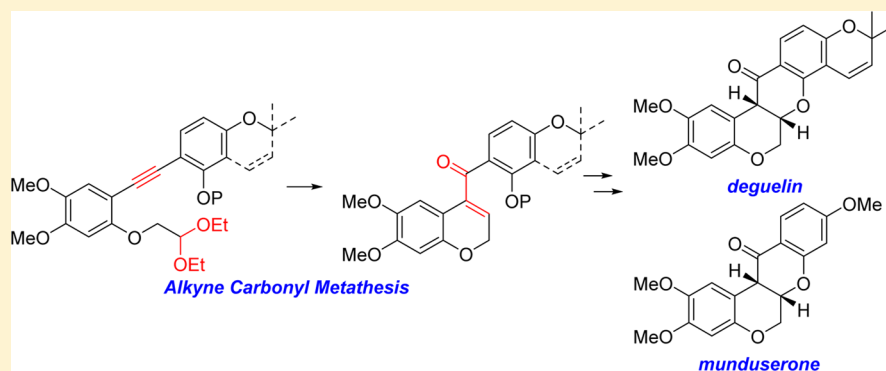


Alkyne Carbonyl Metathesis As a Means To Make 4-Acyl Chromenes: Syntheses of (±)-Deguelin and (±)-Munduserone

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Supporting Information



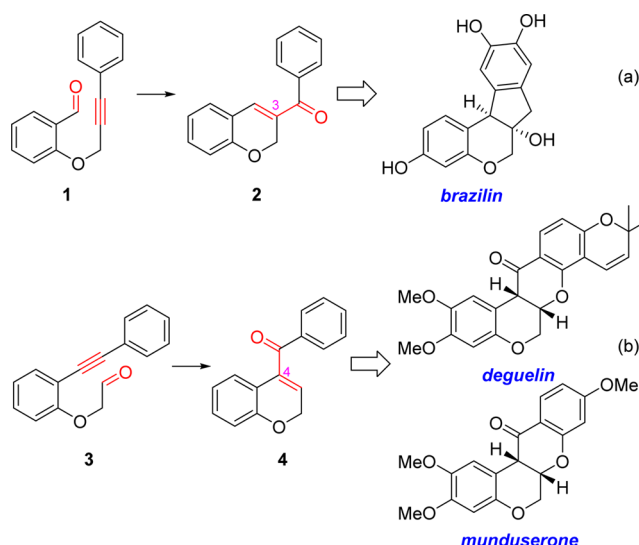
ABSTRACT: A highly convergent synthetic approach to rotenoid natural products is described. Successful pairing of two building blocks for Sonogashira cross-coupling and intramolecular alkyne carbonyl metathesis allows ready access to 4-acylchromene, a key substructure of these natural products, leading to syntheses of (±)-deguelin and (±)-munduserone in high overall yields.

INTRODUCTION

Acid-catalyzed metathesis of an alkyne and an aldehyde suitably positioned within one molecular framework is a useful way to make synthetically useful carbo- or heterocycles.¹ Despite many reaction conditions developed for inter- and intramolecular alkyne carbonyl metathesis (ACM), to the best of our knowledge, only a few examples where ACM is applied to the total synthesis of natural products have been disclosed.² As shown in Scheme 1a, we recently demonstrated highly efficient assembly of 3-acylchromene **2** from **1** by this protocol in the course of our total synthesis of brazilin.³ As an extension, we envisioned that 4-acylchromene **4**, a regioisomer of **2**, could be formed via alkyne aldehyde metathesis of **3** (Scheme 1b).⁴ As this core structure was found in many rotenoid natural products (Figure 1),⁵ we decided to pursue the feasibility of this idea being applied to the total synthesis of rotenoids. Here we wish to describe a concise and highly convergent synthetic route to two rotenoid natural products, (±)-deguelin^{6,7} and (±)-munduserone,⁸ involving construction of 4-acylchromene via ACM.

Our retrosynthetic analysis for the synthesis of deguelin is illustrated in Scheme 2. With the above-mentioned strategy in mind, the enone **5** was deemed as an advanced intermediate for our approach. As conversion of **5** to deguelin is well established,⁹ construction of **5** would constitute a formal synthesis of deguelin. We recognized that the enone unit in **5** could be assembled via ACM of diarylalkyne **6**, which in turn could be prepared by two possible Sonogashira coupling

Scheme 1. Synthetic Plans to Make Chromene Structures



reactions (a and b).¹⁰ As **7** and **8** were more readily accessible from commercially available starting materials, we decided to pursue the Sonogashira coupling approach (a) first.

Received: September 14, 2015

Published: November 2, 2015

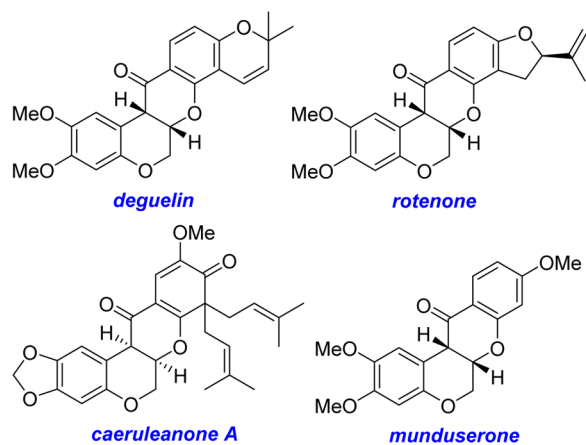


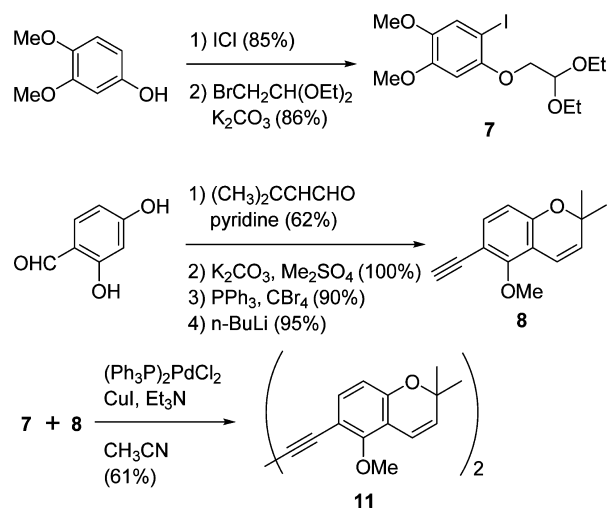
Figure 1. Some rotenoid natural products.

RESULTS AND DISCUSSION

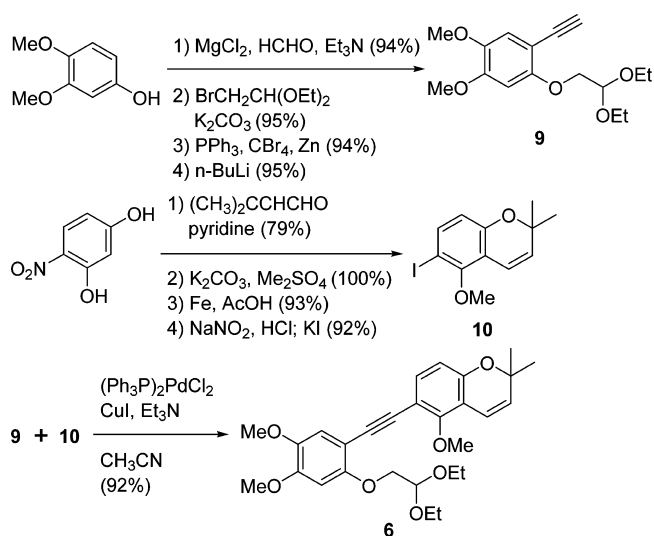
For Sonogashira coupling approach (a), both components, 7 and 8, were easily prepared in high overall yields as shown in Scheme 3. Regioselective iodination of 3,4-dimethoxyphenol followed by alkylation with bromoacetaldehyde diethylacetal provided the iodide 7. Synthesis of the alkyne partner 8 began with cyclization of 2,4-dihydroxybenzaldehyde with 3-methyl-2-butenal in the presence of pyridine, which produced the known aldehyde.¹¹ O-Methylation and subsequent conversion of aldehyde to alkyne under Corey–Fuchs protocol¹² uneventfully afforded the alkyne 8. Unfortunately, however, Sonogashira cross-coupling with these two fragments did not lead to the desired product 6. Only, the homodimer 11 was observed in 61% yield.

