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Studies on the Total Synthesis of Hirtellanine A: Regioselective Synthesis of Benzopyran

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The total synthesis of Hirtellanine A was accomplished by two different synthetic approaches. Hirtellanine A was assembled using a one-pot, tandem acid-mediated deprotection and tautomerization cascade starting from quinone derivative **23**. The key features of the synthesis include a Houben–Hoesch reaction of aryl cyanide **3** with phloroglucinol, a one-pot sequential boronation, a Suzuki–Miyaura cross-coupling of aryl bromide **33** with aryl iodide **26**, and a base-mediated regioselective Claisen rearrangement for the benzopyran construction.

Introduction

Recently, more than 40 new flavonoids were isolated from the roots of *Campylotropis hirtella* (Franch.) Schindl.[1–5] Most of these flavonoids strongly inhibited mitogen-induced splenocyte proliferation. Of these flavonoids, Hirtellanine A (Figure 1) showed very strong B lymphocyte suppression activity (IC_{50} = 0.06 μM) and strong T lymphocyte suppression activity (IC_{50} = 0.92 μM). Compared with Cyclosporin A, Hirtellanine A has a higher B lymphocyte suppression activity and a lower cytotoxicity.[1] However, the amount of Hirtellanine A in the roots of *Campylotropis hirtella* is very low,[6] so a practical synthesis of Hirtellanine A is needed to provide sufficient quantities of Hirtellanine A for additional biological evaluation.

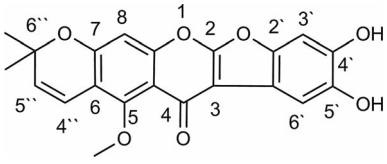

Figure 1. Structure of Hirtellanine A.

In this paper, we document the results of our studies towards the first total synthesis of Hirtellanine A.[7]

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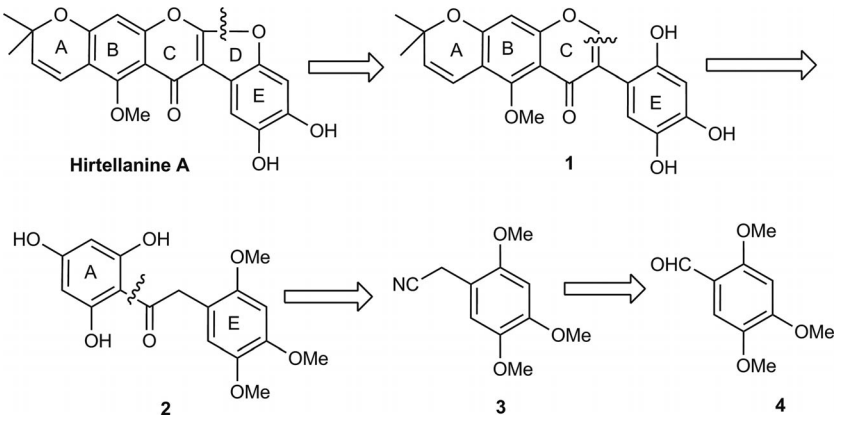
Results and Discussion

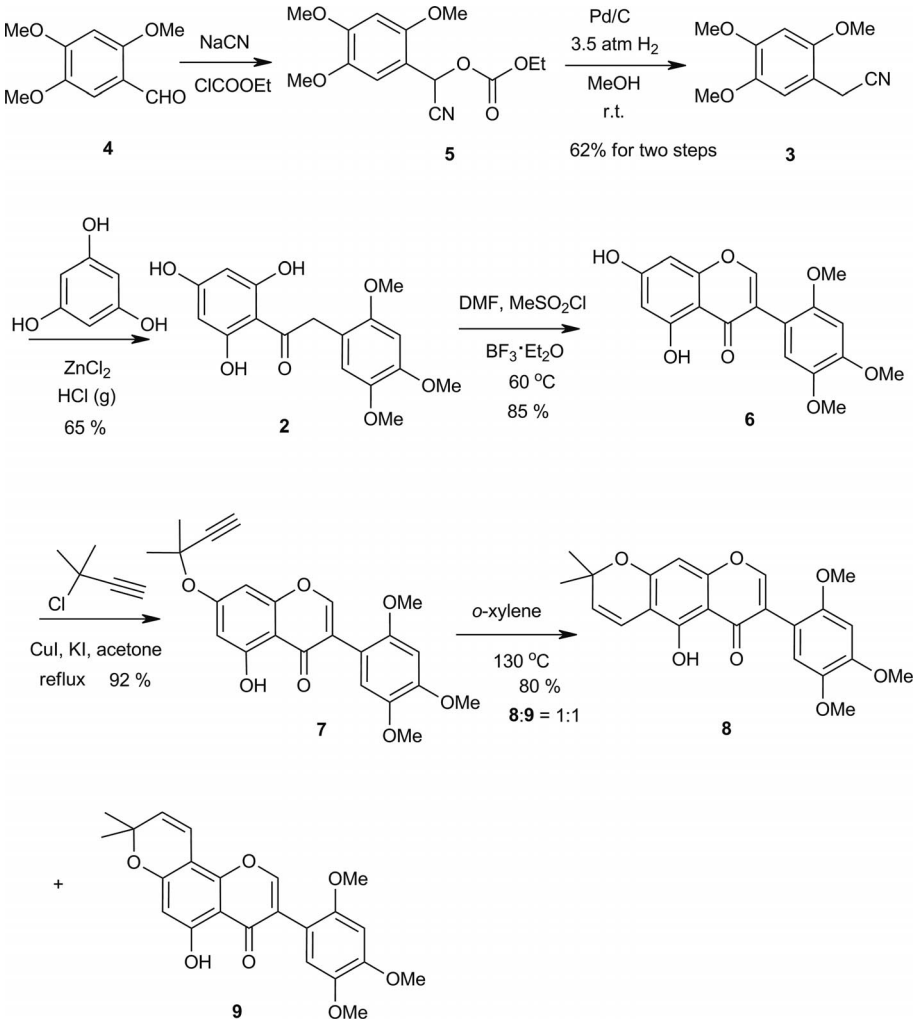
Synthesis of Hirtellanine A Using a Houben–Hoesch Reaction as the Key Step

Our retrosynthetic analysis of Hirtellanine A is shown in Scheme 1. A Houben–Hoesch reaction with aryl cyanide **3** would give intermediate **2**, which could be followed by a Vilsmeier–Haack reaction and a Claisen alkylation to provide key intermediate **1**. An intramolecular Michael addition with subsequent dehydrogenation of 2,4,5-trihydroxy isoflavone derivative **1** was expected to form the Hirtellanine A skeleton.

As a prelude to the total synthesis, we initially set out to prepare intermediate **8** to probe the oxidative cyclization reaction that could deliver the skeleton of Hirtellanine A. As shown in Scheme 2, the synthesis of intermediate **8** started with commercially available 2,4,5-trimethoxybenzaldehyde **4**, which was converted to intermediate **5** by a benzoin condensation reaction. Crude **5** was used directly in a hydrogenation reaction to deliver aryl acetonitrile **3** in a modest overall yield.[8] The Houben–Hoesch reaction was used for the coupling of **3** with phloroglucinol. The coupling reaction went quite smoothly under very mild reaction conditions, and key intermediate **2** was obtained in 65% yield.[9] Compound **2** was subsequently subjected to a BF_3·Et_2O-induced Vilsmeier–Haack-type reaction to give isoflavone **6**.[10] However, attempts to synthesize benzopyran **8** suffered from a lack of regioselectivity in the cyclization. *O*-Alkylation[11] of compound **6** was followed by a thermal Claisen rearrangement to form a 1:1 mixture of **8** and **9** in 80% overall yield.[12] The polarities of **8** and **9** were very similar, and it was extremely difficult to separate these two isomers by flash column chromatography.



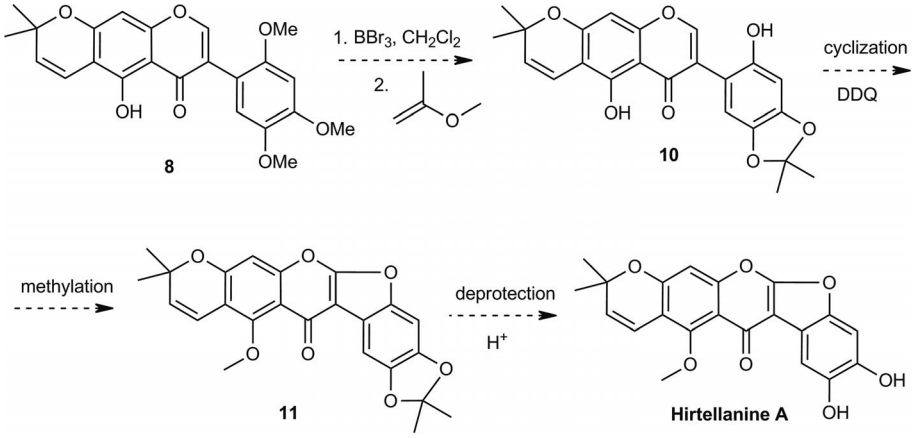
Scheme 1. Retrosynthetic analysis of Hirtellanine A.



