd. for $C_{39}H_{35}O_8/C_{39}H_{34}NaO_8$ 631.2326/653.2146; found 631.2334/653.2145 $[M^+ + H]$ / $[M^+ + Na]$.

5,7-Bis(benzyloxy)-2-(3,4,5-trimethoxyphenyl)-8-(3,4-dimethoxyphenyl)-4H-chromen-4-one (**14**)

8-Iodoflavone **9** (0.100 g, 0.15 mmol), $(Ph_3P)_4Pd$ (0.010 g, 0.009 mmol), DME (10 ml), and 3,4-dimethoxyphenylboronic acid [122775-35-3] (0.070 g, 0.41 mmol), recrystallization from EtOH gave **14** (0.072 g, 73%). ^{1}H NMR ($CDCl_3$) δ 7.58 (d, $J = 8$ Hz, 2H), 7.40 (ddm, $J = 8$, 8 Hz, 2H), 7.32 (ddm, $J = 7$, 8 Hz, 2H), 7.29 (m, 1H), 7.28 (m, 1H), 7.22 (d, $J = 8$ Hz, 2H), 7.00 (dd, $J = 2$, 8 Hz, 1H), 6.97 (d, $J = 8$ Hz, 1H), 6.95 (d, $J = 2$ Hz, 1H), 6.77 (s, 2H), 6.63 (s, 1H), 6.56 (s, 1H), 5.29 (s, 2H), 5.07 (s, 2H), 3.95 (s, 3H), 3.92 (s, 3H), 3.81 (s, 3H), 3.72 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 177.9, 160.1, 159.7, 158.9, 156.2, 153.4 (2C), 149.2, 148.5, 140.6, 136.6, 136.1, 128.7 (2C), 128.7 (2C), 128.1, 127.9, 126.8 (4C), 126.4, 125.1, 123.5, 114.4, 112.7, 110.7, 109.8, 107.4, 102.9 (2C), 96.4, 71.3, 70.6, 61.0, 56.1, 55.9 (2C), 55.9. IR (KBr): 3050, 3030, 3005, 2936, 2836, 1642, 1595, 1500, 1457, 1419, 1387, 1341, 1250, 1226, 1189, 1170, 1129, 1058, 1028,912, 837, 734 cm^{-1}. HRMS (ESI) calcd. for $C_{40}H_{37}O_9/C_{40}H_{36}NaO_9$ 661.2432/683.2252; found 661.2422/691.2247 $[M^+ + H]$ / $[M^+ + Na]$.

5,7-Bis(benzyloxy)-2,8-bis(3,4,5-trimethoxyphenyl)-4H-chromen-4-one (**15**)

8-Iodoflavone **9** (0.100 g, 0.15 mmol), $(Ph_3P)_4Pd$ (0.010 g, 0.009 mmol), DME (10 ml), and 3,4,5-trimethoxyphenylboronic acid [182163-96-8][20] (0.070 g, 0.39 mmol), purification by column chromatography (DCM/Et_2O gradient) gave **15** (0.060 g, 58%). ^{1}H NMR ($CDCl_3$) δ 7.58 (d, $J = 8$ Hz, 2H), 7.40 (ddm, $J = 7$, 8 Hz, 2H), 7.30 (m, 4H), 7.20 (dd, $J = 2$, 8 Hz, 2H), 6.80 (s, 2H), 6.66 (s, 1H), 6.65 (s, 2H), 6.57 (s, 1H), 5.30 (s, 2H), 5.07 (s, 2H), 3.90 (s, 3H), 3.85 (s, 3H), 3.78 (s, 6H), 3.73 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 177.9, 160.2, 159.6, 159.0, 156.0, 153.4 (2C), 152.8 (2C), 140.8, 137.7, 136.4, 136.0, 128.7 (2C), 128.6 (2C), 128.1, 127.9, 127.9, 126.9 (2C), 126.8 (2C), 126.2, 112.8, 109.6, 108.2 (2C), 107.3, 102.9 (2C), 96.3, 71.2, 70.6, 61.0, 60.8, 56.1 (2C), 56.0 (2C). IR (KBr): 3001, 2939, 2839, 1640, 1601, 1498, 1490, 1459, 1452, 1420,

1401, 1348, 1337, 1301, 1250, 1228, 1172, 1137, 1110, 1058, 1005, 910, 839, 823, 734, 697 cm^{-1}. HREIMS calcd. for $C_{41}H_{39}O_{10}/C_{41}H_{38}NaO_{10}$ 691.2538/713.2357; found 691.2548/713.2330 $[M^+ + H]$ / $[M^+ + Na]$.

