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The first practical decagram-scale synthesis of a lamellarin analogue, and a mild new deprotection of lamellarin isopropyl ethers

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Abstract: Modular syntheses of naturally occurring lamellarin ε (**5**) and the synthetic analogue dehydrolamellarin J (**6**), both of them promising lead candidates for anticancer activity, were accomplished in high overall yields. Key steps in these routes are a late-stage installation of the central pyrrole core by [4 + 1] cyclocondensation between ethyl bromoacetate and an enaminone possessing the remaining components of the lamellarin skeleton; and our recently revealed demethylative lactonization for building the chromenone components. Additionally, a mild and nearly quantitative new method for cleaving isopropyl-protected phenols at room temperature with the comparatively green reagent methanesulfonic acid has been developed. The feasibility of exploiting the simplicity and efficiency of the new reactions on a multi-gram scale was demonstrated by preparing over 25 g of dehydrolamellarin J, one of the most cytotoxic anticancer agents in the lamellarin family, without the need for chromatographic purification of intermediates.

Introduction

Lamellarins occupy a prominent position among the numerous plant- and animal-derived natural products possessing the pyrrolo[2,1-*a*]isoquinoline ring system.[1] These marine metabolites have been isolated from sponges, molluscs and ascidians, and almost 60 of them are extensively oxygenated pentacyclic compounds in which an additional 2*H*-chromen-2-one unit is fused to the pyrrole ring, which also carries a pendent aryl substituent at C-1 (Figure 1, conventional lamellarin numbering shown).[2,3] The intense interest in the synthesis[4] and properties of these alkaloids, the first examples of which were reported more than 30 years ago,[5] is chiefly due to their impressive biological activity, aspects of which have been comprehensively covered in a recent review that also summarizes the numerous published syntheses of natural lamellarins and some synthetic analogues,[2] as well as in other important reviews.[6,7] Bioactivity manifested by these compounds includes anti-HIV-1-integrase activity, cardiovascular and immunomodulatory effects, antioxidant and antibacterial properties and, most notably, antiproliferative activity against some cancer cell lines.[6]

One of the most striking properties of several anticancer lamellarins is their ability to reverse resistance to currently available chemotherapeutic drugs, even in multi-drug resistant cancer cell lines and at sub-cytotoxic doses.[6,8] The modes of

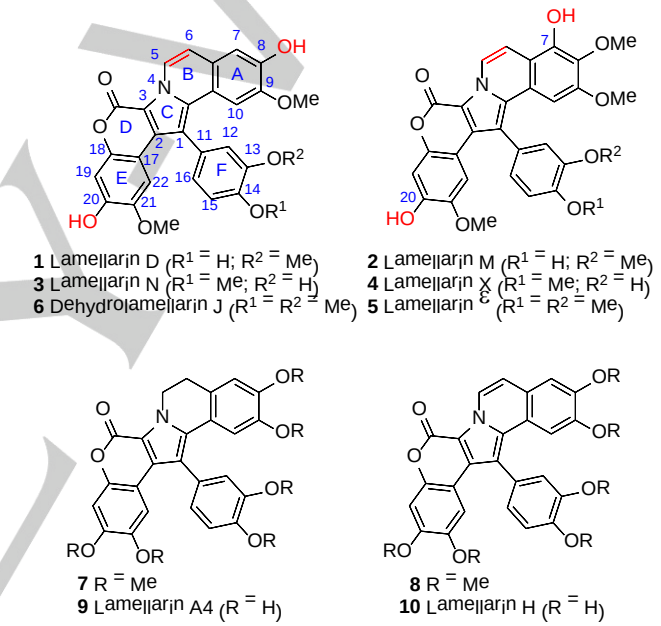


Figure 1. Natural and synthetic lamellarins **1**–**10**. Components in red in structures **1**–**6** are regarded as essential for biological activity.

action displayed by the most active natural and synthetic lamellarins, particularly lamellarin D (**1**), include the inhibition of nuclear and mitochondrial topoisomerase I (in some cases at the nanomolar level) as well as a number of protein kinases; and modification of mitochondrial function.[6] The ability of **1**, for instance, to bypass the nucleus and promote mitochondrial apoptosis, although by an as-yet unknown mechanism, appears to be unprecedented for chemotherapeutics in general,[9] and offers an exciting new target in the treatment of multi-drug resistant cancers.[10]

Structure–activity relationship studies for those lamellarins that display the greatest cytotoxicity towards cancer cells indicate that the oxidation pattern of aromatic rings A and E and a C-5/C-6 double bond are crucial for activity, while ring F is amenable to change.[11,12] In general, potent cytotoxicity is associated with a hydroxy substituent at either C-7 or C-8, while the phenol at C-20 is indispensable. Although hydroxylation of

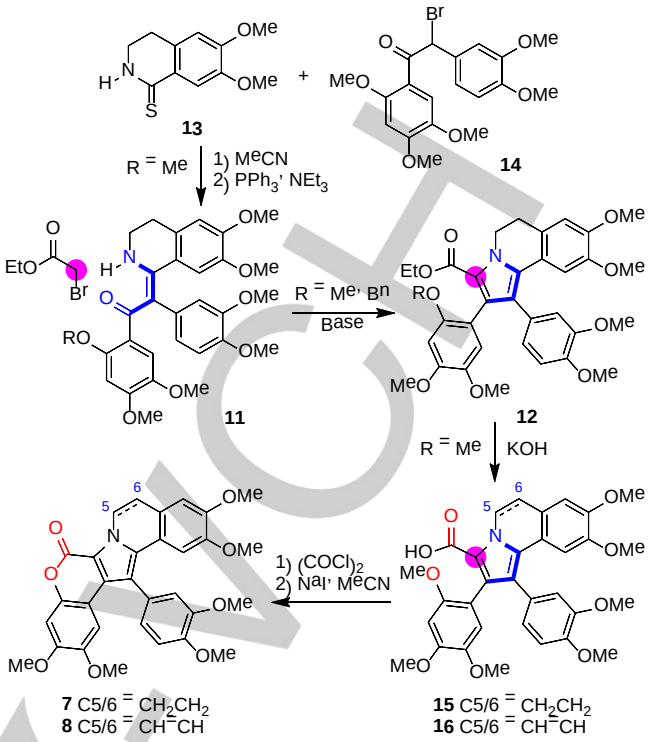
ring F has also been considered important for bioactivity,[13] alkaloids and analogues with no hydroxylation in this ring retain potency.[11] Among the most effective cytotoxins are lamellarins D (**1**), M (**2**), N (**3**), X (**4**), ε (**5**), and a synthetic analogue, dehydrolamellarin J (**6**).[11]

Two recent publications from our research group dealing with the modular synthesis of several lamellarins and analogues included a number of innovative features. The first of these articles showcased an efficient, relatively "green", route to lamellarin G trimethyl ether (**7**), the crux of which was the formation of the central pyrrole ring by a [4 + 1] cyclocondensation between ethyl bromoacetate and a sterically crowded enaminone **11** (R = Bn) possessing all of the remaining skeletal carbon atoms of the target, thereby giving a 1,2-diaryl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline **12** (Scheme 1, **11** → **12**).[14] The second article contained an improved method for constructing the enaminone **11** (R = Me) by Eschenmoser sulfide contraction[15,16] between the dihydroisoquinolinethione **13** and the α-bromoketone **14** (Scheme 1, **13** + **14** → **11**); more significantly, we devised a method for introducing the chromen-2-one unit by an unprecedented intramolecular demethylative lactonization of carboxylic acids **15** and **16** containing a neighboring aryl methyl ether (Scheme 1, **15** → **7** and **16** → **8**).[17] This route also provided the first gram-scale syntheses of **7**, lamellarin D trimethyl ether (**8**), lamellarin A4 (**9**) and lamellarin H (**10**) in the highest overall yields reported to date, and with relatively little need for purification of intermediates. As indicated in the introductory paragraph, although the lamellarins contain a myriad of substitution patterns, only a select few impart highly potent cytotoxicity.

In the present article we have focused our efforts on developing a practical and flexible method for the synthesis of lamellarins that meet the crucial structural requirements for pharmacophoric efficacy.[11] We now report applications of our novel synthetic approaches to the synthesis of the naturally-occurring lamellarin ε (**5**)[18] and the synthetic compound dehydrolamellarin J (**6**),[19] which were chosen as representatives of the different ring A and E substitution patterns found in the most cytotoxic analogues. However, the free phenolic substituents in these targets needed to be protected throughout the reaction sequences. For reasons to be made clear subsequently, we selected isopropyl as the protecting group. Fortuitously, it also provided an opportunity for developing and disclosing a new and significantly improved procedure for the cleavage of aryl isopropyl ethers. In addition, we reveal procedural adaptations for scaling up the synthesis of **6**, which has permitted the manufacture of more than 25 g of this compound – the largest quantity of any lamellarin ever made – without the need for chromatographic purification of intermediates.

