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REGIOSELECTIVE SYNTHESIS OF 2,4-DIFFERENTIALLY ARYLATED PYRROLES AND ITS APPLICATION TO THE SYNTHESIS OF LAMELLARINS

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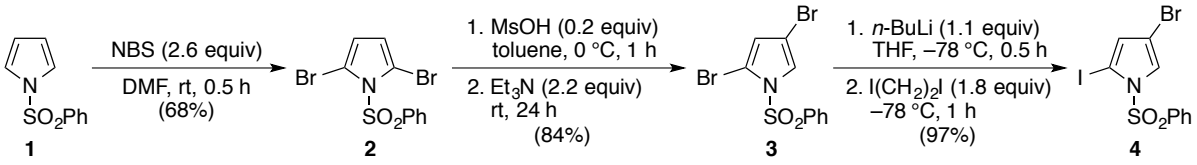
Abstract – An efficient method for the synthesis of 2,4-differentially arylated pyrroles has been developed via stepwise palladium-catalyzed Suzuki–Miyaura coupling of *N*-benzenesulfonyl-4-bromo-2-iodopyrrole with different arylboronic acids. This method has been applied to the new synthesis of the marine natural products lamellarins.

INTRODUCTION

Pyrrole derivatives are found in a wide range of natural products with a broad spectrum of biological activities.[1] They are also embedded in some pharmaceutical agents.[2] In addition, they are utilized as valuable building blocks for the preparation of functional materials bearing unique electronic and photo-physical properties.[3] Therefore, a variety of synthetic methods for *de novo* ring construction and regioselective functionalization of the pyrrole core have been developed.[4] In the last decade, several strategies for the synthesis of 2,4-differentially arylated pyrroles have been reported. They involve the interesting key reactions such as ring formation from 1,3-diaryl-4-nitrobutan-1-ones,[5] carbanion induced pyrrole synthesis from azirines and ketones,[6] ozonolysis of homoallylic ketones followed by Paal–Knorr condensation,[7] gold-catalyzed reaction with *N*-tosyl alkynyl aziridines,[8] rhodium-catalyzed transannulation of *N*-tosyl-1,2,3-triazoles with terminal alkynes[9] or alkenyl alkyl ethers,[10] copper-catalyzed denitrogenative annulation of vinyl azides with aryl acetaldehydes,[11] cyclocondensation of enones with aminoacetonitriles,[12] selenium-catalyzed reaction of γ-nitro substituted carbonyl compounds with carbon monoxide,[13] and gold-catalyzed reaction of *N*-(2,2-dimethoxyethyl)benzamide with terminal alkynes.[14] All of these approaches consist of *de novo* ring construction of the pyrrole core

This paper is dedicated to Professor Dr. Lutz F. Tietze on the occasion of his 75th birthday

and some of them suffer from drawbacks such as hard accessibility of starting materials, multiple synthetic steps, and harsh reaction conditions. Of interest, another approach involving regioselective 2,4-diarylation of preexisting pyrrole core via cross-coupling strategy has not been reported. This is probably due to hard availability of 2,4-dihalogenated pyrrole precursors by direct electrophilic halogenation reactions. Recently, however, we reported that *N*-benzenesulfonyl-2,4-dibromopyrrole (**3**) and *N*-benzenesulfonyl-4-bromo- 2-iodopyrrole (**4**) can be prepared in short steps from readily available *N*-benzenesulfonylpyrrole (**1**) via *N*-benzenesulfonyl-2,5-dibromopyrrole (**2**) intermediate (Scheme 1).[15]



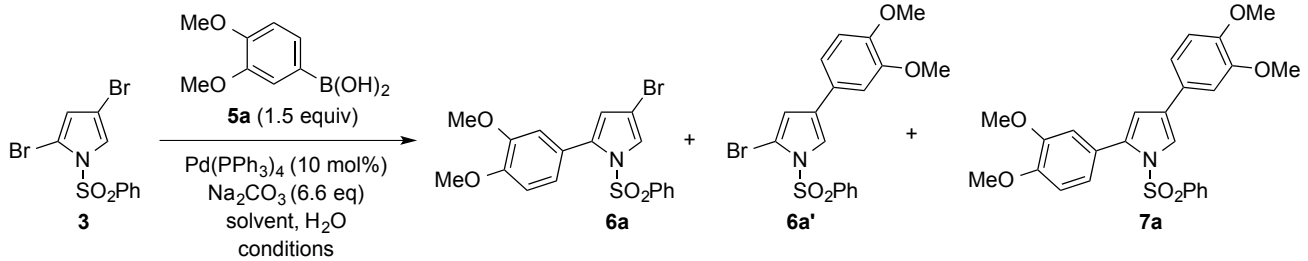
Scheme 1

In this paper, we report a straightforward and regioselective synthesis of 2,4-differentially arylated pyrroles via stepwise Suzuki-Miyaura cross-coupling of *N*-benzenesulfonyl-4-bromo-2-iodopyrrole (**4**). A new synthesis of lamellarin class marine alkaloids using this key reaction will also be described.

RESULTS AND DISCUSSION

Initially, we examined palladium-catalyzed Suzuki–Miyaura cross-coupling of *N*-benzenesulfonyl-2,4-dibromopyrrole (**3**) with 3,4-dimethoxyphenylboronic acid (**5a**) (Table 1). When **3** was treated with 1.5 equiv of **5a** in the presence of 10 mol% of $Pd(PPh_3)_4$ and 6.6 equiv of Na_2CO_3 in a mixture of THF and water at 65 °C for 7 h, a 1:1 mixture of regioisomers (**6a**) and (**6a'**) was obtained in 19% yield and

Table 1. Palladium-catalyzed Suzuki–Miyaura cross-coupling of *N*-benzenesulfonyl-2,4-dibromopyrrole (**3**) with arylboronic acid (**5a**)



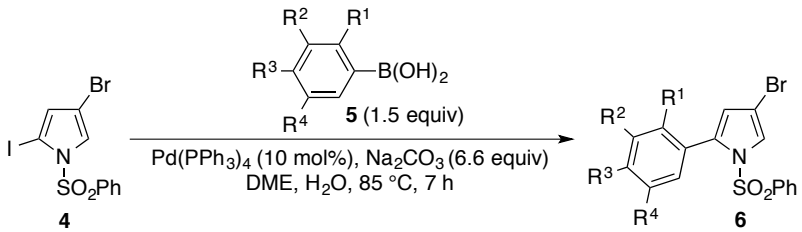
entry	solvent	conditions	**6a** + **6a'** (%)[a]	**6a** : **6a'** [b]	**7a** (%)[a]	**3** (%)[a]
1	THF	65 °C, 7 h	19	1:1	–	61
2	DME	85 °C, 7 h	41	1.4:1	24	26

[a] Isolated yield. [b] The ratio of **6a** to **6a'** were estimated by ^{1}H NMR analysis of the inseparable mixture.

unreacted **3** was recovered in 61% yield after column chromatography (entry 1). Since all attempts to separation of **6a** and **6a'** were failed, the ratio of **6a** to **6a'** was determined by ^{1}H NMR analysis of the mixture. When the solvent was changed to DME and the reaction temperature was raised to 85 °C, a 1.4:1 mixture of **6a** and **6a'** was isolated in 41% yield, accompanied by 2,4-diarylpyrrole (**7a**) (24%) and unreacted **1a** (26%) (entry 2). These results suggested that the reactivity of the bromo groups at C2 and C4 is similar and differentiation of them in the palladium-catalyzed cross-coupling is difficult. Thus, further investigation of the cross-coupling of **3** under different conditions was not performed.

We next examined the cross-coupling of *N*-benzenesulfonyl-4-bromo-2-iodopyrrole (**4**). The results were summarized in Table 2. Of our delight, **4** was reacted with 1.5 equiv of **5a** in the presence of 10 mol% of $Pd(PPh_3)_4$ and 6.6 equiv of Na_2CO_3 in a mixture of DME and water at 85 °C for 7 h, 2-arylated pyrrole (**6a**) was obtained in 83% yield as a single regioisomer (entry 1). Under the similar conditions, a variety of arylboronic acids (**5b–g**), which possess electron-donating, electron-withdrawing, or sterically demanding substituent at the aryl ring, were also reacted to produce the corresponding 2-arylated pyrroles (**6b–g**) selectively in good yields (entries 2–7).

