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Practical and efficient entry to isoflavones by Pd(0)/C-mediated Suzuki–Miyaura reaction. Total synthesis of geranylated isoflavones

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Abstract—A scalable synthesis of isoflavones taking advantage of the Suzuki–Miyaura reaction catalyzed by Pd(0)/C is described. The approach developed has been extended to the total synthesis of 7-*O*-geranylformononetin, griffonianone D, and conrauinone D, which did not display cytotoxicity against human HeLa carcinoma cells. In addition, this study established unambiguously the absolute configuration of natural griffonianone D.

1. Introduction

Isoflavones constitute an important class of natural products that possess a number of interesting biological activities including antioxidative,[1] antitumor,[2] anti-inflammatory,[3] or estrogenic properties.[4] The relationship between the consumption of isoflavonoids and the reduction of cardiovascular disease and cancer has been demonstrated in many reports,[5] increasing the interest for the search and the synthesis of new active compounds. While an impressive number of isoflavones have been isolated to date,[6] we were interested in their less common geranylated congeners (Fig. 1). Several reasons motivated us to focus on this family of products: (1) to date, no total synthesis has been disclosed, (2) we could take advantage of the chemistry previously developed in our laboratory, and (3) no information regarding the anticancer activity has been reported for this class of isoflavones.

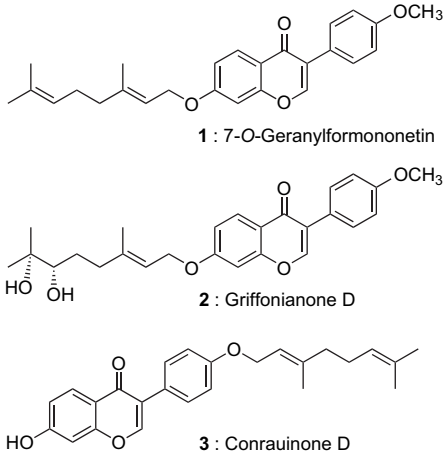
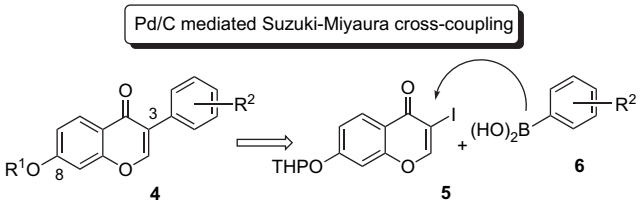


Figure 1. Selected examples of geranylated isoflavones.

In this paper we report the total synthesis of 7-*O*-geranylformononetin **1**, griffonianone D **2**, and conrauinone D **3** using the chemistry of Pd(0)/C.

2. Results and discussion

The approach adopted is directly inspired by our studies on Suzuki–Miyaura cross-coupling using Pd(0)/C, a practical and inexpensive catalyst (Scheme 1). We recently studied the Suzuki–Miyaura cross-coupling of 2-iodocycloenones with boronic acid partners catalyzed both by Pd(0)/C.[7] The



Scheme 1. General retrosynthetic strategy.

Keywords: Pd/C; Suzuki–Miyaura reaction; Isoflavones; 7-*O*-Geranylformononetin; Griffonianone D; Conrauinone D.
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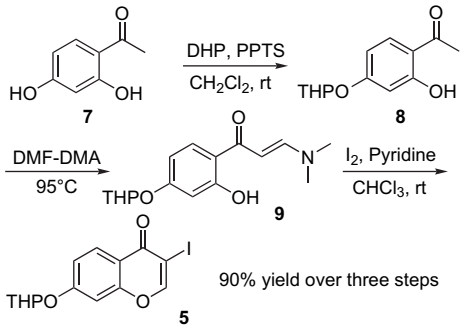
optimum conditions feature inexpensive reagents and solvents with low toxicity rendering the method environmentally benign, very practicable, and scalable.[8] This catalyst system would be particularly appropriate for the preparation of biologically active compounds. The iodochromanone **5** would be an excellent platform for the development of a small library of isoflavones **4**. A number of biologically active natural products such as daidzein,[9] or glycitin[10] possess this structural scaffold with variously substituted aromatic rings at C3 and a substituted (or not) hydroxyl at C8.