These unwanted results led us to evaluate the second Sonogashira coupling approach (Scheme 4). Alkyne 9 was obtained in a high overall yield by employing a series of reactions involving *ortho*-formylation,¹³ alkylation, and Corey–Fuchs alkyne synthesis. Iodide 10 was prepared by following slightly modified literature procedures.¹⁴ Thus, reaction of commercially available 2-nitrosorcinol with 3-methyl-2-butenal and methylation gave 5-methoxy-6-nitrochromene.

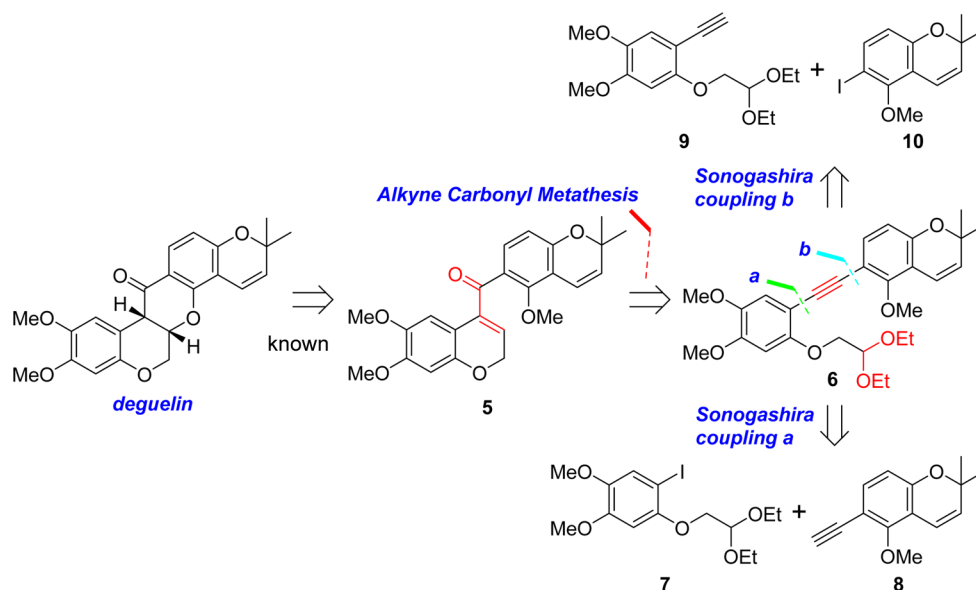
Scheme 3. First Synthetic Approach



Scheme 4. Second Synthetic Approach



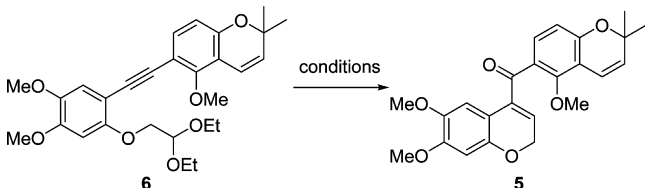
Scheme 2. Retrosynthetic Plan for the Synthesis of Deguelin



Nitro reduction and diazotization followed by iodide treatment furnished the iodide **10**. At this time, to our delight, desired Sonogashira coupling reaction of **9** and **10** occurred at 70 °C to give the coupled product in 92% yield. When the reaction was carried out at room temperature, **6** was isolated in 70% yield.

Having established a firm route to the alkyne **6**, we directed our attention to ACM of **6** to form the 4-acylchromene unit, a substructure of rotenoid natural products. When we first treated **6** in hot formic acid as reported by Taylor, surprisingly, no conversion was observed (Table 1, entry 1). Use of InCl_3

Table 1. Synthesis of **5** via ACM of **6**^a



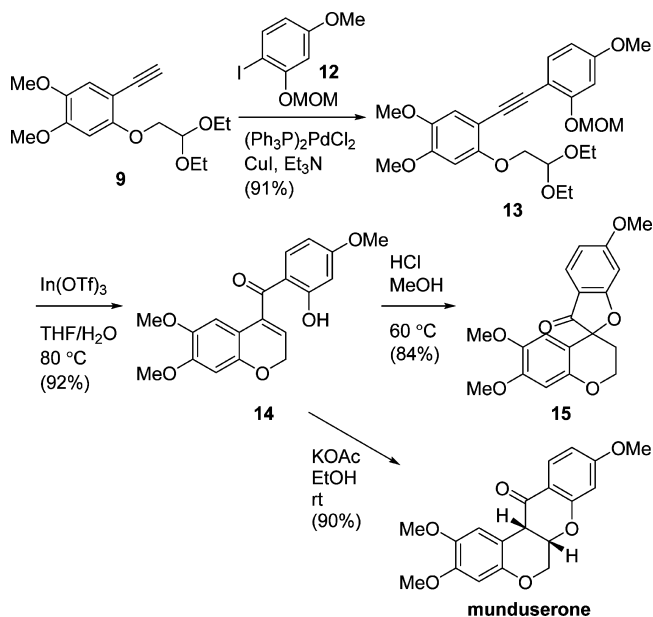
entry	catalyst (equiv)	solvent	temperature (°C)	time (h)	yield (%) ^b
1	HCO_2H	^c	100	12	nr
2	InCl_3 (1.0)	THF/ H_2O (4:1)	80	12	nr
3	TFA-HCl	DCM	80	16	^d
4	FeCl_3 (1.0)	THF/ H_2O (4:1)	80	16	^d
5	$\text{In}(\text{OTf})_3$ (1.0)	THF/ H_2O (4:1)	80	12	94
6	$\text{In}(\text{OTf})_3$ (0.4)	THF/ H_2O (4:1)	80	36	93.5
7	$\text{In}(\text{OTf})_3$ (0.2)	THF/ H_2O (4:1)	80	48	84.6
8	$\text{Cu}(\text{OTf})_2$ (0.4)	THF/ H_2O (4:1)	80	36	34
9	$\text{Sc}(\text{OTf})_3$ (0.4)	THF/ H_2O (4:1)	80	36	83
10	$\text{Yb}(\text{OTf})_3$ (0.4)	THF/ H_2O (4:1)	80	36	82

^aA mixture of **6** (0.1 mmol) and catalyst in solvent (1 mL) was heated at the temperature indicated above. ^bIsolated yield (%). ^c HCO_2H was used as solvent. ^dA complex mixture.

did not induce ACM either (entry 2). While the reaction under the influence of TFA-HCl or FeCl_3 (1.0 equiv) resulted in a complex mixture, exposure of **6** to $\text{In}(\text{OTf})_3$ (1.0 equiv) in THF/ H_2O (4:1) at 80 °C provided the desired 4-acylchromene **5** in 94% yield (entries 3–5).¹⁵ Decreasing the amount of catalyst to 0.4 equiv gave a comparable yield of product, although a longer reaction time was needed (entry 6). Further reduction of $\text{In}(\text{OTf})_3$ (0.2 equiv) led to 84.6% of **5** after extended reaction time (entry 7). Screening of other catalysts revealed that this transformation is effective in the presence of $\text{Cu}(\text{OTf})_2$, $\text{Sc}(\text{OTf})_3$, or $\text{Yb}(\text{OTf})_3$ but in lower efficiency (entries 8–10).

