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1 REGULAR PAPER

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

4

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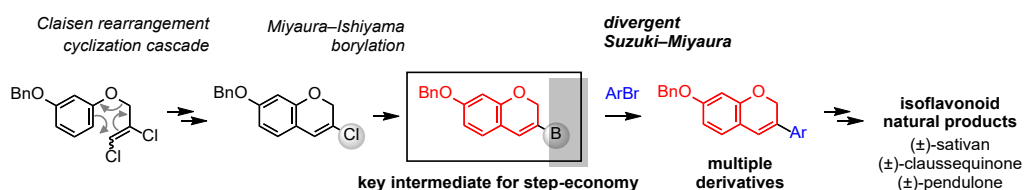
14 ABSTRACT

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

20

21 Graphical Abstract

22



23

24

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

26 Introduction

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

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

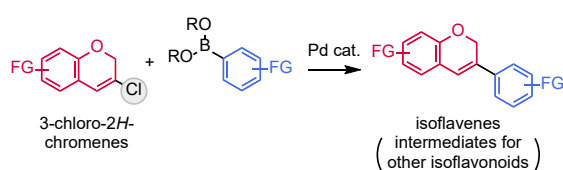
43 To realize a more step-economical synthesis, we planned on inverting the cross-coupling nucleophile and
44 electrophiles; this can be achieved by the cross coupling a 3-boryl-2*H*-chromene and aryl bromides instead of our
45 previously used 3-chloro-2*H*-chromene and arylboronic acids, as AC-ring and B-ring units, respectively (**Scheme**
46 **1d**). This method requires one additional step for the chlorine–boron exchange of a 3-chloro-2*H*-chromene to prepare
47 a 3-boryl-2*H*-chromene. However, because aryl bromides can be used directly in aimed cross coupling, this 3-boryl-
48 2*H*-chromene-based strategy is able to skip each borylation step.

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

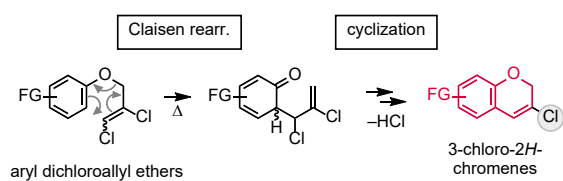
53 products (the three isoflavene derivatives) were then converted to three isoflavonoid natural products (one isoflavan
 54 and two isoflavanquinones) in one or two steps. This report provides rare insight into the preparation, reaction, and
 55 application of 3-boryl-2*H*-chromene. In addition, the 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

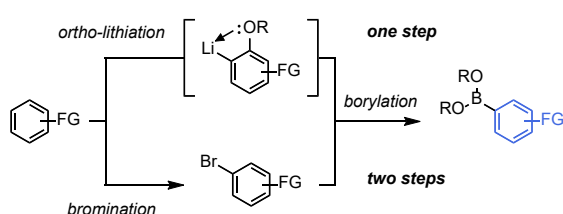
a. Suzuki–Miyaura approach to isoflavenes



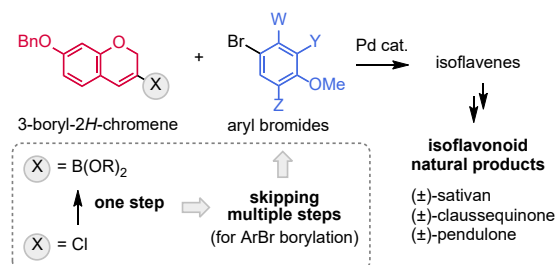
b. Claisen rearrangement cyclization cascade



