

Practical Synthesis of Glaziovianin A, a Cytotoxic Isoflavone, and Its O^7-Propargyl Analogue

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Glaziovianin A and its O^7-propargyl analogue are potent cytotoxic isoflavones. We found that the O^7-propargyl analogue completely arrested cell-cycle progression. We have achieved the large-scale synthesis of glaziovianin A and its O^7-propargyl analogue for further in vivo experimentation.

Glaziovianin A (**1**), a novel isoflavone, was isolated from the leaves of *Ateleia glazioviana* Baillon (Legminosae) as a cytotoxic compound against human leukemia HL-60 cells (Figure 1).[1] Glaziovianin A (**1**) exhibits a broad spectrum of cytotoxicity against a panel of 39 human cancer cell lines (termed JFCR39).[2] The pattern of the differential cytotoxicities of glaziovianin A (**1**) obtained using the software program COMPARE suggested that glaziovianin A (**1**) inhibits cancer cell proliferation by disrupting tubulin polymerization. Inhibitors of tubulin polymerization are used as anticancer agents, especially for breast cancer.[3] We reported the results of our synthesis[4] and structure–cytotoxicity relationship study of glaziovianin A (**1**).[5] We found that the cytotoxicity of O^7-modified glaziovianin A analogues, such as the allyl, the benzyl, and the propargyl ethers instead of the methyl ether at O^7 were more active than glaziovianin A (**1**) itself. In particular, O^7-propargyl analogue **2** completely arrested cell-cycle progression at 1 μM. We also showed that glaziovianin A (**1**) and O^7-propargyl analogue **2** extended the time lag of microtubule polymerization in vitro.[6] Thus, we planned to provide a practical supply of **1** and **2** for further in vivo experiments. Although we have previously accomplished the synthesis of glaziovianin A (**1**),[4] the route involved low-yield steps. In this paper, we describe the practical synthesis of glaziovianin A (**1**) and O^7-propargyl analogue **2**.

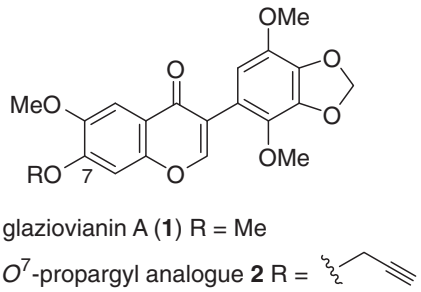
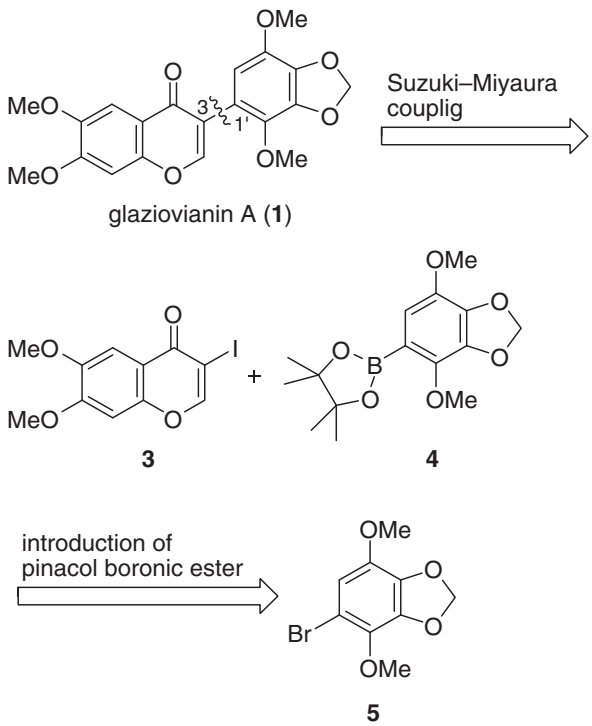


Figure 1. The structures of glaziovianin A (**1**) and its O^7-propargyl analogue **2**.

The retrosynthetic analysis of glaziovianin A (**1**) is shown in Scheme 1. Our strategy involved a key segment coupling between iodochromone **3** and pinacol boronate **4** using the Suzuki–Miyaura coupling.[7] Pinacol boronate **4** might be obtained from known aryl bromide **5**.[8]

In our previous report,[4] we prepared pinacol boronate **4** by using a Pd(0)-mediated cross-coupling reaction between aryl bromide **5**[8] and bis(pinacolato)diboron (Scheme 2).[9] However, this coupling reaction yield was low and not reproducible (0%–44%). On the other hand, the treatment of acetal **6** with *n*-BuLi at room temperature, followed by the addition of trimethyl



Scheme 1. The retrosynthetic analysis of glaziovianin A (**1**).

