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Demethylative Lactonization Provides a Short Cut to High-Yielding Syntheses of Lamellarins

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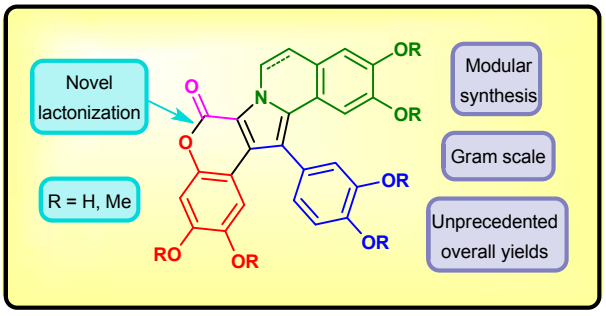


ABSTRACT: Modular gram-scale syntheses of the trimethyl ethers of lamellarins G (**6**) and D (**7**) were achieved from readily accessible precursors in the highest overall yields reported to date (**6**, six steps, 82%; **7**, seven steps, 86%). A novel demethylative lactonization between an aryl methyl ether and a neighbouring carboxylic acid was developed for creating the chromenone unit of the targets in order to avoid the need for additional protection and deprotection steps. The central pyrrole core was constructed in a late-stage [4 + 1] condensation between ethyl bromoacetate and an enaminone possessing the remaining components of the lamellarin skeleton. Exhaustive demethylation of both permethyl ethers **6** and **7** gave the polyphenolic natural lamellarins A4 (**3**) and H (**5**) respectively.

INTRODUCTION

Alkaloids are well represented among the astonishing diversity of natural products isolated from marine organisms.[1] The lamellarins, which occur in minor or trace amounts in a range of molluscs, sponges and tunicates, form a particularly noteworthy family of nitrogen-containing marine metabolites.[2] These compounds and related natural products have attracted the attention of many research groups worldwide, and several useful reviews dedicated to their isolation, synthesis[3] and remarkable biological activity[4] have been published.[5] Since the first members of the family were reported by Faulkner and co-workers in 1985,[6] more than 70 lamellarins and related alkaloids have been isolated to date.[7] The common structural feature of the lamellarins is a substituted pyrrole ring that, in the majority of typical cases, forms the core of a fused pentacyclic system, as shown in **1** (Figure 1, showing conventional lamellarin numbering[6]). These pentacyclic lamellarins are highly oxygenated, and also bear an additional aryl substituent at C-1. Furthermore, the bond between C-5 and C-6 may be saturated, as in lamellarins G (**2**) and A4 (**3**); or unsaturated, as in lamellarins D (**4**) and H (**5**). The saturated and unsaturated modifications are representative of lamellarin classes variously designated as Types 1a and 1b,[2] or Types I and II,[5b] respectively. The enduring interest in the lamellarins is principally due to their significant biological activity, especially the potency of certain members of the series as anticancer agents.[4, 8]

We recently reported an efficient, comparatively green route to lamellarin G trimethyl ether (**6**) in which the key feature was the construction of the pyrrole ring in a [4 + 1] manner by reaction of ethyl bromoacetate with a sterically crowded enaminone

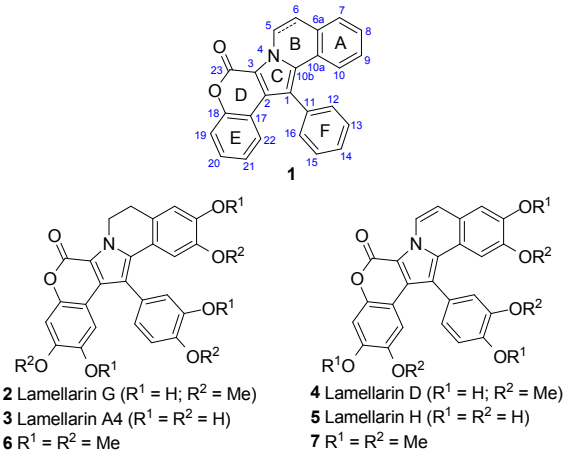
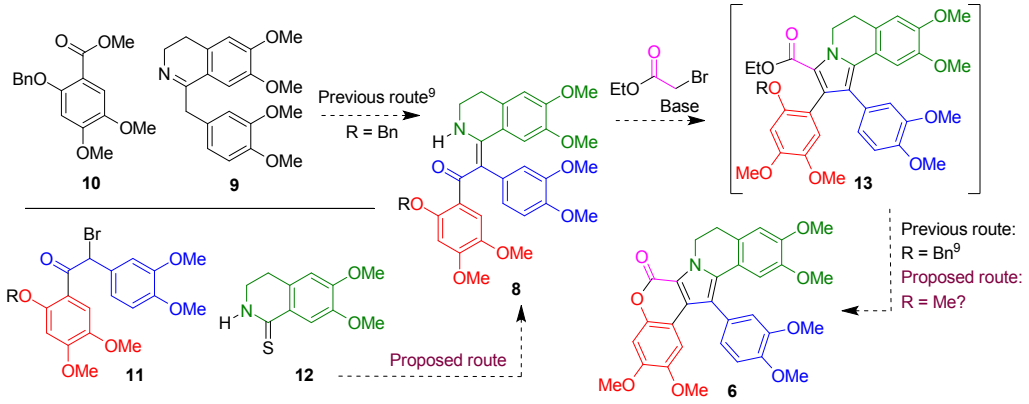


Figure 1. The lamellarin core **1** with conventional numbering;[6] and natural and synthetic lamellarins **2**–**7**.

Scheme 1. Outline of previous and proposed routes to key enaminone **8**, and further conversion into lamellarin G trimethyl ether (**6**).