Results and Discussion

For our proposed syntheses of lamellarin ε (**5**) and dehydrolamellarin J (**6**), our previously reported strategy for making the permethyl ethers **7** and **8** needed to be modified, since protection of the obligatory phenols could not be avoided. While the key steps so successfully employed in our previous route[17] (Eschenmoser sulfide contraction, pyrrole formation and



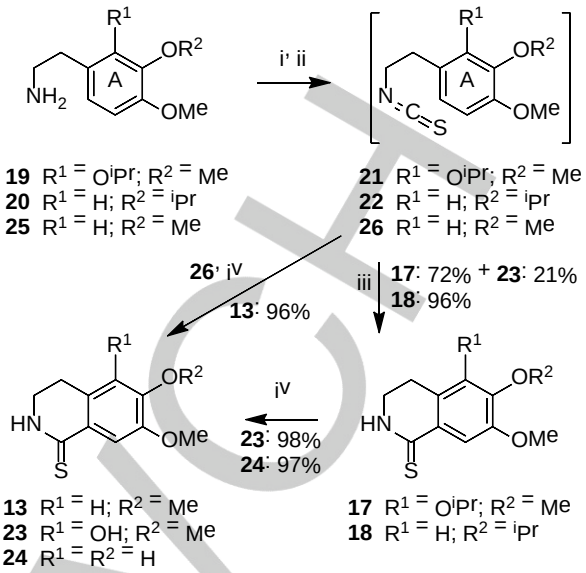
Scheme 1. The key enaminone, pyrrole and lactone formation steps in our previous syntheses of lamellarin G trimethyl ether (**7**) and lamellarin D trimethyl ether (**8**).[14,17]

demethylative lactonization) remained the same, the changes required were in the precursors for rings A and E, where protection of the incipient phenols was necessary. Benzyl and especially isopropyl ethers feature prominently in routes to these rings by other workers.[2-4] Our strategy for making the 3,4-dihydroisoquinolinethione precursors for the sulfide contraction entailed treating appropriately substituted phenylethylamines with carbon disulfide and ethyl chloroformate to give isothiocyanate intermediates, cyclization of which under acidic conditions was expected to yield the desired thiones.[20] Initial experiments ruled out the use of benzyl ethers as protecting groups, since they were invariably cleaved under acidic cyclization conditions, giving mixtures of uncharacterizable products in some of which the benzyl substituents appeared to have migrated to other sites in the compounds. Such intramolecular and intermolecular migration in aryl benzyl ethers under acidic conditions is certainly precedented.[21] The alternative selection of isopropyl is not without potential problems since acid-induced migration in isopropyl aryl ethers, though rare, is not unknown.[22] However, our choice of isopropyl turned out to be fortunate, since not only was it remarkably stable under optimized conditions for isoquinolinethione formation (see below), but it also led to the discovery of a novel method for its removal at the end of the synthetic route.

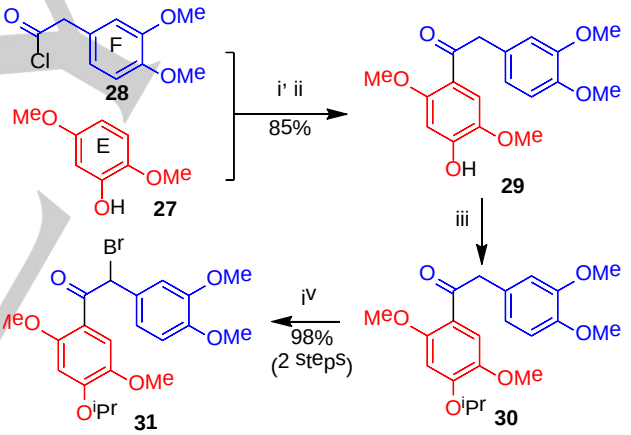
Our route to the requisite isopropyl-protected isoquinolinethiones **17** and **18** is shown in Scheme 2. Both isopropyl-protected phenylethylamines **19**[23] and **20**,[24] the requisite building blocks for lamellarins **5** and **6**, are known compounds, and were readily made according to the reported procedures by Henry reaction of the corresponding aldehydes with nitromethane, followed by reduction of the resulting

nitrostyrenes with lithium aluminum hydride. Conversion of these amines into the corresponding isothiocyanate intermediates **21** and **22** with carbon disulfide followed by reaction with ethyl chloroformate was straightforward. These intermediates were used immediately in the next step without purification. Unfortunately, attempted cyclization of **22** to the thione **18** with polyphosphoric acid at 80−90 °C,[25] the method we previously used for making the 3,4-dimethoxy analogue,[17] failed because the isopropyl protecting groups did not survive the reaction conditions even though the desired cyclization appeared to have taken place. Other acidic reagents (neat methanesulfonic acid, trifluoroacetic acid, trifluoromethanesulfonic acid, aluminum trichloride, boron trifluoride) also led to some cyclization, but with concomitant loss of the protecting group and, in some cases, with the formation of significant amounts of by-products. No reaction of the isothiocyanates was found with camphorsulfonic acid, *p*-toluenesulfonic acid or acetic acid. To our gratification, however, the use of *dilute* methanesulfonic acid in dichloromethane at ambient temperature brought about the desired reactions. Under these conditions, products **17** and **18**, both of which retained the protecting group, were isolated in yields of 72% and 96%, respectively, on a multi-gram scale after purification by column chromatography. In the case of **17**, however, the reaction required 18 hours for completion, and some of the isopropyl protecting group was also lost, giving the free phenol analogue **23** (21%). This fortuitous discovery suggested that the use of methanesulfonic acid might be fine-tuned to effect not only what appears to be a novel procedure for cyclizing isothiocyanates to isoquinolinethiones, but also for cleaving aryl isopropyl ethers to the parent phenols, since we hypothesized that **23** was probably formed owing to the extended reaction time. Indeed, treating **17** with neat methanesulfonic acid caused clean deprotection to **23** in 98% isolated yield within 30 minutes at room temperature without destroying the thiocarbonyl group. Similar treatment of thione **18** also brought about clean and nearly quantitative formation of phenol **24** (97%). Thus in the course of these investigations we appear to have discovered two new reactions mediated by methanesulfonic acid: cyclization of isothiocyanates to isoquinolinethiones, and mild deprotection of aryl isopropyl ethers. We are currently exploring further applications of these reactions; in the meantime, we can report that conversion of homoveratrylamine (**25**) into the corresponding thione **13** proceeds in 96% yield when the intermediate isothiocyanate **26** is treated with neat methanesulfonic acid at ambient temperature. We had previously accomplished this transformation in 92% overall yield under more vigorous conditions with polyphosphoric acid at 80-90 °C.[17]

For both target compounds **5** and **6**, the precursor of ring E was 2,5-dimethoxyphenol (**27**) which, though commercially available, was conveniently prepared by Baeyer–Villiger oxidation of 2,5-dimethoxybenzaldehyde.[26] Initial *in situ* ester formation between homoveratroyl chloride (**28**) and **27** followed by *para*-Fries rearrangement[27] proceeded satisfactorily with 1% phosphorus pentoxide in methanesulfonic acid (a diluted version of Eaton's reagent[28]), giving essentially pure deoxybenzoin product **29** in 85% yield after trituration with diethyl ether (Scheme 3). This appears to be a novel reagent for the rearrangement. Interestingly, decomposition occurred with Eaton's reagent itself (7.7% P_2O_5), while lower yields (50–60%) were obtained if phosphorus pentoxide was omitted. The oxide

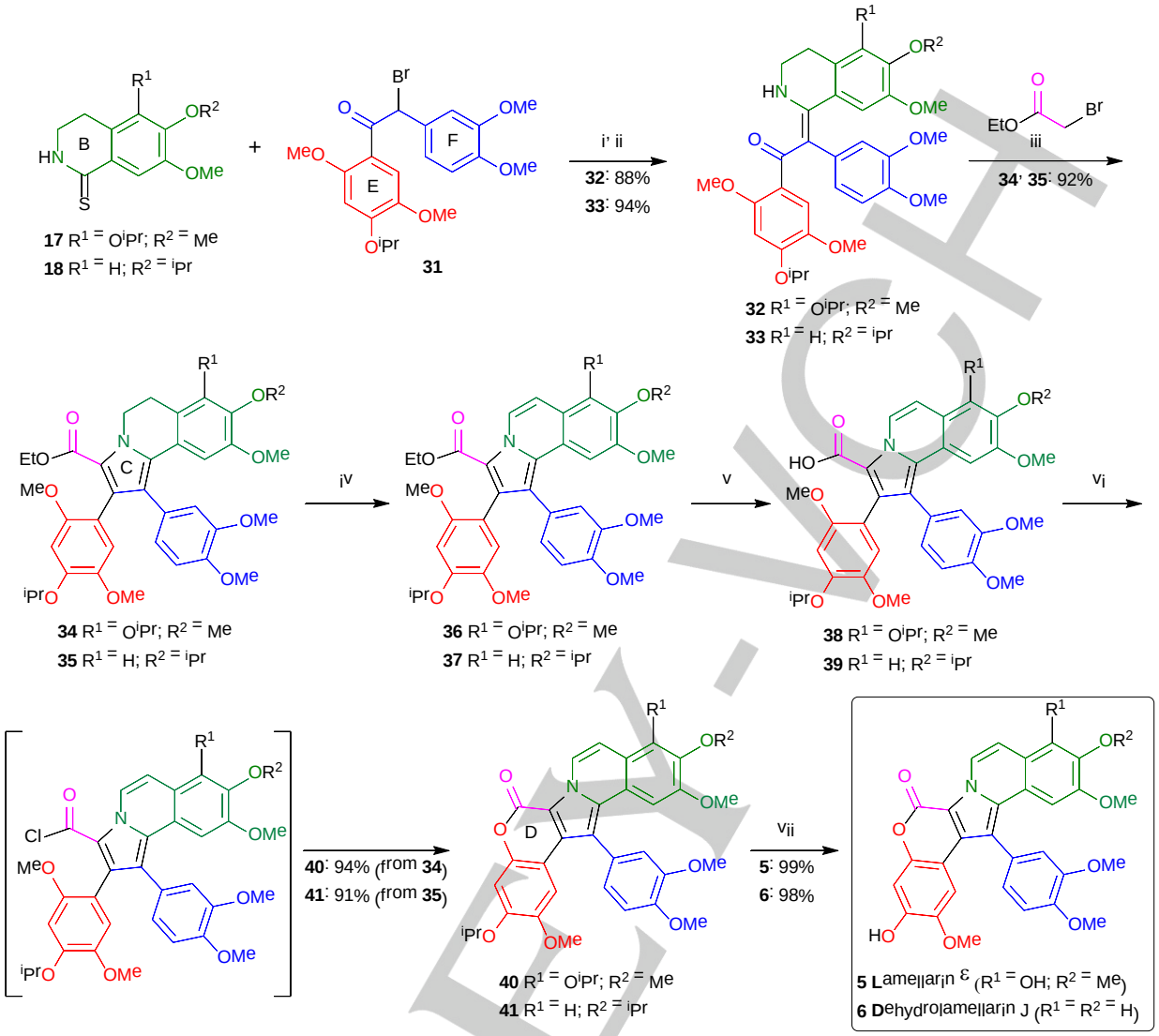


Scheme 2. Conversion of arylethylamines into 3,4-dihydroisoquinoline thiones. Reagents and conditions: (i) CS_2, NEt_3, 0 °, then rt, 1 h; (ii) add $ClCO_2Et$, NEt_3, rt, overnight; (iii) dilute $MeSO_3H$ in CH_2Cl_2, rt, 18 h (for **17**) or 4 h (for **18**); (iv) neat $MeSO_3H$, rt, 0.5 h.



