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Design and Synthesis of Lamellarin D Analogues Targeting Topoisomerase I

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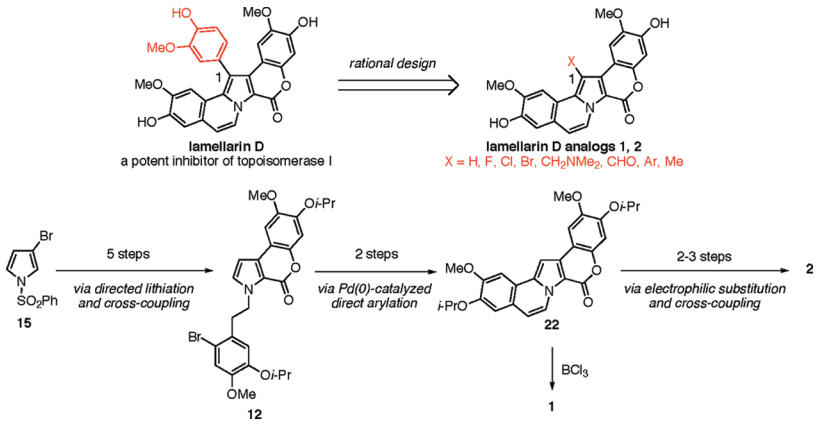

A general synthetic route to rationally designed lamellarin D analogues, 1-dearyllamellarin D (**1**) and 1-substituted 1-dearyllamellarin D (**2**), has been developed. The key pentacyclic intermediate **22** was prepared by palladium-catalyzed direct arylation of **12**, which in turn was synthesized via C-2-selective lithiation of **15** followed by palladium-catalyzed cross-coupling as the key reactions. Compound **22** was converted to a wide range of C-1-substituted analogues **2** via regioselective electrophilic substitution and palladium-catalyzed cross-coupling reactions.

Introduction

Lamellarins are a family of marine alkaloids possessing a common 14-phenyl-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo-[2,1-*a*]isoquinoline ring system.[1] Since the first isolation of lamellarins A−D by Faulkner et al. in 1985, more than 30 lamellarins (A−Z and α−χ, including their acetate and sulfate derivatives) have been isolated from mollusks, ascidians, and sponges.[2] These differ in the number and position of the OH and OMe groups on the common scaffold. Lamellarins have attracted considerable attention owing to their antitumor activity. In 1996, Quesada et al. reported that the triacetates of lamellarins D, K, and N exhibit potent cytotoxicity against both multidrug-resistant (MDR) cancer cell lines and their corresponding parental cell lines.[3] In addition, they demonstrated that lamellarin I reverses

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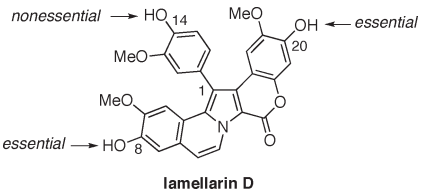


FIGURE 1. Structure−activity relationships of lamellarin D in regard to cytotoxicity.

MDR by direct inhibition of P-glycoprotein-mediated drug efflux at noncytotoxic doses. Following these significant discoveries, synthetic endeavors for lamellarin alkaloids have been initiated by several research groups.[4−9] In 1997, we achieved the first total synthesis of lamellarins D and H by means of *N*-ylide-mediated cyclization.[6a] Using this method, we prepared a range of differentially substituted non-natural lamellarin D analogues and evaluated their cytotoxicity against a HeLa cell line.[10a] Structure−activity relationship study indicated that the hydroxyl groups at C-8 and C-20 positions (lamellarin numbering[2a]) of lamellarin D are essential for its potent cytotoxicity, whereas the hydroxyl group at C-14 is less important (Figure 1).[10a]

Recently, Bailly et al. reported that lamellarin D is a potent inhibitor of topoisomerase I.[11] This enzyme relaxes supercoils generated during DNA replication and transcription via reversible single-strand cleavage and religation. Topoisomerase I inhibitors stabilize the topoisomerase I-DNA cleavage complex and inhibit the religation step.[12] This action by the inhibitors causes single-strand DNA breakages that are transformed into

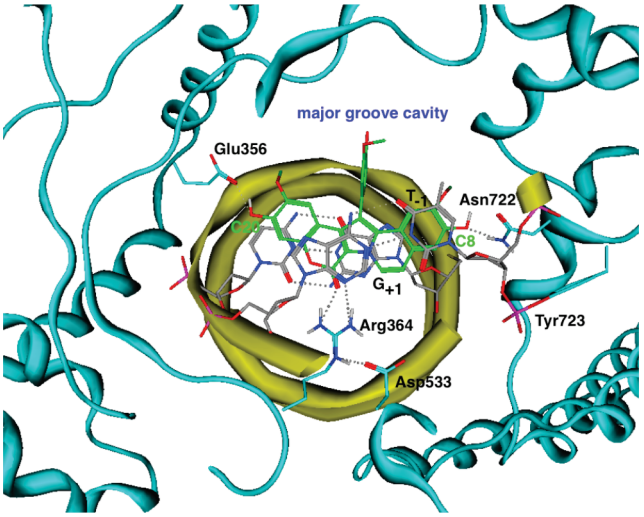
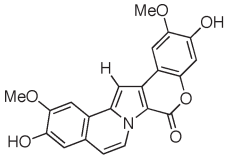
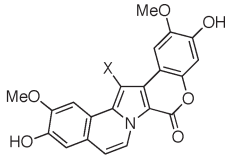


FIGURE 2. Lamellarin D−DNA−topoisomerase I ternary complex model.[14]

double-strand breakages lethal for growing cells. Bailly has proposed[11] a theoretical model of a lamellarin D-DNA-topoisomerase I ternary complex based on the topotecan-DNA-topoisomerase I crystallographic data.[13] According to this model, lamellarin D intercalates at the site of DNA cleavage and is stabilized with both the +1(C-G) and −1(A-T) base pairs forming stacking interactions. Hydrogen bonds between lamellarin D and the specific amino acid residues of topoisomerase I further stabilize the ternary complex. The hydroxyl groups at C-8 and C-20 and the carbonyl oxygen are at a hydrogen bond distance from Asn722, Glu356, and Arg364, respectively. On the other hand, the aryl group at C-1 is directed toward the major groove cavity and does not have any direct interaction with the protein (Figure 2).[14]

This model clearly indicates that the planar pentacyclic lamellarin core that has the hydroxyl groups at C-8 and C-20 is essential for this activity, while the aryl group at C-1 is trivial. Therefore, it is reasonable to assume that simplified 1-dearyllamellarin D (**1**), and more interestingly 1-substituted 1-dearyllamellarin D (**2**) that has a variety of functional groups X at C-1, may hold potent topoisomerase I inhibitory activity. To investigate this idea, we have developed a general synthetic route to this type of novel and promising lamellarin D analogues.





Results and Discussion

Attempted Synthesis of 1-Dearyllamellarin D (1) via Oxidative Cyclizations. In 2003,[6b] we devised a short and flexible

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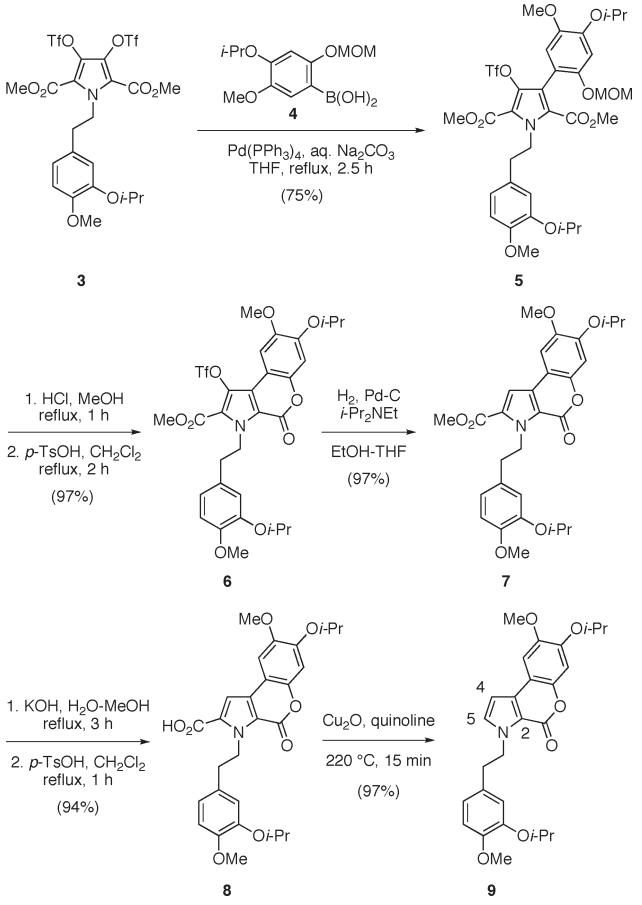
(14) According to ref 11, the lamellarin D−DNA−topoisomerase I ternary complex model shown in Figure 1 was reproduced by means of MOE program (Chemical Computing Group Inc.).

route to 3,4-diarylpyrrole marine alkaloids using Hinsberg-type pyrrole synthesis and palladium-catalyzed Suzuki–Miyaura coupling as the key reactions. This synthetic strategy has been applied successfully to the total synthesis of lamellarins D, L, N[6c] and α 20-sulfate.[6d] In these syntheses, the key pentacyclic framework of lamellarins was constructed by oxidative cyclizations, such as phenyliodine(III) bis(trifluoroacetate) (PIFA)-mediated cyclization[15] and palladium(II)-mediated decarboxylative ring closure.[16] We first attempted to apply this approach for the synthesis of 1-dearyllamellarin D (**1**).

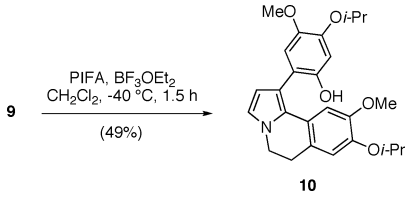
Synthesis of substrates **8** and **9** for the oxidative cyclizations is shown in Scheme 1. Suzuki–Miyaura coupling of the known 3,4-dihydroxypyrrole bistriflate **3**[6c] with 1.2 equiv of arylboronic acid **4**[6c] in the presence of 2 mol % of $Pd(PPh_3)_4$ afforded monocoupling product **5** in 75% yield. This compound was treated with hydrochloric acid in methanol to remove the MOM protecting group. The crude product was treated with a catalytic amount of *p*-toluenesulfonic acid in refluxing dichloromethane to afford lactone **6** in 97% yield. The trifluoromethanesulfonyloxy group on the pyrrole ring was cleanly hydrogenolyzed with H_2 over 5% Pd–C to yield **7**. Alkaline hydrolysis of **7** followed by acid-catalyzed relactonization afforded acid **8**. Decarboxylation of **8** by heating in hot quinoline over copper(I) oxide afforded **9** in excellent yield.

