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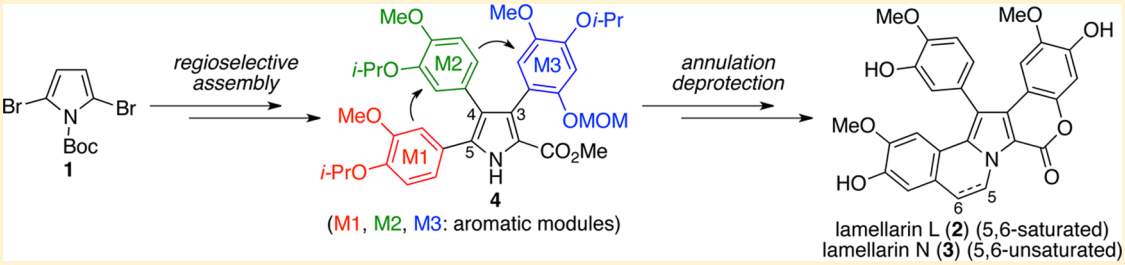
Modular Synthesis of Lamellarins via Regioselective Assembly of 3,4,5-Differentially Arylated Pyrrole-2-carboxylates

Masashi Komatsubara, Teppei Umeki, Tsutomu Fukuda, and Masatomo Iwao*

Division of Chemistry and Materials Science, Graduate School of Engineering, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan

Supporting Information



ABSTRACT: A modular synthesis of lamellarins via 3,4,5-differentially arylated pyrrole-2-carboxylate intermediates has been developed. The key reactions employed are Br−Li exchange−methoxycarbonylation of 2,5-dibromo-1-(*tert*-butoxycarbonyl)-1*H*-pyrrole (**1**) followed by palladium-catalyzed iterative Suzuki−Miyaura coupling of the pyrrole core. The 3,4,5-triarylpyrrole **4** thus synthesized was readily converted to 5,6-saturated lamellarin L (**2**) and 5,6-unsaturated lamellarin N (**3**) via lactonization followed by annulation of the pyrrole nitrogen and lateral aromatic ring at C5 using 2-bromoethyl phenyl sulfide or bromoacetaldehyde dimethyl acetal as two-carbon homologation agents. In principle, this strategy allows the production of diverse lamellarins in short steps with high yields using readily accessible arylboronic acids as aromatic modules.

INTRODUCTION

Lamellarins are polycyclic marine alkaloids that share a common 14-phenyl-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one ring system.[1] In rare cases, however, lamellarins possess a simple and nonfused 3,4-diarylpyrrole-2-carboxylate structure.[2d,e] Since the first discovery of lamellarins A−D from *Lamellaria* sp. by Faulkner and co-workers in 1985,[2a] approximately 50 lamellarins (A−Z, α−χ, and A1−A6, including their acetate and sulfate derivatives) have been isolated from various marine organisms such as tunicates and sponges.[2] These compounds differ in the number and position of the OH and OMe groups on the common scaffold and the degree of unsaturation of the C5−C6 bond. Lamellarins are of interest because they exhibit a wide range of useful biological activities. For example, the triacetates of lamellarins D, K, and N (Figure 1) display potent cytotoxicity against multi-drug-resistant (MDR) cancer cell lines at low nanomolar concentrations, while lamellarin I effectively increases the cytotoxicity of approved anticancer agents on MDR cancer cell lines via inhibition of P-glycoprotein-mediated drug efflux at nontoxic doses.[3] A major molecular target of the anticancer agent lamellarin D has been identified as topoisomerase I.[4] Lamellarin D also induces apoptosis of cancer cell lines by direct inhibition of the mitochondrial function.[5] In contrast, lamellarin N is a potent inhibitor of disease-relevant protein kinases, such as CDK1, CDK5, GSK-3, PIM1, and DYRK1A,[6] while lamellarin α 20-sulfate and related lamellarin sulfates

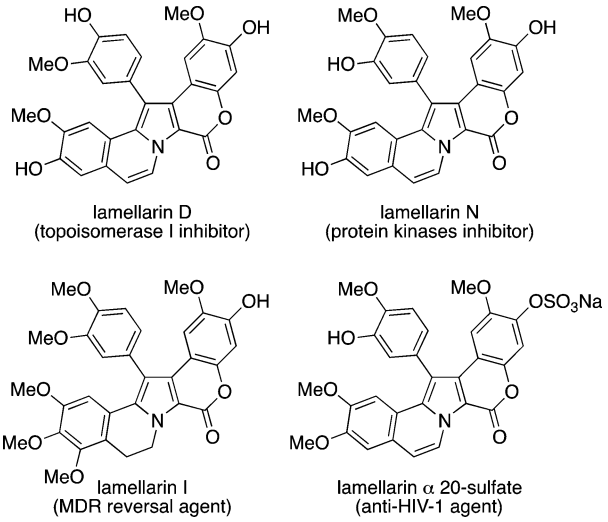


Figure 1. Biologically active lamellarins.

exhibit anti-HIV-1 activity at noncytotoxic concentrations by inhibiting virus entry[7] or the integration step.[2j,8]

Because of these significant biological activities, various synthetic methods for the preparation of lamellarins have been developed.[1h,9,10] These syntheses can be classified into two

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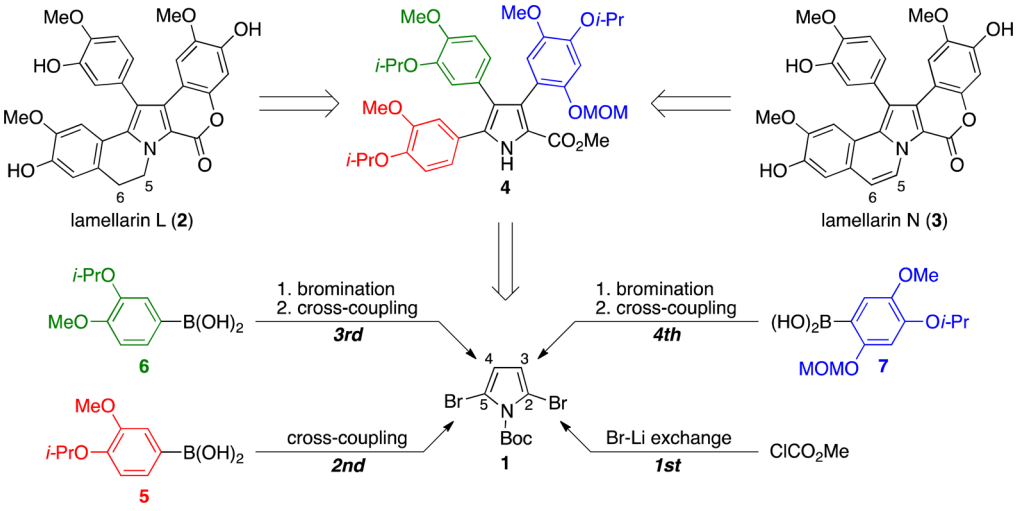
Scheme 1. Synthetic Plan for Lamellarins L and N



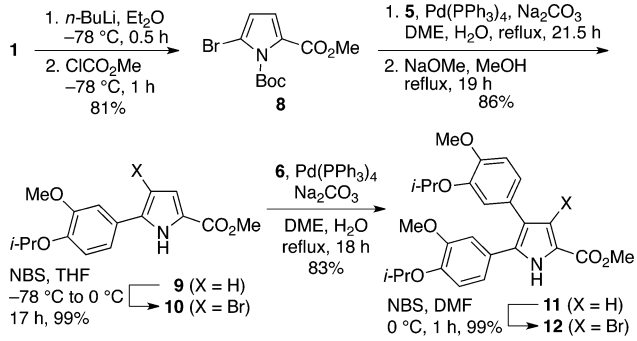
major categories depending on the method used to produce the central pyrrole core. One utilizes ring-formation reactions using appropriately substituted acyclic precursors, while the other employs the functionalization of preexisting pyrroles. The latter class of syntheses are particularly attractive because a wide range of lamellarin analogues can be produced easily via simple modification of the aromatic building blocks decorating the pyrrole ring. In fact, such modular approaches starting from simple pyrrole derivatives have been developed by Handy,[9h] Álvarez,[9i,j] Bach,[11] and Banwell.[9q] Herein we describe a new modular synthesis of lamellarins starting from readily available 2,5-dibromo-1-(*tert*-butoxycarbonyl)-1*H*-pyrrole (**1**). Our synthesis is distinct from the previous approaches in the arylation sequence of the pyrrole core and the final pentacyclic ring construction method.