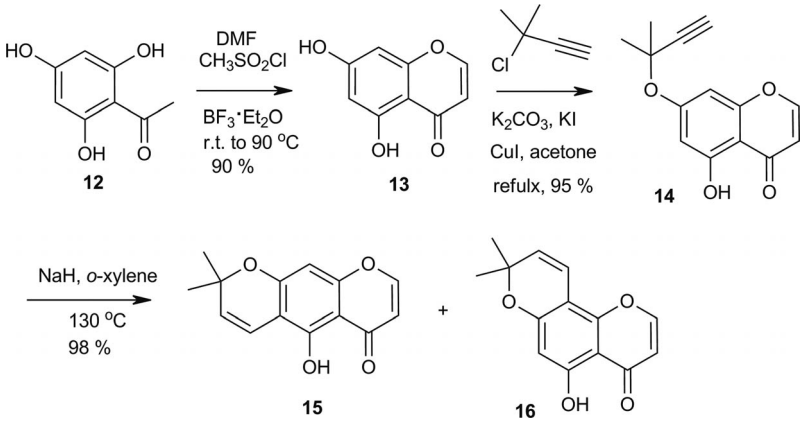
Scheme 2. Synthesis of intermediate **8**.

It was assumed that the demethylation and subsequent cyclization of the mixture of **8** and **9**, as shown in Scheme 3, could lead to the separation of the two isomeric products. Unfortunately, the yield of the demethylation reaction[13] was very low, and the mixture of products was too complex for the desired compound to be identified. The in situ protection of *ortho*-phenolic groups with 2-methoxypropene to give **10** was also attempted, but a similarly complex mixture of products was observed here also. Thus, we decided to give up this approach.

To efficiently convert **7** into **8**, a regioselective alkylation of **7** had to be developed. The necessary conditions for a



Scheme 3. Unsuccessful synthetic route to Hirtellanine A.



Scheme 4. Synthesis of important intermediate **15**.

regioselective Claisen rearrangement could easily be evaluated using readily available flavanone **14**.

Compound **14** was obtained from commercially available acetylphloroglucinol **12** in 90% yield by a Vilsmeier–Haack formylation and subsequent cyclization.[10] As shown in Scheme 4, intensive screening of the reaction conditions was performed to identify appropriate reagents and reaction conditions that would give the regioselective Claisen rearrangement of **14**.

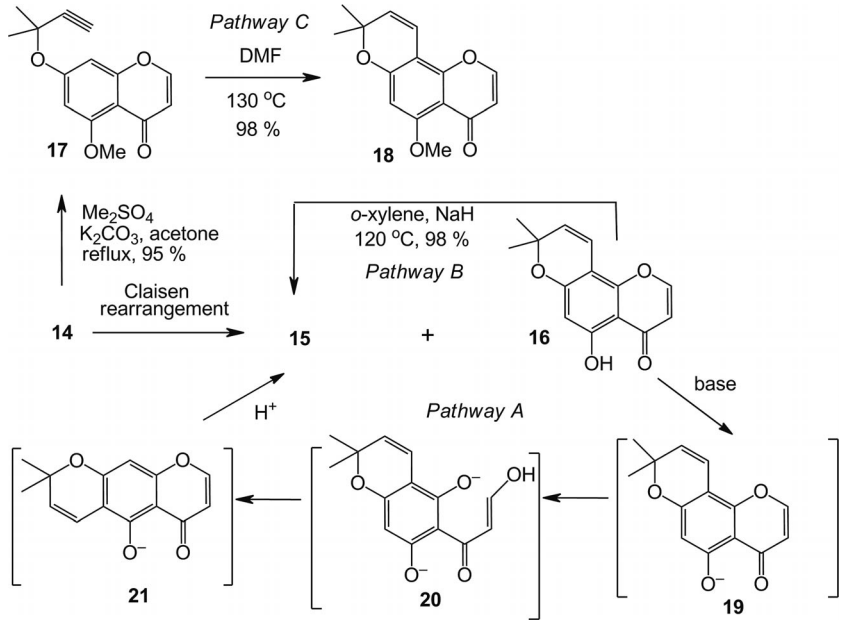
A variety of reaction conditions[14] were attempted, but none of those reaction conditions gave satisfactory results. Interestingly, as shown in Table 1, we observed that the polarity of the solvents significantly affected the regioselectivity of this reaction. Further investigation revealed that the presence of a strong base could control the regioselectivity effectively. NaH was among the best of the reagents tested, and **15** was obtained in approximately quantitative yield. As shown in Scheme 5, the Claisen rearrangement process is a thermodynamically controlled reaction (pathway A), and compound **16** should be the major product of the reaction. However, compound **15** has a linear structure, and probably has a lower enthalpy than **16**. Thus, under the strongly alkaline conditions, the C-ring of compound **16** was opened and reclosed to form **15** (pathway B). This assumption was further confirmed by the results of the Claisen rearrangement of **17**, which gave **18** in 98% yield (pathway C).

Table 1. Optimization of the reaction conditions for the rearrangement of **14**.

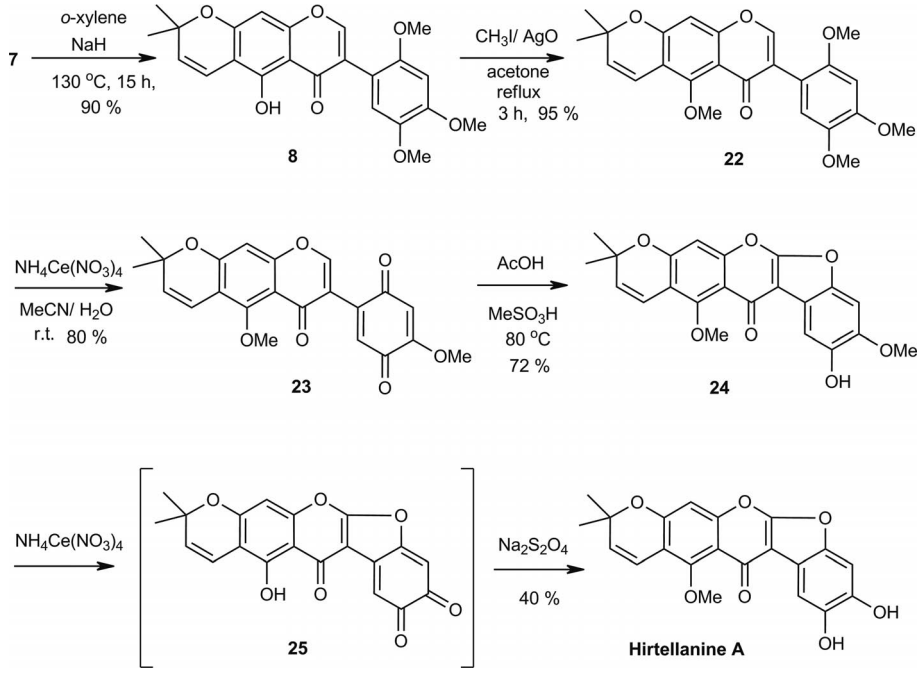
Conditions	Temp. [°C]	Time	Yield [%][a]	**15**:**16**
AcOH	120	20 h	98	22:78
DMF	130	30 h	98	20:80
DMA	130	30 h	83	26:74
Toluene	20	50 h	70[b]	47:53
Xylene	130	30 h	98	60:40
DMF, MW	165	15 min	98	22:78
DMSO, MW	210	18 min	90	24:76
DEA, MW	220	8 min	88	32:68
Dioxane, $PtCl_4$	70	5 h	8	31:69
Pyridine	120	20 h	98	24:76
Xylene, $Ca(OH)_2$[c]	130	20 h	98	87:13
Xylene, Cs_2CO_3[c]	130	16 h	98	96:4
Xylene, KOH[c]	130	16 h	95[d]	>99:trace[e]
Xylene, NaH[c]	130	16 h	98	>99:trace[e]

[a] Calculated based on the signals in the ^1H NMR spectrum. [b] Approximately 30% of **14** was recovered. [c] 6 equiv. of base was used. [d] Approximately 5% of **13** was obtained. [e] Observed by HPLC. DMA = *N*,*N*′-dimethylaniline; DEA = *N*,*N*′-diethylaniline; MW = microwave irradiation.

Having established the optimized regioselective reaction conditions, we re-examined the Claisen rearrangement of **7**



Scheme 5. Regioselectivity and proposed mechanism for the rearrangement of **14**.