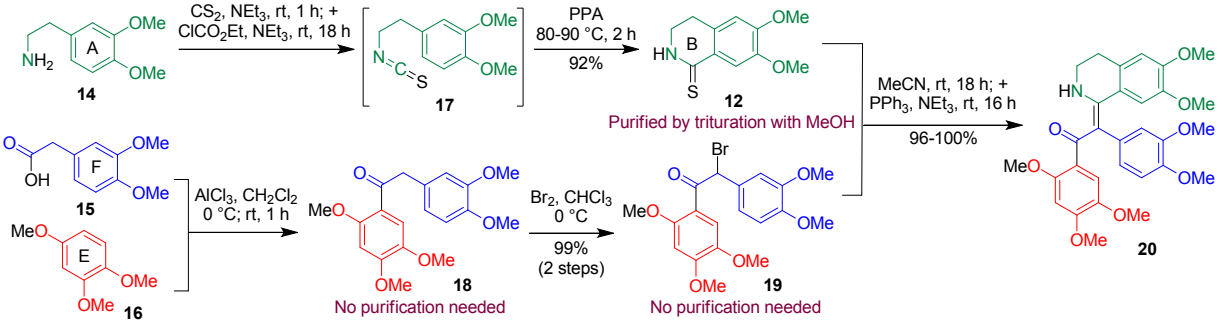
possessing all of the remaining skeletal carbon atoms of the target (Scheme 1).[9] This [4 + 1] formation of the heterocyclic core at a late stage of the synthesis, uncommon in reported lamellarin syntheses,[10, 11] has the advantage of giving a fully substituted pyrrole, thereby blocking the otherwise reactive pyrrole sites. We now report an alternative enaminone-based route that affords gram quantities of the trimethyl ethers of lamellarins G (**6**) and D (**7**) in the highest yields reported to date, and with relatively little need for purification of intermediates. In this article we also introduce a novel reaction: a simple and exceptionally efficient demethylative lactonization for the construction of ring D that avoids the protection–deprotection strategies common to many previously reported lamellarin syntheses.[3] The two naturally occurring polyphenolic lamellarins A4 (**3**) and H (**5**), were also obtained by exhaustive demethylation of (**6**) and (**7**), respectively.

RESULTS AND DISCUSSION

In our previous route to lamellarin G trimethyl ether (**6**), we constructed the pivotal enaminone **8** (R = Bn) by acylation of dihydropapaverine (**9**) with the benzyl-protected ester **10**[9] (Scheme 1, top). However, in view of our extensive experience in the synthesis and use of enaminones as intermediates en route to alkaloids and other nitrogen heterocycles,[12, 13] we felt that the route to **6** and related lamellarins could benefit from a more versatile synthesis of **8** and analogues by using an Eschenmoser sulfide contraction[14, 15] between α-bromoketones such as **11** and the dihydroisoquinolinethione **12** (Scheme 1, bottom). Furthermore, since microwave heating of **8** with ethyl bromoacetate and potassium phosphate, although very successful in our previous route, suffered from competing alkylation of phosphate anion and the consequent contamination of the resulting 5,6-dihydropyrrolo[2,1-*a*]isoquinoline intermediate **13** (R = Bn),[9] we believed that there was room for improvement in this step. Most pressing in our minds, however, was the need for improving the final step entailing lactonization of the intermediate **13** to form ring D. In our earlier approach it was necessary to protect the phenol destined to become the ring oxygen, since the trioxygenated ring E is otherwise susceptible to oxidative decomposition. We, like others before us,[16] chose to mask the phenol as a benzyl ether; other workers have used allyl,[11a] isopropyl[17] or methoxymethyl[18] ethers and even mesylate[19] as protecting groups. The undesirable consequence of these approaches is the need for additional protection and deprotection steps in the overall reaction sequence. In view of the widespread commercial availability of potential methoxy-containing aromatic precursors for ring E, we speculated that it might be possible to avoid these additional steps if lactonization could be effected simply from an aromatic methyl ether. Accomplishing the lactonization by intramolecular reaction of an anisole with an acyl moiety is unprecedented in lamellarin chemistry, and constitutes a significant challenge in selectivity given the presence of methoxy substituents elsewhere in the targets. Our hopes in this regard were fueled by the chance finding of a small quantity of lactone-containing product when preparing an acid chloride from intermediates akin to **13** (R = Me), as will be described below.

Our synthesis of the trimethyl ethers of lamellarins G (**6**) and D (**7**) as well as lamellarins A4 (**3**) and H (**5**) began with three cheap, readily available precursors: homoveratrylamine (**14**), homoveratric acid (**15**) and 1,2,4-trimethoxybenzene (**16**) (Scheme 2). The thiolactam **12** needed for the Eschenmoser sulfide contraction was obtained in two telescoped steps from homoveratrylamine (**14**) by adaptation of a reported method,[20] entailing formation of an intermediate isothiocyanate **17** by treatment of **14** with carbon disulfide and ethyl chloroformate, followed by cyclization with polyphosphoric acid at 80-90 °C. Trituration of the crude product with methanol afforded spectroscopically pure dihydroisoquinolinethione **12** in 92% yield. The brominated reaction partner was made in two steps: Friedel–Crafts acylation between homoveratroyl chloride (generated *in situ* from **15** with oxalyl chloride) and **16** was immediately followed by enolic bromination of the resulting deoxybenzoin **18** with molecular bromine in chloroform. No purification was required after either step, and no bromination of the electron-rich aromatic rings was observed when the rate of bromine addition was carefully controlled. The bromoketone **19**, obtained in quantitative yield, was used without further purification in the subsequent Eschenmoser sulfide contraction step as it is unstable, especially on exposure to light. Simply mixing the two intermediates **12** and **19** (the latter in 5% molar excess) in acetonitrile allowed for the *in situ* formation of the thioiminium ether salt, from which the sulfur was extruded under standard Eschenmoser sulfide contraction conditions with triphenylphosphine and triethylamine. After chromatographic separation from the resulting phosphine sulfide, the heptamethoxylated enaminone **20** was obtained in consistent yields of 96-100%. The signal for the N–H substituent in the ^{1}H NMR spectrum, located far downfield at 13.24 ppm, indicated

Scheme 2. Synthesis of the key enaminone **20**.



intramolecular hydrogen bonding with the carbonyl substituent of the enaminone (δ_C 192.1), thereby establishing that **20** is the (*Z*)-geometric isomer.

In our previous synthesis of lamellarin G trimethyl ether (**6**), we constructed the pyrrole ring C by microwave heating of the intermediate enaminone with excess ethyl bromoacetate and tripotassium phosphate.[9] We found that we could replace the phosphate by sodium bicarbonate, thereby avoiding the formation of alkylated phosphate by-products. Thus conventional heating of enaminone **20** in neat ethyl bromoacetate (1.5 mL/gram of enaminone; 6–8 equiv.) in the presence of the inorganic base at 80–85 °C for two days and subjecting the entire crude mixture to chromatography on silica gel provided the tricyclic product **21** in yields of 95-97% (Scheme 3). Alternatively, chromatography could be avoided entirely by recrystallizing the residue from methanol, which provided **21** in 90-92% yield. It was necessary to use the brominating agent as solvent because yields were adversely affected if concentrations were reduced when using other solvents.