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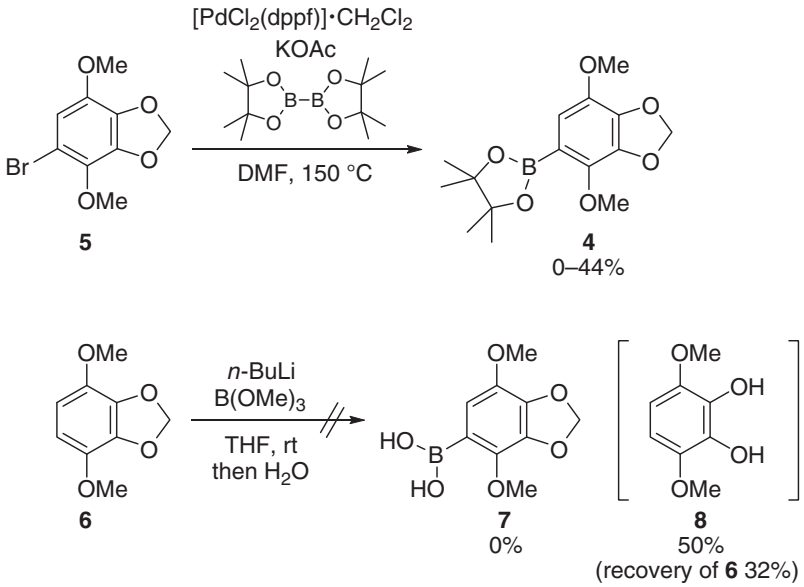
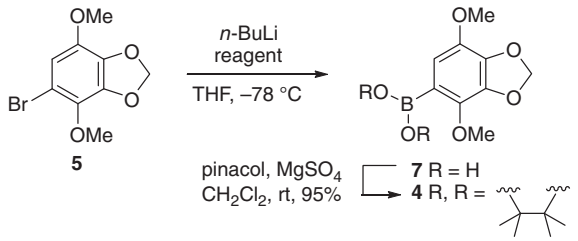
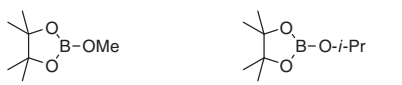


Scheme 2. Unsuccessful synthetic route of pinacol boronate **4** or boronic acid **7**.

Table 1. The Preparation of Pinacol Boronate **4** or Boronic Acid **7**



Entry	Reagent	Product	Yield/%
1	$B(OMe)_3$, then H_2O	**7**	56 (100 mg scale)
2	$B(O\text{-}i\text{-}Pr)_3$, then H_2O	**7**	90 (300 mg scale)
3	**9**	**4**	75 (100 mg scale)
4	**10**	**4**	80 (100 mg scale)
5	**10**	**4**	91 (1 g scale)

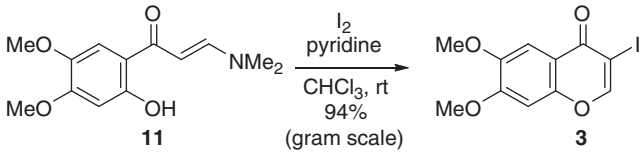


9 methoxyboronic acid pinacol ester

10 isopropoxyboronic acid pinacol ester

borate, gave undesired catechol **8** instead of desired boronic acid **7**. Namely, the methylene acetal of **6** was expected to be deprotonated more easily than the aromatic proton of acetal **6** in these reaction conditions.

We therefore investigated the preparation of pinacol boronate **4** or boronic acid **7** by a bromine–lithium exchange of aryl bromide **5** followed by the reaction with boron compound, because the bromine–lithium exchange can be carried out at a lower temperature (Table 1). We attempted the bromine–lithium exchange of aryl bromide **5** with *n*-BuLi at −78 °C followed by a reaction with trimethyl borate to give the desired aryl boronic acid **7** in 56% yield (Entry 1). In Entry 2, the reaction with triisopropyl borate afforded aryl boronic acid **7** in 90% yield. Aryl boronic acid **7** was converted into pinacol boronate **4** in 95% yield. We next attempted a one-step conversion to form pinacol boronate **4** from aryl bromide **5**. The bromine–lithium exchange of aryl bromide **5** followed by a reaction with methoxyboronic acid pinacol ester (**9**) afforded the desired pinacol boronate **4** in 75% yield (Entry 3). The reaction with isopropoxyboronic acid pinacol ester (**10**) gave pinacol boronate **4** in 80% yield (Entry 4). These reaction conditions could be used in the gram-scale synthesis of pinacol boronate **4** (91% yield) (Entry 5).