RESULTS AND DISCUSSION

Lamellarins L (**2**) and N (**3**) were selected as the synthetic targets because these lamellarins possess the same aromatic moiety but differ in the degree of unsaturation of the C5−C6 bond. The synthetic plan to obtain them from **1** is shown retrosynthetically in Scheme 1. We attempted to synthesize the pentacyclic framework from the 3,4,5-triarylpyrrole-2-carboxylate **4** via lactonization followed by annulation of the pyrrole nitrogen and lateral aromatic ring at C5. Hence, the key triarylpyrrole **4** was assembled from **1** as follows: (1) methoxycarbonylation of **1** at C2 via restricted Br−Li exchange; (2) palladium-catalyzed Suzuki−Miyaura cross-coupling at C5 with boronic acid **5**; (3) regioselective bromination at C4 followed by cross-coupling with **6**; and (4) final bromination at C3 followed by cross-coupling with **7**.

Our initial study was focused on the regioselective synthesis of 3,4,5-differentially arylated pyrrole-2-carboxylates based on the concept described above. The synthesis of the intermediate 4,5-diaryl-3-bromopyrrole-2-carboxylate **12** is shown in Scheme 2. The starting 2,5-dibromopyrrole **1** was readily prepared from commercially available pyrrole in two steps by a known procedure.[10j,12] Br−Li exchange of **1** with 1.0 equiv of *n*-BuLi in Et_2O at −78 °C for 0.5 h followed by reaction with methyl chloroformate afforded the monomethoxycarbonylated compound **8** in 81% yield. Palladium-catalyzed Suzuki−Miyaura coupling[13] of **8** with the known arylboronic acid **5**[9k] under standard conditions [$Pd(PPh_3)_4$ (10 mol %), Na_2CO_3, H_2O, DME, reflux, 19 h] afforded a mixture of *N*-deprotected **9** and its *N*-Boc precursor. Thus, the crude cross-coupling product was treated with sodium methoxide to afford **9** in 86% yield as the only product. Subsequent reaction of **9** with NBS in THF yielded 4-bromo-substituted compound **10** selectively in excellent yield. The regioselectivity was controlled by the *meta*-directing methoxycarbonyl group at C2. Similar regioselectivity has been established for electrophilic substitutions of pyrroles bearing an electron-withdrawing group at C2.[14] Cross-coupling of **10** with boronic acid **6**[9k] was successfully performed under conditions similar to those described above to afford 4,5-diarylpyrrole **11**. Reaction of this compound with NBS in THF yielded a mixture of products in which the electron-rich aromatic rings at C4 and C5 were preferentially brominated. In contrast, when DMF was used as the solvent instead of THF, the desired C3-brominated pyrrole **12** was obtained selectively in excellent yield. The nucleophilicity of the pyrrole ring may be enhanced by coordination of DMF to the acidic pyrrole N−H.

Scheme 2. Synthesis of 4,5-Diaryl-3-bromopyrrole-2-carboxylate 12



Next, the cross-coupling of **12** with a range of arylboronic acids **13a−e** and **7**[9k] was explored under two different sets of conditions as follows: conditions A: $Pd(PPh_3)_4$ (10 mol %), $Ar-B(OH)_2$ (1.5 equiv), Na_2CO_3 (6.6 equiv), DME, H_2O, reflux, 18 h; conditions B: $Pd(dba)_2$ (10 mol %), dppf (10 mol %), $Ar-B(OH)_2$ (1.5 equiv), Na_2CO_3 (6.6 equiv), DME, H_2O, reflux, 18 h. The results are summarized in Table 1. Generally, when $Pd(PPh_3)_4$ was used as the catalyst (conditions A), the yields of the cross-coupling products were modest. In

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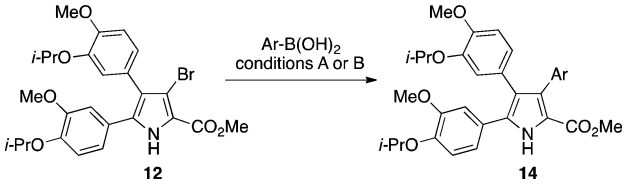
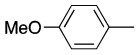
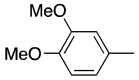
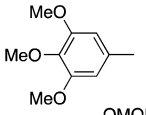
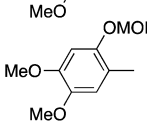
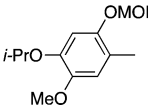
Table 1. Palladium-Catalyzed Cross-Coupling of 12 with Arylboronic Acids



entry	Ar-B(OH)$_2$	Ar	14	yield (%)[a] conditions A[b]	yield (%)[a] conditions B[c]
1	**13a**		**14a**	67	87
2	**13b**		**14b**	64	81
3	**13c**		**14c**	60	84
4	**13d**		**14d**	62	85
5	**13e**		**14e**	37	84
6	**7**		**4**	42	92

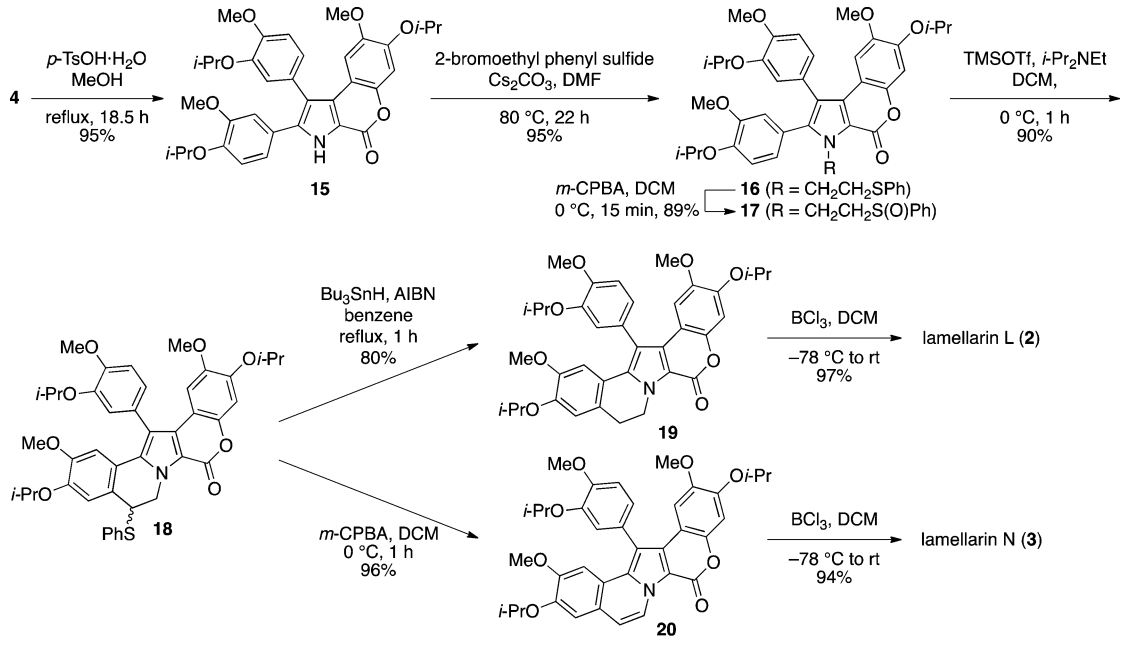
[a]Isolated yields. [b]$Pd(PPh_3)_4$ (10 mol %), Ar−$B(OH)_2$ (1.5 equiv), Na_2CO_3 (6.6 equiv), DME, H_2O, reflux, 18 h. [c]$Pd(dba)_2$ (10 mol %), dppf (10 mol %), Ar−$B(OH)_2$ (1.5 equiv), Na_2CO_3 (6.6 equiv), DME, H_2O, reflux, 18 h.

particular, when sterically congested *o*-(methoxymethoxy)-arylboronic acids **13e** and **7** were employed, the yields of the cross-coupling products decreased considerably. In these reactions, unreacted bromide **12** and debrominated **11** were recovered as an inseparable mixture. In contrast, the cross-coupling reactions under conditions B using $Pd(dba)_2$ as the palladium source and dppf as the ligand gave the desired products consistently in good yields (>80%).

With a regioselective route to 3,4,5-differentially arylated pyrrole-2-carboxylates established, we focused on their conversion to the lamellarins. Initially, we investigated the annulation between the pyrrole nitrogen and the lateral aromatic ring using an alkylation−Pummerer cyclization sequence (Scheme 3).[15,16] Thus, compound **4** was treated with *p*-TsOH in aqueous methanol to give lactone **15**, which was alkylated with commercially available 2-bromoethyl phenyl sulfide in the presence of Cs_2CO_3 to afford sulfide **16**. Oxidation of **16** with 1.0 equiv of *m*-CPBA afforded sulfoxide **17** in good yield, accompanied by a small amount of the starting sulfide. Pummerer reaction of **17** upon treatment with TFAA (10 equiv) in DCM at room temperature for 2 h gave uncyclized sulfide **16** in 42% yield. This unusual deoxygenation reaction via a sulfuran intermediate has been previously reported.[17] The desired Pummerer cyclization, however, proceeded under Craig's conditions (TMSOTf/Hünig's base)[18] to afford **18** in excellent yield (90%). Notably, the ^1H and ^{13}C NMR spectra of **18** at room temperature were quite complex. However, when both spectra were recorded in toluene-d_8 at higher temperature around 90 °C, peak coalescence occurred, and much simpler spectra were obtained. These results suggested that **18** existed as a diastereomeric mixture at room temperature as a result of slow rotation of the aromatic ring at C1. The activation energy for the rotation was estimated to be 74−75 kJ/mol by variable-temperature ^1H NMR spectroscopy (see the Supporting Information). This value is in good agreement with those obtained from our previous studies.