For the synthesis of munduserone, the alkyne **9** was coupled with **12**¹⁶ at room temperature to furnish **13** in 91% yield (Scheme 5). Again, ACM of **13** delivered **14** in excellent yield. We initially anticipated direct conversion of **13** to munduserone via a domino ACM/MOM deprotection/6-endo-trig cyclization sequence. No cyclization occurred under these conditions. When **14** was treated with hot HCl/MeOH previously used for the synthesis of munduserone, however, spirocyclic **15** was isolated in 84% yield as a consequence of 5-exo-trig cyclization.¹⁷ After screening several conditions, we finally

Scheme 5. Total Synthesis of Munduserone

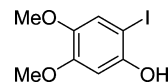


found that treatment of **14** with KOAc in EtOH at room temperature cleanly provided munduserone.

In summary, we have developed a highly efficient and convergent strategy for the synthesis of rotenoid natural products. Successful matching of two building blocks for Sonogashira cross-coupling and effective ACM enabled us to accomplish the syntheses of (\pm)-deguelin and (\pm)-munduserone.¹⁸ Application of ACM to other natural product synthesis is currently underway, and the results will be reported in due course.

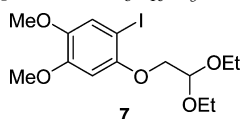
EXPERIMENTAL SECTION

General Methods. Unless specified, all reagents and starting materials were purchased from commercial sources and used as received without purification. “Concentrated” refers to the removal of volatile solvents via distillation using a rotary evaporator. “Dried” refers to pouring onto, or passing through, anhydrous magnesium sulfate followed by filtration. Flash chromatography was performed using silica gel (230–400 mesh) with hexanes, ethyl acetate, and dichloromethane as eluent. All reactions were monitored by thin-layer chromatography on 0.25 mm silica plates (F-254) visualizing with UV light. ¹H and ¹³C NMR spectra were recorded on 400 MHz NMR spectrometer and were described as chemical shifts, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant in hertz (Hz), and number of protons. IR spectra were recorded on FT-IR using diamond ATR technique and were described as wavenumbers (cm^{-1}). HRMS were measured with electrospray ionization (ESI) and Q-TOF mass analyzer.

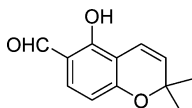


2-Iodo-4,5-dimethoxyphenol. To a stirred solution of 3,4-dimethoxyphenol (1.0 g, 6.49 mmol) in diethyl ether (50 mL) at 0 °C was added ICl (0.33 mL, 6.49 mmol). After being stirred at rt for 2 h, the reaction mixture was quenched with aqueous sodium sulfite solution (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with brine, dried over anhydrous MgSO_4 , and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography on silica gel (hexanes:EtOAc, 4:1) gave the title compound as a brown oil (1.54 g, 85%). ¹H NMR (400 MHz, CDCl_3) δ 6.78 (s, 1H), 6.58 (s, 1H), 5.39 (s, 1H), 3.81 (s, 3H), 3.79 (s, 3H); ¹³C NMR (100 MHz, CDCl_3)

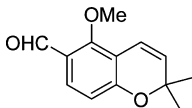
δ 149.2, 145.7, 143.3, 112.0, 109.4, 100.7, 56.7, 56.1; HRMS (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_8H_{10}IO_3$ 280.9669, found 280.9664.



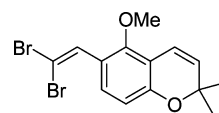
1-(2,2-Diethoxyethoxy)-2-iodo-4,5-dimethoxybenzene (7). To a stirred solution of 2-iodo-4,5-dimethoxyphenol (300 mg, 1.07 mmol) in DMF (5 mL) were added K_2CO_3 (887 mg, 6.43 mmol) and bromoacetaldehyde diethyl acetal (0.226 mL, 1.50 mmol). The resulting mixture was stirred at 150 °C for 16 h. The reaction mixture was cooled down to room temperature, neutralized with cold saturated aqueous NH_4Cl solution, and extracted with $EtOAc$ (3×20 mL). The combined organic layer was washed with H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography on silica gel (hexanes: $EtOAc$, 4:1) furnished 7 as a colorless oil (0.365 g, 86%). 1H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 1H), 6.64 (s, 1H), 4.85 (t, $J = 5.2$ Hz, 1H), 4.03 (d, $J = 5.2$ Hz, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.76–3.82 (m, 2H), 3.65–3.71 (m, 2H), 1.25 (t, $J = 7.0$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 148.4, 144.1, 114.1, 113.5, 101.3, 101.0, 71.7, 63.4, 56.6, 56.3, 15.5; IR (ATR) 2974, 2935, 1624, 1506, 1440, 1211 cm^{-1} ; HRMS (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{14}H_{22}IO_5$ 397.0506, found 397.0510.



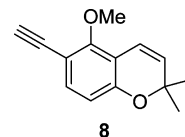
5-Hydroxy-2,2-dimethyl-2H-chromene-6-carbaldehyde.¹⁹ To a vial charged with 2,4-dihydroxybenzaldehyde (1 g, 7.24 mmol) were added 3-methyl-2-butenal (1.39 mL, 14.48 mmol) and pyridine (1.17 mL, 14.48 mmol). Then the reaction mixture was heated at 140 °C for 12 h. After being cooled down to room temperature, the reaction mixture was treated with 2 N HCl solution and extracted with ethyl acetate (3×20 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography on silica gel (hexanes: $EtOAc$, 19:1) gave the title compound as a white solid (916.7 mg, 62%). mp: 67.0–68.3 °C; 1H NMR (400 MHz, $CDCl_3$) δ 11.64 (s, 1H), 9.64 (s, 1H), 7.27 (d, $J = 8.6$ Hz, 1H), 6.67 (d, $J = 10.0$ Hz, 1H), 6.41 (d, $J = 8.5$ Hz, 1H), 5.59 (d, $J = 10.0$ Hz, 1H), 1.45 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 160.6, 158.8, 134.8, 128.7, 115.3, 115.2, 109.5, 108.9, 78.3, 28.5; IR (ATR) 2974, 2920, 1624, 1485, 1331, 1109 cm^{-1} ; HRMS (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{12}H_{13}O_3$ 205.0859, found 205.0862.



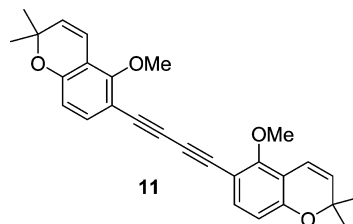
5-Methoxy-2,2-dimethyl-2H-chromene-6-carbaldehyde.^{19a,c} To a stirred solution of 5-hydroxy-2,2-dimethyl-2H-chromene-6-carbaldehyde (600 mg, 2.94 mmol) in acetone (6 mL) were added K_2CO_3 (810 mg, 5.88 mmol) and dimethyl sulfate (0.42 mL, 4.41 mmol). After the reaction mixture was stirred at rt for overnight, the solid was filtered, and the filtrate was concentrated under reduced pressure to afford the crude product. Purification by flash chromatography on silica gel (hexanes: $EtOAc$, 9:1) furnished 5-methoxy-2,2-dimethyl-2H-chromene-6-carbaldehyde as a colorless oil (641 mg, 100%). 1H NMR (400 MHz, $CDCl_3$) δ 10.13 (s, 1H), 7.60 (d, $J = 8.6$ Hz, 1H), 6.60 (d, $J = 8.6$ Hz, 1H), 6.55 (d, $J = 10.0$ Hz, 1H), 5.65 (d, $J = 10.1$ Hz, 1H), 3.85 (s, 3H), 1.42 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.3, 160.0, 159.9, 130.5, 129.8, 122.5, 115.8, 114.4, 113.4, 77.5, 64.4, 28.2; IR (ATR) 2970, 1625, 1569, 1524, 1358, 1208 cm^{-1} ; HRMS (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{13}H_{15}O_3$ 219.1016, found 219.1014.