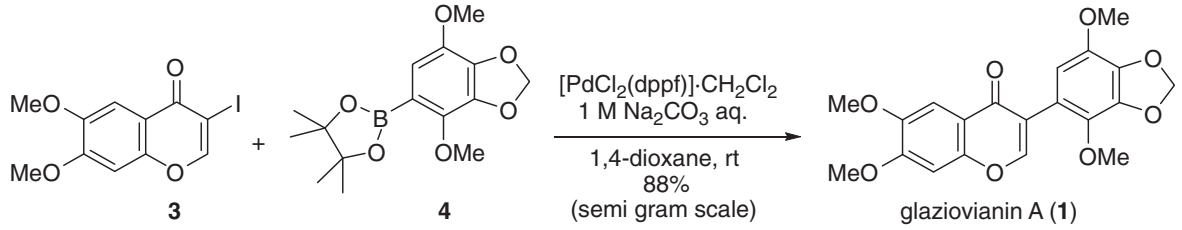


Scheme 3. The synthesis of iodochromone **3**.

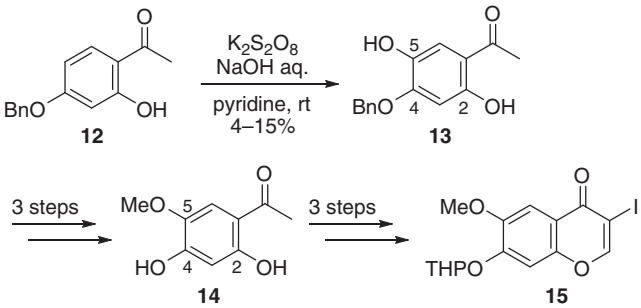
We next examined the preparation of iodochromone **3** (Scheme 3). We reported that the iodinative cyclization of enamine **11**[10] was effected in $CHCl_3$ as a solvent.[4] However, this cyclization yield was not reproducible in the gram-scale synthesis. Our reexamination of iodinative cyclization uncovered satisfactory conditions, i.e., $CHCl_3$ at room temperature in the presence of pyridine.[11] We assume that a small amount of acids would be neutralized by pyridine. This modification increased the reproducibility, and the procedure was applicable to the gram-scale of this cyclization without decreasing the yield.

The semi-gram-scale of the Suzuki–Miyaura coupling[7] reaction between pinacol boronate **4** and iodochromone **3** proceeded smoothly to give glaziovianin A (**1**) (Scheme 4). Thus, we have established a large-scale synthetic route of glaziovianin A (**1**). From this synthetic work, we synthesized one gram of glaziovianin A (**1**).

Next, we attempted the large-scale synthesis of the O^7-propargyl analogue **2** of glaziovianin A. The preparation of O^7-propargyl analogue **2** requires O^7-THP-protected iodochromone **15** as the Suzuki–Miyaura coupling partner of pinacol



Scheme 4. The semi-gram-scale synthesis of glaziovianin A (**1**).



Scheme 5. The previous synthesis of O^7-THP-protected iodochromone **15**.

boronate **4**.[5] In our previous work, iodochromone **15** was prepared from 2,4-dihydroxy-5-methoxyacetophenone (**14**) (known compound) (Scheme 5).[5] However, the preparation of 2,4-dihydroxy-5-methoxyacetophenone (**14**) included a low-yield step.[12] Elbs' persulfate oxidation of acetophenone **12** into 4-benzyloxy-2,5-dihydroxyacetophenone (**13**) thus showed low yields (4%–15% yield), and we therefore attempted to establish an efficient route for synthesizing the O^7-propargyl analogue **2** of glaziovianin A.