Desulfurization of **18** with Raney Ni in ethanol with reflux for 11 h yielded an inseparable mixture of 5,6-saturated **19** and 5,6-unsaturated **20** (1:5 from ^1H NMR analysis). In contrast, radical desulfurization using Bu_3SnH/AIBN[17b] in refluxing

Scheme 3. Total Synthesis of Lamellarins L and N



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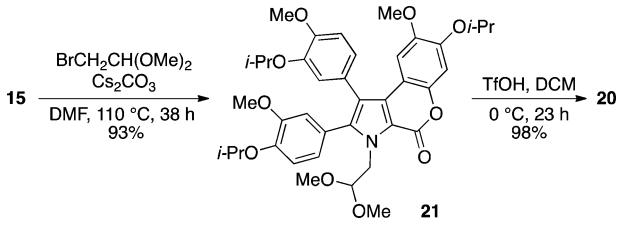
benzene provided **19** selectively in 80% yield, while treatment of **18** with 1.0 equiv of *m*-CPBA in DCM at 0 °C for 1 h afforded **20** in excellent yield. The intermediate sulfoxide was not isolated under these reaction conditions because of easy elimination of the phenylsulfinyl group. Deprotection of the isopropyl groups of **19** and **20** using excess BCl_3 produced lamellarin L (**2**) and lamellarin N (**3**), respectively.[9k]

An alternative annulation using bromoacetaldehyde dimethyl acetal was also investigated. This type of reagent has been employed frequently in the synthesis of isoquinoline alkaloids.[19] Thus, lactone **15** was alkylated with bromoacetaldehyde dimethyl acetal using Cs_2CO_3 as the base to afford **21** in 93% yield (Scheme 4). Recently, Chen and Xu reported the

Scheme 4. Alternative Synthesis of Lamellarin N



cyclization of a similar acetal to give the lamellarin framework.[9n] Their reaction conditions (TFAA, TFA, reflux) were applied, and lamellarin **20** was obtained in 63% yield. However, it was found that the cyclization proceeds more efficiently under milder conditions (cat. TfOH, DCM, 0 °C, 23 h) to afford **20** in essentially quantitative yield. This two-step cyclization is apparently more convenient than the Pummerer route for the synthesis of 5,6-unsaturated lamellarins.

CONCLUSION

We have developed a new modular synthesis of lamellarins via regioselective assembly of 3,4,5-differentially arylated pyrrole-2-carboxylates followed by annulation of the pyrrole nitrogen and the lateral aromatic ring at C5. The overall yields of the lamellarins are quite high [e.g., the total yield of **3** from **1** via the $BrCH_2CH(OMe)_2$ annulation route is 42%]. Hence, because of the ready availability of a wide range of arylboronic acids, the synthetic route described herein should be exceptionally useful for the production of structurally diverse natural and artificial lamellarins in short reaction sequences.

EXPERIMENTAL SECTION

General Information. Melting points are uncorrected. IR spectra are reported in terms of wavenumber of absorption (cm^{-1}). ^1H NMR spectra were recorded at 400 MHz and are reported relative to Me_4Si (δ 0.0). Data for ^1H NMR spectra are reported as follows: chemical shift (δ, ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C NMR spectra were recorded at 100 MHz and are reported relative to Me_4Si (δ 0.0). Data for ^{13}C NMR spectra are reported in terms of chemical shift. High-resolution mass spectrometry (HRMS) was performed on a double-focusing magnetic sector mass spectrometer equipped with an FAB ion source. Elemental analysis was performed for C, H, and N. Column chromatography was conducted on silica gel 60N, 63–210 μm or Chromatorex NH-DM1020. Flash chromatography was conducted on silica gel 60N, 40–50 μm. Solvents were dried and distilled by standard methods if necessary. The yields of the compounds were estimated after chromatographic purification, unless otherwise mentioned. The chromatographically purified samples were used for the subsequent reactions without further purifications such as recrystallization.

Methyl 5-Bromo-1-(*tert*-butoxycarbonyl)-1*H*-pyrrole-2-carboxylate (8). Under an argon atmosphere, a hexane solution of *n*-BuLi (1.51 M, 9.9 mL, 15.0 mmol) was added dropwise to a solution of 2,5-dibromo-1-(*tert*-butoxycarbonyl)-1*H*-pyrrole (**1**)[10j,12] (4.87 g, 15.0 mmol) in Et_2O (85 mL) at −78 °C. After 30 min of stirring, a solution of methyl chloroformate (1.50 mL, 19.5 mmol) in Et_2O (4.5 mL) was added at −78 °C, and the mixture was stirred for an additional 1 h at −78 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl and allowed to warm to room temperature. The products were extracted with Et_2O, and the extract was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography using silica gel 60N (hexane–ethyl acetate = 20:1) to give **8** as a pale-blue oil (3.69 g, 81%). IR (KBr): 1775, 1718, 1442, 1300, 1159, 1092, 845, 751 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.63 (s, 9H), 3.83 (s, 3H), 6.23 (d, J = 3.9 Hz, 1H), 6.83 (d, J = 3.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.5, 51.8, 86.4, 107.1, 113.3, 118.6, 125.2, 148.1, 159.7. HR-FAB-MS (m/z) Calcd for $C_{11}H_{15}BrNO_4$ [$(M + H)^+$]: 304.0184. Found: 304.0155.

Methyl 5-(4-Isopropoxy-3-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (9). Under an argon atmosphere, a mixture of **8** (3.06 g, 10.1 mmol), **5**[9k] (3.17 g, 15.1 mmol), $Pd(PPh_3)_4$ (1.17 g, 1.01 mmol), Na_2CO_3 (7.04 g, 66.5 mmol), DME (185 mL), and degassed water (20 mL) was refluxed for 21.5 h. After cooling to room temperature, the mixture was evaporated, and the products were extracted with DCM. The extract was washed with brine, dried over Na_2SO_4, and evaporated. The residue was passed through a column of silica gel 60N (hexane–ethyl acetate = 3:1) to give a mixture of **9** and its *N*-Boc precursor (4.03 g). To the mixture was added a solution of NaOMe prepared from sodium (566 mg, 24.6 mmol) in MeOH (50 mL), and the mixture was refluxed for 19 h. After the mixture was cooled to room temperature, the solvent was evaporated, and the products were extracted with Et_2O. The extract was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography over silica gel 60N (toluene–ethyl acetate = 10:1) to give **9** as a colorless solid (2.52 g, 86%). Recrystallization from Et_2O–hexane gave colorless granules. Mp 116.5–117 °C. IR (KBr): 3315, 1670, 1486, 1247, 1136, 954, 799 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.38 (d, J = 6.1 Hz, 6H), 3.85 (s, 3H), 3.90 (s, 3H), 4.55 (sep, J = 6.1 Hz, 1H), 6.44 (dd, J = 2.7 and 3.9 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 6.95 (dd, J = 2.4 and 3.9 Hz, 1H), 7.07 (d, J = 2.1 Hz, 1H), 7.12 (dd, J = 2.1 and 8.3 Hz, 1H), 9.50 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 51.5, 56.1, 71.5, 107.4, 109.1, 115.9, 117.0, 117.5, 122.5, 124.8, 137.3, 147.3, 150.7, 161.8. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.30; H, 6.80; N, 4.79.

Methyl 4-Bromo-5-(4-isopropoxy-3-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (10). Under an argon atmosphere, NBS (308 mg, 1.73 mmol) was added portionwise to a solution of **9** (500 mg, 1.73 mmol) in THF (25 mL) at −78 °C. After 1 h of stirring at −78 °C, the mixture was allowed to warm to 0 °C and stirred for an additional 17 h at the same temperature. To the mixture was added powdered Na_2SO_3 (218 mg, 1.73 mmol). The suspension was stirred for 1 h and then passed through a pad of Celite. The filtrate was evaporated, and the residue was purified by column chromatography over silica gel 60N (hexane–ethyl acetate = 3:1) to give **10** as a pale-brown solid (629 mg, 99%). Recrystallization from hexane gave colorless needles. Mp 92–93 °C. IR (KBr): 3303, 1683, 1481, 1246, 1205, 1139, 1037, 1006, 768 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.40 (d, J = 6.1 Hz, 6H), 3.83 (s, 3H), 3.91 (s, 3H), 4.59 (sep, J = 6.1 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 2.8 Hz, 1H), 7.18 (dd, J = 2.1 and 8.4 Hz, 1H), 7.26 (d, J = 2.1 Hz, 1H), 9.41 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 51.8, 56.1, 71.4, 95.7, 111.4, 115.2, 119.1, 119.9, 121.7, 123.1, 134.1, 147.8, 150.2, 161.1. HR-FAB-MS (m/z) Calcd for $C_{16}H_{18}BrNO_4$ (M^+): 367.0419. Found: 367.0443.

