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Construction of Pentacyclic Lamellarin Skeleton via Grob Reaction: Application to Total Synthesis of Lamellarins H and D

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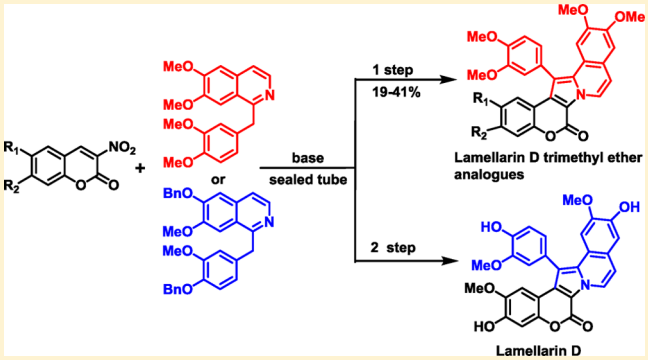
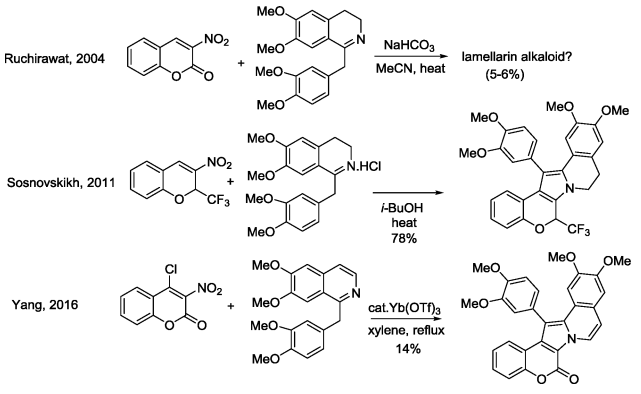
Supporting Information

ABSTRACT: An efficient construction of phenyl-substituted coumarin-pyrrole-isoquinoline-fused pentacycle via base-promoted Grob-type coupling of 3-nitrocoumarin and papaverine in a sealed tube is reported. This reaction is further applied to the total synthesis of lamellarin H in three linear steps and lamellarin D in eight linear steps with overall yields of 31% and 14%, respectively.



Having a unique pyrrolocoumarin structure, lamellarin D is a natural product isolated from marine mollusks and ascidians.[1] It exhibits potent cytotoxic activities against multidrug-resistant tumor cell lines[2] and is a potent DNA topoisomerase I inhibitor.[3] Owing to its intriguing biological properties along with the difficulty in obtaining bulk quantities from natural sources, the synthesis of lamellarin D and related alkaloids has attracted considerable attention from organic and medicinal chemists over the past three decades.[4] Previous lamellarin D synthetic approaches can be generally classified into two categories. One involves the construction of the pyrrole core as the key step; the other refers to the functionalization of the pre-existing pyrrole to the target.[5] Recently, a third approach has emerged, which involves the direct annulation of a pyrrole ring onto functionalized coumarin derivatives to afford the lamellarin pentacyclic core via the coupling of 3,4-dihydropapavarine with 3-nitrocoumarin. This approach is highly attractive since the coumarin/pyrrole-fused lamellarin skeleton can be constructed in a high atom-economical fashion without any protection/deprotection. Unfortunately, Ruchirawat[6] has reported that this coupling reaction suffered from poor yield (only 5−6%), which may be attributed to the lactone ring opening of the coumarin moiety during the reaction. Nevertheless, this strategy has been employed later by Sosnovskikh[7] to prepare trifluoromethyl-substituted lamellarin analogues by replacing 3-nitrocoumarin with 3-nitro-2-(trifluoromethyl)-2*H*-chromenes. Also, we have reported the construction of the lamellarin pentacycle by $Yb(OTf)_3$-catalyzed coupling of papaverine with 4-chloro-3-nitrocoumarin[8] (Scheme 1). Among the aforementioned reactions, none has engaged in a direct coupling of papaverine with 3-nitrocoumarin, in which the target lamellarin alkaloid can be generated in a single step. Therefore, the method installing the pyrrole ring onto appropriately substituted coumarins to afford alamellarin skeleton remains highly sought until today. Herein, we described, for the very first time, the successful construction of phenyl-substituted coumarin-pyrrole-isoquinoline-fused pentacycle (lamellarin skeleton) via Grob coupling[9] of commercial and inexpensive papaverine with 3-nitrocoumarins in a sealed tube. This methodology was further applied to the total synthesis of biologically active lamellarins H, D, and 501 (Figure 1).

Scheme 1. Previous Synthesis of Lamellarin Alkaloids and Analogues via Coupling of 3-Nitrocoumarins and Papaverine Derivatives



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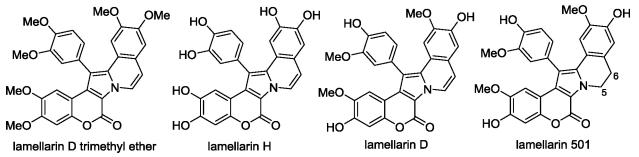
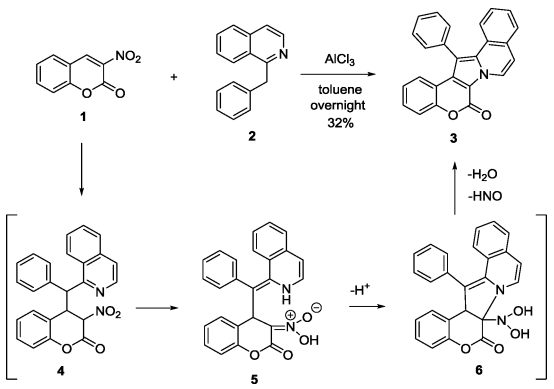


Figure 1. Structures of lamellarins D trimethyl ether, H, D, and 501.

In the present investigation, we chose 1-benzylisoquinoline rather than 1-benzyl-3,4-dihydroisoquinoline as one of the model substrates due to the fact that the latter is susceptible to oxidation at the benzylic carbon. Additionally, the use of 1-benzylisoquinoline also gives an added advantage of possessing the pre-existing C5−C6 double bond (see Figure 1 for atom numbering) which plays a pivotal role in imparting biological activity.[3a] Keeping these in mind, we initiated our studies by investigating the direct coupling of 3-nitrocoumarin (**1**)[10] with 1-benzylisoquinoline (**2**) as shown in Scheme 2. To our delight,

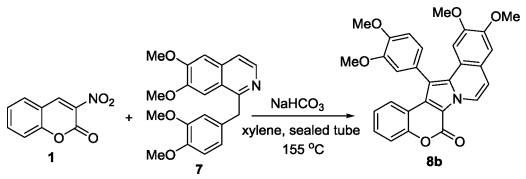
Scheme 2. Synthesis of Lamellarin Core 3



simple refluxing of a mixture of **1** and **2** in the presence of 1 equiv of $AlCl_3$ in toluene overnight led to the formation of the desired lamellarin core **3** in 32% yield. We envisioned that the mechanism for this reaction presumably involves $AlCl_3$-mediated formation of Michael adduct **4** which further undergoes isomerization to generate the enamine **5**. The intramolecular cyclization of **5** via nucleophilic addition of the amine nitrogen to the iminium carbon generates the cyclized dihydroxyamine **6**. Final elimination of water and hyponitrous acid from **6** gives the aromatized phenyl-substituted pentacyclic lamellarin core **3** (Scheme 2).[7a]

Since the hydroxyl and methoxy substituents on the lamellarin alkaloids are indispensable for their biological activities,[11] our next aim was to introduce the methoxy groups onto the lamellarin core (**3**) by replacing 1-benzylisoquinoline (**2**) with commercially available natural product papaverine (**7**). To our disappointment, reaction of **1** and papaverine under the conditions shown in Scheme 2 gave the desired coupled product **8b** in extremely low yield. In an effort to search for the reaction conditions that could enhance the reaction conversion and maximize the formation of lamellarin derivative **8b**, the coupling reaction between 3-nitrocoumarin (**1**) and papaverine (**7**) under various bases, solvents, temperatures, and different reaction conditions were examined (Scheme 3). Among these examinations, xylene was found to be the most effective solvent. Also, the effect of pressure was studied by performing the coupling reaction in a sealed tube. The reactions carried out in a closed sealed tube system usually gave better yields and

Scheme 3. Synthesis of 8b



higher conversions than those of the open system reactions (see Table S1 in the Supporting Information for optimization results). Among the various conditions explored, sodium bicarbonate, xylene, and a sealed tube with the temperature between 150−160 °C were found to be effective combinations. Hence these conditions were employed to all subsequent coupling reactions.

Figure 2 lists the structures and yields of various prepared lamellarin derivatives **8a−h** and **9a−h**. Lamellarins **8b−h** were

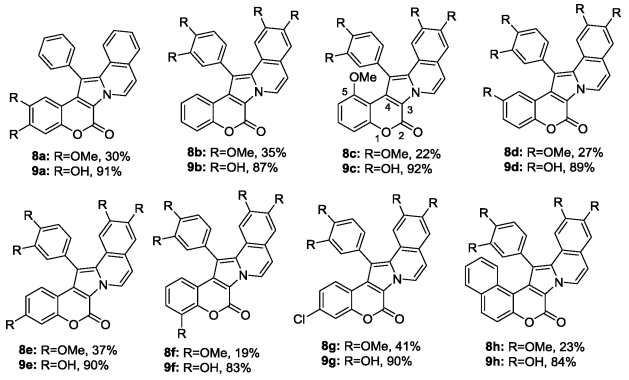


Figure 2. Structures of the prepared **8a−h** and **9a−h**.

synthesized by $NaHCO_3$-mediated coupling of substituted 3-nitrocoumarins and papaverine (**7**) in a sealed tube in moderate yields 19−41% (an average of 20% of **7** was recovered). The methoxy groups on the coumarin moiety of these lamellarins can be readily introduced by employing the appropriately substituted 3-nitrocoumarins (**8c−f**)[12] as the starting material. Other substituents such as the chloro (**8g**) and naphthyl moiety (**8h**)[13] were also incorporated into the lamellarin structure to demonstrate the scope of the coupling reaction. Further exhaustive demethylation of **8a−h** with an excess of boron tribromide (18 equiv) gave the corresponding hydroxyl substituted lamellarin derivatives **9a−h** in good yields. The methoxy group substituted at the C-5 position of the coumarin ring of **8c** survived the deprotection, presumably due to the presence of the nearby benzene moiety which sterically hindered the approach of BBr_3 to the C-5 methoxy group (see **8c** in Figure 2 for atom numbering). Generally, this methodology provides a quick access to lamellarin derivatives with different substituents on the coumarin moiety.

