Total Synthesis of Grossularines-1 and -2

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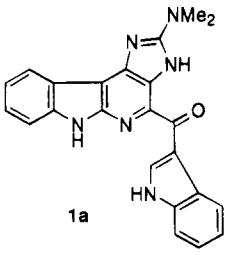
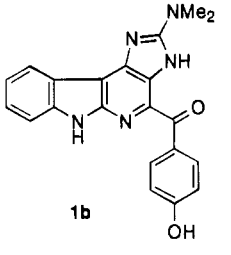
The first total syntheses of grossularines-1 (**1a**) and -2 (**1b**) have been completed. The cross-coupling reaction between ethyl 3-iodoindole-2-carboxylate (**6**) and the directed metalation-derived imidazole **9b** gave the ethyl 3-(5-imidazolyl)indole-2-carboxylate **11b**. Hydrolysis of the ester group of **11b**, followed by Curtius rearrangement, yielded the 2-isocyanatoindole **13b**. The thermal electrocyclic reaction of **13b** was carried out to provide the desired tetracyclic pyrido[2,3-*b*]indole ring system **14b**, which was converted into the triflate **15b**. The three-component cross-coupling reaction of the triflate **15b**, carbon monoxide, and *p*-(OMOM)phenylboronic acid (**17**) followed by hydrolysis gave grossularine-2 (**1b**) in low yield. In addition, the palladium-catalyzed carbonylation of the triflate **15b** afforded the *N*-deprotected methyl ester **19a** or the methyl ester **19b** depending on the amounts of triethylamine used. Compound **19a** was treated with either *p*-(OMOM)phenyllithium or 3-(*N*-TIPS)indolyllithium to obtain grossularine-2 (**1b**) and grossularine-1 (**1a**) (37%), respectively. By contrast, when **19b** was treated with the same aryllithium reagents, grossularine-2 (**1b**) (51%) and grossularine-1 (**1a**) (63%) were produced, respectively.

Grossularine-1 (**1a**) and -2 (**1b**) were isolated in 1989 from *Dendrodoa grossularia* (Stylidae), a tunicate collected in Britany.[1] The structures of both compounds were determined by spectroscopic evidence including X-ray analysis[2] for grossularine-2 (**1b**). These substances are the first examples of naturally occurring pyrido[2,3-*b*]indoles possessing interesting antitumor properties[3] and are challenging targets owing to their unique tetracyclic structure. One synthetic approach to the tetracyclic pyrido[2,3-*b*]indole ring system based on a strategy involving the directed ortho-metalation cross-coupling reaction between 7-bromo-4,6-dichloro-2-(dimethylamino)imidazo[4,5-*c*]pyridine and *o*-iodoacetanilide and subsequent intramolecular cyclization was communicated by Achab and co-workers in 1993.[4]



1a



1b

We are currently interested in the synthesis of heteroaromatic compounds containing a nitrogen atom by thermal electrocyclic reactions[5] of either conjugated hexatriene or monoazahexatriene systems including one double bond of an aromatic or heteroaromatic portion.[6,7] Recently, we reported the first total synthesis of grossularine-2 (**1b**)[8] by using the thermal electrocyclic reaction of a 2-azahexatriene system including the indole 2,3-bond and the imidazole 4,5-bond with a tautomeric process as an extended use of the modified Eloy's pyridoannelation.[9] We now describe the first total synthesis of grossularine-1 (**1a**) and the improved total synthesis of grossularine-2 (**1b**) together with the details of our preliminary work.

In our retrosynthetic analysis (Scheme 1), we planned that the acyl groups at the C-2 position of **1** would be derived from either the tetracyclic pyrido[2,3-*b*]indole **3** or its methyl ester **2**. Next, we considered that the tetracyclic pyrido[2,3-*b*]indole **3** would be obtained by a thermal electrocyclic reaction of 3-imidazolylindole-2-isocyanate **4**, a 2-azahexatriene system, derived from a cleavage of the 2,3-bond of pyrido[2,3-*b*]indole **3**. The precursor of **4** would be the carboxylic acid and its derivative **5**, which might be derived from a cross-coupling reaction between the 3-iodoindole derivative **6** and the *N*-substituted imidazole **7**.

Therefore, we preliminarily investigated a cross-coupling reaction between ethyl 3-iodoindole-2-carboxylate (**6**)[10] and 5-bromo-1-methyl-2-(methylthio)imidazole (**9a**), prepared from 1-methyl-2-(methylthio)imidazole (**8a**)[11] by NBS,[12] for the synthesis of the precursor of the

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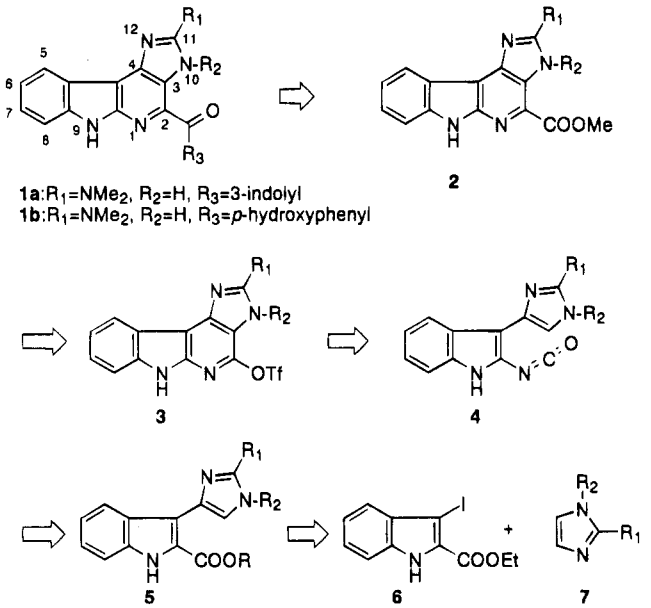
Scheme 1



2-azahexatriene system **4** and subsequent construction of the tetracyclic pyrido[2,3-*b*]indole ring (Scheme 2). Treatment of the readily available 5-bromoimidazole **9a** with *n*-BuLi followed by addition of trimethyltin chloride gave the stannylimidazole **10a**, which was used in the cross-coupling reaction[13] with 3-iodoindole **6** in the presence of $Pd(PPh_3)_4$ to yield the 3-(5-imidazolyl)indole **11a** (96% based on **6**). Hydrolysis of the ester **11a** with Na_2CO_3 and subsequent Curtius rearrangement with diphenyl phosphorazidate (DPPA) afforded the isocyanate **13a**, the so-called 2-azahexatriene system (65% from **11a**). The thermal electrocyclic reaction of **13a** was carried out in *o*-dichlorobenzene at 180 °C for 5 min to give the desired tetracyclic pyrido[2,3-*b*]indole **14a** in 72% yield.