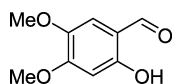
6-(2,2-Dibromovinyl)-5-methoxy-2,2-dimethyl-2H-chromene. To a stirred solution of CBr_4 (1.67 g, 5.4 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C was added PPh_3 (2.64 g, 10.08 mmol). Then aldehyde (550 mg, 2.52 mmol) dissolved in dry CH_2Cl_2 (10 mL) was dropwise added into the reaction mixture. After the cooling bath was removed, the reaction mixture was stirred for 30 min. Then the reaction mixture was quenched with water (50 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography on silica gel (hexanes: $EtOAc$, 19:1) gave the title compound as a colorless oil (895 mg, 95%). 1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, $J = 8.9$ Hz, 1H), 7.51 (s, 1H), 6.55–6.60 (m, 2H), 5.64 (d, $J = 10.0$ Hz, 1H), 3.74 (s, 3H), 1.43 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 154.2, 132.5, 130.7, 129.1, 121.3, 116.7, 114.7, 113.3, 88.8, 76.5, 62.7, 28.2; IR (ATR) 2974, 2934, 1635, 1590, 1524, 1459, 1289, 1113 cm^{-1} ; HRMS (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{14}H_{15}Br_2O_2$ 372.9433, found 372.9439.



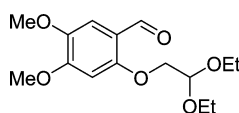
6-Ethynyl-5-methoxy-2,2-dimethyl-2H-chromene (8). To a stirred solution of 6-(2,2-dibromovinyl)-5-methoxy-2,2-dimethyl-2H-chromene (850 mg, 2.27 mmol) in dry THF (10 mL) at –78 °C under nitrogen atmosphere was dropwise added $n-BuLi$ (1.6 M in hexane, 4.26 mL, 6.82 mmol). After being stirred at –78 °C for 30 min, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with $EtOAc$ (3×20 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography on silica gel (hexanes: $EtOAc$, 9:1) furnished compound 8 as a colorless oil (462 mg, 95%). 1H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, $J = 8.4$ Hz, 1H), 6.60 (d, $J = 10.0$ Hz, 1H), 6.51 (d, $J = 8.5$ Hz, 1H), 5.63 (d, $J = 10.0$ Hz, 1H), 3.93 (s, 3H), 3.20 (s, 1H), 1.42 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 154.8, 134.1, 130.6, 116.7, 114.9, 112.5, 107.6, 80.4, 79.98, 76.6, 61.8, 28.1; IR (ATR) 3291, 2975, 2935, 1635, 1593, 1470, 1368 cm^{-1} ; HRMS (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{14}H_{15}O_2$ 215.1067, found 215.1073.



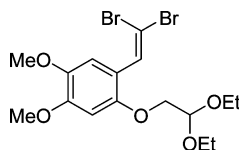
1,4-Bis(5-methoxy-2,2-dimethyl-2H-chromen-6-yl)buta-1,3-diyne (11). In a flask charged with compound 8 (50 mg, 0.23 mmol) and compound 7 (92 mg, 0.23 mmol) in acetonitrile (1.0 mL) and Et_3N (0.07 mL, 0.47 mmol) were added $(Ph_3P)_2PdCl_2$ (16 mg, 0.023 mmol) and CuI (8.9 mg, 0.047 mmol), and the reaction mixture was stirred at 70 °C under nitrogen atmosphere for 1 h. The solvent was removed in vacuo to yield the crude product. Purification by flash chromatography on silica gel (hexanes: $EtOAc$, 9:1) gave compound 11 as an off white solid (30.3 mg, 61%). mp: 140.2–141.9 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, $J = 8.5$ Hz, 2H), 6.60 (d, $J = 10.0$ Hz, 2H), 6.51 (d, $J = 8.5$ Hz, 2H), 5.64 (d, $J = 10.0$ Hz, 2H), 3.98 (s, 6H), 1.43 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 155.2, 134.6, 130.6, 116.7, 114.8, 112.6, 107.2, 78.7, 62.1, 28.2; IR (ATR) 2926, 1629, 1586, 1460, 1370, 1111 cm^{-1} ; HRMS (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{28}H_{27}O_4$ 427.1904, found 427.1907.



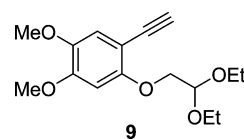
2-Hydroxy-4,5-dimethoxybenzaldehyde.²⁰ To a solution of 3,4-dimethoxyphenol (1.0 g, 6.49 mmol) in dry THF (8.0 mL) were added anhydrous magnesium chloride (1.25 g, 12.97 mmol), triethylamine (2.76 mL, 19.46 mmol), and paraformaldehyde (592 mg, 19.46 mmol). After being stirred at 80 °C for 8 h, the reaction mixture was cooled down to room temperature, quenched with 2 N HCl, and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography on silica gel (hexanes:EtOAc, 4:1) gave the title compound as a white solid (1.11 g, 94%). mp: 103.9–105.2 °C; ¹H NMR (400 MHz, CDCl₃) δ 11.39 (s, 1H), 9.68 (s, 1H), 6.89 (s, 1H), 6.45 (s, 1H), 3.92 (s, 3H), 3.86 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 194.1, 159.5, 157.3, 143.0, 113.3, 112.97, 100.3, 56.6, 56.5; IR (ATR) 2839, 1622, 1506, 1440, 1248, 1144 cm⁻¹; HRMS (ESI-QTOF) *m/z* [M + H]⁺ calcd for C₉H₁₁O₄ 183.0652, found 183.0652.



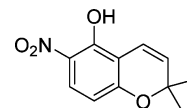
2-(2,2-Diethoxyethoxy)-4,5-dimethoxybenzaldehyde. To a stirred solution of 2-hydroxy-4,5-dimethoxybenzaldehyde (500 mg, 2.74 mmol) in DMF (5 mL) were added K₂CO₃ (1.52 g, 10.98 mmol) and bromoacetaldehyde diethyl acetal (0.495 mL, 3.29 mmol). After being stirred at 150 °C for 2 h, the reaction mixture was cooled down to room temperature, mixed with cold saturated aqueous NH₄Cl solution, and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with H₂O and brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography on silica gel (hexanes:EtOAc, 4:1) furnished title compound as a colorless oil (0.778 g, 95%). ¹H NMR (400 MHz, CDCl₃) δ 10.34 (s, 1H), 7.30 (s, 1H), 6.55 (s, 1H), 4.87 (t, *J* = 5.2 Hz, 1H), 4.10 (d, *J* = 5.2 Hz, 2H), 3.94 (s, 3H), 3.88 (s, 3H), 3.76–3.84 (m, 2H), 3.61–3.69 (m, 2H), 1.26 (t, *J* = 7.0 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 188.1, 157.9, 155.8, 144.1, 117.9, 108.7, 100.8, 97.6, 70.4, 63.4, 56.33, 56.29, 15.5; IR (ATR) 2974, 2867, 1665, 1604, 1508, 1276, 1123 cm⁻¹; HRMS (ESI-QTOF) *m/z* [M + Na]⁺ calcd for C₁₅H₂₂NaO₆ 321.1309, found 321.1307.



