Preprint Title	Concise and Scalable Total Syntheses of Lamellarin Z and other Natural Lamellarins: Regiocontrolled Assembly of the Central Pyrrole Core and Cross Dehydrogenative Coupling Enroute to the Pentacyclic Coumarin-Pyrrole-Isoquinoline Scaffold
Authors	Virendra Kumar, Abdus Salam, Dileep Kumar and Tabrez Khan
Publication Date	29 Jul 2020
Article Type	Full Research Paper
Supporting Information File 1	SI total synthesis VK.pdf; 5.9 MB
ORCID® iDs	Tabrez Khan - https://orcid.org/0000-0002-9875-3101

Concise and Scalable Total Syntheses of Lamellarin Z and other Natural Lamellarins: Regiocontrolled Assembly of the Central Pyrrole Core and Cross Dehydrogenative Coupling Enroute to the Pentacyclic Coumarin-Pyrrole-Isoquinoline Scaffold

Virendra Kumar, Abdus Salam, Dileep Kumar and Tabrez Khan*

Address: Organic Synthesis Laboratory, School of Basic Sciences, Indian Institute of Technology Bhubaneswar, Odisha 752050, India.

Email: Tabrez Khan– tabrez@iitbbs.ac.in

Abstract

An efficient construction of the central 1,2,4-trisubstituted pyrrole core via one-pot [3+2] cycloaddition/elimination/aromatization sequence-based domino process and subsequent Pd-mediated cross dehydrogenative coupling between the C-H bonds of pyrrole and the peripheral aryl rings enables rapid access to the pentacyclic coumarin-pyrrole-isoquinoline scaffolds which were smoothly elaborated to the targeted lamellarins alkaloids. The total synthesis of lamellarins Z and S with the highest overall yield reported till date, besides the synthesis of several other natural lamellarins have been realized in 5-6 steps with overall yields ranging from 20-27%.

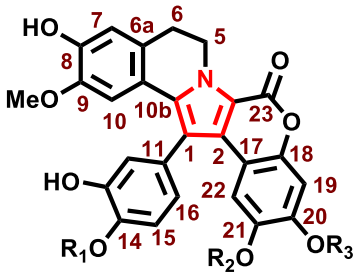
Keywords

aziridine; cross-dehydrogenative coupling; domino process; lamellarins; total synthesis

Introduction

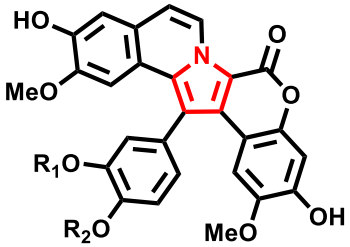
Lamellarins constitute one of the most attractive marine pyrrole alkaloids which have engaged the attention of synthetic organic and medicinal chemists for more than past two decades [1, 2] and continue to do so [3]. The underlying fact behind the world-wide attention enjoyed by these secondary metabolites is their interesting structural architecture comprising of a highly oxygenated pentacyclic coumarin-pyrrole-isoquinoline scaffold, typically in the type I and type II lamellarins (Figure 1) [4]. Also, the type III lamellarins with a relatively simple non-fused 3,4-diarylated pyrrole core with diverse oxygenation patterns on the aryl rings have been considered attractive targets for total synthesis [5]. Besides striking structural attributes, lamellarins have also equally fascinated the chemists with their interesting bioactivity profile including antitumor activity, multi-drug resistant (MDR) reversal activity in cancer cells, HIV integrase inhibitor activity, antibacterial and antioxidant activity among others [1,4a, 6]. Several reviews pertaining to the synthetic contributions from various groups and SAR development in the context of lamellarins are testimony to the enormous popularity enjoyed by these marine pyrrole alkaloids [1,2,4a,6].