At this stage the critical lactonization needed to be optimized. As mentioned above, the chance discovery of small amounts of lactone-containing product upon preparing the acid chloride from **21** suggested a completely new approach to the formation of ring D of the target alkaloids without the need for additional protecting groups. It seemed highly probable that the lactonization was facilitated by the proximity of the *ortho*-methoxy substituent on ring E to the acyl component on ring C, and that a selective halide-mediated demethylation then occurred *via* a cyclic intermediate such as **22**. Accordingly, hydrolysis of **21** with aqueous potassium hydroxide in an ethanol–water mixture gave a quantitative yield of carboxylic acid **23** (used without the need for further purification), from which the corresponding acid chloride **24** was prepared *in situ* by reaction with oxalyl chloride. We then attempted to improve the putative demethylative cyclization by adding the more nucleophilic iodide ion in the form of tetrabutylammonium iodide. While this accelerated the rate of the reaction, it still required high temperatures and long reaction times, with concomitant decomposition of the material being problematic and yields of lamellarin G trimethyl ether (**6**) never exceeding 60%. Eventually, we found that by adding sodium iodide in acetonitrile to the crude acid chloride, the lactonization could be forced to completion by way of what may possibly be a novel Finkelstein conversion of the acyl chloride **24** to the more reactive acyl iodide **25**, as evinced by the copious precipitation of sodium chloride. Not only was this reaction found to occur rapidly at room temperature, but the isolated yields of the desired lamellarin derivative **6** were consistently above 90%, even when the reaction was performed on a multi-gram scale. As judged by NMR spectroscopy, the product was remarkably pure directly after work-up, and there were no detectable byproducts. The overall yield of **6** based on homoveratrylamine (**14**) was 82% – the highest yield reported for this lamellarin derivative to date! The previous record was a 69% overall yield in seven linear steps from 3,4-dimethoxyphenylacetonitrile.[21]

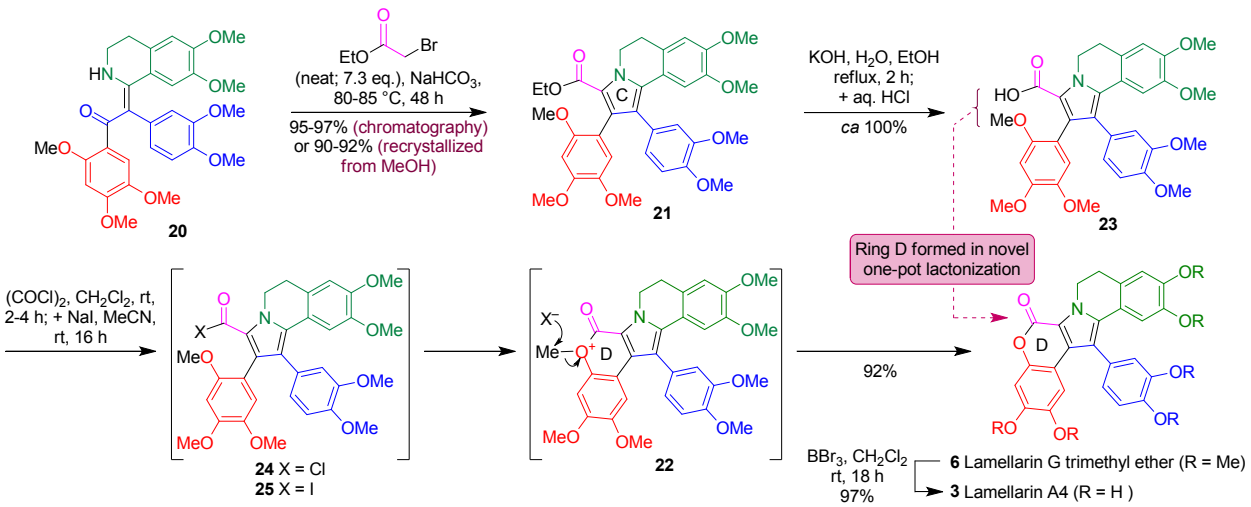
Exhaustive *O*-demethylation of **6** with boron tribromide at room temperature, as reported by other workers,[22] provided the natural product lamellarin A4 (**3**) in 97% yield. It is worth noting that extensive NMR spectroscopic data for **3**, mentioned in passing as a metabolite of a didemnid ascidian and referred to as 5,6-dihydrolamellarin H, were reported as long ago as 1996.[23] However, the natural occurrence of the compound was overlooked in subsequent reviews of the lamellarins.[2–5] The name lamellarin A4 was assigned in a later isolation from *Didemnum* sp.[24] Synthetic compound **3**, named as tris-desmethyl lamellarin G, was recently asserted not to have been previously reported.[22]

Lamellarin D trimethyl ether (**7**), the ring B-unsaturated equivalent of **6**, has previously been made from **6** by oxidation with 5,6-dichloro-2,3-dicyanobenzoquinone (DDQ).[16d] We have found that DDQ oxidation of intermediate **21** prior to lactonization provides the shortest reaction times and the highest yields, without any detectable by-products being formed. In addition, the oxidation did not require heating, as has been the case for conventional late-stage lamellarin oxidations. Thus treating **21** with DDQ in dichloromethane at room temperature afforded the ring B-unsaturated analogue **26** as a foam within four hours (Scheme 4). Finally, application of our novel lactonization procedure after hydrolysis of **26** to the carboxylic acid **27** and *in situ* conversion into the acid chloride followed by treatment with sodium iodide in acetonitrile provided more than a gram of lamellarin D trimethyl ether (**7**) in yields consistently above 96%. Once again, no purification of the intermediates was required, and the final product could easily be purified by recrystallization. The overall yield of **7** based on homoveratrylamine (**14**) was 86%. This is the highest reported yield for lamellarin derivative **7** to date. To complete the reaction sequence, global demethylation of **7** with boron tribromide[18b, 22, 25] provided lamellarin H (**5**) in 98% yield.

CONCLUSION

In this article we report efficient syntheses of two naturally occurring lamellarins (lamellarins A4 and H) and two synthetic lamellarin analogues (the trimethyl ethers of lamellarins D and

Scheme 3. Synthesis of lamellarin G trimethyl ether (**6**) and lamellarin A4 (**3**).