In addition to the preparation of lamellarin derivatives, this Grob coupling reaction strategy was also employed for the synthesis of naturally occurring alkaloids such as lamellarin H. As outlined in Scheme 4, the synthesis of lamellarin H began with the piperidine-catalyzed condensation of commercially available *o*-hydroxy-2,4-dimethoxybenzaldedyde (**10**) with ethyl nitroacetate in the Dean−Stark trap to yield the 6,7-dimethoxy-3-nitrocoumarin (**11**). The subsequent coupling of **11** with papaverine (**7**) in a sealed tube afforded lamellarin D trimethyl ether (**12**) in 40% yield (~20% of **7** was recovered). Final

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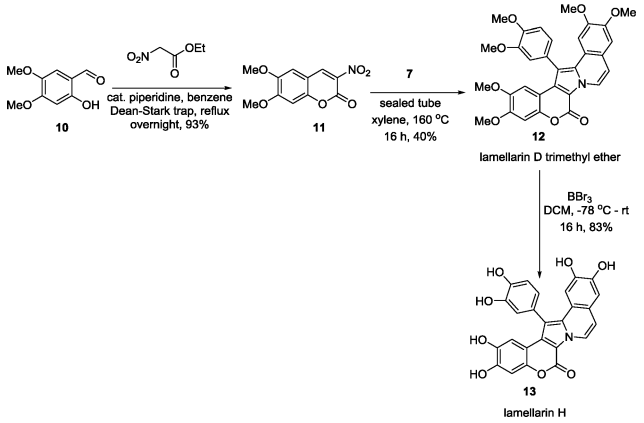
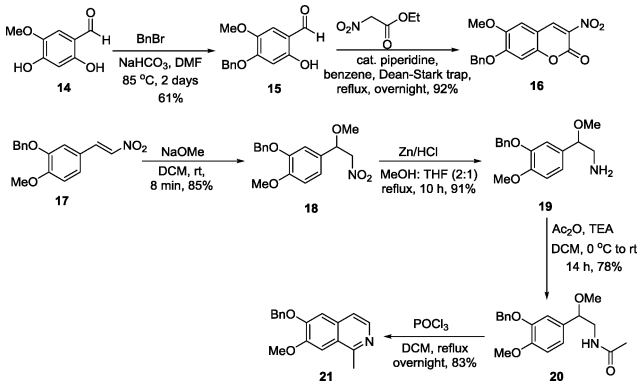
Scheme 4. Synthesis of Lamellarin D Trimethyl Ether and Lamellarin H



exhaustive demethylation of **12** with an excess of boron tribromide at low temperature furnished lamellarin H (**13**). With this methodology, lamellarin H was prepared in three steps with an overall yield of 31% from the benzaldedyde **10**. To the best of our knowledge, this synthetic scheme represents the shortest route for both lamellarin D trimethyl ether and lamellarin H preparations ever reported in the literature.[8,14]

After successfully realizing the preparation of lamellarin H via Grob pyrrolocoumarin synthesis, we believe that the same approach could lead us to prepare biologically important lamellarin D using appropriately substituted coumarins and isoquinolines. Scheme 5 depicts the preparation of the two key

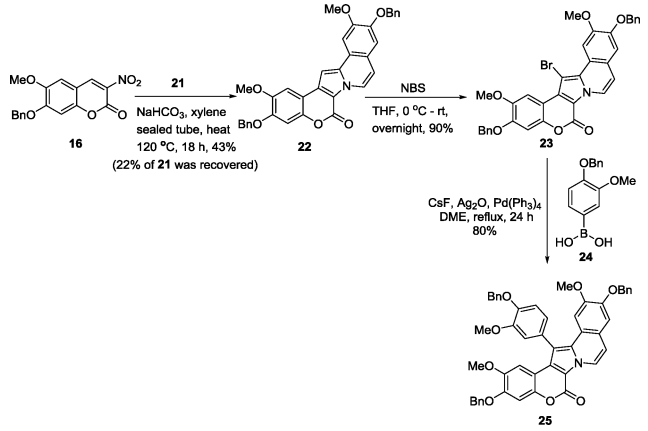
Scheme 5. Preparation of 3-Nitrocoumarin 16 and 1-Methylisoquinoline 21



building blocks 3-nitrocoumarin **16** and 1-methylisoquinoline **21** for the crucial Grob coupling reaction. The 3-nitrocoumarin **16** was synthesized in two steps by selective benzylation at the C-4 hydroxyl group of aldehyde **14** followed by condensation of the benzylated aldehyde **15** with ethyl nitroacetate to give the 3-nitrocoumarin **16** in 56% overall yield. On the other hand, compound **21** was prepared by methoxylation at the β-position of the commercial nitrostyrene **17** with sodium methoxide to give compound **18** which was subsequently reduced by zinc in HCl to yield the amine **19**. The amine **19** was then treated with acetic anhydride to generate the corresponding amide **20**. Final $POCl_3$-promoted Bischler–Napieralski cyclization of **20** furnished the protected 1-methylisoquinoline **21**.

With compounds **16** and **21** in hand, we then pursued the lamellarin D synthesis by coupling of the two building blocks as shown in Scheme 6. The $NaHCO_3$-mediated coupling of 3-

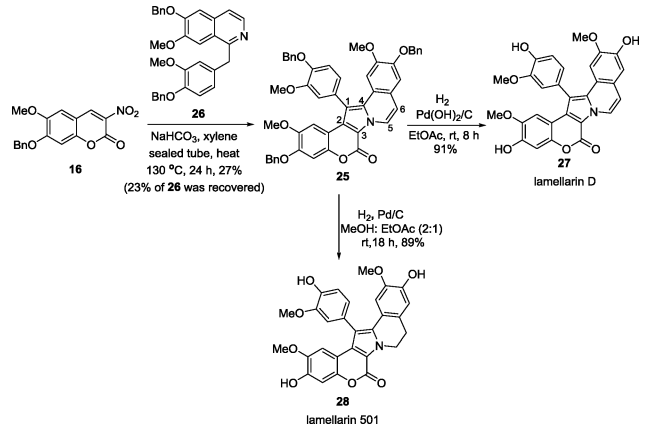
Scheme 6. Synthesis of OBn-Protected Lamellarin D (25)



nitrocoumarin **16** and 1-methylisoquinoline **21** in a sealed tube gave the lamellarin pentacycle core **22** in 43% yield (22% of **21** was recovered), presumably proceeding with a similar reaction mechanism as described in Scheme 2. Bromination of **22** by NBS in THF at room temperature overnight afforded the brominated pentacycle **23**.[15] The Suzuki coupling[16] of **23** with phenylboronic acid **24** in DME yielded the protected lamellarin **25**.

Alternatively, the OBn-protected lamellarin D (**25**) can also be synthesized by coupling of 3-nitrocoumarin **16** with appropriately substituted benzylisoquinoline **26** (prepared according to the literature procedure[14a] in four steps from **17**) in a sealed tube to give the compound **25** in 27% yield (23% of **26** was recovered). The subsequent $Pd(OH)_2$-catalyzed debenzylation of **25** in EtOAc under a hydrogen atmosphere furnished the target lamellarin D (**27**).[13] In the case of Pd/C catalysis, the double bond at C-5 and C-6 of **25** was also hydrogenated, resulting in the lamellarin 501 (**28**) (see **25** in Scheme 7 for atom numbering). Essentially, lamellarin D was prepared in 12% and 14% overall yields over six and eight linear steps starting from the commercial β-nitrostyrene **17** by virtue of the successful Grob coupling reaction. This synthetic scheme represents the shortest route for lamellarin D

Scheme 7. Synthesis of Lamellarin D (27) and Lamellarin 501 (28)



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preparation reported to date.[14a,c,17] Even though the conversion of this coupling reaction requires improvement, the successful preparation of pentacycles **22** and **25** via coupling of 3-nitrocoumarin **16** with respective 1-methylisoquinoline **21** and benzylisoquinoline **26** clearly demonstrates the wide scope of the Grob reaction in the construction of the pentacyclic lamellarin skeleton. We envision the rapid synthesis of lamellarins H, D, and their analogues via Grob-type reaction may greatly facilitate the process for the development of lamellarin-based anticancer drugs.[1c]

CONCLUSION

We have demonstrated that the phenyl-substituted pentacyclic lamellarin skeleton can be efficiently constructed via $NaHCO_3$-mediated Grob coupling of 3-nitrocoumarin and 1-benzylisoquinoline or papaverine in sealed tube. The scope of the reaction was illustrated by the preparation of eight lamellarin derivatives **8a**–**h** in two steps, along with concise synthesis of the natural product lamellarin H in three steps with an overall yield of 31%. Moreover, the Grob coupling was successfully employed as a key step to two total syntheses of lamellarin D in six and eight linear steps with overall yields of 12% and 14%, respectively. Finally, the molecular structure of lamellarin D (**27**) was unambiguously confirmed by the X-ray crystallography.

