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Modular Total Synthesis of Lamellarin D

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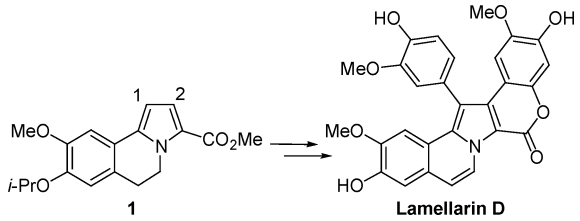

A modular total synthesis of lamellarin D, a marine alkaloid with potent cytotoxic as well as topoisomerase I inhibition properties, has been accomplished. A sequential and regioselective bromination/Suzuki cross-coupling procedure was applied for the introduction of aryl groups at positions 1 and 2 of scaffold **1**. Microwave-assisted 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) oxidation to yield pyrroloisoquinoline **15**, followed by phenol group deprotection and subsequent lactonization, gave lamellarin D (18% in eight steps from **1**).

Lamellarin D is a potent cytotoxic agent first isolated in 1985 by Faulkner and co-workers from the marine prosobranch mollusc *Lamellaria* sp.[1] Since then, a family of more than 30 lamellarins has been isolated from natural sources, and several synthetic strategies have been reported.[2] Recently, lamellarin D was identified as a potent inhibitor of topoisomerase I, thus providing some insight regarding its biological mechanism of action.[3] Furthermore, a structure−activity relationship (SAR) study with derivatives of lamellarin D afforded candidates for in vivo preclinical development of their antitumor activity.[4] The total synthesis of lamellarin D was achieved utilizing a modification of the strategy developed by Banwell and co-workers for the synthesis of lamellarin K.[5] This strategy allowed the preparation of several derivatives by acylation of the free phenolic sites.

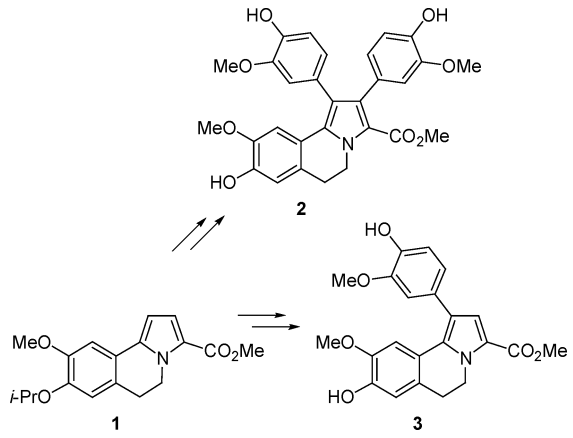

FIGURE 1. Structures of compounds **1**−**3**.

In addition, Ishibashi et al. described a synthetic route to lamellarin D[6] which they used for the preparation and biological evaluation of 10 derivatives that differ from the natural product in the substitution pattern of the nonheterocyclic aromatic rings. Important conclusions about the relation between substitution and activity were reached from that study.[7]

To prepare libraries of biologically active analogues of such natural products for lead discovery and/or optimization in medicinal chemistry, it is essential to have robust and versatile chemistries at hand. To that end, we have developed an efficient and highly convergent synthetic route to lamellarin D.

In a previous communication, we described the utility of methyl 5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-carboxylate **1** as a scaffold for the synthesis of open-chain lamellarin analogue **2**, which contains two methoxyphenols on the pyrrole ring, and for the simplified lamellarin analogue **3** (Figure 1).[8]

Derivative **2** differs from lamellarin D in lacking the lactone ring and the aromatization of the isoquinoline ring, structural modifications that afford conformational flexibility, whereas compound **3** lacks the entire aryl ring at position 2 of the scaffold. Compounds **2** and **3** were obtained using a synthetic procedure based on selective halogenation of the pyrrole ring followed by a Pd(0)-catalyzed Suzuki cross-coupling reaction.