The stage was now set for the implementation of the oxidative cyclizations. First, we tested PIFA-mediated cyclization developed by Kita.[15] Surprisingly, treatment of **9** with PIFA-$BF_3\cdot OEt_2$ in dichloromethane at −40 °C did not produce the expected pentacyclic compound but afforded the abnormally cyclized **10** in 49% yield (Scheme 2). The structure of **10** was confirmed by analyses of its NOESY, HMQC, and HMBC spectra. This type of decarbonylative cyclization at the 2 position of similar pyrrole derivatives has recently been reported by Banwell.[17] The results, however, are quite puzzling because the substrates possessing an aryl group at C-4 of the pyrrole ring undergo normal cyclization

SCHEME 1. Synthesis of 8 and 9 for Oxidative Cyclizations



SCHEME 2. Unusual Cyclization of 9 with PIFA-$BF_3\cdot OEt_2$



to provide the lamellarin skeleton in excellent yields.[6b–d] This discrepancy may be rationalized by following mechanistic considerations. It is well-known that PIFA-mediated aromatic substitutions proceed via initial single-electron transfer (SET) from electron-rich aromatic rings followed by an attack of nucleophiles to the cation radical intermediate.[15a] Therefore, in substrate **9**, the cation radical should be generated at the most electron-rich pyrrole ring.[18,19] This intermediate will be intercepted by the pendant aromatic ring at C-2, presumably owing to the easy extrusion of carbon monoxide via radical-mediated fragmentation.[20] In the

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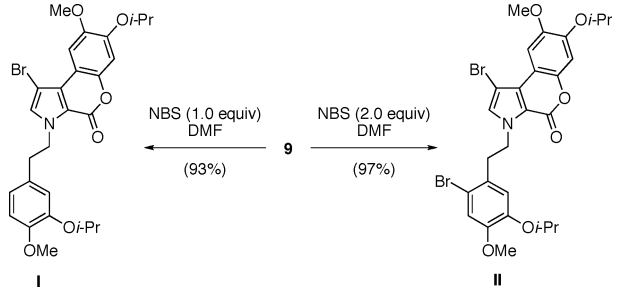
(18) Bromination of **9** with 1.0 equiv of NBS in DMF afforded monobromide **I** in 93% yield, whereas bromination with 2.0 equiv of NBS yielded dibromide **II** in 97% yield. These results suggest relative reactivity of the pyrrole ring and the pendant aromatic ring against elecrophilic reagents.



(19) For PIFA-mediated cyclization, coupling, and functionalization of pyrroles, see: (a) Moreno, I.; Tellitu, I.; Domínguez, E.; SanMartín, R. *Eur. J. Org. Chem.* **2002**, 2126–2135. (b) Dohi, T.; Morimoto, K.; Maruyama, A.; Kita, Y. *Org. Lett.* **2006**, *8*, 2007–2010. (c) Dohi, T.; Morimoto, K.; Takenaga, N.; Goto, A.; Maruyama, A.; Kiyono, Y.; Tohma, H.; Kita, Y. *J. Org. Chem.* **2007**, *72*, 109–116.

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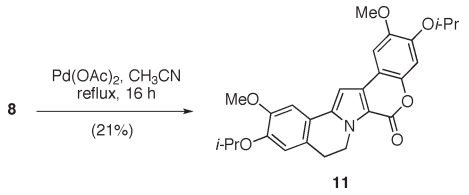
SCHEME 3. Palladium(II)-Mediated Decarboxylative Ring Closure of 8



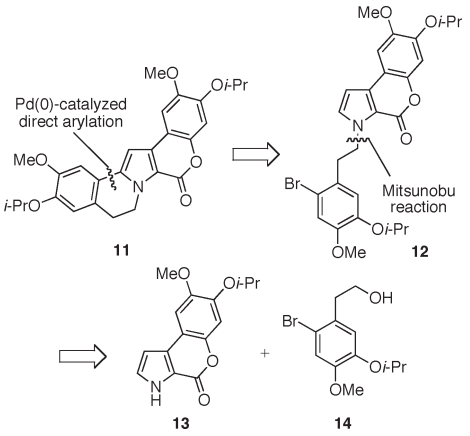
substrate that has an aryl ring at C-4, however, the interaction between the π-electron system of the pyrrole and PIFA may be prohibited by the sterically demanding aryl ring.[21] Thus, the SET occurs at the pendant aromatic ring preferentially, and the resulting cation radical cyclizes to the most nucleophilic C-5 of the pyrrole ring to produce the lamellarin skeleton.

Next, palladium(II)-mediated decarboxylative ring closure of **8** was tested (Scheme 3). In this reaction, the desired compound **11**[22] was obtained in 21% yield by heating a mixture of **8** and 1.1 equiv of $Pd(OAc)_2$ in acetonitrile. The yield, however, is much lower than that obtained in similar cyclizations performed in natural product synthesis.[6b,c] The low yield may be accounted for by the sensitivity of the pyrrole moiety of **11** under oxidative conditions.

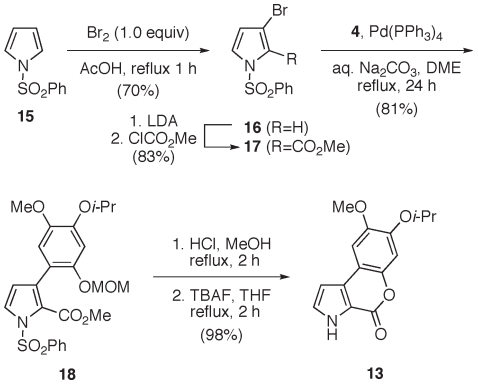
Synthesis of 1-Dearyllamellarin D (1) via Palladium(0)-Catalyzed Direct Arylation. Owing to failure to produce a sufficient amount of **11** by application of the previously established procedures, we decided to develop a new synthetic route. Transition-metal-catalyzed direct arylation has been recognized as a useful way to produce a variety of biaryl derivatives.[23] In this reaction, aryl halides or pseudohalides and simple arenes are employed as the cross-coupling partners. An intramolecular version of this reaction has been frequently employed in the syntheses of carbo- and heterocyclic compounds, including biologically significant natural products.[23] In the field of lamellarin syntheses, Albericio and Álvarez, for example, have utilized palladium-catalyzed intramolecular direct arylation in their modular syntheses of lamellarin D.[8c,d] As shown retrosynthetically in Scheme 4, we anticipated that compound **11** could be obtained in good yield by direct arylation of **12** because unfavorable oxidative conditions are precluded. The precursor **12**, in turn, can be easily prepared by convergent assembly of the pyrrole-lactone **13** and the bromo-alcohol **14** by means of a Mitsunobu reaction.[24]

Synthesis of the pyrrole-lactone **13** was achieved using a combination of directed lithiation and palladium-catalyzed cross-coupling reactions[25] (Scheme 5). *N*-Benzenesulfonylpyrrole (**15**) was brominated with 1.0 equiv of bromine in

SCHEME 4. Retrosynthetic Analysis of 11



SCHEME 5. Synthesis of the Pyrrole-lactone 13



acetic acid at reflux temperature to afford *N*-benzenesulfonyl-3-bromopyrrole (**16**) in 70% yield.[26,27] Directed lithiation of **16** with LDA in THF at −78 °C followed by a reaction with methyl chloroformate produced 2-methoxycarbonylated pyrrole **17** regioselectively in 83% yield.[28] Suzuki−Miyaura coupling of **17** with the boronic acid **4**[6c] afforded **18** in 81% yield. Deprotection of MOM (HCl/MeOH) and the benzenesulfonyl group (TBAF)[27] produced the desired lactone **13** in excellent yield.

Bromo-alcohol **14** was prepared using a modified Jordis procedure[29a] (Scheme 6). Wittig reaction of *O*-isopropylisovanillin (**19**) with the ylide generated from (methoxymethyl)triphenylphosphonium chloride and potassium *tert*-butoxide afforded the enol ether **20** in 93% yield as an *E*/*Z* mixture. Acid-catalyzed hydrolysis of **20** followed by reduction of the resulting aldehyde with sodium borohydride produced **21** in 88% yield. Bromination of **21** with NBS in DMF afforded **14** in 83% yield.

Mitsunobu reaction of the lactone **13** with alcohol **14** using diisopropyl azodicarboxylate (DIAD) and triphenylphosphine afforded **12** in 77% yield (Scheme 7). Intramolecular direct arylation of **12** in the presence of 5 mol % of $Pd(PPh_3)_4$

(21) The SET from aromatic ring to PIFA is sensitive to the steric hindrance of the aromatic substrate, see: Dohi, T.; Ito, M.; Morimoto, K.; Iwata, M.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 1301–1304.

(22) Synthesis of **11** using Banwell's intramolecular [3 + 2]cycloaddition strategy[5a] was described in a patent; see: Bailly, C.; Francesch Solloso, A; Mateo Urbano, M. C.; Jimenez Guerrero, J. A.; Pastor Del Catillo; A.; Cuevas Marchante, C. WO Patent 2004014917, 2004; *Chem. Abstr.* **2004**, *140*, 199492.

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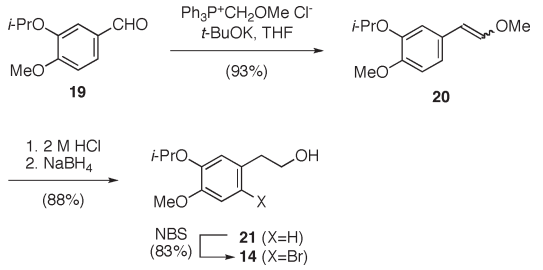
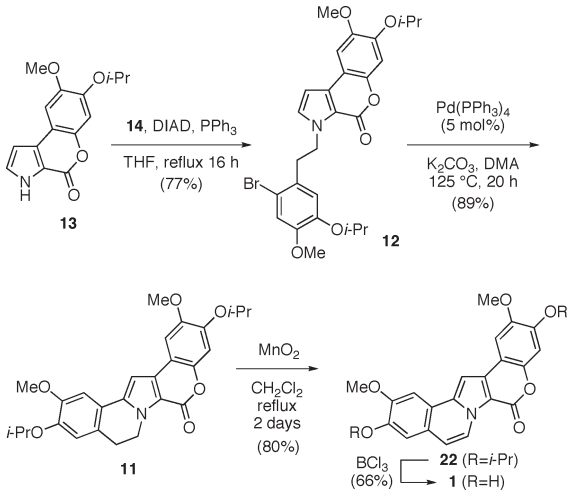
SCHEME 6. Synthesis of the Bromo-alcohol 14



SCHEME 7. Synthesis of 1-Dearyllamellarin D (1)

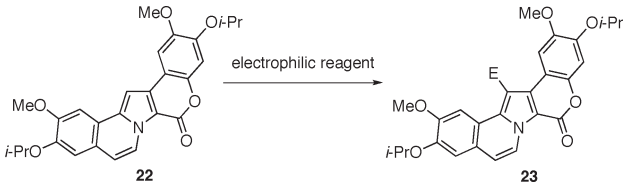


and K_2CO_3 in dimethyl acetamide (DMA) at 125 °C afforded **11** in 89% yield. Dehydrogenation of **11** using active manganese dioxide under mild conditions (CH_2Cl_2, reflux, 2 days) produced **22** in good yield. Attempted dehydrogenation using conventional DDQ[6d] (CH_2Cl_2, reflux, 18 h) resulted in decomposition of the starting material. Finally, selective deprotection of the isopropyl groups with 6.0 equiv of BCl_3[6c] afforded 1-dearyllamellarin D (**1**) in 66% yield.