Scheme 3. Synthesis of isopropyl-protected bromodeoxybenzoin **31**. Reagents and conditions: (i) **27** + **28**, CH_2Cl_2, rt, then evaporate solvent; (ii) P_2O_5 (1%) in $MeSO_3H$, rt, overnight; (iii) Me_2CHBr (3.5 eq.), DMF, K_2CO_3, 60 °C, 2 h; (iv) Br_2 (1 eq.), $CHCl_3$, 0 °C.

seems to be necessary to remove traces of moisture in the solvent, which otherwise cause some hydrolysis of the acyl species. Protection of the phenol was effected with isopropyl bromide in *N*,*N*-dimethylformamide at 60 °C. The choice of solvent for the O-isopropylation was found to be crucial; in less polar solvents such as acetone or acetonitrile, it appeared that alkylation of the benzoin enolate on carbon was a competing reaction. The protected intermediate **30**, obtained in approximately 98% yield, was immediately treated with molecular bromine in chloroform at 0 °C to afford the α-bromoketone **31** in almost quantitative yield. The reaction was



Scheme 4. Completion of the syntheses of lamellarin ε (**5**) and dihydrolamellarin J (**6**). Reagents and conditions: (i) **17/18** + **31**, MeCN, rt, 16 h; (ii) add PPh_3 (1 eq.), NEt_3 (1.2 eq.) in MeCN, rt, 16 h; (iii) EtO_2CCH_2Br (neat; 6–8 eq.), $NaHCO_3$, 80–85 °C, 48 h; (iv) DDQ, CH_2Cl_2, rt, 18 h (for **36**) or 4 h (for **37**); (v) KOH, H_2O, EtOH, reflux; (vi) $(COCl)_2$ (2 eq.), 0 °C, then rt, 2–4 h; (vii) add NaI, MeCN, rt, 16 h; (viii) $MeSO_3H$ (neat), rt, 30 min.

found to take place with no detectable bromination of the aromatic rings under these conditions. However, compound **31** decomposed quite rapidly and did not survive storage; it needed to be prepared fresh before its use in the sulfide contraction step.

Sulfide contraction of the isopropyl protected thiolactams **17** and **18** with the bromoketone **31** proceeded uneventfully even on a multi-gram scale, and afforded enaminones **32** and **33**in yields of 88% and 94%, respectively, after chromatography (Scheme 4). The ensuing [4 + 1] cyclisation with ethyl bromoacetate gave the pyrrolo[2,1-*a*]isoquinolines **34** and **35**, both in 92% yield, after chromatographic separation from excess ethyl bromoacetate. Oxidation of ring B in these two intermediate with DDQ to give the unsaturated intermediates **36** and **37** was followed by ester hydrolysis to the corresponding carboxylic acids **38** and **39**. Application of our new demethylative lactonization protocol[17] thereafter provided the isopropyl-protected lamellarin scaffolds **40** and **41** in yields of 94% and 91%, respectively over the three steps from the pyrrole-containing intermediates **34** and **35**. Purification of the intermediates in the intermediate steps was unnecessary, since the final isopropylated products could be separated from inorganic and other by-products by filtration through a short pad of silica gel followed by trituration with hot methanol.

The deprotection of isopropyl ethers in rings A and E, a standard transformation in published syntheses of lamellarins, has usually been accomplished with boron trichloride[2–4] or, occasionally, with aluminum trichloride.[23,29] For example, a patented procedure for deprotecting the isopropylated intermediate **41** with aluminum trichloride gave only a 26% yield of dehydrolamellarin J (**6**).[30] On the other hand, boron trichloride is toxic, expensive and awkward to handle, although reported yields of the liberated phenols have generally been in excess of 90%. However, our accidental finding of methanesulfonic acid-mediated isopropyl ether cleavage without migration of the isopropyl group to the electron-rich aryl rings during the synthesis of isoquinolinethiones, as reported above, provided a perfect opportunity for testing this novel procedure on the two lamellarin precursors **40** and **41**. We found to our delight

that treating these protected lamellarins with neat methanesulfonic acid at room temperature for only 30 minutes led to complete deprotection even when performed without exclusion of air, and gave almost quantitative yields of pure lamellarin ε (**5**) and dehydrolamellarin J (**6**) after precipitation of the desired products merely upon addition of water to the reaction mixture. Furthermore, we were able to characterize isopropyl methanesulfonate as a by-product of the reaction, indicating that the putative isopropyl cation is effectively trapped by methanesulfonate – a surprising finding for such a relatively non-nucleophilic anion. Since methanesulfonic acid is regarded as a green and sustainable solvent,[31] its use thus provides a cheap, simple, safe, relatively eco-friendly and scalable alternative to the toxic and less desirable Lewis acids conventionally used for deprotecting aryl isopropyl ethers. The overall yield of lamellarin ε (**5**) from the substituted phenylethylamine **19** by our route was 55% over seven steps, while the overall yield of dehydrolamellarin J (**6**) from amine **20** was 75%. It is worth mentioning that the efficient removal of isopropyl substituents from *N*-isopropylamides with methanesulfonic acid has been reported, although a temperature of 90 °C was required for the cleavage, and reaction times varied from 2 to 72 hours.[32]

Our success with these relatively short, high-yielding modular syntheses of lamellarins suggested that we should be able to increase the scale even further in order to obtain multi-gram quantities of these valuable compounds. As proof of concept, we chose to prepare at least 25 g of the highly bioactive lamellarin analogue dehydrolamellarin J (**6**), the cytotoxicity of which towards various cancer cell lines is similar to (and in some cases exceeds) that of lamellarin D (**1**),[11] usually regarded as the front runner in the field.[6] The sequence of reactions from the phenylethylamine **20** to the target **6** was essentially as shown in Schemes 2–4, but with the important difference that we were able to avoid chromatographic purification of the intermediates without materially affecting the yields. Thus the dihydroisoquinolinethione **18**, made from **20** in 81% yield on a 30 g scale, was purified by recrystallization from methyl *tert*-butyl ether. From this point on, reactions were carried out in duplicate in order to assess the reproducibility of the transformations. The enaminone **33**, made in two batches of more than 30 g each, was purified via its hydrochloride salt, neutralization of which afforded the desired product in 90-92% yield. The pivotal pyrrole formation with ethyl bromoacetate proceeded well to give two 27 g batches of intermediate **35** (76-77%), purification of which was accomplished by precipitation from suitable solvents followed by trituration with methanol. Oxidation of ring B with DDQ on two batches of over 20 g each gave almost quantitative yields of the unsaturated analogue **37**.

Of greatest interest was whether our novel demethylative lactonization procedure would work well on a large scale. The conversion of **37** into the substituted lamellarin **41** proceeded beyond expectations: the intermediate carboxylic acid **39** (13 g and 22 g), made by hydrolyzing **37** (14 g and 23 g) with potassium hydroxide in water, underwent the oxalyl chloride/sodium iodide-mediated cyclization to give the desired product **41** in 99% and 96% yields after recrystallization from methanol. The final cleavage of the isopropyl protecting groups was done on batches of *ca* 10 g and 20 g, and afforded dehydrolamellarin J (**6**) (10 g, 96%; and 16.5 g, 97%) simply by precipitating the product from the reaction mixture with water. In this way we achieved our target of making over 25 g of the exceptionally potent lamellarin derivative **6** without chromatography of the intermediates – a quantity that, to our knowledge, exceeds even that in which simpler inactive model compounds such as **7** and **8** have previously been made. The overall average yield of dehydrolamellarin J (**6**) from thiolactam **18** on this large scale was 63% over six steps.

Conclusion

In this article we report the total syntheses of the potent cytotoxins lamellarin ε (**5**) and dehydrolamellarin J (**6**) using our previously reported methods for installing the pyrrole core[14] and the 2-chromenone component.[17] In addition, we demonstrate novel uses for the relatively cheap and "green" reagent[31] methanesulfonic acid, including cyclization of (2-isothiocyanatoethyl)benzenes to 3,4-dihydroisoquinoline-1(2*H*)-thiones; a role in a Fries rearrangement; and, most usefully, the rapid deprotection of isopropyl aryl ethers at ambient temperature. A scaled-up synthesis of dehydrolamellarin J (**6**) produced batches of 10 g and 20 g without chromatographic purification of intermediates while still maintaining excellent efficiency and affordability. We have thereby prepared the largest quantities of this compound (or, indeed, of any lamellarin reported in the periodical literature) to date. Our procedures should lend themselves to the convenient and procedurally simple synthesis of other pentacyclic lamellarins as well as numerous new synthetic derivatives.

Experimental Section

General remarks: 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 vapour. Solvents for reaction or chromatography were dried and purified, where necessary, by standard methods. All reactions were performed under an inert atmosphere of argon in oven-dried glassware. Room temperature refers to ambient laboratory temperatures of 18–25 °C. Melting points were recorded on a JM 626 melting-point apparatus with microscope and a digital thermometer. ^{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 signals recorded in $CDCl_3$ solution are 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 (2.50 ppm). Chemical shifts (δ) of ^{13}C signals are referenced to the central peaks of $CDCl_3$ (77.16 ppm) or DMSO-d_6 (39.52 ppm). High resolution mass spectra were obtained on a Bruker Compact Q-TOF mass spectrometer in electrospray positive ionization mode.