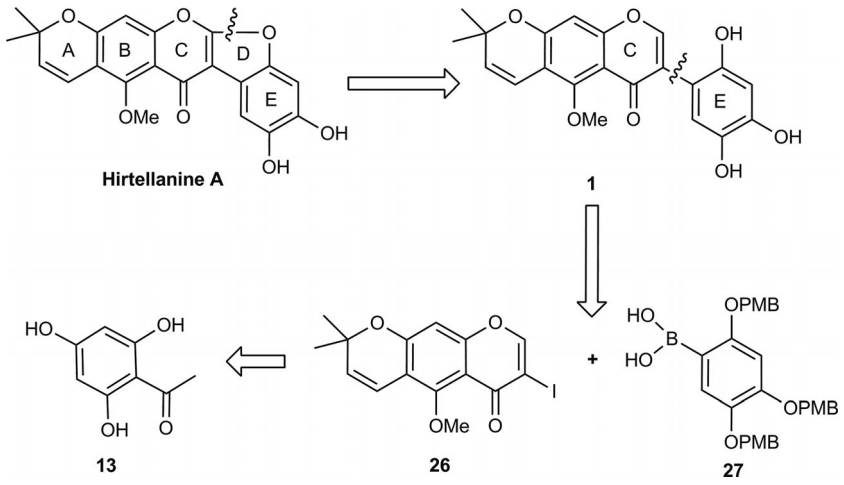


Scheme 6. The linear synthetic approach to Hirtellanine A.

in the presence of NaH in *o*-xylene (Scheme 6). As expected, the reaction gave **8** very cleanly in 90% yield. Subsequently, the methylation of **8** with methyl iodide gave compound **22** in 95% yield.[15] Oxidative demethylation with cerium ammonium nitrate removed the two *para*-methyl groups to yield quinone **23**.[16] To remove the third methyl group on the quinone ring, **23** was treated with methylsulfonic acid, but cyclization product **24** was obtained in 70% yield and the methoxy group remained intact. Theoretically, this reaction occurred by a Michael addition with a tautomerization cascade of double bonds. Finally, an oxidation–reduction system was used to successfully remove the methyl group and give Hirtellanine A in 40% yield.[17]

Synthesis of Hirtellanine A with a Suzuki Coupling as the Key Step

As we had developed an efficient synthetic route to compound **15** using a regioselective Claisen rearrangement, a convergent synthesis of Hirtellanine A was conceived based on the retrosynthetic analysis shown in Scheme 7.

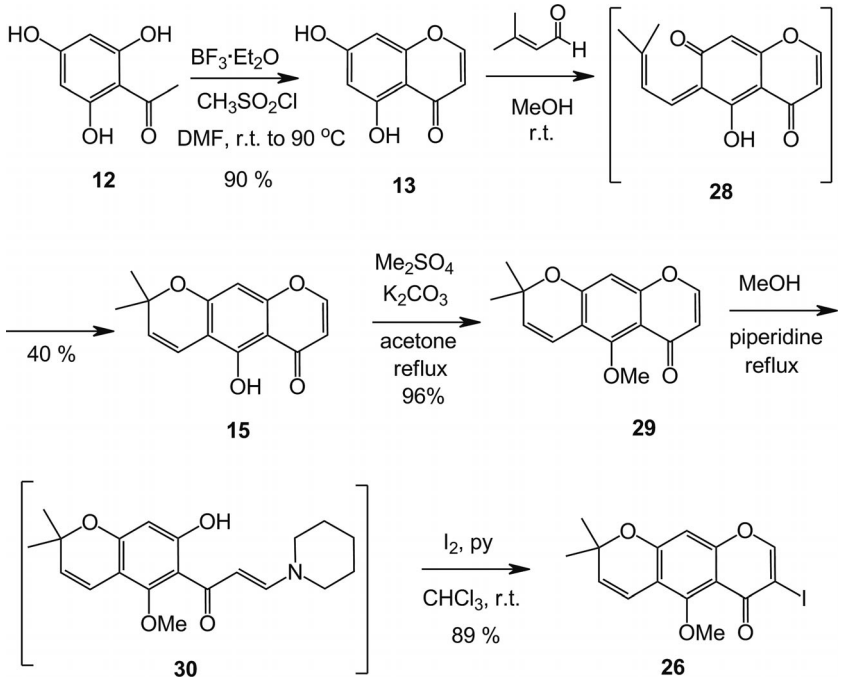


Scheme 7. Retrosynthetic analysis of Hirtellanine A.

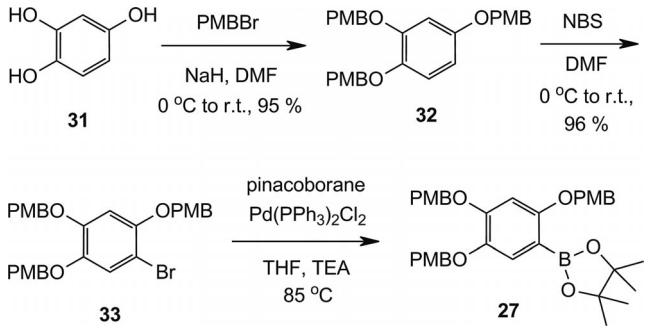
Compound **15** could be obtained from a regioselective Claisen rearrangement as shown in Scheme 4. It could also be obtained from a $Ca(OH)_2$-induced, tandem, regioselective Knoevenagel electrocyclic reaction[18] (Scheme 8) of **13** with 3-methyl-2-butenal in 40% yield. Again, various reaction conditions were explored using reagents such as EDDA (ethylenediammonium diacetate),[19] CaO,[20] DBU (1,8-diazabicycloundec-7-ene),[21] and $CaCl_2$/KOH.[22] The reaction with $Ca(OH)_2$ gave the best result. The methylation of **15** under standard conditions with Me_2SO_4 gave **29** in 96% yield. The γ-pyrone ring of **29** was opened with piperidine in MeOH, and the product was treated with I_2 in the presence of pyridine (2 equiv.) to yield **26** in 89% overall yield.[23]

After a sufficient amount of fragment **26** had been obtained, we focused our efforts on the synthesis of fragment **27**. As shown in Scheme 9, the three hydroxy groups of 1,2,4-Phloroglucinol (**31**) were protected by using *p*-methoxybenzyl bromide.[24] Subsequent bromination[25] with NBS (*N*-bromosuccinimide) at room temperature gave compound **33**, which was expected to deliver key intermediate **27** using a palladium-catalyzed boronation.[26,27] We first chose isopropyl boronate as the boronating reagent, and the reaction was performed in the presence of butyllithium under an Ar atmosphere at –78 °C.

However, the reaction mixture was complex, and the product was not stable during workup. Thus, various boronate reagents and reaction conditions were tested. The



Scheme 8. Synthesis of fragment **26**.

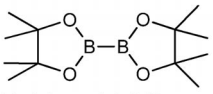
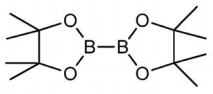
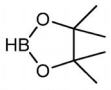


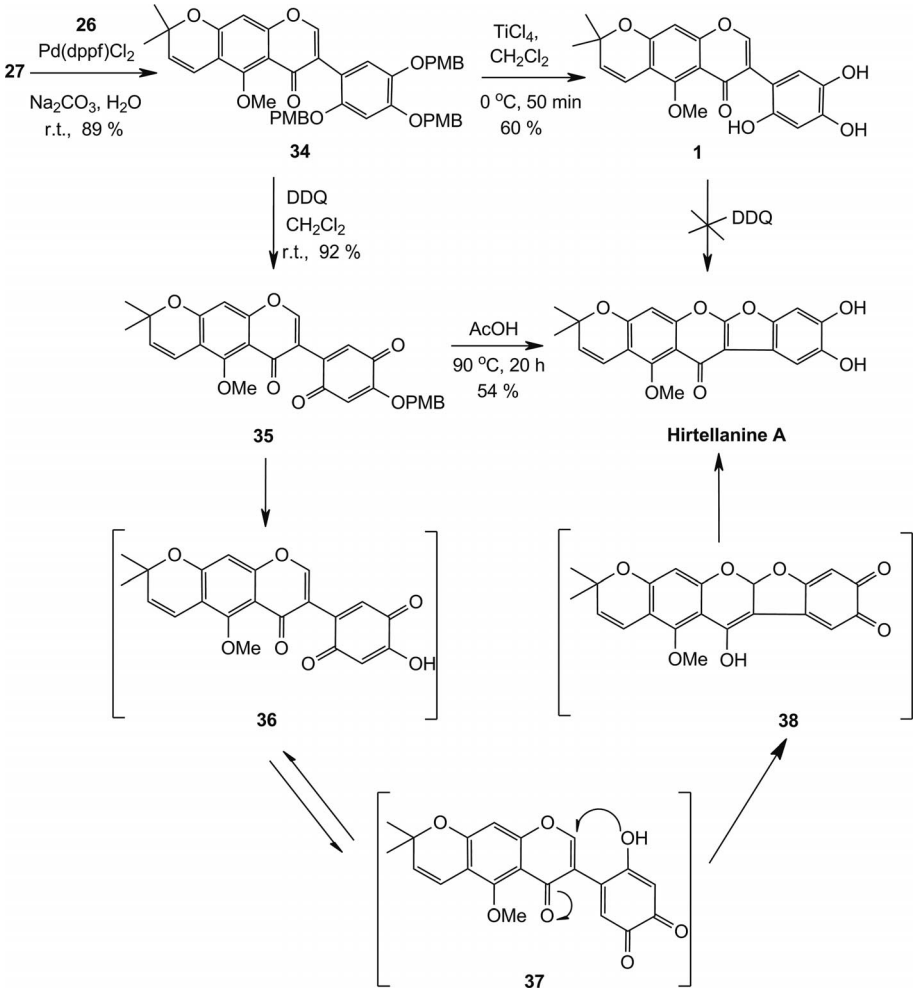
Scheme 9. Synthesis of fragment **27**.

results are shown in Table 2. Both bis(pinacolato)diboron and pinacolborane were examined with different solvents and catalysts. Pinacolborane gave the best results with a palladium catalyst.[28] It is also worth noting that reactions with freshly distilled THF gave better yields than those performed in dioxane under the same reaction conditions.