Synthesis of 1-Substituted 1-Dearyllamellarin D (2) via Regioselective C-1 Functionalization of 22. An efficient synthesis of **1** being established, we focused on the synthesis of a variety of 1-substituted 1-dearyllamellarin D (**2**) via regioselective functionalization of intermediate **22**. At first, we tested electrophilic substituion reactions of **22**.[30] As shown in Table 1, a range of electrophilic reagents reacted smoothly with **22** to afford 1-substituted products **23a**−**e** in good yield. Integrity of the 1-substituted structures of these products was unambiguously confirmed by analyses of their HMQC and HMBC spectra.

To obtain a wider range of lamellarin D analogues, we next examined Suzuki−Miyaura coupling of the bromide **23a** (Table 2). The reaction of **23a** with the boronic acid **24a**[6c] under the standard conditions (10 mol % of $Pd(PPh_3)_4$, aq Na_2CO_3, DME, reflux, 24 h) recovered the starting material **23a** in 95% yield (entry 1). Failure of the reaction may be accounted for by severe steric hindrance at the C-1 position of **23a**. Recently, Qiu et al. reported that the CsF-Ag_2O system is an excellent promoter in the Suzuki−Miyaura coupling of a highly congested tetrabromoperylene derivative.[31] Thus, we tested this promoter in the cross-coupling of **23a**. As shown in entry 2 of the table, dramatic improvement was observed and the desired **25a** was isolated in 69% yield. Compound **25a** thus obtained was shown by spectroscopic comparisons to be identical with an authentic sample prepared previously in our laboratories.[6c] Because the conversion of **25a** to lamellarin D (**1**) has already been reported,[6c] a new and diverted total synthesis[32] of lamellarin D has been thus achieved. Reactions of **23a** with other boronic acids **24b**−**d** afforded the corresponding 1-arylated compounds **25b**−**d** in good yields under similar conditions (entries 3−5). Cross-coupling with trimethylboroxine (**24e**)[33] gave the 1-methylated compound **25e** (entry 6).

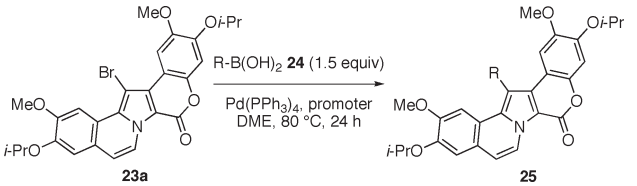
TABLE 1. Electrophilic Substitution Reaction of 22

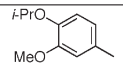
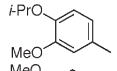
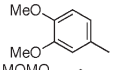
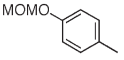


entry	electrophilic reagent	E	23	yield (%)
1	NBS	Br	**23a**	92
2	NCS	Cl	**23b**	96
3	SELECTFLUOR[a]	F	**23c**	53
4	$Me_2N^+{=}CH_2 \cdot I^-$	CH_2NMe_2	**23d**	97
5	$POCl_3$, DMF	CHO	**23e**	99

[a] 1-Chloromethyl-4-fluoro-1,4-diazabicyclo[2.2.2]octane bis(tetrafluoroborate).

TABLE 2. Palladium-Catalyzed Suzuki−Miyaura Coupling of 23a



entry	24	R	promoter	25	yield (%)
1	**24a**		A[a]	**25a**	0
2	**24a**		B[b]	**25a**	69
3	**24b**		B[b]	**25b**	87
4	**24c**		B[b]	**25c**	79
5	**24d**	Ph	B[b]	**25d**	81
6	**24e**[c]	Me	B[b]	**25e**	82

[a] Aqueous Na_2CO_3 (6.6 equiv). [b] CsF (2.0 equiv) and Ag_2O (1.2 equiv). [c] Trimethylboroxine was used.

(30) DFT calculation of **22** indicated high atomic charge and extended HOMO at the C-1 position. The calculation suggested that electrophilic substitution reaction could occur at C-1 selectively. See Supporting Information.

(31) Qiu, W.; Chen, S.; Sun, X.; Liu, Y.; Zhu, D. *Org. Lett.* **2006**, *8*, 867–870.

(32) Wilson, R. M.; Danishefsky, S. J. *J. Org. Chem.* **2006**, *71*, 8329–8351.

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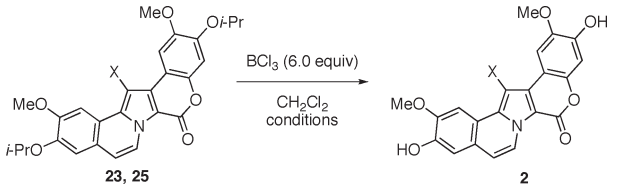
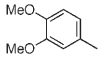
TABLE 3. Deprotection of Isopropyl Groups



entry	substrate	X	conditions	2	yield (%)
1	**23a**	Br	A[a]	**2a**	88
2	**23b**	Cl	B[b]	**2b**	52
3	**23c**	F	A[a]	**2c**	37
4	**23d**	CH_2NMe_2	C[c]	**2d**	53
5	**23e**	CHO	A[a]	**2e**	58
6	**25b**		A[a]	**2f**	84
7	**25d**	Ph	A[a]	**2g**	97
8	**25e**	Me	A[a]	**2h**	64

[a] −78 °C, 0.5 h → rt, 3 h. [b] −78 °C, 1 h → rt, 3 h. [c] −78 °C, 1 h → rt, 5 h.

Finally, selective deprotection of the isopropyl groups of **23** and **25** was performed (Table 3). Treatment of **23a**−**e**, **25b**, **25d**, and **25e** with 6.0 equiv of boron trichloride[6c] in dichloromethane at −78 °C and then at room temperature produced a variety of 1-substituted 1-dearyllamellarin D analogues **2a**−**h**. The yields of the products were dependent on the substituent at C-1.

Conclusion

We have developed an efficient route for the synthesis of 1-dearyllamellarin D (**1**) using directed lithiation, Suzuki−Miyaura coupling, and palladium-catalyzed direct arylation as the key reactions. Several electrophilic substitution reactions of the key intermediate **22** proceeded at C-1 selectively under mild conditions. The 1-brominated compound **23a** thus prepared underwent Suzuki−Miyaura coupling with arylboronic acids and trimethylboroxine using Ag_2O−CsF as a promoter. We believe the procedures described herein are highly useful for the synthesis of lamallarin analogues that have a variety of substituents at the C-1 position of the pentacyclic lamellarin framework. Biological evaluations of the analogues **1** and **2a**−**h** prepared in this study are in progress. The results will be reported in due course.

Experimental Section

Dimethyl *N*-[2-(3-Isopropoxy-4-methoxyphenyl)ethyl]-3-(4-isopropoxy-5-methoxy-2-methoxymethoxyphenyl)-4-(trifluoromethanesulfonyloxy)pyrrole-2,5-dicarboxylate (5). Under an argon atmosphere, a two-necked, round-bottomed flask was charged with bistriflate **3**[6c] (2.02 g, 3.00 mmol), boronic acid **4**[6c] (0.972 g, 3.60 mmol), $Pd(PPh_3)_4$ (69 mg, 0.06 mmol) and Na_2CO_3 (2.10 g, 14.8 mmol). The flask was evacuated and refilled with argon. To this mixture were added THF (60 mL) and degassed water (6 mL) sequentially. The mixture was refluxed for 2.5 h, cooled to room temperature, and evaporated. The product was extracted with dichloromethane, 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 (toluene−ethyl acetate = 10:1) to give **5** as colorless solid (1.69 g, 75%). Recrystallization from dichloromethane−hexane gave colorless powder. Mp 165−166 °C; IR (KBr) 1730, 1518, 1414, 1216, 1132, 1025, 989 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (d, J = 6.0 Hz, 6H), 1.38 (d, J = 6.0 Hz, 6H), 3.02 (t, J = 7.0 Hz, 2H), 3.34 (s, 3H), 3.58 (s, 3H), 3.81 (s, 3H), 3.82 (s, 3H), 3.91 (s, 3H), 4.52 (sep, J = 6.0 Hz, 1H), 4.57 (sep, J = 6.0 Hz, 1H), 6.71−6.74 (m, 2H), 6.76−6.80 (m, 2H), 6.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 22.2, 37.6, 48.7, 51.7, 51.8, 55.8, 56.1, 56.6, 71.4, 71.8, 96.0, 105.4, 112.2, 112.3, 115.3, 116.9, 117.1, 118.1 (q, J = 321 Hz), 118.5, 121.6, 124.2, 130.2, 136.2, 145.3, 147.3, 148.0, 149.3, 149.4, 159.3, 161.2. Anal. Calcd for $C_{33}H_{40}F_3NO_{13}S$: C, 53.01; H, 5.39; N, 1.87. Found: C, 52.94; H, 5.32; N, 1.71.

Methyl 3,4-Dihydro-7-isopropoxy-3-[2-(3-isopropoxy-4-methoxyphenyl)ethyl]-8-methoxy-4-oxo-1-(trifluoromethanesulfonyloxy)-[1]benzopyrano[3,4-*b*]pyrrole-2-carboxylate (6). To a solution of **5** (4.29 g, 5.74 mmol) in methanol (420 mL) was added concd HCl (42.0 mL) at room temperature. After being refluxed for 1 h, the mixture was cooled to room temperature, quenched with water, and evaporated under reduced pressure. The product was extracted with dichloromethane, and the extract was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was dissolved in dichloromethane (330 mL), and *p*-toluenesulfonic acid monohydrate (273 mg, 1.44 mmol) was added. The mixture was refluxed for 2 h, cooled to room temperature, and evaporated. The residue was purified by column chromatography over silica gel 60N (hexane−ethyl acetate = 3:1) to give **6** as white solid (3.75 g, 97%). Recrystallization from dichloromethane−hexane gave colorless powder. Mp 121−122 °C; IR (KBr) 1737, 1517, 1425, 1258, 1228, 1159, 1139 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (d, J = 6.2 Hz, 6H), 1.44 (d, J = 6.1 Hz, 6H), 3.03 (t, J = 7.3 Hz, 2H), 3.81 (s, 3H), 3.88 (s, 3H), 3.92 (s, 3H), 4.49 (sep, J = 6.2 Hz, 1H), 4.61 (sep, J = 6.2 Hz, 1H), 5.14 (t, J = 7.3 Hz, 2H), 6.66 (dd, J = 1.8 and 8.2 Hz, 1H), 6.76 (d, J = 1.8 Hz, 1H), 6.76 (d, J = 8.2 Hz, 1H), 6.92 (s, 1H), 7.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 22.1, 37.5, 48.8, 52.4, 56.1, 56.2, 71.4, 71.7, 103.2, 105.2, 106.1, 112.1, 115.6, 116.7, 118.5 (q, J = 321 Hz), 120.1, 121.6, 123.2, 129.4, 129.5, 146.0, 147.4, 147.6, 148.9, 149.3, 153.9, 158.9. Anal. Calcd for $C_{30}H_{32}F_3NO_{11}S$: C, 53.65; H, 4.80; N, 2.09. Found: C, 53.35; H, 4.82; N, 1.88.

