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A concise synthesis of (±)-pseudodeflectusin, an antitumor isochroman derivative isolated from *Aspergillus* sp.

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Abstract—A novel and concise synthesis of (±)-pseudodeflectusin (**1**), an antitumor isochroman derivative isolated from the culture broth of *Aspergillus pseudodeflectus*, was accomplished by starting from 4-(*tert*-butyldimethylsilyloxy)-1-pentyne (**3**) and diethyl 3-oxopentanedicarboxylate (**5**).

1. Introduction

In 2004, Mizushina and his co-workers isolated pseudodeflectusin from the culture broth of *Aspergillus pseudodeflectus*.[1] Pseudodeflectusin is an isochroman derivative exhibiting cytotoxicity against several human cancer cell lines such as HeLa-S3, HL-60, etc., and its LD_{50} value for HL-60 cells was reported to be 39 μM. The originally proposed structure for pseudodeflectusin (**1**, in Fig. 1) was just a planar structure, and the absolute configurations of two stereogenic centers were not determined. On the other hand, Proksch and his co-workers reported the isolation of aspergione B from *Aspergillus versicolor* in 2003.[2] The proposed structure for aspergione B (**2**) was identical with **1** concerning isochromanol framework but different from **1** in the northwestern portion. However, both the NMR spectral data reported for pseudodeflectusin and aspergione B were in good agreement with each other. It meant that pseudodeflectusin and aspergione B should be the same compound, and either of the proposed structures might be in error. Kobayashi and his co-workers have clarified this problem by their first syntheses of (+)-**1** and (±)-**2**, and proven that **1** is correct.[3] They were also able to determine the absolute stereochemistry of the naturally occurring **1** as shown in Figure 1.

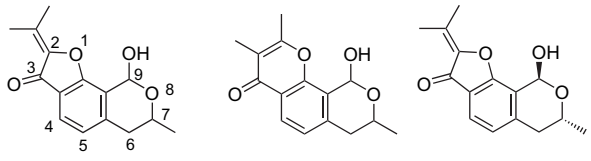

Figure 1. Structure of pseudodeflectusin.

We became interested in the biological activities and the unique structure of **1** and undertook a project to synthesize it. Although the absolute configuration of the natural **1** was unknown at the beginning, the first enantioselective synthesis was reported last year as mentioned above.[3] Therefore, we turned to focus on the development of a new and concise synthetic route to (±)-**1**. Herein, we report a short-step and straightforward synthesis of (±)-pseudodeflectusin (**1**) in detail.

2. Results and discussion

Our basic strategy is shown in Scheme 1. One of the crucial points in the synthesis of **1** should be the construction of the 2-isopropylidenefuran-3-one portion. For this point, we assigned the intermediate **A** as an appropriate precursor, because an isopropylidene moiety was preparable from a carboxylate group by nucleophilic dimethylation followed by dehydration. For the construction of the furan-3-one framework of **A**, we envisioned adopting Dieckmann condensation,[4] which was also employed in Kobayashi's synthesis.[3] In our strategy, the envisaged intermediates **A** and **B**