Methyl 4-(3-Isopropoxy-4-methoxyphenyl)-5-(4-isopropoxy-3-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (11). Under an argon atmosphere, a mixture of **10** (1.00 g, 2.72 mmol), **6**[9k] (857 mg, 4.08 mmol), $Pd(PPh_3)_4$ (315 mg, 0.272 mmol), Na_2CO_3 (1.90 g, 17.9 mmol), DME (50 mL), and degassed water (6 mL) was refluxed for 18 h. After cooling to room temperature, the mixture was

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evaporated, and the products were extracted with DCM. The extract was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography over silica gel 60N (hexane−ethyl acetate = 3:1) to give **11** as a pale-yellow solid (1.02 g, 83%). Recrystallization from Et_2O−hexane gave a colorless powder. Mp 78.5−79 °C. IR (KBr): 3290, 1689, 1464, 1238, 1137, 1014, 769 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.25 (d, J = 6.1 Hz, 6H), 1.37 (d, J = 6.1 Hz, 6H), 3.67 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 4.33 (sep, J = 6.1 Hz, 1H), 4.53 (sep, J = 6.1 Hz, 1H), 6.82 (d, J = 8.3 Hz, 1H), 6.83 (d, J = 1.9 Hz, 1H), 6.85 (d, J = 8.3 Hz, 1H), 6.86 (d, J = 1.9 Hz, 1H), 6.89 (dd, J = 1.9 and 8.3 Hz, 1H), 6.93 (dd, J = 1.9 and 8.3 Hz, 1H), 7.01 (d, J = 2.6 Hz, 1H), 9.17 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 22.0, 51.6, 55.8, 56.0, 71.1, 71.4, 111.9, 111.9, 115.5, 116.2, 116.6, 120.2, 121.1, 121.4, 123.5, 124.8, 128.2, 133.1, 147.0, 147.2, 149.0, 150.2, 161.7. HR-FAB-MS (m/z) Calcd for $C_{26}H_{31}NO_6$ (M^+): 453.2151. Found: 453.2165.

Methyl 3-Bromo-4-(3-isopropoxy-4-methoxyphenyl)-5-(4-isopropoxy-3-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (12). Under an argon atmosphere, NBS (525 mg, 2.95 mmol) was added portionwise to a solution of **11** (1.34 g, 2.95 mmol) in DMF (45 mL) at 0 °C. After 1 h of stirring at 0 °C, the mixture was diluted with water, and the products were extracted with ethyl acetate. The extract was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography over silica gel 60N (hexane−ethyl acetate = 2:1) to give **12** as a colorless solid (1.55 g, 99%). Recrystallization from DCM−hexane gave a colorless powder. Mp 124.5−125 °C. IR (KBr): 3262, 1660, 1471, 1247 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.29 (d, J = 6.1 Hz, 6H), 1.35 (d, J = 6.1 Hz, 6H), 3.57 (s, 3H), 3.86 (s, 3H), 3.91 (s, 3H), 4.42 (sep, J = 6.1 Hz, 1H), 4.51 (sep, J = 6.1 Hz, 1H), 6.70 (d, J = 2.0 Hz, 1H), 6.81 (d, J = 8.3 Hz, 1H), 6.82−6.89 (m, 4H), 9.39 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 22.0, 51.7, 55.7, 55.9, 71.1, 71.3, 106.2, 111.5, 111.7, 115.2, 118.3, 119.1, 119.5, 123.5, 123.7, 124.4, 126.0, 133.5, 146.9, 147.4, 149.6, 150.0, 160.9. Anal. Calcd for $C_{26}H_{30}BrNO_6$: C, 58.65; H, 5.68; N, 2.63. Found: C, 58.48; H, 5.57; N, 2.60.

Methyl 4-(3-Isopropoxy-4-methoxyphenyl)-5-(4-isopropoxy-3-methoxyphenyl)-3-phenyl-1*H*-pyrrole-2-carboxylate (14a). Under an argon atmosphere, a mixture of **12** (133 mg, 0.249 mmol), **13a** (45.6 mg, 0.374 mmol), $Pd(dba)_2$ (14.3 mg, 24.9 μmol), dppf (13.8 mg, 24.9 μmol), Na_2CO_3 (174 mg, 1.64 mmol), DME (5.0 mL), and degassed water (0.4 mL) was refluxed for 18 h. After cooling to room temperature, the mixture was evaporated, and the products were extracted with DCM. The extract was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography over silica gel 60N (DCM) to give **14a** as a pale-yellow solid (115 mg, 87%). Recrystallization from Et_2O−hexane gave a colorless powder. Mp 150−150.5 °C. IR (KBr): 3293, 1671, 1442, 1244, 1137 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.07 (d, J = 6.1 Hz, 6H), 1.36 (d, J = 6.1 Hz, 6H), 3.57 (s, 3H), 3.70 (s, 3H), 3.78 (s, 3H), 4.11 (sep, J = 6.1 Hz, 1H), 4.52 (sep, J = 6.1 Hz, 1H), 6.50 (d, J = 2.0 Hz, 1H), 6.57 (dd, J = 2.0 and 8.3 Hz, 1H), 6.67 (d, J = 8.3 Hz, 1H), 6.75 (d, J = 2.0 Hz, 1H), 6.83 (d, J = 8.3 Hz, 1H), 6.91 (dd, J = 2.0 and 8.3 Hz, 1H), 7.16−7.25 (m, 5H), 9.27 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 22.0, 51.3, 55.7, 55.8, 70.9, 71.3, 111.5, 111.9, 115.3, 117.9, 118.7, 119.7, 123.5, 123.6, 124.6, 126.6, 126.9, 127.3, 130.8, 131.8, 132.8, 134.3, 146.6, 147.1, 148.8, 150.0, 161.8. HR-FAB-MS (m/z) Calcd for $C_{32}H_{35}NO_6$ (M^+): 529.2464. Found: 529.2472.

Methyl 4-(3-Isopropoxy-4-methoxyphenyl)-5-(4-isopropoxy-3-methoxyphenyl)-3-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (14b). According to the procedure described for the preparation of **14a**, **12** (100 mg, 0.188 mmol), **13b** (42.9 mg, 0.282 mmol), $Pd(dba)_2$ (10.8 mg, 18.8 μmol), and dppf (10.4 mg, 18.8 μmol) were reacted. After purification by column chromatography over silica gel 60N (hexane−ethyl acetate = 2:1), **14b** was obtained as a colorless solid (84.7 mg, 81%). Recrystallization from DCM−Et_2O gave a colorless powder. Mp 214.5−215 °C. IR (KBr): 3364, 1717, 1509, 1243, 1129 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.09 (d, J = 6.1 Hz, 6H), 1.36 (d, J = 6.1 Hz, 6H), 3.57 (s, 3H), 3.75 (s, 3H), 3.78 (s, 3H), 3.79 (s, 3H), 4.14 (sep, J = 6.1 Hz, 1H), 4.52 (sep, J = 6.1 Hz, 1H), 6.51 (d, J = 2.0 Hz, 1H), 6.57 (dd, J = 2.0 and 8.3 Hz, 1H), 6.68 (d, J = 8.3 Hz, 1H), 6.74 (d, J = 2.0 Hz, 1H), 6.76−6.81 (m, 2H), 6.83 (d, J = 8.3 Hz, 1H), 6.90 (dd, J = 2.0 and 8.3 Hz, 1H), 7.12−7.17 (m, 2H), 9.11 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 22.0, 51.3, 55.1, 55.7, 55.8, 70.9, 71.3, 111.5, 111.9, 112.9, 115.3, 117.8, 118.8, 119.7, 123.5, 123.7, 124.6, 126.5, 127.0, 131.6, 131.9, 132.8, 146.6, 147.0, 148.8, 150.0, 158.4, 161.8. HR-FAB-MS (m/z) Calcd for $C_{33}H_{37}NO_7$ (M^+): 559.2570. Found: 559.2585.