EXPERIMENTAL SECTION

Instrumentation. Melting points were determined on a Mel-Temp melting point apparatus in open capillaries and are uncorrected. Infrared (IR) spectra were recorded using a 1725XFT-IR spectrophotometer. High resolution mass spectra (HRMS) were obtained on a Thermo Fisher Scientific Finnigan MAT95XL spectrometer using a magnetic sector analyzer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100, or 150 MHz) spectra were recorded on a Varian VXR300 or Bruker 400/600 spectrometer. Chemical shifts were reported in parts per million on the δ scale relative to an internal standard (tetramethylsilane, or appropriate solvent peaks) with coupling constants given in hertz. ^{1}H NMR multiplicity data are denoted by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), ABdq (AB doublet quartet), and ABddq (AB doublet doublet quartet). Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel 60G-254 plates (25 mm) and developed with the solvents mentioned. Visualization was accomplished by using portable UV light, a ninhydrin spray, and an iodine chamber. Flash chromatography was performed in columns of various diameters with Merck silica gel (230–400 mesh ASTM 9385 kieselgel 60H) by elution with the solvent systems. Solvents, unless otherwise specified, were reagent grade and distilled once prior to use. All new compounds exhibited satisfactory spectroscopic and analytical data.

Synthesis of 3-Nitrocoumarin Derivatives. A mixture of appropriately substituted *o*-hydroxybenzaldehyde (1 equiv), ethyl nitroacetate (1.2 equiv), and piperidine (1.2 equiv) in benzene was placed in a round-bottom flask and fitted with a Dean–Stark trap. The mixture was heated at 110 °C for 6 h. After the mixture cooled to room temperature, the product was precipitated. The solid was filtered, washed with plenty of 2–5% EA/hexanes, and dried under vacuum to remove the excess ethyl nitroacetate.

3-Nitrocoumarin.[12a] Pale-yellow solid; 640 mg; yield 82%; mp 138–140 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.73 (s, 1H), 7.79 (td, J = 8.8, 1.6 Hz, 1H), 7.74 (dd, J = 8.0, 1.6 Hz, 1H), 7.48–7.44 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.9, 152.0, 142.4, 136.2, 134.9, 130.7, 126.0, 117.1, 116.2; IR ν_{max} (KBr) 3483, 2970, 1732, 1717, 1606, 1520, 1365, 1253, 1118, 977 cm^{-1}; HRMS (EI) m/z calcd for $C_9H_5NO_4$ [M$^+$] 191.0219, found 191.0215.

6,7-Dimethoxy-3-nitrocoumarin (11).[12b] Saffron yellow solid; 580 mg; yield 93%; mp 268–270 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 9.05 (s, 1H), 7.36 (s, 1H), 7.13 (s, 1H), 4.02 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (Acetone-d_6, 150 MHz) δ 158.2, 153.5, 153.1, 148.5, 144.1, 133.1, 111.0, 110.1, 100.5, 57.2, 56.6; IR ν_{max} (KBr) 3461, 2947, 1717. 1616, 1520, 1367, 1227, 1002, 849, 770 cm^{-1}; HRMS (EI) m/z calcd for $C_{11}H_9NO_6$ [M$^+$] 251.0430, found 251.0426.

5-Methoxy-3-nitrocoumarin.[12a] Brown solid; 612 mg; yield 84%; mp 116–118 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.16 (s, 1H), 7.71 (t, J = 8.6 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 4.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.4, 155.9, 152.1, 138.5, 137.5, 133.1, 109.0, 107.5, 106.2, 56.6; IR ν_{max} (KBr) 2944, 1746, 1602, 1470, 1336, 1230, 1090, 971, 772 cm^{-1}; HRMS (EI) m/z calcd for $C_{10}H_7NO_5$ [M$^+$] 221.0324, found 221.0331.

6-Methoxy-3-nitrocoumarin.[12a] Pale brown solid; 592 mg; yield 81%; mp 159–161 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.71 (s, 1H), 7.39 (s, 1H), 7.38 (d, J = 2.4 Hz, 1H), 7.11 (d, J = 2.4 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.2, 152.1, 149.6, 142.1, 135.2, 124.8, 118.3, 116.6, 111.2, 56.1; IR ν_{max} (KBr) b3473, 2949, 1738, 1607, 1525, 1364, 1227, 1030, 815, 773 cm^{-1}; HRMS (EI) m/z calcd for $C_{10}H_7NO_5$ [M$^+$] 221.0324, found 221.0321.

7-Methoxy-3-nitrocoumarin.[12a] Yellow solid; 618 mg; yield 85%; mp 148–150 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.80 (s, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.03 (dd, J = 8.8, 2.4 Hz, 1H), 6.90 (d, J = 2.4 Hz, 1H), 4.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.0, 157.8, 152.4, 143.2, 132.1, 131.7, 115.1, 109.8, 100.7, 56.4; IR ν_{max} (KBr) 3461, 2970, 1739, 1716, 1621, 1598, 1383, 1132, 1000, 846 cm^{-1}; HRMS (EI) m/z calcd for $C_{10}H_7NO_5$ [M$^+$] 221.0324, found 221.0322.

8-Methoxy-3-nitrocoumarin.[12a] Dark brown solid; 575 mg; yield 79%; mp 170–172 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.73 (s, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.33–7.29 (m, 2H), 4.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.5, 147.3, 144.6, 142.6, 135.1, 126.0, 121.5, 117.5, 116.9, 56.5; IR ν_{max} (KBr) 3442, 3011, 1728, 1717, 1603, 1572, 1463, 1371, 1332, 1091 cm^{-1}; HRMS (EI) m/z calcd for $C_{10}H_7NO_5$ [M$^+$] 221.0324, found 221.0317.

7-Chloro-3-nitrocoumarin.[12c] Off-white solid; 640 mg; yield 89%; mp 128–130 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.73 (s, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.46 (dd, J = 8.4, 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.1, 151.2, 142.9, 141.8, 134.5, 131.5, 126.8, 117.5, 114.8; IR ν_{max} (KBr) 3441, 2857, 1723, 1615, 1522, 1337, 1206, 1074, 976, 869 cm^{-1}; HRMS (EI) m/z calcd for $C_9H_4ClNO_4$ [M$^+$] 224.9829, found 224.9830.

2-Nitro-3*H*-benzo[*f*]coumarin.[12d] Brown solid; 560 mg; yield 80%; mp 194–196 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.60 (s, 1H), 8.35 (d, J = 8.4 Hz, 1H), 8.27 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.87 (td, J = 7.2, 1.2 Hz, 1H), 7.72 (t, J = 8.0 Hz, 1H), 7.56 (d, J = 9.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.5, 152.0, 138.8, 138.5, 133.4, 130.4, 130.1, 129.7, 129.6, 127.4, 121.5, 116.5, 111.1; IR ν_{max} (KBr) 3441, 2970, 1737, 1714, 1552, 1439, 1365, 1228, 1022, 820 cm^{-1}; HRMS (EI) m/z calcd for $C_{13}H_7NO_4$ [M$^+$] 241.0475, found 241.0380.

Synthesis of Lamellarin Core (3). To a mixture of 3-nitrocoumarin **1** (209 mg, 1.09 mmol, 1.2 equiv), 1-benzylisoquinoline **2** (200 mg, 0.912 mmol, 1 equiv), and $AlCl_3$ (243 mg, 1.82 mmol, 2 equiv) in a flame-dried 50 mL round-bottom flask was added toluene (20 mL) under a nitrogen atmosphere. The mixture was degassed and refluxed overnight. After the reaction mixture was cooled down to room temperature, the solvent was evaporated *in vacuo*. The crude mixture was purified by column chromatography to give the lamellarin core as pale yellow compound **3**. R_f = 0.40 (40% EtOAc/hexanes); 105 mg; yield 32%; mp 222–224 °C (Lit.[8] 222–224 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.36 (d, J = 7.2 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.67–7.63 (m, 3H), 7.58–7.53 (m, 2H), 7.52–7.49 (m, 2H), 7.47–7.43 (m, 1H), 7.35 (td, J = 7.6, 1.6 Hz, 1H), 7.25 (td, J = 8.0, 1.2 Hz, 1H), 7.15 (d, J = 7.2 Hz, 1H), 7.11 (dd, J = 8.0, 1.6 Hz, 1H), 7.00 (td, J = 8.4, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 155.3, 151.7, 135.6, 134.1, 130.9, 129.9, 129.7, 128.7, 128.7, 128.4, 128.2, 127.5, 127.3, 125.0, 124.4, 124.4, 124.2, 123.9, 117.9, 117.4, 114.3, 113.5, 109.4; IR ν_{max} (KBr) 3463, 2970, 1738, 1538, 1411, 1367, 1229, 1048, 968, 898 cm^{-1}; HRMS (EI) m/z calcd for $C_{25}H_{15}NO_2$ [M$^+$] 361.1103, found 361.1106.

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Synthesis of Lamellarin Derivatives. Mixtures of a 3-nitrocoumarin derivative (1.2 equiv), 1-benzylisoquinoline/papaverine (1 equiv), and $NaHCO_3$ (2.2 equiv) in xylene (25 mL) were placed in a 50 mL flame-dried sealed tube under an argon atmosphere. The sealed tube was closed tightly with a Teflon ring screw cap and was heated to 160 °C for 16 h. After the mixture was cooled down to room temperature, the solvent was evaporated *in vacuo* and the crude mixture was purified by column chromatography to afford lamellarin derivatives **8a−h**. During the purification, the starting material papaverine (about 20%) was recovered.

8a. R_f = 0.30 (50% EtOAc/hexanes); off-white solid; 155 mg; yield 30%; mp 248−250 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.34 (d, J = 7.6 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.75−7.49 (m, 4H), 7.68 (s, 1H), 7.64 (s, 1H), 7.51 (td, J = 8.0, 1.2 Hz, 1H), 7.28 (td, J = 8.0, 1.2 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H), 6.97 (s, 1H), 6.53 (s, 1H), 3.92 (s, 3H), 3.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 155.6, 149.5, 146.6, 145.5, 135.8, 134.0, 131.4, 129.7, 129.4, 128.5, 128.1, 127.4, 127.3, 124.9, 124.5, 124.4, 113.1, 113.0, 109.7, 108.7, 104.8, 100.5, 56.1, 55.3; IR ν_{max} (KBr) 3461, 2970, 1708, 1428, 1360, 1216, 1008, 788, 728 cm^{-1}; HRMS (EI) m/z calcd for $C_{27}H_{19}NO_4$ [M$^+$] 421.1314, found 421.1311.