Type I lamellarins



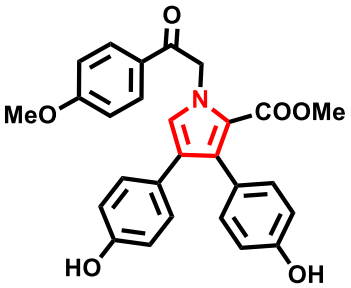
lamellarin S ($R_1 = R_2 = R_3 = H$)
lamellarin Z ($R_1 = R_2 = H$; $R_3 = Me$)
lamellarin G ($R_1 = R_3 = Me$; $R_2 = H$)
lamellarin L ($R_1 = R_2 = Me$; $R_3 = H$)

Type II lamellarins



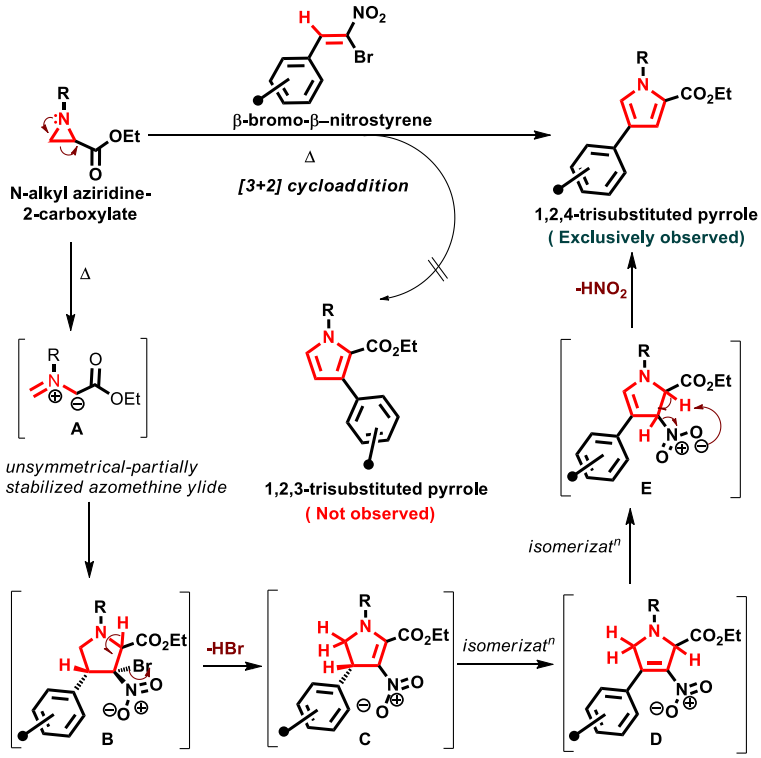
lamellarin D ($R_1 = Me$; $R_2 = H$)
lamellarin N ($R_1 = H$; $R_2 = Me$)

Type III lamellarins



lamellarin O

From the total synthesis perspective, most of the approaches reported towards lamellarins could be segregated into two categories. The first category of modular approaches originating from a commercially available pyrrole core involves functionalization of the heterocyclic core enroute to the natural alkaloid; while the second category involves the construction of the functionalized central pyrrole core enroute to the natural product [1b,2a]. Though, most of the second category approaches emanate from isoquinoline derivatives, recently some innovative approaches involving the construction of the pre-functionalized pyrrole core have surfaced in the literature [3a,7]. One such approach was recently reported by us [8], which discloses a novel one-pot domino process involving [3+2] cycloaddition of unactivated aziridine with *β*-bromo-*β*-nitrostyrene which interestingly affords 1,2,4-trisubstituted pyrrole core in a highly regioselective manner instead of the expected 1,2,3-trisubstituted pyrrole core (Scheme 1) [8,9]. Also, subsequent elaboration of the 1,2,4-trisubstituted pyrrole core to several natural and unnatural lamellarins was then demonstrated in an elegant manner with reasonably good overall yield [10].