Methyl 3,4-Dihydro-7-isopropoxy-3-[2-(3-isopropoxy-4-methoxyphenyl)ethyl]-8-methoxy-4-oxo-[1]benzopyrano[3,4-*b*]pyrrole-2-carboxylate (7). A mixture of **6** (3.75 g, 5.58 mmol), 5% Pd−C (2.81 g), *i*-Pr_2NEt (1.17 mL, 6.72 mmol), ethanol (100 mL), and THF (100 mL) was vigorously stirred under hydrogen atmosphere at room temperature for 20 h. The mixture was filtered through a pad of Celite, and the filtrate was evaporated. The residue was purified by column chromatography over silica gel 60N (hexane−ethyl acetate = 3:1) to give **7** as colorless solid (2.84 g, 97%). Recrystallization from dichloromethane−hexane gave colorless needles. Mp 137.5−138 °C; IR (KBr) 1736, 1707, 1512, 1442, 1267, 1233, 1181, 1141 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (d, J = 6.0 Hz, 6H), 1.43 (d, J = 6.2 Hz, 6H), 3.02 (t, J = 7.6 Hz, 2H), 3.82 (s, 3H), 3.90 (s, 3H), 3.93 (s, 3H), 4.51 (sep, J = 6.0 Hz, 1H), 4.58 (sep, J = 6.0 Hz, 1H), 5.13 (t, J = 7.6 Hz, 2H), 6.78 (s, 2H), 6.84 (s, 1H), 6.92 (s, 1H), 7.11 (s, 1H), 7.21 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 22.1, 37.8, 48.4, 52.0, 56.1, 56.5, 71.4, 71.7, 103.7, 104.7, 108.0, 109.3, 112.0, 116.8, 119.2, 121.6, 128.8, 130.4, 130.9, 145.9, 147.3, 147.6, 148.2, 149.1, 155.0, 160.7. Anal. Calcd for $C_{29}H_{33}NO_8$: C, 66.53; H, 6.35; N, 2.68. Found: C, 66.30; H, 6.42; N, 2.55.

3,4-Dihydro-7-isopropoxy-3-[2-(3-isopropoxy-4-methoxyphenyl)ethyl]-8- methoxy-4-oxo-[1]benzopyrano[3,4-*b*]pyrrole-2-carboxylic Acid (8). Under an argon atmosphere, a suspension of **7** (2.60 g, 4.97 mmol) in a degassed mixture of 40% aqueous KOH (200 mL) and ethanol (200 mL) was refluxed for 3 h. The solution was cooled to room temperature and concentrated

under reduced pressure. The pH of the solution was adjusted to 2 with concd HCl, and the product was extracted with dichloromethane. The extract was washed with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was dissolved in dichloromethane (400 mL) and *p*-toluenesulfonic acid monohydrate (0.237 g, 1.25 mmol) was added. The mixture was refluxed for 1 h and cooled to room temperature. The mixture was washed with water, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography over silica gel 60N (dichloromethane−methanol = 20:1) to give **8** as pale yellow solid (2.38 g, 94%). Recrystallization from dichloromethane−hexane gave pale yellow powder. Mp 197.5−198 °C; IR (KBr) 1737, 1681, 1513, 1263, 1233, 1178, 1143 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (d, J = 6.1 Hz, 6H), 1.43 (d, J = 6.1 Hz, 6H), 3.06 (t, J = 7.7 Hz, 2H), 3.81 (s, 3H), 3.96 (s, 3H), 4.53 (sep, J = 6.1 Hz, 1H), 4.60 (sep, J = 6.1 Hz, 1H), 5.17 (t, J = 7.7 Hz, 2H), 6.80 (s, 2H), 6.88 (s, 1H), 6.93 (s, 1H), 7.15 (s, 1H), 7.40 (s, 1H), 9.00 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 22.1, 37.8, 48.6, 56.1, 56.5, 71.5, 71.8, 103.6, 104.7, 109.1, 109.8, 112.1, 116.9, 120.2, 121.7, 128.8, 129.8, 130.3, 145.9, 147.3, 147.7, 148.3, 149.2, 155.0, 164.6. Anal. Calcd for $C_{28}H_{31}NO_8$: C, 66.00; H, 6.13; N, 2.75. Found: C, 65.70; H, 6.16; N, 2.69.

7-Isopropoxy-3-[2-(3-isopropoxy-4-methoxyphenyl)ethyl]-8-methoxy-[1]benzopyrano[3,4-*b*]pyrrol-4(3*H*)-one (9). Under an argon atmosphere, a mixture of **8** (1.20 g, 2.36 mmol) and copper(I) oxide (337 mg, 2.36 mmol) in quinoline (60 mL) was heated at 220 °C for 15 min. After cooling to room temperature, the mixture was filtered through a pad of Celite to remove copper(I) oxide. The filtrate was diluted with dichloromethane and washed successively with 6 M aqueous HCl 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 **9** as colorless solid (1.06 g, 97%). Recrystallization from dichloromethane−hexane gave colorless prisms. Mp 161−162 °C; IR (KBr) 1694, 1519, 1269, 1237, 1135 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (d, J = 6.0 Hz, 6H), 1.42 (d, J = 6.0 Hz, 6H), 3.05 (t, J = 6.9 Hz, 2H), 3.81 (s, 3H), 3.93 (s, 3H), 4.41 (sep, J = 6.0 Hz, 1H), 4.59 (sep, J = 6.0 Hz, 1H), 4.60 (t, J = 6.9 Hz, 2H), 6.41 (d, J = 2.8 Hz, 1H), 6.61−6.66 (m, 2H), 6.76 (d, J = 8.0 Hz, 1H), 6.82 (d, J = 2.8 Hz, 1H), 6.95 (s, 1H), 7.10 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 22.1, 37.7, 50.9, 56.0, 56.6, 71.4, 71.6, 100.5, 103.8, 104.8, 110.4, 112.1, 114.9, 116.8, 121.4, 130.5, 131.2, 132.8, 146.1, 147.3, 147.4, 147.7, 149.2, 155.4. Anal. Calcd for $C_{27}H_{31}NO_6$: C, 69.66; H, 6.71; N, 3.01. Found: C, 69.40; H, 6.78; N, 2.91.

1-(2-Hydroxy-4-isopropoxy-5-methoxyphenyl)-8-isopropoxy-9-methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline (10). Under an argon atmosphere, a solution of PIFA (52.0 mg, 0.121 mmol) and $BF_3 \cdot OEt_2$ (30.0 μL, 0.243 mmol) in dichloromethane (0.24 mL) was added dropwise to a solution of **9** (50.0 mg, 0.107 mmol) in dichloromethane (6 mL) at −40 °C. After being stirred for 1.5 h, the mixture was quenched with saturated NH_4Cl and allowed to warm to room temperature. The product was extracted with dichloromethane, 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 **10** as unstable gray foam (23.0 mg, 49%). IR (KBr) 3454, 1508, 1244, 1208, 1165, 1110, 1008 cm^{-1}; ^1H NMR (500 MHz, benzene-d_6) δ 1.14 (d, J = 6.0 Hz, 6H), 1.22 (d, J = 6.0 Hz, 6H), 2.49 (br s, 2H), 3.33 (s, 3H), 3.38 (s, 3H), 3.41 (t, J = 6.5 Hz, 2H), 4.29 (sep, J = 6.0 Hz, 1H), 4.36 (sep, J = 6.0 Hz, 1H), 5.55 (br s, 1H), 6.32 (d, J = 2.7 Hz, 1H), 6.41 (d, J = 2.7 Hz, 1H), 6.64 (s, 1H), 6.86 (s, 1H), 7.01 (s, 1H), 7.20 (s, 1H); ^{13}C NMR (125 MHz, benzene-d_6) δ 22.1, 22.4, 29.3, 44.7, 55.0, 56.5, 71.3, 71.8, 104.8, 108.1, 111.0, 114.2, 115.5, 116.3, 117.6, 120.9, 123.4, 123.8, 126.8, 145.4, 146.2, 148.7, 148.8, 150.8; HREIMS m/z calcd for $C_{26}H_{31}NO_5$ (M^+) 437.2202, found 437.2202.

8,9-Dihydro-3,11-diisopropoxy-2,12-dimethoxy-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (11).[22] Under an argon atmosphere, a mixture of **9** (100 mg, 0.196 mmol) and $Pd(OAc)_2$ (48.0 mg, 0.214 mmol) in acetonitrile (58 mL) was refluxed for 16 h. The mixture was cooled to room temperature and evaporated. The residue was dissolved in dichloromethane and filtered through a pad of Celite to remove palladium black. The filtrate was evaporated, and the residue was purified by column chromatography over silica gel 60N (hexane−ethyl acetate = 1:1−1:3) to give **11** as colorless solid (19.0 mg, 21%). Recrystallization from dichloromethane−hexane gave colorless needles. Mp 180−180.5 °C; IR (KBr) 1697, 1509, 1426, 1274, 1239, 1142, 1003 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (d, J = 5.8 Hz, 12H), 3.08 (t, J = 6.8 Hz, 2H), 3.95 (s, 3H), 3.96 (s, 3H), 4.56 (sep, J = 5.8 Hz, 1H), 4.60 (sep, J = 5.8 Hz, 1H), 4.70 (t, J = 6.8 Hz, 2H), 6.78 (s, 1H), 6.81 (s, 1H), 6.93 (s, 1H), 7.18 (s, 1H), 7.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 22.1, 28.3, 42.3, 56.3, 56.5, 71.6, 71.6, 95.3, 103.8, 104.8, 108.3, 110.2, 115.0, 115.1, 120.1, 125.7, 131.2, 140.2, 146.0, 147.3, 147.7, 148.3, 149.7, 155.5. Anal. Calcd for $C_{27}H_{29}NO_6$: C, 69.96; H, 6.31; N, 3.02. Found: C, 69.87; H, 6.32; N, 2.84.

***N*-Benzenesulfonyl-3-bromopyrrole (16).** A solution of bromine (52.6 g, 329 mmol) in acetic acid (200 mL) was added dropwise to a solution of **15**[26] (68.2 g, 329 mmol) in acetic acid (600 mL) at room temperature, and the mixture was refluxed for 1 h. The mixture was cooled to room temperature and evaporated. To the residue was added saturated aqueous $NaHCO_3$, and the mixture was extracted with dichloromethane. The extract was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography over silica gel 60N (hexane−toluene = 2:1) to give 3-bromopyrrole **16** as colorless solid (65.6 g, 70%). Recrystallization from methanol gave colorless granules. Mp 66.5−67 °C; IR (KBr) 1369, 1173, 1057, 728, 620, 588 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.29 (dd, J = 1.6 and 3.3 Hz, 1H), 7.09 (dd, J = 2.4 and 3.3 Hz, 1H), 7.18 (dd, J = 1.6 and 2.4 Hz, 1H), 7.51−7.56 (m, 2H), 7.61−7.67 (m, 1H), 7.85−7.89 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 102.2, 116.4, 119.7, 121.3, 127.0, 129.6, 134.3, 138.4. Anal. Calcd for $C_{10}H_8BrNO_2S$: C, 41.97; H, 2.82; N, 4.89. Found: C, 41.67; H, 2.52; N, 4.82.