The assembly of fragments **26** and **27** was performed using a Suzuki–Miyaura coupling as the key reaction.[29] The coupling occurred very smoothly at room temperature in high overall yield. However, some debrominated by-product was observed, and compound **32** was recovered. To avoid the decomposition of boronated compound **27** during the reaction and purification, the Suzuki–Miyaura coupling

Table 2. Exploration of reaction conditions for the conversion of **33** into **27** (TEA = triethylamine).

Entry	Reagent	Conditions	Yield (%)
1	$B(OiPr)_3$ isopropyl borate	*n*BuLi, THF, –78 °C, 30 min	20 (boronic acid)
2	 bis(pinacolato)diboron	$Pd(dppf)Cl_2$ or $Pd(PPh_3)_2Cl_2$, K_2CO_3, dioxane, 85 °C, 20 h	0
3	 bis(pinacolato)diboron	$Pd(dppf)Cl_2$, K_2CO_3, DMF, 150 °C, 5 h	15
4	 pinacolborane	$Pd(PPh_3)_2Cl_2$, TEA, THF (or dioxane), reflux	90



Scheme 10. Synthesis of Hirtellanine A and the proposed mechanism for the cascade tautomerization.

reaction was performed in a one-pot procedure tandem to the boronation. After the boronation reaction finished, the reaction mixture was cooled down to room temperature, and **26**, $Pd(dppf)Cl_2$ [dppf = 1,1′-bis(diphenylphosphanyl)-ferrocene], and an excess of aqueous Na_2CO_3 were added. The reaction mixture was stirred at room temperature overnight, and coupling product **34** was obtained in a very high yield. Normally, boric esters are rather difficult to purify due to their instability. This one-pot tandem reaction avoids the difficult purification of the boric ester and improves the efficiency of the process.

Removal of the *p*-methoxybenzyl (PMB) protecting groups of **34** under acidic conditions gave compound **1** in reasonable yield.[30] However, the oxidative cyclization of **1** with various oxidizing agents was tried without success, and only complex mixtures of products were obtained in all cases. DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) has been reported as a reagent for the removal of the PMB protecting group.[31] We performed the reaction with an excess of DDQ, and we hoped that oxidative cyclization would occur after the PMB protecting groups had been removed. Interestingly, DDQ only removed the two PMB groups in the *para* positions, and quinone **35** was obtained in 92% yield. The expected cyclization was blocked by the remaining PMB protecting group. Fortunately, treatment of **35** with various acids ($MeSO_3H/CHCl_3$, AcOH, HCl/EtOH) led to the formation of the desired product, Hirtellanine A, exclusively. It was assumed that tautomerization took place after the removal of the PMB group. This conversion involved the following mechanistic steps (Scheme 10): tautomerization, intramolecular oxy-Michael addition, and subsequent cascade tautomerizations, and led to the formation of Hirtellanine A in 54% yield.

Conclusions

In summary, we have developed a practical synthetic approach to Hirtellanine A by two different routes. The linear synthesis started from commercially available 2,4,5-trimethoxybenzaldehyde **4**, and the synthesis of Hiretellanine A was accomplished in nine steps with an overall yield of 4.3%. The convergent synthesis started from 2,4,6-trihydroxyacetophenone **12**, and the overall yield of the synthesis was over 30% in eight steps. Compared with the linear synthetic route of Hirtellanine A, this convergent approach avoided the protection and deprotection steps, and the final one-pot, tandem deprotection, tautomerization, intramolecular oxy-Michael addition and subsequent cascade tautomerization improved the synthetic efficiency.[32] In addition, a base-mediated, highly regioselective Claisen rearrangement was discovered, which may have wider applications in the synthesis of biologically significant molecules of the same class in the future.

Experimental Section

2,4,5-Trimethoxybenzeneacetonitrile (3): 1,3,4-Trimethoxybenzaldehyde (5.88 g, 30 mmol) was dissolved in dichloromethane (60 mL), and tetrabutylammonium iodide (554 mg, 1.5 mmol) and ethyl chloroformate (3.14 mL, 33 mmol) were added. The solution was stirred, and KCN (4.09 g, 63 mmol) in water (60 mL) was added dropwise over a period of 90 min. The biphasic solution was stirred at room temperature until TLC indicated that no starting material remained. The mixture was transferred into a separation funnel with the aid of CH_2Cl_2 (200 mL), and the organic phase was washed with water (120 mL), saturated aqueous $NaHCO_3$ solution (120 mL), and brine (120 mL). The organic phase was dried and filtered through a pad of SiO_2 to give the intermediate as a brown oil. The crude product was dissolved in MeOH (100 mL), and Pd/C (10%; 3 g) was added. The slurry was hydrogenated at room temperature (3.5 atm H_2). After 3 d, the reaction mixture was filtered. The solvent was removed in vacuo, and the residue was purified by column chromatography (ethyl acetate/petroleum ether, 1:6) to give **3** (3.85 g, 62%) as a white solid, m.p. 81–83 °C. ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 6.96 (s, 1 H), 6.74 (s, 1 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 3.74 (s, 3 H), 3.68 (s, 2 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 151.8, 150.6, 143.6, 118.7, 114.8, 110.3, 98.4, 56.5, 56.0, 55.8, 17.4 ppm. IR (film): $\tilde{\nu}$ = 3437, 2960, 2249, 1612, 1520, 1450, 1230, 1028, 845 cm^{-1}.

1,4,6-Trihydroxy-2-(2′,4′,5′-trimethoxyphenyl)acetophenone (2): Zinc chloride (350 mg, 26.2 mmol) was added to an ice-cold solution of phloroglucinol (942 mg, 7.47 mmol) and compound **3** (1.29 g, 6.23 mmol) in ether (35 mL) at 0 °C. Dry HCl gas was passed through the solution for 30 min with continuous stirring. The passage of the gas was discontinued, and the mixture was stirred for an additional 20 h at 20 °C. Dry HCl gas was passed through the solution again for 10 min, and the mixture was stirred for an additional 16 h at 20 °C. Water (35 mL) was added to the flask, and the mixture was heated at reflux for 3 h with stirring. The solution was allowed to cool to room temperature, and then it was extracted with ethyl acetate (2 × 60 mL). After drying and concentrating the extract, the residue was purified by flash column chromatography (ethyl acetate/petroleum ether, 1:3) to give **2** (1.35 g, 65%) as a white solid, m.p. 201–203 °C. ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 11.66 (br s, 2 H), 9.20 (br s, 1 H), 6.80 (s, 1 H), 6.68 (s, 1 H), 5.96 (s, 2 H), 4.33 (s, 2 H), 3.82 (s, 3 H), 3.72 (s, 6 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 203.2, 164.6, 164.5, 152.6, 149.4, 143.4, 117.2, 116.4, 104.7, 98.6, 95.2, 56.5, 55.9, 55.85, 44.6 ppm. IR (film): $\tilde{\nu}$ = 3414, 3362, 1632, 1603, 1520, 1207, 1032, 829 cm^{-1}. MS-ESI: *m*/*z* (%) = 335.1 (100) [M + 1]$^+$. HRMS (ESI$^+$): calcd. for $C_{17}H_{19}O_7$ [M + 1]$^+$ 335.1125; found 335.1129.

5,7-Dihydroxy-2′,4′,5′-trimethoxyisoflavone (6): $BF_3{\cdot}Et_2O$ (2.54 mL, 20 mmol) was added dropwise to a solution of compound **2** (1.67 g, 5 mmol) in anhydrous DMF (20 mL) at room temperature over 50 min, and then a solution of methanesulfonyl chloride (1.16 mL, 15 mmol) in anhydrous DMF (5 mL) was added. The mixture was heated at 90 °C for 3 h, and then it was allowed to cool to room temperature. With vigorous stirring, the reaction solution was slowly poured into ice/water (80 mL). After stirring for 30 min, the solution was extracted with ethyl acetate (3 × 80 mL), and the organic phase was washed with saturated aqueous $NaHCO_3$ (50 mL) and water (50 mL). After the extract was dried and concentrated, the crude product was purified by column chromatography (ethyl acetate/petroleum ether, 1:3) to give **6** (1.46 g, 85%) as a yellow solid, m.p. 230–232 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.89 (s, 1 H), 10.86 (s, 1 H), 8.18 (s, 1 H), 6.87 (s, 1 H), 6.76 (s, 1 H), 6.38 (s, 1 H), 6.21 (s, 1 H), 3.81 (s, 3 H), 3.70 (s, 3 H), 3.68 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 180.7, 164.9, 162.5, 158.3, 156.1, 152.7, 150.6, 143.0, 120.9, 116.7, 111.3, 105.0, 99.6, 99.2, 94.4, 67.7, 57.0,

56.6 ppm. IR (film): $\tilde{\nu}$ = 3375, 2960, 2833, 1661, 1525, 1279, 1207, 1034, 812 cm^{-1}. MS-ESI: *m*/*z* (%) = 345.1 (100) $[M + 1]^+$. HRMS (ESI^+): calcd. for $C_{18}H_{17}O_7$ $[M + 1]^+$ 345.0969; found 345.0973.

