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A step-economical divergent approach to isoflavenes based on Suzuki–Miyaura cross coupling of a 3-boryl-2*H*-chromene with aryl bromides: Application to total synthesis of isoflavonoid natural products

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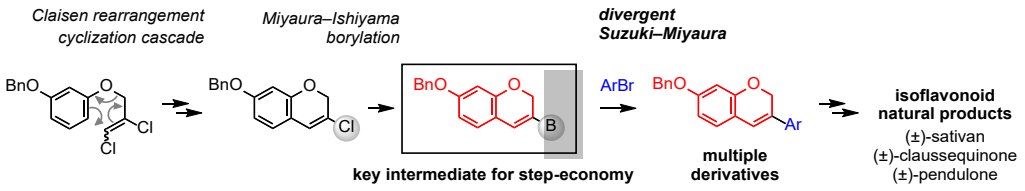
ABSTRACT

We present a step-economical divergent synthetic approach for isoflavene derivatives using the Suzuki–Miyaura cross coupling of a 3-boryl-2*H*-chromene and three aryl bromides. 3-boryl-2*H*-chromene, which is not a well-explored species, was prepared via Miyaura–Ishiyama borylation of a 3-chloro-2*H*-chromene obtained through a Claisen rearrangement cyclization cascade reaction. Further conversion of the cross coupling products, three isoflavene derivatives, afforded three isoflavonoid natural products with one or two additional reaction steps.

Graphical Abstract



Keywords: isoflavonoid, total synthesis, Claisen rearrangement, cascade reaction, Suzuki–Miyaura cross coupling

Introduction

Isoflavonoids are aromatic compounds that typically have a 3-arylchromane core structure consisting of a fused aromatic A ring and oxane C ring, with another aromatic B ring at its C3 position (Sajid, Stone and Kaur **2021**). Along with their structural diversity on their A–C rings, isoflavonoids have various bioactivities, such as antioxidant, anticancer, and antibacterial activities (Al-Maharik **2019**). Due to their potential usefulness, many isoflavonoid syntheses have been developed over the years (Donnelly and Boland **1995**; Boland and Donnelly **1998**).

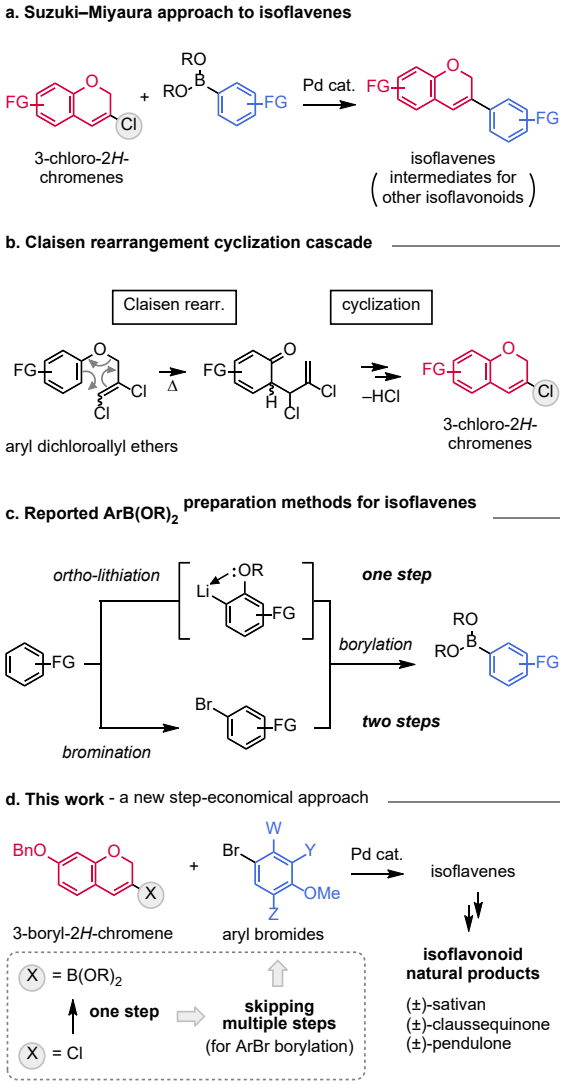
Among them, we have been working on Suzuki–Miyaura cross coupling-based syntheses of isoflavenes and their applications in supplying isoflavonoid natural products (**Scheme 1a**) (Kohno *et al.* **2014**; Kang *et al.* **2022**; Uchida, Kang and Takikawa **2023**). Our syntheses feature 3-chloro-2*H*-chromenes as the cross-coupling electrophiles, which serve as isoflavonoid AC-ring moieties. These chromenes are easily preparable from their corresponding phenols by Williamson etherification and Claisen rearrangement cyclization cascade (CRCC) reaction (**Scheme 1b**). On the other hand, their B-ring arylboronic acid partners are synthesized from their corresponding arenes through several transformation combinations. While some arylboronic acids can be prepared in one step through alkoxy-directed *ortho*-lithiation (**Scheme 1c** top) (Kang *et al.* **2022**), the others require two-step reactions of bromination and borylation (**Scheme 1c** bottom) (Koo *et al.* **2013**; Kohno *et al.* **2014**; Kang *et al.* **2022**; Uchida, Kang and Takikawa **2023**). Although these two methods are regioselectively complementary to each other, the latter takes one more step than the former and occasionally requires protocol/process optimization for the second borylation steps.

To realize a more step-economical synthesis, we planned on inverting the cross-coupling nucleophile and electrophiles; this can be achieved by the cross coupling a 3-boryl-2*H*-chromene and aryl bromides instead of our previously used 3-chloro-2*H*-chromene and arylboronic acids, as AC-ring and B-ring units, respectively (**Scheme 1d**). This method requires one additional step for the chlorine–boron exchange of a 3-chloro-2*H*-chromene to prepare a 3-boryl-2*H*-chromene. However, because aryl bromides can be used directly in aimed cross coupling, this 3-boryl-2*H*-chromene-based strategy is able to skip each borylation step.