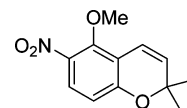
1-(2,2-Dibromovinyl)-2-(2,2-diethoxyethoxy)-4,5-dimethoxybenzene. After a suspension of Zn dust (328 mg, 5.03 mmol), PPh₃ (1.32 g, 5.03 mmol), and CBr₄ (1.68 g, 5.03 mmol) in dry CH₂Cl₂ (10 mL) was stirred at rt under N₂ for 6 h, aldehyde (0.5 g, 1.68 mmol) was added to the reaction mixture. After being stirred at rt for 3 h, the reaction mixture was passed through a pad of Celite, and the Celite pad was washed with CH₂Cl₂. The filtrate was concentrated under reduced pressure to afford the crude product. Purification by flash chromatography on silica gel (hexanes:EtOAc, 9:1) furnished the title compound as a colorless oil (0.716 g, 94%). ¹H NMR (400 MHz, CDCl₃) δ 7.63 (s, 1H), 7.38 (s, 1H), 6.52 (s, 1H), 4.81 (t, *J* = 5.2 Hz, 1H), 3.99 (d, *J* = 5.2 Hz, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 3.76–3.85 (m, 2H), 3.61–3.69 (m, 2H), 1.27 (t, *J* = 7.0 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 150.9, 150.3, 143.2, 132.1, 116.4, 111.8, 100.9, 98.7, 87.6, 70.9, 63.4, 56.6, 56.1, 15.6; IR (ATR) 2969, 2880, 1646, 1540, 1378, 1297, 1160 cm⁻¹; HRMS (ESI-QTOF) *m/z* [M + Na]⁺ calcd for C₁₆H₂₂Br₂NaO₅ 474.9726, found 474.9722.



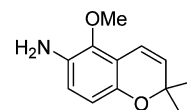
1-(2,2-Diethoxyethoxy)-2-ethynyl-4,5-dimethoxybenzene (9). To a stirred solution of 1-(2,2-dibromovinyl)-2-(2,2-diethoxyethoxy)-4,5-dimethoxybenzene (620 mg, 1.36 mmol) in dry THF (10 mL) at –78 °C under nitrogen atmosphere was dropwise added *n*-BuLi (1.6 M in hexane, 1.28 mL, 2.05 mmol). After being stirred at –78 °C for 30 min, the reaction mixture was quenched with saturated aqueous NH₄Cl solution and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography on silica gel (hexanes:EtOAc, 9:1) furnished compound 9 as an off white solid (382 mg, 95%). mp: 56.3–57.7 °C; ¹H NMR (400 MHz, CDCl₃) δ 6.88 (s, 1H), 6.53 (s, 1H), 4.81 (t, *J* = 5.6 Hz, 1H), 4.04 (d, *J* = 5.2 Hz, 2H), 3.83 (s, 3H), 3.79 (s, 3H), 3.74–3.77 (m, 2H), 3.64–3.66 (m, 2H), 3.17 (s, 1H), 1.21 (t, *J* = 7.1 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 155.5, 150.6, 143.3, 115.9, 103.0, 101.0, 99.4, 80.2, 79.9, 71.3, 63.3, 56.4, 56.0, 15.4; IR (ATR) 3237, 2970, 1607, 1506, 1276, 1206 cm⁻¹; HRMS (ESI-QTOF) *m/z* [M + H]⁺ calcd for C₁₆H₂₃O₅ 295.1540, found 295.1547.



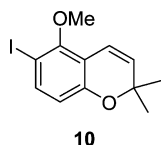
2,2-Dimethyl-6-nitro-2H-chromen-5-ol. To a vial charged with 2-nitroresorcinol (600 mg, 3.87 mmol) were added 3-methyl-2-butenal (0.75 mL, 7.74 mmol) and pyridine (0.63 mL, 7.74 mmol). Then the reaction mixture was heated at 140 °C for 4 h. After being cooled down to room temperature, the reaction mixture was treated with 2 N HCl solution and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography on silica gel (hexanes:EtOAc, 19:1) gave the title compound as a yellow solid (676 mg, 79%). mp: 123.9–125.0 °C; ¹H NMR (400 MHz, CDCl₃) δ 11.22 (s, 1H), 7.89 (d, *J* = 9.4 Hz, 1H), 6.69 (d, *J* = 10.1 Hz, 1H), 6.38 (d, *J* = 9.3 Hz, 1H), 5.63 (d, *J* = 10.1 Hz, 1H), 1.46 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 160.9, 152.3, 129.2, 127.8, 126.1, 115.3, 110.1, 109.8, 78.9, 28.5; IR (ATR) 2975, 2928, 1594, 1436, 1244, 1075 cm⁻¹; HRMS (ESI-QTOF) *m/z* [M + Na]⁺ calcd for C₁₁H₁₁NNaO₄ 244.0580, found 244.0588.



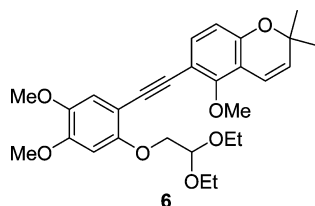
5-Methoxy-2,2-dimethyl-6-nitro-2H-chromene.¹⁴ To a stirred solution of 2,2-dimethyl-6-nitro-2H-chromen-5-ol (600 mg, 2.71 mmol) in acetone (6 mL) were added K₂CO₃ (750 mg, 5.42 mmol) and dimethyl sulfate (0.39 mL, 4.07 mmol). After being stirred at rt for overnight, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to afford the crude product. Purification by flash chromatography on silica gel (hexanes:EtOAc, 19:1) furnished 5-methoxy-2,2-dimethyl-6-nitro-2H-chromene as a yellow oil (638 mg, 100%). ¹H NMR (400 MHz, CDCl₃) δ 7.78 (d, *J* = 9.1 Hz, 1H), 6.61 (d, *J* = 9.6 Hz, 1H), 6.59 (d, *J* = 8.7 Hz, 1H), 5.74 (d, *J* = 10.1 Hz, 1H), 3.91 (s, 3H), 1.46 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 158.7, 151.2, 136.6, 131.5, 126.7, 116.2, 115.9, 112.4, 77.96, 63.1, 28.3; IR (ATR) 2974, 2933, 1575, 1514, 1209, 1071 cm⁻¹; HRMS (ESI-QTOF) *m/z* [M + H]⁺ calcd for C₁₂H₁₄NO₄ 236.0917, found 236.0921.



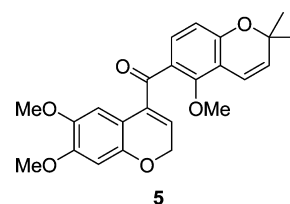
5-Methoxy-2,2-dimethyl-2H-chromen-6-amine.¹⁴ To a stirred solution of 5-methoxy-2,2-dimethyl-6-nitro-2H-chromene (350 mg, 1.49 mmol) in acetic acid (4 mL) was added Fe powder (415 mg, 7.44 mmol), and the reaction mixture was stirred at 80 °C for 4 h. The reaction mixture was neutralized with saturated NaHCO₃ solution and extracted with ethyl acetate (3 × 15 mL). The combined organic layer was washed with brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography on silica gel (hexanes:EtOAc, 9:1) furnished 5-methoxy-2,2-dimethyl-2H-chromen-6-amine as a brown solid (284 mg, 93%). mp: 123.9–125.0 °C; ¹H NMR (400 MHz, CDCl₃) δ 6.57 (d, *J* = 9.9 Hz, 1H), 6.53 (d, *J* = 8.5 Hz, 1H), 6.44 (d, *J* = 8.5 Hz, 1H), 5.65 (d, *J* = 9.9 Hz, 1H), 3.75 (s, 3H), 3.49 (s, 2H), 1.39 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 145.9, 143.2, 133.1, 131.4, 117.2, 115.99, 115.3, 112.4, 75.1, 60.8, 27.5; IR (ATR) 3353, 2973, 2934, 1480, 1287, 1053 cm⁻¹; HRMS (ESI-QTOF) *m/z* [M + H]⁺ calcd for C₁₂H₁₆NO₂ 206.1176, found 206.1179.