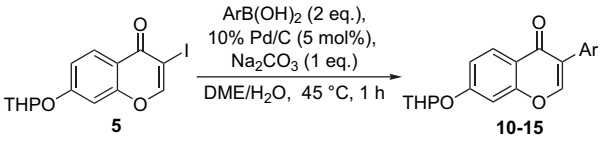
Precursor **5** was prepared in three steps in high yield, starting from commercially available 2,4-dihydroxyacetophenone **7** (Scheme 2).[11] Selective protection of the 4-hydroxyl gave the THP ether **8**, which upon condensation with *N*,*N*-dimethylformamide dimethylacetal provided the 3-(dimethylamino)-2′-hydroxyacrylophenone **9**. The crude **9** was directly treated with I_2 to furnish the corresponding iodochromanone **5**. This optimized sequence, involving three synthetic operations, required only one chromatographic purification to give pure **5** in 90% yield over three steps, on a multigram scale (>11 g).

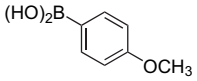
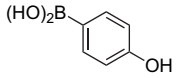
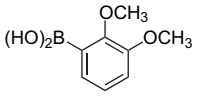
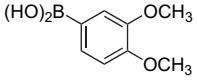
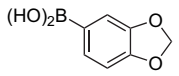
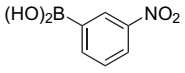


Scheme 2. Preparation of the iodochromanone **5**.

Having appreciable quantities of **5** to hand, we focused on the preparation of a small library by solution-phase Suzuki–Miyaura[12] reaction using Pd/C as heterogenous catalyst.[13] Six parallel reactions were conducted on a 1 mmol-scale (with respect to **5**) for only 1 h at 45 °C with Pd(0)/C as a catalyst under ligand free conditions. Excellent yields of cross-coupled products were obtained as indicated in Table 1. We particularly focused on the introduction of electron-rich boronic acids since natural isoflavones are often poly-oxygenated. This did not constitute a problem since the method worked equally well with electron-poor boronic acid (entry 6). These heterogenous conditions compete favorably with usual homogenous conditions. Indeed, in a similar approach, Westwell[2b] described Suzuki–Miyaura reactions of iodochromanones under homogenous conditions ($Pd(PPh_3)_4$) in refluxing benzene for 20 h. Although we did not recycle the catalyst in this study, we previously showed that it is possible to reuse it at least five times with good catalytic efficiency.[7] It is important to note that the conditions developed for the Suzuki–Miyaura reaction using Pd(0)/C as catalyst could be easily scaled-up since no drop in yields of cross-coupled products was observed by working on multigram quantity of **5**. Moreover, the heterogenous nature of the catalyst renders the method particularly well suited for large-scale applications.

Table 1. Synthesis of isoflavones by Pd(0)/C-mediated Suzuki–Miyaura reaction



Entry	$ArB(OH)_2$	Product	Yield (%)[a]
1		**10**	73
2		**11**	86
3		**12**	75
4		**13**	89
5		**14**	94
6		**15**	90

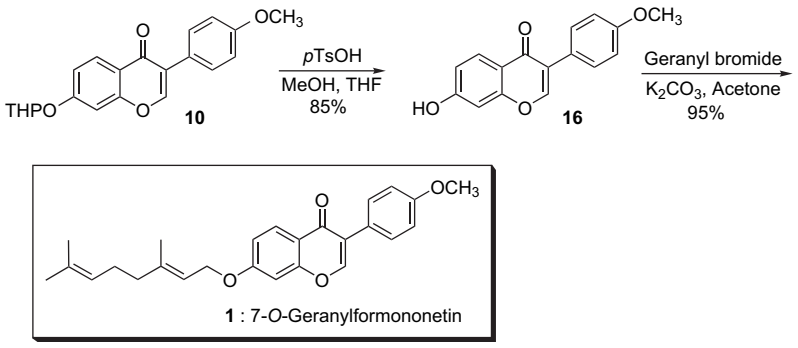
[a] Yields are for isolated products.

We then turned our attention toward the preparation of geranylated isoflavones **1**–**3** using **10** and **11** as synthetic intermediates. Several geranylated isoflavones have been isolated from *Millettia* species[14] that are plants essentially found in Africa. Many species of the genus *Millettia* exhibit interesting biological activities. For instance, *Millettia griffoniana*, found in the central part of Cameroon, is used in traditional medicine as an oral treatment for boils. It should be noted that isoflavones **1**–**3** have never been synthesized and the configuration of griffonianone D **2** remained unknown at the time we started our work.

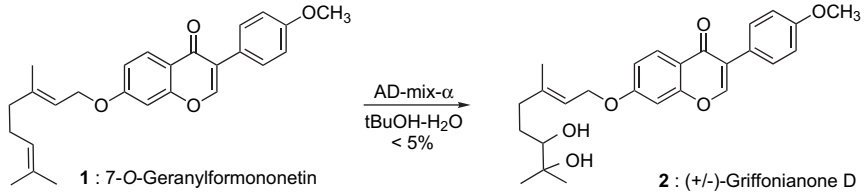
Starting from isoflavone **10**, cleavage of the THP protecting group under acidic conditions followed by an etherification of the liberated phenol with geranyl bromide furnished 7-*O*-geranylformononetin **1**[14a] in good yield (six steps from 2,4-dihydroxyacetophenone **7**, 53% overall) (Scheme 3).