Dibromination of the scaffold was accomplished in excellent yield using an excess of NBS in THF. Furthermore, regioselective monobromination was achieved in excellent yield by modifying the reaction time and the amount of NBS. Both compounds, **2** and **3**, proved to have cytotoxic effects on cancer cell lines; thus, the preparation and evaluation of a library of related compounds is in progress.

The total synthesis of lamellarin D described in the present paper is based on the findings described for preparation of **2** and **3**. This new protocol involves two

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(1) Andersen, R. J.; Faulkner, J.; Chun-heng, H.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1985**, *107*, 5493.

(2) For a recent review, see: Cironi, P.; Albericio, F.; Álvarez, M. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Joule, J. A., Eds.; Pergamon: Oxford, UK, 2004; Vol. 16, pp 1.

(3) Facompré, M.; Tardy, C.; Bal-Mahieu, C.; Colson, P.; Pérez, C.; Manzanares, I.; Cuevas, C.; Bailly, C. *Cancer Res.* **2003**, *63*, 7392.

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(5) Banwell, M.; Flynn, B.; Hockless, D. *Chem. Commun*. **1997**, 259.

(6) Ishibashi, F.; Miyazaki, Y.; Iwao, M. *Tetrahedron* **1997**, *53*, 5951.

(7) Ishibashi, F.; Tanabe, S.; Oda, T.; Iwao M. *J. Nat. Prod*. **2002**, *65*, 500.

(8) Olsen, C. A.; Parera, N.; Albericio, F.; Álvarez, M. *Tetrahedron Lett*. **2005**, *46*, 2041.

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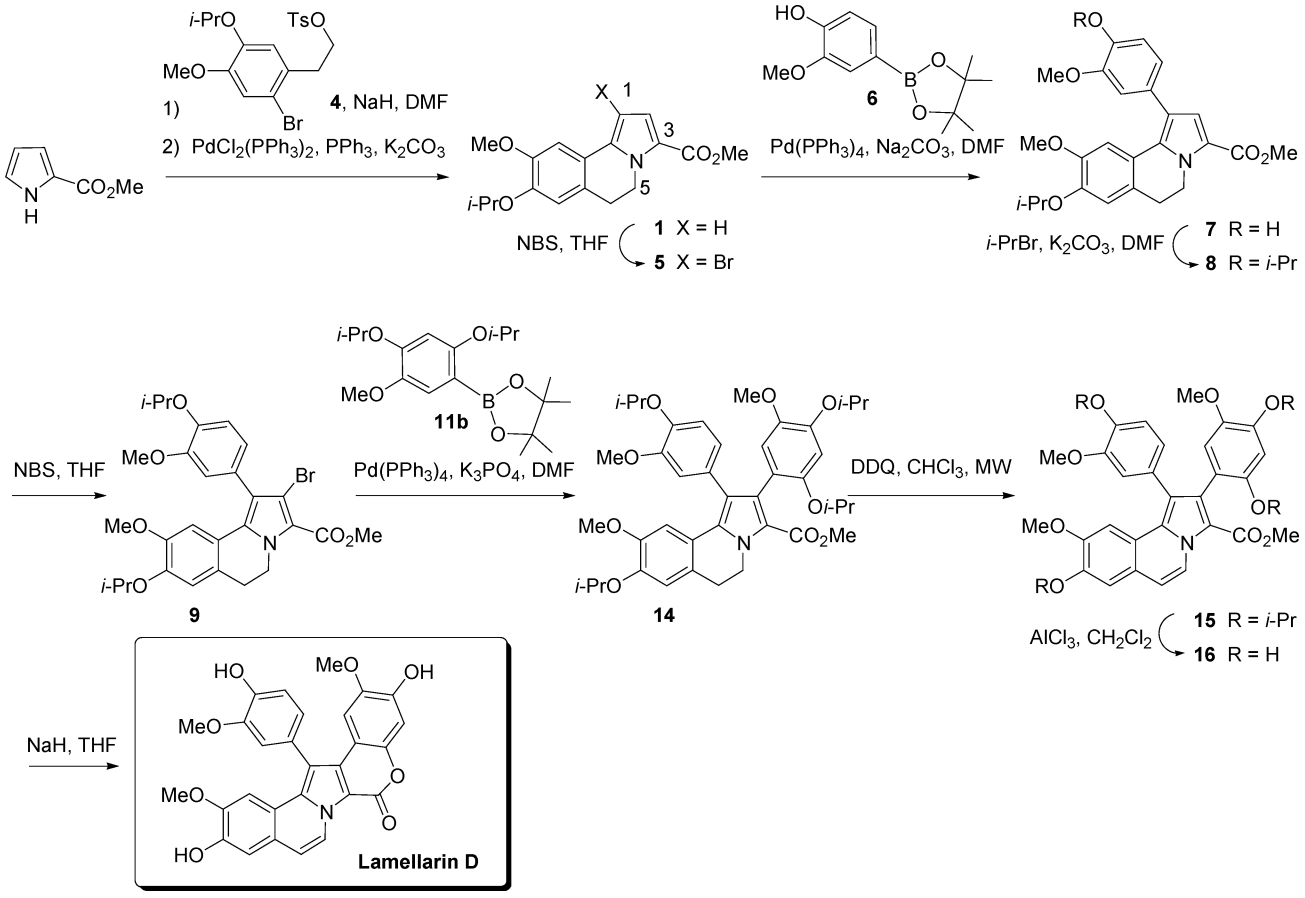
SCHEME 1. Synthesis of Lamellarin D