Table 2. Palladium-catalyzed Suzuki–Miyaura cross-coupling of *N*-benzenesulfonyl-4-bromo-2-iodopyrrole (**4**) with arylboronic acids (**5**)



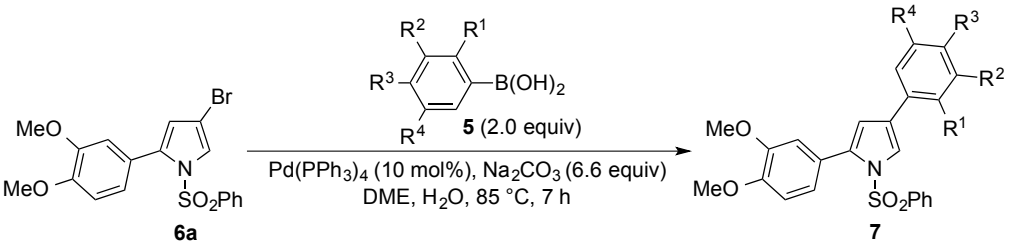
entry	**5**	R^1	R^2	R^3	R^4	**6**	yield (%)[a]
1	**5a**	H	OMe	OMe	H	**6a**	83
2	**5b**	H	H	OMe	H	**6b**	70
3	**5c**	H	H	H	H	**6c**	63
4	**5d**	H	H	Cl	H	**6d**	71
5	**5e**	OMe	H	H	H	**6e**	76
6	**5f**	H	OMe	OMe	OMe	**6f**	73
7	**5g**	H	O*i*-Pr	OMe	H	**6g**	78

[a] Isolated yield.

Since regioselective synthesis of 2-arylated 4-bromopyrroles (**6**) was achieved, we next examined the conversion of **6** to 2,4-differentially arylated pyrroles (**7**) via second cross-coupling. The examples using 4-bromo-2-(3,4-dimethoxyphenyl)pyrroles (**6a**) as a starting material were summarized in Table 3.

When **6a** was treated with 2.0 equiv of arylboronic acids (**5**) in the presence of 10 mol% of $Pd(PPh_3)_4$ and 6.6 equiv of Na_2CO_3 in a mixture of DME and water at 85 °C for 7 h, the corresponding 2,4-differentially arylated pyrroles (**7**) were obtained in 61–74% yields (entries 1–6).

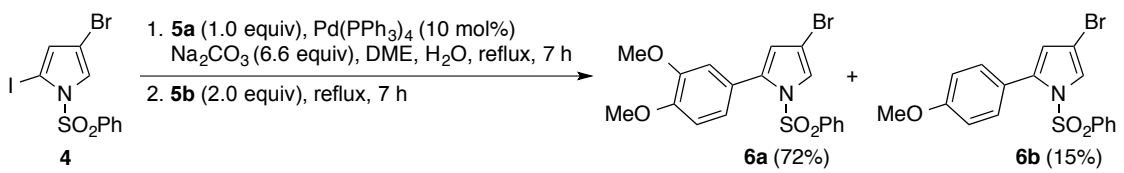
Table 3. Palladium-catalyzed Suzuki–Miyaura cross-coupling of 4-bromo-2-(3,4-dimethoxyphenyl)-pyrrole (**6a**) with arylboronic acids (**5**)



entry	**5**	R^1	R^2	R^3	R^4	**7**	yield (%)
1	**5b**	H	H	OMe	H	**7b**	68
2	**5c**	H	H	H	H	**7c**	66
3	**5d**	H	H	Cl	H	**7d**	71
4	**5e**	OMe	H	H	H	**7e**	66
5	**5f**	H	OMe	OMe	OMe	**7f**	61
6	**5h**	H	OMe	O*i*-Pr	H	**7g**	74

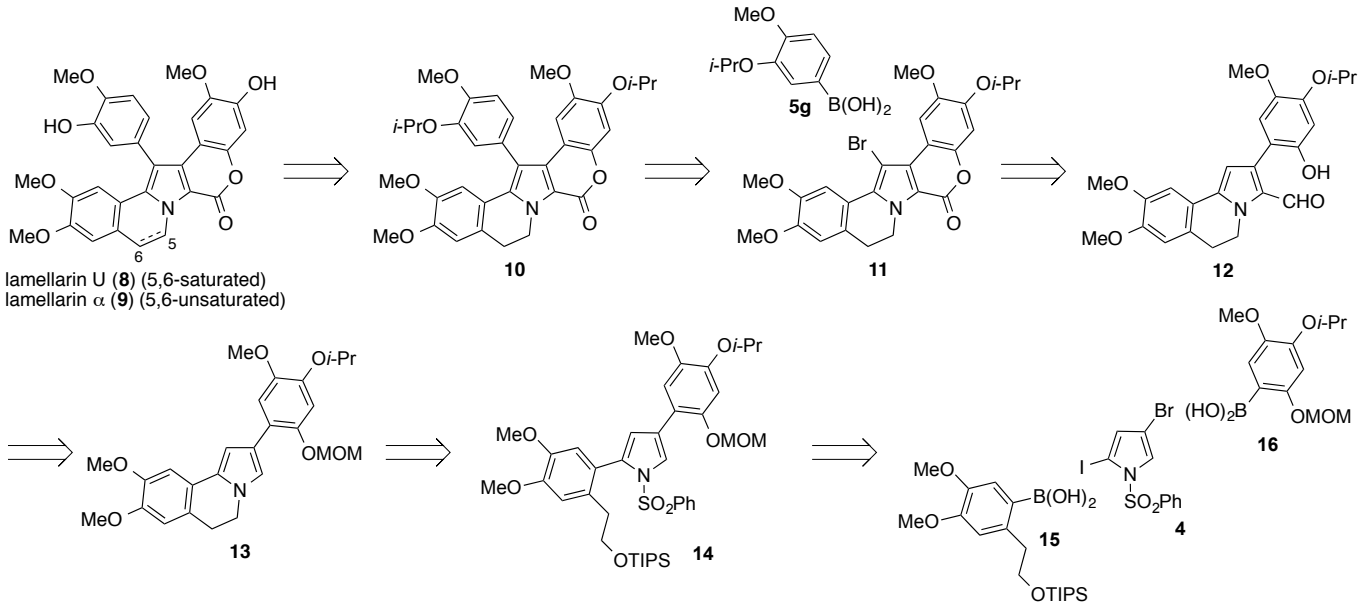
[a] Isolated yield.

The results described above suggested that 2,4-differentially arylated pyrroles could be obtained directly from **4** by sequential treatment with different arylboronic acids in one-pot. Thus, **4** was reacted with 1.0 equiv of **5a** in the presence of 10 mol% of $Pd(PPh_3)_4$ and 6.6 equiv of Na_2CO_3 in a mixture of DME and water under reflux for 7 h and then the mixture was reacted with 2.0 equiv of **5b** under reflux for 7 h in the same pot. However, the expected **7b** was not isolated and only mono-coupling products (**6a**) and (**6b**) were obtained in 72% and 15% yields, respectively (Scheme 2). Although we tested different conditions [solvent (DMF, dioxane) and catalyst ($Pd(dba)_2$/dppf)], **7b** was not produced in all attempts. The reason of the failure is not clear at the present stage.



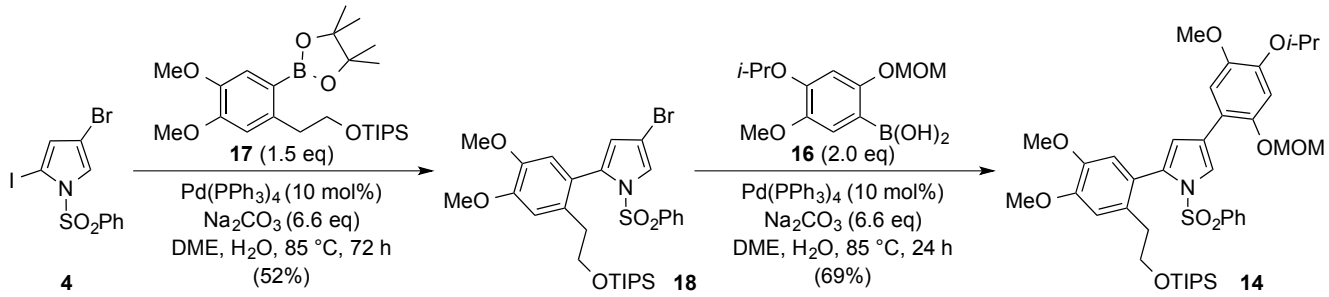
Scheme 2

Having established the method for the synthesis of 2,4-differentially arylated pyrroles, we next applied this method for the synthesis of lamellarin type natural products which possess various interesting biological activities.[16] We selected lamellarins U (**8**) and α (**9**) as the target compounds. These lamellarins exhibit cytotoxicity against several cancer cell lines with IC_{50} values in micromolar range.[17] In addition, their sulfate derivatives are known to possess anti-HIV activity.[18] Our retrosynthetic analysis of **8** and **9** is shown in Scheme 3. The conversion of lamellarin U diisopropyl ether (**10**) to the target lamellarins U (**8**) and α (**9**) has been established by Banwell[19] and Faulkner,[18b] respectively. The compound (**10**) can be obtained from pentacyclic bromide (**11**) and arylboronic acid (**2g**) by Suzuki-Miyaura coupling.[20] The pentacyclic compound (**11**) will be produced by oxidative lactonization[21] of **12** followed by regioselective bromination. Compound (**12**) can be produced by Vilsmeier-Haack reaction of **13** which in turn may be produced by intramolecular alkylation of **14**. Finally, 2,4-diarylpyrrole (**14**) can be prepared from **4** by using stepwise cross-coupling with arylboronic acids (**15**) and (**16**).



