Synthesis of Glaziovianin A: A Potent Antitumor Isoflavone

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Glaziovianin A (**1**) is a novel isoflavone derivative isolated from the leaves of the Brazilian tree *Astelia glazioviana*. Glaziovianin A (**1**) showed cytotoxic activity and was suggested to be an inhibitor of tubulin polymerization. We achieved the total synthesis of glaziovianin A (**1**) by using the Suzuki–Miyaura coupling as a key step.

Glaziovianin A (**1**) is a novel isoflavone derivative isolated from the leaves of the Brazilian tree *Astelia glazioviana* by Yokosuka et al. in 2007 (Figure 1).[1] Glaziovianin A (**1**) showed cytotoxic activity against HL-60 cells with an IC_{50} value of 0.29 μM. The pattern of the differential cytotoxicities in the Japanese Foundation for Cancer Research 39 cell line of glaziovianin A (**1**), as determined using the program COMPARE, has suggested that the activity of **1** involves the inhibition of tubulin polymerization.[2] Inhibitors of tubulin polymerization, such as vinblastin, have become clinically important drugs against breast cancer.[3] We planned an efficient and scalable synthesis of glaziovianin A (**1**), which will provide a practical supply for further biological studies.

Our synthetic route to glaziovianin A (**1**) involved the Suzuki–Miyaura coupling at C-1′–C-3 (Scheme 1).[4] We therefore synthesized 3-iodochlomone derivative **2** and boronate compound **3**.

Preparation of the boronate compounds **3** required optimization (Table 1). Thus, preparation of arylboronic acid **3a** was attempted by the lithiation of **4**[5] followed by treatment with trimethyl borate (**6**) or triisopropyl borate (**7**), but the desired compound **3a** could not be obtained (Entries 1 and 2). Bromine–lithium exchange of aryl bromide **5**[6] followed by reaction with **6** or **7** gave only debromo compound **4** (Entries 3 and 4). Next, we attempted the direct borylation of the aryl bromide **5** with pinacolborane (**8**) catalyzed by Pd^0,[7] but the arylboronate **3b** could not be obtained (Entry 5). An attempt at the cross-coupling

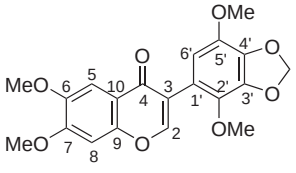
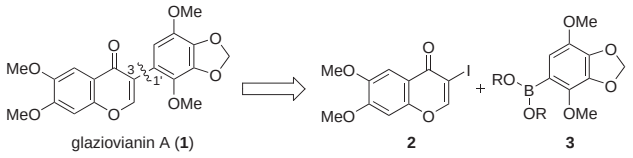
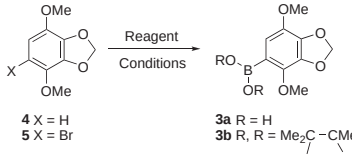


Figure 1. Structure of glaziovianin A (**1**).

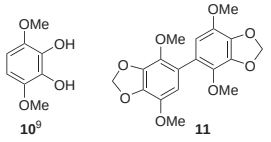


Scheme 1. Retrosynthetic analysis of glaziovianin A (**1**).

Table 1. Study of the borylation of arenes **4** and **5**



Entry	Substrate	Reagent	Conditions	Yield
1	**4**	$B(OMe)_3$ **6**	*n*-BuLi, THF, rt	**4**: 85%
2	**4**	$B(O\text{-}i\text{-}Pr)_3$ **7**	*n*-BuLi, THF, rt	**4**: 62%, **10**: 25%
3	**5**	**6**	*n*-BuLi, THF, rt	**4**: 79%
4	**5**	**7**	*t*-BuLi, THF, rt	**4**: 72%, **10**: 17%
5	**5**	**8**	$Pd(OAc)_2$, Et_3N, DPEphos 1,4-dioxane, 60 °C	**4**: 76%
6	**5**	**9**	$PdCl_2$(dppf), KOAc DMF, 60 °C	**4**: 40%, **11**: 15%
7	**5**	**9**	$PdCl_2$(dppf), KOAc DMF, 100 °C	**3b**: 12%, **4**: 39%, **11**: 1%
8	**5**	**9**	$PdCl_2$(dppf), KOAc DMF, 150 °C	**3b**: 44%, **4**: 40%, **11**: 3%



reaction of the bis(pinacolato)diboron (**9**) with **5** to **3b** failed by using $PdCl_2$(dppf) and KOAc in DMF at 60 °C (Entry 6).[8] However, the reactions at higher temperature gave the desired arylboronate **3b** (Entries 7 and 8). The reaction at 150 °C gave the desired arylboronate **3b** in 44% yield along with a small amount of the homocoupling dimer **11** (Entry 8).