sequential brominations and cross-coupling reactions using differently substituted arylboronic esters, followed by oxidation to give the aromatic isoquinoline ring, and lactonization to afford lamellarin D (Scheme 1). Key steps of this procedure are the regioselective bromination of the tricyclic system **8** in the presence of two highly activated benzene rings and the efficient preparation and introduction of building block **11b**.

N-Alkylation of methyl pyrrole-2-carboxylate[9] with tosylate **4**,[10] followed by Heck cyclization, gave scaffold **1**. Regioselective bromination of position 1 followed by Pd(0)-catalyzed cross-coupling with commercially available boronic ester **6** furnished compound **7**. Protection of the phenol as an isopropoxyether was achieved by reaction with 2-bromopropane in DMF using K_2CO_3 as a base.[11] The regioselective bromination of **8** to give compound **9** was achieved in 84% yield by treatment with NBS in THF at 70 °C for 1.5 h.[12] The electrophilic substitution occurs on the pentagonal heterocycle exclusively, and no traces of bromination on the activated benzene rings were observed in these conditions. Similar regioselectivity was also described for the synthesis of lamellarin G trimethyl ether.[13]

Preparation of the 2,4-diisopropoxy-5-methoxyphenylboranes **11a** and **11b** needed for the second Pd(0)-catalyzed cross-coupling reaction required optimization. Thus, the syntheses were attempted from bromobenzene derivative **10**[14] by employing bromine−lithium exchange followed by reaction with borolane **12a** or **12b**, respectively (Table 1, entries 1 and 2). The phenylboronic acid derivative **11a** was obtained in lower yield than the borolane **11b**, and its purification and manipulation were more tedious. Furthermore, boronic acid **11a** was inefficient to introduce the second aryl moiety through cross-coupling reaction with **9** using $Pd(PPh_3)_4$ and Na_2CO_3, as in the previous reaction for the preparation of **7**; thus, coupling with **11b** was investigated in detail. Preparation of **11b** was attempted by Pd(0)-catalyzed reaction between bromide **10** and pinacolborane **13** (entries 3 and

(9) Methyl pyrrole-2-carboxylate was obtained from pyrrole by acylation with trichloroacetyl chloride as described by Harbuck, J. W.; Rapoport, H. *J. Org. Chem.* **1972**, *37*, 3618. The 2-trichloroacetylpyrrole was treated with a solution of NaOMe in MeOH at 0 °C to furnish the methyl ester.