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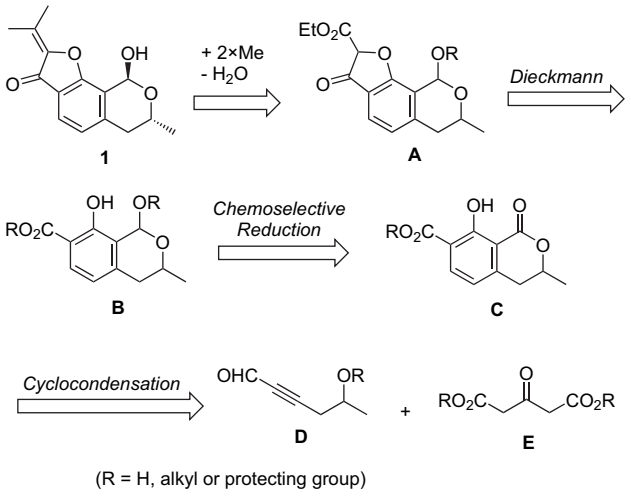
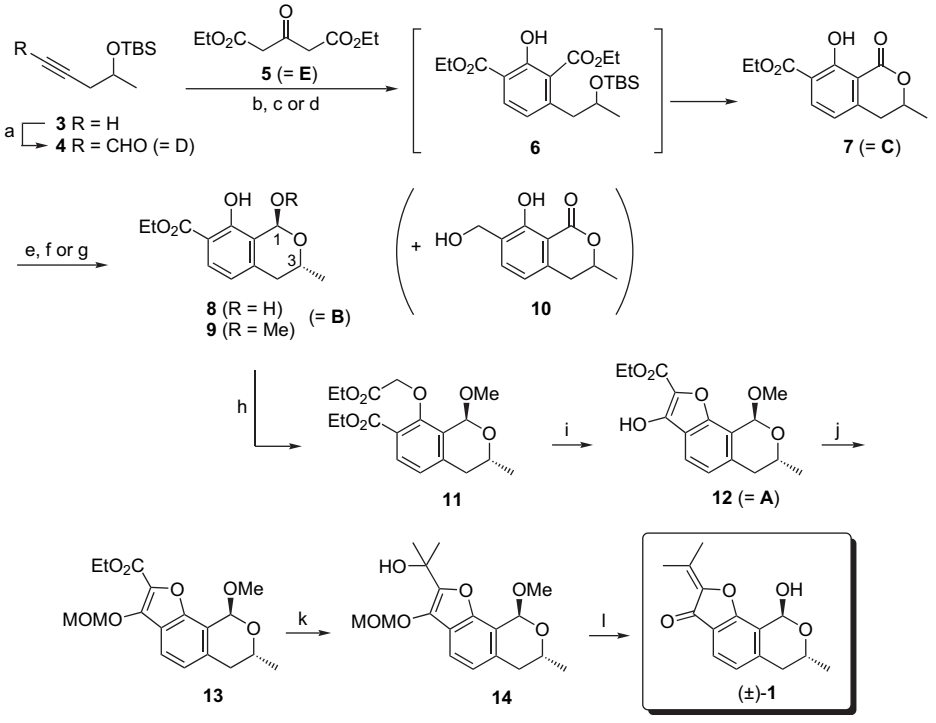


Scheme 1. Synthetic plan for (±)-**1**.

were not *lactones* but *acetals*. That was the key point of our synthetic plan. Because we were worried that reduction of the lactone to the corresponding lactol in the later stage might be problematic, we ventured on the chemoselective reduction of **C** to **B**. In other words, another crucial point was this chemoselective reduction. For the synthesis of **C**, we were purposed to establish a new route to **C** based on the cyclocondensation of **D** with **E**, although **C** has already reported as not only racemic[5] but also optically active[3,6] forms.

Scheme 2 shows our synthetic route to (±)-**1**. Our starting material was the known alkyne **3**, which was easily prepared from commercially available 4-pentyn-2-ol.[7] First, we prepared an aldehyde **4**[6c] (=**D**) from the starting alkyne **3** according to the conventional manner. The next key cyclocondensation of **4** with **5** (=**E**) was performed based on the reported procedure.[8] Our first trial of this cyclocondensation was not so successful under the originally reported conditions: NaH, THF, room temperature, affording the cycloadduct **6** in 36% yield. Although the use of K_2CO_3 as a base made the yield worse (19%), the improved yield (54%) was observed by changing a base to Cs_2CO_3. Very recently, we have realized that the identical cyclocondensation was reported by McClay and his co-workers independently,[6c,9] but our modified method was more efficient than theirs in yield.[10] The cycloadduct **6** was then converted to the corresponding lactone **7** (83%; =**C**) by treatment with *p*-TsOH. We then intended to obtain **7** from **4** in one-pot process. This attempt was achieved by the cyclocondensation of **4** with **5** in the presence of Cs_2CO_3 and the following acidic work-up to give the desired **7** in 43% yield.