Scheme 3

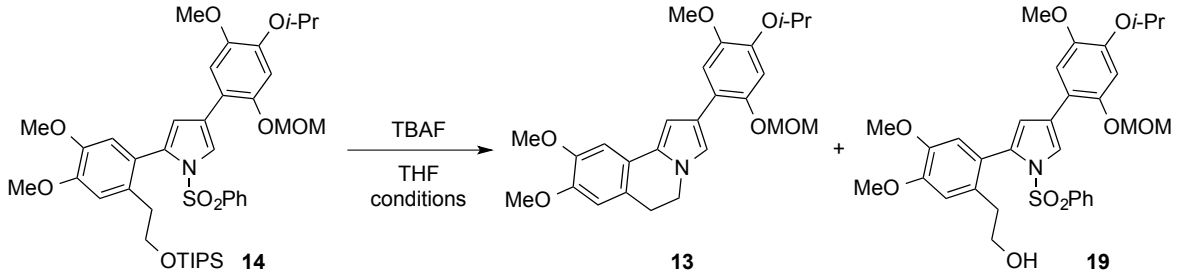
Based on this analysis, we first carried out the synthesis of 2,4-diarylpyrrole (**14**) (Scheme 4). Due to difficulty to produce pure boronic acid (**15**), we employed the corresponding pinacol borate (**17**) for the initial cross-coupling reaction. When **4** was reacted with 1.5 equiv of **17** under the established conditions for 7 h, desired 2-arylated 4-bromopyrrole (**18**) was obtained only in 36% yield. However, the yield of **18** was improved to 52% by elongation of the reaction time (72 h). The second cross-coupling of **18** with arylboronic acid (**16**) proceeded smoothly to produce the 2,4-diarylpyrrole (**14**) in 69% yield.



Scheme 4

Next, we attempted fluoride-induced cyclization of **14** to the tricyclic compound (**13**) (Table 4).[22] When **14** was treated with 1.0 equiv of TBAF in THF at room temperature for 24 h, the desired cyclization product (**13**) was obtained in 27% yield accompanied by a major amount of the simply desilylated alcohol (**19**) (entry 1). Of our delight, when the reaction temperature was elevated to 65 °C, the yield of **13** was increased to 68% (entry 2). The best yield of **13** (87%) was achieved by using 1.2 equiv of TBAF at 65 °C for 48 h (entry 4).

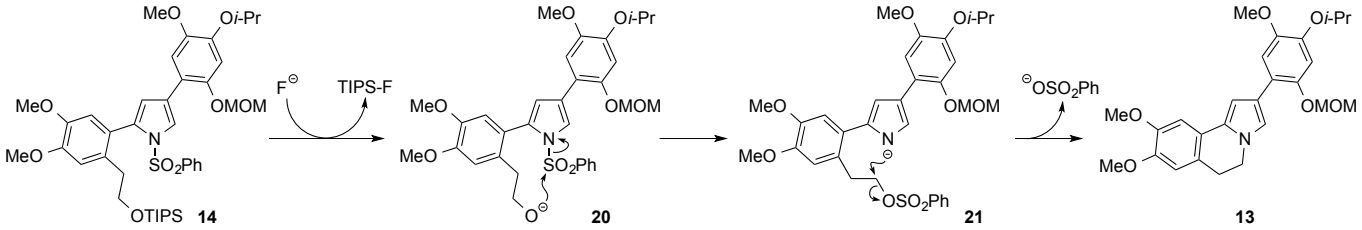
Table 4. Fluoride-induced cyclization of **14**



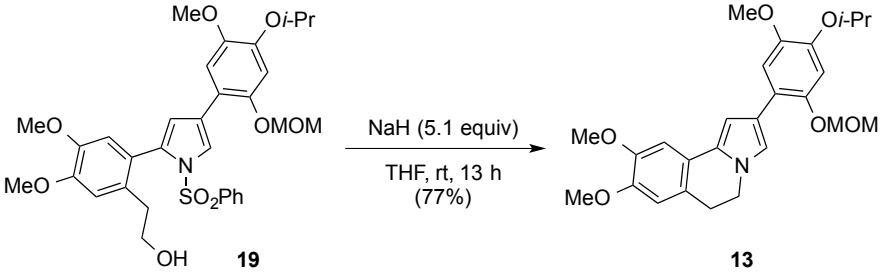
entry	TBAF (equiv)	conditions	**13** (%)[a]	**19** (%)[a]
1	1.0	rt, 24 h	27	60
2	1.0	65 °C, 24 h	68	15
3	1.2	65 °C, 24 h	83	5
4	1.2	65 °C, 48 h	87	4

[a] Isolated yield.

The mechanism of this cyclization may be accounted for by the sequence shown in Scheme 5: (1) deprotection of triisopropylsilyl (TIPS) group of **14** by treatment with TBAF to produce **20**, (2) attack of the resulting alkoxide group onto the phenylsulfonyl group of the pyrrole nitrogen to afford benzenesulfonate (**21**), (3) intramolecular displacement of the sulfonate group by the pyrrolic anion leads to the cyclization product (**13**). The successful cyclization of the alcohol (**19**) to **13** in the presence of NaH supports this mechanism (Scheme 6).

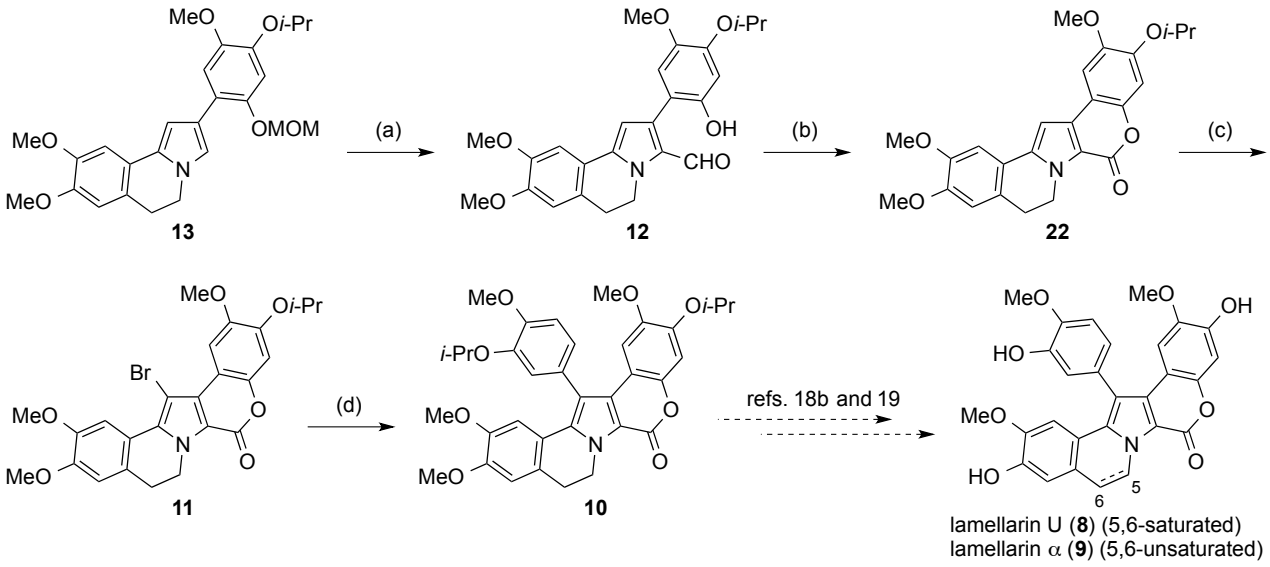


Scheme 5



Scheme 6

Since sufficient amount of 2-aryl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline (**13**) was obtained, we next focused on its conversion to lamellarins U (**8**) and α (**9**) (Scheme 7).



Scheme 7. *Reagents and conditions:* (a) $POCl_3$ (3.0 equiv), DMF, 60 °C, 20 h (96%); (b) $Pd(OAc)_2$ (10 mol%), PPh_3 (30 mol%), PhBr (1.2 equiv), K_2CO_3 (1.1 equiv), DMF, 120 °C, 12 h (68%); (c) NBS (1.03 equiv), DMF, 0 °C, 24 h (93%); (d) $Pd(PPh_3)_4$ (10 mol%), 3-isopropoxy-4-methoxyphenylboronic acid (**5g**) (1.5 equiv), Na_2CO_3 (6.6 equiv), DME, water, 85 °C, 24 h (59%).