G). Several features of our syntheses are particularly noteworthy.

- The syntheses are both modular and operationally simple. All four compounds were made in six to eight steps from relatively cheap precursors (homoveratrylamine, homoveratric acid, 1,2,4-trimethoxybenzene and ethyl bromoacetate). Furthermore, only a single chromatographic separation was required.
- We have discovered a novel late-stage method for making the alkaloids' chromenyl lactone ring by a demethylative cyclization between a methoxylated aromatic system and a nearby carboxylic acid situated on the pyrrole ring. This has the advantage of avoiding the need for additional protection and deprotection steps for the incipient phenol, since a simple readily available anisole serves as the precursor.
- Although ours are not the shortest syntheses of lamellarins on record, the overall yields are outstanding and are, in fact, higher than any hitherto reported in the literature for any lamellarin,[3] let alone those we have chosen as examples (*cf* 82% for lamellarin G trimethyl ether, compared with a previously reported highest yield of 69%[20]). In addition, no other lamellarin synthesis reported in the periodicals literature to date has yielded gram quantities of the target products.

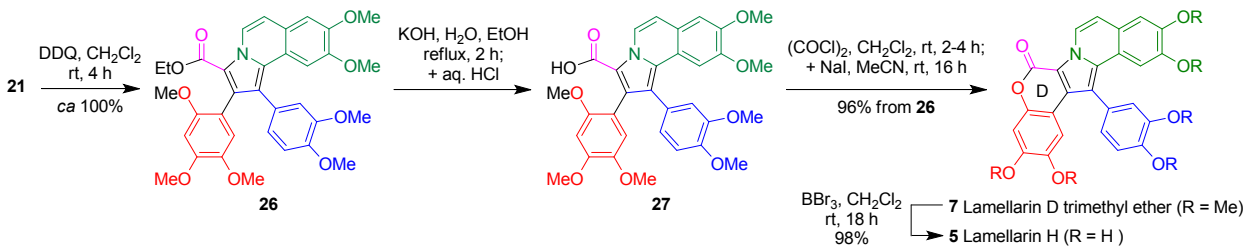
We believe that our new lactonization in particular represents a game-changing strategy in the quest for efficient and workable routes to pharmacologically valuable lamellarins. The methods reported in this article should, with suitable modifications, be readily applicable to the synthesis of virtually all known naturally occurring pentacyclic lamellarin alkaloids, and should also provide a convenient route to numerous new synthetic derivatives.

EXPERIMENTAL

Solvents for reaction or chromatography were dried and purified, where necessary, by standard methods. All other chemicals and deuterated solvents were purchased from commercial sources (Merck, Sigma-Aldrich) and used as received. Merck silica gel (particle size 0.063–0.200 mm) was used for conventional silica gel chromatography, and Merck silica gel (particle size 0.04–0.063 mm) for flash column chromatography. Thin-layer chromatography (TLC) was carried out on Merck silica gel 60 F_{254} plates, and compounds were visualized using UV light and/or by exposure to iodine vapor. All reactions were performed under an inert atmosphere of argon in oven-dried glassware. An oil bath was used for conventional heating. Melting points were recorded on a JM 626 melting-point apparatus with microscope and a digital thermometer. Room temperature refers to ambient laboratory temperatures of 18–25 °C.

^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded on Bruker Avance I 300 MHz, Avance III 400 MHz and Avance III 500 MHz spectrometers at frequencies of 300 MHz, 400 MHz and 500 MHz, respectively, for ^{1}H spectra; and at frequencies of 75 MHz, 101 and 126 MHz, respectively, for ^{13}C spectra. Chemical shifts (δ) of ^{1}H and ^{13}C signals recorded in $CDCl_3$ solution are

Scheme 4. Synthesis of lamellarin D trimethyl ether (**7**) and lamellarin H (**5**).



reported as parts per million (ppm) downfield from Me_4Si as internal reference, while spectra recorded in DMSO-d_6 are referenced to the central peak of the solvent. High resolution mass spectra were obtained on a Bruker Compact Q-TOF mass spectrometer. Samples were diluted to a concentration of approx. 10 ppm in MeOH, and introduced by injection into a Dionex Ultimate 3000 UHPLC system. The ionization mode was electrospray positive with a capillary voltage of 4500 V and a desolvation temperature of 220 °C using N_2 gas at 9 L min^{-1}.

6,7-Dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (12). (Method adapted from ref. 20). NEt_3 (11.6 mL, *ca* 83 mmol, 1 equiv) and CS_2 (7.5 mL, *ca* 9.5 g, 125 mmol, 1.5 equiv) were added to a solution of 2-(3,4-dimethoxyphenyl)ethylamine (**14**) (15.0 g, 82.8 mmol) in dry CH_2Cl_2 (150 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h, then again cooled to 0°C. Ethyl chloroformate (7.9 mL, *ca* 9.0 g, *ca* 83 mmol, 1 equiv) was added dropwise, which caused the immediate precipitation of triethylammonium chloride. After stirring at room temperature for 1 h, additional NEt_3 (11.6 mL, 1 equiv) was added and the reaction was left to stir overnight (18 h). Aqueous NaOH solution (10%, 100 mL) was added to maintain alkalinity during extraction, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated to provide 4-(2-isothiocyanatoethyl)-1,2- dimethoxybenzene (**17**) as an oil that was used immediately without further purification. The crude isothiocyanate was dissolved in CH_2Cl_2 (10 mL) and added dropwise to stirring polyphosphoric acid (25 g), which was heated to 80-90 °C. The organic solvent evaporated on contact with the hot acid, product began to precipitate immediately, and the mixture turned red. The reaction mixture was stirred for an additional 2 h. On cooling, water (300 mL) was added, which caused further precipitation of the product. Stirring was continued for 30 min, after which the product was filtered through a glass sinter and washed with additional water. The crude solid product was then triturated under boiling methanol (250 mL); and after cooling was filtered and dried to provide the pure product 6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (**12**) (17.0 g, 76.1 mmol, 92%); pale yellow powder, m.p. 231-232 °C (lit.,[20] 223 °C). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.08 (s, 1H), 8.03 (br s, 1H, NH), 6.61 (s, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.55 (td, J = 7.0, 3.4 Hz, 2H), 2.95 (t, J = 7.0 Hz, 2H). ^{1}H NMR (500 MHz, DMSO-d_6, δ): 10.17 (br s, 1H, NH), 7.90 (s, 1H), 6.87 (s, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.37 (td, J = 7.0, 3.3 Hz, overlapping with H_2O), 2.85 (t, J = 7.0 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6, δ): 191.2, 152.7, 147.5, 128.8, 125.6, 114.3, 110.4, 56.3, 55.0, 41.5, 27.1.