8b. R_f = 0.25 (50% EtOAc/hexanes); pale white solid; 261 mg; yield 35%; mp 250−252 °C (Lit.[18a] 254−256 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.28 (d, J = 7.2 Hz, 1H), 7.44 (dd, J = 8.0, 0.4 Hz, 1H), 7.37 (dd, J = 7.6, 1.6 Hz, 1H), 7.32 (td, J = 8.0, 2.8 Hz, 1H), 7.18 (dd, J = 6.4, 1.6 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 7.10−7.09 (m, 3H), 7.68 (s, 1H), 7.04 (d, J = 8.0 Hz, 1H), 4.02 (s, 3H), 3.98 (s, 3H), 3.87 (s, 3H), 3.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 155.1, 151.7, 150.0, 149.9, 149.2, 149.1, 134.4, 128.6, 128.3, 128.0, 124.7, 124.1, 123.8, 123.7, 123.1, 119.1, 118.0, 117.2, 114.0, 112.7, 112.1, 112.0, 108.3, 107.3, 105.2, 56.1, 56.0, 55.9, 55.2; IR ν_{max} (KBr) 3447, 3005, 1737, 1710, 1610, 1505, 1366, 1219, 1024, 753 cm^{-1}; HRMS (EI) m/z calcd for $C_{29}H_{23}NO_6$ [M$^+$] 481.1525, found 481.1534.

8c. R_f = 0.35 (50% EtOAc/hexanes); brown solid; 152 mg; yield 22%; mp 234−236 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.50 (d, J = 7.6 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 7.11−7.07 (m, 4H), 7.03 (s, 1H), 7.01 (d, J = 2.0 Hz, 1H), 6.74 (s, 1H), 6.62 (d, J = 8.0 Hz, 1H), 4.00 (s, 3H), 3.98 (s, 3H), 3.88 (s, 3H), 3.45 (s, 3H), 3.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 156.4, 155.3, 152.8, 149.8, 148.9, 148.8, 147.8, 135.2, 133.1, 128.6, 127.4, 124.9, 123.8, 123.1, 119.4, 114.9, 114.0, 113.1, 110.9, 109.9, 108.7, 108.6, 107.3, 105.9, 105.2, 56.2, 56.1, 55.9, 55.2, 54.7; IR ν_{max} (KBr) 3602, 2969, 1714, 1608, 1435, 1365, 1226, 1027, 855, 787 cm^{-1}; HRMS (EI) m/z calcd for $C_{30}H_{25}NO_7$ [M$^+$] 511.1631, found 511.1634.

8d. R_f = 0.35 (50% EtOAc/hexanes); pale brown solid; 187 mg; yield 27%; mp 252−254 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.30 (d, J = 7.2 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 7.23 (dd, J = 8.4, 2.0 Hz, 1H), 7.19 (s, 1H), 7.16 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 2.0 Hz, 1H), 7.15 (s, 1H), 7.11 (s, 1H), 7.09 (d, J = 7.6 Hz, 1H), 6.94 (dd, J = 8.8, 2.8 Hz, 1H), 6.83 (d, J = 2.8 Hz, 1H), 4.02 (s, 3H), 4.00 (s, 3H), 3.91 (s, 3H), 3.52 (s, 3H), 3.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.4, 155.3, 150.1, 149.9, 149.2, 149.1, 146.0, 134.2, 128.6, 128.0, 124.6, 123.9, 123.2, 119.1, 118.3, 118.1, 115.9, 114.2, 112.7, 112.0, 111.8, 108.6, 107.3, 106.7, 105.2, 56.2, 56.1, 55.9, 55.2, 55.1; IR ν_{max} (KBr) 3461, 2933, 1713, 1690, 1479, 1411, 1225, 1045, 1005, 866, 799 cm^{-1}; HRMS (EI) m/z calcd for $C_{30}H_{25}NO_7$ [M$^+$] 511.1631, found 511.1635.

8e. R_f = 0.30 (60% EtOAc/hexanes); yellow solid; 255 mg; yield 37%; mp 256−258 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.26 (d, J = 7.6 Hz, 1H), 7.22 (d, J = 8.8 Hz, 1H), 7.19 (d, J = 1.6 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 7.11−7.10 (m, 3H), 7.07 (d, J = 7.6 Hz, 1H), 6.98−6.96 (m, 1H), 6.67 (d, J = 8.8, 2.4 Hz, 1H), 4.04 (s, 3H), 4.02 (s, 3H), 3.89 (s, 3H), 3.85 (s, 3H), 3.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 160.0, 155.3, 155.2, 150.1, 149.9, 149.2, 149.1, 134.6, 129.3, 128.1, 124.9, 124.8, 123.8, 123.3, 119.1, 114.1, 112.4, 112.0, 111.6, 111.3, 111.2, 107.5, 107.3, 105.3, 101.6, 56.1, 56.0, 55.9, 55.5, 55.2; IR ν_{max} (KBr) 2936, 1707, 1617, 1431, 1314, 1225, 1139, 1046, 841, 756 cm^{-1}; HRMS (EI) m/z calcd for $C_{30}H_{25}NO_7$ [M$^+$] 511.1631, found 511.1625.

8f. R_f = 0.40 (50% EtOAc/hexanes); dark brown solid; 135 mg; yield 19%; mp 254−256 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.32 (d, J = 7.6 Hz, 1H), 7.20 (dd, J = 8.0, 1.6 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 7.13−7.10 (m, 1H), 7.11 (s, 1H), 7.10 (s, 1H), 7.09 (d, J = 7.2 Hz, 1H), 7.01 (d, J = 7.6 Hz, 1H), 6.69−6.91 (m, 2H), 4.04 (s, 3H), 4.00 (s, 3H), 3.99 (s, 3H), 3.90 (s, 3H), 3.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 154.6, 150.0, 149.9, 149.1, 149.0, 147.8, 141.2, 134.4, 128.7, 128.1, 124.7, 123.8, 123.6, 123.3, 119.2, 118.8, 115.9, 114.2, 112.7, 112.2, 112.0, 110.4, 108.5, 107.4, 105.3, 56.2, 56.1, 56.0, 55.9, 55.2; IR ν_{max} (KBr) 3631, 2837, 1702, 1611, 1503, 1462, 1399, 1264, 1171, 1094 cm^{-1}; HRMS (EI) m/z calcd for $C_{30}H_{25}NO_7$ [M$^+$] 511.1631, found 511.1635.

8g. R_f = 0.30 (50% EtOAc/hexanes); off white solid; 298 mg; yield 41%; mp 296−298 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.24 (d, J = 7.6 Hz, 1H), 7.44 (d, J = 2.0 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.16 (s, 1H), 7.15 (d, J = 2.0 Hz, 1H), 7.11−7.10 (m, 4H), 7.03 (dd, J = 8.8, 2.4 Hz, 1H), 4.02 (s, 3H), 3.97 (s, 3H), 3.87 (s, 3H), 3.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 154.6, 152.0, 150.3, 150.0, 149.3, 149.2, 134.7, 133.8, 128.0, 127.6, 125.0, 124.8, 124.3, 123.7, 123.1, 119.1, 117.6, 116.7, 114.1, 113.1, 112.1, 112.0, 108.0, 107.4, 105.2, 56.13, 56.10, 56.0, 55.3; IR ν_{max} (KBr) 3452, 2970, 1711, 1504, 1428, 1385, 1210, 1030, 858, 755 cm^{-1}; HRMS (EI) m/z calcd for $C_{29}H_{22}ClNO_6$ [M$^+$] 515.1136, found 515.1131.

8h. The compound was recrystallized from 70% DCM/hexanes biphasic system. R_f = 0.40 (1% MeOH/DCM); brown solid; 149 mg; yield 23%; mp 218−220 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.54 (d, J = 7.6 Hz, 1H), 7.88 (d, J = 8.8 Hz, 1H), 7.84 (d, J = 8.8 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.35 (s, 1H), 7.31 (t, J = 7.2 Hz, 1H), 7.43 (d, J = 7.2 Hz, 1H), 7.14 (s, 1H), 7.13 (d, J = 6.4 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 1.6 Hz, 1H), 6.90 (td, J = 8.0, 1.6 Hz, 1H), 4.02 (s, 3H), 4.00 (s, 3H), 3.70 (s, 3H), 3.53 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 155.3, 150.6, 150.0, 149.7, 149.0, 134.6, 130.9, 130.5, 130.0, 129.3, 128.4, 127.7, 127.9, 125.1, 125.0, 124.7, 124.6, 124.5, 123.1, 119.2, 117.8, 115.7, 113.4, 113.2, 113.0, 111.8, 110.3, 107.5, 105.9, 56.3, 56.1, 55.9, 55.4; IR ν_{max} (KBr) 3439, 3004, 1715, 1617, 1416, 1365, 1226, 1049, 989, 810, 752 cm^{-1}; HRMS (EI) m/z calcd for $C_{33}H_{25}NO_6$ [M$^+$] 531.1682, found 531.1683.

Exhaustive Demethylation of Lamellarin Derivatives (9a−h). To an ice cooled solution of lamellarin derivatives **8a−h** (1 equiv) in dry CH_2Cl_2, was added dropwise BBr_3 (1 M solution in DCM, 18.0 equiv) at −78 °C under a nitrogen atmosphere. The resultant deep green reaction mixture was further allowed to stir at room temperature for 16 h. After this, the reaction was carefully quenched by the addition of MeOH (10 mL). The dark colored solution was then concentrated *in vacuo*, and the residue was suspended in water. The resultant precipitate was filtered off and dried *in vacuo* to yield the demethylated lamellarin derivatives **9a−h**.