c. Reported ArB(OR)₂ preparation methods for isoflavenes



d. This work - a new step-economical approach



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

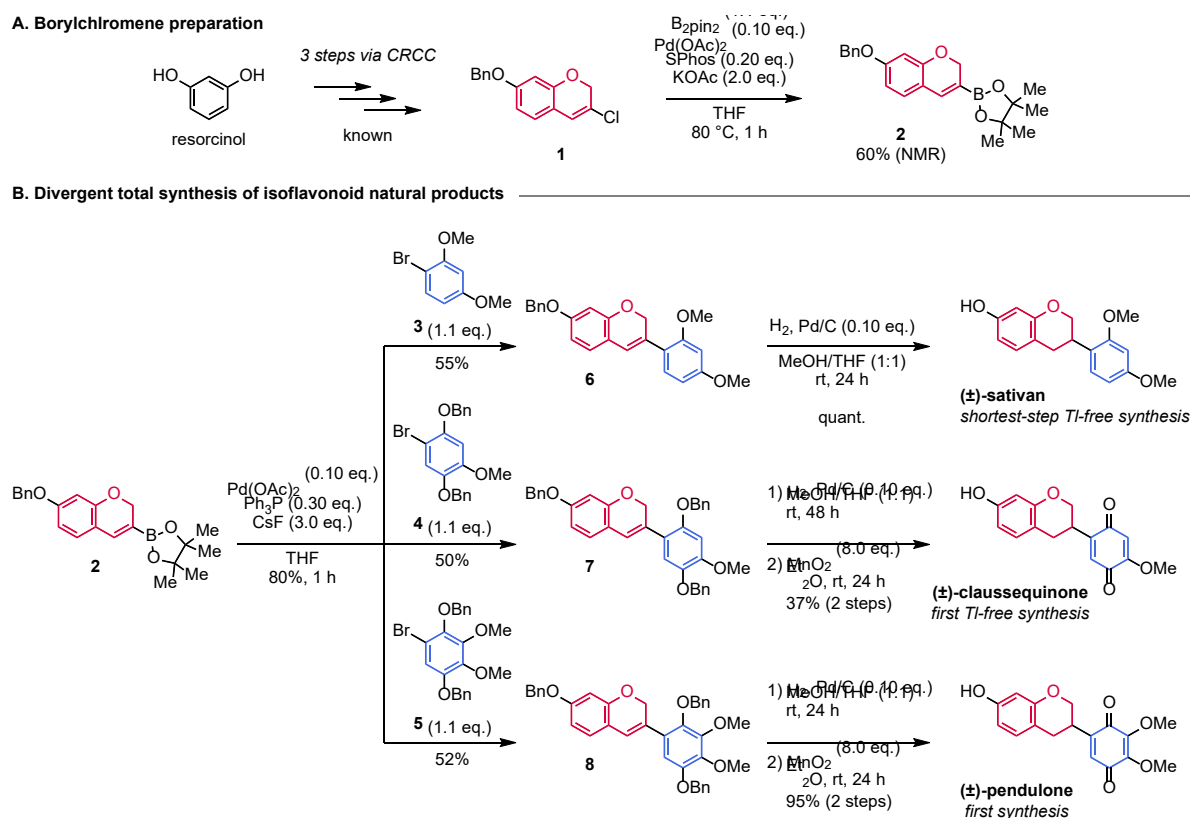
65 Results and discussion

66 We began the present study by synthesizing a 3-boryl-2*H*-chromene (**Scheme 2a**). As a precursor to 3-
67 boryl-2*H*-chromene, we chose known 7-benzyloxy-3-chloro-2*H*-chromene **1** (Kohno *et al.* 2014). This chloro-2*H*-
68 chromene **1** was subjected to a typical Miyaura–Ishiyama borylation condition catalyzed by a Pd(0)/SPhos complex
69 for poorly reactive aryl/alkenyl chlorides (Billingsley, Barder and Buchwald 2007). The yield of the borylation
70 product, 7-benzyloxy-3-(pinacolato)boryl-2*H*-chromene **2**, was estimated to be 60% by its crude ¹H nuclear magnetic
71 resonance spectra wherein triphenylmethane was used as an internal standard (see **Experimental** for details). We
72 failed to isolate **2** using a silica gel column chromatography, which is probably due to its instability in this system.
73 On the other hand, 3-borylchromene **2** was successfully isolated through recrystallization from Et₂O/Hex (1/3) in
74 45% recrystallization yield (27% overall from **1**). To avoid this partial loss of **2** through this recrystallization process,
75 crude **2** was used for the next step without purification.