(10) Tosylate **4** was obtained from the 2-bromo-5-isopropoxy-4-methoxybenzaldehyde as detailed in Supporting Information. A Wittig reaction afforded the styrene, while anti-Markovnikov hydroboration and standard tosylation of the resulting 2-(2-bromo-5-isopropoxy-4-methoxyphenyl)ethanol gave **4**. Preparation of 2-(2-bromo-5-isopropoxy-4-methoxyphenyl) ethanol was described from the same benzaldehyde using a different procedure by: Treu, M.; Jordis, U. *Molecules* **2002**, *7*, 374.

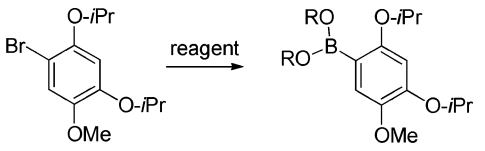
(11) ^{1}H NMR spectra of **7** and **8** differ only in the integrated area of the isopropoxy signals, whereas two $OCH(CH_3)_2$ signals can be observed at 71.4 and 71.6 ppm in the ^{13}C NMR.

(12) This reaction required extensive fine-tuning, as longer reaction times and/or higher temperature resulted in complex mixtures due to additional bromination. Furthermore, oxidation of the dihydroisoquinoline ring was observed by ^{1}H NMR. The reaction could be followed by HPLC.

(13) Handy, S. T.; Zhang, Y.; Bregman, H. *J. Org. Chem.* **2004**, *69*, 2362.

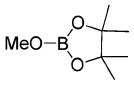
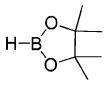
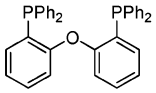
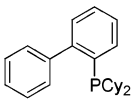
(14) Obtained from 3-isopropoxy-4-methoxybenzaldehyde by Baeyer−Villiger reaction followed by protection of the resulting phenol and bromination; see Supporting Information for details.

TABLE 1. Preparation of Boronic Acid 11a and Boronic Ester 11b



10 **11a** R = H

11b R,R = Me_2C-CMe_2

entry	reagent	conditions	compound yield
1	$B(O\text{-}iPr)_3$ **12a**	*n*BuLi, THF -78 °C, 15 min	**11a** 20%
2	 **12b**	*n*BuLi, THF -78 °C, 15 min	**11b** 59%
3	 **13**	$Pd(OAc)_2$, Et_3N[a]  (DPEphos)	**11b** 80%
4	**13**	$Pd(OAc)_2$, Et_3N[a] 	**11b** 59%

[a] In refluxing dioxane; DPEphos = (oxydi-2,1-phenylene)bis-(diphenylphosphine).

4). $Pd(OAc)_2$ together with (DPEphos)[15] or biphenyl ligand [2-(dicyclohexylphosphino)biphenyl][16]afforded **11b** in good yields.[17,18]

The Suzuki−Miyaura cross-coupling reaction between **11b** and **9** was tested under several experimental conditions without satisfactory yields. The lack of reactivity of boronic ester **11b** could presumably be attributed to its steric hindrance. Ultimately, the problem was solved by using an excess of **11b**, $Pd(PPh_3)_4$ as the catalyst, and K_3PO_4 as a base, instead of K_2CO_3, affording the biaryl derivative **14** in high yield.[17] Handy and co-workers[13] also described the use of a total of 8 equiv of a boronic acid to lead to a 46% yield of the coupling product, in a related structure. Applying our improved protocol with 5 equiv of **11b**, of which 3 equiv were added at the beginning of the reaction and the last 2 equiv by syringe pump over 2.5 h, led to a yield of 87%.

The aromatization of dihydroisoquinoline **14** to give **15** was achieved using DDQ in $CHCl_3$ in a sealed tube with controlled microwave (MW) irradiation at 120 °C for 5 min.[19] Several experimental conditions with a simple analogue were tested for the optimization of this oxidation, and the MW-assisted DDQ method proved to be superior.[20] Cleavage of the four isopropoxyether protecting groups[21] in **15** with $AlCl_3$ followed by lactonization using NaH as a base afforded lamellarin D.