9a. Brown solid; 85 mg; yield 91%; mp charred at 330 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.85 (br s, 1H), 9.21 (d, J = 7.2 Hz, 1H), 8.91 (br s, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.72−7.69 (m, 3H), 7.57−7.53 (m, 3H), 7.37 (d, J = 7.6 Hz, 1H), 7.35−7.33 (m, 1H), 7.30 (dd, J = 8.0, 0.8 Hz, 1H), 6.86 (s, 1H), 6.44 (s, 1H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 154.6, 147.2, 145.3, 142.4, 135.0, 133.2, 130.7, 130.0, 129.3, 128.9, 128.8, 128.4, 127.7, 127.6, 124.2, 123.8, 123.4, 113.1, 113.0, 109.1, 108.3, 107.7, 103.5; IR ν_{max} (KBr) 3292, 1738, 1716, 1668, 1441, 1365, 1227, 1144, 1050, 862 cm^{-1}; HRMS (EI) m/z calcd for $C_{25}H_{15}NO_4$ [M$^+$] 393.1001, found 393.1006.

9b. Gray solid; 77 mg; yield 87%; mp charred at 300 °C (Lit.[8] ≥300 °C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.01 (br s, 1H), 9.53 (br s, 1H), 9.25 (br s, 2H), 9.02 (d, J = 7.6 Hz, 1H), 7.47−7.45 (m, 1H), 7.44−7.41 (m, 1H), 7.24 (d, J = 7.2 Hz, 1H), 7.18 (s, 1H), 7.16−7.13 (m, 2H), 7.08 (s, 1H), 7.01 (d, J = 7.6 Hz, 1H), 6.85 (d, J = 2.0 Hz, 1H), 6.77 (dd, J = 7.6, 2.0 Hz, 1H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 153.9, 151.2, 147.9, 146.8, 146.3, 145.6, 133.9, 128.5, 127.7, 125.4, 123.8, 123.7, 123.6, 121.3, 121.0, 118.1, 117.6, 117.4, 117.1, 117.0, 113.3, 112.4, 111.5, 109.5, 107.1; IR ν_{max} (KBr) 3424, 2970, 1737, 1681, 1504, 1473, 1203, 1108, 1026, 744 cm^{-1}; HRMS (EI) m/z calcd for $C_{25}H_{15}NO_6$ [M$^+$] 425.0899, found 425.0896.

9c. Dark brown solid; 82 mg; yield 92%; mp charred at 300 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 9.13 (d, J = 7.2 Hz, 1H), 7.24 (t, J = 8.4

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Hz, 1H), 6.98 (s, 1H), 6.95 (d, J = 7.2 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.76 (s, 1H), 6.75 (d, J = 1.6 Hz, 1H), 6.61 (d, J = 8.4 Hz, 1H), 6.60 (dd, J = 8.0, 2.0 Hz, 1H), 3.13 (s, 3H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 156.2, 154.1, 152.2, 147.4, 146.4, 145.0, 144.2, 134.8, 130.6, 129.0, 126.7, 124.0, 121.5, 121.0, 118.4, 118.6, 115.5, 114.6, 113.6, 111.3, 110.7, 109.1, 107.9, 107.5, 106.0, 54.9; IR ν_{max} (KBr) 3017, 1736, 1604, 1418, 1365, 1278, 1217, 1095, 867, 763 cm^{-1}; HRMS (EI) m/z calcd for $C_{26}H_{17}NO_7$ [M$^+$] 455.1005, found 455.1002.

9d. Dark brown solid; 77 mg; yield 89%; mp charred at 300 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 9.01 (d, J = 7.2 Hz, 1H), 7.14 (d, J = 8.8 Hz, 1H), 7.07 (s, 1H), 7.02 (s, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.99 (d, J = 7.2 Hz, 1H), 6.89 (d, J = 2.0 Hz, 1H), 6.78 (dd, J = 8.4, 2.0 Hz, 1H), 6.75 (dd, J = 8.0, 2.0 Hz, 1H), 6.69 (d, J = 2.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 154.2, 153.2, 147.8, 146.7, 146.3, 145.6, 144.5, 133.8, 127.8, 125.2, 123.7, 121.3. 121.1, 118.2, 118.2, 117.6, 117.4, 117.1, 116.2, 113.3, 112.5, 111.5, 109.6, 109.2, 107.3; IR ν_{max} (KBr) 3443, 1738, 1621, 1473, 1366, 1227, 1110, 1036, 958, 755 cm^{-1}; HRMS (EI) m/z calcd for $C_{25}H_{15}NO_7$ [M$^+$] 441.0849, found 441.0845.

9e. Dark brown solid; 80 mg; yield 90%; mp charred at 300 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 8.95 (d, J = 7.2 Hz, 1H), 7.14 (s, 1H), 7.03 (s, 1H), 7.00 (d, J = 3.6 Hz, 1H), 6.99 (d, J = 2.8 Hz, 1H), 6.96 (d, J = 7.2 Hz, 1H), 6.87 (d, J = 2.0 Hz, 1H), 6.76 (dd, J = 8.0, 2.0 Hz, 1H), 6.71 (d, J = 2.4 Hz, 1H), 6.47 (dd, J = 8.8, 2.4 Hz, 1H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 158.2, 154.2, 152.7, 147.9, 146.7, 146.3, 145.6, 134.1, 128.8, 125.6, 124.6, 123.9, 121.5, 121.2, 118.9, 117.6, 117.1, 112.8, 112.4, 111.5, 111.4, 109.6, 109.4, 106.0, 103.1; IR ν_{max} (KBr) 3393, 2970, 1737, 1616, 1472, 1366, 1217, 1081, 981, 753 cm^{-1}; HRMS (EI) m/z calcd for $C_{25}H_{15}NO_7$ [M$^+$] 441.0849, found 441.0843.

9f. Dark brown solid; 72 mg; yield 83%; mp >300 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 9.01 (d, J = 7.6 Hz, 1H), 7.13 (s, 1H), 7.03 (s, 1H), 6.99 (t, J = 7.6 Hz, 1H), 6.98 (d, J = 7.6 Hz, 1H), 6.86 (d, J = 2.0 Hz, 1H), 6.82 (s, 1H), 6.80 (d, J = 2.8 Hz, 1H), 6.75 (dd, J = 8.0, 2.0 Hz, 1H), 6.67 (dd, J = 6.4, 3.6 Hz, 1H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 153.9, 147.8, 146.8, 146.3, 145.6, 145.3, 140.0, 133.9, 128.3, 125.5, 123.8, 123.7, 121.5, 121.2, 118.6, 118.2, 117.6, 117.1, 115.1, 114.0, 113.3, 112.5, 111.5, 109.6, 107.2; IR ν_{max} (KBr) 3429, 3016, 1737, 1622, 1584, 1449, 1366, 1285, 1022, 854 cm^{-1}; HRMS (EI) m/z calcd for $C_{25}H_{15}NO_7$ [M$^+$] 441.0849, found 441.0852.

9g. Dark green solid; 80 mg; yield 90%; mp >300 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 8.92 (d, J = 7.2 Hz, 1H), 7.31 (d, J = 1.2 Hz, 1H), 7.134 (d, J = 8.4 Hz, 1H), 7.130 (s, 1H), 7.02 (s, 1H), 7.00 (s, 1H), 6.99 (dd, J = 6.8, 2.0 Hz, 1H), 6.98 (d, J = 4.0 Hz, 1H), 6.87 (d, J = 2.0 Hz, 1H), 6.76 (dd, J = 8.0, 2.0 Hz, 1H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 153.0, 151.6, 148.0, 146.9, 146.4, 145.7, 134.2, 132.5, 126.9, 125.0, 124.7, 124.1, 123.8, 121.3, 120.9, 118.1, 117.4, 117.2, 117.0, 116.7, 113.6, 112.5, 111.5, 109.5, 106.8; IR ν_{max} (KBr) 3460, 1737, 1607, 1475, 1421, 1366, 1280, 1164, 1031, 782 cm^{-1}; HRMS (EI) m/z calcd for $C_{25}H_{14}ClNO_6$ [M$^+$] 459.0510, found 459.0509.

9h. Dark brown solid; 75 mg; yield 84%; mp >330 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 9.21 (d, J = 7.2 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.78 (t, J = 8.8 Hz, 1H), 7.77 (s, 1H), 7.446 (t, J = 8.4 Hz, 1H), 7.454 (s, 1H), 7.28 (t, J = 8.4 Hz, 1H), 7.11 (s, 1H), 7.08 (d, J = 7.2 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.90 (t, J = 8.0 Hz, 1H), 6.80 (d, J = 2.0 Hz, 1H), 6.76 (dd, J = 8.0, 2.0 Hz, 1H); ^{13}C NMR (DMSO- d_6, 150 MHz) δ 154.0, 149.9, 147.7, 146.6, 146.0, 145.5, 134.2, 130.6, 130.0, 128.4, 128.0, 127.7, 127.5, 127.4, 124.7, 124.5, 124.1, 122.7, 120.9, 118.7, 118.2, 117.5, 116.6, 113.9, 113.8, 112.6, 111.5, 110.3, 109.1; IR ν_{max} (KBr) 3438, 1737, 1715, 1515, 1366, 1228, 1160, 1033, 869, 753 cm^{-1}; HRMS (EI) m/z calcd for $C_{29}H_{17}NO_6$ [M$^+$] 475.1056, found 475.1050.