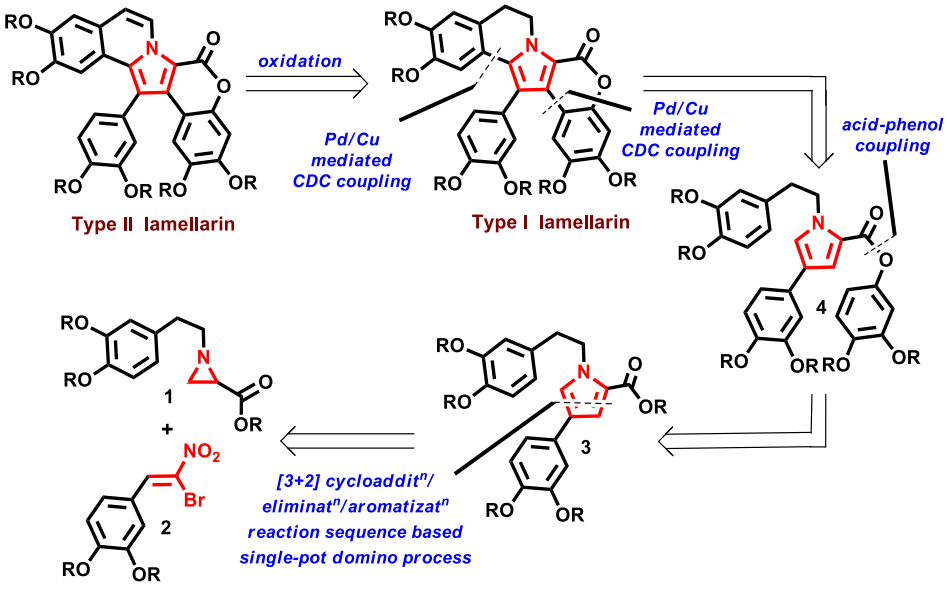
Scheme 1: One-step domino process for the synthesis of functionalized central pyrrole core.

Our continuing interest in marine pyrrole alkaloids (MPAs) [8,10] gave us the realization that despite numerous synthetic efforts towards various members of the lamellarin family, there still exist some members for which either no chemical synthesis subsists or there are very few reports. This prompted us to further validate the generality and flexibility of our already reported synthetic strategy towards lamellarins by demonstrating its applicability for the total synthesis of lamellarins Z [11,12], G, and S besides other frequently targeted biologically significant lamellarins L, N and D. In this article, we present the details of our synthetic investigation in the context of these natural marine pyrrole alkaloids (MPAs).

Results and Discussion

A concise retrosynthetic strategy as depicted in Scheme 2 and similar to the one explored by us earlier [10] to access the targeted type I and type II lamellarins was

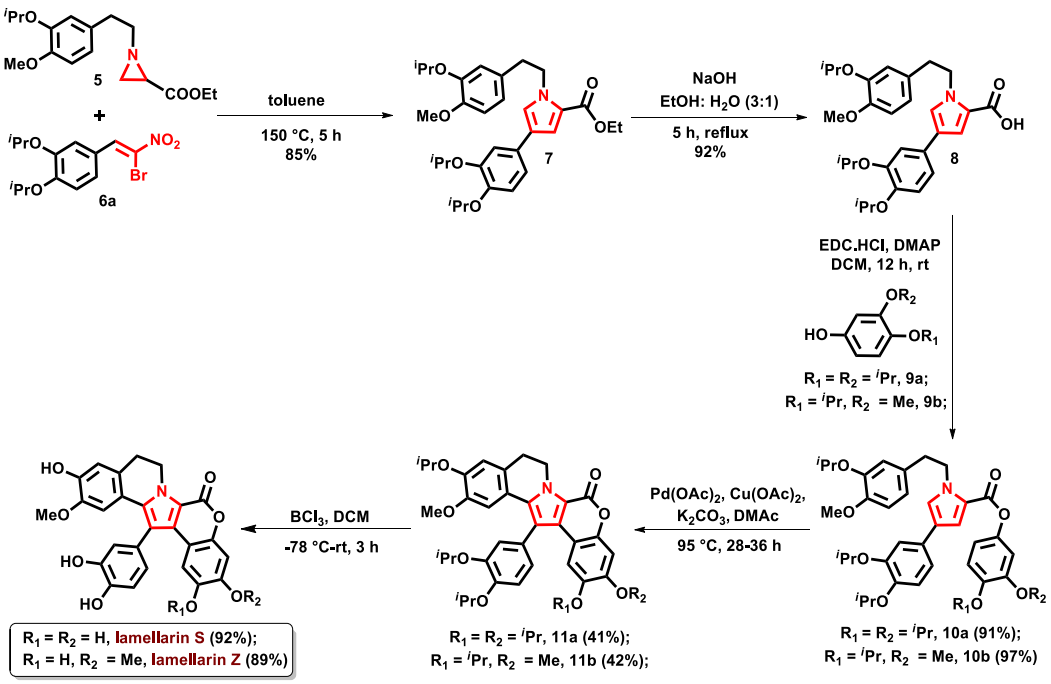
adopted in order to facilitate the rapid acquisition of the pentacyclic coumarin-pyrrole-isoquinoline scaffold. Annulation of aziridine-2-carboxylate (**1**) with substituted *β*-bromo-*β*-nitrostyrene (**2**) as per our reported condition [8] was planned to arrive at the pyrrole-2-carboxylate (**3**). Swapping of the alkyl ester in **3** with appropriately substituted phenyl esters through a straightforward 2-step synthetic manoeuvre was the next planned task to access the key intermediate (**4**). Then, a crucial one-pot Pd-mediated cross dehydrogenative coupling (CDC) reaction between sp^2 C-H bonds of central pyrrole core and peripheral aryl rings was conceptualized to arrive at the pentacyclic type I lamellarin scaffold [10,13], from which the type II lamellarin scaffold could also be accessed through a dehydrogenation reaction.