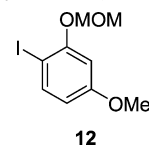
6-Iodo-5-methoxy-2,2-dimethyl-2H-chromene (10). To a stirred solution of 5-methoxy-2,2-dimethyl-2H-chromen-6-amine (300 mg, 1.46 mmol) in concentrated HCl (3 mL) at 0 °C was added a solution of NaNO₂ (111 mg, 1.61 mmol) dissolved in H₂O (5 mL), and the mixture was stirred at 0 °C for 1 h. Then a solution of KI (267 mg, 1.61 mmol) dissolved in H₂O (5 mL) was dropwise added at 0 °C. Then the mixture was slowly warmed up to room temperature and stirred for overnight. The mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic layer was washed with brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography on silica gel (hexanes:EtOAc, 19:1) furnished **10** as a brown oil (425 mg, 92%). ¹H NMR (400 MHz, CDCl₃) δ 7.44 (d, *J* = 8.6 Hz, 1H), 6.57 (d, *J* = 10.0 Hz, 1H), 6.40 (d, *J* = 8.6 Hz, 1H), 5.64 (d, *J* = 10.0 Hz, 1H), 3.78 (s, 3H), 1.42 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 155.6, 154.7, 138.1, 131.3, 117.3, 116.1, 115.0, 80.0, 76.3, 61.9, 27.9; IR (ATR) 2974, 2877, 1556, 1414, 1163 cm⁻¹; HRMS (ESI-QTOF) *m/z* [M + H]⁺ calcd for C₁₂H₁₄IO₂ 317.0033, found 317.0029.



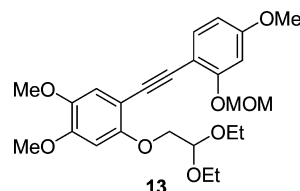
6-((2,2-Diethoxyethoxy)-4,5-dimethoxyphenyl)ethynyl)-5-methoxy-2,2-dimethyl-2H-chromene (6). In a flask charged with compound **10** (100 mg, 0.32 mmol) and compound **9** (111 mg, 0.38 mmol) in acetonitrile (1.5 mL) and Et₃N (0.5 mL) were added (Ph₃P)₂PdCl₂ (22 mg, 0.032 mmol) and CuI (0.6 mg, 0.003 mmol), and the reaction mixture was stirred at 70 °C under nitrogen atmosphere for 4 h. The solvent was removed in vacuo to yield the crude product. Purification by flash chromatography on silica gel (hexanes:EtOAc, 9:1) gave compound **6** as a colorless oil (140.4 mg, 92%). ¹H NMR (400 MHz, CDCl₃) δ 7.21 (d, *J* = 8.4 Hz, 1H), 6.93 (s, 1H), 6.62 (d, *J* = 10.0 Hz, 1H), 6.56 (s, 1H), 6.51 (d, *J* = 8.4 Hz, 1H), 5.61 (d, *J* = 5.2 Hz, 1H), 4.84 (t, *J* = 5.1 Hz, 1H), 4.09 (d, *J* = 5.1 Hz, 2H), 4.01 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.73–3.80 (m, 2H), 3.61–3.68 (m, 2H), 1.41 (s, 6H), 1.20 (t, *J* = 7.0 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 156.9, 154.5, 154.1, 150.0, 143.4, 133.3, 130.4, 116.9, 115.3, 114.7, 112.2, 109.0, 105.0, 101.0, 99.8, 88.8, 88.7, 76.4, 71.3, 63.1, 61.6, 56.5, 56.1, 28.0, 15.4; IR (ATR) 2974, 2933, 1509, 1369, 1217, 1070 cm⁻¹; HRMS (ESI-QTOF) *m/z* [M + H]⁺ calcd for C₂₈H₃₅O₇ 483.2377, found 483.2378.



(6,7-Dimethoxy-2H-chromen-4-yl)(5-methoxy-2,2-dimethyl-2H-chromen-6-yl)methanone (5). In a vial containing compound **6** (50 mg, 0.1 mmol) in THF-H₂O (4:1, 1 mL) was added In(OTf)₃ (23.3 mg, 0.04 mmol), and the resulting reaction mixture was stirred at 80 °C for 24 h. The reaction mixture was cooled down to rt and concentrated in vacuo to yield the crude product. Purification by flash chromatography on silica gel (hexanes:EtOAc, 9:1) gave compound **5** as a colorless gum (39.4 mg, 93.5%). ¹H NMR (400 MHz, CDCl₃) δ 7.33 (d, *J* = 8.5 Hz, 1H), 7.29 (s, 1H), 6.57–6.61 (m, 2H), 6.49 (s, 1H), 6.13 (t, *J* = 4.1 Hz, 1H), 5.67 (d, *J* = 5.2 Hz, 1H), 4.80 (d, *J* = 4.1 Hz, 2H), 3.85 (s, 3H), 3.78 (s, 3H), 3.74 (s, 3H), 1.44 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 194.0, 157.5, 156.3, 150.2, 148.9, 143.6, 135.7, 131.8, 130.7, 128.3, 124.7, 116.6, 114.96, 112.1, 111.9, 109.0, 100.6, 77.0, 64.9, 63.3, 56.4, 56.0, 28.2; IR (ATR) 2925, 2851, 1634, 1588, 1507, 1369, 1267, 1150 cm⁻¹; HRMS (ESI-QTOF) *m/z* [M + H]⁺ calcd for C₂₄H₂₄NaO₆ 431.1465, found 431.1466.

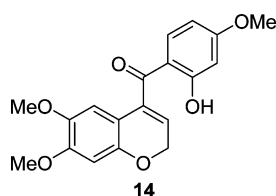


1-Iodo-4-methoxy-2-(methoxymethoxy)benzene (12).²¹ To a stirred suspension of NaH (48 mg, 1.2 mmol) in DMF (1 mL) at 0 °C was added a solution of 2-iodo-5-methoxyphenol (300 mg, 1.2 mmol) in DMF (2 mL). Then methoxymethyl chloride (0.182 mL, 1.61 mmol) was dropwise added at 0 °C. Then the mixture was slowly warmed up to room temperature and stirred for 30 min. The reaction mixture was quenched with cold water and extracted with ethyl acetate (3 × 15 mL). The combined organic layer was washed with water and brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography on silica gel (hexanes:EtOAc, 19:1) furnished **12** as a brown oil (328 mg, 93%). ¹H NMR (400 MHz, CDCl₃) δ 7.62 (d, *J* = 8.6 Hz, 1H), 6.69 (d, *J* = 2.7 Hz, 1H), 6.38 (dd, *J* = 2.7, 8.7 Hz, 1H), 5.22 (s, 2H), 3.78 (s, 3H), 3.51 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 161.3, 156.9, 139.2, 109.2, 102.4, 95.1, 75.9, 56.5, 55.6; IR (ATR) 2838, 1736, 1591, 1245, 1148 cm⁻¹; HRMS (ESI-QTOF) *m/z* [M + H]⁺ calcd for C₉H₁₂IO₃ 294.9826, found 294.9827.

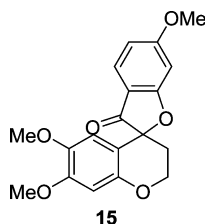


1-(2,2-Diethoxyethoxy)-4,5-dimethoxy-2-((4-methoxy-2-(methoxymethoxy)phenyl)ethynyl)benzene (13). A flask charged with compound **12** (100 mg, 0.34 mmol), compound **9** (110 mg, 0.37 mmol), (Ph₃P)₂PdCl₂ (11.9 mg, 0.017 mmol), and CuI (0.65 mg, 0.0034 mmol) was evacuated and refilled with nitrogen. Then Et₃N (2 mL) was added, and the reaction mixture was stirred at rt for 1 h. The solvent was removed in vacuo to yield the crude product. Purification by flash chromatography on silica gel (hexanes:EtOAc, 4:1) gave compound **13** as an off white solid (142.5 mg, 91%). mp: 95.3–96.8 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.39 (d, *J* = 8.4 Hz, 1H), 6.95 (s, 1H), 6.71 (s, 1H), 6.57 (s, 1H), 6.54 (d, *J* = 8.6 Hz, 1H), 5.27 (s, 2H), 4.85 (t, *J* = 4.9 Hz, 1H), 4.14 (d, *J* = 4.9 Hz, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.73–3.77 (m, 2H), 3.62–3.69 (m, 2H), 3.53 (s, 3H), 1.21 (t, *J* = 6.9 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 160.8, 158.9, 154.6, 149.97, 143.6, 134.0, 115.5, 107.3, 106.9, 105.3, 102.5, 101.1, 100.5, 95.4, 88.7, 88.4, 71.6, 63.1, 56.5, 56.4, 56.1, 55.5, 15.5; IR

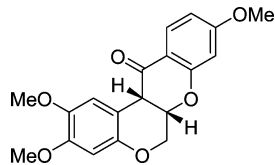
(ATR) 2954, 2899, 1609, 1514, 1267, 1071 cm^{-1} ; HRMS (ESI-QTOF) m/z $[M + \text{Na}]^+$ calcd for $\text{C}_{25}\text{H}_{32}\text{NaO}_8$ 483.1989, found 483.1988.