Methyl 3-(3,4-Dimethoxyphenyl)-4-(3-isopropoxy-4-methoxyphenyl)-5-(4-isopropoxy-3-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (14c). According to the procedure described for the preparation of **14a**, **12** (104 mg, 0.195 mmol), **13c** (53.3 mg, 0.293 mmol), $Pd(dba)_2$ (11.2 mg, 19.5 μmol), and dppf (10.8 mg, 19.5 μmol) were reacted. After purification by column chromatography over silica gel 60N (hexane−ethyl acetate = 1:1), **14c** was obtained as a colorless solid (96.7 mg, 84%). Recrystallization from Et_2O−hexane gave a colorless powder. Mp 68.5−69.5 °C. IR (KBr): 3310, 1713, 1440, 1250, 1138, 1029 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.11 (d, J = 6.1 Hz, 6H), 1.36 (d, J = 6.1 Hz, 6H), 3.58 (s, 3H), 3.66 (s, 3H), 3.75 (s, 3H), 3.79 (s, 3H), 3.85 (s, 3H), 4.16 (sep, J = 6.1 Hz, 1H), 4.52 (sep, J = 6.1 Hz, 1H), 6.55 (d, J = 1.9 Hz, 1H), 6.58 (dd, J = 1.9 and 8.3 Hz, 1H), 6.69 (d, J = 8.3 Hz, 1H), 6.74 (d, J = 1.9 Hz, 1H), 6.76 (d, J = 1.9 Hz, 1H), 6.77 (d, J = 8.3 Hz, 1H), 6.83 (dd, J = 1.9 and 8.3 Hz, 1H), 6.83 (d, J = 8.3 Hz, 1H), 6.91 (dd, J = 1.9 and 8.3 Hz, 1H), 9.19 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 22.1, 51.3, 55.7, 55.7, 55.8, 55.9, 71.1, 71.4, 110.3, 111.7, 111.9, 114.5, 115.4, 117.7, 118.9, 119.7, 123.4, 123.5, 123.7, 124.6, 126.6, 127.1, 131.5, 132.8, 146.7, 147.1, 147.8, 147.8, 148.9, 150.1, 161.7. HR-FAB-MS (m/z) Calcd for $C_{34}H_{39}NO_8$ (M^+): 589.2676. Found: 589.2676.

Methyl 4-(3-Isopropoxy-4-methoxyphenyl)-5-(4-isopropoxy-3-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)-1*H*-pyrrole-2-carboxylate (14d). According to the procedure described for the preparation of **14a**, **12** (100 mg, 0.188 mmol), **13d** (79.7 mg, 0.376 mmol), $Pd(dba)_2$ (10.8 mg, 18.8 μmol), and dppf (10.4 mg, 18.8 μmol) were reacted. After purification by column chromatography over silica gel 60N (hexane−ethyl acetate = 2:1), **14d** was obtained as a colorless solid (98.6 mg, 85%). Recrystallization from Et_2O−hexane gave a colorless powder. Mp 161.5−162 °C. IR (KBr): 3317, 1725, 1505, 1241, 1126 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.12 (d, J = 6.1 Hz, 6H), 1.36 (d, J = 6.1 Hz, 6H), 3.58 (s, 3H), 3.66 (s, 6H), 3.78 (s, 3H), 3.80 (s, 3H), 3.82 (s, 3H), 4.18 (sep, J = 6.1 Hz, 1H), 4.52 (sep, J = 6.1 Hz, 1H), 6.48 (s, 2H), 6.56 (d, J = 1.8 Hz, 1H), 6.61 (dd, J = 1.8 and 8.3 Hz, 1H), 6.72 (d, J = 8.3 Hz, 1H), 6.76 (d, J = 1.8 Hz, 1H), 6.84 (d, J = 8.3 Hz, 1H), 6.92 (dd, J = 1.8 and 8.3 Hz, 1H), 9.26 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 22.0, 51.4, 55.7, 55.9, 56.0, 60.8, 71.1, 71.3, 108.4, 111.7, 111.8, 115.2, 117.6, 118.8, 119.7, 123.5, 123.7, 124.4, 127.1, 129.4, 131.4, 132.9, 136.8, 146.7, 147.2, 149.0, 150.0, 152.2, 161.7. Anal. Calcd for $C_{35}H_{41}NO_9$: C, 67.84; H, 6.67; N, 2.26. Found: C, 67.54; H, 6.70; N, 2.51.

Methyl 3-(4,5-Dimethoxy-2-methoxymethoxyphenyl)-4-(3-isopropoxy-4-methoxyphenyl)-5-(4-isopropoxy-3-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (14e). According to the procedure described for the preparation of **14a**, **12** (1.55 g, 2.91 mmol), **13e** (1.06 g, 4.37 mmol), $Pd(dba)_2$ (167 mg, 0.291 mmol), and dppf (161 mg, 0.291 mmol) were reacted. After successive purification by column chromatography over silica gel 60N (toluene−ethyl acetate = 5:1) and column chromatography over Chromatorex NH-DM1020 (toluene−ethyl acetate = 3:1), **14e** was obtained as a colorless solid (1.58 g, 84%). Recrystallization from Et_2O−hexane gave a colorless powder. Mp 75.5−76 °C. IR (KBr): 3308, 1694, 1511, 1441, 1245, 1013 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.11 (d, J = 6.1 Hz, 6H), 1.36 (d, J = 6.1 Hz, 6H), 3.27 (s, 3H), 3.59 (s, 3H), 3.68 (s, 3H), 3.71 (s, 3H), 3.77 (s, 3H), 3.85 (s, 3H), 4.12 (sep, J = 6.1 Hz, 1H), 4.52 (sep, J = 6.1 Hz, 1H), 4.59 (d, J = 6.8 Hz, 1H), 4.82 (d, J = 6.8 Hz, 1H), 6.58 (dd, J = 2.0 and 8.4 Hz, 1H), 6.59 (d, J = 2.0 Hz, 1H), 6.63 (s, 1H), 6.66 (d, J = 8.4 Hz, 1H), 6.79 (d, J = 2.0 Hz, 1H), 6.79 (s, 1H), 6.83 (d, J = 8.4 Hz, 1H), 6.92 (dd, J = 2.0 and 8.4 Hz, 1H), 9.21 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 21.8, 22.1, 51.3, 55.6, 55.7, 55.9, 55.9, 56.3, 71.2, 71.4, 96.7, 101.8, 111.5, 112.0, 115.3, 115.4, 116.6, 118.3, 118.8, 119.8, 123.1, 123.8, 124.8, 127.4,

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127.6, 132.6, 143.7, 146.7, 147.1, 148.8, 148.9, 150.0, 150.1, 161.7. Anal. Calcd for $C_{36}H_{43}NO_{10}$: C, 66.55; H, 6.67; N, 2.16. Found: C, 66.45; H, 6.89; N, 2.12.

Methyl 4-(3-Isopropoxy-4-methoxyphenyl)-5-(4-isopropoxy-3-methoxyphenyl)-3-(4-isopropoxy-5-methoxy-2-methoxymethoxyphenyl)-1*H*-pyrrole-2-carboxylate (4). According to the procedure described for the preparation of **14a**, **12** (532 mg, 0.999 mmol), **7**[9k] (407 mg, 1.51 mmol), $Pd(dba)_2$ (58.2 mg, 0.101 mmol), and dppf (55.1 mg, 99.4 μmol) were reacted. After purification by flash chromatography over silica gel 60N (toluene−ethyl acetate = 5:1), **4** was obtained as a colorless solid (621 mg, 92%). Recrystallization from Et_2O−hexane gave a colorless powder. Mp 72−73 °C. IR (KBr): 3330, 1716, 1509, 1441, 1244, 1112 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.11 (d, *J* = 6.0 Hz, 3H), 1.11 (d, *J* = 6.0 Hz, 3H), 1.35 (d, *J* = 6.0 Hz, 3H), 1.37 (d, *J* = 6.0 Hz, 6H), 1.37 (d, *J* = 6.0 Hz, 3H), 3.25 (s, 3H), 3.59 (s, 3H), 3.64 (s, 3H), 3.71 (s, 3H), 3.77 (s, 3H), 4.13 (sep, *J* = 6.0 Hz, 1H), 4.49 (sep, *J* = 6.0 Hz, 1H), 4.52 (sep, *J* = 6.0 Hz, 1H), 4.57 (d, *J* = 6.8 Hz, 1H), 4.80 (d, *J* = 6.8 Hz, 1H), 6.58 (dd, *J* = 1.9 and 8.1 Hz, 1H), 6.60 (d, *J* = 1.9 Hz, 1H), 6.62 (s, 1H), 6.66 (d, *J* = 8.1 Hz, 1H), 6.78 (d, *J* = 1.8 Hz, 1H), 6.80 (s, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 6.92 (dd, *J* = 1.8 and 8.3 Hz, 1H), 9.19 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 22.1, 22.2, 51.3, 55.5, 55.7, 55.9, 56.4, 71.0, 71.3, 96.7, 105.5, 111.4, 111.9, 115.3, 116.0, 117.1, 117.9, 118.8, 119.8, 123.0, 123.8, 124.7, 127.4, 127.7, 132.5, 144.9, 146.6, 147.0, 147.2, 148.7, 149.9, 150.0, 161.8. Anal. Calcd for $C_{38}H_{47}NO_{10}$: C, 67.34; H, 6.99; N, 2.07. Found: C, 67.25; H, 7.28; N, 2.03.