Scheme 2: Retrosynthetic Strategy towards Type I and Type II lamellarins.

Toward the operationalization of the devised retrosynthetic plan outlined in Scheme 2, initially, we choose to target lamellarins S and Z. In this context, the N-substituted aziridine-2-carboxylate (**5**) was subjected to annulation with *β*-bromo-*β*-nitrostyrene (**6a**) as depicted in Scheme 3 under our reported optimized condition [8] to arrive exclusively at the pyrrole-2-carboxylate (**7**) in good yield. The ethyl ester (**7**) was then elaborated to the phenyl esters (**10a**,**b**) through a 2-step synthetic manoeuvre

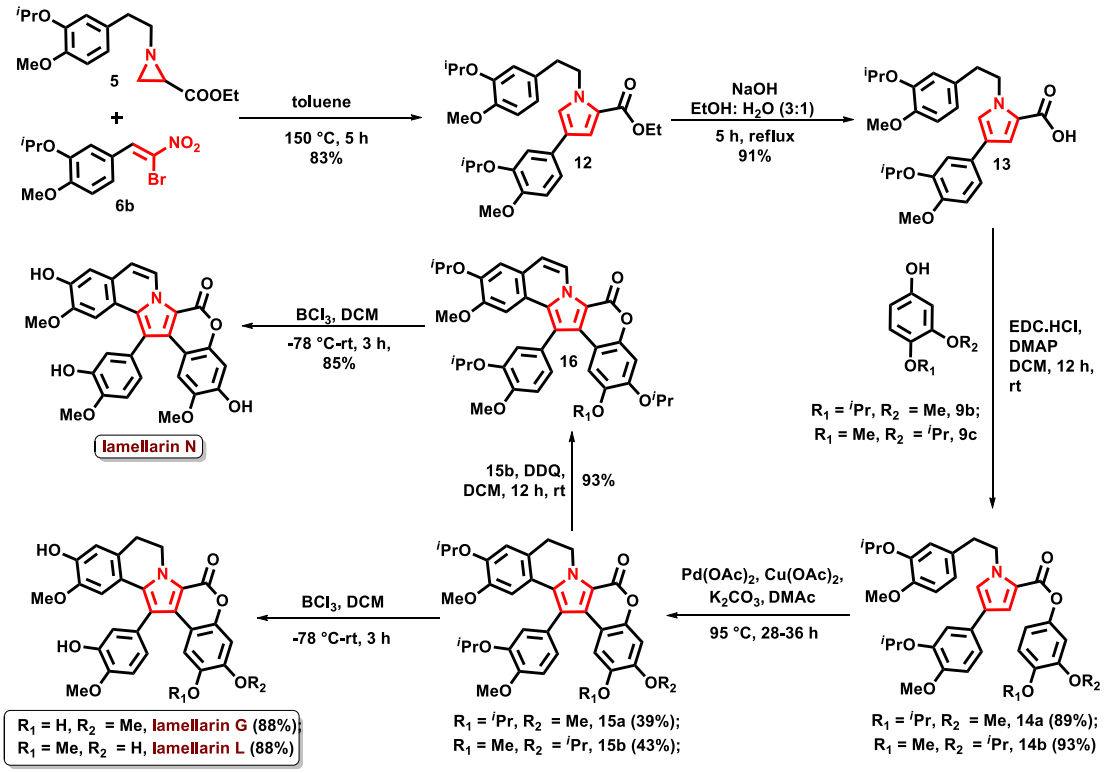
involving hydrolysis followed by EDC.HCl mediated coupling of the resultant pyrrole-2-carboxylic acid (**8**) with phenol **9a**,**b** [14,15]. After having access to **10a**,**b** we then executed the key Pd-mediated CDC reaction in presence of $Cu(OAc)_2$ as cooxidant to establish two C-C bonds in a consecutive manner between the central pyrrole core and the appended phenyl rings in the ester functionality as well as the phenyl ring of phenethyl substitution on the pyrrole-N-atom, to arrive at the pentacyclic lactones (**11a**,**b**) in moderate yields [10,13]. Subsequently, exhaustive deisopropylation of the isopropyl ethers present on the aryl rings using BCl_3 smoothly delivered the target MPAs, lamellarin S and lamellarin Z in excellent yields. The NMR spectral data of the synthetic lamellarins S and Z were found to be in decent agreement with the data reported for the natural products [16,17].



