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A GENERAL METHOD FOR THE SYNTHESIS OF *N*-UNSUBSTITUTED 3,4-DIARYLPYRROLE-2,5-DICARBOXYLATES

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Abstract – A general method for the synthesis of *N*-unsubstituted 3,4-diarylpyrrole-2,5-dicarboxylates (**3**) has been developed. The key reactions involved are the Hinsberg-type synthesis of dimethyl *N*-benzyl-3,4-dihydroxypyrrole-2,5-dicarboxylate (**6**) followed by palladium-catalyzed Suzuki-Miyaura coupling of its bis-triflate derivative (**7**). The *N*-benzyl protecting group of the resulting 3,4-diarylpyrrole-2,5-dicarboxylates (**8**) is cleanly removed under hydrogenolytic or solvolytic conditions.

INTRODUCTION

Pyrrole moieties possessing two aryl groups at the 3- and 4-positions appear frequently in marine natural products, such as lamellarins,[1] lukianols,[2] ningalins,[3] storniamides,[4] polycitones,[5] purpurone,[6] halitulin,[7] and dictyodendrins.[8] These natural products have attracted considerable attention due to their unique structures and highly useful biological activities. As the result, a number of synthetic approaches have been developed so far.[1b,9] These syntheses can be divided into two classes depending on the construction method of 3,4-diarylpyrrole scaffold. The first employed *de novo* ring construction of the pyrrole ring *via* titanium-mediated reaction,[10] biomimetic synthesis,[11] *N*-ylide-mediated cyclization,[12] intra- or intermolecular [3+2] cycloaddition,[13,14] Diels-Alder cyclization of azadiene,[15] vinylogous iminium ion-mediated ring formation,[16,17] and aminoquinone-mediated cyclization.[18] The second utilized regioselective arylation of preexisting pyrrole core by palladium-catalyzed cross-coupling and related reactions.[19]

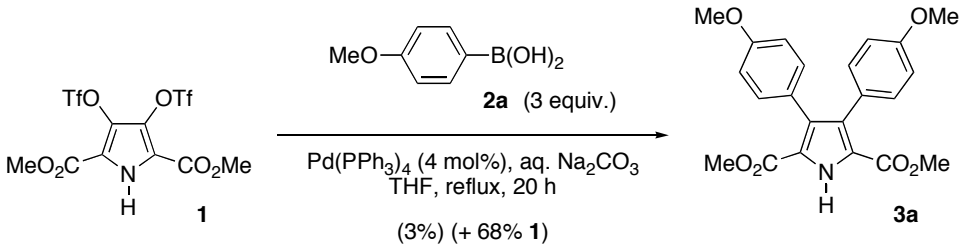
In 2003, we reported a short and flexible route to 3,4-diarylpyrrole marine alkaloids.[20] The key reactions involved are the synthesis of *N*-substituted dimethyl 3,4-dihydroxypyrrole-2,5-dicarboxylates *via*

This paper is dedicated to Professor Emeritus, Tohoku University, Keiichiro Fukumoto on the occasion of his 75th birthday.

Hinsberg-type reaction followed by palladium-catalyzed Suzuki-Miyaura coupling of their bis-triflate derivatives. This strategy has been successfully applied to the total synthesis of biologically significant lamellarins D, L, N and α 20-sulfate.[21] In this paper, we report further application of this strategy for the synthesis of *N*-unsubstituted dimethyl 3,4-diarylpyrrole-2,5-dicarboxylates.

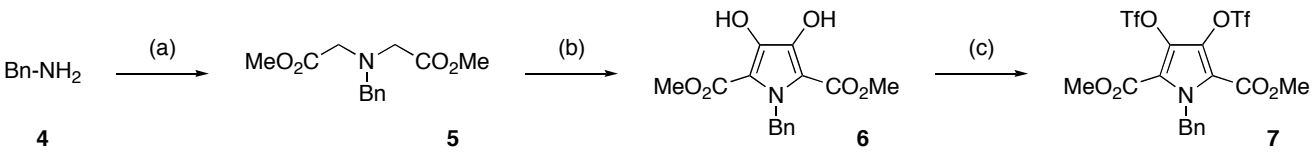
RESULTS AND DISCUSSION

Initially, we examined Suzuki-Miyaura coupling of dimethyl 3,4-bis(trifluoromethanesulfonyloxy)-pyrrole-2,5-dicarboxylate (**1**) with 4-methoxyphenylboronic acid (**2a**). Under the previously established conditions,[20] bis-triflate (**1**) was treated with **2a** (3.0 equiv.) and aqueous Na_2CO_3 in the presence of a catalytic amount of $Pd(PPh_3)_4$ in refluxing THF for 20 h, however, only trace amount (3%) of the desired 3,4-bis(4-methoxyphenyl)pyrrole (**3a**) was obtained and unreacted **1** was recovered in 68% yield (Scheme 1).



Scheme 1

This result suggested *N*-protection of bis-triflate (**1**) may be indispensable for the smooth cross-coupling.[22] Thus, we decided to test the cross-coupling of *N*-benzyl protected bis-triflate (**7**). The synthesis of **7** is shown in Scheme 2. Benzylamine (**4**) was alkylated with methyl bromoacetate to give *N*-benzyliminodiacetate (**5**) in 90% yield. Hinsberg reaction of **5** with dimethyl oxalate using NaH as a base afforded 3,4-dihydroxypyrrole (**6**) in 88% yield. The conventional conditions using NaOMe in MeOH afforded **6** in much lower yield (58%).[23] Triflation of **6** with trifluoromethanesulfonic anhydride in pyridine gave the bis-triflate (**7**) in 96% yield.

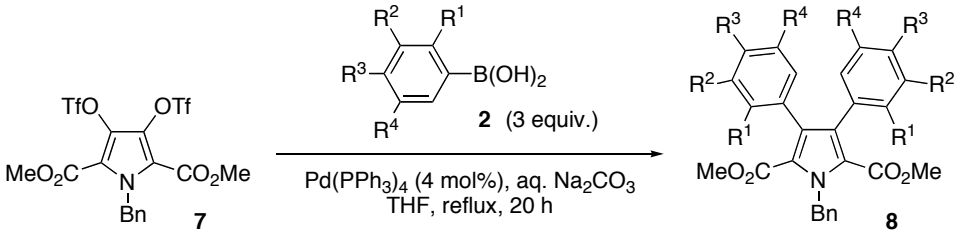


Scheme 2. *Reagents and conditions:* (a) $BrCH_2CO_2Me$ (2.1 equiv.), $NaHCO_3$, MeCN, reflux, 2 h (90%). (b) $(CO_2Me)_2$, NaH, THF, reflux, 3 h (88%). (c) Tf_2O (2.2 equiv.), pyridine, 0 °C, 1 h (96%).

The results of the cross-coupling of **7** with a variety of arylboronic acids (**2a-i**) are summarized in Table 1.

In contrast to the reaction of **1**, **7** reacted with **2a-i** quite smoothly to give 3,4-diarylated products **8a-i** in excellent yields. The reactions were not affected by electronic or steric effects of the substituents on the aryl ring of the boronic acids.