Treatment of **13** under Vilsmeier-Haack condition gave C3-selectively formylated compound (**12**) in 96% yield.[21] Under the reaction conditions, methoxymethyl (MOM) protecting group was cleaved. The

phenolic aldehyde (**12**) was converted to the lactone (**22**) by palladium-catalyzed Tamaru oxidation.[21,23] Bromination of **22** with NBS gave regioselectively brominated compound (**11**) in 93% yield. Cross-coupling of **11** with arylboronic acid (**5g**) yielded lamellarin U diisopropyl ether (**10**). Because the conversion of **10** to lamellarins U (**8**) and α (**9**) has been reported,[18b,19] the formal synthesis of these lamellarins were thus achieved.

In conclusion, we have developed a new method for the synthesis of 2,4-differentially arylated pyrrole derivatives by stepwise cross-coupling of *N*-benzenesulfonyl-4-bromo-2-iodopyrrole (**4**). This method was successfully applied for the synthesis of lamellarins U (**8**) and α (**9**).

EXPERIMENTAL

Melting points were determined with a Yanagimoto micro melting points apparatus and are uncorrected. IR spectra were obtained with a Thermo Nicolet Nexus 670 NT FT-IR instrument and are reported in terms of frequency of absorption (cm^{-1}). NMR spectra were recorded on a JEOL JNM-AL400 instrument (400 MHz for ^1H and 100 MHz for ^{13}C) or a Varian NMR System 500PS SN instrument (500 MHz for ^1H and 125 MHz for ^{13}C). Chemical shifts for ^1H NMR are expressed in parts per million (ppm) relative to tetramethylsilane (δ 0.0 ppm). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, dd = double of doublets, t = triplet, sep = septet, m = multiplet, br s = broad signal), coupling constant (Hz), and integration. Chemical shifts for ^{13}C NMR are expressed in ppm relative to tetramethylsilane (δ 0.0 ppm). Data for ^{13}C NMR spectra are reported in terms of chemical shift. High resolution mass spectra were recorded on a JEOL JMS-T100TD (direct analysis in real time mass spectrometry, DARTMS). Column chromatography was conducted on silica gel 60N, 63–210 μm (Kanto Chemical Co., Inc.). Tetrabutylammonium fluoride (TBAF) was purchased from Kanto Chemical Co., Inc. as a 1 M solution in THF and was treated with molecular sieves (4 Å) before use.

Typical procedure for Suzuki–Miyaura cross-coupling of *N*-benzenesulfonyl-2,4-dibromopyrrole (3) with 3,4-dimethoxyphenylboronic acid (5a). Under an argon atmosphere, a mixture of *N*-benzenesulfonyl-2,4-dibromopyrrole (**3**) (44.3 mg, 0.121 mmol), **5a** (33.1 mg, 0.182 mmol), $Pd(PPh_3)_4$ (14.0 mg, 12.1 μmol), Na_2CO_3 (84.7 mg, 0.799 mmol), an appropriate solvent (4.0 mL), and degassed water (0.4 mL) was heated in a sealed tube at solvent-refluxing temperature (65 or 85 °C) for 7 h. After cooling to rt, the mixture was evaporated, and the products were extracted with CH_2Cl_2. The residue was purified by column chromatography over silica gel 60N (hexane–toluene = 1:2 to toluene–EtOAc = 20:1) to give a regioisomeric mixture of **6a** and **6a'**, unreacted **3**, and **7a**. Since all attempts to separation of **6a** and **6a'** by column chromatography were failed, the ratio of **6a** to **6a'** was determined by

integration of ^{1}H NMR absorption of H3 of each regioisomer (δ H3 of **6a**: 6.13; δ H3 of **6a'**: 6.58). The results were shown in Table 1.

***N*-Benzenesulfonyl-4-bromo-2-(3,4-dimethoxyphenyl)-1*H*-pyrrole (6a).** ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.79 (s, 3H), 3.92 (s, 3H), 6.13 (d, J = 2.0 Hz, 1H), 6.68–6.72 (m, 2H), 6.78 (d, J = 8.8 Hz, 1H), 7.31–7.37 (m, 4H), 7.47 (d, J = 2.0 Hz, 1H), 7.50–7.55 (m, 1H).

***N*-Benzenesulfonyl-2-bromo-4-(3,4-dimethoxyphenyl)-1*H*-pyrrole (6a').** ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.90 (s, 3H), 3.93 (s, 3H), 6.58 (d, J = 2.2 Hz, 1H), 6.87 (d, J = 8.3 Hz, 1H), 6.96 (d, J = 2.0 Hz, 1H), 7.01 (dd, J = 2.0 and 8.3 Hz, 1H), 7.53–7.57 (m, 2H), 7.63–7.68 (m, 1H), 7.67 (d, J = 2.2 Hz, 1H), 7.95–7.99 (m, 2H).

***N*-Benzenesulfonyl-2,4-bis(3,4-dimethoxyphenyl)-1*H*-pyrrole (7a).** Colorless semisolid. IR (KBr): 1511, 1258, 1235, 1163, 1133, 1102, 1025 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.82 (s, 3H), 3.90 (s, 3H), 3.93 (s, 3H), 3.94 (s, 3H), 6.42 (d, J = 2.0 Hz, 1H), 6.78 (d, J = 1.8 Hz, 1H), 6.78 (dd, J = 1.8 and 8.6 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H), 7.05 (d, J = 2.0 Hz, 1H), 7.09 (dd, J = 2.0 and 8.3 Hz, 1H), 7.30–7.35 (m, 2H), 7.38–7.42 (m, 2H), 7.48–7.52 (m, 1H), 7.67 (d, J = 2.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.9, 55.9, 56.0, 56.0, 108.8, 110.0, 111.5, 114.0, 114.4, 117.9, 118.4, 123.5, 123.5, 126.3, 127.2, 127.3, 128.8, 133.6, 136.7, 138.4, 147.7, 148.4, 149.3, 149.3. HRMS (*m*/*z*) Calcd for $C_{26}H_{26}NO_6S$ [(M+H)$^+$]: 480.14808. Found: 480.15043.

Typical procedure for Suzuki-Miyaura cross-coupling of *N*-benzenesulfonyl-4-bromo-2-iodopyrrole (4) with arylboronic acids (5). Under an argon atmosphere, a mixture of *N*-benzenesulfonyl-4-bromo-2-iodopyrrole (**4**) (50.0 mg, 0.121 mmol), **5** (0.182 mmol), $Pd(PPh_3)_4$ (14.0 mg, 12.1 μmol), Na_2CO_3 (84.7 mg, 0.799 mmol), DME (4.0 mL), and degassed water (0.4 mL) was heated in a sealed tube at 85 °C for 7 h. After cooling to rt, the mixture was evaporated, and the products were extracted with CH_2Cl_2. 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 to give **6**. The results were summarized in Table 2.

***N*-Benzenesulfonyl-4-bromo-2-(3,4-dimethoxyphenyl)-1*H*-pyrrole (6a).** According to the typical procedure, 3,4-dimethoxyphenylboronic acid (**5a**) (33.1 mg, 0.182 mmol) was reacted. After chromatographic purification over silica gel 60N (toluene–EtOAc = 20:1), **6a** was obtained as a pale purple solid (42.2 mg, 83%). Recrystallization from CH_2Cl_2–hexane gave pale purple granules. Mp 143.5–144.5 °C. IR (KBr): 1517, 1449, 1371, 1251, 1188, 1128, 1028, 613 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.79 (s, 3H), 3.92 (s, 3H), 6.13 (d, J = 2.0 Hz, 1H), 6.68–6.72 (m, 2H), 6.78 (d, J = 8.8 Hz, 1H), 7.31–7.37 (m, 4H), 7.47 (d, J = 2.0 Hz, 1H), 7.50–7.55 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.8, 55.9, 100.9, 110.0, 114.3, 117.6, 122.3, 122.3, 123.7, 127.4, 128.9, 133.9, 136.4, 138.0, 147.8, 149.6. HRMS (*m*/*z*) Calcd for $C_{18}H_{17}BrNO_4S$ [(M+H)$^+$]: 422.00617. Found: 422.00816.

***N*-Benzenesulfonyl-4-bromo-2-(4-methoxyphenyl)-1*H*-pyrrole (6b).** According to the typical procedure, 4-methoxyphenylboronic acid (**5b**) (27.7 mg, 0.182 mmol) was reacted. After chromatographic purification over silica gel 60N (hexane–EtOAc = 5:1), **6b** was obtained as a pale gray solid (33.2 mg, 70%). Recrystallization from CH_2Cl_2–hexane gave colorless granules. Mp 114–115 °C. IR (KBr): 1470, 1365, 1255, 1186, 1170, 1135, 817, 589 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.84 (s, 3H), 6.10 (d, J = 1.9 Hz, 1H), 6.80–6.84 (m, 2H), 7.06–7.11 (m, 2H), 7.30–7.36 (m, 4H), 7.45 (d, J = 1.9 Hz, 1H), 7.48–7.56 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 101.0, 113.0, 117.6, 122.2, 122.2, 127.3, 128.9, 132.3, 133.9, 136.4, 138.1, 160.1. HRMS (*m/z*) Calcd for $C_{17}H_{15}BrNO_3S$ [$(M+H)^+$]: 391.99560. Found: 391.99503.