In conclusion, the preparation of lamellarin D has been accomplished in eight steps (18% overall yield) from scaffold **1**. The strategy is based on two consecutive, regioselective bromination−Suzuki cross-coupling steps for introducing the appropriate aryl groups in positions 1 and 2 of scaffold **1**. Synthesis of an *ortho*-substituted borolane (**11b**) and its coupling to compound **9** were optimized, and high yields were obtained in the remaining sequence leading to lamellarin D.

In addition to our previous report on open-chain lamellarins, the methodology reported herein can be exploited for the preparation of analogues of the natural product by utilizing the concept of diverted total synthesis (DTS).[22]

Experimental Section

2-(2,4-Diisopropoxy-5-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (11b). A mixture of **10** (1.59 g, 5.3 mmol), Et_3N (28.9 mL, 21 mmol), $Pd(OAc)_2$ (62.4 mg, 0.28 mmol), DPEphos (0.29 mg, 0.54 mmol), and **13** (2.36 mL, 15.76 mmol) in dioxane (5.3 mL) was heated at 100 °C for 13.5 h. After cooling to room temperature, the reaction mixture was quenched with saturated NH_4Cl, and the aqueous solution was extracted with Et_2O. The organic solution was dried, filtered, and concentrated. The resulting oil was purified by flash chromatography (SiO_2 previously deactivated with 5% Et_3N). Elution with hexane/AcOEt (70:30) afforded **11b** (1.47 g, 79%) as a brown syrup: IR (film) ν 2976, 2929, 1407, 1371, 1145, 1112, 1032. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.29 (d, 6H, J = 6.0 Hz, 2Me); 1.33 (s, 12H, 4Me); 1.35 (d, 6H, J = 6.0 Hz, 2Me); 3.84 (s, 3H, OMe); 4.24 (h, 1H, J = 6.0 Hz); 4.53 (h, J = 6.0 Hz, 1H); 6.51 (s, 1H); 7.14 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.9 (q, 2Me); 22.2 (q, 2Me); 24.8 (q, 4Me); 56.4 (q); 71.0 (d); 75.0 (d); 83.2 (s, C4, C5); 107.8

(15) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwn, P. W. N. M.; Goubitz, K. Fraange, *J. Organometallics* **1995**, *14*, 3081.

(16) Wolfe, J. P.; Singer, R. A.; Bryant, H. Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.

(17) Other catalysts such as $PdCl_2(dppf)_2$ were inefficient for this transformation: Baudoin, O.; Guénard, D.; Guéritte, F. *J. Org. Chem.* **2000**, *65*, 9268.

(18) Reaction of **10** with bis(neopentyl glycolato)diboron catalyzed by $Pd(OAc)_2$ and DPEphos afforded the debrominated compound, 2,4-diisopropoxy-1-methoxybenzene, instead of the desired building block **11b**.

(19) A doublet at 9.24 ppm in the ^1H NMR spectrum, characteristic of H-5, verified the formation of **15**.

(20) Oxidation of methyl 1,2-bis(2-thienyl)pyrrolo[2,1-*a*]isoquinoline-3-carboxylate using either (i) DDQ in $CHCl_3$ at reflux temperature, (ii) MnO_2 in refluxing toluene or pyridine, or (iii) Pd−C in toluene or decalin were unsuccessful (unpublished results).

(21) Protection of phenol groups as isopropoxyethers was previously demonstrated to be very efficient in the solid-phase synthesis of lamellarins: Cironi, P.; Manzanares, I.; Albericio, F.; Álvarez, M. *Org. Lett.* **2003**, *5*, 2959. Marfil, M.; Albericio, F.; Álvarez, M. *Tetrahedron* **2004**, *60*, 8659.

(22) For an example of DTS, see: Gaul, C.; Njadarson, J. T.; Shan, D.; Diorn, D. C.; Wu, K.-D.; Tong, W. T.; Huang, X.-Y.; Moore, M. A. S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 11326 and references therein.

(d); 118.9 (d); 145.2 (s); 150.4 (s); 158.2 (s). MS(CI) 350 (M, 100); 351 (M + 1, 92); 352 (M + 2, 48); 353 (M + 3, 12).