Table 1. Palladium-catalyzed cross-coupling of bis-triflate (**7**) with arylboronic acids (**2**)



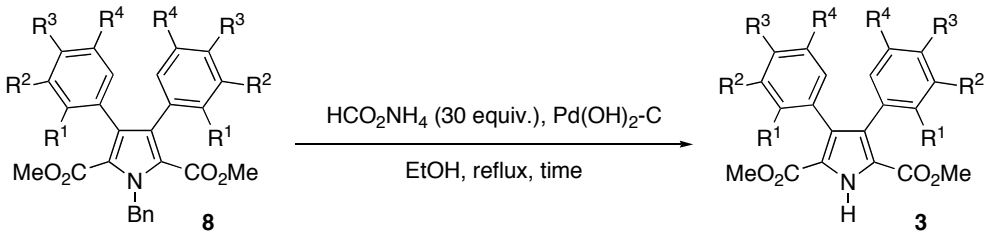
entry	**2**	R^1	R^2	R^3	R^4	**8**	yield (%)[a]
1	**2a**	H	H	OMe	H	**8a**	99
2	**2b**	H	H	H	H	**8b**	98
3	**2c**	H	H	O*i*-Pr	H	**8c**	quant.
4	**2d**	H	H	F	H	**8d**	99
5	**2e**	H	H	Cl	H	**8e**	98
6	**2f**	OMe	H	H	H	**8f**	97
7	**2g**	H	OMe	OMe	H	**8g**	99
8	**2h**	H	OMe	OMe	OMe	**8h**	96
9	**2i**	OMOM	H	OMe	OMe	**8i**	99

[a] Isolated yield.

Having established the cross-coupling reactions of **7**, we next carried out debenzylation of **8** to produce *N*-unsubstituted 3,4-diarylpyrroles (**3**). The results are summarized in Table 2. 3,4-Diarylpyrroles (**8a-i**) were treated with Pearlman's catalyst[24] and ammonium formate in refluxing EtOH to give the debenzylated compounds (**3**) in excellent yields, except for compound (**8e**). In this case, hydrogenolysis of C-Cl bonds on the aryl groups also proceeded and 3,4-diphenylpyrrole (**3b**) was isolated (entry 5). Fortunately, however, deprotection of **8e** was cleanly effected under solvolytic conditions[25] (Scheme 3).

Since an efficient synthesis of 3,4-symmetrically arylated pyrroles (**3a-i**) was established, we next examined the stepwise cross-coupling with different arylboronic acids to produce 3,4-unsymmetrically arylated pyrrole (**11**) (Scheme 4). Thus, the bis-triflate (**7**) was treated with 1.0 equiv. of 3,4-dimethoxyphenylboronic acid (**2g**) to give the mono-arylated pyrrole (**9**) in 75% yield accompanied by 8% of **8g**. The second cross-coupling of **9** with 4-methoxyphenylboronic acid (**2a**) gave the 3,4-differentially arylated pyrrole (**10**) in excellent yield. Hydrogenolysis of **10** gave the deprotected **11** in 69% yield.

Table 2. Debenzylation of 3,4-diarylpyrrole (**8**)

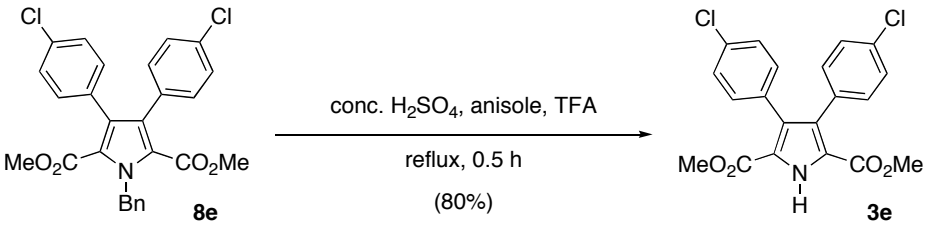


entry	**8**	R^1	R^2	R^3	R^4	time (h)	**3**	yield (%)[a]
1	**8a**	H	H	OMe	H	1	**3a**	97
2	**8b**	H	H	H	H	1	**3b**	quant.
3	**8c**	H	H	O*i*-Pr	H	3	**3c**	95
4	**8d**	H	H	F	H	3	**3d**	89
5	**8e**	H	H	Cl	H	2	**3e**	0[b]
6	**8f**	OMe	H	H	H	1	**3f**	88
7	**8g**	H	OMe	OMe	H	1.5	**3g**	95
8	**8h**	H	OMe	OMe	OMe	2	**3h**	96
9	**8i**	OMOM	H	OMe	OMe	1	**3i**	94

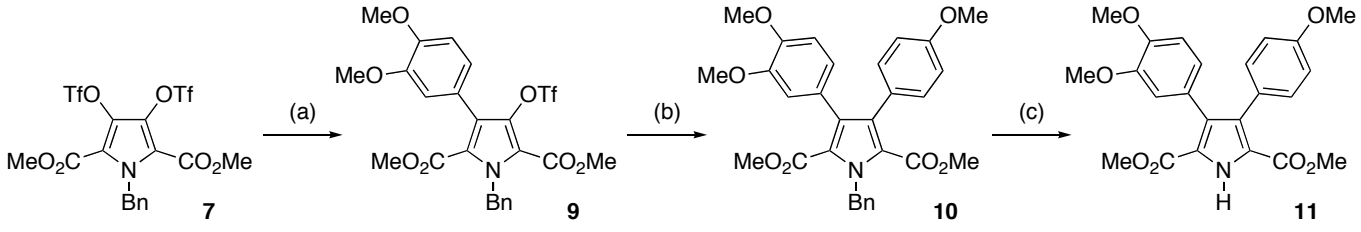
[a] Isolated yield.

[b] Dimethyl 3,4-diphenylpyrrole-2,5-dicarboxylate (**3b**) was obtained (85%).

Finally, we briefly describe the utility of our procedure for the synthesis of natural products. Recently,