7-(1′′,1′′-Dimethylpropargyloxy)-5-hydroxy-2′,4′,5′-trimethoxyisoflavone (7): Potassium carbonate (836 mg, 6.06 mmol), potassium iodide (840 mg, 5.05 mmol), the catalyst CuI (4 mg, 0.02 mmol), and then 3-chloro-3-methyl-1-butyne (0.24 mL, 2.22 mmol) were added to a solution of **6** (695 mg, 2.02 mmol) in dry acetone (30 mL) at room temperature under an Ar atmosphere. The reaction mixture was heated at reflux for 3 h. Then the mixture was allowed to cool, the acetone solvent was removed under reduced pressure, and water (35 mL) was added. The mixture was extracted with ethyl acetate (2× 50 mL). After being dried and concentrated, the residue was purified by chromatography (ethyl acetate/petroleum ether, 1:4) to give product **7** (762 mg, 92%) as a yellow solid, m.p. 110–112 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 12.77 (s, 1 H), 7.88 (s, 1 H), 6.88 (s, 1 H), 6.81 (d, *J* = 2.0 Hz, 1 H), 6.69 (d, *J* = 2.0 Hz, 1 H), 6.62 (s, 1 H), 3.92 (s, 3 H), 3.85 (s, 3 H), 3.78 (s, 3 H), 2.69 (s, 1 H), 1.73 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.1, 162.21, 162.06, 157.5, 155.2, 152.2, 150.4, 143.3, 120.8, 115.4, 111.1, 107.2, 103.0, 98.5, 97.6, 85.0, 75.4, 73.0, 75.0, 56.8, 56.4, 29.8 (2 C) ppm. IR (film): $\tilde{\nu}$ = 3437, 3283, 2937, 1655, 1516, 1304, 1207, 1134, 1036 cm^{-1}.

Isoflavone 8 and Isoflavone Derivative 9

Method A: A solution of compound **7** (82 mg, 0.2 mmol) in *o*-xylene (10 mL) was stirred at 130 °C for 20 h under an argon atmosphere. Then the mixture was allowed to cool to room temperature, the reaction solution was concentrated, and the crude product was purified by column chromatography (ethyl acetate/petroleum ether, 1:15 to 1:9) to give products **8** (32 mg, 40%) and **9** (32 mg, 40%) as pale yellow solids.

Method B: NaH (60% dispersed in oil, 240 mg, 6 mmol) was added to a solution of **7** (410 mg, 1 mmol) in *o*-xylene (40 mL). The suspension was heated at 130 °C for 20 h. Then the mixture was allowed to cool to room temperature, and ice/water (30 mL) was added. The aqueous phase was neutralized to pH 5 with hydrochloric acid (1 M). The acidic aqueous phase was extracted with ethyl acetate (2× 30 mL). The combined organic extracts were washed with brine (30 mL), dried and concentrated. The residue was purified by silica gel chromatography (ethyl acetate/petroleum ether, 1:5) to give product **8** (385 mg, 94%) as a pale yellow solid.

Data for 8: M.p. 190–192 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 13.18 (s, 1 H), 7.82 (s, 1 H), 6.87 (s, 1 H), 6.73 (d, *J* = 10.0 Hz, 1 H), 6.62 (s, 1 H), 6.33 (s, 1 H), 5.62 (d, *J* = 9.6 Hz, 1 H), 3.92 (s, 3 H), 3.84 (s, 3 H), 3.77 (s, 3 H), 1.46 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.0, 159.6, 157.5, 157.1, 154.8, 152.2, 150.4, 143.3, 128.3, 120.7, 115.8, 115.4, 111.1, 106.4, 105.8, 98.4, 95.1, 78.2, 57.0, 56.8, 56.4, 28.5 (2 C) ppm. IR (film): $\tilde{\nu}$ = 3435, 2935, 1653, 1572, 1520, 1205, 1150, 1034 cm^{-1}. MS-ESI: *m*/*z* (%) = 411.1 (100) $[M + 1]^+$. HRMS (ESI^+): calcd. for $C_{23}H_{23}O_7$ $[M + 1]^+$ 411.1438; found 411.1452.

Data for 9: M.p. 146–148 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 12.94 (s, 1 H), 7.90 (s, 1 H), 6.88 (s, 1 H), 6.69 (d, *J* = 10.0 Hz, 1 H), 6.62 (s, 1 H), 6.28 (s, 1 H), 5.59 (d, *J* = 10.0 Hz, 1 H), 3.92 (s, 3 H), 3.85 (s, 3 H), 3.78 (s, 3 H), 1.47 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.1, 162.4, 159.6, 154.7, 152.4, 152.2, 150.4, 143.3, 127.6, 120.8, 115.4, 114.9, 111.0, 106.4, 101.4, 100.5, 98.4, 78.2, 57.1, 56.8, 56.4, 28.4 (2 C) ppm. IR (film): $\tilde{\nu}$ = 3437, 2972, 2932, 1661, 1578, 1518, 1464, 1213, 1150, 1032, 821 cm^{-1}.

5,7-Dihydroxychromen-4-one (13): $BF_3{\cdot}Et_2O$ (15.2 mL, 120 mmol) was added dropwise to a solution of acetylphloroglucinol **12** (5.58 g, 30 mmol) in anhydrous DMF (50 mL) over 50 min. A solution of methanesulfonyl chloride (6.95 mL, 90 mmol) in anhydrous DMF (15 mL) was added to the mixture, which was then heated at 90 °C for 3 h. The reaction mixture was then allowed to cool, and was slowly poured into ice/water (120 mL) with vigorous stirring. The crude product was filtered and washed with water to give a dark yellow solid (6.8 g). The filtrate was extracted with ethyl acetate (3× 60 mL). The combined crude product was purified by chromatography (ethyl acetate/petroleum ether, 1:5–1:2) to give **13** (4.82 g, 90.3%) as a yellow solid, m.p. 255 °C (Decomposed). ^1H NMR (400 MHz, [D_6]acetone): δ = 12.76 (s, 1 H), 8.07 (d, *J* = 6.0 Hz, 1 H), 6.39 (s, 1 H), 6.26 (s, 1 H), 6.23 (d, *J* = 6.0 Hz, 1 H) ppm. IR (film): $\tilde{\nu}$ = 3084, 3005, 2930, 2878, 2741, 2629, 1647, 1616, 1612, 1553, 1499, 1466, 1425, 1369, 1313, 1234, 1188, 1167, 1117, 1032, 978 cm^{-1}. ESI-MS: *m*/*z* (%) = 179.1 (100) $[M + 1]^+$.

7-(1′,1′-Dimethylpropargyloxy)-5-hydroxychromone (14): K_2CO_3 (2.51 g, 18.18 mmol), KI (2.52 g, 15.15 mmol), CuI (12 mg, 0.06 mmol), and then 3-chloro-3-methyl-1-butyne (0.71 mL, 6.36 mmol) were added to a solution of **13** (1.08 g, 6.06 mmol) in dry acetone (50 mL) at room temperature under an Ar atmosphere. The reaction mixture was heated at reflux for 3 h. Then the mixture was allowed to cool, and the acetone solvent was removed under reduced pressure. Water (60 mL) was added, and the mixture was extracted with ethyl acetate (2× 60 mL). After the extract was dried and concentrated, the residue was purified by chromatography (ethyl acetate/petroleum ether, 1:5) to give product **14** (1.41 g, 95.2%) as a yellow solid, m.p. 112–113 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 12.47 (s, 1 H), 7.75 (d, *J* = 6.0 Hz, 1 H), 6.77 (d, *J* = 2.0 Hz, 1 H), 6.69 (d, *J* = 2.0 Hz, 1 H), 6.22 (d, *J* = 5.6 Hz, 1 H), 2.68 (s, 1 H), 1.72 (s, 6 H) ppm. ESI-MS: *m*/*z* (%) = 245.2 (100) $[M + 1]^+$.