Synthesis of Lamellarin D Trimethyl Ether (12). A 100 mL flame-dried sealed tube was charged with 6,7-dimethoxy-3-nitrocoumarin (**11**, 0.444 g, 1.77 mmol, 1.2 equiv), papaverine **7** (0.500 g, 1.47 mmol, 1 equiv), and $NaHCO_3$ (0.273 g, 3.24 mmol, 2.2 equiv) in anhydrous xylene (35 mL) under an argon atmosphere. The sealed tube was closed tightly with a Teflon ring screw cap and was subjected to heat at 160 °C for 16 h. After the dark colored reaction mixture was cooled down to room temperature, the solvent was evaporated *in vacuo*. The residue was dissolved in DCM (50 mL), filtered, and washed with copious amounts of DCM. The resulting solvent was concentrated *in vacuo*, and the product was purified over column chromatography to afford lamellarin D trimethyl ether **12** as a pale yellow solid. R_f = 0.45 (2% MeOH/DCM); 317 mg; yield 40%; mp 278−280 °C (Lit.[8] 278−280 °C); During the purification, unreacted papaverine **7** was recovered (97 mg, ∼20%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.24 (d, J = 7.2 Hz, 1H), 7.28 (s, 1H), 7.26 (dd, J = 6.4, 1.6 Hz, 1H), 7.19−7.17 (m, 3H), 7.11 (s, 1H), 7.07 (d, J = 7.6 Hz, 1H), 6.95 (s, 1H), 6.76 (s, 1H), 4.02 (s, 3H), 4.01 (s, 3H), 3.91 (s, 3H), 3.90 (s, 3H), 3.50 (s, 3H), 3.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 155.5, 150.1, 149.9, 149.5, 149.2, 149.0, 146.7, 145.5, 134.4, 129.4, 128.2, 124.8, 124.1, 123.3, 119.1, 114.4, 112.3, 111.9, 110.9, 109.9, 107.8, 107.4, 105.3, 105.0, 100.5, 56.3, 56.2, 56.01, 56.00, 55.5, 55.2; IR ν_{max} (KBr) 2944, 1746, 1602, 1520, 1470, 1365, 1230, 1128, 971, 772 cm^{-1}; HRMS (EI) m/z calcd for $C_{31}H_{27}NO_8$ [M$^+$] 541.1737, found 541.1740.

Synthesis of Lamellarin H (13). To a solution of lamellarin D trimethyl ether **12** (0.200 g, 0.37 mmol, 1 equiv) in dry CH_2Cl_2 (39 mL) was carefully added dropwise BBr_3 (1 M solution in DCM, 6.65 mL, 6.65 mmol, 18.0 equiv) at −78 °C under a nitrogen atmosphere. The resultant dark green reaction mixture was further allowed to stir at room temperature for 16 h. Afterward, the reaction was carefully quenched by the addition of MeOH (15 mL). The dark colored solution was then concentrated *in vacuo*, and the residue was suspended in water. The resultant precipitate was filtered off and dried *in vacuo* to yield lamellarin H (**13**) as a gray solid; 140 mg; yield 83%; mp >300 °C (Lit.[8] > 300 °C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.98 (br s, 1H), 9.76 (br s, 1H), 9.40 (br s, 1H), 9.19 (br s, 2H), 9.50 (d, J = 7.6 Hz, 1H), 8.90 (br s, 1H), 7.15 (d, J = 7.2, Hz, 1H), 7.14 (s, 1H), 7.00 (d, J = 7.6 Hz, 1H), 6.96 (s, 1H), 6.81 (s, 1H), 6.80 (d, J = 2.0 Hz, 1H), 6.72 (dd, J = 7.6, 2.0 Hz, 1H), 6.58 (s, 1H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 154.3, 147.7, 146.8, 146.6, 146.2, 145.5, 145.3, 142.1, 134.0, 128.9, 125.4, 123.8, 121.5, 121.2, 118.1, 117.6, 117.0, 112.6, 111.44, 111.42, 109.64, 109.57, 108.8, 106.3, 103.4; IR ν_{max} (KBr) 3430, 2970, 1737, 1556, 1417, 1366, 1210, 1082, 957, 753 cm^{-1}; HRMS (EI) m/z calcd for $C_{25}H_{15}NO_8$ [M$^+$] 457.0798, found 457.0793.

4-(Benzyloxy)-2-hydroxy-5-methoxybenzaldehyde (15).[18b] To a mixture of 2,4-dihydroxy-5-methoxybenzaldehyde (1.5 g, 8.9 mmol, 1 equiv) and $NaHCO_3$ (0.9 g, 10.7 mmol, 1.2 equiv) in dry DMF (50 mL) was added BnBr (1.27 mL, 10.7 mmol, 1.2 equiv) at room temperature under a nitrogen atmosphere. The resultant solution was then heated at 85 °C for 2 days (typically 48−56 h). After the solution cooled to room temperature, the reaction was quenched with water and the product was extracted with EtOAc (50 mL × 3). The combined organic layer was washed with brine (2 times), dried over $MgSO_4$, and evaporated *in vacuo*. The residue was further purified by flash column chromatography to afford the product **15** as a white solid; R_f = 0.45 (30% EtOAc/hexanes); 1.40 g; yield 61%; mp 92−94 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.34 (s, 1H), 9.70 (s, 1H), 7.45−7.34 (m, 5H), 6.94 (s, 1H), 6.51 (s, 1H), 5.20 (s, 2H), 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 197.0, 159.1, 156.3, 143.2, 135.4, 128.7, 128.3, 127.3, 113.7, 113.0, 101.5, 70.8, 56.6; IR ν_{max} (KBr) 3440, 2970, 1737, 1651, 1503, 1369, 1269, 1235, 1142, 1023, 984 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{14}O_4$ [M$^+$] 258.0892, found 258.0893.

7-(Benzyloxy)-6-methoxy-3-nitrocoumarin (16). To a solution of 4-(benzyloxy)-2-hydroxy-5-methoxybenzaldehyde (**15**, 2.0 g, 10.3 mmol, 1 equiv) in benzene (100 mL) was added ethyl nitroacetate (1.51 g, 11.33 mmol, 1.1 equiv) and a catalytic amount of piperidine at room temperature. The resulting mixture was then refluxed with a Dean−Stark trap overnight. After the mixture cooled to room temperature, the dark yellow solution was concentrated under reduced pressure and the residue was thoroughly washed with 5% EtOAc/hexanes to remove excess ethyl nitroacetate and a trace of piperidine. The vacuum-dried residue resulted in product **16** as a brown-yellow solid; R_f = 0.45 (100% DCM); 2.65 g; yield 92%; mp 208−210 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.76 (s, 1H), 7.45−7.36 (m, 5H), 7.00 (s,

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1H), 6.91 (s, 1H), 5.28 (s, 2H), 3.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 156.4, 152.5, 148.1, 143.1, 134.5, 131.5, 129.0, 128.9, 128.8, 127.4, 109.2, 109.1, 101.2, 71.7, 56.5; IR ν_{max} (KBr) 3472, 1736, 1728, 1519, 1363, 1280, 1188, 1004, 866, 769 cm^{-1}; HRMS (EI) m/z calcd for $C_{17}H_{13}NO_6$ [M$^+$] 327.0743, found 327.0740.

2-(Benzyloxy)-1-methoxy-4-(1-methoxy-2-nitroethyl) Benzene (18).[14a] To a solution of compound **17** (2.0 g, 7.0 mmol, 1 equiv) in dry DCM (50 mL) was added a freshly prepared saturated methanolic solution of NaOMe (4 mL) at room temperature under a nitrogen atmosphere. After the resultant dark brown solution was stirred for 8 min, the reaction was quenched by adding AcOH (3 mL). The organic layer was washed with copious amounts of water (100 mL × 3), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was further purified by flash column chromatography to afford product **18** as a yellow solid; R_f = 0.35 (30% EtOAc/hexanes); 1.90 g; yield 85%; mp 97−99 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46 (d, J = 7.2 Hz, 1H), 7.45 (s, 1H), 7.392 (td, J = 8.0, 0.8 Hz, 1H), 7.388 (s, 1H), 7.34 (d, J = 7.2 Hz, 1H), 6.924 (d, J = 1.2 Hz, 1H), 6.923 (s, 1H), 6.90 (d, J = 0.8 Hz, 1H), 5.19 (s, 2H), 4.85 (dd, J = 10.0, 3.2 Hz, 1H), 4.55 (ABdq, J = 12.8, 10.0 Hz, 1H), 4.33 (ABdq, J = 12.8, 3.2 Hz, 1H), 3.92 (s, 3H), 3.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 150.3, 148.5, 136.6, 128.6, 128.0, 128.0, 127.4, 120.0, 112.1, 111.8, 80.5, 79.6, 71.0, 56.8, 56.0; IR ν_{max} (KBr) 3444, 3004, 1737, 1714, 1552, 1363, 1222, 1026, 810, 730 cm^{-1}; HRMS (EI) m/z calcd for $C_{17}H_{19}NO_5$ [M$^+$] 317.1263, found 317.1270.

2-(3-(Benzyloxy)-4-methoxyphenyl)-2-methoxyethan-1-amine (19).[14a] To a suspension of 2-(benzyloxy)-1-methoxy-4-(1-methoxy-2-nitroethyl)benzene (**18**, 1.5 g, 4.73 mmol, 1 equiv) in MeOH/THF (2:1) (150 mL) was added zinc powder (3.0 g) at room temperature, and the mixture was stirred for 10 min at that temperature. Upon careful addition of concentrated HCl (12 M, 4 mL), the slurry was subjected to reflux for 10 h. After the reaction was cooled down to room temperature, the solution was concentrated *in vacuo* and the residue was redissolved in DCM. The organic layer was washed with water and a brine solution twice, dried, and concentrated under reduced pressure to afford **19** as an off-white spongy hygroscopic solid. The crude product **19** was taken to the next step without further purification; R_f = 0.15 (5% MeOH/DCM); 1.23 g; yield 91%; mp 76−78 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.44 (d, J = 8.4 Hz, 1H), 7.43 (s, 1H), 7.36 (td, J = 8.4, 1.6 Hz, 1H), 7.35 (s, 1H), 7.30 (d, J = 6.8 Hz, 1H), 7.02 (d, J = 2.0 Hz, 1H), 6.99 (s, 1H), 6.95 (dd, J = 8.4, 2.0 Hz, 1H), 5.12 (s, 2H), 4.41 (dd, J = 9.2, 4.0 Hz, 1H), 3.85 (s, 3H), 3.21 (s, 3H), 3.05 (ABdq, J = 12.8, 9.2 Hz, 1H), 3.00 (ABdq, J = 12.8, 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 151.5, 149.6, 138.4, 131.0, 129.4, 128.9, 128.8, 121.4, 114.1, 113.5, 80.6, 72.1, 56.8, 56.6, 46.6; IR ν_{max} (KBr) 3452, 2970, 1715, 1606, 1515, 1429, 1365, 1257, 1086, 815 cm^{-1}; HRMS (EI) m/z calcd for $C_{17}H_{21}NO_3$ [M$^+$] 287.1521, found 287.1519.