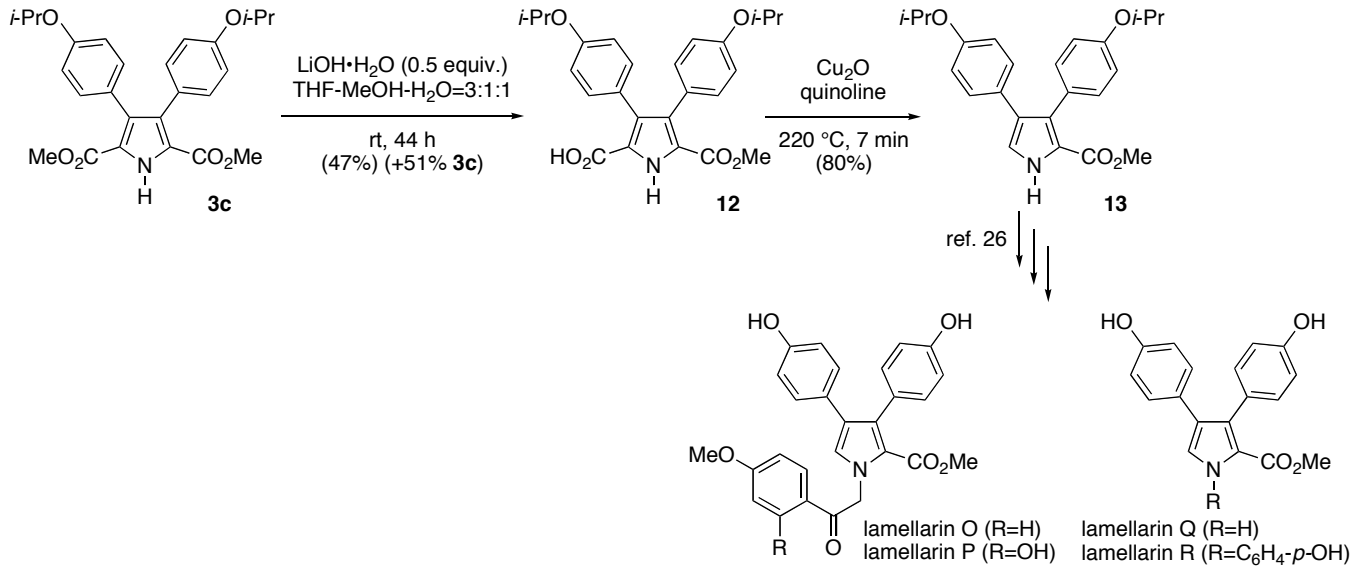


Scheme 3



Scheme 4. *Reagents and conditions:* (a) **2g** (1 equiv.), $Pd(PPh_3)_4$ (2 mol%), aq. Na_2CO_3, THF, reflux, 4 h (**9**: 75%, **8g**: 8%). (b) **2a** (1.5 equiv.), $Pd(PPh_3)_4$ (4 mol%), aq. Na_2CO_3, THF, reflux, 20 h (96%). (c) HCO_2NH_4 (30 equiv.), $Pd(OH)_2$-C, EtOH, reflux, 3 h (69%).

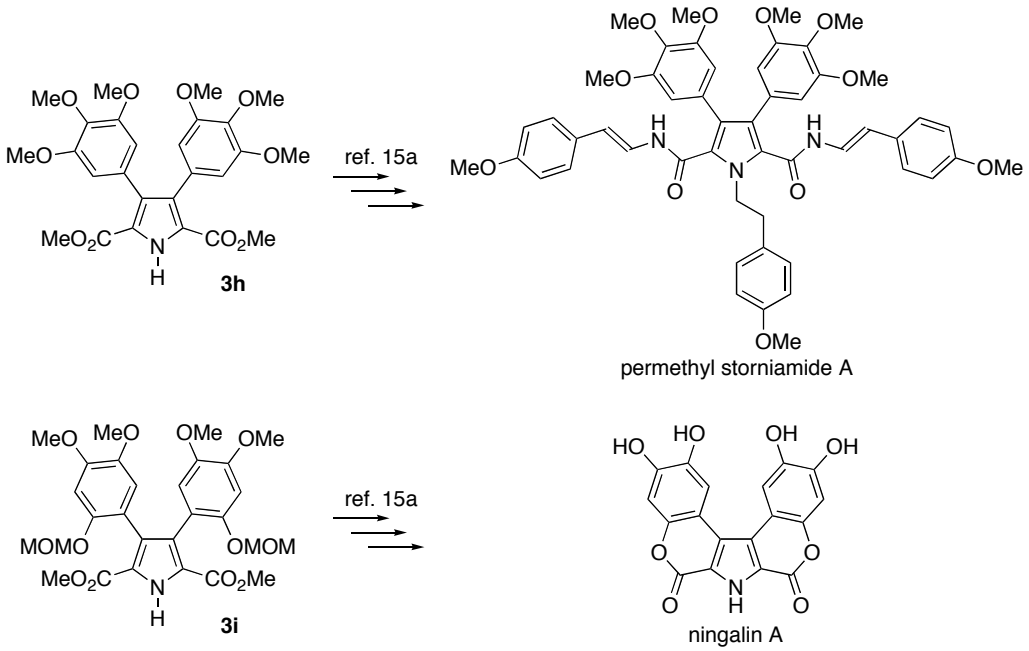
we reported the short-step synthesis of lamellarins O, P, Q, and R using **13** as a common intermediate.[26] This key intermediate was prepared in two steps from **3c** by partial hydrolysis and decarboxylation (Scheme 5).



Scheme 5

It is also noteworthy, that the 3,4-diarylpyrroles (**3h**) and (**3i**) were utilized as the key intermediates in the synthesis of permethyl storniamide A and ningalin A, respectively, by Boger *et al.*[15a] (Scheme 6).

In conclusion, we have developed an efficient procedure to produce *N*-unsubstituted



Scheme 6

3,4-diarylpyrrole-2,5-dicarboxylates. This method can be utilized for the synthesis of 3,4-diarylpyrrole marine natural products and their analogues.

EXPERIMENTAL

Melting points were determined with a Yanagimoto micro melting points apparatus and are uncorrected. IR spectra were obtained with a Perkin-Elmer System 2000 instrument. NMR spectra were recorded on a JEOL JNM-AL400 instrument (400 MHz for ^{1}H and 100 MHz for ^{13}C) using tetramethylsilane as an internal standard. High resolution mass spectra were recorded on a JEOL JMS-700N spectrometer. Flash chromatography was conducted on Silica Gel 60N, 40-50 μm (Kanto Chemical Co., Inc.). Column chromatography was conducted on Silica Gel 60N, 63-210 μm (Kanto Chemical Co., Inc.) or Chromatorex NH-DM1020 silica gel (Fuji Silysia Chemical Ltd.). Dry THF were distilled from Na-benzophenone ketyl under argon immediately before use.

Dimethyl 3,4-bis(trifluoromethanesulfonyloxy)pyrrole-2,5-dicarboxylate (1)

Under an argon atmosphere, a suspension of dimethyl oxalate (2.36 g, 20.0 mmol) and NaH (60% dispersion in mineral oil, 1.63 g, ca. 40.8 mmol, prewashed with hexane) in THF (10 mL) was heated to reflux. To this suspension was added dropwise a solution of dimethyl iminodiacetate (1.61 g, 10.0 mmol) in THF (30 mL) under reflux. After being refluxed for additional 3 h, the reaction mixture was cooled to rt, quenched with acetic acid (3 mL) and evaporated under reduced pressure. The residue was poured into ice-cold water and the suspension was acidified with 2 M aqueous HCl to pH 3. The precipitated solid was collected by filtration, washed with water, and dried under reduced pressure to give dimethyl 3,4-dihydroxypyrrole-2,5-dicarboxylate as pale yellow powder (1.50 g, 70%). Recrystallization from MeOH gave pale yellow powder. Mp 180-210 °C (decomp) (sealed capillary); IR (KBr): 3399, 3302, 1701, 1565, 1500, 1438, 1311, 1194, 1157 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6): δ 3.84 (s, 6H), 7.53 (s, 2H), 9.89 (s, 1H); ^{13}C NMR (100 MHz, acetone-d_6): δ 51.7, 109.9, 138.5, 162.4. *Anal*. Calcd for $C_8H_9NO_6$: C, 44.66; H, 4.22; N, 6.51. Found: C, 44.90; H, 4.33; N, 6.30.