Methyl *N*-Benzenesulfonyl-3-bromopyrrole-2-carboxylate (17). Under an argon atmosphere, a hexane solution of *n*-butyllithium (1.53 M, 29.3 mL, 44.8 mmol) was added dropwise to a solution of diisopropylamine (8.40 mL, 59.9 mmol) in THF (150 mL) at −78 °C. After being stirred for 15 min, the mixture was allowed to warm to 0 °C and immediately recooled to −78 °C. A solution of **16** (8.58 g, 30.0 mmol) in THF (90 mL) was added dropwise to the mixture at −78 °C. After being stirred for 1 h, a solution of methyl chloroformate (5.22 mL, 67.5 mmol) in THF (60 mL) was added dropwise, and the mixture was stirred for 30 min at −78 °C. The reaction mixture was allowed to warm to room temperature, quenched with saturated aqueous NH_4Cl, and evaporated. The products were extracted with diethyl ether, 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−toluene = 1:2) to give **17** as colorless solid (8.54 g, 83%). Recrystallization from diethyl ether−hexane gave colorless prisms. Mp 77−77.5 °C; IR (KBr) 1720, 1452, 1360, 1257, 1174, 1144, 600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 6.40 (d, J = 3.4 Hz, 1H), 7.53−7.58 (m, 3H), 7.62−7.68 (m, 1H), 7.93−7.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.1, 109.7, 115.3, 123.3, 126.8, 127.9, 129.0, 134.1, 138.7, 159.3. Anal. Calcd for $C_{12}H_{10}BrNO_4S$: C, 41.88; H, 2.93; N, 4.07. Found: C, 41.76; H, 2.80; N, 4.00.

Methyl *N*-Benzenesulfonyl-3-(4-isopropoxy-5-methoxy-2-methoxymethoxyphenyl)pyrrole-2-carboxylate (18). Under an argon atmosphere, a degassed solution of Na_2CO_3 (11.6 g, 0.109 mol) in water (32.0 mL) was added to a solution of **17** (5.66 g, 16.4 mmol),

4[6c] (6.70 g, 24.8 mmol) and $Pd(PPh_3)_4$ (1.15 g, 0.995 mmol) in DME (300 mL) at room temperature, and the mixture was refluxed for 24 h. The mixture was cooled to room temperature and evaporated. The products were extracted with dichloromethane, 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 (toluene−ethyl acetate = 10:1) to give **18** as yellow solid (6.59 g, 81%). Recrystallization from dichloromethane−hexane gave colorless prisms. Mp 131.5−132.5 °C; IR (KBr) 1736, 1512, 1374, 1232, 1179, 1113, 959, 608 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (d, J = 6.1 Hz, 6H), 3.19 (s, 3H), 3.62 (s, 3H), 3.79 (s, 3H), 4.52 (sep, J = 6.1 Hz, 1H), 4.86 (s, 2H), 6.40 (d, J = 3.2 Hz, 1H), 6.75 (s, 1H), 6.77 (s, 1H), 7.52−7.58 (m, 3H), 7.61−7.67 (m, 1H), 8.00−8.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 51.9, 55.9, 56.6, 71.6, 96.6, 105.9, 114.1, 114.3, 116.6, 122.6, 125.4, 127.8, 128.9, 131.1, 133.8, 139.3, 145.5, 147.8, 148.6, 161.3. Anal. Calcd for $C_{24}H_{27}NO_8S$: C, 58.88; H, 5.56; N, 2.86. Found: C, 58.97; H, 5.66; N, 2.75.

7-Isopropoxy-8-methoxy[1]benzopyrano[3,4-*b*]pyrrol-4(3*H*)-one (13). To a solution of **18** (6.28 g, 12.8 mmol) in methanol (400 mL) was added concd HCl (40 mL). The mixture was refluxed for 2 h, cooled to room temperature, and evaporated. The products were extracted with dichloromethane, and the extract was washed with water and brine, dried over Na_2SO_4, and evaporated. Under an argon atmosphere, the residue was dissolved in THF (350 mL), and a THF solution of TBAF (1.0 M, 19.5 mL, 19.5 mmol) was added dropwise to the mixture at room temperature. After being refluxed for 2 h, the mixture was cooled to room temperature, quenched with water, and evaporated. The products were extracted with dichloromethane, 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 = 2:1) to give **13** as white solid (3.45 g, 98%). Recrystallization from dichloromethane−hexane gave colorless powder. Mp 190.5−191 °C; IR (KBr) 3220, 1699, 1444, 1255, 1217, 1107, 1066 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (d, J = 6.2 Hz, 6H), 3.96 (s, 3H), 4.59 (sep, J = 6.2 Hz, 1H), 6.66 (t, J = 2.3 Hz, 1H), 7.00 (s, 1H), 7.19 (s, 1H), 7.44 (t, J = 2.7 Hz, 1H), 11.24 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 56.5, 71.7, 102.5, 104.0, 105.1, 110.5, 116.2, 129.6, 130.8, 145.9, 147.7, 147.8, 156.7. Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.91; H, 5.54; N, 5.00.

3-Isopropoxy-4,β-dimethoxystyrene (20). Under an argon atmosphere, potassium *tert*-butoxide (17.5 g, 156 mmol) was added portionwise to a suspension of (methoxymethyl)-triphenylphosphonium chloride (44.6 g, 130 mmol) in THF (260 mL) at 0 °C. After 15 min, a solution of **19** (20.2 g, 104 mmol) in THF (70 mL) was added dropwise, and the solution was stirred for 2 h at 0 °C and then for 4 h at room temperature. The mixture was quenched with water and evaporated. The residue was extracted with dichloromethane, 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) and then by distillation (93−94 °C, 0.07 mmHg) to give 21.6 g (93%) of **20** [(*E*)-isomer:(*Z*)-isomer = ca. 1:1] as colorless oil. IR (neat): 1645, 1510, 1462, 1263, 1212, 1138, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (d, J = 6.2 Hz, 6H), 1.36 (d, J = 6.2 Hz, 6H), 3.65 (s, 3H), 3.73 (s, 3H), 3.81 (s, 3H), 3.82 (s, 3H), 4.46−4.57 (m, 2H), 5.14 (d, J = 7.0 Hz, 1H), 5.75 (d, J = 12.8 Hz, 1H), 6.03 (d, J = 7.0 Hz, 1H), 6.76−6.81 (m, 4H), 6.91 (d, J = 12.8 Hz, 1H), 7.08 (dd, J = 2.0 and 8.4 Hz, 1H), 7.25 (d, J = 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 22.2, 56.0, 56.1, 56.4, 60.5, 71.4, 71.6, 104.8, 105.5, 111.8, 112.5, 113.5, 116.5, 118.3, 121.4, 129.0, 129.3, 146.5, 146.8, 147.4, 147.7, 148.7, 149.0; HREIMS m/z calcd for $C_{13}H_{18}O_3$ (M^+) 222.1256, found 222.1243.

2-(3-Isopropoxy-4-methoxyphenyl)ethanol (21).[29b] Under an argon atmosphere, 2 M aqueous HCl (13 mL) was added to a solution of **20** (19.6 g, 88.2 mmol) in THF (400 mL) at room temperature. After being refluxed for 2 h, the mixture was cooled to room temperature and evaporated. The product was extracted with diethyl ether, washed with water, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, and evaporated. The residue was dissolved in ethanol (350 mL), and $NaBH_4$ (6.67 g, 0.176 mol) was added portionwise to the solution at 0 °C. The mixture was stirred for 30 min at 0 °C and then for 16 h at room temperature. The mixture was quenched with water and evaporated. The product was extracted with dichloromethane, 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 **21** as colorless oil (16.3 g, 88%). Bp 99−103 °C (0.2 mmHg, bulb-to-bulb); IR (neat) 3407, 1511, 1261, 1233, 1137, 1111, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (d, J = 6.0 Hz, 6H), 1.82 (br s, 1H), 2.77 (t, J = 6.6 Hz, 2H), 3.80 (t, J = 6.6 Hz, 2H), 3.82 (s, 3H), 4.51 (sep, J = 6.0 Hz, 1H), 6.76 (dd, J = 1.9 and 7.9 Hz, 1H), 6.78 (d, J = 1.9 Hz, 1H), 6.82 (d, J = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 38.7, 56.1, 63.7, 71.5, 112.3, 117.1, 121.5, 131.0, 147.3, 149.2; HREIMS m/z calcd for $C_{12}H_{18}O_3$ (M^+) 210.1256, found 210.1252.

2-(2-Bromo-5-isopropoxy-4-methoxyphenyl)ethanol (14).[29] A solution of NBS (14.0 g, 78.7 mmol) in DMF (30 mL) was added dropwise to a solution of **21** (16.3 g, 77.5 mmol) in DMF (80 mL) at 0 °C. The mixture was stirred for 20 h at 0 °C and diluted with water. The product was extracted with dichloromethane, 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 **14** as pink solid (18.5 g, 83%). Recrystallization from dichloromethane−hexane gave colorless needles. Mp 67.5−68.5 °C; IR (KBr) 3336, 3258, 1514, 1263, 1215, 1170, 1029, 850 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (d, J = 6.2 Hz, 6H), 2.92 (t, J = 6.7 Hz, 2H), 3.82 (s, 3H), 3.83 (t, J = 6.7 Hz, 2H), 4.49 (sep, J = 6.2 Hz, 1H), 6.82 (s, 1H), 7.02 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 38.9, 56.2, 62.3, 71.9, 114.9, 116.4, 118.6, 129.7, 146.6, 149.8. Anal. Calcd for $C_{12}H_{17}BrO_3$: C, 49.84; H, 5.93. Found: C, 49.79; H, 6.15.

3-[2-(2-Bromo-5-isopropoxy-4-methoxyphenyl)ethyl]-7-isopropoxy-8-methoxy[1]benzopyrano[3,4-*b*]pyrrol-4(3*H*)-one (12). Under an argon atmosphere, triphenylphosphine (8.23 g, 31.4 mmol) and DIAD (6.2 mL, 31.5 mmol) were added in sequence to a mixed solution of **13** (4.29 g, 15.7 mmol) and **14** (9.07 g, 31.4 mmol) in THF (500 mL). After being refluxed for 16 h, the mixture was cooled to room temperature, diluted with water, and evaporated. The product was extracted with dichloromethane, 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 a mixture of **12** and diisopropyl hydrazinedicarboxylate. The latter hydrazine derivative was easily removed by bulb-to-bulb distillation (130 °C, 0.1 mmHg) to leave **12** as white solid (6.61 g, 77%). Recrystallization from dichloromethane−hexane gave colorless powder. Mp 139−140 °C; IR (KBr) 1718, 1501, 1262, 1233, 1208, 1111, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (d, J = 5.9 Hz, 6H), 1.43 (d, J = 5.9 Hz, 6H), 3.20 (t, J = 6.9 Hz, 2H), 3.82 (s, 3H), 3.93 (s, 3H), 4.27 (sep, J = 5.9 Hz, 1H), 4.58 (sep, J = 5.9 Hz, 1H), 4.64 (t, J = 6.9 Hz, 2H), 6.40 (d, J = 2.6 Hz, 1H), 6.51 (s, 1H), 6.84 (d, J = 2.6 Hz, 1H), 6.95 (s, 1H), 7.00 (s, 1H), 7.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 21.9, 37.8, 48.8, 56.2, 56.6, 71.6, 71.7, 100.6, 103.8, 104.8, 110.4, 114.4, 115.0, 116.0, 117.9, 129.1, 131.3, 132.9, 146.1, 146.8, 147.4, 147.7, 149.8, 155.4. Anal. Calcd for $C_{27}H_{30}BrNO_6$: C, 59.56; H, 5.55; N, 2.57. Found: C, 59.29; H, 5.55; N, 2.43.