General procedure for preparing 3,4-dihydroisoquinolinethiones 13, 17, 18, 23: NEt_3 (1.00 mmol, 1 equiv) and CS_2 (1.50 mmol, 1.5 equiv) were added to a solution of the phenylethylamine (1.00 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C under an atmosphere of Ar. The reaction mixture was stirred at room temperature for 1 h, then again cooled to 0°C. Ethyl chloroformate (1.00 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 (1.00 mmol, 1 equiv) was added and the reaction was left to stir overnight. Aqueous NaOH solution (10%, 10 mL) was added to maintain alkalinity during extraction, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated to provide the isothiocyanate intermediates as oils, which were used immediately without further purification. Methanesulfonic acid (0. 28 mL, *ca* 4.3 equiv) was added dropwise with stirring to a solution of the isothiocyanate (1 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The solution was allowed to warm to room temperature and stirred until an NMR spectrum of the mixture indicated that the reaction was complete. The reaction was then quenched with saturated aqueous $NaHCO_3$ solution and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL), at which point the extracts were no longer yellow. The combined organic phases were dried over $MgSO_4$, filtered, and the solvent was removed to provide an oily residue, which was purified by chromatography on silica gel (40% EtOAc in hexane) to provide the thiolactams as yellow solids, which were further purified if necessary as described below.

6,7-Dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (13): Prepared from homoveratrylamine (**25**) (5.00 g, 27.3 mmol) via the isothiocyanate intermediate **26** according to the general procedure, but using neat $MeSO_3H$ (25 mL) for the cyclization. The reaction time for thiolactam formation was 0.5 h. After addition of water (100 mL), collection of the resulting solid by filtration, washing with MeOH (100 mL) and drying, thione **13** (5.90 g, 26.4 mmol, 96%) was obtained as a spectroscopically homogeneous cream-colored crystalline solid, m.p. 221-222 °C (lit.,[20a] 223 °C); spectroscopic details are as described previously.[17]

5-Isopropoxy-6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (17) and 5-hydroxy-6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (23): Prepared from 2-(2-isopropoxy-3,4-dimethoxyphenyl)ethylamine (**19**)[23] (7.07 g, 29.5 mmol) via the isothiocyanate intermediate **21** according to the general procedure. The reaction time for thiolactam formation was 18 h. A by-product, isopropyl methanesulfonate, co-eluted with **17**, but was removed by triturating the crude solid with Et_2O:hexane (1:1), and collecting the desired thione **17** (6.00 g, 72%) by filtration. Some deprotected phenol **23** (1.50 g, 6.27 mmol, 21%) was obtained from later fractions after chromatography. *5-Isopropoxy-6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione* (**17**): spectroscopically homogeneous yellow crystalline solid, R_f = 0.40 (hexane:EtOAc 3:2); m.p. 114-116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.36 (br s, 1H), 7.94 (s, 1H), 4.52 (septet, *J* = 6.2 Hz, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 3.47 (td, *J* = 6.9, 3.4 Hz, 2H), 2.95 (t, *J* = 6.9 Hz, 2H), 1.27 (d, *J* = 6.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.0, 151.8, 147.0, 146.5, 127.8, 122.3, 110.7, 75.6, 60.6, 56.1, 41.7, 22.6 (2 × C), 21.8. HRMS (ESI) Found: $[M + H]^+$, 282.1160; $C_{14}H_{20}NO_3S^+$ requires 282.1158. *5-Hydroxy-6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione* (**23**): pale yellow solid, m.p. 214–215 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.29 (br s, 1H), 9.22 (s, 1H), 7.57 (s, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.32 (td, *J* = 7.0, 3.5 Hz, 2H, partly obscured by water), 2.75 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 191.1, 150.6, 146.0, 139.7, 127.9, 115.7, 106.1, 60.3, 55.7, 40.8, 20.4.

6-Isopropoxy-7-methoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (18): Prepared from 2-(4-isopropoxy-3-methoxyphenyl)ethylamine (**20**)[24b] (3.01 g, 14.4 mmol) via the isothiocyanate intermediate **22** according to the general procedure. The reaction time for thiolactam formation was 4 h. After chromatographic purification, thione **18** (3.47 g, 96%) was obtained as a spectroscopically homogeneous yellow crystalline solid, R_f = 0.35 (hexane:EtOAc 3:2); m.p. 120-121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (t, *J* = 3.3 Hz, 1H, NH), 8.00 (s, 1H), 6.57 (s, 1H), 4.57 (septet, *J* = 6.1 Hz, 1H), 3.86 (s, 3H), 3.52 (td, *J* = 7.0, 3.3 Hz, 2H), 2.84 (t, *J* = 7.0 Hz, 2H), 1.32 (d, *J* = 6.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.3, 151.3, 148.5, 127.8, 125.1, 114.7, 111.9, 71.2, 56.0, 41.6, 27.3, 21.8 (2 × C). HRMS (ESI) Found: $[M + H]^+$, 252.1051; $C_{13}H_{18}NO_2S^+$ requires 252.1053.

Alternative route to 5-hydroxy-6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (23): 5-Isopropoxy-6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (**17**) (123 mg, 0.44 mmol) was stirred at room temperature in neat methanesulfonic acid (0.60 mL) for 30 min. Addition of ice-cold water induced precipitation of the product, which was collected by filtration. The filter paper was extracted with warm MeOH (100 mL), which was evaporated to give thione **23** (102 mg, 0.43 mmol, 98%); characterization as described above.

6-Hydroxy-7-methoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (24): 6-Isopropoxy-7-methoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (**18**) (1.00 g, 3.98 mmol) was stirred at room temperature in neat methanesulfonic acid (5.0 mL) for 30 min. The precipitate resulting from addition of ice-cold water was collected by filtration, washed with water and dried to yield thione **24** (809 mg, 3.87 mmol, 97%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.08 (t, *J* = 3.3 Hz, 1H, NH), 9.89 (s, 1H), 7.90 (s, 1H), 6.64 (s, 1H), 3.79 (s, 3H), 3.33 (td, *J* = 6.9, 3.3 Hz, 2H), 2.76 (t, *J* = 6.9 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 190.8, 150.8, 146.2, 128.7, 124.3, 114.8, 113.6, 55.7, 41.0, 26.5.

2-(3,4-Dimethoxyphenyl)-1-(4-hydroxy-2,5-dimethoxyphenyl)ethanone (29): Oxalyl chloride (2.4 mL, *ca* 28 mmol) was added to an ice-cooled solution of 3,4-dimethoxyphenylacetic acid (5.0 g, 25.5 mmol) in dry CH_2Cl_2 (75 mL) under Ar, 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 (**28**), obtained as an orange oil, was used immediately without purification. 2,5-Dimethoxyphenol (**27**)[26] (3.92 g, 25.4 mmol, 1 equiv) in dry CH_2Cl_2 (10 mL) was then added to the crude acid chloride **28** using additional dry CH_2Cl_2 (*ca* 5 mL) to ensure quantitative transfer. The solvent was removed *in vacuo*, and the reaction vessel was flushed with Ar. A dilute solution of P_2O_5 in methanesulfonic acid (1%; 20 mL; prepared at least a day in advance to allow for complete formation of the active species) was added to the well-mixed residue at room temperature. HCl gas was immediately produced, and the solution turned dark brown. This was left to stir overnight at room temperature, after which time ice water (250 mL) was added. The solution was then neutralized by adding solid $NaHCO_3$ with vigorous stirring until bubbling ceased and the dark color lightened to pale amber. Extraction with CH_2Cl_2 (3 × 100 mL) followed by drying of the combined organic extracts over $MgSO_4$, filtration and removal of solvent gave a thick amber oil to which Et_2O (150 mL) was added with swirling. Crystals immediately started to precipitate. These were collected by filtration, washed with hexane and dried to yield the substituted deoxybenzoin **29** (7.19 g, 21.6 mmol, 85% based on 3,4-dimethoxyphenylacetic acid) as a cream colored solid, m.p. 152-154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 6.84–6.72 (m, 3H), 6.57 (s, 1H), 6.24 (s, 1H), 4.24 (s, 2H), 3.86 (s, 3H), 3.85 and 3.84 (2 × s, 6H), 3.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.7, 155.6, 151.3, 148.8, 147.7, 140.8, 128.4, 121.9, 118.7, 113.0, 112.9, 111.2, 99.2, 56.4, 56.0, 55.94, 55.86, 49.6. HRMS (ESI) Found: $[M + H]^+$, 333.1338; $C_{18}H_{21}O_6^+$ requires 333.1333. *Note:* The compound could be used in the subsequent reaction without further purification. However, it can be recrystallized from MeOH if required although at least 24 h are necessary for complete crystallization, and repeated recrystallization of material obtained from the mother liquors from MeOH–H_2O is necessary in order to obtain comparable yields.

2-(3,4-Dimethoxyphenyl)-1-(4-isopropoxy-2,5-dimethoxyphenyl)ethanone (30): 2-Bromopropane (5 mL, *ca* 53 mmol) and K_2CO_3 (8.29 g, 60 mmol) were added to a solution of 2-(3,4-dimethoxyphenyl)-1-(4-hydroxy-2,5-dimethoxyphenyl)ethanone (**29**) (5.00 g, 15.0 mmol) in DMF (50 mL). The mixture was heated at 60 °C for 2 h until TLC showed that the reaction was complete. Water (800 mL) was added, and the mixture was extracted with EtOAc (100 mL). The organic phase was washed successively with water (3 × 500 mL) and brine (100 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide the isopropylated deoxybenzoin **30** (5.52 g, 14.7 mmol, 98%) as an amber oil that was sufficiently pure for subsequent use. ^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.42 (s, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 6.80–6.77 (m, 1H), 6.76 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.51 (s, 1H), 4.65 (septet, *J* = 6.1 Hz, 1H), 4.25 (s, 2H), 3.90 (s, 3H), 3.86 (s, 6H), 3.82 (s, 3H), 1.41 (d, *J* = 6.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6, 154.9, 152.4, 148.7, 147.6, 144.2, 128.3, 121.7, 119.0, 113.8, 112.9, 111.1, 99.6, 71.7, 56.3, 56.1, 55.9, 55.8, 49.6, 22.0 (2 × C). HRMS (ESI) Found: $[M + H]^+$, 375.1812; $C_{21}H_{27}O_6^+$ requires 375.1802.