***N*-(2-(3-(Benzyloxy)-4-methoxyphenyl)-2-methoxyethyl) Acetamide (20).** To an ice cooled solution of amine **19** (1.0 g, 3.5 mmol, 1 equiv) and TEA (1.1 equiv) in DCM was added dropwise Ac_2O (1.32 mL, 4 equiv, 13.4 mmol) under a nitrogen atmosphere at 0 °C. The solution was allowed to stir for an additional 14 h at room temperature before it was quenched by water. The crude reaction mixture was then extracted with DCM. The organic layer was washed with water and a brine solution (3 times each), dried over $MgSO_4$, and evaporated under reduced pressure. The pure product **20** was obtained after filter-column separation as an off-white solid; R_f = 0.45 (5% MeOH/DCM); 890 mg; yield 78%; mp 85−87 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44 (d, J = 7.2 Hz, 1H), 7.43 (s, 1H), 7.36 (s, 1H), 7.36 (t, J = 8.8 Hz, 1H), 7.30 (d, J = 4.8 Hz, 1H), 6.89−6.82 (m, 2H), 6.88 (s, 1H), 5.79 (br s, 1H), 5.15 (s, 2H), 4.14 (dd, J = 8.8, 4.0 Hz, 1H), 3.89 (s, 3H), 3.61 (ABddq, J = 11.6, 8.8, 4.0 Hz, 1H), 3.14 (s, 3H), 3.13−3.10 (m, 1H), 1.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 170.0, 149.5, 148.1, 136.9, 131.2, 128.5, 127.9, 127.4, 119.4, 112.1, 111.6, 81.7, 70.9, 56.5, 56.0, 45.6, 23.3; IR ν_{max} (KBr) 3442, 2942, 1714, 1630, 1511, 1365, 1246, 1097, 1011, 824 cm^{-1}; HRMS (EI) m/z calcd for $C_{19}H_{23}NO_4$ [M$^+$] 329.1627, found 329.1626.

6-(Benzyloxy)-7-methoxy-1-methylisoquinoline (21).[18c] To a vigorously stirred solution of amide **20** (2.0 g, 6.0 mmol, 1 equiv) in dry DCM (50 mL) was cautiously added $POCl_3$ (2.3 mL, 24.2 mmol, 4 equiv), and the mixture was refluxed overnight. The solution was neutralized by adding the aq. NaOH (20%) solution, and the crude compound was extracted by DCM (30 mL × 5). The collected organic layer was again washed with water and a brine solution (3 times), dried over $MgSO_4$, and concentrated *in vacuo*. The flash column chromatography of the residue afforded the 6-(benzyloxy)-7-methoxy-1-methylisoquinoline (**21**) as a pale yellow solid. R_f = 0.40 (5% MeOH/DCM); 1.40 g; yield 83%; mp 138−140 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27 (d, J = 5.6 Hz, 1H), 7.516 (d, J = 7.2 Hz, 1H), 7.507 (s, 1H), 7.43 (s, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.37 (d, J = 7.2 Hz, 1H), 7.35 (d, J = 5.6 Hz, 1H), 7.32 (s, 1H), 7.12 (s, 1H), 5.32 (s, 2H), 4.07 (s, 3H), 2.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 155.8, 151.6, 150.2, 140.7, 136.0, 132.5, 128.7, 128.2, 127.3, 123.3, 118.2, 107.0, 104.0, 70.7, 56.0, 22.3; IR ν_{max} (KBr) 3460, 2949, 1737, 1619, 1504, 1365, 1217, 1054, 855, 699 cm^{-1}; HRMS (EI) m/z calcd for $C_{18}H_{17}NO_2$ [M$^+$] 279.1259, found 279.1257.

2-(4-(Benzyloxy)-3-methoxyphenyl)-*N*-(2-(3-(benzyloxy)-4-methoxyphenyl)-2-methoxyethyl)acetamide.[14a] To an ice cooled mixture of amine **19** (1.0 g, 3.48 mmol, 1 equiv) and 4-benzyloxy-3-methoxy phenylacetic acid (1.04 g, 3.83 mmol, 1.1 equiv) in dry DCM (100 mL) was added *N,N′*-dicyclohexylcarbodiimide (DCC) (1.08 g, 5.22 mmol, 1.5 equiv) in one portion under a nitrogen atmosphere. The mixture was stirred at room temperature for 2 days. The progress of the reaction was monitored constantly by TLC, and more DCC (0.4 equiv × 2) was added. The precipitate was then filtered off, and the solvent was washed with water and brine (×2), dried over $MgSO_4$, and evaporated to dryness. The residue was further purified by column chromatography to afford a pale yellow solid. R_f = 0.45 (5% MeOH/DCM); 1.43 g; yield 76%; mp 93−95 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47−7.44 (m, 4H), 7.39 (s, 1H), 7.34 (s, 1H), 7.41−7.30 (m, 4H), 6.87 (d, J = 8.0 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.81 (d, J = 1.6 Hz, 1H), 6.78 (d, J = 1.6 Hz, 1H), 6.74 (dd, J = 8.0, 2.0 Hz, 1H), 6.69 (dd, J = 8.0, 2.0 Hz, 1H), 5.75 (t, J = 6.8 Hz, 1H), 5.17 (s, 2H), 5.14 (s, 2H), 4.10−4.06 (m, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.59−3.49 (m, 3H), 3.18−3.09 (m, 4H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 171.1, 149.9, 149.6, 148.2, 147.4, 137.0, 136.9, 131.2, 128.51, 128.46, 127.8, 127.7, 127.4, 127.2, 127.1, 121.5, 119.8, 114.3, 112.9, 112.1, 111.6, 81.6, 71.0, 70.9, 56.5, 56.0, 55.9, 45.5, 43.4; IR ν_{max} (KBr) 3005, 2938, 1738, 1716, 1512, 1365, 1217, 1026, 781, 695 cm^{-1}; HRMS (EI) m/z calcd for $C_{33}H_{35}NO_6$ [M$^+$] 541.2464, found 541.2456.

6-(Benzyloxy)-1-(4-(benzyloxy)-3-methoxybenzyl)-7-methoxy Isoquinoline (26).[14a] To a solution of 2-(4-(benzyloxy)-3-methoxyphenyl)-*N*-(2-(3-(benzyloxy)-4-methoxyphenyl)-2-methoxyethyl)acetamide (1.0 g, 1.85 mmol, 1 equiv) in DCE (70 mL) was added $POCl_3$ (0.8 mL, 4 equiv) at room temperature. The resulting mixture was refluxed for 18 h under a nitrogen atmosphere, and the progress of the reaction was monitored by TLC. After the reaction mixture cooled down to room temperature, it was neutralized by the addition of aqueous NaOH (20%) solution. The crude compound was extracted with DCM and washed thoroughly with water and a brine solution (50 mL × 3). The collected organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography to yield a pale yellow solid. R_f = 0.35 (5% MeOH/DCM); 730 mg; yield 80%; mp 147−149 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 8.24 (d, J = 6.0 Hz, 1H), 7.60 (d, J = 6.0 Hz, 1H), 7.53 (d, J = 6.8 Hz, 1H), 7.52 (s, 1H), 7.49 (s, 1H), 7.44−7.42 (m, 4H), 7.412−7.31 (m, 5H), 6.97 (d, J = 2.0 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.79 (dd, J = 8.4, 2.0 Hz, 1H), 5.28 (s, 2H), 5.06 (s, 2H), 4.57 (s, 2H), 3.88 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (CD_3OD, 150 MHz) δ 159.1, 153.6, 152.0, 151.4, 148.1, 140.4, 138.7, 137.8, 135.3, 134.4, 129.6, 129.4, 129.2, 128.9, 128.8, 128.7, 124.4, 121.9, 120.6, 116.2, 114.0, 108.2, 105.8, 72.4, 71.7, 56.5, 56.4, 42.1; IR ν_{max} (KBr) 3449, 3328, 2929, 1737, 1713, 1623, 1365, 1227, 1144, 1025 cm^{-1}; HRMS (EI) m/z calcd for $C_{32}H_{29}NO_4$ [M$^+$] 491.2097, found 491.2097.

Synthesis of Lamellarin D Pentacycle (22). A flame-dried 50 mL glass sealed tube fitted with a Teflon ring screw cap was charged with 6-(benzyloxy)-7-methoxy-1-methylisoquinoline (**21**, 150 mg,

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0.536 mmol, 1 equiv), 7-(benzyloxy)-6-methoxy-3-nitrocoumarin (**16**, 211 mg, 0.644 mmol, 1.2 equiv), $NaHCO_3$ (90 mg, 1.07 mmol, 2 equiv), and anhydrous xylene (15 mL) under an argon atmosphere. The sealed tube was tightly closed by Teflon screw and heated to 120 °C for 18 h. After the reaction mixture cooled to room temperature, it was filtered-off and washed with DCM (20 mL × 2) and the collective organic solvent was concentrated *in vacuo*. The crude product was purified by column chromatography to yield lamellarin D pentacycle **22** as a pale-white solid; 128 mg; yield 43%; the starting material isoquinoline **21** (34 mg, 22%) was recovered during the purification process; R_f = 0.40 (1% MeOH/DCM); mp 254−256 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.02 (d, J = 7.2 Hz, 1H), 7.54 (s, 1H), 7.51−7.32 (m, 10H), 7.31 (s, 1H), 7.12 (s, 1H), 7.11 (s, 1H), 6.95 (s, 1H), 6.93 (d, J = 7.2 Hz, 1H), 5.27 (s, 2H), 5.19 (s, 2H), 4.10 (s, 3H), 4.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.3, 150.6, 150.0, 149.2, 146.8, 146.4, 138.4, 136.3, 136.2, 132.1, 128.8, 128.7, 128.21, 128.16, 127.6, 127.3, 124.0, 123.3, 118.6, 112.2, 109.95, 109.56, 109.2, 105.1, 104.5, 102.9, 91.4, 71.0, 70.9, 56.5, 56.2; IR ν_{max} (KBr) 3444, 1737, 1711, 1453, 1366, 1218, 1147, 1018, 844, 737, 694 cm^{-1}; HRMS (EI) m/z calcd for $C_{35}H_{27}NO_6$ [M$^+$] 557.1838, found 557.1835.