Then, we turned our attention toward the preparation of griffonianone D **2** from 7-*O*-geranylformononetin **1** by a selective Sharpless asymmetric dihydroxylation (SAD). Unfortunately, we obtained griffonianone D **2** with a very low yield and only under its racemic form. This result was attributed to the very low solubility of both **1** and **2** in the solvent system used in this study. We obtained a complex mixture of compounds where starting material **1** was the major product recovered (Scheme 4).

Considering that introduction of the chirality on **1** would be problematic, we reasoned that the chiral diol could be introduced on the geranyl backbone prior to its coupling to the chromanone core **10** (Scheme 5). Following this pathway, geraniol **17** was acetylated and selectively dihydroxylated using the SAD conditions to furnish (*S*)-**18** with good yield

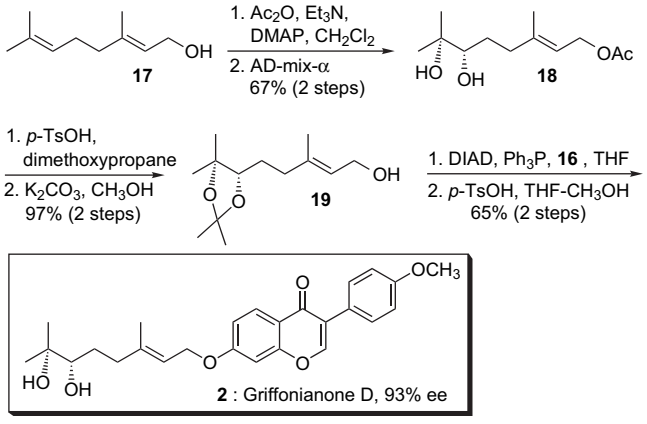


Scheme 3. Synthesis of 7-*O*-geranylformononetin.



Scheme 4. Synthesis of griffonianone D.

over two steps (67%).[15,16] After two protective group manipulations, alcohol **19** was reacted with isoflavone **16** under Mitsunobu[17] conditions to give the corresponding cross-coupled product. Finally, cleavage of the acetonide furnished griffonianone D **2**[14e] in 93% enantiomeric excess whose NMR data perfectly match those reported for the natural product (seven steps, 36% overall). In addition, the value and sign of the optical rotation were equally in good agreement. Consequently the configuration of natural griffonianone D **2** was unambiguously assigned as the (*S*)-isomer.



Scheme 5. Synthesis of griffonianone D.

On the other hand, conrauinone D **3**[14c] was easily accessed from isoflavone **11** by a two-step sequence. The free phenol of the aryl group attached at C3 was geranylated and the THP protecting group cleaved to afford conrauinone D **3** (six steps from 2,4-dihydroxyacetophenone **7**, 55% overall) (Scheme 6).

As part of a program devoted to the discovery of natural products with anticancer activity, we evaluated synthetic isoflavones **1**–**3** whose cytotoxicities were unknown. Unfortunately, 7-*O*-geranylformononetin **1**, griffonianone D **2**, and conrauinone D **3** did not exhibit in vitro cytotoxicity against human HeLa carcinoma cells.

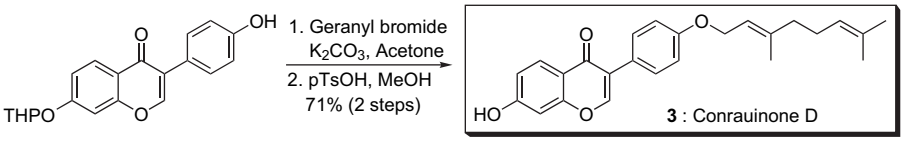
3. Conclusion

In summary, we have described the first total synthesis of 7-*O*-geranylformononetin **1**, griffonianone D **2**, and conrauinone D **3**. The synthetic route developed appears to be extremely efficient and practical. Notably, we successfully applied the Pd/C-mediated Suzuki–Miyaura cross-coupling reaction to the construction of the isoflavone core. Although these isoflavones did not induce apoptosis of tumoral cells, the chemistry described herein opens a way for the synthesis of either natural or non-natural isoflavones with biological activities.