The next step was the crucial chemoselective reduction of the lactone functionality in **7** leaving the ester intact. This chemoselective reduction was successfully performed by treatment with DIBAL in toluene at −78 °C to furnish the desired lactol **8** (=**B**) in 15–67% yield.[11] The lactol **8** was then treated with *p*-TsOH in MeOH to give the corresponding methyl acetal **9** (91%). However, this reduction was somewhat problematic, and the isolated yield fluctuated considerably from case to case. Because this fluctuation might depend mainly on work-up and/or isolation processes but not on reduction itself, we endeavored to obtain **9** directly from **7** by skipping the isolation of **8**. As a result, the desired **9** was successfully obtained in 58% yield (based on the recovered SM) by quenching with MeOH–AcOH. On the



Scheme 2. Synthesis of (±)-**1**. *Reagents and conditions*: (a) *n*-BuLi, THF, DMF (91%); (b) Cs_2CO_3, THF (54% for **6**); (c) *p*-TsOH, EtOH (83% for **6**→**7**); (d) Cs_2CO_3, THF, then dil HCl (43% for **4**→**7**); (e) DIBAL, toluene, −78 °C (15–67% for **7**→**8**); (f) *p*-TsOH, MeOH (91% for **8**→**9**); (g) DIBAL, toluene, −78 °C, then MeOH, AcOH (58% for **7**→**9**); (h) $BrCH_2CO_2Et$, K_2CO_3, acetone, reflux (90%); (i) *t*-BuOK, THF (93%); (j) MOMCl, DBU, CH_2Cl_2; (k) MeLi, THF; (l) *p*-TsOH, aq THF (43% based on **12** in 3 steps).

other hand, the undesired product **10** was also yielded (19%). Both **8** and **9** were isolated as a single diastereomer, respectively, in these reactions. Even though their relative configurations between OH or OMe at C-1 and Me at C-3 were not carefully examined, these were tentatively assigned as trans based on the spectral similarity to the reported **1**.[12]

For the construction of the benzofuranone portion of **12** (=**A**) employing Dieckmann condensation,[4] the phenolic hydroxyl group of **9** was etherified with $BrCH_2CO_2Et$ in the presence of K_2CO_3 to give **11** (90%). The diester **11** was subjected to Dieckmann condensation by treatment with *t*-BuOK in THF to afford the adduct **12** (93%). It should be mentioned that the keto–enol equilibrium was observed as a matter of course, and the enol form was predominant. The next and remaining subject was the construction of the isopropylidenefuranone framework. In other words, the final crucial step was conversion of the ethoxycarbonyl group of **12** into the isopropylidene group. Our initial attempts to convert **12** to **1** by treatment with excess MeLi and the following acidic work-up did not work.[13] Thus, we turned to prepare the corresponding MOM enol ether **13**.[14] The MOM ether **13**, prepared by treatment with MOMCl and DBU in CH_2Cl_2, was exposed to excess MeLi to give the tertiary alcohol **14**. The resulting unstable alcohol **14** was finally treated with *p*-TsOH in aq THF to give (±)-**1** (43% based on **12** in 3 steps). The various spectral data of synthetic (±)-**1** were in good accord with those of the reported.[1,3] The overall yield was 8.2% in 8 steps based on the starting alkyne **3**.

3. Conclusion

In conclusion, a novel and concise synthesis of (±)-pseudodeflectusin (**1**) was completed in 8 steps from the known alkyne **3** with an overall yield of 8.2%. An alkynal–acetone dicarboxylate cyclocondensation, a chemoselective reduction, and an isopropylidenation have been employed as the key steps. The total number of steps and the overall yield of our synthesis are shorter and better than the reported synthesis (11 steps; 2.0%).