Dealkylation to form Polyhydroxy Flavones

A solution of boron tribromide (1 M) in DCM was added to a solution of the protected flavone in dry DCM (volume). The mixture was stirred for the specified time. MeOH (2 × volume) was added to quench the reaction, and the solution was evaporated under vacuum. The residue was purified as specified. Experiments are summarized as follows: protected flavone (mass, amount), 1 M BBr_3 (volume, amount), and DCM (volume), reaction time, purification method, product (mass yield, % yield).

8-Benzyl-5,7-dihydroxy-2-(3,4-dihydroxyphenyl)-4H-chromen-4-one (**16**)

Protected flavone **10** (0.085 g, 0.15 mmol), 1 M BBr_3 (3 ml, 3.00 mmol), and DCM (10 ml), 2 h, chromatography on silica (5:1, DCM/MeOH) gave tetrahydroxyflavone **16** (0.053, 94%). ^{1}H NMR (methanol-d_6) δ 7.54 (d, $J = 2$ Hz, 1H), 7.42 (dd, $J = 2$, 8 Hz, 1H), 7.33 (d, $J = 6$ Hz, 2H), 7.27 (dd, $J = 6$, 7 Hz, 2H), 7.13 (d, $J = 6$ Hz, 1H), 6.97 (d, $J = 8$ Hz, Hz, 1H), 6.58 (s, 1H), 6.38 (s, 1H), 4.23 (s, 2H). ^{13}C NMR (methanol-d_6) δ 184.2, 166.3, 163.7, 161.3, 156.7, 150.9, 147.0, 142.1, 129.3 (2C), 129.2 (2C), 126.8, 123.9, 120.4, 116.7, 114.2, 107.7, 105.3, 103.7, 99. 6, 29.2. IR (KBr): 3205, 1602, 1575, 1516, 1451, 1394, 1363, 1330, 1261, 1193, 1121, 1012, 989, 841, 814, 786, 696 cm^{-1}. HRMS (ESI) calcd. 377.1020 for $C_{22}H_{17}O_6$; found 377.1030 $[M^+ + H]$.

8-Bromo-5,7-dihydroxy-2-(3,4-dihydroxyphenyl)-4H-chromen-4-one (**17**)

Protected flavone **11** (0.370 g, 0.66 mmol), 1 M BBr_3 (3 ml, 3.00 mmol), DCM (10 ml), 2 h, chromatography on silica (5:1, DCM/MeOH) gave tetrahydroxyflavone **17** (0.172 g, 71%). ^{1}H NMR (methanol-d_6) δ 7.67 (d, $J = 2$ Hz, 1H), 7.59 (dd, $J = 2$, 8 Hz, 1H), 7.04 (d, $J = 8$ Hz, 1H), 6.72 (s, 1H), 6.52 (s, 1H). ^{13}C NMR (methanol-d_6) δ 183.7, 167.0, 166.3, 161.5, 155.5, 151.5, 147.1, 123.3, 120.6, 116.8, 114.4, 108.8, 103.7, 100.1, 89.5. IR (KBr): 3350, 1652, 1601, 1560, 1436, 1390, 1254, 1125 cm^{-1}. HRMS (ESI) calcd. for $C_{15}H_{10}{}^{79}BrO_{10}/C_{15}H_{10}{}^{81}BrO_{10}$ 364.9655/366.9635; found 364.9692/366.9674 $[M^+ + H]$.

5,7-Dihydroxy-2-(3,4-dihydroxyphenyl)-8-(4-hydroxyphenyl)-4H-chromen-4-one (**18**)