8,9-Dihydro-3,11-diisopropoxy-2,12-dimethoxy-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (11).[22] Under an argon atmosphere, a mixture of **13** (6.60 g, 12.1 mmol), K_2CO_3 (3.69 g, 26.7 mmol) and $Pd(PPh_3)_4$ (701 mg, 0.607 mmol) in *N*,*N*-dimethylacetamide (85 mL) was heated at 125 °C for 20 h. After cooling to room temperature, the mixture was diluted with water and extracted with dichloromethane. 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 (dichloromethane−ethyl acetate = 20:1) to give **11** as colorless solid (5.01 g, 89%). The spectroscopic data of this product are identical with those described above.

3,11-Diisopropoxy-2,12-dimethoxy-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (22). A mixture of **11** (1.26 g, 2.72 mmol) and activated MnO_2 (< 5 μm, 12.6 g, 145 mmol) in dichloromethane (200 mL) was refluxed for 48 h. After cooling to room temperature, the mixture was passed through a pad of Celite and evaporated. The residue was purified by column chromatography over silica gel 60N (dichloromethane−ethyl acetate = 20:1) to give **22** as pale yellow solid (1.00 g, 80%). Recrystallization from dichloromethane−hexane gave colorless needles. Mp 180−181 °C; IR (KBr) 1698, 1489, 1440, 1276, 1220, 1148, 1108 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.44 (d, *J* = 6.2 Hz, 6H), 1.48 (d, *J* = 6.2 Hz, 6H), 3.99 (s, 3H), 4.06 (s, 3H), 4.59 (sep, *J* = 6.2 Hz, 1H), 4.72 (sep, *J* = 6.2 Hz, 1H), 6.93 (d, *J* = 7.3 Hz, 1H), 6.94 (s, 1H), 7.05 (s, 1H), 7.07 (s, 1H), 7.26 (s, 1H), 7.48 (s, 1H), 9.00 (d, *J* = 7.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 21.9, 56.2, 56.5, 71.3, 71.5, 91.2, 103.5, 104.5, 105.2, 109.0, 109.6, 110.4, 112.0, 118.2, 123.2, 124.0, 132.1, 138.4, 146.6, 147.2, 148.5, 149.2, 151.0, 155.3. Anal. Calcd for $C_{27}H_{27}NO_6$: C, 70.27; H, 5.90; N, 3.03. Found: C, 70.07; H, 5.93; N, 2.89.

3,11-Dihydroxy-2,12-dimethoxy-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (1). Under an argon atmosphere, a heptane solution of BCl_3 (1.0 M, 390 μL, 0.390 mmol) was added dropwise to a solution of **22** (30.0 mg, 65.0 μmol) in dichloromethane (6.5 mL) at −78 °C. After being stirred for 30 min at the same temperature, the reaction mixture was allowed to warm to room temperature and stirred for 3 h. The mixture was quenched with saturated $NaHCO_3$, and the product was 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 (dichloromethane−ethyl acetate = 20:1) to give **1** as gray powder (16.1 mg, 66%). Mp 234−246 °C (dec) (sealed capillary); IR (KBr) 3441, 1689, 1457, 1284, 1217, 1146 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.95 (s, 3H), 4.03 (s, 3H), 6.89 (s, 1H), 7.15 (d, *J* = 7.3 Hz, 1H), 7.20 (s, 1H), 7.53 (s, 1H), 7.62 (s, 1H), 7.77 (s, 1H), 8.83 (d, *J* = 7.3 Hz, 1H), 9.82 (s, 1H), 9.94 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.8, 55.9, 92.2, 103.5, 104.9, 105.6, 107.5, 108.1, 111.2, 112.0, 117.1, 121.9, 123.8, 131.9, 138.2, 145.3, 146.0, 148.1, 148.8, 149.5, 154.1; HREIMS *m*/*z* calcd for $C_{21}H_{15}NO_6$ (M^+) 377.0899, found 377.0892.

14-Bromo-3,11-diisopropoxy-2,12-dimethoxy-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (23a). A solution of NBS (234 mg, 1.31 mmol) in DMF (6.0 mL) was added dropwise to a solution of **22** (601 mg, 1.30 mmol) in DMF (20.0 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C and for 14 h at room temperature. The solution was diluted with water, and the product was extracted with dichloromethane. 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 (dichloromethane−ethyl acetate = 20:1) to give **23a** as pale yellow solid (647 mg, 92%). Recrystallization from dichloromethane−hexane gave colorless powder. Mp 212−213 °C; IR (KBr) 1706, 1515, 1433, 1271, 1215, 1110, 1042 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.46 (d, *J* = 6.2 Hz, 6H), 1.49 (d, *J* = 6.2 Hz, 6H), 3.93 (s, 3H), 3.99 (s, 3H), 4.60 (sep, *J* = 6.2 Hz, 1H), 4.72 (sep, *J* = 6.2 Hz, 1H), 6.86 (s, 1H), 6.86 (d, *J* = 7.3 Hz, 1H), 6.98 (s, 1H), 8.18 (s, 1H), 8.66 (s, 1H), 9.06 (d, *J* = 7.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 22.0, 56.0, 56.2, 71.1, 71.4, 82.2, 102.9, 105.2, 105.2, 108.1, 108.8, 110.0, 113.0, 118.1, 122.6, 124.9, 127.9, 132.1, 146.3, 146.5, 148.4, 148.8, 150.0, 154.4. Anal. Calcd for $C_{27}H_{26}BrNO_6$: C, 60.01; H, 4.85; N, 2.59. Found: C, 59.93; H, 4.83; N, 2.46.

14-Chloro-3,11-diisopropoxy-2,12-dimethoxy-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (23b). A solution of NCS (8.8 mg, 65.9 μmol) in DMF (1.0 mL) was added dropwise to a solution of **22** (30.0 mg, 65.0 μmol) in DMF (3.0 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C and for 12 h at room temperature. The solution was diluted with water, and the product was extracted with dichloromethane. 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 (dichloromethane−ethyl acetate = 20:1) to give **23b** as colorless solid (30.8 mg, 96%). Recrystallization from dichloromethane−hexane gave colorless powder. Mp 225.5−226.5 °C; IR (KBr) 1712, 1512, 1461, 1436, 1272, 1220, 1110, 1042 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.46 (d, *J* = 6.2 Hz, 6H), 1.49 (d, *J* = 6.2 Hz, 6H), 3.92 (s, 3H), 3.95 (s, 3H), 4.59 (sep, *J* = 6.2 Hz, 1H), 4.70 (sep, *J* = 6.2 Hz, 1H), 6.81 (d, *J* = 7.3 Hz, 1H), 6.83 (s, 1H), 6.96 (s, 1H), 7.88 (s, 1H), 8.33 (s, 1H), 8.95 (d, *J* = 7.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 22.0, 55.9, 56.2, 71.1, 71.4, 98.0, 102.9, 105.0, 105.4, 106.8, 108.5, 110.0, 112.8, 117.8, 122.4, 124.6, 126.5, 131.4, 146.4, 146.6, 148.4, 148.7, 150.2, 154.4. Anal. Calcd for $C_{27}H_{26}ClNO_6$: C, 65.39; H, 5.28; N, 2.82. Found: C, 65.20; H, 5.27; N, 2.69.

14-Fluoro-3,11-diisopropoxy-2,12-dimethoxy-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (23c). SELECTFLUOR (23.4 mg, 66.1 μmol) was added to a solution of **22** (30.0 mg, 65.0 μmol) in acetnitrile (1.0 mL) containing H_2O (100 μL) at 0 °C. After being stirred for 15 h at 0 °C, the mixture was quenched with water. The product was extracted with dichloromethane, 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 (dichloromethane−ethyl acetate = 20:1) to give **23c** as gray solid (16.6 mg, 53%). Recrystallization from dichloromethane−hexane gave colorless needles. Mp 208.5−209.5 °C; IR (KBr) 1703, 1505, 1476, 1280, 1227, 1109, 1046 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.45 (d, *J* = 6.1 Hz, 6H), 1.48 (d, *J* = 6.1 Hz, 6H), 3.95 (s, 3H), 3.98 (s, 3H), 4.59 (sep, *J* = 6.1 Hz, 1H), 4.70 (sep, *J* = 6.1 Hz, 1H), 6.82 (d, *J* = 7.2 Hz, 1H), 6.88 (s, 1H), 7.01 (s, 1H), 7.36 (s, 1H), 7.64 (s, 1H), 8.84 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 22.0, 55.9, 56.3, 71.3, 71.5, 102.6 (d, *J* = 4.3 Hz), 103.2, 104.9 (d, *J* = 8.5 Hz), 106.0 (d, *J* = 3.1 Hz), 107.2, 110.3, 112.3, 116.6 (d, *J* = 10.4 Hz), 116.8 (d, *J* = 3.7 Hz), 122.1, 123.3 (d, *J* = 19.5 Hz), 123.5, 138.2 (d, *J* = 244 Hz), 146.1, 147.1, 148.4, 148.8, 150.9, 154.7. Anal. Calcd for $C_{27}H_{26}FNO_6$: C, 67.63; H, 5.47; N, 2.92. Found: C, 67.48; H, 5.48; N, 2.78.

14-(*N*,*N*-Dimethylaminomethyl)-3,11-diisopropoxy-2,12-dimethoxy-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (23d). A mixture of **22** (200 mg, 0.433 mmol) and *N*,*N*-dimethylmethyleneammonium iodide (241 mg, 1.30 mmol) in dichloromethane (7.0 mL) was refluxed for 24 h. After cooling, saturated $NaHCO_3$ was added, and the product was extracted with dichloromethane. 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 (dichloromethane−ethyl acetate = 20:1) to give **23d** as white solid (218 mg, 97%). Recrystallization from dichloromethane−hexane gave yellow powder. Mp 214.5−215.5 °C; IR (KBr) 1698, 1428, 1264, 1229, 1180, 1113, 1057 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.45 (d, *J* = 6.2 Hz, 6H), 1.48 (d, *J* = 6.2 Hz, 6H), 2.49 (s, 6H), 4.00 (s, 3H), 4.05 (s, 3H), 4.10 (br s, 2H), 4.61 (sep, *J* = 6.2 Hz, 1H), 4.74 (sep, *J* = 6.2 Hz, 1H), 6.95 (d, *J* = 7.3 Hz, 1H), 6.96 (s, 1H), 7.09

(s, 1H), 7.91 (s, 1H), 8.39 (s, 1H), 9.23 (d, $J = 7.3$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 22.0, 44.9, 54.3, 56.2, 56.5, 71.2, 71.4, 103.5, 107.3, 107.7, 108.2, 110.1, 110.4, 112.7, 119.1, 123.0, 125.2, 130.4, 136.5, 146.4, 146.7, 147.9, 148.5, 150.6, 155.2. Anal. Calcd for $C_{30}H_{34}N_2O_6$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.18; H, 6.71; N, 5.32.