7-Isopropoxy-1-(3-isopropoxy-4-methoxyphenyl)-2-(4-isopropoxy-3-methoxyphenyl)-8-methoxy[1]benzopyrano[3,4-*b*]pyrrol-4(3*H*)-one (15). Under an argon atmosphere, a solution of **4** (143 mg, 0.211 mmol) and *p*-TsOH·H_2O (10.5 mg, 55.2 μmol) in MeOH (10 mL) was refluxed for 18.5 h. After cooling to room temperature, the mixture was quenched with saturated aqueous $NaHCO_3$ and evaporated. The products were extracted with DCM, and the extract was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography over silica gel 60N (hexane−ethyl acetate = 3:1) to give **15** as a pale-yellow solid (121 mg, 95%). Recrystallization from DCM−hexane gave a colorless powder. Mp 216−217 °C. IR (KBr): 3276, 1691, 1442, 1267, 1143, 1111 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (br d, *J* = 6.1 Hz, 3H), 1.32 (br d, *J* = 6.1 Hz, 3H), 1.37 (d, *J* = 6.1 Hz, 6H), 1.41 (d, *J* = 6.1 Hz, 6H), 3.49 (s, 3H), 3.79 (s, 3H), 3.92 (s, 3H), 4.47 (sep, *J* = 6.1 Hz, 1H), 4.54 (sep, *J* = 6.1 Hz, 1H), 4.58 (sep, *J* = 6.1 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 6.81 (s, 1H), 6.93 (s, 1H), 6.97 (d, *J* = 1.8 Hz, 1H), 6.99 (dd, *J* = 2.1 and 8.5 Hz, 1H), 7.01 (d, *J* = 8.1 Hz, 1H), 7.04 (dd, *J* = 1.8 and 8.1 Hz, 1H), 7.16 (d, *J* = 2.1 Hz, 1H), 10.71 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 22.0, 55.7, 55.8, 56.2, 71.2, 71.2, 71.5, 103.6, 105.1, 110.6, 111.3, 112.3, 114.7, 115.1, 117.2, 118.2, 120.2, 123.5, 123.8, 127.4, 129.1, 139.3, 146.2, 146.8, 147.3, 147.5, 147.6, 149.9, 150.0, 156.1. Anal. Calcd for $C_{35}H_{39}NO_8$: C, 69.87; H, 6.53; N, 2.33. Found: C, 69.63; H, 6.75; N, 2.18.

7-Isopropoxy-1-(3-isopropoxy-4-methoxyphenyl)-2-(4-isopropoxy-3-methoxyphenyl)-8-methoxy-3-[2-(phenylsulfanyl)-ethyl][1]benzopyrano[3,4-*b*]pyrrol-4(3*H*)-one (16). Under an argon atmosphere, a solution of **15** (190 mg, 0.316 mmol), 2-bromoethyl phenyl sulfide (315 μL, 2.09 mmol), and Cs_2CO_3 (680 mg, 2.09 mmol) in DMF (15 mL) was stirred for 22 h at 80 °C. After cooling to room temperature, the mixture was diluted with water, and the products were extracted with ethyl acetate. The extract was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography over silica gel 60N (hexane−ethyl acetate = 2:1) to give **16** as a colorless solid (222 mg, 95%). Recrystallization from DCM−hexane gave a colorless powder. Mp 180−181 °C. IR (KBr): 1701, 1440, 1261, 1137, 1033 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.15 (br s, 3H), 1.27 (br s, 3H), 1.40 (d, *J* = 6.1 Hz, 6H), 1.40 (d, *J* = 6.1 Hz, 6H), 3.28 (t, *J* = 7.5 Hz, 2H), 3.47 (s, 3H), 3.64 (s, 3H), 3.84 (s, 3H), 4.33 (sep, *J* = 6.1 Hz, 1H), 4.53 (sep, *J* = 6.1 Hz, 1H), 4.56 (sep, *J* = 6.1 Hz, 1H), 4.61−4.78 (m, 2H), 6.66 (d, *J* = 1.7 Hz, 1H), 6.73 (d, *J* = 1.7 Hz, 1H), 6.75 (dd, *J* = 1.7 and 8.3 Hz, 1H), 6.78 (d, *J* = 8.3 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 6.88 (dd, *J* = 1.7 and 8.3 Hz, 1H), 6.90 (s, 1H), 6.93 (s, 1H), 7.03−7.15 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 22.1, 33.8, 45.7, 55.8, 55.9, 56.0, 71.0, 71.2, 71.4, 103.4, 105.3, 110.2, 111.6, 114.1, 114.5, 114.5, 118.6, 118.7, 122.0, 123.3, 123.8, 125.9, 126.6, 127.8, 128.6, 128.8, 135.1, 143.0, 146.2, 146.5, 146.9, 147.3, 147.9, 149.6, 149.7, 155.5. Anal. Calcd for $C_{43}H_{47}NO_8S$: C, 69.99; H, 6.42; N, 1.90. Found: C, 69.87; H, 6.62; N, 1.87.

7-Isopropoxy-1-(3-isopropoxy-4-methoxyphenyl)-2-(4-isopropoxy-3-methoxyphenyl)-8-methoxy-3-[2-(phenylsulfinyl)-ethyl][1]benzopyrano[3,4-*b*]pyrrol-4(3*H*)-one (17). Under an argon atmosphere, *m*-chloroperbenzoic acid (28.0 mg, 0.162 mmol) was added portionwise to a solution of **16** (120 mg, 0.162 mmol) in DCM (9 mL) at 0 °C. After 15 min of stirring at 0 °C, the mixture was quenched with saturated aqueous $NaHCO_3$, and the products were extracted with DCM. The extract was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography over silica gel 60N (hexane−ethyl acetate = 1:1) to give **17** as a colorless solid (108 mg, 89%). Recrystallization from DCM−hexane gave a colorless powder. Mp 182.5−183.5 °C. IR (KBr): 1711, 1441, 1262, 1032 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.14 (br s, 3H), 1.26 (br s, 3H), 1.40 (d, *J* = 6.1 Hz, 12H), 3.24−3.33 (m, 1H), 3.42−3.51 (m, 1H), 3.47 (s, 3H), 3.68 (s, 3H), 3.84 (s, 3H), 4.25−4.38 (m, 1H), 4.56 (sep, *J* = 6.1 Hz, 2H), 4.66 (br s, 1H), 4.87 (br s, 1H), 6.66 (d, *J* = 1.8 Hz, 1H), 6.73 (br s, 1H), 6.81 (dd, *J* = 1.8 and 8.3 Hz, 1H), 6.83−6.87 (m, 2H), 6.86 (d, *J* = 8.3 Hz, 1H), 6.90 (s, 1H), 6.91 (s, 1H), 7.44−7.51 (m, 3H), 7.53−7.58 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 21.8, 22.1, 40.3, 55.7, 55.9, 56.0, 57.7, 71.1, 71.2, 71.5, 103.3, 105.3, 110.0, 111.6, 114.3, 114.5, 118.5, 118.9, 121.4, 123.3, 123.8, 124.0, 126.4, 128.4, 129.2, 131.0, 143.2, 143.3, 146.2, 146.6, 147.0, 147.5, 148.1, 149.6, 149.9, 155.5. Anal. Calcd for $C_{43}H_{47}NO_9S$: C, 68.51; H, 6.28; N, 1.86. Found: C, 68.19; H, 6.46; N, 1.78.