Under an argon atmosphere, trifluoromethanesulfonic anhydride (3.70 mL, 22.6 mmol) was added as a neat liquid to a solution of dimethyl 3,4-dihydroxypyrrole-2,5-dicarboxylate (2.19 g, 10.2 mmol) in pyridine (20 mL) at 0 °C. After being stirred for 3 h, the reaction mixture was quenched with water at the same temperature and allowed to warm to rt. The product was extracted with Et_2O and the extract was washed successively with 3 M aqueous HCl, water, and brine, and dried over Na_2SO_4. The solvent was removed by evaporation and the residue was purified by column chromatography over Silica Gel 60N (hexane-EtOAc=2:1) to give **1** as colorless solid (4.27 g, 87%). Recrystallization from Et_2O-hexane gave colorless needles. Mp 122-122.5 °C; IR (KBr): 3307, 3273, 1738, 1714, 1439, 1297,

1228, 1135 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.00 (s, 6H), 10.42 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 52.9, 115.9, 118.4 (q, *J*= 320 Hz), 127.4, 158.0. *Anal.* Calcd for $C_{10}H_7F_6NO_{10}S_2$: C, 25.06; H, 1.47; N, 2.92. Found: C, 24.99; H, 1.22; N, 2.87.

Suzuki-Miyaura coupling of bis-triflate (1) with arylboronic acids (2a).

Under an argon atmosphere, a degassed solution of Na_2CO_3 (700 mg, 6.60 mmol) in water (2.0 mL) was added to a solution of **1** (479 mg, 1.00 mmol), **2a** (456 mg, 3.00 mmol) and $Pd(PPh_3)_4$ (46.2 mg, 40.0 μmol) in THF (20 mL) at rt and the mixture was refluxed for 20 h. The mixture was cooled to rt and evaporated under reduced pressure. The residue was diluted with water, adjusted to pH 3 with 1 M aqueous HCl, and saturated with NaCl. The products were extracted with CH_2Cl_2 and the extract was washed successively with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified successively by flash chromatography over Silica Gel 60N (toluene-EtOAc=5:1~EtOAc) and column chromatography over Chromatorex NH-DM1020 silica gel (hexane-EtOAc=3:1) to give **3a** as colorless solid (12.0 mg, 3%) and unreacted **1** (326 mg, 68%).

Dimethyl *N*-benzyliminodiacetate (5)

Methyl bromoacetate (90 mL, 0.951 mol) was added as a neat liquid to a suspension of benzylamine (**4**) (49 mL, 0.449 mol) and $NaHCO_3$ (159 g, 1.89 mol) in MeCN (700 mL) at rt. The mixture was refluxed for 2 h and then cooled to rt. After removal of inorganic salts by filtration, the filtrate was evaporated under reduced pressure. The residue was purified by distillation (112 °C/ 0.2 mmHg) to give **5** as pale yellow oil (101 g, 90%). IR (neat): 1746, 1454, 1436, 1202, 1010 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.56 (s, 4H), 3.70 (s, 6H), 3.91 (s, 2H), 7.23-7.29 (m, 1H), 7.29-7.35 (m, 2H), 7.35-7.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.5, 54.0, 58.0, 127.4, 128.4, 129.0, 138.1, 171.6. HREIMS *m/z*. Calcd for $C_{13}H_{17}NO_4$ (M^+): 251.1158. Found: 251.1155.

Dimethyl *N*-benzyl-3,4-dihydroxypyrrole-2,5-dicarboxylate (6)

Under an argon atmosphere, a suspension of dimethyl oxalate (14.9 g, 126 mmol) and NaH (60% dispersion in mineral oil, 10.0 g, ca. 250 mmol, prewashed with hexane) in THF (80 mL) was heated to reflux. To this suspension was added dropwise a solution of **5** (15.7 g, 62.5 mmol) in THF (150 mL) under reflux. After being refluxed for additional 3 h, the reaction mixture was cooled to rt, quenched with acetic acid (16 mL) and evaporated under reduced pressure. The residue was poured into ice-cold water and the suspension was acidified with 2 M aqueous HCl to pH 3. The precipitated solid was collected by filtration, washed with water, and dried under reduced pressure to give **6** as pale brown powder (16.8 g, 88%). Recrystallization from MeOH gave pale brown powder. Mp 166.5-167 °C; IR

(KBr): 3365, 1692, 1658, 1509, 1461, 1296, 1195, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.85 (s, 6H), 5.75 (s, 2H), 6.90-6.94 (m, 2H), 7.16-7.20 (m, 3H), 7.65 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.3, 51.8, 111.0, 125.6, 126.9, 128.4, 138.9, 139.4, 162.5. *Anal*. Calcd for $C_{15}H_{15}NO_6$: C, 59.01; H, 4.95; N, 4.59. Found: C, 59.07; H, 4.85; N, 4.55.

Dimethyl *N*-benzyl-3,4-bis(trifluoromethanesulfonyloxy)pyrrole-2,5-dicarboxylate (7)

Under an argon atmosphere, trifluoromethanesulfonic anhydride (18.2 mL, 108 mmol) was added as a neat liquid to a solution of **6** (15.0 g, 49.1 mmol) in pyridine (75 mL) at 0 °C. After being stirred for 1 h, the reaction mixture was quenched with water at the same temperature and allowed to warm to rt. The product was extracted with Et_2O and the extract was washed successively with 3 M aqueous HCl, water, and brine, and dried over Na_2SO_4. The solvent was removed by evaporation and the residue was purified by column chromatography over Silica Gel 60N (hexane-EtOAc=5:1) to give **7** as colorless solid (26.9 g, 96%). Recrystallization from Et_2O-hexane gave colorless granules. Mp 70.5-71 °C; IR (KBr): 1745, 1438, 1289, 1248, 1211, 1134 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 6H), 6.19 (s, 2H), 6.95-7.02 (m, 2H), 7.21-7.34 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.8, 52.4, 117.6, 118.4 (q, J= 320 Hz), 126.0, 127.6, 128.3, 128.7, 136.2, 158.0. *Anal*. Calcd for $C_{17}H_{13}F_6NO_{10}S_2$: C, 35.86; H, 2.30; N, 2.46. Found: C, 35.64; H, 2.12; N, 2.42.

Suzuki-Miyaura coupling of bis-triflate (7) with arylboronic acids (2). General procedure

Under an argon atmosphere, a degassed solution of Na_2CO_3 (2.10 g, 19.8 mmol) in water (6.0 mL) was added to a solution of **7** (3.02 mmol), **2** (9.02 mmol) and $Pd(PPh_3)_4$ (140 mg, 0.121 mmol) in THF (60 mL) at rt and the mixture was refluxed for 20 h. The mixture was cooled to rt and evaporated under reduced pressure. The product was extracted with CH_2Cl_2 and the extract was washed successively with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography to give **8**.

Dimethyl *N*-benzyl-3,4-bis(4-methoxyphenyl)pyrrole-2,5-dicarboxylate (8a)

According to the general procedure, **7** (1.72 g, 3.02 mmol) and **2a** (1.37 g, 9.02 mmol) were reacted. After chromatographic purification over Silica Gel 60N (toluene~toluene-EtOAc=10:1), **8a** was obtained as colorless solid (1.45 g, 99%). Recrystallization from CH_2Cl_2-hexane gave colorless granules. Mp 142-143 °C; IR (KBr): 1717, 1694, 1534, 1431, 1293, 1246, 1203, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.52 (s, 6H), 3.75 (s, 6H), 6.01 (s, 2H), 6.69-6.73 (m, 4H), 6.93-6.96 (m, 4H), 7.07-7.11 (m, 2H), 7.18-7.24 (m, 1H), 7.26-7.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.7, 51.4, 55.1, 112.7, 124.4, 126.2, 126.4, 126.9, 128.4, 130.9, 131.4, 138.6, 158.1, 162.0. *Anal*. Calcd for $C_{29}H_{27}NO_6$: C, 71.74; H,

5.61; N, 2.88. Found: C, 71.52; H, 5.62; N, 2.84.