2-(3,4-Dimethoxyphenyl)-1-(2,4,5-trimethoxyphenyl)ethanone (18). (a) Oxalyl chloride (4.8 mL, *ca* 56 mmol) was added to an ice-cooled solution of 3,4-dimethoxyphenylacetic acid (**15**) (10.0 g, 51.0 mmol) in dry CH_2Cl_2 (150 mL), which caused the solution to turn a deep orange color. Addition of a few drops of dry DMF by syringe resulted in the immediate formation of CO and CO_2 gas bubbles. The ice bath was removed and the solution was left to stir until bubbling ceased (*ca* 2 h). The solvent was removed by rotary evaporation, and the crude product was further dried under vacuum (*ca* 0.1 Torr) to remove any residual oxalyl chloride. 3,4 Dimethoxyphenylacetyl chloride was obtained as an orange oil, and was used immediately without purification. This crude acid chloride was dissolved in dry CH_2Cl_2 (150 mL), to which was added a solution of 1,2,4-trimethoxybenzene (**16**) (8.56 g, 50.9 mmol, 1 equiv) in CH_2Cl_2 (50 mL) A little additional CH_2Cl_2 was used to ensure quantitative transfer. The stirred mixture was then cooled to 0 °C and anhydrous $AlCl_3$ (6.790 g, 50.9 mmol, 1 equiv) was added in portions, which caused the solution to turn a deep brown-black color. The reaction mixture was allowed to warm to room temperature and stirred for 1 h before the addition of ice water (100 mL) followed by aqueous HCl solution (1 M) to hydrolyze any remaining aluminum adducts. The resulting clear phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent removed to provide **18** (17.61 g, 50.8 mmol, 99% based on acid **15**) as a pale purple solid. The material was spectroscopically pure and was used without further purification, although it could be recrystallized as a colorless crystalline solid from MeOH if required. M.p. 127-128 °C (lit.,[26] 121 °C). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.41 (s, 1H), 6.81 (d, J = 8.1 Hz, 1H), 6.80–6.71 (m, 2H), 6.50 (s, 1H), 4.25 (s, 2H), 3.94 (s, 3H), 3.92 (s, 3H), 3.86 and 3.85 (overlapping s, 9H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, δ): 197.6, 155.1, 153.9, 148.7, 147.7, 143.2, 128.3, 121.7, 118.8, 113.1, 112.9, 111.2, 96.4, 56.2, 56.1, 55.9, 55.8, 49.6. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{23}O_6^+$ 347.1489; Found 347.1490.

2-Bromo-2-(3,4-dimethoxyphenyl)-1-(2,4,5-trimethoxyphenyl)ethanone (19). 2-(3,4-Dimethoxyphenyl)-1-(2,4,5-trimethoxyphenyl)ethanone (**18**) (5.00 g, 14.4 mmol) was dissolved in $CHCl_3$ (100 mL) and the solution was cooled in an ice bath. An accurately prepared solution of Br_2 (2.30 g, 14.4 mmol, 1 equiv) in $CHCl_3$ (50 mL) was transferred to a dropping funnel, and one drop was added to the ketone solution. After 1 min it was assumed that enough HBr had formed to catalyze enolic bromination. The remainder of the Br_2 solution was then added dropwise at 0 °C to the persistently amber solution of ketone at a rate of about 1-2 drops per second such that its red color was discharged immediately before the addition of the succeeding drop. Once addition was complete (*ca* 1 h), saturated aqueous $NaHCO_3$ solution was added to quench the cold reaction mixture, which caused the color to clear considerably. The phases were separated, and the aqueous phase was further extracted with $CHCl_3$ (2 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide the bromoketone **19** (6.14 g, *ca* 100%) as a sticky foam. The material was used immediately as it proved susceptible to rapid decomposition, especially in the presence of light. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.44 (s, 1H), 7.11 (s, 1H), 7.01 (d, J = 8.2 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.68 (s, 1H), 6.45 (s, 1H), 3.94 (s, 3H), 3.91 (s, 6H), 3.87 (s, 6H).^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, δ): 191.1, 154.74, 154.70, 149.5, 149.1, 143.6, 129.1, 122.0, 116.4, 113.7, 112.5, 110.7, 96.3, 56.33, 56.29, 56.16, 56.0, 55.9, 55.6. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{22}{}^{79}BrO_6^+$ 425.0594; Found 425.0532 (minor signal); $[M - HBr]^+$ Calcd for $C_{19}H_{21}O_6^+$ 345.1333. Found 345.1327 (major signal).

(*Z*)-2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)-2-(3,4-dimethoxyphenyl)-1-(2,4,5-trimethoxyphenyl)ethanone (20). 6,7-Dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (**12**) (5.98 g, 26.8 mmol) was added to a solution of the bromoketone **19** (12.0 g, 28.2 mmol, 1.05 equiv) in dry MeCN (150 mL), and the resulting solution

was stirred at room temperature for 18 h to ensure complete salt formation, after which time Ph_3P (7.03 g, 26.8 mmol, 1 equiv) was added. The solution was stirred for 5 min until the phosphine had dissolved, after which NEt_3 (4.5 mL, *ca* 32 mmol, 1.2 equiv) in MeCN (50 mL) was added at a rate of about 1 drop per second. The solution soon turned bright yellow, indicating the successful formation of the deeply colored enaminone. The reaction mixture was stirred at room temperature overnight. The solvent was then removed *in vacuo* and the residue was purified by flash column chromatography (50–100% EtOAc in hexane). The yellow fractions containing the enaminone were combined and evaporated to give the desired product **20** as a bright yellow solid (14.3 g, 26.7 mmol, *ca* 100%), m.p. 98-99 °C. [Note: yields of 96-100% were consistently obtained when the experiment was repeated several times on different scales.] ^{1}H NMR (300 MHz, $CDCl_3$, δ): 13.24 (br s, 1H), 6.64 (s, 1H), 6.60–6.51 (m, 3H), 6.46 (dd, J = 8.2, 1.7 Hz, 1H), 6.40 (s, 1H), 6.27 (s, 1H), 3.87 (s, 3H), 3.80 (s, 3H), 3.75 (s, 3H), 3.66 (s, 3H), 3.60 (s, 3H), 3.55–3.40 and 3.54 (overlapping m and s, 5H), 3.15 (s, 3H), 3.03–2.74 (m, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, δ): 192.1, 158.8, 150.1, 149.5, 149.1, 148.2, 146.9, 146.0, 142.4, 133.7, 132.1, 125.8, 125.0, 121.4, 116.5, 114.2, 112.2, 110.5, 109.9, 107.0, 96.9, 56.4, 56.2, 56.0, 55.81, 55.79, 55.1, 39.2, 28.8. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{30}H_{34}NO_8^+$ 536.2279; Found 536.2271.