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

85 These natural products were first isolated from leguminous plants, namely *Medicago sativa* (alfalfa),
86 *Cyclolobium claussei* (native to South America), and *Millettia pendula* (native to Southeast Asia), respectively
87 (Ingham and Millar 1973; Bonde, Millar and Ingham 1973; Braga de Oliveira *et al.* 1971; Hayashi *et al.* 1978). They
88 have been reported to exhibit various bioactivities, including anticancer (Peng, Xiong and Peng 2020; Choi *et al.*
89 2009; Cheng *et al.* 2022), antileishmanial (Araújo *et al.* 2022; Takahashi *et al.* 2006), schistosomicidal (Xiao *et al.*
90 2014), antiplasmodial (Su *et al.* 2015) activities, etc.

91 Sativan has already been synthesized in both racemic and enantioenriched forms in seven previous reports
 92 (see **Table S1** in Supplementary data). Although the shortest racemic synthesis (Hashimoto *et al.* **2011**) was
 93 established with four overall steps, it required a conventional oxidative rearrangement mediated by toxic thallium(III)
 94 nitrate. The second shortest-step synthesis (Jiang *et al.* **2020**) was achieved without thallium by using Pd-catalyzed
 95 asymmetric α -arylation of a chromanone, which consisted of seven overall steps from resorcinol. The synthesis of
 96 claussequinone was reported only once before (Farkas *et al.* **1974**), and it was also based on the conventional
 97 thallium-based reaction to form its racemate. In regards to pendulone, however, no synthesis has been reported so
 98 far.
 99



100

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

104

105 The C=C bond reduction and removal of the benzyl group of isoflavene **6** were carried out under a typical
106 Pd/C-catalyzed hydrogenation condition to form (±)-sativan quantitatively. This synthesis is the shortest thallium-
107 free synthesis, which is comprised of six overall steps (see **Table S1** in Supplementary data). Similar transformations
108 of **7** and **8** were performed under the same conditions, followed by MnO₂-mediated selective oxidation of the resulting
109 hydroquinone moieties to give (±)-claussequinone and (±)-pendulone in two steps in yields of 37% and 95%,
110 respectively. It is noteworthy that these syntheses are the first thallium-free synthesis of claussequinone and the first
111 synthesis of pendulone. The ¹H and ¹³C spectral data for these three isoflavonoid natural products were in good
112 agreement with those reported previously (see **Tables S2–S4** in Supplementary data).

113

114 **Conclusion**

115 We have established a new convergent and step-economical method for isoflavene synthesis using a
116 divergent Suzuki–Miyaura cross coupling of a 3-boryl-2*H*-chromene and multiple aryl bromides. Although 3-boryl-
117 2*H*-chromene has rarely been reported, 3-(pinacolato)boryl-2*H*-chromene **2** was successfully prepared in 60% yield
118 via Miyaura–Ishiyama borylation of known 3-chloro-2*H*-chromene **1**, which is obtained through CRCC. The
119 subsequent Suzuki–Miyaura cross coupling of 3-boryl-2*H*-chromene **2** and aryl bromides **3–5** proceeded smoothly
120 under standard conditions to give isoflavene derivatives **6–8** in moderate yields of 55%, 50%, and 52%, respectively.
121 This method enabled the omission of the bromine–boron exchange steps for aryl bromides **3–5** to give multiple
122 isoflavenes **6–8** in fewer steps than the previous 3-chloro-2*H*-chromene-based methods. The conversion of the
123 resulting isoflavene derivatives in one or two steps by catalytic hydrogenation (and selective oxidation of B rings)
124 enabled facile access to three natural isoflavonoids: the shortest-step synthesis of (±)-sativan among the reported
125 thallium-free methods, the first thallium-free synthesis of (±)-claussequinone, and the first synthesis of (±)-pendulone.
126 This new method would also facilitate the synthesis of other isoflavonoid natural products.