The 3-iodochromone derivative **2** was synthesized from commercially available 2-hydroxy-4,5-dimethoxyacetophenone (**12**) by the reported method for the preparation of 3-halogenated chromones (Scheme 2).[10] Condensation of **12** with *N*,*N*-dimethylformamide dimethyl acetal gave enamine **13** in quantitative yield. The attempts to achieve iodinative cyclization of enamine **13** are summarized in Table 2. Reaction of enamine **13** with iodine in MeOH did not give iodochromone **2** because of the low solubility (Entry 1). The cyclization in toluene afforded the desired iodochromone **2** in 44% yield (Entry 2).[11] Treatment of **13** with iodine in CH_2Cl_2 gave iodochromone **2** in 65% yield (Entry 3). The cyclization was the most efficiently effected in $CHCl_3$ (Entry 4). Addition of pyridine was not effective in this case (Entry 5).[12]

With both segments, iodochromone **2** and arylboronate **3b**, in hand, we attempted the Suzuki–Miyaura coupling by using $PdCl_2$(dppf)[13] to furnish glaziovianin A (**1**) in 80% yield (Scheme 3).

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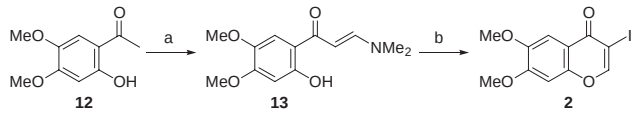
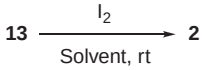


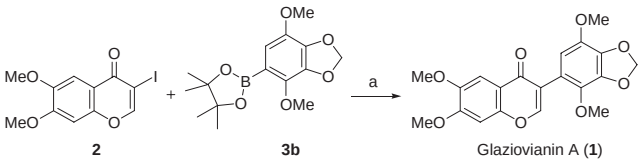
Reagents and conditions: a) $(MeO)_2CHNMe_2$, quant. b) I_2, $CHCl_3$, rt, 73% (see Table 2).

Scheme 2. Synthesis of iodochromone **2**.

Table 2. Study of iodinative cyclization



Entry	Solvent	Yield
1	MeOH	0% (recovery of **13**: 88%)
2	Toluene	44%
3	CH_2Cl_2	65%
4	$CHCl_3$	73%
5	Pyridine, $CHCl_3$	73%



Reagents and conditions: a) $PdCl_2$(dppf), 1M Na_2CO_3 aq., 1,4-dioxane, rt, 80%.

Scheme 3. Synthesis of glaziovianin A (**1**).

Synthetic glaziovianin A (**1**) gave spectral data (^{1}H NMR, ^{13}C NMR, HRMS, IR, and UV) in full agreement with those of the natural glaziovianin A (**1**),[14] completing the total synthesis. The cytotoxic activities of synthetic glaziovianin A (**1**) against HeLa cells and U87 human glioblastoma cells had the same IC_{50} values as those of natural glaziovianin A (**1**).[15]

In summary, we achieved a concise and semigram scale synthesis of glaziovianin A (**1**) by using the Suzuki–Miyaura coupling as a key step. Further structure–activity relationship studies are now in progress.

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9 The methylene acetal unit of compound **4** was hydrolyzed by acidic workup with 1 M HCl to give catechol **10** (Entries 2 and 4), however, compound **10** was not detected in Entries 1 and 3 somehow.
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14 Glaziovianin A (**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; HR-ESI-MS m/z 409.0894, calcd for $C_{20}H_{19}NaO_8$ $[M + Na]^+$ 409.0899; IR (film) ν_{max} 3002, 2941, 2838, 1638, 1606, 1505, 1454, 1428, 1297, 1271, 1228, 1150, 1062, 1035 cm^{-1}; UV (MeOH) λ_{max} 317.0 ($\log \varepsilon$ 4.02), 256.5 nm (4.21), mp 185.0–187.0 °C.
15 Natural and synthetic glaziovianin A (**1**) showed cytotoxic activities against HeLa cells with an IC_{50} of 5.0 and 5.3 μM, and against U87 cells with an IC_{50} of 7.9 and 8.3 μM, respectively. These biological assays were carried out by Prof. T. Usui, Graduate School of Life and Environmental Sciences, University of Tsukuba.

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