2-Bromo-2-(3,4-dimethoxyphenyl)-1-(4-isopropoxy-2,5-dimethoxyphenyl)ethanone (31): The deoxybenzoin **30** (4.02 g, 107.4 mmol) was dissolved in $CHCl_3$ (200 mL) and the solution was cooled in an ice bath. An accurately prepared solution of Br_2 (110 mmol, 1 equiv) in $CHCl_3$ (100 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 catalyse enolic bromination. The remainder of the Br_2 solution was then added dropwise 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, 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 × 150 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide the bromoketone **31** (4.84 g, *ca* 99%) as a greenish gel. This product was used immediately as it proved susceptible to rapid decomposition, especially in the presence of light. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.12 (d, *J* = 2.1 Hz, 1H), 7.02 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.69 (s, 1H), 6.46 (s, 1H), 4.64 (septet, *J* = 6.1 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 1.42 and 1.41 (2 × overlapping d, *J* = 6.1 and 6.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.0, 154.7, 153.4, 149.5, 149.1, 144.6, 129.2, 122.0, 116.4, 114.4, 112.5, 110.8, 99.2, 71.4, 56.4, 56.3, 56.0, 55.9, 55.7, 22.0 (2 × C). HRMS (ESI) Found: $[M + H]^+$, 453.0912; $C_{21}H_{26}{}^{79}BrO_6^+$ requires 453.0907.

General method for the synthesis of enaminones 32 and 33 by Eschenmoser sulfide contraction: Immediately after synthesis as described above, the bromoketone **31** (1.05 mmol) was dissolved in dry MeCN (30 mL), to which was added the relevant dihydroisoquinoline-1(2*H*)-thione (1 mmol). The mixture was stirred for 18 h at room temperature to ensure complete salt formation, after which time Ph_3P (1 equiv) was added. The solution was stirred for 5 min until the phosphine had dissolved, after which NEt_3 (1.2 equiv) in MeCN (10 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. Once the reaction mixture had been stirred at room temperature overnight, the solvent was removed 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 products as bright yellow solids that were purified by careful column chromatography on silica gel. [*Note*: Replacing PPh_3 by the relatively volatile $P(OMe)_3$ simplified the purification of the enaminones because both it and the corresponding sulfide can be removed by co-evaporation with ethanol, followed by acid–base extractive purification. However, the yields of enaminone were consistently lower (78–82%).]

(*Z*)-2-(3,4-Dimethoxyphenyl)-1-(4-isopropoxy-2,5-dimethoxyphenyl)-2-(5-isopropoxy-6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)ethanone (32): This product (7.00 g) partially contaminated with an inseparable quantity of Ph_3PS was obtained from 5-isopropoxy-6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (**17**) (3.200 g, 113.7 mmol) by the general procedure. The purity of **32** was estimated as 90% by NMR spectroscopy against DMF added as internal reference, indicating an approximate yield of 88%. The compound could be used in the subsequent cyclization without detriment, after which the contaminant was readily removed by chromatography or recrystallization. Bright yellow solid, R_f = 0.50 (EtOAc); m.p. 74-76°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.23 (br t, *J* = 3.7 Hz, 1H), 6.59–6.48 (m, 3H), 6.45 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.30 (s, 1H), 6.26 (s, 1H), 4.47 and 4.42 (2 × overlapping septets, *J* = 6.1 and 6.1 Hz, 2H), 3.81 (s, 3H), 3.74 (s, 3H), 3.62 (s, 3H), 3.57 (s, 3H), 3.52 (s, 3H), 3.44 (s, 2H), 3.12 (s, 3H), 2.92 (br s, 2H), 1.29 (d, *J* = 6.0 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.4, 158.9, 150.2, 149.5, 148.1, 147.12 (2 × C), 147.09, 146.9, 144.2, 143.8, 133.7, 126.3, 126.0, 125.6, 124.3, 116.6, 113.0, 111.0, 110.4, 107.2, 102.0, 75.6, 72.1, 60.5, 56.5, 56.1, 55.8, 55.7, 55.1, 39.1, 22.5 (2 × C), 22.0 (2 × C). HRMS (ESI) Found: $[M + H]^+$, 622.3027; $C_{35}H_{44}NO_9^+$ requires 622.3011.

(*Z*)-2-(3,4-Dimethoxyphenyl)-1-(4-isopropoxy-2,5-dimethoxyphenyl)-2-(6-isopropoxy-7-methoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)ethanone (33): This product (2.91 g, 49.2 mmol, 94%) was obtained from 6-isopropoxy-7-methoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (**18**) (1.32 g, 52.5 mmol) by the general procedure. Bright yellow solid, R_f = 0.40 (EtOAc); m.p. 89-90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.24 (br s, 1H), 6.62 (s, 1H), 6.58–6.52 (m, 2H), 6.50 (s, 1H), 6.46 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.41 (s, 1H), 6.30 (s, 1H), 4.57 (septet, *J* = 6.1 Hz, 1H), 4.42 (septet, *J* = 6.1 Hz, 1H), 3.73 (s, 3H), 3.62 (s, 3H), 3.58 (s, 3H), 3.53 (s, 3H), 3.60–3.40 (br m, 2H), 3.11 (s, 3H), 2.95–2.80 (br m, 2H), 1.37 (d, *J* = 6.1 Hz, 6H), 1.29 (d, *J* = 6.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.1, 158.9, 149.4, 148.6, 148.2, 147.1, 146.94, 146.91, 144.2, 133.7, 131.8, 126.1, 125.7, 121.2, 116.6, 114.7, 113.0, 112.7, 110.5, 106.9, 102.0, 72.1, 71.0, 56.5, 56.1, 55.80, 55.75, 55.2, 39.2, 28.8, 22.04 (2 × C), 22.00 (2 × C). HRMS (ESI) Found: $[M + H]^+$, 592.2908; $C_{34}H_{42}NO_8^+$ requires 592.2905.

General procedure for formation of pyrroles 34 and 35 from enaminones 32 and 33: The enaminone (1.00 g, 1.6–1.8 mmol) was dissolved in ethyl bromoacetate (1.5 mL; *ca* 2.26 g, *ca* 13.5 mmol, *ca* 6–8 equiv; some CH_2Cl_2 can be used to ensure homogeneity, as it evaporates over the course of the reaction), to which was added $NaHCO_3$ (1.50 g, 179 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 an almost colorless state. The total crude product was dissolved in a small quantity of CH_2Cl_2 and loaded onto a column of flash silica gel. Gradient elution with 0–50% EtOAc:hexane mixtures provide the pyrrole-fused products. (Alternatively, the product was dissolved in CH_2Cl_2 and filtered to remove insoluble material. After evaporation of the solvent, the residue was dissolved in Et_2O (5 mL gram^{-1} of starting enaminone), and hexane was added to induce 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. Additional product could be obtained by further treatment of the mother liquors.)

Ethyl 1-(3,4-dimethoxyphenyl)-7-isopropoxy-2-(4-isopropoxy-2,5-dimethoxyphenyl)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (34): Compound **34** (1.762 g, *ca* 92%) was obtained from (*Z*)-2-(3,4-dimethoxyphenyl)-1-(4-isopropoxy-2,5-dimethoxyphenyl)-2-(5-isopropoxy-6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)ethanone (**32**) (2.00g, *ca* 90% pure) according to the general procedure after purification by chromatography. Alternatively, **34** (3.10 g, *ca* 80%) was obtained from **32** (3.90, *ca* 90% pure) after recrystallization from MeOH. White solid, R_f = 0.30 (hexane:EtOAc 3:2); m.p. 72-76 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 6.69 (d, *J* = 1.8 Hz, 1H), 6.57 (s, 2H), 6.47 (s, 1H), 4.65–4.40 (m, 4H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 6H), 3.64 (s, 3H), 3.61 (s, 3H), 3.55 (s, 3H), 3.33 (s, 3H), 3.09 (br t, *J* = 6.7 Hz, 2H), 1.34 and 1.32 (2 × overlapping d, *J* = 6.1 and 6.2 Hz, 12H), 0.96 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 151.5, 151.4, 148.4, 148.1, 147.5, 146.4, 144.1, 141.5, 130.6, 128.4, 128.2, 123.9, 123.2, 122.2, 120.4, 119.3, 117.8, 116.7, 114.0, 110.8, 104.9, 102.4, 75.5, 72.1, 60.5, 59.6, 56.5, 56.3, 55.9, 55.7, 55.2, 42.7, 23.0, 22.7 (2 × C), 22.1 (2 × C), 13.8. HRMS (ESI) Found: $[M + H]^+$, 690.3252; $C_{39}H_{48}NO_{10}^+$ requires 690.3273.

Ethyl 1-(3,4-dimethoxyphenyl)-8-isopropoxy-2-(4-isopropoxy-2,5-dimethoxyphenyl)-9-methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (35): Compound **35** (2.35 g, 3.56 mmol, 92%) was

obtained from (*Z*)-2-(3,4-dimethoxyphenyl)-1-(4-isopropoxy-2,5-dimethoxy-phenyl)-2-(6-isopropoxy-7-methoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)ethanone (**33**) (2.27 g, 3.84 mmol) according to the general procedure as a colorless gel that gradually solidified after purification by chromatography; R_f = 0.30 (hexane:EtOAc 3:2); m,p. 160-161 °C (from MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.76–6.71 (m, 3H), 6.69 (d, *J* = 1.8 Hz, 1H), 6.57 (s, 1H), 6.47 (s, 1H), 4.61 (br t, *J ca* 7.5 Hz, 2H), 4.51 (septet, *J* = 6.0 Hz, 2H), 4.06 (q, *J* = 7.2 Hz, 2H), 3.82 (s, 3H), 3.62 (s, 3H), 3.61 (s, 3H), 3.54 (s, 3H), 3.33 (s, 3H), 3.03 (t, *J* = 6.6 Hz, 2H), 1.37 (d, *J* = 6.0 Hz, 6H), 1.33 (d, *J* = 6.0 Hz, 6H), 0.96 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0, 151.5, 148.4 (2 × C), 147.5, 146.4, 146.3, 144.1, 131.0, 128.4, 128.3, 125.7, 123.1, 121.5, 121.3, 119.0, 118.0, 116.8, 114.7, 114.0, 110.8, 109.3, 102.5, 72.1, 71.4, 59.6, 56.5, 56.3, 55.9, 55.7, 55.3, 42.8, 29.0, 22.1 (4 × C), 13.8. HRMS (ESI) Found: $[M + H]^+$, 660.3147; $C_{38}H_{46}NO_9^+$ requires 660.3167.