On the basis of this model experiment, we chose the readily available 2-(dimethylamino)-1-[[(trimethylsilyl)-ethoxy]methyl]imidazole (**9b**), prepared from 2-(dimethylamino)imidazole (**8b**)[14] with [(trimethylsilyl)ethoxy]-methyl chloride (SEM-Cl) (83%), as the other component of the cross-coupling reaction for the synthesis of tetracyclic pyrido[2,3-*b*]indole **14b** (Scheme 2). To this end, treatment of the SEM-imidazole **9b** with *t*-BuLi, followed by addition of tributyltin chloride, gave the stannylimidazole **10b**, which was subjected to the cross-coupling reaction with 3-iodoindole **6** in the presence of $Pd(PPh_3)_4$ to yield the 3-(5-imidazolyl)indole **11b** (82% based on **6**) [80% yield based on **6** in the case of $PdCl_2(PPh_3)_2$]. Hydrolysis of **11b** with Na_2CO_3 gave the carboxylic acid **12b**, which was treated with DPPA at 60 °C in the presence of triethylamine to provide the isocyanate **13b** (86% yield from **11b**) as the required 2-azahexatriene system. The thermal electrocyclic reaction of **13b** was carried out in *o*-dichlorobenzene at 170 °C for 5 min to give the tetracyclic pyrido[2,3-*b*]indole **14b** (88%). This compound **14b** was converted into the mesylate **15a** in order to elucidate the regiochemistry of the directed metalation cross-coupling reaction described above. In the 2D-NOESY NMR spectrum of **15a**, the correlation was observed between methylene protons (δ 5.72) of the *N*-SEM group on the imidazole ring and the aromatic proton (δ 8.16) of C-5 position of pyrido[2,3-*b*]indole ring. Consequently, it was demonstrated that the proposed metalation cross-coupling reaction between **6** and **9b** has regioselectively proceeded at the C-5 position of the SEM-imidazole **9b**.[15] Furthermore, **14b** was converted into the triflate **15b** with trifluoromethanesulfonic anhydride and pyridine (94%) as an access to the goal.

At a final stage (Scheme 3), we attempted the Suzuki cross-coupling reaction.[16] The three-component cross-coupling reaction between the triflate **15b**, carbon monoxide, and 4-[(methoxymethyl)oxy]phenylboronic acid (**17**) ((methoxymethyl)oxy = OMOM) was carried out at 80 °C in the presence of $PdCl_2(PPh_3)_2$, K_2CO_3, and LiCl in anisole to provide the tetracyclic 2-benzoylpyrido[2,3-*b*]-indole **18a** (19%) along with 2-phenylpyrido[2,3-*b*]indole **18b** (58%) (method A). Subsequent hydrolysis of the *N*-SEM group of **18a** with diluted acid gave grossularine-2 (**1b**) (81%), which was confirmed by spectral data to be identical with natural grossularine-2 (**1b**).[1,8] However, a similar application of the Suzuki cross-coupling reaction to the synthesis of grossularine-1 (**1a**) failed.

We next turned our attention toward devising an improved route for introducing the suitable acyl groups to the C-2 position of pyrido[2,3-*b*]indole and utilized a palladium-catalyzed carbonylation of aryl triflates by the procedure of Ortar and co-workers[17] to obtain the key compound **19** (Scheme 3). Namely, the palladium-catalyzed carbonylation was carried out under a carbon monoxide atmosphere in the presence of triethylamine, palladium acetate, 1,1-bis(diphenylphosphino)ferrocene (dppf), and methanol to yield either the *N*-deprotected methyl ester **19a** (93%) or the methyl ester **19b** (77%) depending upon the amounts of triethylamine.

The nucleophilic addition reaction of the methyl esters **19** was investigated by using the aryllithium derivatives prepared from *p*-(OMOM)phenyl bromide (**16**)[18] with *n*-BuLi (or *t*-BuLi) or 3-bromo-1-(triisopropylsilyl)indole (**20**)[19] (triisopropylsilyl = TIPS) with *t*-BuLi *in situ*. For the improved synthesis of grossularine-2 (**1b**), the reaction of **19a** with *p*-(OMOM)phenyllithium and subsequent hydrolysis with diluted acid gave the desired grossularine-2 (**1b**) (method B; 61%). By contrast, treatment of **19b** with *p*-(OMOM)phenyllithium followed by hydrolysis with the same acid yielded grossularine-2 (**1b**) (method C; 51%). On the other hand, the reaction of **19a** with 3-indolyllithium and subsequent hydrolysis with diluted acid afforded grossularine-1 (**1a**) (method B; 37%). Moreover, treatment of **19b** with 3-indolyllithium followed by hydrolysis with the same acid provided grossularine-1 (**1a**) (method C; 63%). The spectral data of these synthetic materials were identical with those of