Ethyl 1-(3,4-dimethoxyphenyl)-8,9-dimethoxy-2-(2,4,5-trimethoxyphenyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (21). (a) The enaminone **20** (2.00 g, 3.73 mmol)) was dissolved in ethyl bromoacetate (3.0 mL; *ca* 4.53 g, *ca* 27.1 mmol, *ca* 7.3 equiv), to which was added solid $NaHCO_3$ (3.0 g, 35.7 mmol). The mixture was stirred under an atmosphere of argon gas at 80-85 °C for 48 h, after which time the solution had gone from bright yellow-orange to deep red and then to almost colorless. The total reaction mixture was loaded directly onto a column of flash silica gel (100 g) with a small quantity of CH_2Cl_2 to ensure quantitative transfer of soluble components. Chromatography was performed under slight positive pressure with increasing polarity of the eluent from 0-50% EtOAc in hexane to provide **21** (2.19 g, 3.62 mmol, 97%); characterization described below.

(b) The reaction was repeated with enaminone **20** (2.00 g, 3.73 mmol), ethyl bromoacetate (3.0 mL) and $NaHCO_3$ (3.0 g) as described in (a). Once the reaction was complete, the total reaction mixture was dissolved in enough CH_2Cl_2 to produce an easily filterable suspension of solids (*ca* up to twice the volume of residual ethyl bromoacetate) and filtered. The solid residue was washed with additional CH_2Cl_2 until the filtrate was no longer colored. The solvent was removed *in vacuo*, and Et_2O (5 mL/gram of starting enaminone) was added, followed by sufficient hexane (*ca* 20 mL/gram of starting enaminone) to inducing a lasting turbidity. Soon crystals began to develop, and after a few hours these were collected by filtration, washed with hexane and triturated under boiling MeOH. After cooling, the crystals were collected by filtration, washed with MeOH and dried to give the dihydropyrrolo[2,1-*a*]isoquinoline **21** (2.07 g, 3.43 mmol, 92%) as a white solid, m.p. 94-96 °C (from MeOH). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 6.76 (s, 2H), 6.74–6.68 (m, 3H), 6.60 (s, 1H), 6.45 (s, 1H), 4.62 (br t, J = 5.5 Hz, 2H), 4.07 (q, J = 7.1 Hz, 2H), 3.87 (s, 6H), 3.83 (s, 3H), 3.66 (s, 3H), 3.64 (s, 3H), 3.56 (s, 3H), 3.35 (s, 3H), 3.06 (br t, J = 6.3 Hz, 2H), 0.98 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, δ): 162.3, 151.8, 148.8, 148.7, 148.3, 147.9, 147.5, 142.6, 131.2, 128.8, 128.6, 126.2, 123.4, 122.0, 121.4, 119.4, 117.0, 116.3, 114.3, 111.2, 111.0, 109.1, 97.6, 59.9, 56.7, 56.4, 56.24, 56.19, 56.1, 55.6, 43.2, 29.4, 14.3. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{34}H_{38}NO_9^+$ 604.2541; Found 604.2538.

1-(3,4-Dimethoxyphenyl)-8,9-dimethoxy-2-(2,4,5-trimethoxyphenyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylic acid (23). A solution of KOH (4.5 g, 80 mmol) in water (10 mL) was added to the ethyl ester **21** (1.30 g, 2.15 mmol), followed by EtOH (100 mL) to ensure complete dissolution of the ester. The pale yellow solution was heated to reflux for 2 h, after which most of the EtOH was removed by rotary evaporation until the potassium carboxylate began to precipitate. The mixture was acidified with aqueous HCl (1 M), causing the free carboxylic acid to begin precipitating and turning the supernatant liquid bright yellow. The mixture was then extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts containing the dissolved carboxylic acid were washed with aqueous HCl (1 M; 100 mL) and brine (100 mL), dried over $MgSO_4$ and evaporated *in vacuo* to provide the carboxylic acid **23** (1.24 g, 2.15 mmol, 100%) as an off-white solid, m.p. 154-156 °C (from MeOH). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 6.96 (s, 1H, CO_2H, exchanges with D_2O), 6.92–6.86 (m, 2H), 6.84 (d, J = 6.6 Hz, 1H), 6.73 (s, 1H), 6.69 (s, 1H), 6.63 (s, 1H), 6.50 (s, 1H), 4.10 (t, J = 6.5 Hz, 2H), 3.87, 3.86 and 3.86 (3 × overlapping s, 9H), 3.69 (s, 3H), 3.63 (s, 3H), 3.51 (s, 3H), 3.39 (s, 3H), 3.06 (t, J = 6.5 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, δ): 150.8, 148.8, 147.41 147.36, 147.30, 146.7, 142.4, 130.1, 125.6, 124.0, 123.1, 122.5, 120.0, 119.33, 119.29, 116.0, 115.1, 114.1, 111.3, 111.1, 107.6, 97.7, 77.2, 56.2, 56.1, 56.0, 55.94, 55.88 (2 C), 55.3, 44.7, 29.5. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{32}H_{34}NO_9^+$ 576.2228; Found 576.2232 (minor signal); $[M - CO_2]^+$ Calcd for $C_{31}H_{34}NO_7^+$ 532.2300; Found 532.2322 (major signal).