(6,7-Dimethoxy-2H-chromen-4-yl)(2-hydroxy-4-methoxyphenyl)methanone (**14**). In a vial containing compound **13** (50 mg, 0.11 mmol) in THF- H_2O (4:1) (1 mL) was added $\text{In}(\text{OTf})_3$ (12.2 mg, 0.022 mmol), and the resulting reaction mixture was stirred at 80 °C for 16 h. The reaction mixture was cooled down to rt and concentrated in vacuo to yield the crude product. Purification by flash chromatography on silica gel (hexanes:EtOAc, 4:1) gave compound **14** as a colorless gum (34.2 mg, 92%). ^1H NMR (400 MHz, CDCl_3) δ 12.59 (s, 1H), 7.61 (d, $J = 9.0$ Hz, 1H), 6.69 (s, 1H), 6.50 (s, 1H), 6.48 (s, 1H), 6.38 (dd, $J = 1.9, 8.8$ Hz, 1H), 5.88 (t, $J = 3.8$ Hz, 1H), 4.85 (d, $J = 3.8$ Hz, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 198.5, 166.98, 166.6, 150.7, 148.7, 143.9, 134.9, 134.5, 122.2, 113.4, 112.1, 108.5, 107.8, 101.1, 100.9, 64.7, 56.6, 56.1, 55.8; IR (ATR) 2935, 2836, 1609, 1505, 1251, 1121 cm^{-1} ; HRMS (ESI-QTOF) m/z $[M + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{19}\text{O}_6$ 343.1176, found 343.1174.



6,6',7'-Trimethoxy-3H-spiro[benzofuran-2,4'-chroman]-3-one (**15**). To a stirred solution of **14** (20 mg, 0.058 mmol) in dry MeOH (1.0 mL) was added 1N solution of HCl in ether (1.0 mL), and the resulting reaction mixture was stirred at 60 °C for 2 h. Then the reaction mixture was cooled to rt, quenched with saturated aqueous NaHCO_3 solution, and concentrated under reduced pressure. The resulting crude mixture was extracted with EtOAc (3 \times 5 mL). The combined organic layer was washed with H_2O and brine, dried over anhydrous MgSO_4 , and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography on silica gel (hexanes:EtOAc, 4:1) furnished compound **15** as an off white solid (16.8 mg, 84%). mp: 55.2–56.8 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.65 (d, $J = 8.6$ Hz, 1H), 6.71 (dd, $J = 2.0, 8.7$ Hz, 1H), 6.55 (d, $J = 1.8$ Hz, 1H), 6.45 (s, 1H), 6.22 (s, 1H), 4.51 (td, $J = 4.1, 11.1$ Hz, 1H), 4.30 (dt, $J = 2.2, 11.4$ Hz, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 3.65 (s, 3H), 2.38–2.45 (m, 1H), 2.03–2.07 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 199.9, 174.1, 169.0, 151.7, 151.0, 144.1, 126.2, 113.6, 112.2, 109.4, 109.1, 101.1, 96.4, 85.9, 62.7, 56.6, 56.1, 56.0, 32.2; IR (ATR) 2929, 1698, 1607, 1508, 1281, 1156 cm^{-1} ; HRMS (ESI-QTOF) m/z $[M + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{19}\text{O}_6$ 343.1176, found 343.1178.



Munduserone. In a vial containing compound **14** (20 mg, 0.058 mmol) was added ethanol saturated with potassium acetate (0.5 mL), and the mixture was stirred at rt for 30 min. Water and EtOAc were added to the reaction mixture. Layers were separated, and the aqueous layer was extracted with EtOAc (2 \times 5 mL). The combined organic layer was dried over anhydrous MgSO_4 and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography on silica gel (hexanes:EtOAc, 4:1) furnished

munduserone as a white solid (18 mg, 90%). mp: 169.3–170.8 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.87 (d, $J = 8.8$ Hz, 1H), 6.76 (s, 1H), 6.57 (dd, $J = 2.2, 8.9$ Hz, 1H), 6.45 (s, 1H), 6.42 (d, $J = 2.1$ Hz, 1H), 4.94 (t, $J = 3.2$ Hz, 2H), 4.63 (dd, $J = 3.0, 12.1$ Hz, 1H), 4.18 (d, $J = 12.0$ Hz, 1H), 3.85 (d, $J = 3.9$ Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 189.4, 166.7, 162.9, 149.6, 147.5, 144.0, 129.5, 112.9, 110.9, 110.4, 104.8, 101.1, 100.8, 72.5, 66.5, 56.4, 56.0, 55.8, 44.7; IR (ATR) 2920, 2851, 1675, 1607, 1514, 1252, 1194 cm^{-1} ; HRMS (ESI-QTOF) m/z $[M + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{19}\text{O}_6$ 343.1176, found 343.1178.

■ ASSOCIATED CONTENT

📄 Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02160.

^1H and ^{13}C NMR spectra of synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (2014R1A2A1A11050491).