Dimethyl *N*-benzyl-3,4-diphenylpyrrole-2,5-dicarboxylate (8b)

According to the general procedure, **7** (1.71 g, 3.00 mmol) and **2b** (1.10 g, 9.00 mmol) were reacted. After chromatographic purification over Silica Gel 60N (toluene), **8b** was obtained as colorless solid (1.25 g, 98%). Recrystallization from Et_2O-pentane gave colorless needles. Mp 138-139 °C; IR (KBr): 1716, 1435, 1296, 1228, 1201, 1173 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.49 (s, 6H), 6.05 (s, 2H), 7.01-7.06 (m, 4H), 7.09-7.25 (m, 9H), 7.27-7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.6, 51.4, 124.4, 126.2, 126.4, 126.9, 127.1, 128.3, 130.2, 131.1, 134.0, 138.4, 161.8. *Anal*. Calcd for $C_{27}H_{23}NO_4$: C, 76.22; H, 5.45; N, 3.29. Found: C, 76.05; H, 5.38; N, 3.22.

Dimethyl *N*-benzyl-3,4-bis(4-isopropoxyphenyl)pyrrole-2,5-dicarboxylate (8c)

According to the general procedure, **7** (5.29 g, 9.29 mmol) and **2c** (5.02 g, 27.9 mmol) were reacted. After chromatographic purification over Silica Gel 60N (toluene~toluene-EtOAc=10:1), **8c** was obtained as colorless solid (5.02 g, quant.). Recrystallization from Et_2O-pentane gave colorless. Mp 140-141 °C; IR (KBr): 1713, 1531, 1435, 1298, 1244, 1201, 1182 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.30 (d, *J*= 6.1 Hz, 12H), 3.52 (s, 6H), 4.43-4.53 (m, 2H), 6.00 (s, 2H), 6.68-6.72 (m, 4H), 6.90-6.94 (m, 4H), 7.07-7.10 (m, 2H), 7.18-7.23 (m, 1H), 7.26-7.31 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 49.6, 51.3, 69.7, 114.7, 124.3, 126.2, 126.2, 126.9, 128.3, 130.8, 131.4, 138.6, 156.3, 162.0. *Anal*. Calcd for $C_{33}H_{35}NO_6$: C, 73.18; H, 6.51; N, 2.59. Found: C, 73.31; H, 6.63; N, 2.47.

Dimethyl *N*-benzyl-3,4-bis(4-fluorophenyl)pyrrole-2,5-dicarboxylate (8d)

According to the general procedure, **7** (1.71 g, 3.00 mmol) and **2d** (1.26 g, 9.01 mmol) were reacted. After chromatographic purification over Silica Gel 60N (toluene), **8d** was obtained as colorless solid (1.37 g, 99%). Recrystallization from CH_2Cl_2-hexane gave colorless granules. Mp 126.5-127.5 °C; IR (KBr): 1714, 1534, 1436, 1299, 1225, 1201, 1176 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.52 (s, 6H), 6.05 (s, 2H), 6.84-6.91 (m, 4H), 6.95-7.01 (m, 4H), 7.08-7.11 (m, 2H), 7.20-7.26 (m, 1H), 7.27-7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.8, 51.5, 114.3 (d, *J*= 21 Hz), 124.5, 126.3, 127.1, 128.5, 129.9 (d, *J*= 3.3 Hz), 130.3, 131.9 (d, *J*= 8.3 Hz), 138.4, 161.6 (d, *J*= 245 Hz), 161.6. *Anal*. Calcd for $C_{27}H_{21}F_2NO_4$: C, 70.28; H, 4.59; N, 3.04. Found: C, 70.56; H, 4.61; N, 2.98.

Dimethyl *N*-benzyl-3,4-bis(4-chlorophenyl)pyrrole-2,5-dicarboxylate (8e)

According to the general procedure, **7** (1.71 g, 3.00 mmol) and **2e** (1.41 g, 9.02 mmol) were reacted. After chromatographic purification over Silica Gel 60N (toluene), **8e** was obtained as colorless solid (1.45

g, 98%). Recrystallization from CH_2Cl_2-hexane gave colorless prisms. Mp 128-129 °C; IR (KBr): 1707, 1455, 1434, 1292, 1196, 1171, 1102, 1020 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.52 (s, 6H), 6.05 (s, 2H), 6.93-6.96 (m, 4H), 7.07-7.11 (m, 2H), 7.14-7.18 (m, 4H), 7.20-7.25 (m, 1H), 7.27-7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.8, 51.6, 124.5, 126.3, 127.1, 127.6, 128.5, 129.9, 131.6, 132.4, 132.7, 138.2, 161.5. *Anal*. Calcd for $C_{27}H_{21}Cl_2NO_4$: C, 65.60; H, 4.28; N, 2.83. Found: C, 65.54; H, 4.27; N, 2.72.

Dimethyl *N*-benzyl-3,4-bis(2-methoxyphenyl)pyrrole-2,5-dicarboxylate (8f)

According to the general procedure, **7** (564 mg, 0.990 mmol) and **2f** (453 mg, 2.98 mmol) were reacted. After successive purification by column chromatography over Silica Gel 60N (toluene-EtOAc=20:1~10:1) and column chromatography over Silica Gel 60N (hexane-CH_2Cl_2=1:5), **8f** was obtained as colorless solid (466 mg, 97%). Recrystallization from CH_2Cl_2-Et_2O gave colorless granules. Mp 168.5-169.5 °C; IR (KBr): 1721, 1698, 1438, 1291, 1248, 1201, 1176, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.47 (s, 6H), 3.57 (s, 6H), 6.10 (s, 2H), 6.69-6.77 (m, 4H), 6.86-6.90 (m, 2H), 7.09-7.15 (m, 4H), 7.16-7.22 (m, 1H), 7.25-7.31 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.6, 51.2, 55.3, 110.0, 119.6, 124.0, 125.1, 126.2, 126.7, 127.2, 127.9, 128.3, 131.3, 138.9, 156.8, 161.9. *Anal.* Calcd for $C_{29}H_{27}NO_6$: C, 71.74; H, 5.61; N, 2.88. Found: C, 71.62; H, 5.71; N, 2.72.

Dimethyl *N*-benzyl-3,4-bis(3,4-dimethoxyphenyl)pyrrole-2,5-dicarboxylate (8g)

According to the general procedure, **7** (1.71 g, 3.00 mmol) and **2g** (1.64 g, 9.01 mmol) were reacted. After chromatographic purification over Silica Gel 60N (toluene-EtOAc=5:1), **8g** was obtained as colorless solid (1.62 g, 99%). Recrystallization from CH_2Cl_2-hexane gave colorless needles. Mp 154.5-155.5 °C; IR (KBr): 1718, 1532, 1439, 1318, 1235, 1206, 1178, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.56 (s, 6H), 3.65 (s, 6H), 3.84 (s, 6H), 6.00 (s, 2H), 6.55 (d, *J*= 1.7 Hz, 2H), 6.61 (dd, *J*= 1.7 and 8.1 Hz, 2H), 6.71 (d, *J*= 8.1 Hz, 2H), 7.11-7.14 (m, 2H), 7.20-7.26 (m, 1H), 7.28-7.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.6, 51.5, 55.7, 110.1, 113.8, 122.7, 124.3, 126.3, 126.6, 127.0, 128.4, 130.6, 138.4, 147.5, 147.7, 162.0. *Anal*. Calcd for $C_{31}H_{31}NO_8$: C, 68.25; H, 5.73; N, 2.57. Found: C, 68.09; H, 5.86; N, 2.51.