Zhang and Botting reported the synthesis of 2,4-dihydroxy-5-methoxy-[1′,2′-$^{13}C_2$]acetophenone from 3-[1,2-$^{13}C_2$]acetoxy-4-methoxyphenol by using the Fries rearrangement.[13] We followed the reported procedure (Scheme 6). The treatment of 3-acetoxy-4-methoxyphenol (**17**) prepared from isovanillin (**16**),[14] with BF_3·OEt_2 (without solvent) thus afforded 2,4-dihydroxy-5-methoxyacetophenone (**14**), which was converted into the THP ether **18** in 73% yield in two steps. These reaction conditions could be used in the gram-scale synthesis. The THP ether **18** was transformed into the O^7-THP-protected iodochromone **15** by our reported procedure in the gram-scale synthesis. With pinacol boronate **4** and O^7-THP-protected iodochromone **15** in hand, we attempted the semi-gram-scale of Suzuki–Miyaura coupling[7] by a strategy that was the same as that used for glaziovianin A (**1**). As a result, the desired coupling compound **20** was obtained in 81% yield. Coupling compound **20** was converted into the O^7-propargyl analogue **2** of glaziovianin A by our established procedure on the semi-gram-scale.

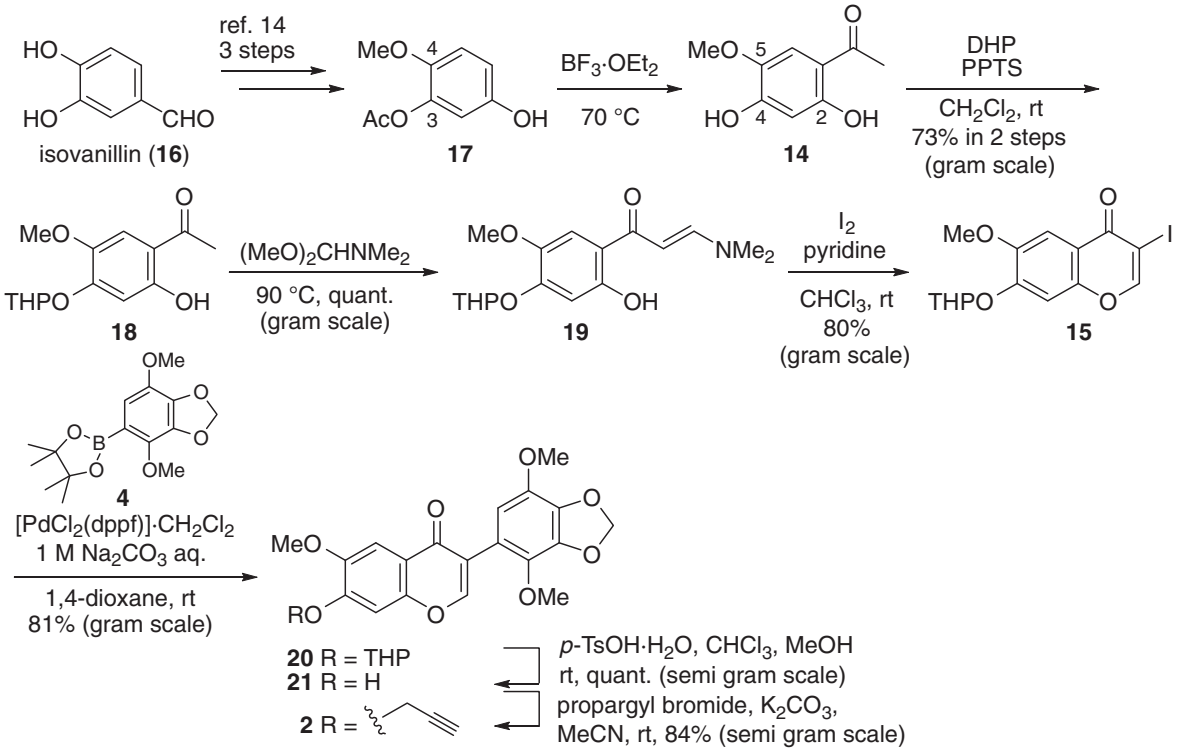
In conclusion, we have established the practical synthesis of glaziovianin A (**1**), a cytotoxic isoflavone, and its O^7-propargyl analogue **2**. To provide a supply for further biological studies, we synthesized one gram of glaziovianin A (**1**) and its O^7-propargyl analogue **2**. Further studies including animal experiments with glaziovianin A (**1**) and its O^7-propargyl analogue **2** are in progress.

Experimental

General. All reagents and dry solvents were used as obtained from commercial supplies unless otherwise noted. Organic solvents for moisture-sensitive reactions were distilled by standard procedure. Column chromatography was performed using silica gel (75–200 or 45–75 μm). All moisture-sensitive reactions were performed under an atmosphere of argon or nitrogen, and the starting materials were azeotropically dried with benzene before use. Infrared (IR) spectra were recorded on a FT IR system and only selected peaks are reported. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were run at various field strengths as indicated. The ^{1}H and ^{13}C chemical shifts (δ) are reported in parts per million (ppm) downfield relative to tetramethylsilane (TMS), $CHCl_3$ (δ_H 7.26), and $CDCl_3$ (δc 77.0). Coupling constants (J) are reported in Hz. Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High-resolution mass spectra (HRMS) were recorded by electrospray ionization (ESI)/time-of-flight (TOF) experiments. Melting points are uncorrected.