***N*-Benzenesulfonyl-4-bromo-2-phenyl-1*H*-pyrrole (6c).** According to the typical procedure, phenylboronic acid (**5c**) (22.2 mg, 0.182 mmol) was reacted. After chromatographic purification over silica gel 60N (hexane–EtOAc = 7:1), **6c** was obtained as a colorless oil (27.8 mg, 63%). IR (KBr): 1448, 1378, 1238, 1187, 1131, 1090, 1058, 731, 606 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.15 (d, J = 1.9 Hz, 1H), 7.14–7.19 (m, 2H), 7.26–7.41 (m, 7H), 7.47 (d, J = 1.9 Hz, 1H), 7.49–7.55 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 101.1, 117.9, 122.5, 127.3, 127.5, 128.8, 128.9, 130.0, 131.0, 134.0, 136.5, 138.0. HRMS (*m/z*) Calcd for $C_{16}H_{13}BrNO_2S$ [$(M+H)^+$]: 361.98504. Found: 361.98415.

***N*-Benzenesulfonyl-4-bromo-2-(4-chlorophenyl)-1*H*-pyrrole (6d).** According to the typical procedure, 4-chlorophenylboronic acid (**5d**) (28.5 mg, 0.182 mmol) was reacted. After chromatographic purification over silica gel 60N (hexane–toluene = 2:1 to toluene–EtOAc = 20:1), **6d** was obtained as a colorless oil (34.3 mg, 71%). IR (KBr): 1378, 1187, 1131, 1091, 1057, 725, 618, 541 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.15 (d, J = 1.9 Hz, 1H), 7.09–7.13 (m, 2H), 7.26–7.30 (m, 2H), 7.33–7.39 (m, 4H), 7.47 (d, J = 1.9 Hz, 1H), 7.51–7.58 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 101.2, 118.3, 122.9, 127.2, 127.8, 128.5, 129.1, 132.1, 134.2, 135.1, 135.2, 137.9. HRMS (*m/z*) Calcd for $C_{16}H_{12}BrClNO_2S$ [$(M+H)^+$]: 395.94606. Found: 395.94694.

***N*-Benzenesulfonyl-4-bromo-2-(2-methoxyphenyl)-1*H*-pyrrole (6e).** According to the typical procedure, 2-methoxyphenylboronic acid (**5e**) (27.7 mg, 0.182 mmol) was reacted. After chromatographic purification over silica gel 60N (hexane–EtOAc = 7:1), **6e** was obtained as a pale brown oil (35.9 mg, 76%). IR (KBr): 1473, 1449, 1375, 1251, 1235, 1186, 1132, 1091, 1058, 753, 729, 607 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.55 (s, 3H), 6.14 (d, J = 1.9 Hz, 1H), 6.80 (d, J = 8.3 Hz, 1H), 6.87 (t, J = 7.5 Hz, 1H), 6.94 (dd, J = 1.9 and 7.5 Hz, 1H), 7.33–7.42 (m, 5H), 7.46 (d, J = 1.9 Hz, 1H), 7.51–7.57 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.2, 100.7, 110.3, 117.9, 119.1, 119.5, 121.8, 127.4, 128.8, 130.9, 132.0, 133.0, 133.7, 138.4, 158.6. HRMS (*m/z*) Calcd for $C_{17}H_{15}BrNO_3S$ [$(M+H)^+$]: 391.99560. Found: 391.99286.

***N*-Benzenesulfonyl-4-bromo-2-(3,4,5-trimethoxyphenyl)-1*H*-pyrrole (6f).** According to the typical procedure, 3,4,5-trimethoxyphenylboronic acid (**5f**) (38.6 mg, 0.182 mmol) was reacted. After chromatographic purification over silica gel 60N (hexane–EtOAc = 4:1), **6f** was obtained as a yellow oil (39.8 mg, 73%). IR (KBr): 1584, 1509, 1449, 1375, 1337, 1239, 1186, 1128, 608, 589 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.75 (s, 6H), 3.89 (s, 3H), 6.17 (d, J = 1.9 Hz, 1H), 6.35 (s, 2H), 7.31–7.39 (m, 4H), 7.49 (d, J = 1.9 Hz, 1H), 7.50–7.55 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.1, 61.0, 100.6, 108.5, 117.4, 122.4, 125.0, 127.5, 128.9, 133.9, 136.2, 137.9, 138.6, 152.2. HRMS (*m/z*) Calcd for $C_{19}H_{19}BrNO_5S$ [$(M+H)^+$]: 452.01673. Found: 452.01751.

***N*-Benzenesulfonyl-4-bromo-2-(3-isopropoxy-4-methoxyphenyl)-1*H*-pyrrole (6g).** According to the typical procedure, 3-isopropoxy-4-methoxyphenylboronic acid (**5g**)[24] (38.2 mg, 0.182 mmol) was reacted. After successive purification by column chromatography over silica gel 60N (hexane–EtOAc = 4:1) and column chromatography over silica gel 60N (toluene–EtOAc = 50:1), **6g** was obtained as a yellow oil (42.4 mg, 78%). IR (KBr): 1514, 1479, 1375, 1254, 1186, 1128, 1091, 1058, 1022, 728, 605, 587 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.35 (d, J = 6.1 Hz, 6H), 3.89 (s, 3H), 4.43 (sep, J = 6.1 Hz, 1H), 6.11 (d, J = 1.9 Hz, 1H), 6.67 (dd, J = 2.0 and 8.3 Hz, 1H), 6.77 (d, J = 2.0 Hz, 1H), 6.77 (d, J = 8.3 Hz, 1H), 7.29–7.38 (m, 4H), 7.45 (d, J = 1.9 Hz, 1H), 7.48–7.54 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 56.0, 71.3, 100.9, 110.7, 117.6, 118.3, 122.3, 122.3, 123.8, 127.3, 128.9, 133.9, 136.6, 138.0, 146.2, 150.9. HRMS (*m/z*) Calcd for $C_{20}H_{21}BrNO_4S$ [$(M+H)^+$]: 450.03747. Found: 450.03822.

Typical procedure for Suzuki-Miyaura cross-coupling of *N*-benzenesulfonyl-4-bromo-2-(3,4-dimethoxyphenyl)pyrrole (6a) with arylboronic acids (5). Under an argon atmosphere, a mixture of *N*-benzenesulfonyl-4-bromo-2-(3,4-dimethoxyphenyl)pyrrole (**6a**) (51.1 mg, 0.121 mmol), arylboronic acid (**5**) (0.242 mmol), $Pd(PPh_3)_4$ (14.0 mg, 12.1 μmol), Na_2CO_3 (84.7 mg, 0.799 mmol), DME (4.0 mL), and degassed water (0.4 mL) was heated in a sealed tube at 85 °C for 7 h. After cooling to rt, the mixture was evaporated, and the products were extracted with with CH_2Cl_2. 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 to give **7**. The results were summarized in Table 3.

***N*-Benzenesulfonyl-2-(3,4-dimethoxyphenyl)-4-(4-methoxyphenyl)-1*H*-pyrrole (7b).** According to the typical procedure, 4-methoxyphenylboronic acid (**5b**) (36.8 mg, 0.242 mmol) was reacted. After chromatographic purification over silica gel 60N (hexane–EtOAc = 2:1 to 1:1), **7b** was obtained as a pale green oil (37.1 mg, 68%). IR (KBr): 1510, 1448, 1364, 1252, 1175, 1094, 1027, 728, 599 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.81 (s, 3H), 3.83 (s, 3H), 3.93 (s, 3H), 6.41 (d, J = 2.0 Hz, 1H), 6.76–6.83 (m, 3H), 6.89–6.94 (m, 2H), 7.28–7.34 (m, 2H), 7.37–7.41 (m, 2H), 7.44–7.52 (m, 3H), 7.65 (d, J = 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 55.8, 55.9, 110.1, 114.0, 114.3, 114.4, 118.4, 123.5,

123.6, 125.9, 126.7, 127.2, 127.2, 128.8, 133.5, 136.7, 138.5, 147.7, 149.3, 158.9. HRMS (*m*/*z*) Calcd for $C_{25}H_{24}NO_5S$ [$(M+H)^+$]: 450.13752. Found: 450.13914.