Scheme 3: Total synthesis of lamellarin S and lamellarin Z.

Next, our attention turned towards the synthesis of lamellarins G, L, and N. As highlighted in Scheme 4, a similar reaction sequence as described above was adopted for the other lamellarins. The pyrrole ester (**12**) accessed from the annulation of the aziridine-2-carboxylate **5** with *β*-bromo-*β*-nitrostyrene (**6b**)**,** was subjected to

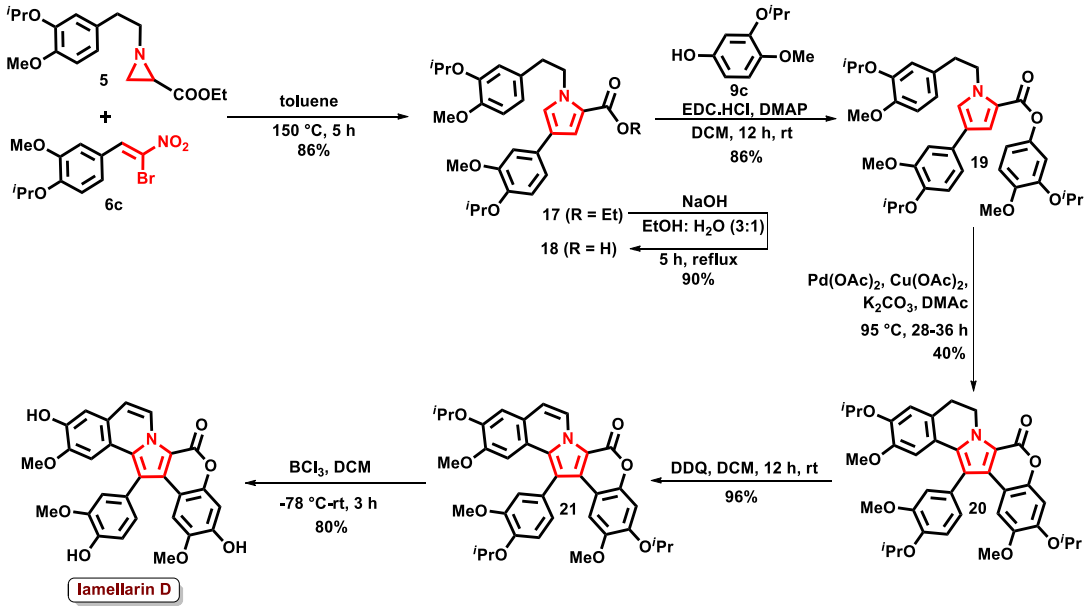
saponification and subsequently, a coupling of the resultant acid (**13**) with **9b**,**c** [15,18] to arrive at the phenyl tethered esters (**14a**,**b**) in excellent yields. Next, the crucial Pd-mediated CDC reaction in presence of $Cu(OAc)_2$ as cooxidant was executed on **14a,b**, to arrive at the pentacyclic lactones (**15a**,**b**) in moderate yields [10,13]. Lastly, BCl_3 mediated selective deprotection of the isopropyl ethers present on the aryl rings efficiently furnished lamellarin G and lamellarin L in 88% yields. On the other hand, the subjection of the pentacyclic lactone (**15b**) first to a DDQ mediated oxidation of the fused dihydroisoquinoline ring, followed by BCl_3 mediated selective deprotection of the isopropyl ethers present on the aryl rings in **16**, effortlessly delivered lamellarin N. Also, the NMR spectral data for the synthetic lamellarins G, L and N were in close agreement with the reported data [19, 20].