Methyl 2-(2,4-diisopropoxy-5-methoxyphenyl)-8-isopropoxy-1-(4-isopropoxy-3-methoxyphenyl)-9-methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (14). 11b (3 mL, 1.88 mmol, 0.63M in DMF), $Pd(PPh_3)_4$ (145 mg, 0.13 mmol), and 2 M K_3PO_4 (1.25 mL) were added to a solution of bromide **9** (350 mg, 0.63 mmol) in DMF (10 mL). The reaction mixture was stirred at 110 °C, and another portion of **11b** (5 mL, 1.25 mmol, 0.25 M in DMF) was added by syringe pump over 2.5 h. After 6 h of heating, the solvent was evaporated, and the residue was dissolved in AcOEt. The organic solution was washed with sodium diethyldithiocarbamate (0.02 M solution), brine, and water, dried, filtered, and concentrated to give a crude material that was purified by column chromatography on silica gel. Elution with hexane/AcOEt (60:40) gave **14** (383 mg, 87%) as a reddish oil: IR (film) ν 2975, 1693, 1438, 1254, 1208, 1111 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.31 (d, 12H, J = 6.0 Hz, 4Me); 1.36 (d, 12H, J = 6.0 Hz, 4Me); 3.00 (m, 2H, C5); 3.33 (s, 3H, OMe); 3.51 (s, 3H, OMe); 3.59 (s, 6H, OMe, CO_2Me) 4.09−4.14 (m, 1H, CH); 4.41−4.55 (m, 3H, CH); 4.64−4.69 (m, 2H, C6); 6.46 (s, 1H); 6.48 (s, 1H); 6.66 (br, 1H); 6.74−6.79 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.0 (q, Me); 22.1 (q, Me); 22.2 (q, Me); 29.0 (t, C6); 42.8 (t, C5); 50.8 (q, CO_2Me); 55.1 (q, OMe); 55.7 (q, OMe); 56.1 (q, OMe); 71.5 (d, OCH); 71.6 (d, OCH); 71.7 (d, OCH); 107.2 (d); 109.1 (d); 114.9 (d); 115.0 (d); 116.0 (d); 116.1 (d); 119.2 (s); 119.5 (s); 121.3 (s); 121.5 (s); 123.3 (d); 125.5 (s); 127.9 (s); 129.1 (s); 130.6 (s); 144.5 (s, C−OMe); 145.7 (s); 145.8 (s); 146.2 (s); 148.5 (s); 149.4 (s, C−OMe); 150.2 (s, C−OMe); 162.7 (s, C═O). MS (MALDI-TOF) 701 (M, 100), 702 (M + 1, 39), 703 (M + 2, 8). HRMS *m/z* calcd for $C_{41}H_{51}NO_9$ 701.3564, found 701.3558.

Methyl 2-(2,4-diisopropoxy-5-methoxyphenyl)-8-isopropoxy-1-(4-isopropoxy-3-methoxyphenyl)-9-methoxypyrrolo-[2,1-*a*]isoquinoline-3-carboxylate (15). A mixture of **14** (411 mg, 0.59 mmol) and DDQ (173 mg, 0.76 mmol) in dry $CHCl_3$ (15 mL) was purged with Ar and irradiated with a microwave at 120 °C for 5 min in a sealed vessel. The organic solution was washed with 2 M NaOH, water, and brine. The solvent was removed to afford a crude residue, which was purified by flash chromatography on silica gel. Elution with hexane/AcOEt (55:45) gave **15** (336 mg, 82%) as a pale yellow oil: IR (film) ν 1684, 1211 cm^{-1}. ^1H NMR (acetone-d_6, 400 MHz) δ 1.25−1.35 (m, 24H); 3.38 and 3.40 (2d, 3H, OMe); 3.54 and 3.59 (2s, 3H, OMe); 3.60 and 3.62 (2s, 3H, OMe); 3.62 (s, OMe); 4.19−4.35 (m, 1H); 4.48−4.59 (m, 2H); 4.72 (h, 1H, J = 5.6 Hz); 6.56 (s, 1H); 6.60 (d, 1H, J = 8.8 Hz); 6.69−6.82 (m, 2H); 6.90−7.13 (m, 2H), 7.28 and 7.16 (2s, 1H); 7.29 (s, 1H); 9.24 (d, 1H, J = 7.6 Hz, H5). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.8 (q, 2Me); 21.9 (q, 2Me); 22.1 (q, 2Me); 22.2 (q, 2Me); 50.7 (q, CO_2Me); 55.2 (q, OMe); 55.5 (q, OMe); 56.1 (q, OMe); 71.2 (d); 71.4 (d); 71.5, 71.6 (d); 71.8 (d); 105.6 (d), 106.6 (d); 107.0 (s); 110.7 (d); 111.7 (d); 113.1 (s); 115.4 (d), 115.6 (d); 115.9 (d), 116.1 (d); 118.2 (s); 119.4 (s); 119.8 (s); 123.3 (d); 129.4 (s); 131.6 (s); 144.3 (s); 146.0 (s); 146.2 (s); 147.3 (s); 149.5 (s); 149.9 (s); 150.2 (s); 162.9 (s, C═O). MS (MALDI-TOF) 699 (M, 100), 700 (M + 1, 59), 701 (M + 2, 17). HRMS *m/z* calcd for $C_{41}H_{49}NO_9$ 699.3407, found 699.3402.