***N*-Benzenesulfonyl-2-(3,4-dimethoxyphenyl)-4-phenyl-1*H*-pyrrole (7c).** According to the typical procedure, phenylboronic acid (**5c**) (29.5 mg, 0.242 mmol) was reacted. After chromatographic purification over silica gel 60N (hexane–EtOAc = 3:1), **7c** was obtained as a pale brown oil (33.4 mg, 66%). IR (KBr): 1503, 1364, 1253, 1176, 1097, 1026, 729, 601 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.81 (s, 3H), 3.93 (s, 3H), 6.46 (d, J = 2.0 Hz, 1H), 6.76–6.83 (m, 3H), 7.24–7.41 (m, 7H), 7.47–7.56 (m, 3H), 7.75 (d, J = 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.9, 55.9, 110.1, 113.9, 114.4, 119.2, 123.5, 123.6, 125.5, 127.1, 127.2, 127.4, 128.8, 128.8, 133.3, 133.6, 136.8, 138.4, 147.8, 149.3. HRMS (*m*/*z*) Calcd for $C_{24}H_{22}NO_4S$ [$(M+H)^+$]: 420.12695. Found: 420.12527.

***N*-Benzenesulfonyl-4-(4-chlorophenyl)-2-(3,4-dimethoxyphenyl)-1*H*-pyrrole (7d).** According to the typical procedure, 4-chlorophenylboronic acid (**5d**) (37.8 mg, 0.242 mmol) was reacted. After chromatographic purification over silica gel 60N (hexane–EtOAc = 3:1 to 2:1), **7d** was obtained as a pale brown solid (38.9 mg, 71%). Recrystallization from CH_2Cl_2–hexane gave a colorless powder. Mp 140–141 °C. IR (KBr): 1500, 1376, 1233, 1174, 1095, 1028, 808, 564 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.81 (s, 3H), 3.93 (s, 3H), 6.41 (d, J = 2.0 Hz, 1H), 6.77 (dd, J = 1.7 and 8.6 Hz, 1H), 6.77 (d, J = 1.7 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 7.29–7.41 (m, 6H), 7.44–7.54 (m, 3H), 7.73 (d, J = 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.8, 55.9, 110.1, 113.6, 114.4, 119.2, 123.3, 123.6, 126.2, 126.7, 127.3, 128.8, 129.0, 131.9, 132.7, 133.7, 136.9, 138.3, 147.8, 149.4. HRMS (*m*/*z*) Calcd for $C_{24}H_{21}ClNO_4S$ [$(M+H)^+$]: 454.08798. Found: 454.08975.

***N*-Benzenesulfonyl-2-(3,4-dimethoxyphenyl)-4-(2-methoxyphenyl)-1*H*-pyrrole (7e).** According to the typical procedure, 2-methoxyphenylboronic acid (**5e**) (36.8 mg, 0.242 mmol) was reacted. After chromatographic purification over silica gel 60N (hexane–EtOAc = 3:1), **7e** was obtained as a colorless solid (35.9 mg, 66%). Recrystallization from CH_2Cl_2–hexane gave colorless granules. Mp 126–130.5 °C (dec). IR (KBr): 1487, 1370, 1257, 1180, 1093, 1023, 729, 607 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.81 (s, 3H), 3.93 (s, 3H), 3.95 (s, 3H), 6.57 (d, J = 1.9 Hz, 1H), 6.80 (s, 3H), 6.94–7.01 (m, 2H), 7.21–7.27 (m, 1H), 7.28–7.34 (m, 2H), 7.38–7.43 (m, 2H), 7.45–7.52 (m, 2H), 7.99 (d, J = 1.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.4, 55.8, 55.9, 110.0, 111.2, 114.5, 115.5, 120.8, 121.9, 122.6, 123.1, 123.6, 123.8, 127.2, 128.0, 128.7, 133.5, 135.4, 138.6, 147.7, 149.2, 156.6. HRMS (*m*/*z*) Calcd for $C_{25}H_{24}NO_5S$ [$(M+H)^+$]: 450.13752. Found: 450.13550.

***N*-Benzenesulfonyl-2-(3,4-dimethoxyphenyl)-4-(3,4,5-trimethoxyphenyl)-1*H*-pyrrole (7f).** According to the typical procedure, 3,4,5-trimethoxyphenylboronic acid (**5f**) (51.3 mg, 0.242 mmol) was reacted. After chromatographic purification over silica gel 60N (hexane–EtOAc = 2:1), **7f** was obtained as a colorless solid (37.7 mg, 61%). Recrystallization from CH_2Cl_2–hexane gave colorless granules.

Mp 158–161 °C. IR (KBr): 1590, 1508, 1463, 1372, 1239, 1162, 1125, 1062, 1028, 1003, 726, 604 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.82 (s, 3H), 3.87 (s, 3H), 3.91 (s, 6H), 3.94 (s, 3H), 6.42 (d, J = 2.0 Hz, 1H), 6.74(s, 2H), 6.78 (d, J = 1.8 Hz, 1H), 6.78 (dd, J = 1.8 and 8.7 Hz, 1H), 6.81 (d, J = 8.7 Hz, 1H), 7.30–7.36 (m, 2H), 7.38–7.42 (m, 2H), 7.49–7.54 (m, 1H), 7.70 (d, J = 2.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.9, 55.9, 56.2, 61.0, 102.8, 110.0, 113.9, 114.4, 119.0, 123.4, 123.6, 127.3, 127.4, 128.8, 129.1, 133.7, 136.7, 137.4, 138.3, 147.8, 149.4, 153.6. HRMS (*m*/*z*) Calcd for $C_{27}H_{28}NO_7S$ [$(M+H)^+$]: 510.15865. Found: 510.15776.

***N*-Benzenesulfonyl-2-(3,4-dimethoxyphenyl)-4-(4-isopropoxy-3-methoxyphenyl)-1*H*-pyrrole (7g).** According to the typical procedure, 4-isopropoxy-3-methoxyphenylboronic acid (**5h**)[24] (50.8 mg, 0.242 mmol) was reacted. After chromatographic purification over silica gel 60N (hexane–EtOAc = 2:1 to 1:1), **7g** was obtained as a pale yellow oil (45.7 mg, 74%). IR (KBr): 1510, 1368, 1252, 1175, 1140, 1098, 1027, 728, 602 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.38 (d, J = 6.1 Hz, 6H), 3.81 (s, 3H), 3.91 (s, 3H), 3.93 (s, 3H), 4.54 (sep, J = 6.1 Hz, 1H), 6.42 (d, J = 2.0 Hz, 1H), 6.76–6.80 (m, 2H), 6.81 (d, J = 8.9 Hz, 1H), 6.90 (d, J = 8.9 Hz, 1H), 7.04–7.08 (m, 2H), 7.29–7.35 (m, 2H), 7.37–7.42 (m, 2H), 7.46–7.52 (m, 1H), 7.67 (d, J = 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 55.9, 55.9, 56.1, 71.6, 109.6, 110.1, 114.0, 114.4, 116.3, 118.0, 118.5, 123.5, 123.6, 126.7, 127.2, 127.4, 128.8, 133.6, 136.7, 138.5, 146.7, 147.8, 149.3, 150.7. HRMS (*m*/*z*) Calcd for $C_{28}H_{30}NO_6S$ [$(M+H)^+$]: 508.17938. Found: 508.17958.

2-(2-Bromo-4,5-dimethoxyphenyl)ethanol (23). Under an argon atmosphere, a solution of NBS (5.36 g, 30.1 mmol) in DMF (20 mL) was added dropwise to a solution of 2-(3,4-dimethoxyphenyl)ethanol (5.00 g, 27.4 mmol) in DMF (10 mL) at 0 °C. After stirring for 22 h, the reaction mixture was quenched with water at the same temperature and allowed to warm to rt. The products were extracted with EtOAc 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–EtOAc = 1:1) to give **23** as a colorless solid (6.45 g, 90%). IR (KBr) 3216, 1509, 1382, 1256, 1217, 1164, 1053, 859, 802 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.46 (br s, 1H), 2.96 (t, J = 6.7 Hz, 2H), 3.84–3.89 (m, 8H), 6.78 (s, 1H), 7.02 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 39.0, 56.1, 56.2, 62.4, 113.8, 114.4, 115.7, 129.7, 148.3, 148.4. HRMS (*m*/*z*) Calcd for $C_{10}H_{14}BrO_3$ [$(M+H)^+$]: 261.01263. Found: 261.01146. These spectroscopic data are in good agreement with those previously reported.[25]

[2-(2-Bromo-4,5-dimethoxyphenyl)ethoxy]triisopropylsilane (24). Under an argon atmosphere, TIPSCl (4.37 mL, 20.4 mmol) was added at rt to a solution of **23** (4.88 g, 18.7 mmol) and imidazole (1.52 g, 22.3 mmol) in DMF (30 mL). After stirring for 2 h, the reaction mixture was quenched with saturated aqueous NH_4Cl. The products were extracted with EtOAc 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–EtOAc = 40:1) to give **24** as a pale yellow oil (7.32 g, 94%). IR (KBr) 1510, 1464, 1258, 1221, 1164, 1102 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.01–1.12 (m, 21H), 2.92 (t, J = 6.8 Hz, 2H), 3.85 (s, 6H), 3.88 (t, J = 6.8 Hz, 2H), 6.83 (s, 1H), 6.99 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.9, 18.0, 39.4, 55.9, 56.2, 62.9, 114.2, 114.3, 115.4, 130.6, 148.0, 148.1. HRMS (*m/z*) Calcd for $C_{19}H_{34}BrO_3Si$ [$(M+H)^+$]: 417.14606. Found: 417.14826.