Bromination of Lamellarin D Pentacycle (23). To a vigorously stirred solution of lamellarin D pentacycle **22** (100 mg, 179.3 mmol, 1 equiv) in THF (25 mL) was added *N*-bromosuccinimide (NBS, 35.1 mg, 197.3 mmol, 1.1 equiv) at 0 °C, and the mixture was stirred for 1 h at that temperature. The reaction mixture was further stirred overnight at room temperature. The precipitate was then filtered-off, washed with hexanes (10 mL × 5), and dried *in vacuo* to yield the compound **23** as a white solid; 103 mg; yield 90%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.18 (d, J = 7.2 Hz, 1H), 8.83 (s, 1H), 8.32 (s, 1H), 7.52−7.37 (m, 9H), 7.05 (s, 1H), 6.92 (d, J = 7.2 Hz, 1H), 6.918 (s, 1H), 5.26 (s, 2H), 5.20 (s, 2H), 4.10 (s, 3H), 4.03 (s, 3H).

Synthesis of Benzyloxy Protected Lamellarin D (25). In a 100 mL round-bottom flask (flame-dried and cooled under Ar atmosphere), **23** (100 mg, 0.157 mmol, 1 equiv), **24** (44 mg, 0.173 mmol, 1.1 equiv), CsF (48 mg, 0.314 mmol, 2 equiv), Ag_2O (55 mg, 0.235 mmol, 1.5 equiv), and $Pd(Ph_3)_4$ (16 mg, 0.016 mmol, 0.1 equiv) were placed under an Ar atmosphere followed by the addition of dried DME (35 mL). The reaction mixture was refluxed for 24 h. After the reaction was completed and the solution was cooled down to room temperature, the solvent was evaporated to dryness, and the residue was redissolved in DCM. The organic layer was washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. The silica gel slurry was made, and the crude product was purified by column chromatography to afford benzyloxy protected lamellarin D **25** as a pale yellow solid; 94 mg; R_f = 0.55 (5% MeOH/DCM); yield 80%; mp 206−208 °C (Lit.[14a] 217−218 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.20 (d, J = 7.2 Hz, 1H), 7.53−7.30 (m, 16H), 7.18−7.12 (m, 1H), 7.16 (s, 1H), 7.14 (s, 1H), 7.12 (s, 1H), 6.98 (d, J = 7.6 Hz, 1H), 6.96 (s, 1H), 6.73 (s, 1H), 5.32 (s, 2H), 5.26 (s, 2H), 5.20 (s, 2H), 3.91 (s, 3H), 3.41 (s, 3H), 3.37 (s, 3H).

Alternate Route to Benzyloxy Protected Lamellarin D (25). A sealed tube with a Teflon screw-stopper (flame-dried and cooled under a stream of nitrogen) was charged with 6-(benzyloxy)-1-(4-(benzyloxy)-3-methoxybenzyl)-7-methoxyisoquinoline (**26**, 150 mg, 0.305 mmol, 1 equiv), 7-(benzyloxy)-6-methoxy-3-nitrocoumarin (**16**, 120 mg, 0.366 mmol, 1.2 equiv), $NaHCO_3$ (52 mg, 0.60 mmol, 2 equiv), and anhydrous xylene (20 mL). The sealed tube was then heated at 130 °C for 24 h. After the mixture cooled to room temperature, the solvent was evaporated to dryness and the residue was redissolved in DCM. The slurry was filtered, and the solid was washed with DCM and concentrated *in vacuo*. The crude product was subjected to column chromatography to give the desired compound **25** as a pale yellow solid; 63 mg; yield 27%; During the purification process, some of the starting material **26** was recovered (34 mg, 23%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.20 (d, J = 8.0 Hz, 1H), 7.53−7.33 (m, 16H), 7.29−7.12 (m, 1H), 7.16 (s, 1H), 7.15 (s, 1H), 7.11 (s, 1H), 6.99 (dd, J = 7.2, Hz, 1H), 6.96 (s, 1H), 6.74 (s, 1H), 5.34 (s, 2H), 5.27 (s, 2H), 5.21 (s, 2H), 3.92 (s, 3H), 3.41 (s, 3H), 3.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 155.5, 150.5, 149.6, 149.2, 148.5, 147.8, 146.4, 146.0, 136.9, 136.3, 136.2, 134.3, 129.3, 128.8, 128.72, 128.70, 128.13, 128.10, 128.0, 127.3, 127.2, 127.0, 126.9, 124.6, 123.9, 123.2, 119.3, 114.9, 114.6, 112.3, 111.0, 110.3, 109.5, 107.9, 105.5, 105.4, 102.7, 71.0, 70.9, 70.8, 56.3, 55.5, 55.2; IR ν_{max} (KBr) 3462, 2947, 1738, 1716, 1423, 1365, 1217, 1017, 857, 753 cm^{-1}; HRMS (EI) m/z calcd for $C_{49}H_{39}NO_8$ [M$^+$] 769.2676, found 769.2672.

Debenzylation of Benzyloxy Protected of Lamellarin D (25): Lamellarin D (27). The mixture of benzyloxy protected lamellarin D (**25**, 100 mg) in 50 mL of EtOAc and $Pd(OH)_2$/C (20%, 50 mg) was hydrogenated at atmospheric pressure overnight at room temperature. The $Pd(OH)_2$/C was removed by filtering over a Celite pad and washed with copious amounts of EtOAc (40 mL × 3). The combined solvent was concentrated *in vacuo* to the dryness. The residue was further sonicated with DCM/hexanes (1:2), and the precipitate was filtered and dried to afford lamellarin D (**27**) as a yellow solid. 59 mg; yield 91%; mp >300 °C (Lit.[14a] ≥300 °C); some of the compound was further recrystallized in DMSO. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.97 (br s, 1H), 9.83 (br s, 1H), 9.33 (br s, 1H), 8.99 (d, J = 7.6 Hz, 1H), 7.20 (d, J = 7.2 Hz, 1H), 7.18 (s, 1H), 7.14 (d, J = 1.6 Hz, 1H), 7.13 (s, 1H), 7.06 (d, J = 8.0 1H), 7.00 (dd, J = 8.0, 2.0 Hz, 1H), 6.86 (s, 1H), 6.70 (s, 1H), 3.76 (s, 3H), 3.37 (s, 3H), 3.33 (s, 3H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 154.3, 148.7, 148.5, 148.3, 147.8, 146.8, 146.3, 144.6, 134.1, 129.0, 125.4, 124.6, 123.8, 122.0, 117.5, 116.4, 115.0, 112.4, 111.5, 110.8, 108.3, 106.4, 105.7, 105.3, 103.7, 56.0, 55.0, 54.5; IR ν_{max} (KBr) 3386, 2928, 2835, 1671, 1589, 1444, 1377, 1270, 1080, 985 cm^{-1}; HRMS (EI) m/z calcd for $C_{28}H_{21}NO_8$ [M$^+$] 499.1267, found 499.1277.

Hydrogenation of Benzyloxy Protected of Lamellarin D (25): Lamellarin 501 (28). To a solution of benzyloxy protected lamellarin D (**25**, 100 mg) in MeOH−EtOAc (2:1, 50 mL) was added Pd/C (10%, ca. 20−25 mg). The resulting solution was stirred under a hydrogen atmosphere for 18 h at room temperature. Once the reaction was complete, the mixture was passed through a Celite pad and washed thoroughly with MeOH (25 mL × 6). The collective organic solvent was dried and concentrated *in vacuo*. The gray residue was further sonicated in hexanes to afford a fine powder of lamellarin 501 (**28**) as a pale gray solid; 58 mg; yield 89%; mp >300 °C (Lit.[17b] ≥250 °C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.32 (br s, 1H), 7.04 (d, J = 7.6 Hz, 1H), 7.03 (s, 1H), 6.90 (dd, J = 7.6, 1.2 Hz, 1H), 6.83 (s, 1H), 6.78 (s, 1H), 6.69 (s, 1H), 6.61 (s, 1H), 4.60 (t, J = 6.4 Hz, 2H), 3.75 (s, 3H), 3.37 (s, 3H), 3.28 (s, 3H), 3.01 (t, J = 6.4 Hz, 2H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 154.3, 148.5, 147.1, 146.9, 146.5, 146.0, 145.7, 144.4, 135.9, 127.7, 127.1, 125.4, 123.4, 118.0, 116.3, 115.3, 114.6, 114.2, 112.2, 109.3, 108.7, 105.1, 103.6, 55.9, 55.0, 54.7, 42.0, 27.5; IR ν_{max} (KBr) 3385, 2832, 1666, 1580, 1473, 1294, 1145, 1029, 953, 856 cm^{-1}; HRMS (EI) m/z calcd for $C_{28}H_{23}NO_8$ [M$^+$] 501.1424, found 501.1428.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01061.

Optimization of the reaction conditions and copies of NMR of the synthesized compounds, and X-ray crystal structure details for **8h** and **27** (PDF)

Crystallographic data for **8h** (CIF)

Crystallographic data for **27** (CIF)

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Notes

The authors declare the following competing financial interest(s): A patent application of this work has been filed.

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