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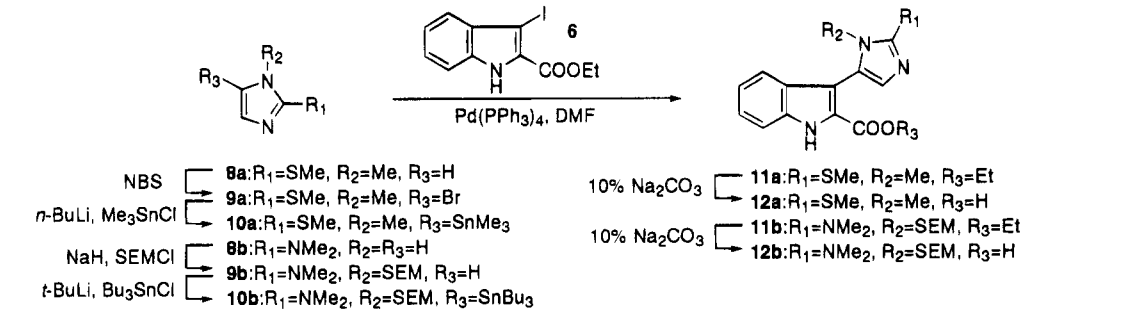
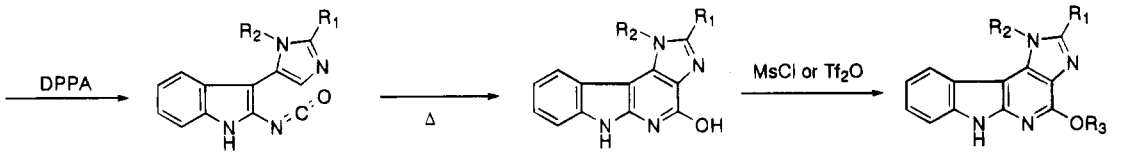
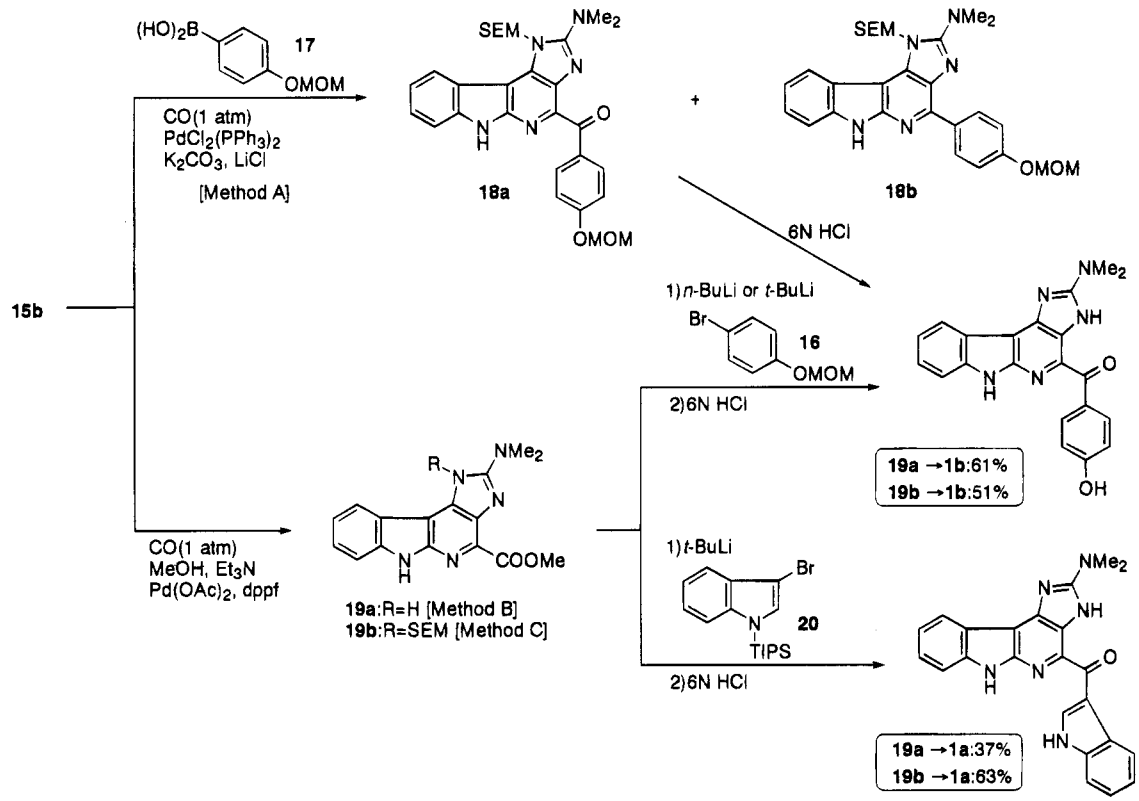
Scheme 2





Scheme 3



previously synthesized grossularine-2 (**1b**) and natural grossularines-1 (**1a**) and -2 (**1b**).

Thus, this new approach based on the thermal electrocyclic reaction of the 2-azahexatriene system provided an effective route to the imidazo[4′,5′:3,4]pyrido[2,3-*b*]-indole ring. In addition, the first total synthesis of grossularine-1 (**1a**) and the improvement of total synthesis of grossularine-2 (**1b**) have been completed. The highest overall yields of **1a** and **1b** from the iodoindole **6** were 28% (**6** → **19b** → **1a**) and 33% (**6** → **19a** → **1b**), respectively.

Experimental Section

General. Most reactions were conducted in flame-dried glassware under an argon atmosphere. All air-sensitive reactions were run under an argon atmosphere, and reagents were added through septa using dried syringes. THF, ether, and anisole were freshly distilled from sodium benzophenone ketyl. DMF was freshly distilled under reduced pressure after drying over CaH_2. NBS was recrystallized from water and was dried in a desiccator under vacuum before use. Silica gel (60–100 mesh, Merck Art 7734) and Sephadex LH-20 (Pharmacia) were used for column chromatography. Melting points are uncorrected. ^1H NMR and ^{13}C NMR were taken with $SiMe_4$ as an internal standard unless otherwise stated. Low and high resolution mass spectra were measured at 70 eV (EI) unless otherwise stated.

5-Bromo-1-methyl-2-(methylthio)imidazole (9a). NBS (3.0 g, 17.2 mmol) was added to a stirred solution of imidazole **8a**[11] (2.0 g, 15.6 mmol) in THF (45 mL) under cooling with ice–water. After being stirred for 3 h at rt, the reaction mixture was diluted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatog-

raphy (silica gel, 50 g) using EtOAc/hexane (2:3) as an eluent to yield the 5-bromoimidazole **9a** (1.9 g, 58%) as an oil: bp 114–115 °C/6 Torr; ^{1}H NMR ($CDCl_3$) δ 2.56 (3H, s), 3.52 (3H, s), 6.97 (1H, s); MS *m/z* 206 (M^+), 208 ($M^+ + 2$). Anal. Calcd for $C_5H_7BrN_2S$: C, 29.00; H, 3.41; N, 13.53. Found: C, 29.05; H, 3.46: N, 13.51.