4. Experimental

4.1. General procedures

Chemical shifts from proton and carbon NMR spectra are reported in parts per million relative to the $CDCl_3$ peak at



Scheme 6. Synthesis of conrauinone D.

7.26 ppm (^{1}H) or 77.0 ppm (^{13}C), DMSO at 2.50 ppm (^{1}H) or 39.52 ppm (^{13}C). Infrared (IR) spectra were recorded as neat samples on NaCl plates or with KBr pellets. Yields refer to isolated material determined to be pure by NMR spectroscopy and thin layer chromatography (TLC), unless specified otherwise in the text. Chiral HPLC was performed with a Chiralpak AD-H column, 0.46×25 cm, flow rate 1 mL/min.

4.2. Chromanone (5)

A solution of DHP (9 mL, 98.7 mmol) in CH_2Cl_2 (54 mL) was added dropwise to a solution of acetophenone (5 g, 32.8 mmol) and PPTS (296 mg) at rt. The resulting mixture was stirred for 4 h at rt, then washed with saturated aqueous $NaHCO_3$ solution, and extracted with CH_2Cl_2 (3×). The collected organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude was diluted with DMF/DMA (6.54 mL, 49.3 mmol) and the resulting mixture was stirred at 95 °C for 3 h. After evaporation of volatiles, the obtained solid was dissolved in $CHCl_3$ (53 mL) and successively treated with pyridine (2.66 mL, 33 mmol) and I_2 (16.7 g, 66 mmol). The resulting mixture was stirred at rt for 12 h. The reaction was hydrolyzed with saturated aqueous $Na_2S_2O_3$ solution and stirred for 30 min at rt. The aqueous phase was extracted with CH_2Cl_2 (3×). The collected organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (20% EtOAc/petroleum ether then 40% EtOAc/petroleum ether) gave **5** (11 g, 90% yield) as a colorless solid. Mp 131–133 °C. IR (KBr) ν 1614, 1649, 2930, 2952, 3059 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.57–1.80 (m, 3H), 1.87–2.07 (m, 3H), 3.60–3.68 (m, 1H), 3.77–3.87 (m, 1H), 5.53 (m, 1H), 7.07–7.11 (m, 2H), 8.13 (d, 1H, J=9.5 Hz), 8.21 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.2, 24.9, 29.9, 62.0, 86.9, 96.5, 103.1, 116.1, 116.4, 127.8, 157.3, 157.6, 161.7, 172.6. HRMS (LSIMS) calcd for $C_{14}H_{13}O_4I$ (M^+) 372.9937, found 372.9941.

4.3. General procedure for the preparation of isoflavones

General procedure: to a solution of iodoenone (372 mg, 1 mmol) in DME (3 mL) and H_2O (3 mL) were added Na_2CO_3 (318 mg, 3 mmol), $ArB(OH)_2$ (1.2 mmol), and Pd/C (53 mg, 5 mol %). The resulting mixture was stirred for 1 h at 45 °C and then filtered. The catalyst was washed with H_2O (3 mL) and CH_2Cl_2 (5 mL). The aqueous phase was extracted twice with CH_2Cl_2. The collected organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude was purified by flash chromatography to give the corresponding cross-coupled product.

4.3.1. Isoflavone (10). Mp 174–175 °C. IR (KBr) ν 1608, 1636, 2928, 3059 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.59–1.80 (m, 3H), 1.89–2.06 (m, 3H), 3.62–3.71 (m, 1H), 3.81–3.91 (m, 1H), 3.83 (s, 3H), 5.55 (m, 1H), 6.96 (d, 2H, J=8.8 Hz), 7.08 (d, 2H, J=6.7 Hz), 7.49 (dd, 2H, J=2.2, 6.7 Hz), 7.91 (s, 1H), 8.20 (d, 1H, J=9.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.3, 25.0, 30.0, 55.3, 62.0, 96.4, 103.2, 113.9, 115.7, 118.9, 124.3, 124.7, 127.6, 130.1, 152.1, 157.7, 159.5, 161.3, 175.9. HRMS (LSIMS) calcd for $C_{21}H_{21}O_5$ (M+H) 353.1389, found 353.1390.

4.3.2. Isoflavone (11). Mp 272–275 °C. IR (KBr) ν 1610, 1625, 2952, 3410 cm^{-1}. ^{1}H NMR (DMSO, 250 MHz) δ 1.59–1.89 (m, 6H), 3.59–3.77 (m, 2H), 5.71 (m, 1H), 6.82 (d, 2H, J=7.6 Hz), 7.13–7.20 (m, 2H), 7.40 (d, 2H, J=7.6 Hz), 8.05 (d, 1H, J=8.9 Hz), 8.36 (s, 1H), 9.53 (s, 1H). ^{13}C NMR (DMSO, 75 MHz) δ 18.3, 24.5, 29.4, 61.7, 95.9, 103.4, 115.0, 115.6, 118.2, 122.3, 123.6, 126.9, 130.0, 153.2, 157.0, 157.2, 160.7, 174.7. HRMS (LSIMS) calcd for $C_{20}H_{18}O_5$ (M^+) 338.1154, found 338.1153.