It is also obvious that the enantiospecific synthesis of **1** is possible according to our developed synthetic route, because not only the starting material (=**3**) but also the key intermediate **C** are known to be in optically active form.[6,15]

4. Experimental

4.1. General

Melting points were measured with YANAKO MP-S9 micro-melting point apparatus. IR spectra were recorded with a Shimadzu IR-408 spectrophotometer. ^{1}H NMR spectra were recorded at 300 MHz on a JEOL JNM-AL300 spectrometer. The peak for $CHCl_3$ in $CDCl_3$ (δ 7.26) was used as the internal standard. Chemical shifts are reported in parts per million on the δ scale and *J*-values are given in hertz. ^{13}C NMR spectra were recorded at 75 MHz on a JEOL JNM-AL300 spectrometer. The peak for $CDCl_3$ (δ 77.0) was used as the internal standard. Mass spectra were measured with a JEOL JMS-SX102A or a HITACHI M-80B spectrometer. Column chromatography was carried out on Kanto Chemical Co., Inc. Silica Gel 60N (spherical, neutral, 63–210 μm). TLC analyses were performed on Merck silica gel plates 60 F_{254}.

4.1.1. 5-*tert*-Butyldimethylsilyloxy-2-hexynal (4). To a solution of **3** (228 mg, 1.15 mmol) in dry THF (10 mL), *n*-BuLi (2.66 M in hexane, 0.52 mL, 1.4 mmol) was added at −78 °C under Ar. After stirring for 30 min at 0 °C, DMF (0.13 mL, 1.7 mmol) was added dropwise. After stirring for 10 min, the reaction mixture was quenched with satd aq NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give **4** (237 mg, 91%) as a colorless oil: ^{1}H NMR δ 0.08 (s, 3H), 0.09 (s, 3H), 0.89 (s, 9H), 1.25 (d, *J*=6.0 Hz, 3H), 2.48 (dd, *J*=17.1, 6.3 Hz, 1H), 2.56 (dd, *J*=17.1, 6.0 Hz, 1H), 4.04 (m, 1H), 9.18 (br s, 1H).

4.1.2. Diethyl 4-(2-*tert*-butyldimethylsilyloxy)propyl-2-hydroxyisophthalate (6). To a stirred and ice-cooled mixture of **5** (10.0 g, 49.5 mmol) and Cs_2CO_3 (18.2 g, 55.9 mmol) in dry THF (110 mL), a solution of **4** (8.26 g, 36.5 mmol) in dry THF (20 mL) was added dropwise under Ar. After stirring at room temperature for 2 days, the reaction mixture was quenched with satd aq NH_4Cl and extracted with hexane. The organic layer was washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give **6** (8.07 g, 54%) as a pale yellow oil: ^{1}H NMR δ −0.21 (s, 3H), −0.08 (s, 3H), 0.83 (s, 9H), 1.15 (d, *J*=6.0 Hz, 3H), 1.39 (t, *J*=7.2 Hz, 3H), 1.41 (t, *J*=7.2 Hz, 3H), 2.72 (d, *J*=6.3 Hz, 2H), 4.00–4.13 (m, 1H), 4.35–4.48 (m, 4H), 6.79 (d, *J*=8.1 Hz, 1H), 7.77 (d, *J*=8.1 Hz, 1H), 11.20 (s, 1H); ^{13}C NMR δ −5.1, −4.9, 14.1, 14.2, 18.0, 24.1, 25.8, 44.1, 61.4, 61.6, 68.9, 110.9, 122.2, 123.8, 130.1, 145.1, 158.7, 167.3, 169.8. This was immediately used for the next step.

4.1.3. 7-Ethoxycarbonyl-8-hydroxy-3-methyl-1-isochromanone (7). *(a) Conversion of **6** to **7***: a solution of **6** (8.07 g, 19.7 mmol) and *p*-TsOH·H_2O (0.1 g, 0.5 mmol) in EtOH (150 mL) was stirred at room temperature overnight. After removal of the solvent under reduced pressure, the residue was diluted with water and extracted with EtOAc. The organic layer was washed with satd aq $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give **7** (4.09 g, 83%) as a pale yellow solid: mp 96–98 °C; IR (Nujol) 1710 (s, C=O), 1665 (s, C=O), 1610 (m, C=C) cm^{-1}; ^{1}H NMR δ 1.39 (t, *J*=7.2 Hz, 3H), 1.52 (d, *J*=6.3 Hz, 3H), 2.95 (d, *J*=7.2 Hz, 2H), 4.39 (q, *J*=7.2 Hz, 2H), 4.69 (m, 1H), 6.73 (d, *J*=7.8 Hz, 1H), 8.01 (d, *J*=7.8 Hz, 1H), 12.13 (s, 1H); ^{13}C NMR δ 14.2, 20.6, 35.1, 61.3, 75.3, 110.2, 117.0, 117.4, 137.6, 145.2, 162.6, 166.1, 167.7; HRMS (EI) *m/z* calcd for $C_{13}H_{14}O_5$: 250.0890, found: 250.0833.