2-(Dimethylamino)-1-[[2′-(trimethylsilyl)ethoxy]methyl]imidazole (9b). A solution of 2-(dimethylamino)imidazole (**8b**) (500 mg, 4.5 mmol) in DMF (5 mL) was added to a stirred suspension of NaH (60% dispersion, 198 mg, 5.0 mmol) in DMF (10 mL) with ice cooling. After the mixture was stirred for 1 h at rt, a solution of SEM-Cl (784 mg, 4.7 mmol) in DMF (5 mL) was added under cooling with ice–water. The reaction mixture was stirred for 20 h at rt and then poured into ice–water. The mixture was extracted with $CHCl_3$, and the organic layer was washed with water and brine and then dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography (silica gel, 30 g) using EtOAc/hexane (1:4) as an eluent to give the SEM-imidazole **9b** as an oil (902 mg, 83%): bp 112–114 °C/2 Torr; ^{1}H NMR ($CDCl_3$) δ 0.00 (9H, s), 0.91 (2H, t, J = 9 Hz), 2.80 (6H, s), 3.53 (2H, t, J = 9 Hz), 5.08 (2H, s), 6.70 (2H, s); MS *m/z* 241 (M^+). Anal. Calcd for $C_{11}H_{23}N_3OSi$: C, 54.73; H, 9.60; N, 17.41. Found: C, 54.70; H, 9.63; N, 17.45.

1-Methyl-2-(methylthio)-5-(trimethylstannyl)imidazole (10a). A solution of *n*-BuLi (1.61 M in hexane, 2.2 mL, 3.48 mmol) was added dropwise to a stirred solution of 5-bromoimidazole **9a** (500 mg, 2.90 mmol) in dry ether (40 mL) at −78 °C. After the mixture was stirred for 30 min at the same temperature, a solution of Me_3SnCl (693 mg, 3.48 mmol) in ether (10 mL) was added. The mixture was stirred at ambient temperature for 12 h and then diluted with ether. The ether layer was washed with aqueous saturated NH_4Cl solution and brine, dried over Na_2SO_4, and evaporated under vacuum to give the stannylimidazole **10a** as an oil. This material was used in the next reaction without further purification: ^{1}H NMR ($CDCl_3$) δ 0.27 (9H, s), 2.52 (3H, s), 3.55 (3H, s), 6.91 (1H, s).

2-(Dimethylamino)-5-(tributylstannyl)-1-[[2′-(trimethylsilyl)ethoxy]methyl]imidazole (10b). A solution of *t*-BuLi (1.57 M in hexane, 4.0 mL, 6.3 mmol) was added dropwise to a stirred solution of the SEM-imidazole **9b** (500 mg, 2.1 mmol) in dry ether (15 mL) at −78 °C. After the mixture was stirred for 1.5 h at −78 °C, a solution of Bu_3SnCl (2.1 g, 6.5 mmol) in ether (10 mL) was added at the same temperature. The reaction mixture was slowly warmed to rt and stirred overnight. The mixture was diluted with ether, and the ether layer was washed with aqueous saturated NH_4-Cl solution and brine and then dried over Na_2SO_4. After removal of the solvent, the crude stannylimidazole **10b** was used without further purification: ^{1}H NMR ($CDCl_3$) δ 0.00 (9H, s), 0.51–1.98 (29H, m), 2.71 (6H, s), 3.40 (2H, t, J = 8.0 Hz), 5.01 (2H, s), 6.69 (1H, s).

Ethyl 3-[1-Methyl-2-(methylthio)imidazol-5-yl]indole-2-carboxylate (11a). A solution of **10a** (2.9 mmol) in dry DMF (30 mL) was added to a mixture of 3-iodoindole **6**[10] (548 mg, 1.74 mmol) and $Pd(PPh_3)_4$ (99.1 mg, 0.087 mmol) in dry DMF (10 mL) at rt. The reaction mixture was heated at 120 °C for 20 h. After being cooled to ambient temperature, the mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and then concentrated under vacuum. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc/hexane (3:7) as an eluent to give the ester **11a** (612 mg, 96%): mp 157–159 °C (Et_2O–petroleum ether); IR (KBr) 3054, 1706 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.63 (3H, t, J = 8.0 Hz), 2.65 (3H, s), 3.40 (3H, s), 4.27 (2H, q, J = 8.0 Hz), 7.10 (1H, s), 6.73–7.56 (4H, m); MS *m/z* 315 (M^+). Anal. Calcd for $C_{16}H_{17}N_3O_2S$: C, 60.93; H, 5.43; N, 13.32. Found: C, 60.85; H, 5.40; N, 13.41.

Ethyl 3-[2-(Dimethylamino)-1-[[2′-(trimethylsilyl)ethoxy]methyl]imidazol-5-yl]indole-2-carboxylate (11b). A solution of **10b** (2.1 mmol) in DMF (15 mL) was added to a mixture of 3-iodoindole **6**[10] (331 mg, 1.1 mmol) and $Pd(PPh_3)_4$ (60.7 mg, 0.053 mmol) in DMF (5 mL) through a cannula at rt. The reaction mixture was heated at 120 °C for 20 h. After the mixture was cooled to rt, the solvent was removed under vacuum. The residue was dissolved in EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4, and evaporated under vacuum. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc/hexane (3:7) as an eluent to give the ester **11b** (370 mg, 82% based on **6**) [80% based on **6** by using $PdCl_2(PPh_3)_2$ (0.053 mmol) instead of $Pd(PPh_3)_4$]: mp 197–198 °C (AcOEt–hexane); IR (KBr) 3053, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.00 (9H, s), 0.86 (2H, t, J = 8.6 Hz), 1.54 (3H, t, J = 7.2 Hz), 3.23 (6H, s), 3.85 (2H, t, J = 8.6 Hz), 4.57 (2H, t, J = 7.2 Hz), 5.28–5.51 (2H, br s), 7.17 (1H, s), 7.29–7.94 (4H, m); MS *m/z* 428 (M^+). Anal. Calcd for $C_{22}H_{32}N_4O_3Si$: C, 61.65; H, 7.53; N, 13.07. Found: C, 61.71; H, 7.55; N, 13.20.

3-[1-Methyl-2-(methylthio)imidazol-5-yl]indole-2-carboxylic Acid (12a). A mixture of the ester **11a** (180 mg, 0.57 mmol) and aqueous 10% Na_2CO_3 (5 mL) in EtOH (5 mL) was stirred at 70 °C for 3 h. After being cooled to rt, the reaction mixture was diluted with water. The mixture was washed with EtOAc. The aqueous layer was adjusted to pH 5 with AcOH under cooling with ice and then extracted with $CHCl_3$. The $CHCl_3$ layer was washed with brine, dried over Na_2SO_4, and evaporated under vacuum to give the carboxylic acid **12a** as white crystals (133 mg, 81%): mp 179–181 °C ($CHCl_3$); IR (KBr) 3232, 1696 cm^{-1}; ^{1}H NMR ($CDCl_3$–MeOH-d_4) δ 2.71 (3H, s), 3.49 (3H, s), 7.29 (1H, s), 7.01–7.58 (4H, m); MS *m/z* 287 (M^+). Anal. Calcd for $C_{14}H_{13}N_3O_2S$: C, 58.52; H, 4.56; N, 14.62. Found: C, 58.55; H, 4.37; N, 14.65.