4.3.3. Isoflavone (12). Mp 151–153 °C. IR (KBr) ν 1609, 1627, 1649, 2950 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.59–1.80 (m, 3H), 1.88–2.06 (m, 3H), 3.62–3.69 (m, 1H), 3.74 (s, 3H), 3.80–3.89 (m, 1H), 3.89 (s, 3H), 5.55 (m, 1H), 6.92–6.98 (m, 2H), 7.07–7.13 (m, 3H), 7.94 (s, 1H), 7.91 (s, 1H), 8.20 (d, 1H, J=8.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.3, 24.9, 29.9, 55.8, 60.6, 61.9, 96.4, 103.3, 112.3, 115.6, 119.0, 121.8, 123.5, 123.7, 126.1, 127.5, 147.3, 152.8, 154.0, 157.7, 161.2, 175.7. HRMS (LSIMS) calcd for $C_{22}H_{22}O_6Na$ (M+Na) 405.1314, found 405.1324.

4.3.4. Isoflavone (13). IR (KBr) ν 1623, 2946, 3015, 3075 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.57–1.76 (m, 3H), 1.86–2.04 (m, 3H), 3.59–3.64 (m, 1H), 3.65–3.90 (m, 1H), 3.88 (s, 3H), 3.90 (s, 3H), 5.52 (m, 1H), 6.89 (d, 2H, J=8.6 Hz), 7.00–7.08 (m, 3H), 7.20 (m, 1H), 7.92 (s, 1H), 8.18 (d, 1H, J=9.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.2, 24.9, 29.9, 55.8, 55.8, 61.9, 96.4, 103.2, 111.0, 112.4, 115.7, 118.8, 120.9, 124.6, 124.6, 127.4, 148.6, 148.9, 152.3, 157.5, 161.3, 175.8. HRMS (EI) calcd for $C_{22}H_{23}O_6$ (M+H) 383.1495, found 383.1496.

4.3.5. Isoflavone (14). Mp 298–300 °C. IR (KBr) ν 1636, 2951 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.59–1.75 (m, 3H), 1.89–2.06 (m, 3H), 3.63–3.67 (m, 1H), 3.80–3.90 (m, 1H), 5.56 (m, 1H), 6.86 (d, 1H, J=8.3 Hz), 6.97 (dd, 1H, J=1.5, 7.9 Hz), 7.06–7.10 (m, 3H), 7.91 (s, 1H), 8.20 (d, 1H, J=9.8 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.3, 25.0, 30.0, 62.0, 96.5, 101.1, 103.3, 108.3, 109.8, 115.8, 118.9, 122.4, 124.9, 125.7, 127.6, 147.6, 147.7, 152.3, 157.7, 161.4, 175.7. HRMS (LSIMS) calcd for $C_{21}H_{19}O_6$ (M+H) 367.1182, found 367.1176.

4.3.6. Isoflavone (15). Mp 166–168 °C. IR (KBr) ν 1602, 1626, 1648, 2953, 3075 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.30–1.77 (m, 3H), 1.89–2.06 (m, 3H), 3.64–3.69 (m, 1H), 3.80–3.90 (m, 1H), 5.57 (m, 1H), 7.09–7.14 (m, 2H), 7.60 (t, 1H, J=8.2 Hz), 7.96 (d, 1H, J=7.9 Hz), 8.06 (s, 1H), 8.18–8.24 (m, 2H), 8.42 (t, 1H, J=2.2 Hz). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 18.3, 24.9, 29.9, 62.0, 96.5, 103.4, 116.2, 118.6, 122.9, 123.2, 123.6, 123.6, 127.6, 129.3, 135.2, 148.3, 153.3, 157.7, 161.8, 175.0. HRMS (LSIMS) calcd for $C_{20}H_{17}NNaO_6$ (M+Na) 390.0954, found 390.0961.