Herein, we describe a new synthetic method for isoflavene derivatives featuring the divergent Suzuki–Miyaura cross coupling of a 3-boryl-2*H*-chromene and three aryl bromides. The 3-boryl-2*H*-chromene, which has rarely been referred to in literature (Anderson *et al.* **2004**; Jang *et al.* **2011**), was prepared by Miyaura–Ishiyama borylation of a known 3-chloro-2*H*-chromene obtained through CRCC (Kohno *et al.* **2014**). The Suzuki–Miyaura

53 products (the three isoflavene derivatives) were then converted to three isoflavonoid natural products (one isoflavan
54 and two isoflavanquinones) in one or two steps. This report provides rare insight into the preparation, reaction, and
55 application of 3-boryl-2*H*-chromene. In addition, the utility of this new approach is highlighted in the shortest-step
56 total synthesis of (±)-sativan among the reported thallium-free methods (Takashima, Kaneko and Kobayashi **2010**; Ji
57 *et al.* **2013**; Yalamanchili *et al.* **2018**; Zhang *et al.* **2018**; Jiang *et al.* **2020**), the first thallium-free synthesis of (±)-
58 calussequinone (Farkas *et al.* **1974**), and the first synthesis of (±)-pendulone.

59



60

61 **Scheme 1.** (a) Reported Suzuki–Miyaura cross coupling-based synthetic methods for isoflavenes; (b) CRCC of aryl
62 2,3-dichloroallyl ethers for 3-chloro-2*H*-chromenes; (c) reported synthetic methods of arylboronic acid derivatives
63 for isoflavene synthesis; (d) a new step-economical approach for isoflavenes with 3-boryl-2*H*-chromene as the
64 substrate

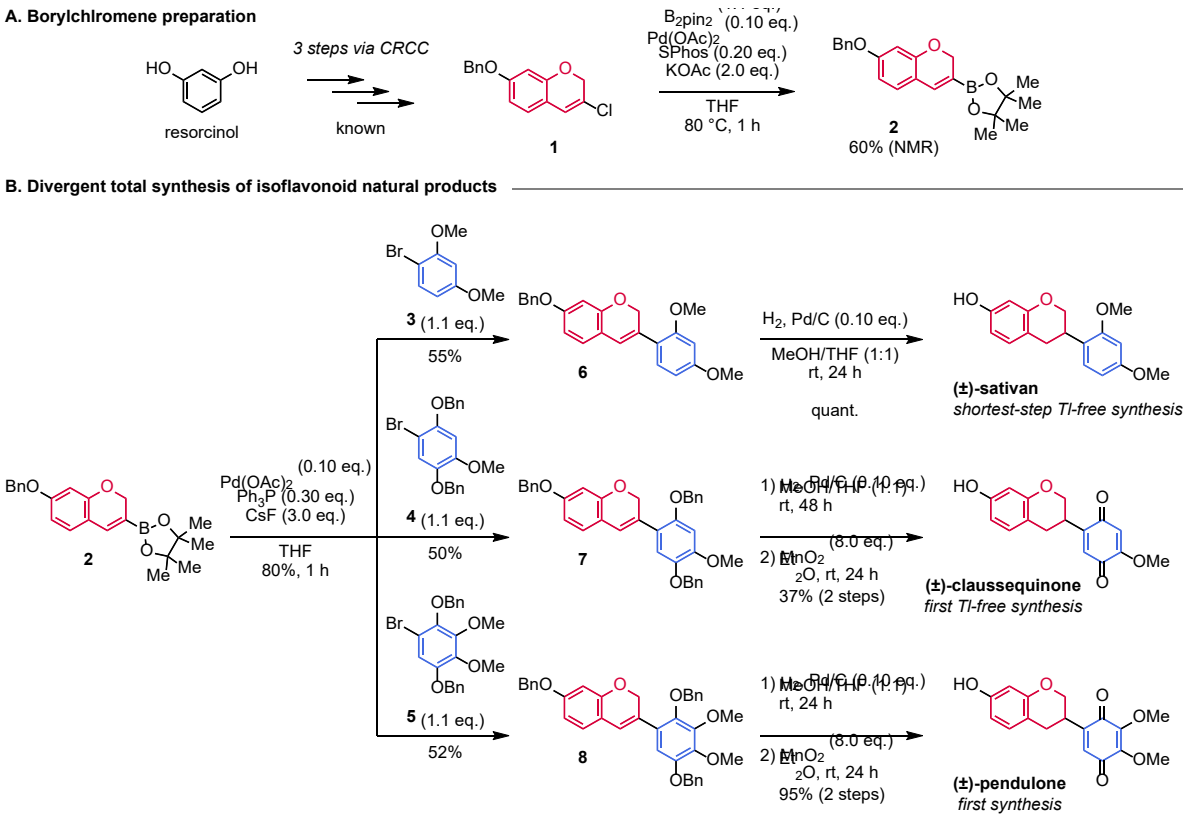
Results and discussion

We began the present study by synthesizing a 3-boryl-2*H*-chromene (**Scheme 2a**). As a precursor to 3-boryl-2*H*-chromene, we chose known 7-benzyloxy-3-chloro-2*H*-chromene **1** (Kohno *et al.* **2014**). This chloro-2*H*-chromene **1** was subjected to a typical Miyaura–Ishiyama borylation condition catalyzed by a Pd(0)/SPhos complex for poorly reactive aryl/alkenyl chlorides (Billingsley, Barder and Buchwald **2007**). The yield of the borylation product, 7-benzyloxy-3-(pinacolato)boryl-2*H*-chromene **2**, was estimated to be 60% by its crude ^{1}H nuclear magnetic resonance spectra wherein triphenylmethane was used as an internal standard (see **Experimental** for details). We failed to isolate **2** using a silica gel column chromatography, which is probably due to its instability in this system. On the other hand, 3-borylchromene **2** was successfully isolated through recrystallization from Et_2O/Hex (1/3) in 45% recrystallization yield (27% overall from **1**). To avoid this partial loss of **2** through this recrystallization process, crude **2** was used for the next step without purification.