2-(4,7-Dimethoxybenzo[*d*][1,3]dioxol-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4). To a stirred solution of aryl bromide **5** (1.03 g, 3.94 mmol) in THF (18.0 mL) was added *n*-BuLi (2.50 M in *n*-hexane, 2.40 mL, 5.90 mmol) at −78 °C. After being stirred at −78 °C for 1 h, isopropoxyboronic acid pinacol ester (**10**) (1.80 mL, 7.88 mmol) was added. The mixture was stirred at −78 °C for 2 h, diluted with H_2O (12 mL) at −78 °C, and extracted with EtOAc (3 × 30 mL). The combined extracts were dried over Na_2SO_4, filtered, and concentrated. The residual solid was purified by column chromatography on silica gel (30 g, *n*-hexane–EtOAc 5:1) to give pinacol boronate **4** (1.10 g, 91%) as a colorless solid: mp 86–90 °C; IR ($CHCl_3$): 3010, 2982, 2938, 1606, 1496, 1458, 1426, 1367, 1144, 1068, 1039 cm^{-1}; ^{1}H NMR (270 MHz, $CHCl_3$): δ 6.85 (s, 1H), 5.98 (s, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 1.33 (s, 12H); ^{13}C NMR (67.8 MHz, $CHCl_3$): δ 143.1, 142.2, 139.3, 139.2, 138.7, 114.1, 101.5, 83.2 (2C), 61.0, 56.6, 24.9 (4C); HRMS (ESI): m/z 331.1329, calcd for $C_{15}H_{21}BNaO_6$ $[M + Na]^+$ 331.1323.

(*E*)-3-(Dimethylamino)-1-(2-hydroxy-4,5-dimethoxyphenyl)prop-2-en-1-one (11). 2′-Hydroxy-4′,5′-dimethoxyacetophenone (1.71 g, 8.71 mmol) was dissolved in *N*,*N*-dimethylformamide dimethyl acetal (1.90 mL, 14.2 mmol) and stirred at 100 °C for 2 h. The reaction mixture was concentrated in vacuo. The residual solid was purified by column chromatography on silica gel (35 g, $CHCl_3$) to give enamine **11** (2.10 g, quant.) as a yellow solid: mp 149–154 °C; IR ($CHCl_3$): 3275, 2950, 1625, 1541, 1506, 1280, 1222, 1101 cm^{-1}; ^{1}H NMR



Scheme 6. The semi-gram-scale synthesis of O^7-propargyl analogue **2**.

(270 MHz, $CHCl_3$): δ 14.3 (s, 1H), 7.84 (d, $J = 12.2$ Hz, 1H), 7.09 (s, 1H), 6.44 (s, 1H), 5.60 (d, $J = 12.2$ Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.17 (br s, 3H), 2.97 (br s, 3H); ^{13}C NMR (67.8 MHz, $CHCl_3$): δ 190.0, 159.9, 154.5, 153.0, 141.6, 113.6, 113.3, 105.2, 90.3, 57.9, 57.4, 40.1 (2C); HRMS (ESI): m/z 274.1038, calcd for $C_{13}H_{17}NNaO_4$ $[M + Na]^+$ 274.1050.

3-Iodo-6,7-dimethoxy-4*H*-chromen-4-one (3). To a stirred solution of enamine **11** (1.07 g, 4.53 mmol) in $CHCl_3$ (22 mL) were added pyridine (650 µL, 8.12 mmol) and I_2 (2.47 g, 9.73 mmol) at 0 °C. After being stirred in the dark at room temperature for 13 h, the mixture was diluted with saturated aqueous $Na_2S_2O_3$ (20 mL) at 0 °C and extracted with $CHCl_3$ (3 × 30 mL). The combined extracts were dried over Na_2SO_4, filtered, and concentrated. The residual solid was purified by column chromatography on silica gel (50 g, $CHCl_3$) to give iodochromone **3** (1.43 g, 94%) as a yellow solid: mp 182–186 °C; IR ($CHCl_3$): 3014, 2972, 2943, 1617, 1507, 1289, 1171, 1065 cm^{-1}; ^{1}H NMR (270 MHz, $CHCl_3$): δ 8.23 (s, 1H), 7.53 (s, 1H), 6.85 (s, 1H), 3.98 (s, 3H), 3.97 (s, 3H); ^{13}C NMR (67.8 MHz, $CHCl_3$): δ 172.3, 156.7, 151.5, 148.6, 134.4, 115.6, 105.3, 103.1, 86.7, 56.5, 56.3; HRMS (ESI): m/z 354.9430, calcd for $C_{11}H_9INaO_4$ $[M + Na]^+$ 354.9438.