*(b) Conversion of **4** to **7***: to a stirred and ice-cooled mixture of **5** (265 mg, 1.31 mmol) and Cs_2CO_3 (750 mg, 2.30 mmol) in dry THF (5 mL), a solution of **4** (237 mg, 1.05 mmol) in dry THF (5 mL) was added dropwise under Ar. After stirring

at room temperature overnight, the reaction mixture was quenched with 1 M HCl (20 mL). This mixture was stirred for 2 days and extracted with ether. The organic layer was washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give **7** (112 mg, 43%).

4.1.4. Ethyl (1*S,3*R**)-1,8-dihydroxy-3-methylisochroman-7-carboxylate (8).** To a stirred solution of **7** (84 mg, 0.34 mmol) in dry toluene (10 mL), DIBAL (0.99 M in toluene, 0.71 mL, 0.70 mmol) was added dropwise at −78 °C under Ar. After stirring for 30 min at −78 °C, the reaction mixture was quenched with MeOH. This was then diluted with satd aq Rochelle's salt and extracted with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give the recovered **7** (14 mg, 17%) and **8** (47 mg, 56%, 67% based on the recovered SM): mp 135–137 °C; IR (Nujol) 3350 (m, O–H), 1665 (s, C=O), 1620 (s, C=C) cm^{-1}; ^1H NMR δ 1.38 (d, J=6.0 Hz, 3H), 1.41 (t, J=7.2 Hz, 3H), 2.56–2.75 (m, 2H), 3.18 (d, J=3.3 Hz, 1H), 4.33–4.48 (m, 3H), 6.20 (d, J=3.3 Hz, 1H), 6.65 (d, J=8.1 Hz, 1H), 7.74 (d, J=8.1 Hz, 1H), 11.33 (s, 1H); ^{13}C NMR δ 14.2, 21.1, 35.8, 61.4, 62.7, 88.4, 110.5, 119.1, 123.4, 129.2, 142.8, 159.0, 170.2; HRMS (EI) m/z calcd for $C_{13}H_{16}O_5$: 252.0995, found: 252.0991.

4.1.5. Ethyl (1*S,3*R**)-8-hydroxy-1-methoxy-3-methylisochroman-7-carboxylate (9).** *(a) Conversion of **8** to **9***: a solution of **8** (47 mg, 0.17 mmol) and p-TsOH·H_2O (5 mg, 0.03 mmol) in MeOH (20 mL) was stirred at room temperature for 2 h. This mixture was diluted with water and extracted with EtOAc. The organic layer was washed with satd aq $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated under reduced pressure to give **9** (45 mg, 91%.) as a white solid: mp 69–70 °C; IR (Nujol) 3350 (w, O–H), 1665 (s, C=O), 1620 (s, C=C) cm^{-1}; ^1H NMR δ 1.37 (d, J=6.0 Hz, 3H), 1.39 (t, J=7.2 Hz, 3H), 2.62 (dd, J=10.5, 17.4 Hz, 1H), 2.71 (dd, J=4.5, 17.4 Hz, 1H), 3.59 (s, 3H), 4.30 (m, 1H), 4.38 (q, J=7.2 Hz, 2H), 5.66 (s, 1H), 6.62 (d, J=8.1 Hz, 1H), 7.73 (d, J=8.1 Hz, 1H), 11.24 (s, 1H); ^{13}C NMR δ 14.2, 21.1, 35.7, 55.4, 61.3, 62.0, 95.0, 110.4, 118.9, 122.5, 129.3, 142.9, 159.3, 170.1; HRMS (EI) m/z calcd for $C_{14}H_{18}O_5$: 266.1153, found: 266.1162.