3-[2-(Dimethylamino)-1-[[2′-(trimethylsilyl)ethoxy]methyl]imidazol-5-yl]indole-2-carboxylic Acid (12b). A mixture of the ester **11b** (217 mg, 0.51 mmol) and aqueous 10% Na_2CO_3 (15 mL) in EtOH (15 mL) was stirred at 70 °C for 2 h. After being cooled to rt, the mixture was diluted with water. The mixture was washed with EtOAc. The aqueous layer was acidified to pH 5 with AcOH under cooling with ice and extracted with *i*-PrOH/$CHCl_3$ (1:5). The organic layer was washed with brine and then dried over Na_2SO_4, and the solvent was removed under reduced pressure to yield the carboxylic acid **12b** (200 mg, 99%): mp 181–183 °C (MeOH–Et_2O); IR (KBr) 3200, 1650 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ −0.32 (9H, s), 0.46 (2H, t, J = 8.0 Hz), 2.86 (6H, s), 2.95 (2H, t, J = 8.0 Hz), 4.95–5.21 (2H, m), 6.75 (1H, br s), 7.09 (1H, t, J = 7.1, 7.1 Hz), 7.29 (1H, t, J = 7.1, 7.1 Hz), 7.42 (1H, d, J = 7.1 Hz), 7.48 (1H, d, J = 7.1 Hz), 12.01 (1H, br s), 13.02 (1H, br s); MS *m/z* 400 (M^+). Anal. Calcd for $C_{20}H_{28}N_4O_3Si$: C, 59.97; H, 7.05; N, 13.99. Found: C, 56.00; H, 6.99; N, 14.11.

2-Isocyanato-3-[1-methyl-2-(methylthio)imidazol-5-yl]indole (13a). A mixture of the carboxylic acid **12a** (126 mg, 0.44 mmol), DPPA (0.284 mL, 1.32 mmol), and Et_3N (0.182 mL, 1.34 mmol) in dry benzene (10 mL) was stirred at 60 °C for 30 min. After being cooled to ambient temperature, the mixture was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc/hexane (3:7) as an eluent to give the isocyanate **13a** (100 mg, 80%): IR (KBr) 3120, 2139 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.67 (3H, s), 3.35 (3H, s), 7.15 (1H, s), 7.08–7.60 (4H, m); MS *m/z* 284 (M^+); HRMS calcd for $C_{14}H_{12}N_4OS$ 284.0723, found 284.0728.

3-[2-(Dimethylamino)-1-[[2′-(trimethylsilyl)ethoxy]methyl]imidazol-5-yl]-2-isocyanatoindole (13b). A mixture of the carboxylic acid **12b** (110 mg, 0.27 mmol), DPPA (0.176 mL, 0.82 mmol), and Et_3N (0.114 mL, 0.82 mmol) in dry benzene (10 mL) was stirred at 60 °C for 30 min. After being cooled to rt, the mixture was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc/hexane (3:7) as an eluent to yield the isocyanate **13b** as a solid (95 mg, 87%): IR (KBr) 3051, 2139 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ −0.30 (9H, s), 0.58 (2H, t, J = 9.0 Hz), 3.33 (6H, s), 3.62 (2H, t, J = 9.0 Hz), 5.06 (2H, br s), 6.83 (1H, s), 7.35–7.62 (4H, m), 9.47 (1H, br s); MS *m/z* 397 (M^+); HRMS calcd for $C_{20}H_{27}N_5O_2Si$ 379.1918, found 379.1930.

2-Hydroxy-12-methyl-11-(methylthio)-9*H*-imidazo[4′,5′:3,4]pyrido[2,3-*b*]indole (14a). A solution of the isocyanate **13a** (60 mg, 0.21 mmol) in *o*-dichlorobenzene (5 mL) was heated at 180 °C for 5 min. After the solution was cooled to rt, the resulting precipitates were filtered off, washed with Et_2O, and dried *in vacuo* to give the analytical pure α-carboline

14a (43 mg, 72%): mp 337–338 °C; IR (KBr) 3112 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.68 (3H, s), 4.17 (3H, s), 7.13 (1H, t, J = 7.1, 7.1 Hz), 7.18 (1H, t, J = 7.1, 7.1 Hz), 7.49 (1H, d, J = 7.1 Hz), 8.03 (1H, d, J = 7.1 Hz); MS m/z 284 (M^+). Anal. Calcd for $C_{14}H_{12}N_4OS$: C, 59.14; H, 4.25; N, 19.70. Found: 59.21; H, 4.35; N, 19.85.

11-(Dimethylamino)-2-hydroxy-12-[[2′-(trimethylsilyl)-ethoxy]methyl]-9*H*-imidazo[4′,5′:3,4]pyrido[2,3-*b*]indole (14b). A solution of the isocyanate **13b** (189 mg, 0.48 mmol) in *o*-dichlorobenzene (20 mL) was heated at 170 °C for 5 min. After being cooled to rt, the mixture was concentrated under reduced pressure. The residue was crystallized from EtOAc to yield the α-carboline **14b** (167 mg, 88%): mp 241–243 °C (EtOAc); IR (KBr) 3100, 1680 cm^{-1}; ^1H NMR (pyridine-d_5, 400 MHz, 80 °C) δ 0.09 (9H, s), 1.09 (2H, t, J = 8 Hz), 3.04 (6H, s), 3.85 (2H, t, J = 8 Hz), 5.88 (2H, s), 7.38 (1H, dt, J = 7.0, 7.0, 2.0 Hz), 7.41 (1H, dt, J = 7.0, 7.0, 2.0 Hz), 7.62 (1H, dd, J = 7.0, 2.0 Hz), 8.42 (1H, dd, J = 7.0, 2.0 Hz), 12.30 (1H, br s); MS m/z 397 (M^+). Anal. Calcd for $C_{20}H_{27}N_5O_2Si$: C, 60.42; H, 6.85; N, 17.62. Found: C, 60.33; H, 6.97; N, 17.54.