Dimethyl *N*-benzyl-3,4-bis(3,4,5-trimethoxyphenyl)pyrrole-2,5-dicarboxylate (8h)

According to the general procedure, **7** (410 mg, 0.720 mmol) and **2h** (455 mg, 2.15 mmol) were reacted. After successive purification by column chromatography over Silica Gel 60N (toluene-EtOAc=10:1~5:1) and column chromatography over Chromatorex NH-DM1020 silica gel (toluene-EtOAc=10:1), **8h** was obtained as colorless solid (418 mg, 96%). Recrystallization from CH_2Cl_2-Et_2O gave colorless granules.

Mp 159.5-160.5 °C; IR (KBr): 1717, 1582, 1434, 1341, 1279, 1239, 1196, 1128, 1099, 1001 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.59 (s, 6H), 3.64 (s, 12H), 3.81 (s, 6H), 5.99 (s, 2H), 6.28 (s, 4H), 7.13-7.18 (m, 2H), 7.22-7.24 (m, 1H), 7.27-7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.7, 51.7, 56.1, 60.9, 107.9, 124.2, 126.4, 127.1, 128.4, 129.4, 130.4, 136.8, 138.2, 152.2, 161.9. *Anal.* Calcd for $C_{33}H_{35}NO_{10}$: C, 65.44; H, 5.82; N, 2.31. Found: C, 65.73; H, 5.87; N, 2.19.

Dimethyl *N*-benzyl-3,4-bis(4,5-dimethoxy-2-methoxymethoxyphenyl)pyrrole-2,5-dicarboxylate (8i)

According to the general procedure, **7** (2.29 g, 4.02 mmol) and **2i** (2.90 g, 12.0 mmol) were reacted. After successive purification by column chromatography over Silica Gel 60N (hexane-EtOAc=1:1) and column chromatography over Chromatorex NH-DM1020 silica gel (hexane-EtOAc=2:1), **8i** was obtained as colorless solid (2.65 g, 99%). Recrystallization from CH_2Cl_2-Et_2O gave colorless granules. Mp 139.5-140.5 °C; IR (KBr): 1722, 1703, 1533, 1439, 1288, 1214, 1078, 1031, 1005 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.28 (s, 6H), 3.55 (s, 6H), 3.56 (s, 6H), 3.83 (s, 6H), 4.83 (br s, 4H), 6.06 (s, 2H), 6.47 (br s, 2H), 6.68 (s, 2H), 7.12-7.16 (m, 2H), 7.19-7.24 (m, 1H), 7.26-7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.5, 51.5, 55.8, 55.9, 56.0, 96.6, 101.7, 114.4, 117.1, 125.3, 126.5, 126.8, 127.0, 128.4, 138.9, 143.7, 148.5, 149.2, 162.2. *Anal.* Calcd for $C_{35}H_{39}NO_{12}$: C, 63.15; H, 5.91; N, 2.10. Found: C, 63.12; H, 5.97; N, 1.99.

Synthesis of dimethyl 3,4-diarylpyrrole-2,5-dicarboxylates (3). General procedure

Under an argon atmosphere, ammonium formate (1.53 g, 24.3 mmol) was added portionwise to a mixture of **8** (0.801 mmol), Pearlman's catalyst (129 mg), and EtOH (16 mL) at rt. After being refluxed for an appropriate reaction time shown in Table 2, the mixture was cooled to rt and passed through a pad of Celite. The filtrate was evaporated under reduced pressure. The residue was purified by column chromatography to give **3**.

Dimethyl 3,4-bis(4-methoxyphenyl)pyrrole-2,5-dicarboxylate (3a)

According to the general procedure, **8a** (389 mg, 0.801 mmol) and Pearlman's catalyst (129 mg) were reacted. After chromatographic purification over Silica Gel 60N (CH_2Cl_2), **3a** was obtained as colorless solid (308 mg, 97%). Recrystallization from CH_2Cl_2-hexane gave colorless needles. Mp 195.5-196 °C; IR (KBr): 3351, 1710, 1537, 1469, 1438, 1311, 1249, 1181 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.77 (s, 12H), 6.73-6.77 (m, 4H), 7.01-7.05 (m, 4H), 9.80 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.7, 55.0, 112.8, 121.0, 125.0, 131.1, 131.8, 158.3, 160.6. *Anal.* Calcd for $C_{22}H_{21}NO_6$: C, 66.83; H, 5.35; N, 3.54. Found: C, 66.75; H, 5.44; N, 3.45.

Dimethyl 3,4-diphenylpyrrole-2,5-dicarboxylate (3b)

According to the general procedure, **8b** (3.68 g, 8.64 mmol) and Pearlman's catalyst (368 mg) were reacted. After chromatographic purification over Silica Gel 60N (CH_2Cl_2), **3b** was obtained as colorless solid (2.89 g, quant.). Recrystallization from CH_2Cl_2-Et_2O gave colorless cube. Mp 195-196 °C; IR (KBr): 3310, 1710, 1462, 1429, 1297, 1242, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.75 (s, 6H), 7.08-7.13 (m, 4H), 7.17-7.21 (m, 6H), 9.89 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.7, 121.1, 126.8, 127.2, 130.6, 131.4, 132.7, 160.5. *Anal.* Calcd for $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.18. Found: C, 71.62; H, 5.19; N, 4.12.

Dimethyl 3,4-bis(4-isopropoxyphenyl)pyrrole-2,5-dicarboxylate (3c)

According to the general procedure, **8c** (7.02 g, 13.0 mmol) and Pearlman's catalyst (751 mg) were reacted. After chromatographic purification over Silica Gel 60N (CH_2Cl_2), **3c** was obtained as colorless solid (5.56 g, 95%). Recrystallization from CH_2Cl_2-pentane gave colorless granules. Mp 148-149 °C; IR (KBr): 3290, 1703, 1534, 1464, 1297, 1246, 1185, 1120, 1106, 955 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.31 (d, J= 6.1 Hz, 12H), 3.77 (s, 6H), 4.44-4.55 (m, 2H), 6.70-6.74 (m, 4H), 6.98-7.02 (m, 4H), 9.80 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 51.7, 69.6, 114.6, 120.9, 124.7, 131.2, 131.8, 156.7, 160.6. *Anal.* Calcd for $C_{26}H_{29}NO_6$: C, 69.16; H, 6.47; N, 3.10. Found: C, 69.16; H, 6.36; N, 3.01.