With key 3-boryl-2*H*-chromene **2** in hand, we next focused on the aimed divergent Suzuki–Miyaura cross coupling of **2** with multiple aryl bromides (**Scheme 2b**). We selected the following three aryl bromides as cross-coupling partners: commercially available 2,4-dimethoxyphenyl bromide **3**, and known aryl bromides **4** and **5**. It is noteworthy that, in our previous study on the abovementioned divergent isoflavonoid synthesis (Uchida, Kang and Takikawa 2023), **4** and **5** were used as precursors for their corresponding arylboronic acids. The divergent Suzuki−Miyaura cross coupling reactions of **2** and **3**–**5** were successfully carried out under standard conditions to afford isoflavene derivatives **6**, **7**, and **8** in 55%, 50%, and 52% yields, respectively. As derivatives **6**–**8** were successfully obtained, we next focused on converting them into the isoflavonoid natural products of (±)-sativan, (±)-claussequinone, and (±)-pendulone.

These natural products were first isolated from leguminous plants, namely *Medicago sativa* (alfalfa), *Cyclolobium clausseni* (native to South America), and *Millettia pendula* (native to Southeast Asia), respectively (Ingham and Millar **1973**; Bonde, Millar and Ingham **1973**; Braga de Oliveira *et al.* **1971**; Hayashi *et al.* **1978**). They have been reported to exhibit various bioactivities, including anticancer (Peng, Xiong and Peng **2020**; Choi *et al.* **2009**; Cheng *et al.* **2022**), antileishmanial (Araújo *et al.* **2022**; Takahashi *et al.* **2006**), schistosomicidal (Xiao *et al.* **2014**), antiplasmodial (Su *et al*. **2015**) activities, etc.

Sativan has already been synthesized in both racemic and enantioenriched forms in seven previous reports (see **Table S1** in Supplementary data). Although the shortest racemic synthesis (Hashimoto *et al.* **2011**) was established with four overall steps, it required a conventional oxidative rearrangement mediated by toxic thallium(III) nitrate. The second shortest-step synthesis (Jiang *et al.* **2020**) was achieved without thallium by using Pd-catalyzed asymmetric α-arylation of a chromanone, which consisted of seven overall steps from resorcinol. The synthesis of claussequinone was reported only once before (Farkas *et al.* **1974**), and it was also based on the conventional thallium-based reaction to form its racemate. In regards to pendulone, however, no synthesis has been reported so far.



Scheme 2. (a) Synthesis of 7-benzyloxy-3-(pinacolato)boryl-2*H*-chromene **2**; (b) divergent total synthesis of the isoflavonoid natural products of (±)-sativan, (±)-claussequinone, and (±)-pendulone through Suzuki–Miyaura cross coupling, catalytic hydrogenation, and hydroquinone-selective oxidation

The C=C bond reduction and removal of the benzyl group of isoflavene **6** were carried out under a typical Pd/C-catalyzed hydrogenation condition to form (±)-sativan quantitatively. This synthesis is the shortest thallium-free synthesis, which is comprised of six overall steps (see **Table S1** in Supplementary data). Similar transformations of **7** and **8** were performed under the same conditions, followed by MnO_2-mediated selective oxidation of the resulting hydroquinone moieties to give (±)-claussequinone and (±)-pendulone in two steps in yields of 37% and 95%, respectively. It is noteworthy that these syntheses are the first thallium-free synthesis of claussequinone and the first synthesis of pendulone. The ^{1}H and ^{13}C spectral data for these three isoflavonoid natural products were in good agreement with those reported previously (see **Tables S2**–**S4** in Supplementary data).

Conclusion

We have established a new convergent and step-economical method for isoflavene synthesis using a divergent Suzuki–Miyaura cross coupling of a 3-boryl-2*H*-chromene and multiple aryl bromides. Although 3-boryl-2*H*-chromene has rarely been reported, 3-(pinacolato)boryl-2*H*-chromene **2** was successfully prepared in 60% yield via Miyaura–Ishiyama borylation of known 3-chloro-2*H*-chromene **1**, which is obtained through CRCC. The subsequent Suzuki–Miyaura cross coupling of 3-boryl-2*H*-chromene **2** and aryl bromides **3**–**5** proceeded smoothly under standard conditions to give isoflavene derivatives **6**–**8** in moderate yields of 55%, 50%, and 52%, respectively. This method enabled the omission of the bromine–boron exchange steps for aryl bromides **3**–**5** to give multiple isoflavenes **6**–**8** in fewer steps than the previous 3-chloro-2*H*-chromene-based methods. The conversion of the resulting isoflavene derivatives in one or two steps by catalytic hydrogenation (and selective oxidation of B rings) enabled facile access to three natural isoflavonoids: the shortest-step synthesis of (±)-sativan among the reported thallium-free methods, the first thallium-free synthesis of (±)-claussequinone, and the first synthesis of (±)-pendulone. This new method would also facilitate the synthesis of other isoflavonoid natural products.