General procedure for DDQ oxidation of ethyl 5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylates 34 and 35: The 5,6-dihydropyrrolo[2,1-*a*]isoquinoline (1 mmol) was dissolved in CH_2Cl_2 (100 mL), to which was added DDQ (1.25 mmol). The solution, which immediately turned a muddy-brown color, was left to stir at room temperature for the specified time. 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. After drying over $MgSO_4$, filtration, evaporation *in vacuo*, the spectroscopically homogeneous products were obtained as foams in quantitative yields.

Ethyl 1-(3,4-dimethoxyphenyl)-7-isopropoxy-2-(4-isopropoxy-2,5-dimethoxyphenyl)-8,9-dimethoxy-pyrrolo[2,1-*a*]isoquinoline-3-carboxylate (36): Compound **36** (1.98 g, 28.8 mmol, 99%) was obtained from ethyl 1-(3,4-dimethoxyphenyl)-7-isopropoxy-2-(4-isopropoxy-2,5-dimethoxyphenyl)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (**34**) (2.00 g, 29.0 mmol) according to the general procedure as a brownish solid foam, m.p. 85-86 °C; reaction time 18 h; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.05 (s, 1H), 6.95–6.73 (m, 3H), 6.61 (s, 1H), 6.48 (s, 1H), 4.70 (septet, *J* = 6.2 Hz, 1H), 4.50 (septet, *J* = 6.1 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.71 (s, 3H), 3.64 (s, 3H), 3.58 (s, 3H), 3.42 (s, 3H), 1.34 (d, *J* = 6.0 Hz, 12H), 0.98 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1, 152.8, 151.5, 148.6, 147.9, 146.6, 146.1, 144.1, 141.5, 131.8, 129.6, 128.8, 123.8, 122.9, 121.9, 119.6, 119.4, 117.8, 116.7, 114.7, 113.4, 110.8 (br), 107.2, 102.3 (br), 101.3, 76.1, 72.1, 60.7, 59.5, 56.6, 56.3, 56.0, 55.8, 55.3, 22.72, 22.70, 22.1 (br, 2 × C), 13.8. HRMS (ESI) Found: $[M + H]^+$, 688.3116; $C_{39}H_{46}NO_{10}^+$ requires 688.3116.

Ethyl 1-(3,4-dimethoxyphenyl)-8-isopropoxy-2-(4-isopropoxy-2,5-dimethoxyphenyl)-9-methoxy-pyrrolo[2,1-a]isoquinoline-3-carboxylate (37): Compound **37** (796 mg, 1.21 mmol, 100%), was obtained from ethyl 1-(3,4-dimethoxyphenyl)-8-isopropoxy-2-(4-isopropoxy-2,5-dimethoxyphenyl)-9-methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (**35**) (800 mg, 1.21 mmol) according to the general procedure as a brownish gel that gradually solidified; m.p. 96-100 °C; reaction time 4 h. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.31 (d, *J* = 7.5 Hz, 1H), 7.26 (s, 1H), 7.04 (s, 1H), 6.92 and 6.91–6.87 (overlapping d and m, *J* = 7.5 Hz, 2H), 6.86–6.80 (m, 2H), 6.62 (s, 1H), 6.48 (s, 1H), 4.66 (septet, *J* = 6.1 Hz, 1H), 4.51 (septet, *J* = 6.1 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 3.70 (s, 3H), 3.64 (s, 3H), 3.57 (br s, 3H), 3.43 (s, 3H), 1.42 (d, *J* = 6.1 Hz, 6H), 1.35 (d, *J* = 6.1 Hz, 6H), 0.97 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2, 151.5, 149.8, 148.5, 147.8, 147.4, 146.6, 144.1, 131.9, 130.2, 128.8, 123.8, 123.5 (2 × C), 119.7, 118.5, 117.9, 116.7, 114.6, 112.9, 111.9, 110.5, 105.6, 102.3, 72.1, 71.1, 59.4, 56.6, 56.3, 56.0, 55.7, 55.3, 22.1 (br, 2 × C), 22.0 (2 × C), 13.8. HRMS (ESI) Found: $[M + H]^+$, 658.3005; $C_{38}H_{44}NO_9^+$ requires 658.3011.

General procedure for hydrolysis of esters 36 and 37: A solution of KOH (4.5 g, 80 mmol) in water (10 mL) was added to the ethyl pyrrolo[2,1-*a*]isoquinoline-3-carboxylates (1.00 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 salt 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 quantitative yields of spectroscopically pure carboxylic acids. The high-resolution mass spectra showed minor or no signals for the molecular ions, but ions for the decarboxylated products were apparent. However, the presence of the carboxylic acid was apparent in the ^{1}H (D_2O-exchangeable proton in the range δ 7.0–7.6) and ^{13}C NMR (C=O *ca* 150 ppm) spectra.

1-(3,4-Dimethoxyphenyl)-7-isopropoxy-2-(4-isopropoxy-2,5-dimethoxyphenyl)-8,9-dimethoxypyrrolo-[2,1-*a*]isoquinoline-3-carboxylic acid (**38**): The acid **38** (1.50 g, 2.27 mmol, *ca* 100%) was obtained according to the general procedure from ethyl 1-(3,4-dimethoxyphenyl)-7-isopropoxy-2-(4-isopropoxy-2,5-dimethoxy-phenyl)-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate (**36**) (1.57 g, 2.28 mmol) as a pale brown solid, m.p. 76-79 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.4 Hz, 1H), 7.54 (s, 1H, CO_2H, exchanges with D_2O), 7.04 (d, *J* = 7.2 Hz, 1H), 7.02–6.95 (m, 3H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.70 (s, 1H), 6.53 (s, 1H), 4.67 (septet, *J* = 6.2 Hz, 1H), 4.50 (septet, *J* = 6.1 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.75 (s, 3H), 3.65 (s, 3H), 3.48 (s, 3H), 3.45 (s, 3H), 1.35 and 1.34 (2 × superimposed d, *J* = 6.4 and 6.0 Hz, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.6, 151.0, 148.9, 147.7, 146.5, 146.0, 144.1, 140.1, 130.5, 124.8, 124.0 (2 × C), 123.1, 122.9, 122.3, 117.9, 116.6, 116.5, 116.1, 114.9, 114.4, 111.3, 105.7, 102.6, 100.5, 75.9, 72.0, 60.6, 56.3, 56.1, 55.9 (2 × C), 55.3, 22.7 (2 × C), 22.2 (2 × C). HRMS (ESI) Found: $[M - CO_2]^+$, 616.2908; $C_{36}H_{42}NO_8^+$ requires 616.2905.

1-(3,4-Dimethoxyphenyl)-8-isopropoxy-2-(4-isopropoxy-2,5-dimethoxyphenyl)-9-methoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylic acid (39): The acid **39** (1.43 g, 2.27 mmol, 100%) was obtained according to the general procedure from ethyl 1-(3,4-dimethoxyphenyl)-8-isopropoxy-2-(4-isopropoxy-2,5-dimethoxy-phenyl)-9-methoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate (**37**) (1.49 g, 2.27 mmol) as an off-white crystalline solid, m.p. 182-184 °C (from MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.2 Hz, 1H), 7.54 (s, 1H, CO_2H, exchanges with D_2O), 7.20 (s, 1H), 6.99 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.96 (d, *J* = 1.8 Hz, 1H), 6.95 (s, 1H), 6.91 (d, *J* = 8.1 Hz, 1H), 6.71 (s, 1H), 6.61 (d, *J* = 1.8 Hz, 1H), 6.53 (s, 1H), 4.59 (septet, *J* = 6.1 Hz, 1H), 4.50 (septet, *J* = 6.1 Hz, 1H), 3.89 (s, 3H), 3.74 (s, 3H), 3.64 (s, 3H), 3.49 (s, 3H), 3.45 (s, 3H), 1.39 (d, *J* = 6.1 Hz, 6H), 1.35 (d, *J* = 6.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.0, 149.8, 148.9, 147.6, 145.9, 145.8, 144.1, 130.6, 125.3, 124.0 (2 × C), 122.83, 122.76, 121.7, 121.1, 116.6, 116.0, 115.7, 114.8, 114.0, 112.1, 111.3, 110.4, 105.0, 102.5, 72.0, 71.2, 56.3, 56.08, 56.07, 55.9, 55.3, 22.2 (2 × C), 22.1 (2 × C). HRMS (ESI) Found: $[M - CO_2]^+$, 586.2834; $C_{35}H_{40}NO_7^+$ requires 586.2799.

Conversion of pyrrolo[2,1-*a*]isoquinoline-3-carboxylic acids 38 and 39 into lamellarin isopropyl ethers 40 and 41 *via* acid chlorides: The carboxylic acid (1.00 mmol) was dissolved in dry CH_2Cl_2 (100 mL), and the solution was cooled to 0 °C under an atmosphere of argon. Oxalyl chloride (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 2-4 h. The solvent was evaporated on a rotary evaporator, and the crude amber-colored acid chloride was dissolved in a solution of NaI in MeCN (1 g in 100 mL; 80 mL). NaCl began to precipitate within 30 min. The suspension was stirred overnight, during which time a dense precipitate of NaCl and desired lamellarin ether was formed. The solvent was removed *in vacuo* and the residue was adsorbed onto silica gel (*ca* 5 g/g of starting material) and washed through a pad of silica gel with EtOAc–hexane (1:1) (*ca* 20 mL/g) until eluents no longer showed a bright blue fluorescent spot at 254 nm by TLC. The solvent was removed and MeOH (50 mL g^{-1}) was added. The suspension was heated to boiling, then allowed to cool to room temperature. The resulting solids, consisting of

spectroscopically homogeneous lamellarin ethers, were collected by filtration. Solutions of the products fluoresce bright purple in direct sunlight.