Chromone Derivative 15

Method A: NaH (60% dispersed in oil, 480 mg, 12 mmol) was added to a solution of **14** (508 mg, 2 mmol) in *o*-xylene (40 mL). The suspension was heated at 130 °C for 20 h. Then the mixture was allowed to cool to room temperature, and ice/water (30 mL) was added. The aqueous phase was neutralized to pH 5 with hydrochloric acid (1 M). The acidic aqueous phase was extracted with ethyl acetate (2× 35 mL). The combined organic extracts were washed with brine (30 mL), dried, and concentrated. The residue was purified by silica gel chromatography (ethyl acetate/petroleum ether, 1:6) to give product **15** (498 mg, 98.0%) as a yellow solid, m.p. 139–141 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 12.86 (s, 1 H), 7.70 (d, *J* = 6.0 Hz, 1 H), 6.71 (d, *J* = 10.0 Hz, 1 H), 6.31 (s, 1 H), 6.19 (d, *J* = 5.6 Hz, 1 H), 5.62 (d, *J* = 10.0 Hz, 1 H), 1.46 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.6, 128.5, 115.6, 111.4, 59.3, 28.6 ppm. IR (film): $\tilde{\nu}$ = 3441, 3070, 2976, 2926, 1655, 1628, 1574, 1481, 1423, 1396, 1313, 1290, 1254, 1165, 1115, 1074, 839, 833, 777, 702, 633, 530, 505 cm^{-1}. ESI-MS: *m*/*z* = 245.2 (100) $[M + 1]^+$. Compound **16** could be converted into **15** in 98.1% yield under similar reaction conditions.

Method B: 3-Methyl-2-butenal (1.33 mL, 13.75 mmol) was added to a stirring mixture of **13** (490 mg, 2.75 mmol) and $Ca(OH)_2$ (407 mg, 5.50 mmol) in methanol (20 mL) at room temperature. The mixture was stirred for 72 h at room temperature, then the methanol was removed in vacuo, and the mixture was diluted with ethyl acetate (40 mL). The separated organic phase was washed with hydrochloric acid (2 M), water, and brine. The dried and concentrated residue was purified by silica gel chromatography (ethyl acetate/petroleum ether, 1:10–1:6) to give product **15** (252 mg, 40.0%) as a yellow solid.

Chromone Derivative 16: A solution of **14** (25 mg, 0.1 mmol) in DMF (3 mL) was heated at 130 °C for 25 h. Then the mixture was allowed to cool to room temperature and ice/water (15 mL) was added. The mixture was extracted with ethyl acetate (2× 20 mL). The organic phase was washed with water (15 mL) and brine (15 mL). The dried and concentrated extract was evaluated by ^{1}H NMR spectroscopy; the residue consisted of a mixture of **15** and **16** in a 1:4 ratio. The residue was purified by preparative TLC (ethyl acetate/petroleum ether, 1:9) to give **16** (20 mg, 80.0%) as a yellow solid, m.p. 112–114 °C. ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 12.83 (s, 1 H), 8.16 (d, J = 6.0 Hz, 1 H), 6.69 (d, J = 10.0 Hz, 1 H), 6.27 (d, J = 6.0 Hz, 1 H), 6.18 (s, 1 H), 5.75 (d, J = 10.0 Hz, 1 H), 1.46 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.1, 128.1, 114.2, 111.2, 99.8, 78.3, 27.6 ppm. IR (film): $\tilde{\nu}$ = 3441, 3076, 2970, 2926, 1655, 1628, 1578, 1466, 1450, 1414, 1383, 1296, 1211, 1155, 1121, 1078, 1013, 914, 837, 783, 702, 563 cm^{-1}. ESI-MS: m/z (%) = 245.2 (100) [M + 1]$^+$.

7-(1,1-Dimethylpropargyloxy)-5-methoxychromone (17): Product **17** was prepared according to the same procedure as for the synthesis of **29**. The reaction gave a yellow solid product in 95.0% yield, m.p. 147–149 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, J = 6.0 Hz, 1 H), 6.95 (s, 1 H), 6.55 (s, 1 H), 6.18 (d, J = 5.6 Hz, 1 H), 3.92 (s, 3 H), 2.70 (s, 1 H), 1.73 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 156.1, 155.7, 154.7, 148.2, 109.9, 94.9, 94.12, 94.10, 80.2, 70.7, 68.1, 51.9, 25.0 ppm. IR (film): $\tilde{\nu}$ = 3447, 3240, 3219, 3072, 2989, 1655, 1618, 1601, 1562, 1470, 1456, 1418, 1286, 1140, 1109, 835, 685 cm^{-1}. HRMS (ESI$^+$): calcd. for $C_{15}H_{15}O_4$ [M + 1]$^+$ 259.0965; found 259.0971.

Chromone Derivative 18: A solution of **17** (26 mg, 0.1 mmol) in DMF (3 mL) was heated at 165 °C by microwave irradiation (100 W) for 18 min. The solution was cooled to room temperature, and then water (10 mL) was added. After filtration and drying, pure **18** (25 mg, 96.2%) was obtained as a yellow solid, m.p. 230–233 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, J = 6.0 Hz, 1 H), 6.69 (d, J = 10.0 Hz, 1 H), 6.30 (s, 1 H), 6.18 (d, J = 5.6 Hz, 1 H), 5.58 (d, J = 10.0 Hz, 1 H), 3.92 (s, 3 H), 1.47 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.0, 160.9, 158.0, 154.4, 152.5, 127.7, 115.3, 114.6, 110.6, 102.8, 96.8, 78.3 56.7, 28.5 ppm. IR (film): $\tilde{\nu}$ = 3447, 3092, 2966, 2927, 2856, 1647, 1593, 1572, 1481, 1389, 1358, 1290, 1202, 1159, 1107, 1030, 833, 781, 704, 528, 442 cm^{-1}. HRMS (ESI$^+$): calcd. for $C_{15}H_{15}O_4$ [M + 1]$^+$ 259.0965; found 259.0970.

Isoflavone Derivative 22: Methyl iodide (0.13 mL, 2.5 mmol) and silver oxide (693 mg, 3 mmol) were added to a solution of **8** (205 mg, 0.5 mmol) in acetone (25 mL). The mixture was heated at reflux for 3 h. After it was allowed to cool to room temperature, the mixture was filtered and washed with acetone (10 mL). The filtrate was concentrated, and the crude product was purified by column chromatography (ethyl acetate/petroleum ether, 1:6) to give product **22** (201 mg, 95%) as a pale yellow solid, m.p. 125–127 °C. ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 7.90 (s, 1 H), 6.93 (s, 1 H), 6.77 (s, 1 H), 6.74 (d, J = 9.6 Hz, 1 H), 6.61 (s, 1 H), 5.88 (d, J = 10.0 Hz, 1 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.77 (s, 3 H), 3.75 (s, 3 H), 1.47 (s, 6 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 173.8, 158.9, 157.9, 155.8, 152.7, 152.3, 150.6, 143.4, 131.2, 123.3, 117.1, 116.0, 113.34, 113.18, 113.10, 100.45, 98.98, 77.8, 62.1, 56.53, 56.24, 55.8, 27.7 (2 C) ppm. IR (film): $\tilde{\nu}$ = 3435, 2935, 1645, 1606, 1514, 1215, 1203, 1031, 831 cm^{-1}. MS-ESI: m/z (%) = 425.2 (100) [M + 1]$^+$. HRMS (ESI$^+$): calcd. for $C_{24}H_{25}O_7$ [M + 1]$^+$ 425.1595; found 425.1601.

Isoflavone Quinone Derivative 23: A solution of cerium ammonium nitrate (274 mg, 0.5 mmol) in water (2 mL) was added to a solution of **22** (85 mg, 0.2 mmol) in acetonitrile (6 mL) in an ice/water bath. After stirring for 1 h, water (20 mL) was added. The solution was extracted with ethyl acetate (2× 35 mL), and the organic phase was washed with water (20 mL) and brine (20 mL). After drying and concentrating, the residue was purified by column chromatography (ethyl acetate/petroleum ether, 1:2) to give **23** (59 mg, 75%) as a pale red solid, m.p. 243–245 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (s, 1 H), 6.73 (d, J = 10.4 Hz, 1 H), 6.61 (s, 1 H), 6.02 (s, 1 H), 5.74 (d, J = 10.0 Hz, 1 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 1.47 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.3, 182.1, 173.7, 171.4, 158.80, 158.17, 155.89, 155.38, 138.0, 134.0, 131.3, 117.1, 116.1, 114.1, 112.9, 108.1, 101.1, 78.2, 63.1, 60.7, 56.6, 28.6 (2 C) ppm. IR (film): $\tilde{\nu}$ = 3437, 3423, 1661, 1641, 1597, 1294, 1198, 1126, 1063 cm^{-1}. MS-ESI: m/z (%) = 395.1 (100) [M + 1]$^+$. HRMS (ESI$^+$): calcd. for $C_{22}H_{19}O_7$ [M + 1]$^+$ 395.1125; found 395.1134.