Experimental

General experimental details

For reactions that required heating, a heat block and an oil bath were used as the heat sources. Column chromatography was performed on Silica Gel 60 N (spherical, neutral), 100–210 μm (purchased from Kanto Chemical Company, Incorporated). Reactions and chromatography fractions were analyzed by TLC on Silica gel 70 F254 TLC Plate-Wako (purchased from FUJIFILM Wako Pure Chemical Corporation), with visualization by UV irradiation at 254 nm, anisaldehyde, and/or 2,4-dinitrophenylhydrazine staining. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-ECZ-400S instrument at 400 and 101 MHz, respectively. Chemical shifts (δ) and coupling constants (*J*) are presented in ppm (relative to internal standards), and Hz, respectively. Me_4Si (δ 0.00), CD_3COCHD_2 (δ 2.05), or CHD_2OD (δ 3.31) was used as internal standard for ^{1}H NMR spectroscopy, while Me_4Si (δ 0.00), $(CD_3)_2CO$ (δ 29.84), or CD_3OD (δ 49.00) was used as internal standard for ^{13}C NMR spectroscopy. ^{13}C NMR spectra were recorded with ^{1}H NMR decoupling. To distinguish mono- (CH_3), di- (CH_2), tri- (CH), and tetra-substituted (C) carbon atoms, DEPT spectra were obtained by variation of selection angle (90° and 135°) parameters (DEPT90 and DEPT135). HRMS data were obtained by a JEOL JMS-T100LP AccuTOF LC-Plus instrument with a JEOL MS-5414DART attachment for ESI and DART, and a JEOL MS700 spectrometer for FAB (with *m*-NBA matrix and NaI) after calibration with PEG-400 or PEG-600. FT-IR spectra were recorded with a ThermoFisher Nicolet iS5 instrument with an iD5 ATR attachment and are reported in terms of frequency absorption (cm^{-1}). All reagents and solvents were purchased from chemical companies and used as received. Dry solvents were purchased for the reactions and used without purification.

Synthesis and characterization of compounds

The NMR data for the natural products ((±)-sativan (Miller, Spencer and Putnam **1989**; Le Bail *et al.* **2000**), (±)-claussequinone (Yahara *et al.* **1989**; Choi *et al*. **2010**; Goulart *et al.* **1993**), (±)-pendulone (Radwan **2008**; Rahman **2011**) were in good agreement with the literature values (see Supplementary data for the spectra, and **Tables S2**–**S4**). The analytical data for the new compounds **2** and **6**–**8**, and the natural products are as follows.

7-Benzyloxy-3-(pinacolato)boryl-2*H*-chromene (2)

A mixture of **1** (546 mg, 2.00 mmol), B_2pin_2 (559 mg, 2.20 mmol), $Pd(OAc)_2$ (44.9 mg, 0.200 mmol), SPhos (169

mg, 0.400 mmol, 97% purity), KOAc (393 mg, 4.00 mmol), and dry THF (20 mL) was stirred at 80 °C for 1 h. The reaction mixture was diluted with EtOAc (60 mL), washed with water (60 mL × 2) and brine (60 mL), dried over Na_2SO_4, decolorized with charcoal, filtered through Celite, and concentrated under reduced pressure. A solution of the crude product was prepared in a 5 mL volumetric flask using dry THF. The yield of the title compound and the concentration of this solution were estimated to be 60.0%, and 0.240 M, respectively by quantitative ^{1}H NMR (relaxation delay = 20 sec) using a 125 µL portion of this solution and triphenylmethane (22.4 mg, 0.100 mmol) as an internal standard. The remaining 0.240 M solution of the title compound was used in the next steps without purification. An analytically pure sample was obtained by recrystallization from Hex/Et_2O (3/1) as a yellowish-brown solid; mp 127–130 °C; ν_{max} 3062, 3031, 2977, 2929, 2852, 1610, 1501, 1380, 1360, 1309, 1269, 1237, 1160, 1137, 1111, 1008 cm^{-1}; δ_H ($CDCl_3$) 7.44 – 7.29 (5H, m), 7.07 (1H, br s), 6.94 (1H, d, J = 8.3), 6.49 (1H, dd, J = 8.3, 2.5), 6.44 (1H, d, J = 2.5), 5.02 (2H, s), 4.85 (2H, d, J = 1.6), 1.29 (12H, s); δ_C ($CDCl_3$) 160.8 (C), 156.7 (C), 137.2 (CH), 136.7 (C), 128.6 (CH), 128.5 (CH), 128.0 (CH), 127.5 (CH), 116.1 (C), 108.1 (CH), 102.3 (CH), 83.6 (C), 70.0 (CH_2), 67.1 (CH_2), 24.8 (CH_3); HRMS (FAB): $[MNa]^+$, found 387.1739. $C_{22}H_{25}BNaO_4^+$ requires 387.1738.

7-Benzyloxy-3-(2,4-dimethoxyphenyl)-2*H*-chromene (6)

A mixture of the above **2** solution in THF (833 µL, 200 µmol, 0.240 M), **3** (48.0 mg, 221 µmol), $Pd(OAc)_2$ (4.5 mg, 20 µmol), PPh_3 (15.7 mg, 59.9 µmol), and dry CsF (91.1 mg, 600 µmol) was stirred at 80 °C for 1 h. The reaction mixture was quenched with water (1 mL) and extracted with EtOAc (1 mL × 3). The organic solution was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2 10 g; Hex/EtOAc=9/1) to yield the title compound (41.2 mg, 55%) as a pale yellow solid; mp 80–83 °C; ν_{max} 3063, 3030, 3001, 2960, 2934, 2836, 1610, 1576, 1505, 1456, 1290, 1269, 1208, 1160, 1127, 1112, 1027 cm^{-1}; δ_H ($CDCl_3$) 7.46 – 7.30 (5H, m), 7.22 (1H, d, J = 8.3), 6.97 (1H, d, J = 8.2), 6.54 (1H, dd, J = 8.2, 2.0), 6.522 (1H, br s), 6.520 (1H, d, J = 2.0), 6.50 (1H, dd, J = 8.3, 2.3), 6.46 (1H, d, J = 2.3), 5.05 (2H, s), 4.99 (2H, d, J = 0.7), 3.83 (3H, s), 3.81 (3H, s); δ_C ($CDCl_3$) 160.7 (C), 159.4 (C), 158.2 (C), 154.7 (C), 136.9 (C), 129.4 (C), 129.3 (CH), 128.6 (CH), 128.0 (CH), 127.5 (CH), 127.3 (CH), 121.1 (CH), 120.8 (C), 117.3 (C), 108.2 (CH), 104.6 (CH), 102.4 (CH), 98.6 (CH), 70.0 (CH_2), 68.3 (CH_2), 55.5 (CH_3), 55.4 (CH_3); HRMS (DART): $[MH]^+$, found 375.1578. $C_{24}H_{23}O_4^+$ requires 375.1591.