11-(Dimethylamino)-2-[(methanesulfonyl)oxy]-12-[[2′-(trimethylsilyl)ethoxy]methyl]-9*H*-imidazo[4′,5′:3,4]pyrido[2,3-*b*]indole (15a). To a solution of **14b** (30 mg, 0.075 mmol) and pyridine (0.018 mL, 0.22 mmol) in dry CH_2Cl_2 (5 mL) was added methanesulfonyl chloride (10.4 mg, 0.091 mmol) at 0 °C. After being stirred at rt overnight, the reaction mixture was diluted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and then concentrated under vacuum. The residue was purified by column chromatography (silica gel, 10 g) with EtOAc/hexane (5:95) as an eluent to yield the mesylate **15a** (35 mg, 98%): mp 197–198 °C ($CHCl_3$–hexane); IR (KBr) 3213, 1402, 1193 cm^{-1}; ^1H NMR ($CHCl_3$, 500 MHz) δ −0.07 (9H, s), 0.91 (2H, t, J = 8 Hz), 3.04 (6H, s), 3.65 (2H, t, J = 8.0 Hz), 3.80 (3H, s), 5.72 (2H, s), 7.24 (1H, dt, J = 8.0, 8.0, 1.0 Hz), 7.44 (1H, dt, J = 8.0, 8.0, 1.0 Hz), 7.54 (1H, br d, J = 8.0 Hz), 8.16 (1H, br d, J = 8.0 Hz); MS m/z 475 (M^+). Anal. Calcd for $C_{21}H_{29}N_5O_4SSi$: C, 53.03; H, 6.15; N, 14.72. Found: C, 53.11; H, 6.30; N, 14.65.

11-(Dimethylamino)-2-[(trifluoromethanesulfonyl)oxy]-12-[[2′-(trimethylsilyl)ethoxy]methyl]-9*H*-imidazo[4′,5′:3,4]pyrido[2,3-*b*]indole (15b). To a solution of **14b** (80 mg, 0.20 mmol) and pyridine (0.05 mL, 0.60 mmol) in dry CH_2Cl_2 (10 mL) was added trifluoromethanesulfonic anhydride (0.04 mL, 0.24 mmol) at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was poured into ice–water, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under vacuum. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc/hexane (1:4) as eluent to yield the triflate **15b** (100 mg, 94%): mp 87–88 °C (EtOAc–hexane); IR (KBr) 3200, 1419, 1197 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.02 (9H, s), 1.06 (2H, t, J = 8.4 Hz), 3.14 (6H, s), 3.72 (2H, t, J = 8.4 Hz), 5.65 (2H, s), 7.30 (1H, t, J = 7.4, 7.4 Hz), 7.49 (1H, t, J = 7.4, 7.4 Hz), 7.53 (1H, d, J = 7.4 Hz), 8.20 (1H, d, J = 7.4 Hz), 8.77 (1H, br s); MS (CI) m/z 530 (M^+ + 1). Anal. Calcd for $C_{21}H_{26}F_3N_5O_4SSi$: C, 47.63; H, 4.95; N, 13.22. Found: C, 47.59; H, 5.06; N, 13.08.

***p*-[(Methoxymethyl)oxy]phenylboronic Acid (17).** A solution of *n*-BuLi (1.63 M in hexane, 7.4 mL, 12.0 mmol) was added dropwise to a stirred solution of *p*-(OMOM)phenyl bromide (2.0 g, 9.2 mmol) in dry THF (25 mL) at −78 °C. After the mixture was stirred for 30 min at the same temperature, a solution of triisopropyl borate (2.3 g, 12.0 mmol) in THF (5 mL) was added rapidly. The mixture was stirred for 30 min at the same temperature and then stirred for a further 1 h at rt. The reaction mixture was partitioned between EtOAc (100 mL) and 10% aqueous HCl (50 mL). The organic layer was washed with brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure followed by crystallization from Et_2O afforded the boronic acid **17** (743 mg, 45%): mp 134–135 °C; ^1H NMR ($CDCl_3$) δ 3.50 (3H, s), 5.17 (2H, s), 7.03 (2H, d, J = 8.0 Hz), 8.03 (2H, d, J = 8.0 Hz). Anal. Calcd for $C_8H_{11}BO_4$: C, 52.80; H, 6.09. Found: C, 52.65; H, 6.21.

11-(Dimethylamino)-2-[4′-[(methoxymethyl)oxy]benzoyl]-12-[[2″-(trimethylsilyl)ethoxy]methyl]-9*H*-imidazo[4′,5′:3,4]pyrido[2,3-*b*]indole (18a) and 11-(Dimethylamino)-2-[4′-[(methoxymethyl)oxy]phenyl]-12-[[2″-(trimethylsilyl)ethoxy]methyl]-9*H*-imidazo[4′,5′:3,4]pyrido[2,3-*b*]indole (18b) (Method A). Into a mixture of phenylboronic acid **17** (73 mg, 0.40 mmol), triflate **15b** (97 mg, 0.18 mmol), $PdCl_2(PPh_3)_2$ (3.8 mg, 0.0054 mmol), K_2CO_3 (152 mg, 1.1 mmol), and LiCl (23 mg, 0.54 mmol) in dry anisole (3 mL) was bubbled carbon monoxide for 5 min, and the mixture was heated at 80 °C for 3 h under a CO atmosphere. After being cooled to rt, the mixture was dissolved in $CHCl_3$. The $CHCl_3$ layer was washed with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 10 g) using MeOH/$CHCl_3$ (1:99) as an eluent to yield **18a** as a yellow solid (19 mg, 19%) and **18b** (54 mg, 58%). **18a**: mp 232–234 °C ($CHCl_3$–hexane); IR (KBr) 1596 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.04 (9H, s), 1.10 (2H, t, J = 8.4 Hz), 3.13 (6H, 2), 3.48 (3H, s), 3.75 (2H, t, J = 8.4 Hz), 5.24 (2H, s), 5.66 (2H, s), 7.05 (2H, d, J = 8.8 Hz), 7.29 (1H, t, J = 7.9, 7.9 Hz), 7.49 (1H, t, J = 7.9, 7.9 Hz), 7.52 (1H, d, J = 7.9 Hz), 8.07 (2H, d, J = 8.8 Hz), 8.29 (1H, d, J = 7.9 Hz), 9.32 (1H, br s); MS m/z 545 (M^+). Anal. Calcd for $C_{29}H_{35}N_5O_4Si$: C, 63.83; H, 6.46; N, 12.83. Found: C, 63.94; H, 6.33; N, 12.82. **18b**: mp 193–195 °C ($CHCl_3$–hexane); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.02 (9H, s), 1.09 (2H, t, J = 8.4 Hz), 3.15 (6H, s), 3.53 (3H, s), 3.73 (2H, t, J = 8.4 Hz), 5.28 (2H, s), 5.70 (2H, s), 7.07 (1H, d, J = 8.0 Hz), 7.21 (1H, t, J = 8.0, 8.0 Hz), 7.22 (2H, d, J = 8.7 Hz), 7.32 (1H, t, J = 8.0, 8.0 Hz), 8.20 (1H, d, J = 8.0 Hz), 8.72 (2H, d, J = 8.7 Hz), 10.23 (1H, br s); MS m/z 517 (M^+). Anal. Calcd for $C_{28}H_{35}N_5O_3Si$: C, 64.96; H, 6.81; N, 13.53. Found: C, 64.62; H, 6.92; N, 13.67.