Dimethyl 3,4-bis(4-fluorophenyl)pyrrole-2,5-dicarboxylate (3d)

According to the general procedure, **8d** (462 mg, 1.00 mmol) and Pearlman's catalyst (49 mg) were reacted. After chromatographic purification over Silica Gel 60N (hexane-CH_2Cl_2=1:5), **3d** was obtained as colorless solid (329 mg, 89%). Recrystallization from CH_2Cl_2-hexane gave colorless needles. Mp 174-175 °C; IR (KBr): 3319, 1725, 1691, 1475, 1463, 1294, 1255, 1223, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.77 (s, 6H), 6.84-6.94 (m, 4H), 7.03-7.09 (m, 4H), 9.90 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.8, 114.4 (d, J= 22 Hz), 121.2, 128.4 (d, J= 3.3 Hz), 130.3, 132.2 (d, J= 8.3 Hz), 160.4, 161.8 (d, J= 246 Hz). *Anal.* Calcd for $C_{20}H_{15}F_2NO_4$: C, 64.69; H, 4.07; N, 3.77. Found: C, 64.58; H, 3.95; N, 3.68.

Dimethyl 3,4-bis(2-methoxyphenyl)pyrrole-2,5-dicarboxylate (3f)

According to the general procedure, **8f** (195 mg, 0.402 mmol) and Pearlman's catalyst (100 mg) were reacted. After chromatographic purification over Silica Gel 60N (CH_2Cl_2~CH_2Cl_2-EtOAc=10:1), **3f** was obtained as colorless solid (140 mg, 88%). Recrystallization from CH_2Cl_2-pentane gave colorless granules. Mp 203-205 °C; IR (KBr): 3290, 1713, 1694, 1470, 1434, 1300, 1270, 1248, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.53 (br s, 6H), 3.72 (s, 6H), 6.76 (dd, J= 1.0 and 7.5 Hz, 2H), 6.78 (dt, J=

1.0 and 7.5 Hz, 2H), 6.98 (dd, *J*= 1.8 and 7.5 Hz, 2H), 7.16 (dt, *J*= 1.8 and 7.5 Hz, 2H), 9.86 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.5, 55.1, 110.2, 119.5, 122.0, 122.7, 127.8, 128.4, 131.6, 157.0, 160.6. *Anal*. Calcd for $C_{22}H_{21}NO_6$: C, 66.83; H, 5.35; N, 3.54. Found: C, 66.76; H, 5.41; N, 3.37.

Dimethyl 3,4-bis(3,4-dimethoxyphenyl)pyrrole-2,5-dicarboxylate (3g)

According to the general procedure, **8g** (546 mg, 1.00 mmol) and Pearlman's catalyst (55 mg) were reacted. After chromatographic purification over Silica Gel 60N (CH_2Cl_2), **3g** was obtained as colorless solid (432 mg, 95%). Recrystallization from CH_2Cl_2-hexane gave colorless needles. Mp 168.5-169.5 °C; IR (KBr): 3313, 1719, 1683, 1531, 1469, 1438, 1319, 1279, 1245, 1138, 1024 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.64 (s, 6H), 3.79 (s, 6H), 3.85 (s, 6H), 6.61-6.63 (m, 2H), 6.71-6.77 (m, 4H), 9.83 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.8, 55.7, 55.7, 110.2, 114.2, 120.9, 123.2, 125.2, 131.1, 147.7, 147.9, 160.6. *Anal.* Calcd for $C_{24}H_{25}NO_8$: C, 63.29; H, 5.53; N, 3.08. Found: C, 63.33; H, 5.47; N, 2.98.

Dimethyl 3,4-bis(3,4,5-trimethoxyphenyl)pyrrole-2,5-dicarboxylate (3h)

According to the general procedure, **8h** (612 mg, 1.01 mmol) and Pearlman's catalyst (67 mg) were reacted. After chromatographic purification over Silica Gel 60N (CH_2Cl_2), **3h** was obtained as colorless solid (502 mg, 96%). Recrystallization from CH_2Cl_2-hexane gave colorless needles. Mp 166-167 °C; IR (KBr): 3273, 1730, 1702, 1586, 1480, 1460, 1412, 1344, 1239, 1124 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.65 (s, 12H), 3.83 (s, 12H), 6.38 (s, 4H), 9.90 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.9, 56.0, 60.8, 108.4, 120.9, 128.0, 131.0, 137.1, 152.2, 160.4. *Anal.* Calcd for $C_{26}H_{29}NO_{10}$: C, 60.58; H, 5.67; N, 2.72. Found: C, 60.57; H, 5.68; N, 2.60.

Dimethyl 3,4-bis(4,5-dimethoxy-2-methoxymethoxyphenyl)pyrrole-2,5-dicarboxylate (3i)

According to the general procedure, **8i** (1.22 g, 1.83 mmol) and Pearlman's catalyst (128 mg) were reacted. After chromatographic purification over Silica Gel 60N (hexane-EtOAc=1:2), **3i** was obtained as colorless solid (993 mg, 94%). Recrystallization from CH_2Cl_2-Et_2O gave colorless granules. Mp 150.5-151.5 °C; IR (KBr): 3277, 1713, 1494, 1233, 1152, 1099, 1011 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.31 (br s, 6H), 3.58 (br s, 6H), 3.77 (s, 6H), 3.84 (s, 6H), 4.61 (br s, 1H), 4.85 (br s, 2H), 5.02 (br s, 1H), 6.50 (br s, 2H), 6.77 (br s, 2H), 9.84 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.7, 55.7, 55.9, 56.1, 96.8, 101.4, 114.5, 122.2, 127.6, 143.6, 149.0, 150.0, 160.8. *Anal*. Calcd for $C_{28}H_{33}NO_{12}$: C, 58.43; H, 5.78; N, 2.43. Found: C, 58.48; H, 5.82; N, 2.26.

Dimethyl 3,4-bis(4-chlorophenyl)pyrrole-2,5-dicarboxylate (3e)

Under an argon atmosphere, a mixture of **8e** (509 mg, 1.03 mmol), anisole (140 μL, 1.29 mmol), and 98% H_2SO_4 (36 μL, 0.68 mmol) in trifluoroacetic acid (1.2 mL) was refluxed for 0.5 h. After being cooled to rt, the mixture was evaporated under reduced pressure. The residue was basified with saturated aqueous $NaHCO_3$ and the mixture was extracted with CH_2Cl_2. The extract was washed successively with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (hexane-CH_2Cl_2=1:5~CH_2Cl_2) to give **3e** as colorless solid (333 mg, 80%). Recrystallization from Et_2O-pentane gave colorless granules. Mp 191.5-193 °C; IR (KBr): 3281, 1713, 1462, 1436, 1298, 1248, 1163, 1091, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.77 (s, 6H), 7.00-7.04 (m, 4H), 7.17-7.21 (m, 4H), 9.92 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.9, 121.3, 127.7, 129.9, 130.9, 131.9, 133.1, 160.2. HREIMS *m/z*. Calcd for $C_{20}H_{15}Cl_2NO_4$ (M^+): 403.0378. Found: 403.0379.