Methyl 2-(2,4-dihydroxy-5-methoxyphenyl)-8-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-9-methoxypyrrolo[2,1-*a*]-isoquinoline-3-carboxylate (16). A solution of **15** (143 mg, 0.20 mmol) and $AlCl_3$ (148 mg, 1.06 mmol) in dry CH_2Cl_2 (1 mL) was stirred at room temperature for 2 h. The reaction mixture was then quenched with saturated NH_4Cl and washed with water and brine. The organic phase was dried, filtered, and concentrated, and the resulting crude material was purified by flash chromatography. Elution with hexane/AcOEt (gradient from 25:75 to pure AcOEt) gave **16** (69.1 mg, 64%) as a light brown solid: IR (film) ν 3426, 1679, 1380, 1268, 1242, 1210 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.51 (s, 3H, Me); 3.55 (s, 3H, Me); 3.66 (s, 3H, Me); 3.77 (s, 3H, Me); 5.43 (br, 1H, OH); 5.56 (s, 1H, OH); 5.61 (s, 1H, OH); 5.87 (s, OH); 6.33−6.92 (m, 3H); 6.92−7.27 (m, 5H); 9.19 (m, 1H, H5). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 51.4 (q, Me); 55.4 (q, Me); 56.0 (q, Me); 56.4 (q, Me); 102.7 (d); 104.8 (d); 110.4 (d); 112.5 (d); 112.7 (s); 113.8 (d); 113.9 (s); 114.0 (d); 114.1 (d); 119.1 (s); 123.4 (d, C5); 124.2 (d); 124.5 (s); 131.3 (s); 140.2 (s); 144.8 (s); 145.8 (s); 146.1 (s); 146.6 (s); 146.7 (s); 148.6 (s); 162.3 (s, C═O). MS (MALDI-TOF) 531 (M, 100), 532 (M + 1, 38), 533 (M + 2, 11). HRMS *m/z* calcd for $C_{29}H_{25}NO_9$ 531.1529, found 531.1524.

Lamellarin D. A mixture of NaH (60% dispersion, 25.7 mg, 0.64 mmol) and **16** (33.9 mg, 0.06 mmol) in THF (3.5 mL) was stirred for 3 h at room temperature and for 1 h at 40 °C. The solvent was removed under reduced pressure, and AcOEt was added to the residue. The organic solution was washed with saturated NH_4Cl, water, and brine and then dried, filtered, and concentrated. The residue was purified by flash chromatography. Elution with AcOEt/MeOH (gradient from 100:0 to 80:20) furnished lamellarin D (23.7 mg, 75%) as a pinkish-white solid. The spectroscopic data were in accordance with previous reports.[1,6]

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Supporting Information Available: Materials and methods, experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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