*(b) Conversion of **7** to **9***: to a stirred solution of **7** (58 mg, 0.23 mmol) in dry toluene (15 mL), DIBAL (0.99 M in toluene, 0.49 mL, 0.49 mmol) was added dropwise at −78 °C under Ar. After stirring for 15 min at −78 °C, the reaction mixture was quenched by the successive addition of MeOH (15 mL) and AcOH (10 mL). After stirring at room temperature for 2 h, this mixture was neutralized with satd aq $NaHCO_3$ and extracted with ether. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give **9** (30 mg, 49%, 58% based on the recovered SM), **7** (7 mg, 12%), and **10** (9 mg, 19%).

10: ^1H NMR δ 1.53 (d, J=6.6 Hz, 3H), 2.92 (d, J=6.9 Hz, 2H), 4.55–4.80 (m, 3H), 6.69 (d, J=7.5 Hz, 1H), 7.44 (d, J=7.5 Hz, 1H), 11.39 (s, 1H).

4.1.6. Ethyl (1*S,3*R**)-8-(ethoxycarbonyl)methoxy-1-methoxy-3-methylisochroman-7-carboxylate (11).** To a solution of **9** (293 mg, 1.10 mmol) in acetone (50 mL), K_2CO_3 (182 mg, 1.32 mmol) and $BrCH_2CO_2Et$ (220 mg, 1.32 mmol) were added. After stirring under reflux for 2 days, the reaction mixture was concentrated under reduced pressure, diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give **11** (348 mg, 90%) as a white solid: mp 45–47 °C; IR (Nujol) 1720 (s, C=O), 1605 (m, C=C) cm^{-1}; ^1H NMR δ 1.30 (t, J=7.2 Hz, 3H), 1.33 (t, J=7.2 Hz, 3H), 1.33 (d, J=6.0 Hz, 3H), 2.61 (dd, J=11.1, 17.1 Hz, 1H), 2.70 (dd, J=4.2, 17.1 Hz, 1H), 3.46 (s, 3H), 4.18–4.35 (m, 1H), 4.28 (q, J=7.2 Hz, 2H), 4.31 (dq, J=1.8, 7.2 Hz, 2H), 4.61 (d, J=15.0 Hz, 1H), 4.74 (d, J=15.0 Hz, 1H), 5.78 (s, 1H), 6.92 (d, J=8.1 Hz, 1H), 7.77 (d, J=8.1 Hz, 1H); ^{13}C NMR δ 14.1, 14.2, 21.0, 35.2, 54.6, 60.8, 61.0, 61.8, 71.6, 95.1, 122.4, 124.5, 129.4, 131.4, 141.3, 156.3, 165.1, 169.1; HRMS (FAB) m/z calcd for $C_{18}H_{24}O_7Na$: 375.1420, found: 375.1420.

4.1.7. Ethyl (7*R,9*S**)-3-hydroxy-9-methoxy-7-methyl-6,9-dihydro-7*H*-furo[3,2-*h*]isochromen-2-carboxylate (12).** To a stirred and ice-cooled solution of **11** (37 mg, 0.11 mmol) in dry THF (10 mL), t-BuOK (30 mg, 0.27 mmol) was added portionwise. After stirring for 5 min, the reaction mixture was diluted with satd aq NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give **12** (30 mg, 93%) as a white solid: mp 88–93 °C; IR (Nujol) 3340 (m, O–H), 1655 (s, C=O), 1605 (m, C=C) cm^{-1}; ^1H NMR δ 1.41 (d, J=6.0 Hz, 3H), 1.45 (t, J=7.2 Hz, 3H), 2.68–2.83 (m, 2H), 3.66 (s, 3H), 4.34 (m, 1H), 4.46 (q, J=7.2 Hz, 2H), 5.90 (s, 1H), 7.02 (d, J=8.1 Hz, 1H), 7.59 (d, J=8.1 Hz, 1H), 8.18 (br s, 1H); ^{13}C NMR δ 14.4, 21.1, 35.5, 55.5, 61.1, 63.0, 94.6, 118.6, 119.3, 120.3, 123.7, 126.3, 136.3, 146.7, 151.1, 162.5; HRMS (EI) m/z calcd for $C_{16}H_{18}O_6$: 304.1103, found: 306.1104.