3,11-Diisopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-2,12-dimethoxy-9-(phenylsulfanyl)-8,9-dihydro-6*H*-[1]-benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (18). Under an argon atmosphere, TMSOTf (48 μL, 0.265 mmol) was added to a solution of **17** (50.0 mg, 66.3 μmol) and *i*-Pr_2NEt (46 μL, 0.264 mmol) in DCM (5.0 mL) at 0 °C. After 1 h of stirring at 0 °C, the mixture was quenched with saturated aqueous $NaHCO_3$, and the products were extracted with DCM. The extract was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography over silica gel 60N (hexane−ethyl acetate = 3:1 containing 1% triethylamine) to give **18** as a colorless solid (43.8 mg, 90%). Mp 94.5−95.5 °C. IR (KBr): 1709, 1418, 1239, 1112, 1034 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 20 °C): δ 1.31−1.41 (m, 18H), 3.34 (s, 1.5H), 3.34 (s, 1.5H), 3.43 (s, 1.5H), 3.45 (s, 1.5H), 3.93 (s, 3H), 4.31−4.37 (m, 1H), 4.46−4.59 (m, 4H), 5.55−5.64 (m, 1H), 6.63 (s, 0.5H), 6.66 (s, 0.5H), 6.67 (s, 0.5H), 6.73 (s, 0.5H), 6.81 (s, 0.5H), 6.82 (s, 0.5H), 6.93 (s, 0.5H), 6.93 (s, 0.5H), 6.94 (d, *J* = 1.9 Hz, 0.5H), 6.98 (dd, *J* = 1.9 and 8.2 Hz, 0.5H), 7.05 (d, *J* = 8.2 Hz, 0.5H), 7.11 (d, *J* = 8.2 Hz, 0.5H), 7.13 (d, *J* = 1.9 Hz, 0.5H), 7.16 (dd, *J* = 1.9 and 8.2 Hz, 0.5H), 7.25−7.34 (m, 3H), 7.41−7.46 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): δ 21.8, 21.8, 21.9, 21.9, 22.0, 22.0, 22.1, 22.1, 22.1, 46.4, 46.4, 47.6, 55.1, 55.1, 55.5, 55.6, 56.3, 56.4, 71.3, 71.4, 71.4, 71.5, 103.6, 104.9, 105.1, 108.8, 108.8, 110.4, 112.6, 112.8, 114.2, 114.8, 114.9, 115.0, 115.1, 117.9, 118.1, 120.2, 120.2, 123.7, 123.9, 125.5, 125.6, 127.7, 127.9, 128.3, 128.5, 128.7, 129.1, 129.1, 132.5, 134.8, 134.9, 135.2, 135.3, 146.1, 146.1, 146.6, 146.6, 147.1, 147.1, 147.4, 147.4, 148.0, 148.1, 149.6, 149.7, 150.1, 150.2, 155.4, 155.5. ^1H NMR (400 MHz, toluene-d_8, 20 °C): δ 1.02 (d, *J* = 6.0 Hz, 1.5H), 1.04 (d, *J* = 6.0 Hz, 1.5H), 1.08 (d, *J* = 6.0 Hz, 1.5H), 1.10 (d, *J* = 6.0 Hz, 1.5H), 1.11 (d, *J* = 6.0 Hz, 3H), 1.13 (d, *J* = 6.0 Hz, 1.5H), 1.15 (d, *J* = 6.0 Hz, 1.5H), 1.17 (d, *J* = 6.0 Hz, 1.5H), 1.18 (d, *J* = 6.0 Hz, 1.5H), 1.20 (d, *J* = 6.0 Hz, 3H), 3.20 (s, 1.5H), 3.21 (s, 1.5H), 3.29 (s, 1.5H), 3.31 (s, 1.5H), 3.39 (s, 1.5H), 3.42 (s, 1.5H), 3.99−4.19 (m, 3.5H), 4.25 (sep, *J* = 6.0 Hz, 0.5H), 4.27 (sep, *J* = 6.0 Hz, 0.5H), 4.43 (sep, *J* = 6.0 Hz, 0.5H), 5.76−5.82 (m, 1H), 6.58 (d, *J* = 8.2 Hz, 0.5H), 6.76 (s, 0.5H), 6.76 (d, *J* = 8.2 Hz, 0.5H), 6.76 (s, 0.5H), 6.81 (s, 0.5H), 6.83−6.86 (m, 1.5H), 6.87 (s,

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0.5H), 6.91 (s, 0.5H), 6.94−7.10 (m, 4H), 7.19 (dd, J = 2.0 and 8.2 Hz, 0.5H), 7.30 (d, J = 2.0 Hz, 0.5H), 7.42−7.49 (m, 2H). ^{13}C NMR (100 MHz, toluene-d_8, 20 °C): δ 21.8, 21.9, 21.9, 22.0, 22.0, 22.1, 22.2, 22.2, 22.2, 22.3, 46.5, 46.6, 47.9, 48.1, 54.7, 54.8, 55.2, 55.3, 55.7, 55.9, 71.0, 71.1, 71.4, 71.4, 71.5, 104.2, 106.0, 106.3, 109.6, 109.7, 111.1, 111.2, 113.5, 113.6, 115.1, 115.6, 115.6, 116.3, 116.5, 119.1, 119.5, 121.2, 121.3, 124.2, 124.5, 126.2, 126.2, 128.3, 128.4, 128.5, 128.6, 129.2, 129.3, 129.4, 133.5, 133.7, 134.7, 134.9, 135.6, 135.6, 147.0, 147.5, 147.5, 147.9, 148.0, 148.0, 148.1, 148.8, 149.1, 150.8, 150.9, 151.0, 151.1, 155.2. ^{1}H NMR (400 MHz, toluene-d_8, 90 °C): δ 1.05−1.23 (m, 18H), 3.24 (s, 3H), 3.33 (s, 3H), 3.50 (s, 3H), 4.12 (dd, J = 3.9 and 14.2 Hz, 1H), 4.17−4.36 (m, 4H), 5.70 (dd, J = 2.6 and 14.2 Hz, 1H), 6.70−7.24 (m, 10H), 7.32−7.42 (m, 2H). ^{13}C NMR (100 MHz, toluene-d_8, 90 °C): δ 22.3, 22.3, 22.4, 22.5, 22.5, 47.3, 48.2, 55.4, 56.1, 56.7, 72.2, 72.4, 106.0, 107.7, 110.9, 112.0, 115.2, 115.7, 115.9, 118.0, 121.2, 121.9, 126.9, 128.6, 128.7, 129.4, 134.0, 135.0, 135.6, 147.6, 148.3, 148.6, 148.7, 149.8, 151.6, 152.0, 155.3. HR-FAB-MS (m/z) Calcd for $C_{43}H_{46}NO_8S$ [(M + H)$^+$]: 736.2944. Found: 736.2947.

3,11-Diisopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-2,12-dimethoxy-8,9-dihydro-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (19). Under an argon atmosphere, Bu_3SnH (26 μL, 96.7 μmol) and AIBN (1.5 mg, 9.1 μmol) were added to a solution of **18** (34.9 mg, 47.4 μmol) in benzene (5.0 mL) at room temperature, and the mixture was refluxed for 1 h. After cooling to room temperature, the mixture was evaporated. The residue was washed with pentane, and the resulting solid was purified by column chromatography over silica gel 60N (hexane−ethyl acetate = 2:1) to give **19** as a colorless solid (23.7 mg, 80%). Recrystallization from DCM−Et_2O gave a colorless powder. Mp 205−206 °C (lit.[9k] 206.5−207.5 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (d, J = 6.1 Hz, 3H), 1.35 (d, J = 6.1 Hz, 3H), 1.37 (d, J = 6.1 Hz, 6H), 1.39 (d, J = 6.1 Hz, 6H), 3.10 (t, J = 6.7 Hz, 2H), 3.34 (s, 3H), 3.43 (s, 3H), 3.92 (s, 3H), 4.46−4.62 (m, 3H), 4.74−4.87 (m, 2H), 6.66 (s, 1H), 6.73 (s, 1H), 6.77 (s, 1H), 6.92 (s, 1H), 7.03−7.11 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 21.9, 22.0, 22.1, 28.7, 42.5, 55.1, 55.5, 56.3, 71.3, 71.4, 103.5, 104.9, 109.2, 110.4, 112.7, 113.7, 114.8, 114.9, 117.9, 120.3, 123.7, 126.4, 128.0, 128.3, 136.0, 146.0, 146.5, 147.0, 147.3, 148.1, 148.7, 150.1, 155.7. These physical and spectroscopic data are in good agreement with those previously reported.[9k]

3,11-Dihydroxy-14-(3-hydroxy-4-methoxyphenyl)-2,12-dimethoxy-8,9-dihydro-6*H*-[1]benzopyrano-[4′,3′:4,5]pyrrolo-[2,1-*a*]isoquinolin-6-one (Lamellarin L) (2). Under an argon atmosphere, a heptane solution of BCl_3 (1.0 M, 307 μL, 0.307 mmol) was added dropwise to a solution of **19** (21.4 mg, 34.1 μmol) in DCM (5.0 mL) at −78 °C, and the mixture was allowed to warm to room temperature. After 2 h of stirring at room temperature, the mixture was quenched with saturated aqueous $NaHCO_3$, and the products were extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography over silica gel 60N (ethyl acetate) to give **2** as a pale-gray powder (16.5 mg, 97%). Mp >300 °C (sealed capillary) [lit.[9k] >300 °C (sealed capillary)]. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.01 (t, J = 6.8 Hz, 2H), 3.29 (s, 3H), 3.38 (s, 3H), 3.83 (s, 3H), 4.51−4.60 (m, 1H), 4.60−4.69 (m, 1H), 6.68 (s, 1H), 6.68 (s, 1H), 6.75 (s, 1H), 6.80 (s, 1H), 6.88−6.92 (m, 2H), 7.16 (d, J = 7.9 Hz, 1H), 9.30 (s, 1H), 9.44 (s, 1H), 9.67 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.4, 41.9, 54.6, 55.0, 56.0, 103.5, 104.9, 108.6, 109.2, 112.2, 113.4, 113.8, 115.2, 117.8, 117.9, 121.6, 127.1, 127.3, 127.3, 135.7, 144.4, 145.6, 145.9, 146.7, 147.0, 147.4, 147.5, 154.2. These physical and spectroscopic data are in good agreement with those previously reported.[9k]