Glaziovianin A (1). All solvents were degassed by freeze–thawing. To a stirred solution of pinacol boronate **4** (650 mg, 2.10 mmol), iodochromone **3** (830 mg, 2.40 mmol), and [$PdCl_2$-(dppf)]·CH_2Cl_2 (dppf: 1,1′-bis(diphenylphosphino)ferrocene) (342 mg, 420 µmol) in 1,4-dioxane (43 mL) was added aqueous 1 M Na_2CO_3 (14.0 mL, 14.0 mmol) at room temperature in a glove box. The mixture was stirred at room temperature under a stream of N_2 for 24 h, diluted with H_2O (15 mL) and EtOAc (40 mL) at room temperature, and separated. The aqueous layer was extracted with EtOAc (3 × 30 mL). The organic layer and extracts were combined, dried over Na_2SO_4, filtered through a pad of Florisil, and concentrated. The residual solid was purified by column chromatography on silica gel (50 g, hexane–EtOAc 5:1) to give glaziovianin A (**1**) (714 mg, 88%) as a white solid: mp 188–190 °C; IR (film): 3002, 2941, 2838, 1638, 1606, 1505, 1454, 1428, 1297, 1271, 1228, 1150, 1062, 1035 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.91 (s, 1H), 7.62 (s, 1H), 6.89 (s, 1H), 6.53 (s, 1H), 6.03 (s, 2H), 4.00 (s, 3H), 3.99 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 175.2, 154.1, 153.3, 152.1, 147.5, 139.0, 138.8, 136.9, 136.6, 121.6, 117.9, 117.7, 110.0, 104.8, 101.7, 99.5, 60.1, 56.9, 56.4, 56.3; HRMS (ESI): m/z 409.0894, calcd for $C_{20}H_{18}NaO_8$ $[M + Na]^+$ 409.0899.

1-[2-Hydroxy-5-methoxy-4-(tetrahydro-2*H*-pyran-2-yloxy)phenyl]ethanone (18). BF_3·OEt_2 (5.00 mL, 40.5 mmol) was added to 3-acetoxy-4-methoxyphenol (**17**) (1.60 g, 8.69 mmol) at room temperature (without solvent). The mixture was stirred at 70 °C for 4 h, then diluted with saturated aqueous NaOAc (50 mL) at room temperature. Saturated aqueous $NaHCO_3$ at room temperature was added to the mixture until no further CO_2 was evolved. The reaction mixture was extracted with EtOAc (3 × 60 mL). The combined extracts were dried over Na_2SO_4 and filtered. Removal of the solvent afforded crude 2,4-dihydroxy-5-methoxyacetophenone (**14**) (1.68 g, crude) as a brown solid, which was used for the next reaction without further purification.

To a stirred solution of crude 2,4-dihydroxy-5-methoxyacetophenone (**14**) (1.31 g, 7.10 mmol) in CH_2Cl_2 (80 mL) were added DHP (DHP: dihydropyran) (3.20 mL, 37.5 mmol) and PPTS (PPTS: pyridinium *p*-toluenesulfonate) (400 mg, 1.59 mmol) at 0 °C. After being stirred at room temperature for 24 h, the reaction mixture was diluted with saturated aqueous

$NaHCO_3$ (30 mL) at 0 °C, and separated. The aqueous layer was extracted with EtOAc (3 × 50 mL). The organic layer and extracts were combined, dried over Na_2SO_4, filtered, and concentrated. The residual solid was purified by column chromatography on silica gel (30 g, hexane–EtOAc 5:1) to give THP ether **18** (1.40 g, 5.18 mmol, 73% in 2 steps) as a white solid: mp 120–131 °C; IR ($CHCl_3$): 3518, 3014, 2950, 1632, 1504, 1372, 1330, 1261, 1228, 1216, 1208 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 12.5 (s, 1H), 7.12 (s, 1H), 6.74 (s, 1H), 5.50 (t, J = 3.0 Hz, 1H), 3.89–3.82 (m, 1H), 3.85 (s, 3H), 3.66–3.62 (m, 1H), 2.56 (s, 3H), 2.01–1.89 (m, 3H), 1.74–1.64 (m, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 201.8, 159.3, 154.2, 142.1, 113.3, 112.3, 104.3, 96.6, 62.1, 57.1, 29.9, 26.2, 24.8, 18.5; HRMS (ESI): m/z 289.1051, calcd for $C_{14}H_{18}NaO_5$ $[M + Na]^+$ 289.1046.