Coumaronochromone Derivative 24: Methanesulfonic acid (0.6 mL) was added to a stirred solution of **23** (40 mg, 0.1 mmol) in glacial acetic acid (3 mL) at room temperature. The reaction proceeded at 90 °C for 4 h and was monitored by HPLC. Then the mixture was allowed to cool to room temperature, and it was poured into cold water (20 mL) and stirred for 15 min. The solution was extracted with ethyl acetate (2× 40 mL), and then the organic phase was washed with saturated sodium hydrogen carbonate (25 mL) and brine (25 mL). The dried and concentrated residue was purified by column chromatography (ethyl acetate/petroleum ether, 1:2 to 1:1) to afford **24** (20 mg, 50%) as an off-white solid. ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 7.52 (s, 1 H), 7.34 (s, 1 H), 6.81 (s, 1 H), 6.77 (d, J = 10.0 Hz, 1 H), 5.92 (d, J = 10.4 Hz, 1 H), 5.62 (s, 1 H, -OH), 3.95 (s, 3 H), 3.93 (s, 3 H), 1.49 (s, 6 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 172.5, 163.4, 157.5, 156.1, 155.8, 147.3, 145.7, 143.0, 132.4, 115.81, 115.46, 114.0, 112.4, 106.6, 101.8, 99.6, 97.6, 78.7, 56.9, 55.6, 28.6 (2 C) ppm. MS-ESI: m/z (%) = 395.1 (100) [M + 1]$^+$. HRMS (ESI$^+$): calcd. for $C_{22}H_{19}O_7$ [M + 1]$^+$ 395.1125; found 395.1135.

Chromone Derivative 29: K_2CO_3 (3.79 g, 28 mmol) was added to a solution of **15** (488 mg, 2 mmol) in dry acetone (50 mL). After stirring for 10 min in an ice/water bath, Me_2SO_4 (1.33 mL, 14 mmol) was added dropwise over 5 min. The mixture was heated at reflux for 3 h under an Ar atmosphere. Then the mixture was allowed to cool to room temperature, and water (30 mL) was added. Stirring was continued for 20 min, and then the acetone solvent was removed under reduced pressure. The mixture was extracted with ethyl acetate (2× 40 mL), and the organic phase was washed with brine (25 mL), dried, and concentrated. The residue was purified by chromatography (ethyl acetate/petroleum ether, 1:5–1:3) to give product **29** (492 mg, 95.4%) as a light yellow solid, m.p. 96–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, J = 6.0 Hz, 1 H), 6.62 (d, J = 10.0 Hz, 1 H), 6.47 (s, 1 H), 6.05 (d, J = 6.0 Hz, 1 H), 5.63 (d, J = 10.0 Hz, 1 H), 3.78 (s, 3 H), 1.35 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.3, 158.97, 158.26, 155.4, 153.27, 153.08, 131.0, 116.1, 113.98, 113.62, 113.34, 101.0, 95.7, 62.9, 28.5 ppm. IR (film): $\tilde{\nu}$ = 3447, 3074, 2978, 2941, 2845, 1661, 1639, 1603, 1558, 1466, 1433, 1400, 1354, 1283, 1252, 1157, 1119, 1097, 1067, 1024, 947, 897, 845, 831, 798, 714, 526, 484 cm^{-1}. HRMS (ESI$^+$): calcd. for $C_{15}H_{15}O_4$ [M + 1]$^+$ 259.0965; found 259.0970.

Chromone Derivative 26: Piperidine (2 mL) was added to a stirred solution of **29** (320 mg, 1.24 mmol) in MeOH (30 mL). The solution was heated at reflux for 2 h and then allowed to cool to room temperature. The solution was concentrated to dryness to give a yellow oil, which was dissolved in CH_2Cl_2 (40 mL). Pyridine (196 mg, 2.48 mmol) and a solution of iodine (788 mg, 6.20 mmol) in CH_2Cl_2 (10 mL) were added. After stirring overnight, Na_2SO_3

(saturated aq.; 30 mL) was added, and the mixture was stirred for an additional 10 min. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (30 mL). The combined organic extracts were washed with H_2O (30 mL), dried, and concentrated. The residue was purified by chromatography (ethyl acetate/petroleum ether, 1:5) to give **26** (424 mg, 89.1%) as an off-white liquid, which solidified after some time to give an off-white solid, m.p. 121–123 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (s, 1 H), 6.65 (d, J = 10.0 Hz, 1 H), 6.51 (s, 1 H), 5.68 (d, J = 6.0 Hz, 1 H), 3.83 (s, 3 H), 1.40 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 158.6, 156.1, 155.4, 131.7, 115.9, 113.9, 111.0, 100.7, 89.0, 78.2, 63.1, 28.7 ppm. IR (film): $\tilde{\nu}$ = 3421, 2943, 2849, 1643, 1603, 1466, 1427, 1350, 1275, 1217, 1123, 1051, 947, 879, 839, 769, 681, 552 cm^{-1}. HRMS (ESI$^+$): calcd. for $C_{15}H_{14}IO_4$ $[M + 1]^+$ 384.9931; found 384.9938.

1,2,4-Tris(*p*-methoxybenzyloxy)benzene (32): NaH (60% dispersed in oil, 1.05 g, 24 mmol) was added to a solution of 1,2,4-triphenol (504 mg, 4 mmol) in DMF (40 mL) in an ice/water bath. PMBBr (3.21 g, 16 mmol) was added dropwise over 20 min with vigorous stirring. The reaction mixture was stirred at 0 °C for 2 h, and at room temperature for 16 h. Ice-water (60 mL) was added slowly, which resulted in the formation of a large amount of a white solid. The product was filtered and washed with water (20 mL) to yield a grey solid. The filtrate was extracted with ethyl acetate (2× 60 mL). The organic phase was washed with water (30 mL) and brine (30 mL), dried, and concentrated. The crude product was purified by chromatography (ethyl acetate/petroleum ether, 1:5–1:3) to give **32** (1.88 g, 97.1%) as white solid, m.p. 99–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.31 (m, 6 H), 6.91–6.82 (m, 7 H), 6.63 (d, J = 2.4 Hz, 1 H), 6.45 (dd, J = 2.4, 8.8 Hz, 1 H), 5.02 (s, 2 H), 4.98 (s, 2 H), 4.88 (s, 2 H), 3.81 (s, 9 H) ppm. IR (film): $\tilde{\nu}$ = 3447, 3009, 2934, 2835, 1612, 1587, 1514, 1460, 1379, 1302, 1250, 1213, 1173, 1111, 1034, 1003, 862, 820, 558, 519 cm^{-1}.

1-Bromo-2,4,5-tris(*p*-methoxybenzyloxy)benzene (33): A solution of NBS (263 mg, 1.47 mmol) in DMF (3 mL) was added dropwise to a solution of **32** (680 mg, 1.4 mmol) in DMF (15 mL) at 0 °C over 5 min. After stirring at 0 °C for 1.5 h, ice/water (40 mL) was slowly added to the reaction mixture, and a large amount of a white solid was formed. After the reaction mixture was filtered and washed with water (20 mL), a grey solid was obtained. The filtrate was extracted with ethyl acetate (2× 30 mL). The organic phase was washed with water and brine, dried, and concentrated. The crude product was purified by chromatography (ethyl acetate/petroleum ether, 1:5–1:2) to give **33** (760 mg, 95.8%) as a white solid, m.p. 82–84 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.26 (m, 6 H), 7.13 (s, 1 H), 6.91–6.86 (m, 6 H), 6.60 (s, 1 H), 4.99 (s, 2 H), 4.97 (s, 2 H), 4.94 (s, 2 H), 3.81 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7, 146.2, 145.3, 140.5, 125.64, 125.44, 125.29, 125.13, 124.99, 117.1, 110.22, 110.18, 101.2, 99.7 ppm. IR (film): $\tilde{\nu}$ = 3447, 3011, 2949, 2908, 2860, 1614, 1516, 1460, 1379, 1304, 1250, 1194, 1173, 1034, 862, 820, 752, 559, 519 cm^{-1}. HRMS (ESI$^+$): calcd. for $C_{30}H_{29}BrNaO_6$ $[M + Na]^+$ 587.1040; found 587.1038.

1-(4′,4′,5′,5′-Tetramethyl-1′,3′,2′-dioxaborolyl)-2,4,5-tris(*p*-methoxybenzyloxy)benzene (27): TEA (0.8 mL, 6 mmol) and pinacolborane (0.75 mL, 5 mmol) were added to a solution of 1-bromo-2,4,5-tris(*p*-methoxybenzyloxy)benzene (564 mg, 1 mmol) and Pd(PPh$_3$)$_2$Cl$_2$ (72 mg, 0.1 mmol) in THF (25 mL) under an Ar atmosphere. The mixture was heated at 80 °C for 20 h. After the reaction mixture had cooled and had been concentrated, it was treated with Et_2O (50 mL). The ether-insoluble black precipitate was removed by filtration through Celite. Then the filtrate was concentrated, and the residue was used directly in the next step. Due to instability during purification by silica gel chromatography, characterization was carried out directly on crude **27**. ^{1}H NMR (400 MHz, [D$_6$]-acetone): δ = 7.46 (d, J = 8.4 Hz, 2 H), 7.36–7.30 (m, 5 H), 6.87–6.85 (m, 6 H), 6.56 (s, 1 H), 5.05 (s, 2 H), 4.99 (s, 2 H), 4.93 (s, 2 H), 3.82 (s, 3 H), 3.81 (s, 6 H), 1.34 (s, 12 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 160.2, 159.84, 159.76, 159.69, 159.39, 133.5, 143.1, 130.36, 130.28, 129.87, 129.71, 129.61, 129.51, 129.44, 128.7, 124.6, 117.4, 113.99, 113.94, 113.77, 113.6, 105.9, 103.8, 102.2, 83.1, 72.31, 72.02, 70.98, 70.60, 70.47, 69.99, 54.88, 54.84, 24.6 ppm. HRMS (ESI$^+$): calcd. for $C_{36}H_{41}BNaO_8$ $[M + Na]^+$ 635.2787; found 635.6789.