■ REFERENCES

- (1) (a) Harding, C. E.; King, S. L. *J. Org. Chem.* **1992**, *57*, 883. (b) Rhee, J. U.; Krische, M. J. *Org. Lett.* **2005**, *7*, 2493. (c) Kurtz, K. C. M.; Hsung, R. P.; Zhang, Y. *Org. Lett.* **2006**, *8*, 231. (d) Jin, T.; Yamamoto, Y. *Org. Lett.* **2008**, *10*, 3137. (e) González-Rodríguez, C.; Escalante, L.; Varela, J. A.; Castedo, L.; Saá, C. *Org. Lett.* **2009**, *11*, 1531. (f) Jin, T.; Yang, F.; Liu, C.; Yamamoto, Y. *Chem. Commun.* **2009**, 3533. (g) Saito, A.; Kasai, J.; Fukaya, H.; Hanzawa, Y. *J. Org. Chem.* **2009**, *74*, 5644. (h) Bera, K.; Jalal, S.; Sarkar, S.; Jana, U. *Org. Biomol. Chem.* **2014**, *12*, 57. (i) Maiti, S.; Biswas, P.; Ghosh, J.; Drew, M. G. B.; Bandyopadhyay, C. *Tetrahedron* **2014**, *70*, 334. (j) Nayak, M.; Kim, I. *Org. Biomol. Chem.* **2015**, *13*, 9697.
- (2) (a) Cuthbertson, J. D.; Godfrey, A. A.; Taylor, R. J. *K. Org. Lett.* **2011**, *13*, 3976. (b) Cuthbertson, J. D.; Unsworth, W. P.; Moody, C. L.; Taylor, R. J. *Tetrahedron Lett.* **2015**, *56*, 3123.
- (3) Jung, Y.; Kim, I. *J. Org. Chem.* **2015**, *80*, 2001.
- (4) Cuthbertson, J. D.; Godfrey, A. A.; Unsworth, W. P.; Taylor, R. J. *K. Heterocycles* **2012**, *84*, 1013.
- (5) (a) Finch, N.; Ollis, W. D. *Proc. Chem. Soc.* **1960**, 176. (b) Crombie, L.; Whiting, D. *Phytochemistry* **1998**, *49*, 1479. (c) Fang, N.; Casida, J. E. *J. Agric. Food Chem.* **1999**, *47*, 2130. (d) Whiting, D. A. *Nat. Prod. Rep.* **2001**, *18*, 583. (e) Bueno Pérez, L.; Pan, L.; Acuña, U. M.; Li, J.; Chai, H.-B.; Gallucci, J. C.; Ninh, T. N.; Carcache de Blanco, E. J.; Soejarto, D. D.; Kinghorn, A. D. *Org. Lett.* **2014**, *16*, 1462.
- (6) For synthesis, see: (a) Fukami, H.; Oda, J.; Sakata, G.; Nakajima, M. *Bull. Agric. Chem. Soc. Jpn.* **1960**, *24*, 327. (b) Fukami, H.; Oda, J.; Sakata, G.; Nakajima, M. *Agric. Biol. Chem.* **1961**, *25*, 252. (c) Omokawa, H.; Yamashita, K. *Agric. Biol. Chem.* **1974**, *38*, 1731. (d) Anzeveno, P. B. *J. Org. Chem.* **1979**, *44*, 2578. (e) Pastine, S. J.; Sames, D. *Org. Lett.* **2003**, *5*, 4053. (f) Garcia, J.; Barluenga, S.; Beebe, K.; Neckers, L.; Winssinger, N. *Chem. - Eur. J.* **2010**, *16*, 9767. (g) Farmer, R. L.; Scheidt, K. A. *Chem. Sci.* **2013**, *4*, 3304. (h) Lee, S.; An, H.; Chang, D.-J.; Jang, J.; Kim, K.; Sim, J.; Lee, J.; Suh, Y.-G. *Chem. Commun.* **2015**, *51*, 9026.
- (7) For selected biological activities of deguelin, see: (a) Gerhäuser, C.; Lee, S. K.; Kosmeder, J. W.; Moriarty, R. M.; Hamel, E.; Mehta, R.

G.; Moon, R. C.; Pezzuto, J. M. *Cancer Res.* **1997**, *57*, 3429. (b) Seiler, N.; Atanassov, C.; Raul, F. *Int. J. Oncol.* **1998**, *13*, 993. (c) Schuler, F.; Yano, T.; Di Bernardo, S.; Yagi, T.; Yankovskaya, V.; Singer, T. P.; Casida, J. E. *Proc. Natl. Acad. Sci. U. S. A.* **1999**, *96*, 4149. (d) Chun, K.-H.; Kosmeder, J. W.; Sun, S.; Pezzuto, J. M.; Lotan, R.; Hong, W. K.; Lee, H.-Y. *J. Natl. Cancer Inst.* **2003**, *95*, 291. (e) Oh, S. H.; Woo, J. K.; Yazici, Y. D.; Myers, J. N.; Kim, W.-Y.; Jin, Q.; Hong, S. S.; Park, H.-J.; Suh, Y.-G.; Kim, K.-W.; Hong, W. K.; Lee, H.-Y. *J. Natl. Cancer Inst.* **2007**, *99*, 949. (f) Kim, J. H.; Kim, J. H.; Yu, Y. S.; Shin, J. Y.; Lee, H.-Y.; Kim, K.-W. *J. Cell. Mol. Med.* **2008**, *12*, 2407. (g) Botta, B.; Menendez, P.; Zappia, G.; de Lima, R. A.; Torge, R.; Monache, G. D. *Curr. Med. Chem.* **2009**, *16*, 3414. (h) Belmain, S. R.; Amoah, B. A.; Nyirenda, S. P.; Kamanula, J. F.; Stevenson, P. C. *J. Agric. Food Chem.* **2012**, *60*, 10055. (i) Wang, Y. P.; Yi, S.; Wen, L.; Zhang, B. P.; Zaho, F.; He, J.; Fang, J.; Zhang, C.; Cui, G.; Chen, Y. *Curr. Cancer Drug Targets* **2014**, *14*, 685.

(8) For synthesis, see: (a) Herbert, J. R.; Ollis, W. D.; Russell, R. C. *Proc. Chem. Soc.* **1960**, 177. (b) Fukui, K.; Nakayama, M.; Harano, T. *Experientia* **1967**, *23*, 613. (c) Nakatani, N.; Matsui, M. *Agric. Biol. Chem.* **1968**, *32*, 769. (d) Omokawa, H.; Yamashita, K. *Agric. Biol. Chem.* **1973**, *37*, 1717. (e) Ahmad-Junaid, S.; Amos, P. C.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 539. (f) Crombie, L.; Josephs, J. L. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2591. (g) Ueno, H.; Miyoshi, H.; Inoue, M.; Niidome, Y.; Iwamura, H. *Biochim. Biophys. Acta, Bioenerg.* **1996**, *1276*, 195. (h) Granados-Covarrubias, E. H.; Maldonado, L. A. *J. Org. Chem.* **2009**, *74*, 5097.

(9) Sames and Pastine converted **5** to deguelin by using BCl_3 -mediated regioselective demethylation and intramolecular oxa-Michael addition in 86% overall yield. See ref **6e**.

(10) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (b) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46. (c) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979. (d) Chinchilla, R.; Nájera, C. *Chem. Soc. Rev.* **2011**, *40*, 5084.

(11) (a) Bandaranayake, W. M.; Crombie, L.; Whiting, D. A. *J. Chem. Soc. D* **1969**, 970. (b) Crombie, L.; Bandaranayake, W. M.; Whiting, D. A. *J. Chem. Soc. C* **1971**, 804.

(12) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.

(13) Hofsløkken, N. U.; Skattebøl, L. *Acta Chem. Scand.* **1999**, *53*, 258.

(14) Chang, D.-J.; An, H.; Kim, K.-s.; Kim, H. H.; Jung, J.; Lee, J. M.; Kim, N.-J.; Han, Y. T.; Yun, H.; Lee, S.; Lee, G.; Lee, S.; Lee, J. S.; Cha, J.-H.; Park, J.-H.; Park, J. W.; Lee, S.-C.; Kim, S. G.; Kim, J. H.; Lee, H.-Y.; Kim, K.-W.; Suh, Y.-G. *J. Med. Chem.* **2012**, *55*, 10863.

(15) Reaction progress was checked by crude NMR due to the same R_f values of **5** and **6**.

(16) For synthesis of **12**, see the [Experimental Section](#) for details.

(17) See the [SI](#) for spectral data to identify the structure of **15**. See also: (a) Carson, D.; Crombie, L.; Kilbee, G. W.; Moffatt, F.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1982**, 779. (b) Dinya, Z.; Keseru, G. M.; Nogradi, M.; Szollosy, A. *ACH - Models Chem.* **2000**, *137* (5–6), 591.

(18) For formal synthesis of deguelin, compound **5** was obtained from two commercially available starting materials in 58% overall yields with 6 steps (based on 2-nitroresorcinol), while total synthesis of munduserone was achieved in 60% overall yield with 7 steps from 3,4-dimethoxyphenol.

(19) (a) Henry, G. E.; Jacobs, H. *Tetrahedron* **2001**, *57*, 5335. (b) Lesch, B.; Toräng, J.; Vanderheiden, S.; Bräse, S. *Adv. Synth. Catal.* **2005**, *347*, 555. (c) Azevedo, C. M. G.; Afonso, C. M. M.; Sousa, D.; Lima, R. T.; Vasconcelos, M. H.; Pedro, M.; Barbosa, J.; Corrêa, A. G.; Reis, S.; Pinto, M. M. M. *Bioorg. Med. Chem.* **2013**, *21*, 2941.

(20) Sinhababu, A. K.; Borchardt, R. T. *J. Org. Chem.* **1983**, *48*, 1941.

(21) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 6716.