3,11-Diisopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-2,12-dimethoxy-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]-isoquinolin-6-one (20). Under an argon atmosphere, *m*-chloroperbenzoic acid (6.6 mg, 38.2 μmol) was added portionwise to a solution of **18** (27.8 mg, 37.8 μmol) in DCM (5 mL) at 0 °C. After 1 h of stirring at 0 °C, the mixture was quenched with saturated aqueous $NaHCO_3$. The products were diluted with water and extracted with DCM. The extract was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography over silica gel 60N (hexane−ethyl acetate = 3:1) to give **20** as a colorless solid (22.7 mg, 96%). Recrystallization from DCM−Et_2O gave colorless needles. Mp 170−171 °C (sealed capillary) (lit.[9k] 169−170 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (d, J = 6.1 Hz, 3H), 1.36 (d, J = 6.1 Hz, 3H), 1.41 (d, J = 6.1 Hz, 6H), 1.44 (d, J = 6.1 Hz, 6H), 3.45 (s, 3H), 3.45 (s, 3H), 3.96 (s, 3H), 4.54 (sep, J = 6.1 Hz, 1H), 4.58 (sep, J = 6.1 Hz, 1H), 4.70 (sep, J = 6.1 Hz, 1H), 6.74 (s, 1H), 6.97 (s, 1H), 7.03 (d, J = 7.4 Hz, 1H), 7.10 (s, 1H), 7.13 (d, J = 1.8 Hz, 1H), 7.15 (d, J = 8.2 Hz, 1H), 7.18 (s, 1H), 7.20 (dd, J = 1.8 and 8.2 Hz, 1H), 9.23 (d, J = 7.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 21.9, 22.0, 55.2, 55.5, 56.4, 71.2, 71.3, 71.4, 103.4, 105.5, 105.6, 107.8, 110.0, 110.4, 111.0, 112.3, 112.7, 118.2, 119.1, 123.2, 124.1, 124.7, 128.3, 129.5, 134.5, 146.6, 146.7, 147.9, 148.2, 148.5, 150.2, 150.2, 155.6. These physical and spectroscopic data are in good agreement with those previously reported.[9k]

3,11-Dihydroxy-14-(3-hydroxy-4-methoxyphenyl)-2,12-dimethoxy-6*H*-[1]benzopyrano-[4′,3′:4,5]pyrrolo[2,1-*a*]-isoquinolin-6-one (Lamellarin N) (3). According to the procedure described for the preparation of **2**, **20** (11.1 mg, 17.7 μmol) and BCl_3 (1.0 M, 180 μL, 0.180 mmol) were reacted. After purification by column chromatography over silica gel 60N (ethyl acetate), **3** was obtained as a pale-gray powder (8.8 mg, 94%). Mp 280−300 °C (dec) (sealed capillary) [lit.[9k] 280−300 °C (dec) (sealed capillary)]. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.40 (s, 3H), 3.40 (s, 3H), 3.87 (s, 3H), 6.76 (s, 1H), 6.87 (s, 1H), 7.00−7.05 (m, 2H), 7.17 (s, 1H), 7.20 (s, 1H), 7.22 (d, J = 7.4 Hz, 1H), 7.25 (d, J = 8.7 Hz, 1H), 9.01 (d, J = 7.4 Hz, 1H), 9.40 (br s, 1H), 9.90 (br s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 54.4, 55.0, 56.0, 103.7, 105.2, 105.6, 106.4, 108.1, 110.4, 111.4, 112.3, 113.6, 117.3, 118.1, 121.9, 122.0, 124.6, 127.3, 128.7, 133.8, 144.5, 146.2, 147.6, 147.7, 147.9, 148.2, 148.4, 154.2. These physical and spectroscopic data are in good agreement with those previously reported.[9k]

3-(2,2-Dimethoxyethyl)-7-isopropoxy-1-(3-isopropoxy-4-methoxyphenyl)-2-(4-isopropoxy-3-methoxyphenyl)-8-methoxy[1]benzopyrano[3,4-*b*]pyrrol-4(3*H*)-one (21). Under an argon atmosphere, a solution of **15** (301 mg, 0.499 mmol), 2-bromo-1,1-dimethoxyethane (390 μL, 3.30 mmol), and Cs_2CO_3 (1.07 g, 3.27 mmol) in DMF (30 mL) was stirred for 38 h at 110 °C. After cooling to room temperature, the mixture was diluted with water, and the products were extracted with ethyl acetate. The extract was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography over silica gel 60N (hexane−ethyl acetate = 2:1) to give **21** as a colorless solid (320 mg, 93%). Recrystallization from DCM−Et_2O gave a colorless powder. Mp 211−211.5 °C. IR (KBr): 1702, 1463, 1271, 1143, 1136 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (br d, J = 6.1 Hz, 3H), 1.27 (br d, J = 6.1 Hz, 3H), 1.36 (d, J = 6.1 Hz, 6H), 1.40 (d, J = 6.1 Hz, 6H), 3.34 (br s, 6H), 3.48 (s, 3H), 3.69 (s, 3H), 3.85 (s, 3H), 4.33 (sep, J = 6.1 Hz, 1H), 4.52 (d, J = 5.4 Hz, 2H), 4.52 (sep, J = 6.1 Hz, 1H), 4.57 (sep, J = 6.1 Hz, 1H), 4.89 (t, J = 5.4 Hz, 1H), 6.75 (d, J = 1.9 Hz, 1H), 6.81 (d, J = 8.3 Hz, 1H), 6.85 (d, J = 8.3 Hz, 1H), 6.86−6.93 (m, 3H), 6.93 (s, 1H), 6.95 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 21.8, 22.0, 47.9, 55.3, 55.5, 55.8, 55.8, 56.0, 71.1, 71.1, 71.4, 103.4, 104.5, 105.4, 110.3, 111.6, 114.3, 114.7, 115.2, 118.6, 118.7, 122.2, 123.9, 123.9, 126.9, 127.8, 144.1, 146.2, 146.6, 146.9, 147.3, 147.6, 149.5, 149.6, 155.8. HR-FAB-MS (m/z) Calcd for $C_{39}H_{47}NO_{10}$ (M$^+$): 689.3200. Found: 689.3193.

3,11-Diisopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-2,12-dimethoxy-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]-isoquinolin-6-one (20). Under an argon atmosphere, 1 drop of TfOH was added to a solution of **21** (31.8 mg, 47.1 μmol) in DCM (2.0 mL) at 0 °C. After 23 h of stirring at 0 °C, Na_2CO_3 (5.0 mg) and $MgSO_4$ (5.0 mg) were added to the mixture. The suspension was allowed to warm to room temperature and then passed through a pad of Celite. The filtrate was evaporated, and the residue was purified by column chromatography over silica gel 60N (DCM−ethyl acetate = 20:1) to give **20** as a colorless solid (28.4 mg, 98%). Recrystallization from DCM−Et_2O gave colorless needles. Mp 169−170 °C (sealed capillary) (lit.[9k] 169−170 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35

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(d, J = 6.1 Hz, 3H), 1.36 (d, J = 6.1 Hz, 3H), 1.41 (d, J = 6.1 Hz, 6H), 1.44 (d, J = 6.1 Hz, 6H), 3.44 (s, 3H), 3.45 (s, 3H), 3.96 (s, 3H), 4.54 (sep, J = 6.1 Hz, 1H), 4.58 (sep, J = 6.1 Hz, 1H), 4.70 (sep, J = 6.1 Hz, 1H), 6.74 (s, 1H), 6.97 (s, 1H), 7.03 (d, J = 7.4 Hz, 1H), 7.10 (s, 1H), 7.13 (d, J = 1.8 Hz, 1H), 7.15 (d, J = 8.2 Hz, 1H), 7.18 (s, 1H), 7.20 (dd, J = 1.8 and 8.2 Hz, 1H), 9.23 (d, J = 7.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 21.9, 22.0, 55.2, 55.5, 56.4, 71.2, 71.3, 71.4, 103.4, 105.5, 105.6, 107.8, 110.0, 110.4, 111.0, 112.3, 112.7, 118.1, 119.1, 123.2, 124.1, 124.7, 128.3, 129.5, 134.5, 146.5, 146.7, 147.9, 148.2, 148.5, 150.2, 150.2, 155.6. These physical and spectroscopic data are in good agreement with those previously reported.[9k]

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of all compounds synthesized in this work and results of the variable-temperature ^{1}H NMR experiment on **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: iwao@nagasaki-u.ac.jp.

Notes

The authors declare no competing financial interest.

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