14-Formyl-3,11-diisopropoxy-2,12-dimethoxy-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (23e). Phosphorus oxychloride (21.0 μL, 229 μmol) was added dropwise to DMF (1.00 mL, 12.9 mmol) at 0 °C. After being stirred for 1 h at 0 °C, **22** (31.8 mg, 68.9 μmol) was added, and the mixture was stirred for 15 min at 0 °C. The reaction mixture was heated at 60 °C, and stirring was continued for 24 h. After cooling, the mixture was quenched with saturated $NaHCO_3$, and the product was extracted with dichloromethane. 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 (dichloromethane−ethyl acetate = 20:1) to give **23e** as pale yellow solid (33.5 mg, 99%). Recrystallization from dichloromethane−hexane gave colorless powder. Mp 228−228.5 °C (sealed capillary); IR (KBr) 1718, 1657, 1517, 1271, 1227, 1180, 1109 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.48 (d, $J = 6.2$ Hz, 6H), 1.52 (d, $J = 6.2$ Hz, 6H), 3.98 (s, 3H), 4.01 (s, 3H), 4.64 (sep, $J = 6.2$ Hz, 1H), 4.78 (sep, $J = 6.2$ Hz, 1H), 6.87 (s, 1H), 7.06 (s, 1H), 7.13 (d, $J = 7.1$ Hz, 1H), 8.19 (s, 1H), 8.54 (s, 1H), 9.25 (d, $J = 7.1$ Hz, 1H), 10.70 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 21.9, 56.2, 56.3, 71.3, 71.5, 102.5, 108.4, 108.5, 109.1, 109.2, 110.5, 112.5, 115.1, 118.0, 122.6, 127.2, 133.9, 139.6, 146.8, 147.4, 149.5, 150.6, 151.0, 154.7, 183.5; HREIMS m/z calcd for $C_{28}H_{27}NO_7$ (M^+) 489.1788, found 489.1792.

Suzuki−Miyaura Coupling of Bromide 23a with Arylboronic Acid 24. General Procedure. Under an argon atmosphere, a mixture of **23a** (31.0 mg, 57.4 μmol), **24** (90.5 μmol), CsF (17.0 mg, 0.112 mmol), Ag_2O (16.0 mg, 69.0 μmol), and $Pd(PPh_3)_4$ (7.0 mg, 6.1 μmol) in DME (2 mL) was heated at 80 °C for 24 h. After cooling, the mixture was diluted with water, and the product was extracted with dichloromethane. The extract was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography to give **25**.

3,11-Diisopropoxy-14-(4-isopropoxy-3-methoxyphenyl)-2,12-dimethoxy-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (25a).[6c] According to the general procedure, **23a** (31.0 mg, 57.4 μmol) and **24a** (19.0 mg, 90.5 μmol) were reacted. After successive purifications by column chromatography over silica gel 60N using different solvent systems (dichloromethane−ethyl acetate = 20:1 and hexane−ethyl acetate = 2:1), **25a** was obtained as pale yellow solid (24.8 mg, 69%). Recrystallization from dichloromethane−hexane gave colorless powder. Mp 190.5−191.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (d, $J = 6.1$ Hz, 6H), 1.44 (d, $J = 6.1$ Hz, 12H), 3.44 (s, 3H), 3.45 (s, 3H), 3.84 (s, 3H), 4.57 (sep, $J = 6.1$ Hz, 1H), 4.64 (sep, $J = 6.1$ Hz, 1H), 4.70 (sep, $J = 6.1$ Hz, 1H), 6.75 (s, 1H), 6.97 (s, 1H), 7.02 (d, $J = 7.4$ Hz, 1H), 7.10 (s, 1H), 7.13 (s, 1H), 7.16−7.19 (m, 3H), 9.22 (d, $J = 7.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 21.8, 21.9, 21.9, 21.9, 21.9, 55.1, 55.4, 56.1, 71.2, 71.4, 71.8, 103.4, 105.4, 105.6, 107.7, 109.9, 110.4, 110.9, 112.2, 115.0, 116.9, 118.9, 123.1, 123.8, 124.6, 128.7, 129.3, 134.3, 146.4, 146.5, 147.0, 147.7, 148.3, 150.0, 151.3, 155.4. These spectroscopic data are identical with those previously reported.[6c]

14-(3,4-Dimethoxyphenyl)-3,11-diisopropoxy-2,12-dimethoxy-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (25b).[22] According to the general procedure, **23a** (130 mg, 0.241 mmol) and **24b** (66.0 mg, 0.363 mmol) were reacted. After successive purifications by column chromatography over silica gel 60N using different solvent systems (dichloromethane−ethyl acetate = 40:1 and toluene−ethyl acetate = 5:1), **25b** was obtained as pale yellow solid (125 mg, 87%). Recrystallization from dichloromethane−hexane gave colorless powder. Mp 208−209 °C; IR (KBr) 1705, 1431, 1261, 1225, 1029 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (d, $J = 6.0$ Hz, 6H), 1.44 (d, $J = 6.0$ Hz, 6H), 3.44 (s, 3H), 3.45 (s, 3H), 3.89 (s, 3H), 4.00 (s, 3H), 4.56 (sep, $J = 6.0$ Hz, 1H), 4.70 (sep, $J = 6.0$ Hz, 1H), 6.74 (s, 1H), 6.95 (s, 1H), 7.01 (d, $J = 7.4$ Hz, 1H), 7.10 (s, 1H), 7.13−7.18 (m, 2H), 7.16 (s, 1H), 7.21−7.25 (m, 1H), 9.21 (d, $J = 7.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 21.8, 21.9, 21.9, 55.2, 55.5, 56.2, 56.3, 71.2, 71.4, 103.4, 105.5, 105.6, 107.8, 109.9, 110.4, 110.9, 111.9, 112.3, 114.5, 119.0, 123.2, 124.2, 124.7, 128.3, 129.4, 134.4, 146.5, 146.6, 147.9, 148.5, 149.0, 149.9, 150.2, 155.6; HREIMS m/z calcd for $C_{35}H_{35}NO_8$ (M^+) 597.2363, found 597.2372.

3,11-Diisopropoxy-2,12-dimethoxy-14-(4-methoxymethoxyphenyl)-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (25c). According to the general procedure, **23a** (30.0 mg, 55.5 μmol) and **24c** (15.2 mg, 83.5 μmol) were reacted. After chromatographic purification over silica gel 60N (dichloromethane−ethyl acetate = 20:1), **25c** was obtained as pale yellow solid (26.1 mg, 79%). Recrystallization from dichloromethane−hexane gave colorless powder. Mp 200−201 °C; IR (KBr) 1703, 1430, 1264, 1179, 1039, 992 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (d, $J = 6.1$ Hz, 6H), 1.43 (d, $J = 6.1$ Hz, 6H), 3.43 (s, 3H), 3.45 (s, 3H), 3.50 (s, 3H), 4.57 (sep, $J = 6.1$ Hz, 1H), 4.69 (sep, $J = 6.1$ Hz, 1H), 5.28 (s, 2H), 6.69 (s, 1H), 6.96 (s, 1H), 7.01 (d, $J = 7.3$ Hz, 1H), 7.09 (s, 1H), 7.12 (s, 1H), 7.28−7.33 (m, 2H), 7.53−7.58 (m, 2H), 9.21 (d, $J = 7.3$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 21.9, 55.1, 55.4, 55.9, 71.3, 71.5, 94.3, 103.6, 105.5, 105.7, 107.9, 110.0, 110.6, 110.7, 112.3, 117.4, 119.1, 123.2, 124.7, 129.4, 129.5, 133.1, 134.5, 146.6, 146.6, 147.9, 148.5, 150.2, 155.6, 157.1; HREIMS m/z calcd for $C_{35}H_{35}NO_8$ (M^+) 597.2363, found 597.2352.

3,11-Diisopropoxy-2,12-dimethoxy-14-phenyl-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (25d). According to the general procedure, **23a** (30.0 mg, 55.5 μmol) and **24d** (10.2 mg, 83.7 μmol) were reacted. After chromatographic purification over silica gel 60N (dichloromethane−ethyl acetate = 20:1), **25d** was obtained as pale yellow solid (24.2 mg, 81%). Recrystallization from dichloromethane−hexane gave colorless powder. Mp 229.5−230.5 °C; IR (KBr) 1705, 1430, 1264, 1227, 1178, 1036 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (d, $J = 6.0$ Hz, 6H), 1.43 (d, $J = 6.0$ Hz, 6H), 3.35 (s, 3H), 3.37 (s, 3H), 4.57 (sep, $J = 6.0$ Hz, 1H), 4.69 (sep, $J = 6.0$ Hz, 1H), 6.61 (s, 1H), 6.96 (s, 1H), 7.02 (d, $J = 7.4$ Hz, 1H), 7.05 (s, 1H), 7.09 (s, 1H), 7.51−7.59 (m, 1H), 7.62−7.67 (m, 4H), 9.23 (d, $J = 7.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 21.9, 55.0, 55.3, 71.2, 71.5, 103.5, 105.4, 105.6, 108.0, 109.9, 110.4, 111.2, 112.4, 119.0, 123.2, 124.7, 128.4, 129.3, 129.5, 132.0, 134.2, 136.3, 146.5, 146.6, 147.8, 148.4, 150.2, 155.6; HREIMS m/z calcd for $C_{33}H_{31}NO_6$ (M^+) 537.2151, found 537.2137.

3,11-Diisopropoxy-2,12-dimethoxy-14-methyl-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (25e). According to the general procedure, **23a** (30.0 mg, 55.5 μmol) and trimethylboroxine (**24e**) (12.0 μL, 85.8 μmol) were reacted. The product was purified by column chromatography over silica gel 60N (dichloromethane−ethyl acetate = 20:1) and subsequently by semipreparative HPLC (COSMOSIL, 5C_{18}-MS-II) (CH_3CN) to give **25e** as pale yellow solid (21.6 mg, 82%). Recrystallization from dichloromethane−hexane gave pale yellow powder. 174.5−187 °C (dec) (sealed capillary); IR (KBr) 1688, 1468, 1430, 1277, 1227, 1053 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (d, $J = 6.1$ Hz, 6H), 1.48 (d, $J = 6.1$ Hz, 6H), 3.06 (s, 3H), 3.99 (s, 3H), 4.05 (s, 3H), 4.62 (sep, $J = 6.1$ Hz, 1H), 4.74 (sep, $J = 6.1$ Hz, 1H), 6.93 (d, $J = 7.4$ Hz, 1H), 7.01 (s, 1H), 7.13 (s, 1H), 7.68 (s, 1H), 7.96 (s, 1H), 9.20 (d, $J = 7.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 21.9, 22.0, 56.2, 56.8, 71.3, 71.5, 103.9, 105.6, 106.3, 107.0, 107.9, 110.9, 111.0, 112.1, 119.8, 123.3, 125.1, 129.2, 134.7, 146.8, 146.8, 148.0, 148.3, 150.4, 155.4; HREIMS m/z calcd for $C_{28}H_{29}NO_6$ (M^+) 475.1995, found 475.2001.