Grossularine-2 (1b) (Method A). A mixture of **18a** (20 mg, 0.037 mmol) and 6 N HCl (1 mL) in MeOH (3 mL) was heated at 60 °C for 30 min. After being cooled to rt, the reaction mixture was adjusted to pH 8–9 with 28% NH_4OH. The resulting precipitates were filtered off and dried *in vacuo* to give grossularine-2 (**1b**) (11 mg, 81%): mp 197 °C (the crystals became black at 169 °C and decomposed at 197 °C) ($CHCl_3$–hexane); IR (KBr) 3432 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 3.28 (6H, s), 6.89 (2H, d, J = 8.5 Hz), 7.20 (1H, dt, J = 6.9, 6.9, 1.2 Hz), 7.39 (1H, dt, J = 6.9, 6.9, 1.2 Hz), 7.44 (1H, d, J = 6.9 Hz), 8.22 (1H, d, J = 6.9 Hz), 8.24 (2H, d, J = 8.5 Hz), 10.98 (1H, s), 11.52 (1H, s); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 191.0, 161.5, 159.9, 146.7, 146.4, 139.5, 133.5 (2C), 132.1, 128.6, 127.9, 125.7, 122.4, 119.6, 118.8, 114.7 (2C), 110.5, 104.9, 39.1 (2C); MS m/z 371 (M^+, 100), 356 (5), 343 (15), 342 (17), 328 (10), 314 (7), 262 (6), 248 (12), 234 (16). Anal. Calcd for $C_{21}H_{17}N_5O_2$: C, 67.91; H, 4.61; N, 18.86. Found: C, 68.03; H, 4.61; N, 18.96.

11-(Dimethylamino)-2-(methoxycarbonyl)-9*H*-imidazo-[4′,5′:3,4]pyrido[2,3-*b*]indole (19a). Into a mixture of triflate **15b** (145 mg, 0.27 mmol), $Pd(OAc)_2$ (1.8 mg, 0.0081 mmol), 1,1′-bis(diphenylphosphino)ferrocene (dppf) (9.0 mg, 0.016 mmol), MeOH (0.221 mL, 5.48 mmol), and Et_3N (0.077 mL, 0.55 mmol) in DMF (1 mL) was bubbled carbon monoxide for 5 min and the resulting mixture stirred at 80 °C for 2 h under a CO atmosphere. After being cooled to rt, the mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 10 g) using MeOH/$CHCl_3$ (1:99) to yield the *N*-deprotected methyl ester **19a** as a yellow solid (79 mg, 93%): mp 279–280 °C dec ($CHCl_3$–hexane); IR (KBr) 3282, 1733 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 3.29 (6H, s), 3.97 (3H, s), 7.22 (1H, dt, J = 7.8, 7.8, 1.0 Hz), 7.42 (1H, dt, J = 7.8, 7.8, 1.0 Hz), 7.46 (1H, d, J = 7.8 Hz), 8.22 (1H, d, J = 7.8 Hz), 10.66 (1H, br s), 10.73 (1H, br s); MS m/z 309 (M^+). Anal. Calcd for $C_{16}H_{15}N_5O_2$: C, 62.13; H, 4.89; N, 22.64. Found: C, 62.22; H, 5.00; N, 22.49.

11-(Dimethylamino)-2-(methoxycarbonyl)-12-[[2′-(trimethylsilyl)ethoxy]methyl]-9*H*-imidazo[4′,5′:3,4]pyrido-[2,3-*b*]indole (19b). A solution of triflate **15b** (145 mg, 0.27 mmol), $Pd(OAc)_2$ (1.8 mg, 0.0081 mmol), dppf (9.0 mg, 0.016 mmol), MeOH (0.22 mL, 5.5 mmol), and Et_3N (0.2 mL, 1.4 mmol) in DMF (1 mL) was bubbled with CO for 5 min and stirred at 80 °C for 4 h under a CO atmosphere. After being

cooled to rt, the mixture was dissolved in $CHCl_3$. The $CHCl_3$ layer was washed with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 10 g) using MeOH/$CHCl_3$ (1:99) as an eluent to yield the methyl ester **19b** as a yellow solid (76 mg, 77%): mp 268–269 °C (MeOH); IR (KBr) 3292, 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.02 (9H, s), 1.08 (2H, t, J = 8.4 Hz), 3.24 (6H, s), 3.72 (2H, t, J = 8.4 Hz), 4.10 (3H, s), 7.27 (1H, t, J = 7.8, 7.8 Hz), 7.51 (1H, t, J = 7.8, 7.8 Hz), 7.55 (1H, d, J = 7.8 Hz), 8.30 (1H, d, J = 7.8 Hz), 10.29 (1H, br s); MS m/z 439 (M^+). Anal. Calcd for $C_{22}H_{29}N_5O_3Si$: C, 60.11; H, 6.65; N, 15.93. Found: C, 60.03; H, 6.71; N, 16.11.

***p*-[(Methoxymethyl)oxy]phenyl Bromide (16).**[18] A solution of *p*-bromophenol (10 g, 57.8 mmol) in DMF (10 mL) was added to a stirred suspension of NaH (60% oil dispersion, 2.8 g, 6.94 mmol) in DMF (40 mL) with ice cooling. After the mixture was stirred at rt for 30 min, a solution of chloromethyl methyl ether (5.2 mL, 79.4 mmol) in DMF (10 mL) was added under cooling with ice–water, and the mixture was stirred at rt for 2 h. After being poured into ice–water, the mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and evaporated under vacuum to give the OMOM ether **16** (11.7 g, 93%): bp 82–84 °C/1.5 Torr; ^1H NMR ($CDCl_3$) δ 3.42 (3H, s), 5.08 (2H, s), 6.85 (2H, d, J = 8.0 Hz), 7.30 (2H, d, J = 8.0 Hz); MS m/z 217 (M^+). Anal. Calcd for $C_8H_9BrO_2$: C, 44.27; H, 4.18. Found: C, 44.31; H, 4.12.