4-(3,4-Dimethoxyphenyl)-2,3,11,12-tetramethoxy-8,9-dihydro-6*H*-chromeno[4',3':4,5]-pyrrolo[2,1-*a*]-isoquinolin-6-one, Lamellarin G trimethyl ether (6). The carboxylic acid **23** (1.50 g, 2.61 mmol) was dissolved in dry CH_2Cl_2 (50 mL), and the solution was cooled to 0 °C under an atmosphere of argon. Oxalyl chloride (0.45 mL, *ca* 5.2 mmol, 2 equiv) was added by syringe, causing the color to become deep orange. The stirred solution was warmed to room temperature, and reaction was judged to be complete by NMR spectroscopy after 4 h. The solvent was evaporated on a rotary evaporator, and the crude amber-colored acid chloride was dissolved in a solution of NaI (1.5 g, 10 mmol) in MeCN (50 mL). NaCl began to precipitate within 30 min. The suspension was stirred overnight, during which time a dense precipitate of NaCl and the desired lamellarin ether 11 was formed. The solvent was removed *in vacuo* and the residue was adsorbed onto silica gel (7.5 g) and washed through a pad of silica gel with EtOAc–hexane (1:1) (*ca* 300 mL) until eluents no longer showed a bright blue fluorescent spot at 254 nm by TLC. The solvent was removed and MeOH (*ca* 75 mL) was added. The suspension was heated to boiling, then allowed to cool to room temperature. The resulting solid was collected by filtration and dried to give lamellarin G trimethyl ether (**6**) (1.31 g, 2.40 mmol, 92%) as a colorless solid, m.p. 248-249 °C (lit., 235-236 °C;[21] 236–238 °C;[27] 238-239 °C[28]). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.13 (dd, J = 8.5, 2.0 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 7.06 (d, J= 1.5 Hz, 1H), 6.90 (s, 1H), 6.76 (s, 1H), 6.72 (s, 1H), 6.67 (s, 1H), 4.79 (d × quintet, J = 6.6 Hz, 2H), 3.96 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.46 (s, 3H), 3.37 (s, 3H), 3.12 (t, J = 6.6 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, δ): 155.5, 149.8, 149.0, 148.9, 148.8, 147.5, 146.1, 145.5, 135.9, 128.2, 128.0, 126.6,

123.6, 120.1. 114.8, 114.0, 113.8, 111.9, 111.0, 110.3, 108.7, 104.5, 100.5, 56.3, 56.2, 56.1, 55.9, 55.5, 55.2, 42.4, 28.7. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{31}H_{30}NO_8^+$ 544.1966; Found 544.1961. The ^1H chemical shifts observed for **6** are within 0.02 ppm of previously reported values, while the ^{13}C chemical shifts are within 0.1 ppm[17a, 22] (See Supporting Information, Table S1).

14-(3,4-Dihydroxyphenyl)-2,3,11,12-tetrahydroxy-8,9-dihydro-6*H*-chromeno[4',3':4,5]pyrrolo-[2,1-*a*]isoquinolin-6-one, Lamellarin A4 (3). Neat BBr_3 (0.18 mL, *ca* 10 equiv) was added to a stirring solution of lamellarin G trimethyl ether (**6**) (102 mg, 0.188 mmol) dissolved in CH_2Cl_2 (50 mL) at room temperature. The mixture was left to stir for 18 h, after which time it was quenched with MeOH (1 mL), followed by water (100 mL). The solution was then extracted with EtOAc (4 × 100 mL), since the polyphenolic lamellarin is poorly soluble in chlorinated solvents. The combined organic phases were dried over $MgSO_4$, filtered and solvent was partially removed on a rotary evaporator until solids began precipitating. Hexane (about half the volume of the remaining solvent) was added to complete the crystallization of the products, which were collected by filtration and dried to give lamellarin A4 (**3**) (84 mg, 0.183 mmol, 97%) as a white solid, m.p. >300 °C (lit.,[22] >300 °C). ^1H NMR (400 MHz, DMSO-d_6, δ): 9.58 (s, 1H), 9.37 (s, 1H), 9.11 (s, 2H), 8.81 (s, 1H), 8.61 (s, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.74 (s, 1H), 6.70 and 6.69 (overlapping d and s, *J* = 2.0 Hz, 2H), 6.63 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.53 (s, 1H), 6.47 (s, 1H), 4.60 (quintet, *J ca* 6.8 Hz, 1H), 4.54 (quintet, *J ca* 6.8 Hz, 1H), 2.95 (br t, *J* = 6.8 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6, δ): 154.9, 146.5, 146.4, 146.3, 145.6, 145.1, 144.0, 142.4, 136.4, 127.9, 126.2, 125.8, 121.7, 118.9, 117.9, 117.2, 115.5, 115.1, 113.9, 112.6, 109.7, 109.3, 103.7, 42.4, 28.3. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{18}NO_8^+$ 460.1027; Found 460.1028. The ^1H chemical shifts observed for 5 are within 0.04 ppm of previously reported values, while the ^{13}C chemical shifts are within 0.5 ppm[22, 24] (See Supporting Information, Table S2).

Ethyl 1-(3,4-dimethoxyphenyl)-8,9-dimethoxy-2-(2,4,5-trimethoxyphenyl)pyrrolo[2,1-*a*]isoquinoline-3-carboxylate (26). The saturated pyrrolo[2,1-*a*]isoquinoline **21** (1.50 g, 2.48 mmol) was dissolved in CH_2Cl_2 (100 mL), to which was added DDQ (0.70 g, 3.10 mmol, 1.25 equiv). The solution, which immediately turned a muddy-brown color, was left to stir at room temperature for 4 h. Aqueous NaOH solution (2 M, 50 mL) was added, and the phases were separated. The aqueous phase was re-extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic fractions were washed with NaOH solution (2M, 50 mL), water (50 mL) and brine (50 mL). After drying over $MgSO_4$, filtration and evaporation *in vacuo*, spectroscopically homogeneous **26** (1.49 g, *ca* 100%) was obtained as a brownish foam, m.p. 95-98 °C. ^1H NMR (500 MHz, $CDCl_3$, δ): 9.32 (d, *J* = 7.6 Hz, 1H), 7.22 (s, 1H), 7.02 (s, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 6.91 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.87–6.83 and 6.85 (overlapping m and d, *J* = 8.0 Hz, 2H), 6.64 (br s, 1H), 6.46 (s, 1H), 4.14 (br q, *J ca* 6 Hz, 2H), 3.96 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.71 (s, 3H), 3.68 (s, 3H), 3.61 (br s, 3H), 3.45 (s, 3H), 0.99 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, δ): 162.1, 151.5, 149.2, 148.8, 148.7, 148.6, 147.9, 142.3, 131.9, 130.2, 128.8, 123.8, 123.7, 123.6, 119.8, 118.6, 116.7, 115.9, 114.7, 113.0, 111.9, 110.9, 107.1, 105.3, 97.2, 59.4, 56.5, 56.4, 56.1, 56.0, 55.9, 55.8, 55.3, 14.0. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{34}H_{36}NO_9^+$ 602.2385; Found 602.2372.