Deprotection of Isopropyl Groups of 23 and 25. General Procedure. Under an argon atmosphere, a heptane solution of BCl_3 (1.0 M, 390 μL, 0.390 mmol) was added dropwise to a solution of **23** or **25** (64.8 μmol) in dichloromethane (6.5 mL) at −78 °C. After being stirred under the conditions shown in Table 3, the mixture was quenched with saturated aqueous $NaHCO_3$, and the product was extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4, and evaporated. The residue was triturated with dichloromethane and filtered to give **2**.

14-Bromo-3,11-dihydroxy-2,12-dimethoxy-6*H*-[1]benzopyrano-[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (2a). According to the general procedure, **23a** (35.0 mg, 64.8 μmol) was reacted to give **2a** as pale gray powder (26.1 mg, 88%). Mp > 300 °C (sealed capillary); IR (KBr) 3439, 1697, 1433, 1281, 1212, 1161, 1045 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.80 (s, 3H), 3.89 (s, 3H), 6.73 (s, 1H), 6.99 (d, J = 7.3 Hz, 1H), 7.07 (s, 1H), 7.99 (s, 1H), 8.49 (s, 1H), 8.79 (d, J = 7.3 Hz, 1H), 9.92 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.2, 55.5, 80.9, 103.5, 104.5, 104.7, 106.9, 107.1, 111.4, 112.8, 116.4, 121.4, 124.8, 127.1, 131.5, 144.4, 146.0, 148.2, 148.3, 148.5, 153.2; HREIMS m/z calcd for $C_{21}H_{14}BrNO_6$ (M^+) 455.0004, found 454.9993.

14-Chloro-3,11-dihydroxy-2,12-dimethoxy-6*H*-[1]benzopyrano-[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (2b). According to the general procedure, **23b** (48.3 mg, 97.4 μmol) was reacted to give **2b** as pale gray powder (20.9 mg, 52%). Mp > 300 °C (sealed capillary); IR (KBr) 3446, 1701, 1437, 1281, 1215, 1159, 1047 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.86 (s, 3H), 3.94 (s, 3H), 6.83 (s, 1H), 7.12 (d, J = 7.4 Hz, 1H), 7.17 (s, 1H), 7.87 (s, 1H), 8.36 (s, 1H), 8.86 (d, J = 7.4 Hz, 1H), 9.97 (br s, 1H), 10.07 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.1, 55.5, 96.3, 103.5, 104.2, 104.8, 105.6, 106.6, 111.3, 112.7, 116.1, 121.2, 124.6, 125.7, 130.8, 144.6, 145.9, 148.2, 148.5, 148.5, 153.2; HREIMS m/z calcd for $C_{21}H_{14}ClNO_6$ (M^+) 411.0510, found 411.0503.

14-Fluoro-3,11-dihydroxy-2,12-dimethoxy-6*H*-[1]benzopyrano-[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (2c). According to the general procedure, **23c** (60.0 mg, 125 μmol) was reacted to give **2c** as pale gray powder (18.1 mg, 37%). Mp > 300 °C (sealed capillary); IR (KBr) 3455, 3222, 1695, 1478, 1432, 1286, 1209, 1160, 1053 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.86 (s, 3H), 3.92 (s, 3H), 6.80 (s, 1H), 7.01 (d, J = 7.3 Hz, 1H), 7.13 (s, 1H), 7.21 (s, 1H), 7.50 (s, 1H), 8.63 (d, J = 7.3 Hz, 1H), 9.92 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.3, 55.7, 101.4 (d, J = 4.8 Hz), 103.6, 104.2 (d, J = 8.9 Hz), 105.3 (d, J = 2.9 Hz), 105.5 (d, J = 3.1 Hz), 111.4, 112.3, 115.0 (d, J = 4.3 Hz), 115.9 (d, J = 9.5 Hz), 120.9, 122.8 (d, J = 19.7 Hz), 123.4, 136.7 (d, J = 242 Hz), 145.2, 145.6, 148.2, 148.6, 149.2, 153.5 (d, J = 2.7 Hz); HREIMS m/z calcd for $C_{21}H_{14}FNO_6$ (M^+) 395.0805, found 395.0808.

14-(*N*,*N*-Dimethylaminomethyl)-3,11-dihydroxy-2,12-dimethoxy-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (2d). According to the general procedure, **23d** (26.3 mg, 50.7 μmol) was reacted to give **2d** as pale gray powder (11.6 mg, 53%). Mp 215−230 °C (dec) (sealed capillary); IR (KBr) 3459, 1673, 1428, 1284, 1238, 1166, 1059 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.43 (s, 6H), 3.93 (s, 3H), 4.00 (s, 3H), 4.08 (s, 2H), 6.89 (s, 1H), 7.18 (d, J = 7.3 Hz, 1H), 7.21 (s, 1H), 7.89 (s, 1H), 8.34 (s, 1H), 9.07 (d, J = 7.3 Hz, 1H), 9.94 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 44.3, 53.4, 55.6, 55.9, 103.8, 106.8, 107.0, 107.2, 107.5, 108.4, 111.4, 112.6, 117.5, 121.8, 124.9, 130.0, 136.0, 144.6, 146.2, 147.7, 148.2, 148.8, 154.1; HREIMS m/z calcd for $C_{24}H_{22}N_2O_6$ (M^+) 434.1478, found 434.1500.

14-Formyl-3,11-dihydroxy-2,12-dimethoxy-6*H*-[1]benzopyrano-[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (2e). According to the general procedure, **23e** (41.5 mg, 84.8 μmol) was reacted to give **2e** as pale yellow powder (20.0 mg, 58%). Mp 185−195 °C (dec) (sealed capillary); IR (KBr) 3417, 1698, 1518, 1419, 1390, 1281, 1157 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.94 (s, 3H), 4.04 (s, 3H), 6.92 (s, 1H), 7.33 (s, 1H), 7.51 (d, J = 7.3 Hz, 1H), 8.51 (s, 1H), 8.62 (s, 1H), 9.25 (d, J = 7.3 Hz, 1H), 10.23 (br s, 2H), 10.79 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.6, 55.8, 103.4, 107.1, 108.4, 109.5, 109.7, 111.1, 111.7, 114.9, 116.6, 121.7, 127.2, 133.0, 139.2, 144.9, 147.0, 149.3, 149.5, 150.5, 153.9, 183.7; HREIMS m/z calcd for $C_{22}H_{15}NO_7$ (M^+) 405.0849, found 405.0861.

14-(3,4-Dimethoxyphenyl)-3,11-dihydroxy-2,12-dimethoxy-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (2f).[7e,22] According to the general procedure, **25b** (57.4 mg, 96.0 μmol) was reacted to give **2f** as pale gray powder (41.2 mg, 84%). Mp 280−295 °C (dec) (sealed capillary); IR (KBr) 3383, 1698, 1433, 1278, 1142, 1026 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.36 (s, 3H), 3.37 (s, 3H), 3.77 (s, 3H), 3.87 (s, 3H), 6.68 (s, 1H), 6.88 (s, 1H), 7.09 (s, 1H), 7.16 (dd, J = 1.9 and 8.1 Hz, 1H), 7.20 (s, 1H), 7.22 (d, J = 1.9 Hz, 1H), 7.22 (d, J = 7.4 Hz, 1H), 7.29 (d, J = 8.1 Hz, 1H), 9.02 (d, J = 7.4 Hz, 1H), 9.84 (br s, 1H), 9.93 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 54.4, 55.0, 55.8, 55.9, 103.7, 105.2, 105.6, 106.4, 108.2, 110.4, 111.4, 112.3, 113.0, 114.6, 117.4, 121.9, 123.6, 124.6, 127.2, 128.8, 133.9, 144.5, 146.2, 147.8, 148.3, 148.5, 148.9, 149.8, 154.2; HREIMS m/z calcd for $C_{29}H_{23}NO_8$ (M^+) 513.1424, found 513.1408.

3,11-Dihydroxy-2,12-dimethoxy-14-phenyl-6*H*-[1]benzopyrano-[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (2g). According to the general procedure, **25d** (24.2 mg, 45.0 μmol) was reacted to give **2g** as pale gray powder (19.8 mg, 97%). Mp 263−280 °C (dec) (sealed capillary); IR (KBr) 3446, 1675, 1425, 1279, 1241, 1200, 1167, 1041 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.27 (s, 3H), 3.29 (s, 3H), 6.51 (s, 1H), 6.86 (s, 1H), 6.94 (s, 1H), 7.18 (s, 1H), 7.19 (d, J = 7.3 Hz, 1H), 7.59−7.72 (m, 5H), 8.98 (d, J = 7.3 Hz, 1H), 9.87 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 54.4, 54.9, 103.8, 105.1, 105.3, 106.7, 108.1, 110.4, 111.6, 112.4, 117.3, 122.0, 124.7, 128.5, 128.6, 129.5, 131.5, 133.7, 135.4, 144.6, 146.3, 147.8, 148.3, 148.6, 154.3; HREIMS m/z calcd for $C_{27}H_{19}NO_6$ (M^+) 453.1212, found 453.1216.

3,11-Dihydroxy-2,12-dimethoxy-14-methyl-6*H*-[1]benzopyrano-[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (2h). According to the general procedure, **25e** (58.5 mg, 123 μmol) was reacted to give **2h** as pale gray powder (31.0 mg, 64%). Mp 280−295 °C (dec) (sealed capillary); IR (KBr) 3384, 1688, 1427, 1280, 1206, 1153, 1052 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.76 (s, 3H), 3.88 (s, 3H), 3.94 (s, 3H), 6.80 (s, 1H), 6.96 (d, J = 7.2 Hz, 1H), 7.12 (s, 1H), 7.45 (s, 1H), 7.72 (s, 1H), 8.81 (d, J = 7.2 Hz, 1H), 9.84 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.0, 55.3, 55.8, 103.8, 104.7, 105.5, 106.1, 106.2, 108.9, 111.6, 111.8, 118.0, 121.6, 124.4, 128.3, 133.9, 144.7, 145.9, 147.4, 147.7, 148.5, 153.8; HREIMS m/z calcd for $C_{22}H_{17}NO_6$ (M^+) 391.1056, found 391.1058.

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Supporting Information Available: General experimental methods, experimental data for **I** and **II**, DFT-calculated atomic charge distribution and HOMO of **22**, Cartesian coordinates of the DFT-optimized geometry of **22**, ^1H NMR and ^{13}C NMR spectra of all compounds synthesized in this work, and NOESY spectrum of **10** and HMQC, HMBC spectra of **10**, **22**, and **23a**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.