Protected flavone **12** (0.085 g, 0.13), 1 M BBr_3 (3 ml, 3.00 mmol), and DCM (10 ml), 2 h, chromatography on silica (5:1, DCM/MeOH) gave pentahydroxyflavone **18** (0.046 g, 94%). ^{1}H NMR (DMSO-d_4) δ 7.36 (d, $J = 8$ Hz, 2H), 7.16 (d, $J = 2$ Hz, 1H), 7.12 (dd, $J = 2$, 8 Hz, 1H), 6.88 (d, $J = 8$ Hz, 2H), 6.80 (d, $J = 8$ Hz, 1H), 6.65 (s, 1H), 6.42 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 182.1, 164.1, 161.3, 159.7, 156.4, 115.6, 154.0, 149.6, 145.6, 132.1 (2C), 122.0, 121.8, 118.8, 115.6, 114.7 (2C), 113.8, 108.1, 103.7, 102.5, 98.7. IR (KBr): 3406, 1650, 1610, 1577, 1555, 1516, 1503, 1411, 1371, 1314, 1256, 1228, 1124, 833, 819 cm^{-1}. HRMS (ESI) calcd. 379.0812 for $C_{21}H_{15}O_7$; found 379.0816 $[M^+ + H]$.

5,7-Dihydroxy-2-(3,4,5-trihydroxyphenyl)-8-(4-hydroxyphenyl)-4H-chromen-4-one (**19**)

Protected flavone **13** (0.0.091 g, 0.14 mmol), 1 M BBr_3 (3 ml, 3.00 mmol), DCM (10 ml), 2 h, chromatography on silica (5:1, DCM/MeOH) gave hexahydroxyflavone **19** (0.045 g, 82%). ^{1}H NMR (methanol-d_4) δ 7.23 (d, $J = 9$ Hz 2H), 6.88 (d, $J = 9$ Hz, 2H), 6.71 (s, 2H), 6.48 (s, 1H), 6.32 (s, 1H). ^{13}C NMR δ 184.2, 166.9, 163.0, 161.6, 157.8, 156.1, 147.2 (2C), 139.1, 133.4 (2C), 124.0, 122.7, 116.1 (2C), 110.1, 107.2 (2C), 105.4, 103.6, 99.9. IR (KBr): 3354, 1653, 1610, 1559, 1501, 1457, 1323, 1252, 1033, 819 cm^{-1}. HRMS (ESI) calcd. for $C_{21}H_{15}O_8$ 395.0761; found 395.0780 $[M^+ + H]$.

5,7-Dihydroxy-2-(3,4,5-trihydroxyphenyl)-8-(3,4-dihydroxyphenyl)-4H-chromen-4-one (**20**)

Protected flavone **14** (0.0.088 g, 0.13 mmol), 1 M BBr_3 (3 ml, 3.00 mmol), DCM (10 ml), 2 h, chromatography on silica (5:1, DCM/MeOH) gave heptahydroxyflavone **20** (0.051 g, 96%). ^{1}H NMR (DMSO-d_6) δ 6.84 (d, $J = 8$ Hz, 1H), 6.80 (d, $J = 2$ Hz, 1H), 6.72 (s, 2H), 6.70 (dd, $J = 2$, 8 Hz, 1H), 6.49 (s, 1H), 6.37 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 182.0, 164.5, 161.3, 159.6, 154.1, 146.1 (2C), 144.6, 144.4, 137.8, 122.3, 122.0, 120.8, 118.4, 115.2, 108.4, 106.1 (2C), 103.7, 102.6, 98.6. IR (KBr): 3412, 1650, 1612, 1560, 1510, 1455, 1400, 1327, 1272, 1032, 834 cm^{-1}. HRMS (ESI) calcd. for $C_{21}H_{15}O_9$ 411.0711; found 411.0667 $[M^+ + H]$.

5,7-Dihydroxy-2,8-bis(3,4,5-trihydroxyphenyl)-4H-chromen-4-one (**21**)

Protected flavone **15** (0.0.095 g, 0.14 mmol), 1 M BBr_3 (3 ml, 3.00 mmol), and DCM (10 ml), 2 h, chromatography on silica (5:1, DCM/MeOH) gave octahydroxyflavone **21** (0.053 g, 89%). ^{1}H NMR (DMSO-d_6) δ 6.75 (s, 2H), 6.47 (s, 1H), 6.38 (s, 2H), 6.31 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 182.0, 164.5, 161.4, 159.5, 154.0, 146.1 (2C), 146.1 (2C), 137.6, 132.2, 132.0, 120.8, 109.8 (2C), 108.8, 108.7, 106.2 (2C), 103.6, 98.7. IR (KBr): 3418, 1651, 1604, 1563, 1531, 1451, 1356, 1265, 1198, 1078, 1034, 838, 697 cm^{-1}. HRMS (ESI) calcd. for $C_{21}H_{15}O_{10}$ 427.0660; found 427.0615 $[M^+ + H]$.

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