4.1.8. (7*R,9*S**)-9-Methoxy-3-methoxymethoxy-7-methyl-6,9-dihydro-7*H*-furo[3,2-*h*]isochromen-2-carboxylate (13).** To a solution of **12** (11.3 mg, 36.9 μmol) in dry CH_2Cl_2 (10 mL), DBU (15 mg, 97 μmol) and MOMCl (6.0 mg, 75 μmol) were added. After stirring at room temperature for 20 min, the reaction mixture was diluted with satd aq NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure to give the crude **13** (10.2 mg) as a white solid: ^1H NMR δ 1.35–1.45 (m, 6H), 2.77 (m, 2H), 3.59 (s, 3H), 3.67 (s, 3H), 4.22–4.50 (m, 3H), 5.39 (m, 2H), 5.94 (s, 1H), 7.03 (d, J=8.1 Hz, 1H), 7.65 (d, J=8.1 Hz, 1H). This was used for the next step without purification.

4.1.9. 2-{(7*R,9*S**)-9-Methoxy-3-methoxymethoxy-7-methyl-6,9-dihydro-7*H*-furo[3,2-*h*]isochromen-2-yl}-2-propanol (14).** To a solution of **13** (11.2 mg) in dry THF (5 mL), MeLi (1.04 M in ether; 0.22 mL, 0.23 mmol) was added dropwise at −78 °C under Ar. After stirring for

30 min, the reaction mixture was quenched with satd aq NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure to give the crude **14** (11.5 mg) as a white solid: ^{1}H NMR δ 1.40 (d, J=6.3 Hz, 3H), 1.68 (s, 6H), 2.74 (m, 2H), 3.13 (br s, 1H), 3.60 (s, 3H), 3.64 (s, 3H), 4.32 (m, 1H), 5.13 (s, 2H), 5.85 (s, 1H), 6.95 (d, J=7.8 Hz, 1H), 7.46 (d, J=7.8 Hz, 1H). This was used for the next step without purification.

4.1.10. (7*R,9*S**)-9-Hydroxy-7-methyl-2-(methylethylidine)-6,9-dihydro-7*H*-furo[3,2-*h*]isochromen-3-one; (±)-pseudodeflectusin (1).** The mixture of **14** and *p*-TsOH·H_2O (20 mg, 0.11 mmol) in THF (2 mL) and H_2O (2 mL) was stirred at room temperature for 2 days. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give (±)-**1** (4.1 mg, 43%) as a white solid: mp 169–170 °C; IR (Nujol) 3380 (s, O–H), 1695 (s, C=O), 1650 (s, C=C), 1610 (s, C=C), 1590 (s, C=C) cm^{-1}; ^{1}H NMR δ 1.40 (d, J=6.0 Hz, 3H), 2.12 (s, 3H), 2.36 (s, 3H), 2.71 (dd, J=10.2, 17.4 Hz, 1H), 2.80 (dd, J=3.9, 17.4 Hz, 1H), 2.99 (d, J=3.6 Hz, 1H), 4.46 (m, 1H), 6.28 (d, J=3.6 Hz, 1H), 6.88 (d, J=7.8 Hz, 1H), 7.61 (d, J=7.8 Hz, 1H); ^{13}C NMR δ 17.4, 20.4, 21.1, 35.9, 62.9, 87.8, 119.4, 122.0, 122.6, 123.7, 132.5, 143.8, 145.2, 162.0, 183.3; HRMS (EI) m/z calcd for $C_{15}H_{16}O_4$: 240.1045, found: 260.1046.

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9. They reported the preparation of dimethyl or methyl esters corresponding to **6** and **7** based on the same strategy.[8]
10. The reported yield of the cyclocondensation was 19%.
11. It was noted that this chemoselective DIBAL reduction was unsuccessful in THF.
12. Our conformational analyses based on MM and MOPAC (PM3) calculations using Spartan® '04 also suggested that the trans-diastereomers were more favorable than the cis-isomers.
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