(*E*)-3-(Dimethylamino)-1-[2-hydroxy-5-methoxy-4-(tetrahydro-2*H*-pyran-2-yloxy)phenyl]prop-2-en-1-one (19). THP ether **18** (2.96 g, 11.1 mmol) was dissolved in *N*,*N*-dimethylformamide dimethyl acetal (2.80 mL, 20.8 mmol). The reaction mixture was stirred at 90 °C for 3 h and concentrated. The residual solid was purified by column chromatography on silica gel (30 g, $CHCl_3$) to give enamine **19** (3.70 g, quant.) as a yellow solid: mp 113–119 °C; IR ($CHCl_3$): 3689, 2949, 1631, 1541, 1507, 1372, 1284, 1222, 1209, 1108 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 14.0 (s, 1H), 7.84 (d, J = 12.4 Hz, 1H), 7.18 (s, 1H), 6.72 (s, 1H), 5.62 (d, J = 12.4 Hz, 1H), 5.46 (t, J = 3.2 Hz, 1H), 3.89 (m, 1H), 3.85 (s, 3H), 3.63 (m, 1H), 3.22 (br s, 3H), 3.17 (br s, 3H), 2.01–1.88 (m, 3H), 1.72–1.61 (m, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 190.2, 160.0, 154.0, 152.7, 141.7, 113.6, 112.9, 105.0, 96.8, 89.8, 62.4, 58.2, 40.3 (2C), 30.2, 25.1, 19.0; HRMS (ESI): m/z 344.1471, calcd for $C_{17}H_{23}NNaO_5$ $[M + Na]^+$ 344.1474.

3-Iodo-6-methoxy-7-(tetrahydro-2*H*-pyran-2-yloxy)-4*H*-chromen-4-one (15). To a stirred solution of enamine **19** (2.03 g, 6.32 mmol) in $CHCl_3$ (40 mL) were added pyridine (900 µL, 11.4 mmol) and I_2 (1.98 g, 7.60 mmol) at 0 °C. After being stirred at room temperature for 15 h in the dark, the mixture was diluted with saturated aqueous $Na_2S_2O_3$ (20 mL) at 0 °C and extracted with $CHCl_3$ (3 × 30 mL). The combined extracts were dried over Na_2SO_4 and concentrated. The residual solid was purified by column chromatography on silica gel (60 g, $CHCl_3$) to give O^7-THP-protected iodochromone **15** (2.03 g, 80%) as a yellow solid: mp 144–148 °C; IR ($CHCl_3$): 3024, 2999, 1640, 1605, 1541, 1503, 1350, 1219, 1203 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 8.22 (s, 1H), 7.55 (s, 1H), 7.20 (s, 1H), 5.55 (t, J = 2.7 Hz, 1H), 3.95 (s, 3H), 3.91–3.82 (m, 1H), 3.68–3.63 (m, 1H), 2.10–1.87 (m, 3H), 1.77–1.62 (m, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 172.2, 156.8, 156.7, 151.7, 148.5, 115.6, 105.2, 103.7, 97.1, 86.2, 62.0, 56.3, 29.9, 24.9, 18.3; HRMS (ESI): m/z 424.9867, calcd for $C_{15}H_{15}INaO_5$ $[M + Na]^+$ 424.9862.