2-{4,5-Dimethoxy-2-[2-(triisopropylsiloxy)ethyl]phenyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (17). Under an argon atmosphere, a pentane solution of *n*-butyllithium (1.53 M, 790 μL, 1.21 mmol) was added dropwise to a solution of **24** (500 mg, 1.20 mmol) in THF (15 mL) at –78 °C. After stirring for 15 min, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (245 μL, 1.20 mmol) was added as a neat liquid and the mixture was then allowed to warm to rt and stirred for an additional 2 h. The mixture was quenched with saturated aqueous NH_4Cl and concentrated. The products were extract with CH_2Cl_2. The extract was washed successively with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography over silica gel 60N (hexane–EtOAc = 7:1) to give **12** as a colorless oil (494 mg, 89%). IR (KBr) 1601, 1519, 1465, 1353, 1216, 1145, 1099 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.01–1.11 (m, 21H), 1.32 (s, 12H), 3.11 (t, J = 7.0 Hz, 2H), 3.85 (t, J = 7.0 Hz, 2H), 3.88 (s, 3H), 3.90 (s, 3H), 6.80 (s, 1H), 7.28 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.0, 18.0, 24.8, 39.0, 55.6, 56.0, 65.8, 83.3, 113.8, 118.2, 140.4, 146.5, 150.8. HRMS (*m/z*) Calcd for $C_{25}H_{46}BO_5Si$ [$(M+H)^+$]: 465.32076. Found: 465.32290.

***N*-Benzenesulfonyl-4-bromo-2-{2-[2-(triisopropylsiloxy)ethyl]-4,5-dimethoxyphenyl}-1*H*-pyrrole (18).** Under an argon atmosphere, a mixture of **4** (412 mg, 1.00 mmol), **17** (697 mg, 1.50 mmol), $Pd(PPh_3)_4$ (116 mg, 0.100 mmol), Na_2CO_3 (700 mg, 6.60 mmol), DME (33 mL), and degassed water (3.3 mL) was refluxed for 72 h. After cooling to rt, the mixture was evaporated and the products were extracted with CH_2Cl_2. The extract was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified successively by column chromatography over silica gel 60N (toluene to toluene–EtOAc = 20:1) and column chromatography over silica gel 60N (hexane–EtOAc = 5:1 to 3:1) to give **18** as a pale brown oil (321 mg, 52%). IR (KBr): 1516, 1378, 1235, 1187, 1137, 1116, 1091, 1055 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.96–1.08 (m, 21H), 2.28–2.39 (m, 2H), 3.59–3.75 (m, 2H), 3.62 (s, 3H), 3.91 (s, 3H), 6.11 (d, J = 1.9 Hz, 1H), 6.23 (s, 1H), 6.81 (s, 1H), 7.35–7.41 (m, 4H), 7.52 (d, J = 1.9 Hz, 1H), 7.54–7.60 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.9, 18.0, 36.7, 55.6, 55.8, 64.3, 100.1, 112.1, 115.0, 118.1, 120.9, 121.3, 127.8, 129.0, 133.7, 133.8, 134.0, 138.2, 145.9, 149.5. HRMS (*m/z*) Calcd for $C_{29}H_{41}BrNO_5SSi$ [$(M+H)^+$]: 622.16581. Found: 622.16655.

***N*-Benzenesulfonyl-4-[4-isopropoxy-5-methoxy-2-(methoxymethoxy)phenyl]-2-{2-[2-(triisopropylsiloxy)ethyl]-4,5-dimethoxyphenyl}-1*H*-pyrrole (14).** Under an argon atmosphere, a mixture of **18** (308 mg, 0.495 mmol), **16**[24] (267 mg, 0.989 mmol), $Pd(PPh_3)_4$ (57.2 mg, 49.5 μmol), Na_2CO_3 (346 mg,

3.26 mmol), DME (18 mL), and degassed water (1.8 mL) was refluxed for 24 h. After cooling to rt, the mixture was evaporated and the products were extracted with CH_2Cl_2. 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 (toluene–EtOAc = 20:1 to 10:1) to give **14** as a pale brown solid (263 mg, 69%). Recrystallization from Et_2O–hexane gave pale brown needles. Mp 113.5–114.5 °C. IR (KBr): 1510, 1372, 1210, 1175, 1149, 1096, 1027 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.93–1.02 (m, 21H), 1.39 (d, J = 6.1 Hz, 6H), 2.37–2.52 (m, 2H), 3.53 (s, 3H), 3.63 (s, 3H), 3.63–3.78 (m, 2H), 3.84 (s, 3H), 3.92 (s, 3H), 4.56 (sep, J = 6.1 Hz, 1H), 5.21 (s, 2H), 6.29 (s, 1H), 6.50 (d, J = 1.9 Hz, 1H), 6.85 (s, 1H), 6.89 (s, 1H), 7.00 (s, 1H), 7.34–7.39 (m, 2H), 7.43–7.47 (m, 2H), 7.51–7.56 (m, 1H), 7.96 (d, J = 1.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.9, 18.0, 18.0, 22.1, 36.9, 55.6, 55.8, 56.1, 56.7, 64.3, 71.8, 95.6, 105.8, 112.0, 112.3, 115.1, 115.4, 115.8, 120.4, 122.2, 122.6, 127.6, 128.8, 132.8, 133.6, 133.7, 138.9, 145.7, 145.8, 146.8, 148.7, 149.2. HRMS (*m/z*) Calcd for $C_{41}H_{58}NO_9SSi$ [$(M+H)^+$]: 768.36015. Found: 768.35959.

Fluoride-induced cyclization of 14. Under an argon atmosphere, a mixture of **14** (50 mg, 65.1 μmol), an appropriate amount of TBAF, and THF (5 mL) was treated in a sealed tube under the conditions described in Table 4. The reaction mixture was quenched with water and evaporated. The products were extracted with CH_2Cl_2, 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–EtOAc = 2:1 to 1:2) to give **13** and **19**. The results were shown in Table 4.

5,6-Dihydro-2-[4-isopropoxy-5-methoxy-2-(methoxymethoxy)phenyl]-8,9-dimethoxypyrrolo[2,1-*a*]-isoquinoline (13). Pale brown needles. Mp 138.5–139.5 °C (CH_2Cl_2–Et_2O). IR (KBr): 1536, 1508, 1272, 1235, 1206, 1148, 1025, 997 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.38 (d, J = 6.1 Hz, 6H), 3.03 (t, J = 6.6 Hz, 2H), 3.51 (s, 3H), 3.89 (s, 3H), 3.89 (s, 3H), 3.95 (s, 3H), 4.09 (t, J = 6.6 Hz, 2H), 4.52 (sep, J = 6.1 Hz, 1H), 5.16 (s, 2H), 6.69 (br s, 1H), 6.71 (s, 1H), 6.85 (s, 1H), 7.08 (s, 1H), 7.09 (s, 1H), 7.12 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.1, 29.0, 44.3, 56.0, 56.1, 56.1, 56.7, 71.8, 96.0, 101.4, 105.9, 106.7, 111.4, 112.3, 118.6, 120.0, 120.5, 122.3, 122.9, 129.7, 145.5, 145.9, 147.3, 147.8, 148.3. HRMS (*m/z*) Calcd for $C_{26}H_{32}NO_6$ [$(M+H)^+$]: 454.22296. Found: 454.22286.

***N*-Benzenesulfonyl-2-[2-(2-hydroxyethyl)-4,5-dimethoxyphenyl]-4-[4-isopropoxy-5-methoxy-2-(methoxymethoxy)phenyl]-1*H*-pyrrole (19).** Pale brown semisolid. IR (KBr): 3530, 1509, 1366, 1262, 1216, 1174, 1148, 1024 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.39 (d, J = 6.1 Hz, 6H), 2.48–2.59 (m, 2H), 3.51 (s, 3H), 3.62 (s, 3H), 3.66–3.74 (m, 2H), 3.86 (s, 3H), 3.94 (s, 3H), 4.55 (sep, J = 6.1 Hz, 1H), 5.19 (d, J = 6.4 Hz, 1H), 5.21 (d, J = 6.4 Hz, 1H), 6.29 (s, 1H), 6.54 (d, J = 1.8 Hz, 1H), 6.79 (s, 1H), 6.87 (s, 1H), 7.01 (s, 1H), 7.36–7.41 (m, 2H), 7.45–7.49 (m, 2H), 7.53–7.58 (m, 1H), 7.92 (d, J = 1.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.1, 36.5, 55.6, 55.9, 56.3, 56.8, 63.2, 71.8, 95.8, 105.8, 111.8,

112.2, 115.3, 115.4, 116.1, 120.4, 122.6, 122.9, 127.5, 128.9, 132.7, 132.8, 133.7, 138.9, 145.8, 146.0, 147.0, 148.7, 149.4. HRMS (*m/z*) Calcd for $C_{32}H_{38}NO_9S$ [$(M+H)^+$]: 612.22673. Found: 612.22954.