127

128 **Experimental**

129 **General experimental details**

130 For reactions that required heating, a heat block and an oil bath were used as the heat sources. Column
131 chromatography was performed on Silica Gel 60 N (spherical, neutral), 100–210 μm (purchased from Kanto
132 Chemical Company, Incorporated). Reactions and chromatography fractions were analyzed by TLC on Silica gel 70
133 F254 TLC Plate-Wako (purchased from FUJIFILM Wako Pure Chemical Corporation), with visualization by UV
134 irradiation at 254 nm, anisaldehyde, and/or 2,4-dinitrophenylhydrazine staining. ^1H and ^{13}C NMR spectra were
135 recorded on a JEOL JNM-ECZ-400S instrument at 400 and 101 MHz, respectively. Chemical shifts (δ) and coupling
136 constants (J) are presented in ppm (relative to internal standards), and Hz, respectively. Me_4Si (δ 0.00), $\text{CD}_3\text{COCHD}_2$
137 (δ 2.05), or CHD_2OD (δ 3.31) was used as internal standard for ^1H NMR spectroscopy, while Me_4Si (δ 0.00),
138 $(\text{CD}_3)_2\text{CO}$ (δ 29.84), or CD_3OD (δ 49.00) was used as internal standard for ^{13}C NMR spectroscopy. ^{13}C NMR spectra
139 were recorded with ^1H NMR decoupling. To distinguish mono- (CH_3), di- (CH_2), tri- (CH), and tetra-substituted (C)
140 carbon atoms, DEPT spectra were obtained by variation of selection angle (90° and 135°) parameters (DEPT90 and
141 DEPT135). HRMS data were obtained by a JEOL JMS-T100LP AccuTOF LC-Plus instrument with a JEOL MS-
142 5414DART attachment for ESI and DART, and a JEOL MS700 spectrometer for FAB (with *m*-NBA matrix and NaI)
143 after calibration with PEG-400 or PEG-600. FT-IR spectra were recorded with a ThermoFisher Nicolet iS5 instrument
144 with an iD5 ATR attachment and are reported in terms of frequency absorption (cm^{-1}). All reagents and solvents were
145 purchased from chemical companies and used as received. Dry solvents were purchased for the reactions and used
146 without purification.

147 **Synthesis and characterization of compounds**

148 The NMR data for the natural products ((\pm)-sativan (Miller, Spencer and Putnam [1989](#); Le Bail *et al.* [2000](#)), (\pm)-
149 claussequinone (Yahara *et al.* [1989](#); Choi *et al.* [2010](#); Goulart *et al.* [1993](#)), (\pm)-pendulone (Radwan [2008](#); Rahman
150 [2011](#)) were in good agreement with the literature values (see Supplementary data for the spectra, and **Tables S2–S4**).
151 The analytical data for the new compounds **2** and **6–8**, and the natural products are as follows.

152 **7-Benzyloxy-3-(pinacolato)boryl-2H-chromene (2)**

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

154 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
155 reaction mixture was diluted with EtOAc (60 mL), washed with water (60 mL × 2) and brine (60 mL), dried over
156 Na₂SO₄, decolorized with charcoal, filtered through Celite, and concentrated under reduced pressure. A solution of
157 the crude product was prepared in a 5 mL volumetric flask using dry THF. The yield of the title compound and the
158 concentration of this solution were estimated to be 60.0%, and 0.240 M, respectively by quantitative ¹H NMR
159 (relaxation delay = 20 sec) using a 125 μL portion of this solution and triphenylmethane (22.4 mg, 0.100 mmol) as
160 an internal standard. The remaining 0.240 M solution of the title compound was used in the next steps without
161 purification. An analytically pure sample was obtained by recrystallization from Hex/Et₂O (3/1) as a yellowish-brown
162 solid; mp 127–130 °C; ν_{max} 3062, 3031, 2977, 2929, 2852, 1610, 1501, 1380, 1360, 1309, 1269, 1237, 1160, 1137,
163 1111, 1008 cm⁻¹; δ_H (CDCl₃) 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),
164 6.44 (1H, d, *J* = 2.5), 5.02 (2H, s), 4.85 (2H, d, *J* = 1.6), 1.29 (12H, s); δ_C (CDCl₃) 160.8 (C), 156.7 (C), 137.2 (CH),
165 136.7 (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 (CH₂),
166 67.1 (CH₂), 24.8 (CH₃); HRMS (FAB): [MNa]⁺, found 387.1739. C₂₂H₂₅BNaO₄⁺ requires 387.1738.