4.3.7. Isoflavone (16). To a solution of **10** (585 mg, 1.66 mmol) in MeOH (30 mL) and THF (30 mL) was added *p*TsOH (32 mg, 0.166 mmol) at rt. The resulting mixture was stirred at 60 °C for 1 h, then Et_3N (0.3 mL, 1.66 mmol) was added, and volatiles were removed under reduced pressure. Purification by flash chromatography (40% EtOAc/petroleum ether then 5% MeOH/EtOAc) provided **16** (379 mg, 85%) as a colorless solid. Mp 261–263 °C [lit.[18]

264–267 °C]. IR (KBr) ν 1609, 1638, 2930, 3132 cm^{-1}. ^1H NMR (DMSO, 250 MHz) δ 3.80 (s, 3H), 6.88–7.01 (m, 4H), 7.49–7.54 (m, 2H), 7.98 (d, 1H, J=8.5 Hz), 8.34 (s, 1H), 10.8 (br s, 1H). ^{13}C NMR (DMSO, 62.5 MHz) δ 55.1, 102.1, 113.6, 115.1, 116.6, 123.1, 124.2, 127.3, 130.0, 153.1, 157.4, 158.9, 162.6, 174.6. HRMS (LSIMS) calcd for $C_{16}H_{12}O_4$ (M^+) 268.0736, found 268.0733.

4.3.8. 7-*O*-Geranylformononetin (1).[14a] To a solution of **16** (129 mg, 0.48 mmol) and K_2CO_3 (99 mg, 0.72 mmol) in acetone (10 mL) was added dropwise geranyl bromide (0.14 mL, 0.72 mmol) at rt. The resulting mixture was refluxed for 2 h and then hydrolyzed with H_2O (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3×). The collected organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography (15% EtOAc/petroleum ether) furnished **1** (172 mg, 95%) as a colorless solid. Mp 113–114 °C. IR (KBr) ν 1630, 2967, 3052 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 1.61 (s, 3H), 1.67 (s, 3H), 1.77 (s, 3H), 2.11 (br s, 4H), 3.84 (s, 3H), 4.64 (d, 2H, J=6.7 Hz), 5.09 (br s, 1H), 5.49 (br t, 1H, J=6.6 Hz), 6.85 (d, 1H, J=2.1 Hz), 6.95–7.01 (m, 3H), 6.95–7.01 (m, 3H), 7.50 (d, 2H, J=8.6 Hz), 7.91 (s, 1H), 8.20 (d, 1H, J=8.6 Hz). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 55.1, 102.1, 113.6, 115.1, 116.6, 123.1, 124.2, 127.3, 130.0, 153.1, 157.4, 158.9, 162.6, 174.6.

4.3.9. Geranyl acetate.[19] To a solution of geraniol (2 g, 12.99 mmol) in CH_2Cl_2 (130 mL) was added, at rt, Et_3N (5.42 mL, 38.96 mmol), Ac_2O (3.07 mL, 32.47 mmol), and DMAP (cat.). The resulting mixture was stirred 8 h at rt and then washed with water. Purification by flash chromatography (5% EtOAc/petroleum ether) gave the title compound (2.44 g, 96%) as a colorless oil. IR (KBr) ν 1670, 1742, 2925, 2968 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.58 (s, 3H), 1.66 (s, 3H), 1.68 (s, 3H), 2.03–2.09 (m, 4H), 2.03 (s, 3H), 4.57 (d, 2H, J=7.1 Hz), 5.06 (m, 1H), 5.32 (br t, 1H, J=7.1 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.4, 17.6, 21.0, 25.6, 26.2, 39.5, 61.3, 118.2, 123.7, 131.8, 142.2, 171.0.

4.3.10. (*S*,*E*)-6,7-Dihydroxy-3,7-dimethyloct-2-enyl acetate (18). To a stirred solution of AD-mix α (3.60 g) in a mixture of *t*-BuOH (13 mL) and H_2O (13 mL) was added successively $CH_3SO_2NH_2$ (2.55 mmol) and geranyl acetate (500 mg, 2.55 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 48 h and then quenched with solid Na_2SO_3. After 30 min of stirring at rt, the reaction was diluted with CH_2Cl_2 and the aqueous phase was extracted with CH_2Cl_2 (3×). The collected organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography (70% EtOAc/petroleum ether) gave **18** (410 mg, 70%) as a colorless oil. IR (KBr) ν 1668, 1731, 2974, 3426 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.15 (s, 3H), 1.20 (s, 3H), 1.37–1.50 (m, 1H), 1.55–1.66 (m, 1H), 1.71 (s, 3H), 2.04 (s, 3H), 2.04–2.15 (m, 2H), 2.27–2.35 (m, 2H), 3.33 (dm, 1H, J=10.5 Hz), 4.58 (d, 2H, J=6.8 Hz), 5.38 (br t, 1H, J=7.1 Hz). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 16.4, 21.0, 23.1, 26.4, 29.4, 36.5, 61.3, 73.0, 78.0, 118.6, 142.0, 171.3. MS (CI/NH_3) m/z 248 (M+NH_4), 188 (M−CH_3CO).