Treatment of 19 with NaH. Under an argon atmosphere, to a suspension of NaH (60% dispersion in mineral oil, 10.0 mg, ca. 0.250 mmol) in THF (3.0 mL) was added **19** (30 mg, 49.0 μmol) at rt. After stirring for 13 h at rt, the mixture was quenched with saturated aqueous NH_4Cl and the products were extracted with CH_2Cl_2. 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–EtOAc = 2:1) to give **13** as a pale brown solid (17.2 mg, 77%).

5,6-Dihydro-2-(2-hydroxy-4-isopropoxy-5-methoxyphenyl)-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline-3-carbaldehyde (12). Phosphorus oxychloride (27.7 μL, 0.298 mmol) was added dropwise to DMF (2.5 mL) at 0 °C. After stirring for 1 h at 0 °C, a solution of **13** (45.0 mg, 99.2 μmol) in DMF (2.0 mL) was added and then the mixture was allowed to warm to rt. The reaction mixture was heated at 60 °C and stirring was continued for 20 h. After cooling to rt, the mixture was quenched with saturated aqueous $NaHCO_3$ and the products were extracted with EtOAc. 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–EtOAc = 1:1) to give **12** as a brown semisolid (41.8 mg, 96%). This compound was rather unstable and was used for the next reaction without further purification. IR (KBr): 3431, 1640, 1504, 1426, 1383, 1234, 1209, 1144, 1109 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.42 (d, J = 6.1 Hz, 6H), 3.07 (t, J = 6.9 Hz, 2H), 3.82 (s, 3H), 3.93 (s, 3H), 3.93 (s, 3H), 4.57 (sep, J = 6.1 Hz, 1H), 4.70 (t, J = 6.9 Hz, 2H), 5.53 (br s, 1H), 6.57 (s, 1H), 6.64 (s, 1H), 6.78 (s, 1H), 6.79 (s, 1H), 7.08 (s, 1H), 9.49 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 28.2, 42.4, 56.1, 56.2, 56.9, 71.3, 103.8, 105.9, 107.5, 111.1, 115.3, 119.4, 125.8, 127.4, 134.3, 138.2, 143.2, 144.1, 147.8, 148.4, 148.8, 149.9, 179.9. HRMS (*m/z*) Calcd for $C_{25}H_{28}NO_6$ [$(M+H)^+$]: 438.19166. Found: 438.19230.

8,9-Dihydro-3-isopropoxy-2,11,12-trimethoxy-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]-isoquinolin-6-one (22). Under an argon atmosphere, a mixture of **12** (36.5 mg, 83.4 μmol), bromobenzene (10.5 μL, 0.100 mmol), $Pd(OAc)_2$ (1.8 mg, 8.3 μmol), triphenylphosphine (6.6 mg, 25 μmol), K_2CO_3 (12.7 mg, 91.8 μmol), and DMF (3.7 mL) was heated in a sealed tube at 120 °C for 12 h. After cooling to rt, the mixture was diluted with water and the products were extracted with EtOAc. 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–EtOAc = 1:1) to give **22** as a colorless solid (24.9 mg, 68%). Recrystallization from CH_2Cl_2–hexane gave a colorless powder. Mp 190.5–191.5 °C. IR (KBr): 1696, 1495, 1444, 1423, 1274, 1242, 1215, 1182, 1148, 1034 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.43 (d, J = 6.1 Hz, 6H), 3.12 (t, J = 6.9 Hz, 2H), 3.94 (s, 3H), 3.97 (s, 3H), 3.98 (s, 3H), 4.59

(sep, *J* = 6.1 Hz, 1H), 4.73 (t, *J* = 6.9 Hz, 2H), 6.80 (s, 1H), 6.80 (s, 1H), 6.96 (s, 1H), 7.19 (s, 1H), 7.19 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 28.3, 42.3, 56.1, 56.2, 56.5, 71.6, 95.4, 103.7, 104.7, 107.5, 110.1, 111.2, 115.1, 119.9, 125.8, 131.2, 140.1, 146.1, 147.3, 147.7, 148.4, 149.8, 155.5. HRMS (*m*/*z*) Calcd for $C_{25}H_{26}NO_6$ [$(M+H)^+$]: 436.17601. Found: 436.17338.

14-Bromo-8,9-dihydro-3-isopropoxy-2,11,12-trimethoxy-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo-[2,1-*a*]isoquinolin-6-one (11). A solution of NBS (4.2 mg, 24 μmol) in DMF (0.5 mL) was added dropwise to a solution of **22** (10.0 mg, 23.0 μmol) in DMF (0.5 mL) at 0 °C. After stirring for 24 h at 0 °C, the mixture was diluted with water and the products were extracted with CH_2Cl_2. 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 (toluene–EtOAc = 3:1) to give **11** as a pale gray solid (11.0 mg, 93%). Recrystallization from CH_2Cl_2–hexane gave a colorless powder. Mp 210–220 °C (dec). IR (KBr): 1701, 1508, 1417, 1268, 1241, 1207, 1164, 1043 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.43 (d, *J* = 6.1 Hz, 6H), 3.06 (t, *J* = 6.7 Hz, 2H), 3.95 (s, 3H), 3.97 (s, 3H), 3.99 (s, 3H), 4.60 (sep, *J* = 6.1 Hz, 1H), 4.77 (t, *J* = 6.7 Hz, 2H), 6.82 (s, 1H), 6.94 (s, 1H), 8.16 (s, 1H), 8.25 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.9, 29.0, 42.6, 56.0, 56.2, 56.4, 71.5, 86.7, 103.4, 104.9, 109.0, 109.6, 111.1, 114.2, 119.2, 127.2, 127.5, 135.3, 146.0, 146.7, 147.7, 147.8, 149.6, 154.8. HRMS (*m*/*z*) Calcd for $C_{25}H_{25}BrNO_6$ [$(M+H)^+$]: 514.08652. Found: 514.08448.

8,9-Dihydro-3-isopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-2,11,12-trimethoxy-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (lamellarin U diisopropyl ether) (10). Under an argon atmosphere, a mixture of **11** (9.9 mg, 19 μmol), **5g** (6.1 mg, 29 μmol), $Pd(PPh_3)_4$ (2.2 mg, 1.9 μmol), Na_2CO_3 (13.5 mg, 0.127 mmol), DME (1.0 mL), and degassed water (100 μL) was heated in a sealed tube at 85 °C for 24 h. After cooling to rt, the solvent was evaporated *in vacuo* and the residue was extracted with CH_2Cl_2. 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 (toluene–EtOAc = 5:1) and subsequently by MPLC (30 g Redi*Sep* Rf Gold® reversed-phase C18 column) (CH_3CN) to give **10** as a colorless solid (6.8 mg, 59%). Recrystallization from CH_2Cl_2–hexane gave a colorless powder. Mp 210.5–211.5 °C. [lit.[18b,19] Mp 213–214 °C]. IR (KBr): 1694, 1509, 1484, 1439, 1416, 1270, 1242, 1213, 1167, 1043 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33 (d, *J* = 6.1 Hz, 3H), 1.34 (d, *J* = 6.1 Hz, 3H), 1.39 (d, *J* = 6.1 Hz, 6H), 3.12 (t, *J* = 6.8 Hz, 2H), 3.37 (s, 3H), 3.44 (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 4.47–4.59 (m, 2H), 4.73–4.87 (m, 2H), 6.67 (s, 1H), 6.72 (s, 1H), 6.76 (s, 1H), 6.92 (s, 1H), 7.05 (d, *J* = 1.6 Hz, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 7.09 (dd, *J* = 1.6 and 8.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.8, 21.9, 22.0, 28.7, 42.4, 55.1, 55.5, 55.9, 56.3, 71.3, 71.4, 103.5, 104.9, 108.6, 110.4, 111.0, 112.7, 113.7, 114.9, 117.9, 120.1, 123.7, 126.6, 128.0, 128.3, 135.9, 146.0, 146.6, 147.1, 147.5, 148.1,

148.9, 150.1, 155.7. HRMS (*m/z*) Calcd for $C_{35}H_{38}NO_8$ [$(M+H)^+$]: 600.25974. Found: 600.25719. These physical and spectroscopic data are in good agreement with those previously reported.[18b,19]

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