1-(3,4-Dimethoxyphenyl)-8,9-dimethoxy-2-(2,4,5-trimethoxyphenyl)pyrrolo[2,1-*a*]isoquinoline-3-carboxylic acid (27). Following the procedure described for the synthesis of carboxylic acid **23**, compound **27** (1.41 g, 2.46 mmol, 100%) was obtained from ethyl 1-(3,4-dimethoxyphenyl)-8,9-dimethoxy-2-(2,4,5-trimethoxyphenyl)pyrrolo[2,1-*a*]isoquinoline-3-carboxylate (**26**) (1.48 g, 2.46 mmol) as a pale brown solid, m.p. 101-106 °C. ^1H NMR (300 MHz, $CDCl_3$, δ): 7.69 (d, *J* = 7.2 Hz, 1H), 7.54 (s, 1H, CO_2H; exchanges with D_2O), 7.19 (s, 1H), 7.00 and 6.98 (overlapping dd and s, *J* = 7.1, 1,8 Hz, 2H), 6.94–6.89 (m, 2H), 6.72 (s, 1H), 6.63 (d, *J* = 7.2 Hz, 1H), 6.52 (s, 1H), 3.93 (s, 3H), 3.89 and 3.88 (2 × s, 6H), 3.75 (s, 3H), 3.68 (s, 3H), 3.53 (s, 3H), 3.49 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, δ): 151.1, 148.9, 148.5, 147.9, 147.7, 147.6, 142.5, 130.5, 125.3, 124.0, 122.9, 121.8, 120.9, 115.6, 115.3, 114.8, 113.9, 111.3, 110.4, 107.9, 104.7, 97.8, 77.3, 56.4, 56.1, 56.04, 55.99, 55.90, 55.8, 55.3. HRMS (ESI) *m/z*: $[M - CO_2]^+$ Calcd for $C_{31}H_{32}NO_7^+$ 530.2173; Found 530.2166.

14-(3,4-Dimethoxyphenyl)-2,3,11,12-tetramethoxy-6*H*-chromeno[4',3':4,5]pyrrolo[2,1-*a*]isoquinolin-6-one, Lamellarin D trimethyl ether (7). Following the procedure described for the synthesis of lamellarin G trimethyl ether (**6**), lamellarin D trimethyl ether (**7**) (1.28 g, 2.36 mmol, 97%) was obtained from carboxylic acid **27** (1.40 g, 2.44 mmol) as a colorless solid, m.p. 283-284 °C (lit.,[22, 25a] 278-280 °C). ^1H NMR (500 MHz, $CDCl_3$, δ): 9.18 (d, *J* = 7.3 Hz, 1H), 7.24 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.19 (d, *J* = 1.5 Hz, 1H), 7.18–7.14 (m, 2H), 7.07 (s, 1H), 7.02 (d, *J* = 7.3 Hz, 1H), 6.87 (s, 1H), 6.74 (s, 1H), 4.00 (s, 3H), 3.98 (s, 3H), 3.91 (s, 3H), 3.85 (s, 3H), 3.49 (s, 3H), 3.47 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, δ): 155.4, 150.1, 150.0, 149.6, 149.2, 149.1, 146.7, 145.5, 134.4, 129.3, 128.3, 124.8, 124.2, 123.3, 119.1, 114.5, 112.3, 112.0, 110.9, 109.9, 107.8, 107.4, 105.3, 105.1, 100.5, 56.3, 56.2, 56.04, 55.97, 55.5, 55.2. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{31}H_{28}NO_8^+$ 542.1809; Found 542.1801. The ^1H chemical shifts observed for 12 are within 0.06 ppm of previously reported values, while the ^{13}C chemical shifts are within 0.2 ppm[22, 25c] (See Supporting Information, Table S3).

14-(3,4-Dihydroxyphenyl)-2,3,11,12-tetrahydroxy-6*H*-chromeno[4',3':4,5]pyrrolo[2,1-*a*]isoquinolin-6-one, Lamellarin H (5). Following the procedure described for the synthesis of lamellarin A4 (**3**), lamellarin H (**5**) (42 mg, 0.0918 mmol, 98%) was obtained from lamellarin D trimethyl ether (**7**) (50 mg, 0.0923 mmol) as a white solid, m.p. >300 °C (lit.,[22] >300 °C). ^1H NMR (400 MHz, DMSO-d_6, δ): 10.04 (s, 1H), 9.81 (s, 1H), 9.47 (s, 1H), 9.26 and 9.25 (2 × s, 2H), 9.05 (d, *J* = 7.3 Hz, 1H), 8.96 (s, 1H), 7.21 and 7.19 (d, *J* = 6.0 Hz, and s, 2H), 7.06 (d, *J* = 7.6 Hz, 1H), 7.02 (s, 1H), 6.87 (s, 1H), 6.86 (d, *J* = 2.0 Hz, 1H), 6.78 (dd, *J* = 7.9, 2.0 Hz, 1H), 6.64 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6, δ): 154.9, 148.1, 147.3, 147.0, 146.7, 146.0, 145.7, 142.5, 134.4, 129.3, 125.9, 124.2, 121.9, 121.6, 118.6, 118.0, 117.5, 113.0, 111.87, 111.85, 110.1, 110.0, 109.3, 106.8, 103.8. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{16}NO_8^+$ 458.0870. Found 458.0865. The ^1H chemical shifts observed for **5** are within 0.07 ppm of previously reported values, while the ^{13}C chemical shifts are within 0.5 ppm[22, 25c] (See Supporting Information, Table S4).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Tabulated comparisons of ^{1}H and ^{13}C NMR spectroscopic data for lamellarins **3**, **5**, **6** and **7** with literature values; and copies of ^{1}H and ^{13}C NMR spectra (PDF).

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