182 **7-Benzyloxy-3-(2,5-dibenzyloxy-3-methoxyphenyl)-2*H*-chromene (7)**

183 A mixture of the above **2** solution in THF (833 μL, 200 μmol, 0.240 M), **4** (87.8 mg, 220 μmol), $Pd(OAc)_2$ (4.5 mg,
184 20 μmol), PPh_3 (15.7 mg, 59.9 μmol), and dry CsF (91.1 mg, 600 μmol) was stirred at 80 °C for 1 h. The reaction
185 mixture was quenched with water (1 mL) and extracted with EtOAc (1 mL × 3). The organic solution was dried over
186 Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2
187 10 g; Hex/EtOAc=9/1−4/1) to yield the title compound (55.8 mg, 50%) as a pale yellow solid; mp 121–124 °C; ν_{max}
188 3088, 3064, 3031, 2932, 2863, 1611, 1505, 1454, 1267, 1216, 1193, 1160, 1111, 1019 cm^{-1}; δ_H ($CDCl_3$) 7.47 – 7.29
189 (15H, m), 6.94 (1H, d, J = 8.3), 6.90 (1H, s), 6.57 (1H, s), 6.54 (1H, dd, J = 8.3, 2.4), 6.49 (1H, d, J = 2.4), 6.44 (1H,
190 br s), 5.11 (2H, s), 5.04 (2H, s), 5.02 (2H, s), 4.95 (2H, d, J = 0.9), 3.86 (3H, s); δ_C ($CDCl_3$) 159.4 (C), 154.6 (C),
191 151.2 (C), 150.3 (C), 142.4 (C), 137.2 (C), 136.8 (C), 136.7 (C), 129.1 (C), 128.62 (CH), 128.59 (CH), 128.1 (CH),
192 128.0 (CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 121.4 (CH), 120.2 (C), 117.2 (C), 115.8 (CH), 108.2
193 (CH), 102.3 (CH), 99.6 (CH), 72.2 (CH_2), 71.7 (CH_2), 70.0 (CH_2), 68.4 (CH_2), 56.3 (CH_3); HRMS (FAB): $[MNa]^+$,
194 found 579.2144. $C_{37}H_{32}NaO_5^+$ requires 579.2142.
195

196 **7-Benzyloxy-3-(2,5-dibenzyloxy-3,4-dimethoxyphenyl)-2*H*-chromene (8)**

197 A mixture of the above **2** solution in THF (833 μL, 200 μmol, 0.240 M), **5** (94.4 mg, 220 μmol), $Pd(OAc)_2$ (4.5 mg,
198 20 μmol), PPh_3 (15.7 mg, 59.9 μmol), and dry CsF (91.1 mg, 600 μmol) was stirred at 80 °C for 1 h. The reaction
199 mixture was quenched with water (1 mL) and extracted with EtOAc (1 mL × 3). The organic solution was dried over
200 Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2
201 10 g; Hex/EtOAc=9/1) to yield the title compound (61.3 mg, 52%) as a sticky yellow oil; ν_{max} 3088, 3064, 3030,
202 3011, 2936, 2875, 1614, 1498, 1454, 1372, 1245, 1160, 1113, 1097, 1049 cm^{-1}; δ_H ($CDCl_3$) 7.49 – 7.27 (15H, m),
203 6.94 (1H, d, J = 8.3), 6.64 (1H, s), 6.56 (1H, dd, J = 8.3, 2.5), 6.51 (1H, d, J = 2.5), 6.46 (1H, br s), 5.11 (2H, s),
204 5.05 (2H, s), 4.95 (2H, d, J = 1.0), 4.90 (2H, s), 3.95 (3H, s), 3.95 (3H, s); δ_C ($CDCl_3$) 159.7 (C), 154.8 (C), 148.8
205 (C), 147.5 (C), 144.4 (C), 143.5 (C), 137.1 (C), 137.0 (C), 136.8 (C), 128.7 (C), 128.60 (CH), 128.58 (CH), 128.5
206 (CH), 128.4 (CH), 128.03 (CH), 128.01 (CH), 127.9 (C), 127.6 (CH), 127.5 (CH), 127.4 (CH), 122.5 (CH), 116.9
207 (C), 108.6 (CH), 108.3 (CH), 102.3 (CH), 75.7 (CH_2), 71.4 (CH_2), 70.1 (CH_2), 68.3 (CH_2), 61.5 (CH_3), 61.4 (CH_3);
208 HRMS (FAB): $[MNa]^+$, found 609.2254. $C_{38}H_{34}NaO_6^+$ requires 609.2248.
209