14-(3,4-Dimethoxyphenyl)-3,10-diisopropoxy-2,11,12-trimethoxy-6H-chromeno[4',3':4,5]-pyrrolo[2,1-*a*]isoquinolin-6-one (40): The lamellarin ether **40** (1.04 g, 1.66 mmol, 94%) was obtained according to the general procedure from 1-(3,4-dimethoxyphenyl)-7-isopropoxy-2-(4-isopropoxy-2,5-dimethoxy-phenyl)-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylic acid (**38**) (1.16 g, 1.76 mmol); pale pink solid, m.p. 183-184 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (d, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.22 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 13.6 Hz, 2H), 6.71 (s, 1H), 4.72 (septet, *J* = 6.1 Hz, 1H), 4.58 (septet, *J* = 6.1 Hz, 1H), 4.00 (s, 3H), 3.91 (s, 3H), 3.90 (s, 3H), 3.45 and 3.44 (overlapping s, 6H), 1.41 (d, *J* = 6.1 Hz, 6H), 1.37 (d, *J* = 6.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6, 153.3, 149.9, 149.1, 147.9, 146.62, 146.58, 146.5, 142.5, 133.8, 129.3, 128.4, 124.1, 122.6, 121.3, 120.8, 114.4, 112.0, 111.8, 109.9, 108.2, 107.8, 105.5, 103.5, 101.4, 76.4, 71.5, 60.7, 56.3, 56.2, 55.5, 55.2, 22.7 (2 × C), 21.85, 21.83. HRMS (ESI) Found: $[M + H]^+$, 628.2546; $C_{36}H_{38}NO_9^+$ requires 628.2541.

14-(3,4-Dimethoxyphenyl)-3,11-diisopropoxy-2,12-dimethoxy-6H-chromeno[4',3':4,5]pyrrolo-[2,1-*a*]-isoquinolin-6-one (41): Lamellarin ether **41** (1.23 g, 2.06 mmol, 91%) was obtained according to the general procedure from 1-(3,4-dimethoxyphenyl)-8-isopropoxy-2-(4-isopropoxy-2,5-dimethoxyphenyl)-9-methoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylic acid (**39**) (1.43 g, 2.27 mmol); pale pink solid, m.p. 207-209 °C (lit.,[33] 208-209 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (d, *J* = 7.3 Hz, 1H), 7.24 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.17–7.10 (m, 4H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.97 (s, 1H), 6.74 (s, 1H), 4.70 (septet, *J* = 6.1 Hz, 1H), 4.58 (septet, *J* = 6.1 Hz, 1H), 4.00 (s, 3H), 3.88 (s, 3H), 3.45 (s, 3H), 3.44 (s, 3H), 1.44 (d, *J* = 6.0 Hz, 6H), 1.41 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6, 150.2, 149.9, 149.0, 148.5, 147.9, 146.7, 146.6, 134.4, 129.5, 128.4, 124.8, 124.2, 123.2, 119.0, 114.5, 112.4, 112.0, 110.9, 110.5, 110.0, 107.9, 105.7, 105.6, 103.5, 71.5, 71.2, 56.3, 56.2, 55.5, 55.2, 21.91, 21.89, 21.85, 21.83. HRMS (ESI) Found: $[M + H]^+$, 598.2437; $C_{35}H_{36}NO_8^+$ requires 598.2435. The ^{1}H chemical shifts observed for **47** are within 0.02 ppm of previously reported values, while the ^{13}C chemical shifts are within 0.1 ppm.[33]

Deprotection of lamellarin isopropyl ethers 40 and 41: To the isopropyl-protected lamellarins (1 g) was added methanesulfonic acid (10 mL) at room temperature. The flask was then swirled to ensure complete dissolution of the solid precursor and the color immediately turned bright yellow. After allowing the solution to stand at room temperature for 30 min, water (100 mL) was added and the precipitated solids were collected by filtration, washed with water and dried under vacuum to provide off-white solids of high purity. For quantitative transfer of residual solids from the filtration head and paper, hot EtOAc was used, followed by evaporation. (The phenolic lamellarins are only sparingly soluble in most cold solvents. Solutions exhibit a bright purple fluorescence in direct sunlight.)

Lamellarin ε, 14-(3,4-Dimethoxyphenyl)-3,10-dihydroxy-2,11,12-trimethoxy-6H-chromeno[4',3':4,5]-pyrrolo[2,1-*a*]isoquinolin-6-one (5): Cyclization of 14-(3,4-dimethoxy-phenyl)-3,10-diisopropoxy-2,11,12-trimethoxy-6*H*-chromeno[4',3':4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (**40**) (1.10 g, 1.75 mmol) according to the general procedure afforded lamellarin ε (**5**) as a white amorphous solid (944 mg, 1.74 mmol, 99%), m.p. 261-262 °C (lit.,[18] 271−275 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.19 (d, *J* = 7.5 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.20 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.16 (d, *J* = 8.1 Hz, 1H), 7.15 (d, *J* = 1.8 Hz, 1H), 6.99 (s, 1H), 6.79 (s, 1H), 6.67 (s, 1H), 6.21 (s, 1H), 5.78 (s, 1H), 4.00 (s, 3H), 3.94 (s, 3H), 3.91 (s, 3H), 3.50 (s, 3H), 3.45 (s, 3H); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.86 (br s, 2H), 8.96 (d, *J* = 7.5 Hz, 1H), 7.44 (d, *J* = 7.5 Hz, 1H), 7.22 and 7.21 (overlapping d, *J* = 8.0 Hz, and d, *J* = 2.0 Hz, 2H), 7.11 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.86 (s, 1H), 6.72 (s, 1H), 6.62 (s, 1H), 3.85 (s, 3H), 3.77 (s, 3H), 3.73 (s, 3H), 3.35 (s, *ca* 6H, obscured by H_2O); ^{13}C NMR (126 MHz, DMSO-d_6) δ 154.7, 153.3, 150.1, 149.3, 148.2, 146.6, 146.0, 144.9, 136.1, 133.6, 129.1, 127.6, 123.9, 121.2, 121.1, 115.1, 114.9, 113.2, 112.0, 108.4, 107.8, 107.2, 105.8, 104.0, 97.5, 60.8, 56.3, 56.2, 55.3, 54.9. HRMS (ESI) Found: $[M + H]^+$, 544.1606; $C_{30}H_{26}NO_9^+$ requires 544.1602. The ^{1}H chemical shifts observed for **5** are within 0.03 ppm of previously reported values (other than for OH signals), while the ^{13}C chemical shifts are within 0.5 ppm[18,19] (Table 1, supplementary page S2).

Dehydrolamellarin J, 14-(3,4-Dimethoxyphenyl)-3,11-dihydroxy-2,12-dimethoxy-6H-chromeno[4',3':4,5]pyrrolo[2,1-*a*]-isoquinolin-6-one, (6): Cyclization of 14-(3,4-dimethoxyphenyl)-3,10-diisopropoxy-2,11,12-trimethoxy-6*H*-chromeno-[4',3':4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (**41**) (199 mg, 0.333 mmol) according to the general procedure afforded dehydrolamellarin J (**6**) (168 mg, 0.327 mmol, 98%) as an amorphous white solid, m.p. >300 °C (decomp.) (lit.,[33] 280–295 °C (decomp.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.95 (br s, 1H), 9.84 (br s, 1H), 9.00 (d, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.21 and 7.20 (overlapping d, *J* = 2.5 and 7.5 Hz, 2H), 7.19 (s, 1H), 7.14 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.08 (s, 1H), 6.87 (s, 1H), 6.67 (s, 1H), 3.87 (s, 3H), 3.7 (s, 3H), 3.37 and 3.36 (overlapping s, 6H); ^{13}C NMR (75 MHz, DMSO) δ 154.3, 149.9, 149.0, 148.6, 148.3, 147.9, 146.3, 144.6, 134.0, 128.9, 127.3, 124.7, 123.7, 122.0, 117.5, 114.7, 113.0, 112.4, 111.5, 110.5, 108.3, 106.5, 105.6, 105.3, 103.8, 56.0, 55.9, 55.1, 54.5. HRMS (ESI) Found: $[M + H]^+$, 514.1492; $C_{29}H_{24}NO_8^+$ requires 514.1496. The ^{1}H chemical shifts observed for **10** are within 0.3 ppm of previously reported values, while the ^{13}C chemical shifts are within 0.1 ppm[32,37] (Table 2, supplementary page S3).

Large scale synthesis of dehydrolamellarin J (6) from 2-(4-isopropoxy-3-methoxyphenyl)ethylamine (20): The average overall yield of dehydrolamellarin J (**6**) over six steps from the readily prepared 6-isopropoxy-7-methoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (**18**) on a large scale was 63%. There was no need for chromatographic purification of intermediates, all of which could be used in subsequent steps after purification by precipitation or recrystallization. The individual stages, with modification of the procedures described above, are outlined below, and stages 2–7 were performed in duplicate as a check on reproducibility.

Stage 1: 6-Isopropoxy-7-methoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (18): The procedure reported above was successfully scaled up with 2-(4-isopropoxy-3-methoxyphenyl)ethylamine (**20**) (32.23 g, 149 mmol) to give the thiolactam **18** (30.52 g, 81%) after recrystallization from methyl *tert*-butyl ether without the need for column chromatography; characterization as described above.