Dimethyl *N*-benzyl-3-(3,4-dimethoxyphenyl)-4-(trifluoromethanesulfonyloxy)pyrrole-2,5-dicarboxylate (9)

Under an argon atmosphere, a degassed solution of Na_2CO_3 (4.23 g, 39.9 mmol) in water (12 mL) was added to a solution of **7** (3.46 g, 6.08 mmol), **2g** (1.10 g, 6.05 mmol) and $Pd(PPh_3)_4$ (140 mg, 0.121 mmol) in THF (120 mL) at rt and the mixture was refluxed for 4 h. The mixture was cooled to rt and evaporated under reduced pressure. The products were extracted with CH_2Cl_2 and the extract was washed successively with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified successively by column chromatography over Silica Gel 60N (toluene~toluene-EtOAc=5:1) and over Silica Gel 60N (CH_2Cl_2) to give **9** as colorless solid (2.54 g, 75%), 3,4-diarylated **8g** (258 mg, 8%), and unreacted **7** (461 mg, 13%). Recrystallization from CH_2Cl_2-hexane gave colorless granules. Mp 131-132 °C; IR (KBr): 1728, 1442, 1425, 1294, 1265, 1212, 1139 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.58 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 3.92 (s, 3H), 6.09 (s, 2H), 6.82-6.90 (m, 3H), 7.01-7.05 (m, 2H), 7.21-7.27 (m, 1H), 7.27-7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 49.6, 51.9, 51.9, 55.8, 55.9, 110.5, 113.2, 117.8, 117.9 (q, *J*= 320 Hz), 121.9, 122.7, 123.2, 123.2, 126.1, 127.3, 128.5, 136.0, 137.3, 148.3, 148.8, 159.1, 160.8. *Anal*. Calcd for $C_{24}H_{22}F_3NO_9S$: C, 51.71; H, 3.98; N, 2.51. Found: C, 51.90; H, 3.93; N, 2.40.

Dimethyl *N*-benzyl-3-(3,4-dimethoxyphenyl)-4-(4-methoxyphenyl)pyrrole-2,5-dicarboxylate (10)

Under an argon atmosphere, a degassed solution of Na_2CO_3 (2.10 g, 19.8 mmol) in water (6.0 mL) was added to a solution of **9** (1.67 g, 3.00 mmol), **2a** (685 mg, 4.51 mmol) and $Pd(PPh_3)_4$ (145 mg, 0.125 mmol) in THF (60 mL) at rt and the mixture was refluxed for 20 h. The mixture was cooled to rt and evaporated under reduced pressure. The products were extracted with CH_2Cl_2 and the extract was

washed successively with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified successively by column chromatography over Silica Gel 60N (toluene-EtOAc=10:1) and over Chromatorex NH-DM1020 silica gel (EtOAc) to give **10** as colorless solid (1.48 g, 96%). Recrystallization from CH_2Cl_2-hexane gave colorless granules. Mp 110.5-112 °C; IR (KBr): 1715, 1535, 1435, 1299, 1245, 1202, 1173, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.53 (s, 3H), 3.55 (s, 3H), 3.62 (s, 3H), 3.75 (s, 3H), 3.83 (s, 3H), 6.01 (s, 2H), 6.51 (d, *J*= 2.0 Hz, 1H), 6.62 (dd, *J*= 2.0 and 8.3 Hz, 1H), 6.70 (d, *J*= 8.3 Hz, 1H), 6.70-6.75 (m, 2H), 6.94-6.98 (m, 2H), 7.09-7.13 (m, 2H), 7.19-7.25 (m, 1H), 7.27-7.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 49.6, 51.4, 51.5, 55.0, 55.6, 55.6, 110.0, 112.7, 113.8, 122.7, 124.2, 124.4, 126.2, 126.5, 126.9, 128.3, 130.6, 130.8, 131.3, 138.5, 147.4, 147.6, 158.1, 161.9, 162.1. *Anal*. Calcd for $C_{30}H_{29}NO_7$: C, 69.89; H, 5.67; N, 2.72. Found: C, 69.73; H, 5.64; N, 2.63.

Dimethyl 3-(3,4-dimethoxyphenyl)-4-(4-methoxyphenyl)pyrrole-2,5-dicarboxylate (11)

Under an argon atmosphere, ammonium formate (1.93 g, 30.6 mmol) was added portionwise to a mixture of **10** (523 mg, 1.01 mmol), Pearlman's catalyst (51 mg), and EtOH (20 mL) at rt. After being refluxed for 3 h, the mixture was cooled to rt and passed through a pad of Celite. The filtrate was evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (CH_2Cl_2) to give **11** as colorless solid (298 mg, 69%). Recrystallization from CH_2Cl_2-pentane gave colorless granules. Mp 181-182 °C; IR (KBr): 3282, 1721, 1702, 1463, 1299, 1249, 1190, 1024 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.61 (s, 3H), 3.77 (s, 3H), 3.77 (s, 3H), 3.79 (s, 3H), 3.85 (s, 3H), 6.56-6.58 (m, 1H), 6.72-6.79 (m, 4H), 7.01-7.06 (m, 2H), 9.82 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 51.7, 55.1, 55.6, 55.6, 110.0, 112.8, 114.2, 120.9, 121.0, 123.3, 125.1, 125.1, 131.1, 131.1, 131.7, 147.6, 147.7, 158.4, 160.6. HREIMS *m/z*. Calcd for $C_{23}H_{23}NO_7$ (M^+): 425.1475. Found: 425.1469.

3,4-Bis(4-isopropoxyphenyl)-5-methoxycarbonylpyrrole-2-carboxylic acid (12)

Under an argon atmosphere, **3c** (2.71 g, 6.00 mmol) and $LiOH \cdot H_2O$ (126 mg, 3.00 mmol) were dissolved in a degassed mixture of THF (36 mL), MeOH (12 mL), and water (12 mL). After being stirred for 44 h at rt, the mixture was acidified with 3 M aqueous HCl to pH 1 and evaporated under reduced pressure. The product was extracted with EtOAc and the extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N [hexane-EtOAc=1:1~EtOAc-water (upper phase)] to give **12** as colorless solid (1.23 g, 47%) and unreacted **3c** (1.38 g, 51%). Recrystallization from CH_2Cl_2-pentane gave colorless powder. Mp 219-220 °C; IR (KBr): 3308, 1700, 1466, 1298, 1242, 1119, 952 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.22 (d, *J*= 6.0 Hz, 12H), 3.64 (s, 3H), 4.47-4.58 (m, 2H), 6.67-6.72 (m, 4H), 6.89-6.95 (m, 4H), 11.94 (br

s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.7, 21.8, 51.1, 68.7, 68.7, 113.9, 114.0, 120.6, 122.5, 125.1, 125.3, 129.4, 130.0, 131.5, 131.6, 155.7, 155.8, 160.1, 161.2. *Anal*. Calcd for $C_{25}H_{27}NO_6$: C, 68.63; H, 6.22; N, 3.20. Found: C, 68.63; H, 6.11; N, 3.14.

Methyl 3,4-bis(4-isopropoxyphenyl)pyrrole-2-carboxylate (13)

Under an argon atmosphere, a mixture of **12** (500 mg, 1.14 mmol) and copper(I) oxide (164 mg, 1.14 mmol) in quinoline (10 mL) was heated at 220 °C for 7 min. The mixture was cooled to rt and passed through a pad of Celite. The filtrate was diluted with CH_2Cl_2, washed successively with 6 M aqueous HCl, water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by flash chromatography over Silica Gel 60N (hexane-EtOAc=3:1) to give **13** as yellow solid (361 mg, 80%). Recrystallization from EtOAc-hexane gave yellow needles. The spectroscopic data are identical with those reported in ref. 26.

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