210 **(±)-Sativan**

211 A mixture of **6** (18.7 mg, 49.9 μmol), Pd/C (5.3 mg, 5.0 μmol, 10 wt%), and MeOH/THF=1/1 (4 mL) was stirred at
212 rt for 24 h. The reaction mixture was diluted with EtOAc (4 mL), filtered through Celite, and concentrated under
213 reduced pressure to yield the title compound (14.3 mg, quant.) as a pale red solid; mp 158–159 °C; ν_{max} 3391 (br),
214 3000, 2936, 2837, 1614, 1587, 1506, 1455, 1207, 1155, 1114, 1030 cm^{-1}; δ_H ($CDCl_3$) 7.02 (1H, d, J = 8.3), 6.94 (1H,
215 d, J = 8.1), 6.49 (1H, d, J = 2.4), 6.46 (1H, dd, J = 8.3, 2.4), 6.38 (1H, dd, J = 8.1, 2.5), 6.35 (1H, d, J = 2.5), 4.67
216 (1H, br s), 4.29 (1H, ddd, J = 10.2, 3.3, 1.8), 3.99 (1H, dd, J = 10.3, 10.2), 3.81 (3H, s), 3.80 (3H, s), 3.56 (1H, dddd,
217 J = 10.7, 10.3, 5.3, 3.3), 2.97 (1H, dd, J = 15.7, 10.7), 2.86 (1H, ddd, J = 15.7, 5.3, 1.8); δ_C ($CDCl_3$) 159.6 (C), 158.3
218 (C), 155.2 (C), 154.7 (C), 130.4 (CH), 127.5 (CH), 121.8 (C), 114.9 (C), 107.8 (CH), 104.0 (CH), 103.2 (CH), 98.7
219 (CH), 70.1 (CH_2), 55.4 (CH_3), 55.3 (CH_3), 31.5 (CH), 30.3 (CH_2); δ_H (CD_3OD) 7.03 (1H, d, J = 8.4), 6.86 (1H, d, J
220 = 8.2), 6.54 (1H, d, J = 2.2), 6.47 (1H, dd, J = 8.4, 2.2), 6.31 (1H, dd, J = 8.2, 2.2), 6.22 (1H, d, J = 2.2), 4.18 (1H,
221 ddd, J = 10.3, 3.2, 1.9), 3.92 (dd, J = 10.3, 10.1), 3.83 (3H, s), 3.77 (3H, s), 3.45 (1H, dddd, J = 10.8, 10.1, 5.1, 3.2),
222 2.91 (1H, dd, J = 15.6, 10.8), 2.77 (1H, dd, J = 15.6, 5.1); δ_C ($CDCl_3$) 161.3 (C), 159.6 (C), 157.6 (C), 156.4 (C),
223 131.2 (CH), 128.6 (CH), 123.0 (C), 114.8 (C), 109.0 (CH), 105.5 (CH), 103.8 (CH), 99.4 (CH), 71.1 (CH_2), 55.9
224 (CH_3), 55.7 (CH_3), 32.9 (CH), 31.5 (CH_2); HRMS (ESI): $[MNa]^+$, found 309.1099. $C_{17}H_{18}NaO_4^+$ requires 309.1097.
225

226 **(±)-Claussequinone**

227 A mixture of **7** (55.7 mg, 100 μmol), Pd/C (10.6 mg, 10.0 μmol, 10 wt%), MeOH/THF=1/1 (4 mL) was stirred at rt
228 for 48 h. The reaction mixture was diluted with EtOAc (4 mL), filtered through Celite, and concentrated under
229 reduced pressure. The resulting residue and MnO_2 (69.6 mg, 800 μmol) were stirred in Et_2O (4 mL) at rt for 24 h.
230 The reaction mixture was filtered through Celite and concentrated under reduced pressure. The resulting mixture was
231 diluted with EtOAc (2 mL), washed with water (2 mL) and brine (2 mL), dried over Na_2SO_4, and concentrated under
232 reduced pressure. The crude product was washed with MeOH/water=1/1 solution to yield the title compound (10.5
233 mg, 37%) as a yellow solid; mp 171–173 °C; ν_{max} 3333 (br), 2920, 2850, 1644, 1602 cm^{-1}; δ_H ($CDCl_3$) 6.91 (1H, d,
234 J = 8.2), 6.49 (1H, d, J = 1.2), 6.41 (1H, dd, J = 8.2, 2.5), 6.32 (1H, d, J = 2.5), 5.97 (1H, s), 4.75 (1H, br s), 4.25
235 (1H, ddd, J = 10.8, 3.0, 1.1), 4.07 (1H, ddd, J = 10.8, 6.2, 1.2), 3.83 (3H, s), 3.46 (1H, ddddd, J = 6.6, 6.2, 6.0, 3.0,
236 1.2), 3.04 (1H, dd, J = 16.1, 6.0), 2.73 (1H, dd, J = 16.1, 6.6); δ_C ($CDCl_3$) 186.7 (C), 182.1 (C), 158.5 (C), 155.1 (C),
237 154.7 (C), 149.2 (C), 130.8 (CH), 130.4 (CH), 112.3 (C), 108.7 (CH), 107.9 (CH), 103.4 (CH), 68.2 (CH_2), 56.3

238 (CH_3), 30.9 (CH), 28.9 (CH_2); δ_H ($(CD_3)_2CO$) 8.20 (1H, s), 6.90 (1H, d, J = 8.3), 6.52 (1H, d, J = 0.9), 6.39 (1H, dd,
239 J = 8.3, 2.4), 6.28 (1H, d, J = 2.4), 6.09 (1H, s), 4.25 (1H, ddd, J = 10.5, 3.1, 1.6), 4.00 (1H, dd, J = 10.5, 7.8), 3.85
240 (3H, s), 3.41 – 3.32 (1H, m), 2.93 (1H, dd, J = 15.8, 5.5), 2.79 (1H, dd, J = 15.8, 8.6); δ_C ($(CD_3)_2CO$) 187.4 (C),
241 182.5 (C), 159.6 (C), 157.8 (C), 155.7 (C), 149.7 (C), 131.5 (CH), 131.1 (CH), 112.6 (C), 109.4 (CH), 108.6 (CH),
242 103.7 (CH), 69.1 (CH_2), 56.7 (CH_3), 32.0 (CH), 29.9 (CH_2, observed by DEPT135); HRMS (ESI): $[MNa]^+$, found
243 309.0749. $C_{16}H_{14}NaO_5^+$ requires 309.0733.
244
245 **(±)-Pendulone**
246 A mixture of **8** (29.3 mg, 49.4 μmol), Pd/C (5.3 mg, 5.0 μmol, 10 wt%), MeOH/THF=1/1 (2 mL) was stirred at rt for
247 24 h. The reaction mixture was diluted with EtOAc (4 mL), filtered through Celite, and concentrated under reduce
248 pressure. The resulting residue and MnO_2 (34.4 mg, 396 μmol) were stirred in Et_2O (3 mL) at rt for 24 h. The reaction
249 mixture was filtered through Celite and concentrated under reduced pressure. The crude product was purified by
250 column chromatography (SiO_2 5 g, Hex/EtOAc=2/1) to yield the title compound (14.8 mg, 95%) as a sticky red oil;
251 ν_{max} 3399 (br), 2985, 2947, 2849, 1651, 1599, 1508, 1456, 1217, 1152, 1115, 1037 cm^{-1}; δ_H ($CDCl_3$) 6.90 (1H, d, J
252 = 8.2), 6.41 (1H, dd, J = 8.2, 2.6), 6.37 (1H, d, J = 1.0), 6.32 (1H, d, J = 2.6), 5.29 (1H, br s), 4.23 (1H, ddd, J =
253 11.1, 3.3, 0.9), 4.04 (1H, ddd, J = 11.1, 6.4, 0.6), 4.02 (3H, s), 4.01 (3H, s), 3.43 (1H, ddddd, J = 6.6, 6.4, 5.9, 3.3,
254 1.0), 3.02 (1H, dd, J = 16.1, 5.9), 2.70 (1H, dd, J = 16.1, 6.6); δ_C ($CDCl_3$) 184.1 (C), 183.5 (C), 155.3 (C), 154.6 (C),
255 146.6 (C), 145.0 (C), 144.5 (C), 131.0 (CH), 130.3 (CH), 112.1 (C), 108.8 (CH), 103.4 (CH), 68.1 (CH_2), 61.4 (CH_3),
256 61.3 (CH_3), 30.8 (CH), 28.9 (CH_2); HRMS (ESI): $[MNa]^+$, found 339.0866. $C_{17}H_{16}NaO_6^+$ requires 339.0839.
257
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261 spectrometry.
262
263 **Supplementary material**
264 Supplementary material is available online at *Bioscience, Biotechnology, and Biochemistry*.
265