4.3.11. (*E*)-3-Methyl-5-((*S*)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl)pent-2-en-1-ol (19). To a solution of **18** (250 mg, 1.09 mmol) in 2,2-dimethoxypropane (20 mL) was added *p*TsOH (72 mg, 0.38 mmol) at rt. After 2 h of stirring at rt, the reaction was quenched with saturated $NaHCO_3$ aqueous solution and extracted with CH_2Cl_2 (3×). The collected organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The oily residue was dissolved in a mixture of CH_3OH (9.3 mL)/H_2O (0.7 mL) and treated with K_2CO_3 (165 mg, 1.19 mmol). After 2 h of stirring, solvents were removed under reduced pressure and the residue was diluted with EtOAc. The organic layer was washed with brine (1×), dried ($MgSO_4$), and concentrated in vacuo to give **19** (240 mg, 97%), which was pure enough for the next step. IR (KBr) ν 1669, 2860, 2935, 2982, 3417 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 1.09 (s, 3H), 1.24 (s, 3H), 1.32 (s, 3H), 1.41 (s, 3H), 1.41–1.69 (m, 2H), 1.69 (s, 3H), 2.00–2.12 (m, 1H), 2.20–2.32 (m, 1H), 3.66 (dd, 1H, J=3.4, 9.6 Hz), 4.16 (d, 2H, J=6.7 Hz), 5.45 (br t, 1H, J=6.7 Hz). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 16.4, 22.9, 26.0, 26.8, 27.5, 28.5, 36.6, 59.3, 80.1, 82.9, 106.6, 123.6, 139.1. HRMS (LSIMS) calcd for $C_{13}H_{24}O_3$ (M^+) 228.1725, found 228.1727.

4.3.12. Protected griffonianone D. To a solution of alcohol **19** (53 mg, 0.233 mmol) and isoflavone **16** (52 mg, 0.194 mmol) in THF (2 mL) was added at rt Ph_3P (102 mg, 0.388 mmol) and DIAD (78 μL, 0.388 mmol). The resulting mixture was stirred for 6 h at 50 °C in a sealed tube. Solvents were removed under reduced pressure and the crude was purified by flash chromatography (20% EtOAc/petroleum ether) to give the title compound contaminated by DIAD residues. ^1H NMR ($CDCl_3$, 250 MHz) δ 1.10 (s, 3H), 1.24 (s, 3H), 1.31 (s, 3H), 1.41 (s, 3H), 1.46–1.76 (m, 2H), 1.80 (s, 3H), 2.09–2.21 (m, 1H), 2.28–2.40 (m, 1H), 3.66 (dd, 1H, J=3.4, 9.2 Hz), 3.83 (s, 3H), 4.64 (d, 2H, J=6.7 Hz), 5.54 (br t, 1H, J=6.4 Hz), 6.84 (d, 1H, J=2.5 Hz), 6.94–7.00 (m, 3H), 7.49 (d, 2H, J=8.6 Hz), 7.91 (s, 1H), 8.19 (d, 1H, J=9.2 Hz).

4.3.13. Griffonianone D (2).[14e] A solution of the impure protected griffonianone D (~0.233 mmol) in MeOH (6 mL) and H_2O (0.2 mL) was treated with *p*TsOH (22 mg) at rt and the mixture was stirred for 5 h at 50 °C. The solution was neutralized with Et_3N, concentrated under reduced pressure, and purified by flash chromatography (60% EtOAc/petroleum ether) to give griffonianone D **2** (66 mg, 65% yield, two steps). ee: 92%, determined by chiral HPLC (hexane/*i*-PrOH=70/30, 32.2 min for (*R*)-griffonianone and 37.3 min for (*S*)-griffonianone). $[\alpha]_D^{22}$ −11.1 (*c* 0.45, $CHCl_3$) [lit.[14e] $[\alpha]_D^{23}$ −7.97 (*c* 0.042, $CHCl_3$)]. Mp 128–130 °C [lit.[12e] 128–129 °C]. IR (KBr) ν 1609, 1636, 2926, 3375 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 1.17 (s, 3H), 1.21 (s, 3H), 1.39–1.71 (m, 2H), 1.65 (br s, 1H), 1.79 (s, 3H), 2.11–2.17 (m, 1H), 2.20–2.45 (m, 1H), 2.35 (br s, 1H), 3.36 (d, 1H, J=10.4 Hz), 3.84 (s, 3H), 4.64 (d, 2H, J=6.4 Hz), 5.55 (br t, 1H, J=6.7 Hz), 6.85 (d, 1H, J=2.5 Hz), 6.95–7.01 (m, 3H), 7.49 (d, 2H, J=8.9 Hz), 7.91 (s, 1H), 8.19 (d, 1H, J=8.8 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.8, 23.3, 26.5, 29.4, 36.5, 55.3, 65.4, 73.0, 78.0, 100.9, 113.9, 115.0, 118.3, 118.8, 124.2, 124.8, 127.7, 130.1, 142.3, 152.0, 157.9, 159.5, 163.2, 175.9.