167

168 **7-Benzyloxy-3-(2,4-dimethoxyphenyl)-2H-chromene (6)**

169 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,
170 20 μmol), PPh₃ (15.7 mg, 59.9 μmol), and dry CsF (91.1 mg, 600 μmol) was stirred at 80 °C for 1 h. The reaction
171 mixture was quenched with water (1 mL) and extracted with EtOAc (1 mL × 3). The organic solution was dried over
172 Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO₂
173 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,
174 3030, 3001, 2960, 2934, 2836, 1610, 1576, 1505, 1456, 1290, 1269, 1208, 1160, 1127, 1112, 1027 cm⁻¹; δ_H (CDCl₃)
175 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
176 (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),
177 3.81 (3H, s); δ_C (CDCl₃) 160.7 (C), 159.4 (C), 158.2 (C), 154.7 (C), 136.9 (C), 129.4 (C), 129.3 (CH), 128.6 (CH),
178 128.0 (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
179 (CH), 70.0 (CH₂), 68.3 (CH₂), 55.5 (CH₃), 55.4 (CH₃); HRMS (DART): [MH]⁺, found 375.1578. C₂₄H₂₃O₄⁺ requires
180 375.1591.

181

182 **7-Benzyloxy-3-(2,5-dibenzyloxy-3-methoxyphenyl)-2H-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), PPh₃ (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 \times 3). The organic solution was dried over
186 Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO₂
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} (CDCl₃) 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} (CDCl₃) 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 (CH₂), 71.7 (CH₂), 70.0 (CH₂), 68.4 (CH₂), 56.3 (CH₃); HRMS (FAB): [MNa]⁺,
194 found 579.2144. C₃₇H₃₂NaO₅⁺ requires 579.2142.

196 **7-Benzyloxy-3-(2,5-dibenzyloxy-3,4-dimethoxyphenyl)-2H-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), PPh₃ (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 \times 3). The organic solution was dried over
200 Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO₂
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} (CDCl₃) 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} (CDCl₃) 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 (CH₂), 71.4 (CH₂), 70.1 (CH₂), 68.3 (CH₂), 61.5 (CH₃), 61.4 (CH₃);
208 HRMS (FAB): [MNa]⁺, found 609.2254. C₃₈H₃₄NaO₆⁺ 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): $[\text{MNa}]^+$, found 309.1099. $\text{C}_{17}\text{H}_{18}\text{NaO}_4^+$ 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 (CH₃), 30.9 (CH), 28.9 (CH₂); δ_{H} ((CD₃)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} ((CD₃)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 (CH₂), 56.7 (CH₃), 32.0 (CH), 29.9 (CH₂, observed by DEPT135); HRMS (ESI): [MNa]⁺, found
243 309.0749. C₁₆H₁₄NaO₅⁺ requires 309.0733.

244

245 (\pm)-Pendulone

246 A mixture of **8** (29.3 mg, 49.4 μ mol), Pd/C (5.3 mg, 5.0 μ mol, 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 MnO₂ (34.4 mg, 396 μ mol) were stirred in Et₂O (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 (SiO₂ 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} (CDCl₃) 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, dddd, $J = 6.6, 6.4, 5.9, 3.3,$
254 1.0), 3.02 (1H, dd, $J = 16.1, 5.9$), 2.70 (1H, dd, $J = 16.1, 6.6$); δ_{C} (CDCl₃) 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 (CH₂), 61.4 (CH₃),
256 61.3 (CH₃), 30.8 (CH), 28.9 (CH₂); HRMS (ESI): [MNa]⁺, found 339.0866. C₁₇H₁₆NaO₆⁺ requires 339.0839.

257

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262

263 Supplementary material

264 Supplementary material is available online at [Bioscience, Biotechnology, and Biochemistry](#).

265

266 **Data availability**

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

269

270 **Author contribution**

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

273

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278

279 **Disclosure statement**

280 The authors declare no potential conflicts of interest.

281

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