Data availability

The authors confirm that the data supporting the findings of this study are available within the article and in its supplementary material.

Author contribution

Y.U., B.K., and H.T. designed the synthetic route and wrote the manuscript. Y.U. conducted the synthetic experiments and characterized the compounds with the guidance of B.K. and H.T.

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Disclosure statement

The authors declare no potential conflicts of interest.

References

Sajid M, Stone SR, Kaur P. Recent Advances in Heterologous Synthesis Paving Way for Future Green-Modular Bioindustries: A Review With Special Reference to Isoflavonoids. *Front Bioeng Biotechnol* 2021;9:673270, DOI: 10.3389/fbioe.2021.673270.

Al-Maharik N. Isolation of naturally occurring novel isoflavonoids: an update. *Nat Prod Rep* 2019;36:1156–1195, DOI: 10.1039/c8np00069g.

Donnelly DMX, Boland GM. Isoflavonoids and neoflavonoids: naturally occurring O-heterocycles. *Nat Prod Rep* 1995;12:321–338, DOI: 10.1039/np9951200321.

Boland GM, Donnelly DMX. Isoflavonoids and related compounds. *Nat Prod Rep* 1998;15:241–260, DOI: 10.1039/a815241y.

Kohno Y, Koso M, Kuse M, Takikawa H. Formal synthesis of soybean phytoalexin glyceollin I. *Tetrahedron Lett* 2014;55:1826–1828, DOI: 10.1016/j.tetlet.2014.01.142.

Kang B, Oe T, Shimizu Y, Takikawa H. Syntheses of three 8-methoxyisoflavans from newly developed 7-benzyloxy-3-chloro-8-methoxy-2*H*-chromene as the precursor. *Tetrahedron* 2022;113:132714, DOI: 10.1016/j.tet.2022.132714.

Uchida Y, Kang B, Takikawa H. Convergent radical-free synthesis of isoflavanquinones: Divergent total synthesis of abruquinones B, E, and P. *Tetrahedron* 2023;136:133362, DOI: 10.1016/j.tet.2023.133362.

Koo JY, Oh S, Cho SR, et al. Total synthesis of eryvarin H and its derivatives and their biological activity as ERRγ inverse agonist. *Org Biomol Chem* 2013;11:5782–5786, DOI: 10.1039/c3ob41264d.

Anderson DR, Mahoney MW, Phillion DP *et al.*, inventors; Pharmacia Corporation, assignee. Mitogen activated protein kinase-activated protein kinase-2 inhibiting compounds. WO patent application 2004-058762A1. July 15, 2004.

Jang H, Zhugralin AR, Lee Y, Hoveyda AH. Highly Selective Methods for Synthesis of Internal (α-) Vinylboronates through Efficient NHC–Cu-Catalyzed Hydroboration of Terminal Alkynes. Utility in Chemical Synthesis and Mechanistic Basis for Selectivity. *J Am Chem Soc* 2011;133:7859–7871, DOI: 10.1021/ja2007643.

Takashima Y, Kaneko Y, Kobayashi Y. Synthetic access to optically active isoflavans by using allylic substitution. *Tetrahedron* 2010;66:197–207, DOI: 10.1016/j.tet.2009.10.116.

Ji W, Gao Q, Lin Y, Gao H, Wang X, Geng Y. Total Synthesis of (±)-Glabridin. *Synth Commun* 2013;44:540–546, DOI: 10.1080/00397911.2013.821616.

Yalamanchili C, Chittiboyina AG, Chandra Kumar Rotte S, Katzenellenbogen JA, Helferich WG, Khan IA. A chiral pool approach for asymmetric syntheses of both antipodes of equol and sativan. *Tetrahedron* 2018;74:2020–2029, DOI: 10.1016/j.tet.2018.03.004.

Zhang J, Zhang S, Yang H et al. A general asymmetric route to enantio-enriched isoflavanes via an organocatalytic annulation of *o*-quinone methides and aldehydes. *Tetrahedron Lett* 2018;59:2407–2411, DOI: 10.1016/j.tetlet.2018.05.016.

Jiang D, Zang Q, Zhang Y, Li H, inventors; Yulin Teachers College, assignee. Method for asymmetrically preparing glabridin with optical purity. CN patent 111362961 B. April 4, 2020.