4.3.14. Protected conrauinone D. To a solution of **11** (64 mg, 0.19 mmol) and K_2CO_3 (39 mg, 0.28 mmol) in

acetone (3.5 mL) was added dropwise geranyl bromide (56 μL, 0.28 mmol) at rt. The resulting mixture was refluxed for 2 h and then hydrolyzed with H_2O (3 mL). The aqueous phase was extracted with CH_2Cl_2 (3×). The collected organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography (10% EtOAc/petroleum ether) furnished the title compound (81 mg, 90%) as a colorless solid. Mp 130–133 °C. IR (KBr) ν 1637, 2842, 2932, 3052 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 1.61 (s, 3H), 1.68 (s, 3H), 1.75 (s, 3H), 1.61–1.74 (m, 3H), 1.89–2.13 (m, 7H), 3.63–3.67 (m, 1H), 3.81–3.91 (m, 1H), 5.10 (br s, 1H), 5.51 (br t, 1H, J=6.1 Hz), 5.55 (br s, 1H), 6.98 (d, 2H, J=8.6 Hz), 7.06–7.10 (m, 2H), 7.49 (d, 1H, J=8.6 Hz), 7.92 (s, 1H), 8.21 (s, 1H, J=9.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.7, 17.7, 18.3, 25.0, 25.7, 26.3, 30.0, 39.5, 62.0, 64.9, 96.5, 103.2, 114.7, 115.7, 118.9, 119.4, 123.8, 124.1, 124.8, 127.6, 130.0, 131.8, 141.3, 152.1, 157.1, 158.9, 161.3, 175.9. HRMS (LSIMS) calcd for $C_{30}H_{34}O_5$ (M^+) 474.2406, found 474.2403.

4.3.15. Conrauinone D (3).[14c] To a solution of protected conrauinone D (72 mg, 0.15 mmol) in a mixture of THF (3 mL) and MeOH (3 mL) was added *p*TsOH (3 mg, 0.015 mmol). The resulting mixture was stirred for 4 h at 60 °C. *p*TsOH was neutralized with Et_3N, solvents were removed under reduced pressure, and the crude was purified by flash chromatography (70% EtOAc/petroleum ether) to give conrauinone D **3** (46 mg, 79%) as a white solid. Mp 186–188 °C [lit.[14c] 188–190 °C]. IR (KBr) ν 1618, 2964, 3232 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.61 (s, 3H), 1.69 (s, 3H), 1.74 (s, 3H), 2.10 (m, 4H), 4.56 (d, 2H, J=6.8 Hz), 5.10 (m, 1H), 5.50 (br t, 1H, J=6.0 Hz), 6.34 (m, 1H), 6.86 (d, 1H, J=2.3 Hz), 6.92 (dd, 1H, J=2.3, 9.1 Hz), 6.98 (dm, 2H, J=6.8 Hz), 7.48 (d, 2H, J=9.0 Hz), 7.92 (s, 1H), 8.19 (d, 1H, J=8.6 Hz). ^1H NMR (DMSO, 250 MHz) δ 1.57 (s, 3H), 1.63 (s, 3H), 1.70 (s, 3H), 2.07 (m, 4H), 4.57 (d, 2H, J=6.4 Hz), 5.07 (m, 1H), 5.44 (br t, 1H, J=6.4 Hz), 6.87 (d, 1H, J=2.2 Hz), 6.92 (d, 1H, J=2.2), 6.97 (d, 2H, J=8.9 Hz), 7.49 (d, 2H, J=8.5 Hz), 7.97 (d, 1H, J=8.9 Hz), 8.33 (s, 1H). ^{13}C NMR (DMSO, 62.5 MHz) δ 16.4, 17.6, 25.5, 25.8, 38.9, 64.4, 102.1, 114.3, 115.2, 116.6, 119.7, 123.2, 123.8, 124.1, 127.3, 130.0, 131.0, 140.2, 153.1, 157.4, 158.1, 162.6, 174.6.

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