O^7-THP Glaziovianin A (20). All solvents were degassed by freeze–thawing. To a stirred solution of pinacol boronate **4** (1.03 g, 3.34 mmol), iodochromone **15** (1.43 g, 3.55 mmol), and $[PdCl_2(dppf)]\cdot CH_2Cl_2$ (250 mg, 306 µmol) in 1,4-dioxane (70 mL) was added aqueous 1 M Na_2CO_3 (22.0 mL, 22.0 mmol) at room temperature in a glove box. The mixture was stirred at room temperature under a stream of N_2 for 24 h, diluted with H_2O (25 mL) and $CHCl_3$ (50 mL) at 0 °C, and separated. The aqueous layer was extracted with $CHCl_3$ (3 × 60 mL). The organic layer and extracts were combined, dried over Na_2SO_4, filtered through a pad of Florisil, and concentrated. The residual solid was purified by column chromatography on silica gel (70 g, hexane–EtOAc 5:1) to give O^7-THP glaziovianin A (**20**) (1.23 g, 81%) as a white solid: mp 189–195 °C; IR ($CHCl_3$): 3007, 2948, 1639, 1607, 1500, 1468, 1430, 1352, 1297 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 7.90 (s, 1H), 7.62 (s, 1H), 7.22 (s, 1H), 6.52 (s, 1H), 6.01 (s, 2H), 5.56 (m, 1H), 3.96 (s, 3H), 3.95–3.88 (m, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.70–3.60 (m, 1H), 2.06–1.97 (m, 3H), 1.72–1.68 (m, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 175.4, 153.5, 151.8, 151.4, 148.2, 139.0, 138.8, 136.9, 136.6, 121.3, 118.4, 118.0, 109.9, 105.3, 104.2, 101.9, 97.1, 62.1, 60.2, 56.9, 56.4, 30.1, 25.1, 18.5; HRMS (ESI): m/z 479.1310, calcd for $C_{24}H_{24}NaO_9$ $[M + Na]^+$ 479.1313.

O^7-Demethyl Glaziovianin A (21). To a stirred solution of O^7-THP glaziovianin A (**20**) (900 mg, 1.97 mmol) in $CHCl_3$ (36 mL) and MeOH (18 mL) was added p-TsOH·H_2O (65.0 mg, 341 µmol) at room temperature. After the mixture was stirred at room temperature for 4 h, Et_3N (600 µL, 4.30 mmol) and H_2O (30 mL) were added at room temperature, and separated. The aqueous layer was extracted with $CHCl_3$ (3 × 50 mL). The organic layer and extracts were combined, dried over Na_2SO_4, filtered, and concentrated. The residual solid was purified by column chromatography on silica gel (20 g, $CHCl_3$) to give O^7-demethyl glaziovianin A (**21**) (732 mg, quant.) as a white solid: mp 225–228 °C; IR ($CHCl_3$): 3610, 3015, 2945, 1635, 1599, 1502, 1461, 1288 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.64 (s, 1H), 6.98 (s, 1H), 6.52 (s, 1H), 6.02 (s, 2H), 4.02 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), OH proton was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 175.3, 153.8, 151.6, 151.8, 148.2, 139.1, 138.8, 137.1, 136.6, 121.2, 118.5, 117.6, 109.7, 105.3, 104.0, 102.0, 60.1, 56.9, 56.6; HRMS (ESI): m/z 395.0745, calcd for $C_{19}H_{16}NaO_8$ $[M + Na]^+$ 395.0737.

O^7-Propargyl Glaziovianin A (2). To a stirred solution of O^7-demethyl glaziovianin A (**21**) (732 mg, 1.97 mmol) in MeCN (60 mL) were added K_2CO_3 (700 mg, 5.06 mmol) and propargyl bromide (2.30 mL, 26.7 mmol) at room temperature. After being stirred at room temperature for 25 h, the mixture was diluted with saturated aqueous $NaHCO_3$ (30 mL) at room temperature and extracted with $CHCl_3$ (3 × 50 mL). The combined extracts were dried over Na_2SO_4 and concentrated. The residual solid was purified by column chromatography on silica gel (30 g, hexane–EtOAc 3:1) to give O^7-propargyl glaziovianin A (**2**) (680 mg, 84%) as a brown solid: mp 165–169 °C; IR ($CHCl_3$): 3306, 3008, 2934, 1638, 1609, 1502, 1470, 1431, 1398, 1267, 1231, 1209, 1099 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.64 (s, 1H), 7.08 (s, 1H), 6.52 (s, 1H), 6.03 (s, 2H), 4.90 (d, J = 2.2 Hz, 2H), 3.99 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 2.61 (t, J = 2.2 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 175.2, 153.5, 151.7, 147.8, 139.0, 138.9, 137.0, 136.7, 132.0, 121.7, 118.5, 117.9, 110.0, 105.4, 101.8, 101.6, 84.1, 77.2, 60.2, 60.1, 56.9, 56.4; HRMS (ESI): m/z 411.1068, calcd for $C_{22}H_{19}O_8$ $[M + H]^+$ 411.1080.

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