319 Farkas L, Gottsegen À, Nóagrádi M, Antus S. Synthesis of sophorol, violanone, lonchocarpan, claussequinone,
320 philenopteran, leiocalycin, and some other natural isoflavonoids by the oxidative rearrangement of chalcones with
321 thallium(III) nitrate. *J Chem Soc, Perkin Trans 1* 1974, 305–312, DOI: 10.1039/p19740000305.
322 Billingsley KL, Barder TE, Buchwald SL. Palladium-Catalyzed Borylation of Aryl Chlorides: Scope, Applications,
323 and Computational Studies. *Angew Chem Int Ed* 2007;46:5359–5363, DOI: 10.1002/anie.200701551.
324 Ingham JL, Millar RL. Sativin: an Induced Isoflavan from the Leaves of *Medicago sativa* L. *Nature* 1973;242:125–
325 126, DOI: 10.1038/242125a0.
326 Bonde MR, Millar RL, Ingham JL. Induction and identification of sativan and vestitol as two phytoalexins from
327 *Lotus corniculatus*. *Phytochemistry* 1973;12:2957–2959, DOI: 10.1016/0031-9422(73)80514-x.
328 Braga de Oliveira A, Gottlieb OR, Gonclaves TMM, Ollis WD. Chemistry of Brazilian Leguminosae. XXXIII.
329 Isoflavanoids of *Cyclobium clausseni* and *Cyclobium vecchii*. *An Acad Bras Cienc* 1971;43:129–130.
330 Hayashi Y, Shirato T, Sakurai K, Takahashi T. Isoflavonoids from the heartwood of *Millettia pendula* benth. *Mokuzai*
331 *Gakkaishi* 1978;24:898–901.
332 Peng F, Xiong L, Peng C. (-)-Sativan Inhibits Tumor Development and Regulates miR-200c/PD-L1 in Triple
333 Negative Breast Cancer Cells. *Front Pharmacol* 2020;11:251, DOI: 10.3389/fphar.2020.00251.
334 Choi C, Choi Y, Cha M et al. Antitumor Components Isolated from the Heartwood Extract of *Dalbergia odorifera*. *J*
335 *Korean Soc Appl Biol Chem* 2009;52:375-379, DOI: 10.3839/jksabc.2009.067.
336 Cheng WC, Wen Y, Chiu YS et al. Pendulone induces apoptosis via the ROS-mediated ER-stress pathway in human
337 non-small cell lung cancer cells. *Toxicol In Vitro* 2022;81:105346, DOI: 10.1016/j.tiv.2022.105346.
338 Araújo IAC, De Paula RC, Alves CL et al. *In vitro* efficacy of isoflavonoids and terpenes against *Leishmania*
339 (*Leishmania*) *infantum* and *L. amazonensis. Exp Parasitol* 2022;242:108383, DOI:
340 10.1016/j.exppara.2022.108383.
341 Takahashi M, Fuchino H, Sekita S, Satake M, Kiuchi F. *In Vitro* Leishmanicidal Constituents of *Millettia pendula*.
342 *Chem Pharm Bull* 2006;54:915–917, DOI: 10.1248/cpb.54.915.
343 Xiao C, Zhang Y, Qiu L, Dong X, Jiang B. Schistosomicidal and Antioxidant Flavonoids from *Astragalus englerianus*.
344 *Planta Med* 2014;80:1727–1731, DOI: 10.1055/s-0034-1383219.

345 Su Q, Krai P, Goetz M, Cassera M, Kingston D. Antiplasmodial Isoflavanes and Pterocarpans from *Apoplanesia*
346 *paniculata*. *Planta Med* 2015;81:1128–1132, DOI: 10.1055/s-0035-1546036.
347 Hashimoto H, Sugai Y, Ishikawa J, Shimotoyodome Y, Ito S, inventors; Kao Corporation, assignee. Ceramide
348 production promoters useful for hair conditioners. JP patent publication 2011-231057A. November 17, 2011.
349 Miller RW, Spencer GF, Putnam AR. (-)-5'-Methoxysativan, a New Isoflavan from Alfalfa. *J Nat Prod* 1989;52:634–
350 636, DOI: 10.1021/np50063a026.
351 Le Bail JC, Champavier Y, Chulia AJ, Habrioux G. Effects of phytoestrogens on aromatase, 3β and 17β-
352 hydroxysteroid dehydrogenase activities and human breast cancer cells. *Life Sci* 2000;66:1281–1291, DOI:
353 10.1016/s0024-3205(00)00435-5.
354 Yahara S, Ogata T, Saijo R et al. Isoflavan and related compounds from *Dalbergia odorifera*. I. *Chem Pharm Bull*
355 1989;37:979–987, DOI: 10.1248/cpb.37.979.
356 Choi CW, Choi YH, Cha MR et al. Yeast α-Glucosidase Inhibition by Isoflavones from Plants of Leguminosae as an
357 in Vitro Alternative to Acarbose. *J Agric Food Chem* 2010;58:9988–9993, DOI: 10.1021/jf101926j.
358 Goulart MOF, Soares NA, Sant'Ana AEG, Tonholo J, Boodts JFC. Investigation of the Electrochemical Reduction
359 of 3R-Claussequinone, in "Dry" DMF and Mixed Water-DMF Solvent: A system Involving Self-Protonation. *J*
360 *Braz Chem Soc* 1993;4:47–53, DOI: 10.5935/0103-5053.19930011.
361 Radwan MM. Isoflavonoids from an Egyptian Collection of *Colutea istria*. *Nat Prod Commun*
362 2008;3:1934578X0800300, DOI: 10.1177/1934578x0800300918.
363 Rahman AA, Samoylenko V, Jain SK et al. Antiparasitic and Antimicrobial Isoflavanquinones from *Abrus schimperi*.
364 *Nat Prod Commun* 2011;6:1934578X1100601, DOI: 10.1177/1934578x1100601120