Isoflavone Derivative 34: TEA (1.32 mL, 9.36 mmol) and pinacolborane (1.17 mL, 7.80 mmol) were added to a solution of **33** (881 mg, 1.56 mmol) and Pd(PPh$_3$)$_2$Cl$_2$ (110 mg, 0.16 mmol) in THF (30 mL) under an Ar atmosphere. The mixture was heated at 80 °C for 20 h. Then the mixture was allowed to cool to room temperature, and **26** (300 mg, 0.78 mmol), Pd(dppf)Cl$_2$ (99 mg, 0.12 mmol), and a solution of Na_2CO_3 (1.18 g, 10.92 mmol) in H_2O (4 mL) were added under an Ar atmosphere. The mixture was stirred at room temperature overnight. After TLC showed that **26** had reacted completely, the reaction mixture was filtered, and the residue was washed with THF (10 mL). The filtrate was concentrated, and ethyl acetate (80 mL) was added. The organic phase was washed with $NaHCO_3$ (saturated aq.; 20 mL) and brine (20 mL). After drying and concentrating, the residue was purified by chromatography (ethyl acetate/petroleum ether, 1:4–1:2) to give **34** (519 mg, 89.5%) as a grey-white solid, m.p. 152–154 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (s, 1 H), 7.34–7.31 (m, 4 H), 7.21 (d, J = 7.2 Hz, 2 H), 7.02 (s, 1 H), 6.88 (br., 4 H), 6.81 (d, J = 7.2 Hz, 2 H), 6.76 (d, J = 10.0 Hz, 1 H), 6.68 (s, 1 H), 6.58 (s, 1 H), 5.72 (d, J = 10.0 Hz, 1 H), 5.05 (s, 2 H), 5.01 (s, 2 H), 4.87 (s, 2 H), 3.86–3.77 (m, 12 H), 1.47 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.9, 159.6, 158.9, 158.0, 155.9, 152.6, 151.8, 150.1, 143.6, 130.8, 129.96, 129.63, 129.29, 122.7, 120.1, 116.4, 114.73, 114.14, 114.01, 113.49, 113.34, 104.2, 100.8, 77.8, 72.6, 71.93, 71.78, 63.0, 55.5, 28.5 ppm. IR (film): $\tilde{\nu}$ = 3447, 2966, 2930, 2835, 1649, 1605, 1516, 1458, 1385, 1248, 1173, 1148, 1063, 1032, 822, 779, 567, 513 cm^{-1}. HRMS (ESI$^+$): calcd. for $C_{45}H_{43}O_{10}$ $[M + 1]^+$ 743.2851; found 743.2831.

Isoflavone Derivative 1: $TiCl_4$ (0.04 mL, 0.4 mmol) was added dropwise to a solution of **34** (50 mg, 0.07 mmol) in CH_2Cl_2 (4 mL) at 0 °C under an Ar atmosphere. After being stirred for 1 h at 0 °C, the reaction solution was quenched by treatment with ice/water (15 mL). The solvent was removed, and the residue was extracted with ethyl acetate (2× 20 mL). The organic phase was washed with water (10 mL) and brine (10 mL). After drying and concentrating, the residue was quickly purified by silica gel chromatography (ethyl acetate/petroleum ether, 1:1–5:1) to give **1** (15.5 mg, 60.3%) as a pale red solid, m.p. 167–169 °C. ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 8.12 (s, 1 H), 6.77 (d, J = 10.4 Hz, 1 H), 6.73 (s, 1 H), 6.71 (s, 1 H), 6.49 (s, 1 H), 5.94 (d, J = 10.0 Hz, 1 H), 3.87 (s, 3 H), 1.54 (s, 6 H) ppm. IR (film): $\tilde{\nu}$ = 3385, 3804, 2972, 2930, 1635, 1605, 1585, 1514, 1466, 1450, 1364, 1286, 1191, 1128, 1065, 959, 883, 831, 781, 698 cm^{-1}. HRMS (ESI$^+$): calcd. for $C_{21}H_{19}O_7$ $[M + 1]^+$ 383.1125; found 383.1128. The compound was unstable, and it decomposed in [D$_6$]acetone overnight; thus, its ^{13}C NMR spectrum could not be obtained.

Isoflavone Quinone Derivative 35: A solution of DDQ (212 mg, 1.68 mmol) in CH_2Cl_2 (2 mL) was added dropwise over 3 min to a solution of **34** (250 mg, 0.34 mmol) in a mixed solvent of CH_2Cl_2 (13 mL) and H_2O (0.15 mL) in an ice/water bath. The reaction proceeded at 0 °C for 30 min and at room temperature for 2 h, and

was monitored by TLC. $NaHCO_3$ (saturated aq.; 15 mL) was added. After stirring for 10 min, CH_2Cl_2 (60 mL) was added. The organic phase was washed with H_2O (20 mL) and brine (20 mL). After drying and concentrating the extract, the residue was purified by chromatography (ethyl acetate/petroleum ether, 1:4–1:2) to give **35** (155 mg, 91.8%) as a yellow solid, m.p. 128–130 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.94 (s, 1 H), 7.33 (d, J = 8.4 Hz, 2 H), 7.22 (s, 1 H), 6.92 (d, J = 8.4 Hz, 1 H), 6.72 (d, J = 10.0 Hz, 1 H), 6.60 (s, 1 H), 6.06 (s, 1 H), 5.74 (d, J = 10.0 Hz, 1 H), 5.00 (s, 2 H), 3.86 (s, 3 H), 3.81 (s, 3 H), 1.46 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.3, 182.1, 173.6, 160.3, 158.81, 158.18, 157.7, 155.9, 155.2, 137.8, 134.1, 131.3, 129.8, 126.3, 117.2, 116.1, 114.51, 114.16, 114.01, 112.9, 109.3, 101.0, 78.2, 71.2, 63.0, 55.6, 28.6 ppm. IR (film): $\tilde{\nu}$ = 3441, 3072, 2972, 2932, 2837, 1639, 1605, 1516, 1466, 1362, 1292, 1234, 1173, 1126, 1063, 960, 827, 781, 520 cm^{-1}. HRMS (ESI^+): calcd. for $C_{29}H_{25}O_8$ $[M + 1]^+$ 501.1544; found 501.1551.

Hirtellanine A

The First Route: A solution of ammonium cerium(IV) nitrate (67 mg, 0.12 mmol) in H_2O (1.2 mL) was added to a solution of **24** (16 mg, 0.04 mmol) in acetonitrile/H_2O (4 mL, 3:1) over 1 min at 0 °C. The solution changed from colorless to deep orange. After 15 min, the reaction was allowed to warm to room temperature, and $Na_2S_2O_4$ (0.25 M aq.; 2 mL) was added. The solution immediately turned pale yellow. The reaction mixture was then extracted with ethyl acetate (2 × 20 mL). The organic phase was dried, filtered, and concentrated in vacuo. The crude product was purified by chromatography (ethyl acetate/petroleum ether, 1:2 to 1:1) to give a white solid (6 mg, 40%).

The Second Route: $MeSO_3H$ (0.4 mL) was added to a solution of **35** (85 mg, 0.17 mmol) in AcOH (4 mL) whilst stirring at room temperature. The reaction ran at 90 °C for 3.5 h, and the reaction progress was monitored by HPLC. After cooling, the reaction solution was added dropwise to cooled water (20 mL) with stirring over 4 min. A large amount of an off-white solid was formed. After filtration, the crude product was suspended in CH_2Cl_2 (6 mL) and filtered. A white solid product (20 mg) was obtained, and the filtrate was concentrated for purification by preparative TLC (ethyl acetate/petroleum ether, 1:1) to give the white solid (15 mg, 54.2%), m.p. 280–282 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.30 (s, 1 H), 9.29 (s, 1 H), 7.34 (s, 1 H), 7.05 (s, 1 H), 6.92 (s, 1 H), 6.67 (d, J = 10.4 Hz, 1 H), 5.93 (d, J = 10.0 Hz, 1 H), 3.81 (s, 3 H), 1.43 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5, 163.2, 157.4, 156.1, 155.7, 145.0, 144.7, 143.0, 132.3, 115.8, 114.3, 113.9, 112.5, 106.7, 101.8, 99.7, 78.6, 28.6 ppm. IR (film): $\tilde{\nu}$ = 3522, 3402, 3310, 3215, 2970, 1633, 1597, 1518, 1456, 1443, 1333, 1180, 1119, 1070, 874, 775, 685, 472 cm^{-1}. HRMS (ESI^+): calcd. for $C_{21}H_{17}O_7$ $[M + 1]^+$ 381.0969; found 381.0976.

Supporting Information (see footnote on the first page of this article): General experimental details, ^1H and ^{13}C NMR spectra of all compounds.

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