3-Bromo-1-(triisopropylsilyl)indole (20). A solution of NBS (325 mg, 1.83 mmol) in THF (5 mL) was added to a stirred solution of the triisopropylindole[19] (500 mg, 1.83 mmol) in THF (3 mL) at −78 °C. After the mixture was stirred at the same temperature for 1 h, water was added and the mixture was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 20 g) using hexane as an eluent to yield the 3-bromoindole **20** (569 mg, 89%): mp 56–58 °C (pentane) (lit.[19] mp 62–64 °C); ^1H NMR ($CDCl_3$) δ 1.12 (18H, d, J = 6.0 Hz), 1.53 (3H, sep, J = 6.0 Hz), 6.85–7.62 (4H, m), 7.16 (1H, s); MS m/z 352 (M^+), 354 (M^+ + 2). Anal. Calcd for $C_{17}H_{26}BrNSi$: C, 57.94; H, 7.44; N, 3.97. Found: C, 57.78; H, 7.42; N, 4.05.

Grossularine-1 (1a) (Method B). A solution of *t*-BuLi (1.62 M in pentane, 0.96 mL, 1.56 mmol) was added dropwise to a stirred solution of the 3-bromoindole **20** (273 mg, 0.78 mmol) in dry THF (7 mL) at −78 °C. After being stirred at −78 °C for 30 min, a solution of **19a** (30 mg, 0.097 mmol) in dry THF (7 mL) was added and the mixture was stirred for 2 h at the same temperature. The reaction was quenched with water (3 mL) and 6 N HCl (3 mL), and then the mixture was heated at 60 °C for 30 min. The mixture was worked up with water and extracted with MeOH/$CHCl_3$ (1:9). The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under vacuum. The residue was purified by column chromatography (Sephadex LH-20) using MeOH as an eluent to yield grossularine-1 (**1a**) (14 mg, 37%): mp 339–341 °C ($CHCl_3$) (lit.[1] mp 350 °C); IR (KBr) 3432, 3282 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 3.32 (6H, s), 7.23 (1H, t, J = 7.2, 7.2 Hz), 7.25–7.29 (2H, M), 7.42 (1H, t, J = 7.2, 7.2 Hz), 7.50 (1H, d, J = 7.2 Hz), 7.55 (1H, m), 8.24 (1H, d, J = 7.2 Hz), 8.54–8.57 (1H, m), 8.65 (1H, br s), 9.20 (1H, br s), 9.44 (1H, d), 9.85 (1H, br s); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 187.0, 159.9, 147.0, 146.5, 139.5, 137.4, 135.8, 133.0, 127.5, 127.3, 125.7, 122.8, 122.6, 121.9, 121.8, 119.9, 119.0, 114.6, 112.2, 110.6, 104.9, 39.2 (2C); MS m/z 394 (M^+, 100), 365 (5), 350 (5), 277 (59), 249 (43), 234 (16), 197 (23), 144 (12). Anal. Calcd for $C_{23}H_{18}N_6O$: C, 70.04; H, 4.60; N, 21.31. Found: C, 69.94; H, 4.77; N, 21.35.

Grossularine-1 (1a) (Method C). A solution of *t*-BuLi (1.62 M in pentane, 0.68 mL, 1.10 mmol) was added to a solution of 3-bromoindole (194 mg, 0.55 mmol) in dry THF (5 mL) at −78 °C under argon. After being stirred for 30 min, a solution of **19b** (30 mg, 0.068 mmol) in THF (7 mL) was added. The mixture was stirred for 10 min at −78 °C and then stirred at −30 °C for 1.5 h. The reaction was quenched with water (3 mL) and 6 N HCl (3 mL). The mixture was heated at 60 °C for 30 min and basified to pH 8 with 28% NH_4OH. The mixture was extracted with MeOH–$CHCl_3$ (1:9). The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (Sephadex LH-20) using MeOH as an eluent to yield grossularine-1 (**1a**) (17 mg, 63%).

Grossularine-2 (1b) (Method B). A solution of *n*-BuLi (1.63 M in hexane, 0.43 mL, 0.70 mmol) was added dropwise to a stirred solution of *p*-(OMOM)phenyl bromide (**16**) (151 mg, 0.70 mmol) in dry THF (3 mL) at −78 °C. After being stirred at −78 °C for 30 min, the solution of **19a** (27 mg, 0.087 mmol) in dry THF (7 mL) was added. The reaction mixture was stirred for 15 min at the same temperature and then stirred for a further 2 h under cooling with ice–water. After being quenched with water (3 mL) and 6 N HCl (3 mL), the mixture was stirred at 60 °C for 30 min. At ambient temperature, the solution was adjusted to pH 8–9 with 28% NH_4OH, and the mixture was extracted with MeOH/$CHCl_3$ (1:9). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography (silica gel, 10 g) with MeOH/$CHCl_3$ (1:98) as an eluent and column chromatography (Sephadex LH-20) using MeOH as an eluent to give the grossularine-2 (**1b**) (20 mg, 61%).

Grossularine-2 (1b) (Method C). A solution of *t*-BuLi (1.62 M in pentane, 0.34 mL, 0.55 mmol) was added to a stirred solution of *p*-(OMOM)phenyl bromide (**16**) (119 mg, 0.55 mmol) in dry THF (5 mL) at −78 °C. After being stirred for 30 min, the solution of **19b** (30 mg, 0.068 mmol) in THF (7 mL) was added to the reaction mixture at the same temperature. The reaction mixture was stirred at −78 °C for 30 min and at −30 °C for further 1.5 h. After being quenched with water (3 mL) and 6 N HCl (3 mL), the mixture was heated at 60 °C for 30 min. The mixture was basified to pH 8 with 28% NH_4OH, and the mixture was extracted with MeOH/$CHCl_3$ (1:9). The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 10 g) with MeOH/$CHCl_3$ (1:98) as an eluent and subsequent column chromatography (Sephadex LH-20) using MeOH as an eluent to give grossularine-2 (**1b**) (13 mg, 51%).

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Supporting Information Available: Copies of ^1H NMR spectra of **14**, **15a**, **1a**, and **1b**, ^{13}C NMR spectra of **1a** and **1b**, the 2D-NOESY spectrum of **15a**, and the HMQC spectrum of **1a** (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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