Stage 2: (Z)-2-(3,4-Dimethoxyphenyl)-1-(4-isopropoxy-2,5-dimethoxyphenyl)-2-(6-isopropoxy-7-methoxy-3,4-dihydroisoquinolin-1(2H)-ylidene)ethanone (33): (i) Immediately after its synthesis as described above, 2-bromo-2-(3,4-dimethoxyphenyl)-1-(4-isopropoxy-2,5-dimethoxy-phenyl)ethanone (**31**) (27.2 g, 60 mmol) was dissolved in dry MeCN (250 mL), to which was added the thiolactam **18** (14.8 g, 58.9 mmol). The mixture was stirred for 18 h at room temperature to ensure complete salt formation, after which time Ph_3P (60 mmol) was added. The solution was stirred for 5 min until the phosphine had dissolved, after which NEt_3 (70 mmol) in MeCN (100 mL) was added at a rate of about 1 drop per second. The solution soon turned bright yellow and was left to stir at room temperature overnight. The solvent was removed and the residue was suspended in Et_2O (1 L) and left to stand in the freezer overnight to ensure complete precipitation of the triphenylphosphine sulfide under a clear supernatant liquid. The solids were filtered and washed with Et_2O (100 mL). A solution of concentrated aqueous HCl (32%; 10mL, *ca* 100 mmol) in ^{i}PrOH (50 mL) was added dropwise to the clear, by now reddish, Et_2O extract with stirring. The HCl salt of the desired enaminone immediately began precipitating from solution as a solid which subsequently formed a thick gel. After standing for 1 h the supernatant Et_2O was decanted and the semisolid residue was washed with Et_2O (2 × 200 mL). Upon addition of saturated aqueous $NaHCO_3$ solution (500 mL) to the semisolid, the liberated enaminone was formed as a bright yellow solid. The desired product was extracted from the solids with Et_2O (2 × 200 mL), and the combined extracts were washed with saturated aqueous $NaHCO_3$ solution (200 mL) and brine (200 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo*. The enaminone **33** (32.1 g, 54.3 mmol, 92%) was obtained as a

spectroscopically homogeneous yellow solid characterization as described above. (ii) Repeating the large scale reaction with isoquinolinethione **18** (14.7 g, 58.5 mmol) and bromoketone **31** (27.9 g, 61.5 mmol) yielded enaminone **33** (31.0 g, 52.4 mmol, 90%).

Stage 3: Ethyl 1-(3,4-dimethoxyphenyl)-8-isopropoxy-2-(4-isopropoxy-2,5-dimethoxyphenyl)-9-methoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (35): (i) The preceding enaminone **33** (32.0 g, 54.1 mmol) was dissolved in ethyl bromoacetate (60 mL. *ca* 90 g, *ca* 539 mmol) to which was added solid $NaHCO_3$ (70 g, 833 mmol). The mixture was stirred under an atmosphere of argon gas at 80-85 °C for 18 h, and then at 95 °C for an additional 2 h, at which point the reaction was complete. CH_2Cl_2 (100 mL) was added, and the suspension was filtered and washed with CH_2Cl_2 until the filtrate was clear. The solvent was evaporated *in vacuo*, and Et_2O (100 mL) and hexane (500 mL) were added to the residue. Crystals of **35** soon began to form. The mixture was left standing overnight at room temperature to ensure complete precipitation of solids. The supernatant liquid was then decanted, and the remaining material was washed with methyl *tert*-butyl ether (MTBE; 2 × 150 mL) and then triturated under MeOH (300 mL). The product was filtered, washed with MeOH (2 × 150 mL) and dried to provide **35** as a pale yellow solid (22.9 g). The Et_2O–hexane supernatant liquid was allowed to evaporate in a beaker overnight, and the semicrystalline residue was triturated under MTBE (200 mL) and allowed to stand for a few hours before being filtered, washed with additional MTBE (2 × 100 mL), triturated under MeOH (100 mL), filtered and dried to provide another batch of **35** (4.10 g). Total yield: 27.0 g (40.9 mmol, 76%); characterization as described above. (ii) Repeating the large scale reaction with enaminone **33** (31.0 g, 52.4 mmol) yielded **35** (26.6 g, 40.3 mmol, 77%).

Stage 4: Ethyl 1-(3,4-dimethoxyphenyl)-8-isopropoxy-2-(4-isopropoxy-2,5-dimethoxyphenyl)-9-methoxy-pyrrolo[2,1-*a*]isoquinoline-3-carboxylate (37): (i) The pyrrolo[2,1-*a*]isoquinoline **35** (25.9 g, 39.3 mmol) was dissolved in CH_2Cl_2 (250 mL), to which was added DDQ (13.0 g, 57.3 mmol). The solution, which immediately turned a muddy brown color, was left to stir at room temperature for 2 h. Aqueous NaOH solution (10%, 250 mL) was added, and the biphasic mixture was left to stir for 1 h before separation of the very dark phases. The aqueous phase was re-extracted with CH_2Cl_2 (3 × 300 mL), at which point the extracts were almost colorless and no longer fluoresced bright blue under 254 nm UV irradiation when spotted on a TLC plate. The combined organic extracts were washed with brine (250 mL) and dried over $MgSO_4$, filtered and evaporated *in vacuo* to give the ring B-unsaturated pyrrolo[2,1-*a*]isoquinoline **37** as a brown solid (25.7 g, 39.1 mmol, 99%); characterization as described above. The product was used in the next step without further purification. (ii) Repeating the large scale reaction with the pyrrolo[2,1-*a*]isoquinoline **35** (20.0 g, 30.3 mmol) yielded the ring-B unsaturated product **37** (19.8 g, 30.1 mmol, 99%).

Stage 5: 1-(3,4-Dimethoxyphenyl)-8-isopropoxy-2-(4-isopropoxy-2,5-dimethoxyphenyl)-9-methoxy-pyrrolo[2,1-*a*]isoquinoline-3-carboxylic acid (39): (i) KOH (45 g, 803 mmol) and water (100 mL) were added to the preceding ethyl pyrrolo[2,1-*a*]isoquinoline-3-carboxylate **37** (23.0 g, 35.0 mmol), followed by EtOH (400 mL). The suspension was heated to reflux, and after about 30 min had become homogeneous. Reflux was maintained 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 × 150 mL). The combined extracts containing the dissolved carboxylic acid were washed with aqueous HCl (1 M; 250 mL) and brine (100 mL), dried over $MgSO_4$ and evaporated *in vacuo* to provide the carboxylic acid **39** as a brown solid that could not be dried completely (22.4 g, 35.6 mmol). It was used in the next step without further purification. (ii) Repeating the large scale reaction with the ester **37** (14.4 g, 21.9 mmol) yielded carboxylic acid **39** (13.1 g, 20.8 mmol, 95%).

Stage 6: 14-(3,4-Dimethoxyphenyl)-3,11-diisopropoxy-2,12-dimethoxy-6*H*-chromeno[4',3':4,5]-pyrrolo[2,1-*a*]isoquinolin-6-one (41): (i) The above carboxylic acid **39** (13.0 g, *ca* 20.6 mmol) was dissolved in dry CH_2Cl_2 (200 mL), and the solution was cooled to 0 °C under an atmosphere of argon. Oxalyl chloride (4 mL, *ca* 5.92 g, *ca* 2.25 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 then dried under high vacuum to yield a brownish solid residue. To this was added a solution of NaI (18 g, 120 mmol) in MeCN (250 mL) at room temperature. NaCl began to precipitate after 30 min, and the evolution of a gas was noted. The suspension was stirred overnight, during which time a dense precipitate of NaCl and desired lamellarin ether had formed. The solvent was removed *in vacuo* and MeOH (250 mL) was added to the residue. The solvent was heated to boiling with stirring; upon cooling the desired protected lamellarin **41** crystallized. This was filtered and washed with MeOH (2 × 100 mL). Although it was spectroscopically pure by NMR analysis, the residual greenish color was removed by dissolving the compound in a minimum of CH_2Cl_2 (100 mL), to which was added MeOH (250 mL). Crystals of purified **41** began to form. After 30 min a portion of the solvent (largely CH_2Cl_2; *ca* 150 mL) was removed by rotary evaporation, and more MeOH (150 mL) was added. After several hours at room temperature, no further crystallization was evident. The solids were collected by filtration and dried to provide the lamellarin derivative **41** compound as a pale yellow solid (12.2 g, 20.4 mmol, 99%). (ii) The lactonization was repeated with carboxylic acid **39** (22.0 g, 34.9 mmol) and oxalyl chloride (5 mL, *ca* 2.8 equiv) in CH_2Cl_2 (200 mL) as described above. After evaporation of the solvent, a solution of NaI (18 g, 120 mmol) in MeCN (250 mL) was added, and the suspension was stirred overnight at room temperature. The subsequent work-up was improved by adding water (150 mL) to dissolve the inorganic salts. The suspension was briefly stirred before being filtered through a sintered glass disc. The solid obtained was washed with MeOH (in which the desired product is insoluble) until the filtrate clear. After drying the substituted lamellarin **41** was obtained as a pale pink solid (19.8 g, 33.1 mmol, 95%).

Stage 7: Dehydrolamellarin J (6): (i) Methanesulfonic acid (150 mL) was added to the isopropyl protected lamellarin **41** (12.2 g, 20.4 mmol) at room temperature, and the mixture was stirred to ensure complete dissolution of the solid. The color immediately turned bright fluorescent yellow. After standing at room temperature for 30 min at room temperature, ice water (300 mL) was added to precipitate the product as a fine powder, the collection of which by filtration through a sintered glass disc proved to be very slow. The isolated product was washed with H_2O and dried under vacuum to provide dehydrolamellarin J (**6**) (10.1 g, 19.7 mmol, 96%) as a pale grey amorphous solid; characterization as described above. (ii) The deprotection step was repeated with the isopropyl protected lamellarin **41** (19.8 g, 33.1 mmol) and methanesulfonic acid (150 mL) at room temperature. The suspension was stirred to ensure complete dissolution of the solid (*ca* 30 min), after which the solution was allowed to stir for a further 30 min. In an improved work-up procedure, water (600 mL) was added to precipitate the product as a fine yellow powder. After 20 min, the mixture was heated to 70 °C, which improved its flow upon filtration through a sintered glass disc. The solid paste thus obtained was washed with hot water (3 × 200 mL at *ca* 80-90 °C) and then dried under vacuum to provide dehydrolamellarin J (**6**) (16.5 g, 32.1 mmol, 97%).

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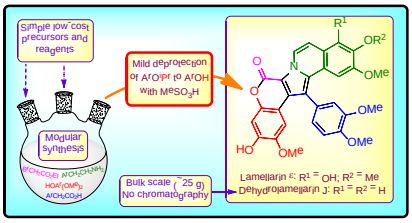
Entry for the Table of Contents



Lamellarin ε and dehydrolamellarin J were synthesized via enaminones by operationally simple routes that included a mild new method for the nearly quantitative deprotectione of isopropyl-protected phenols with methanesulfonic acid. The synthesis of dehydrolamellarin J could be scaled up to provide over 25 g of product without the need for chromatography.