Scheme 4: Total synthesis of lamellarin G, L and N.

In our present synthetic endeavour, the final target left was lamellarin D and the substitution pattern present in it dictated for a forward synthesis as captured in **Scheme 5**. Employing the same aziridine-2-carboxylate (**5**) as used previously (*vide supra*), but

a different *β*-bromo-*β*-nitrostyrene in the form of **6c**, the formation of pyrrole ester (**17**) was facilitated under the optimized condition [8,10]. The pyrrole ester (**17**) was then elaborated to the phenyl tethered pyrrole-2-carboxylate (**19**) through a 2 step synthetic protocol via pyrrole-2-carboxylic acid (**18**). Then, subjection of **19** to the Pd-mediated CDC reaction condition enabled the consecutive C-C bond formation to deliver the pentacyclic isoquinoline-coumarin fused pyrrole **20** [10,13]. With **20** in hand, repetition of a similar sequence of reaction as used for accessing lamellarin N involving DDQ mediated dehydrogenation and BCl_3 facilitated deprotection of the isopropyl ethers, effortlessly furnished the targeted lamellarin D in good yield. Also, the NMR spectral data for the synthetic lamellarin D were in close agreement with the reported data [7b].



Scheme 5: Total synthesis of lamellarin D.

Conclusion

In conclusion, we have successfully demonstrated the adaptation of our recently disclosed one-pot domino process for the construction of the 1,2,4-trisubstituted central pyrrole core with diverse oxygenation pattern on the aryl rings. Also, a further

extension to the pentacyclic lamellarin scaffolds has been demonstrated through a one-pot CDC reaction, thereby enabling a 5-step total synthesis of lamellarins Z and S with the highest overall yields of 27% and 26% respectively, reported till date in the literature.[12,21] Further, the 5-step synthesis of lamellarins G and L accomplished with an overall yield of 26% each, compares reasonably well, either in terms of step economy or overall yield with many of the earlier reported synthesis. Even the 6-step synthesis of lamellarins N and D accomplished with overall yields of 24% and 20% respectively compares satisfactorily with the previous synthetic reports.

Experimental

General Information: All the reagents were purchased from commercial suppliers and used without further purification. While most of the desired solvents supplied by commercial suppliers were dried using the standard drying procedures.[22] All the moisture and air sensitive reactions were performed under a flow of nitrogen or argon atmosphere using flame-dried or oven-dried glassware with magnetic stirring. All purifications were done using column chromatography with 100-200 mesh size SiO_2-gel as the stationary phase. Distilled EtOAc and petroleum ether were typically used for column chromatography. The ^{1}H & $^{13}C\{^{1}H\}$ NMR spectra were recorded on 400 MHz Bruker spectrometer using $CDCl_3$ (H: δ = 7.26 and C: δ = 77.0 ppm) or TMS (δ = 0.0) residual solvent peaks as internal standard and DMSO-d_6 ((H: δ = 2.50 and C: δ = 39.52±0.06 ppm). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, p = quintet/pentet, sept. = septet, dd = doublet of doublet, ddd = doublet of doublet of doublet, td = triplet of doublet, dq = doublet of quartet and m = multiplet. The chemical shifts are reported as δ values (ppm) and the coupling constants (*J*) values are reported in Hz. High Resolution Mass

Spectra (HRMS) were obtained using electron spray ionization (ESI) technique and TOF mass analyzer. IR spectra were recorded on a Bruker FT/IR-460 Plus spectrometer. Melting points were determined on a Buchi M-560 apparatus and are uncorrected. Progress of the reactions were monitored using precoated SiO_2-gel GF254 TLC plates while spot visualizations were done under UV light and using spot developing stains like *p*-anisaldehyde, ceric ammonium molybdate, ninhydrin or $KMnO_4$.

Ethyl 1-(3-isopropoxy-4-methoxyphenethyl) aziridine-2-carboxylate (5): As per our reported protocol,[8,10] in an oven-dried round-bottom flask under N_2 atmosphere, ethyl 2,3-dibromopropanoate[8] (1.3 g, 5.0 mmol) was dissolved in EtOH (5 mL). After the solution was stirred at 0 °C for 10 min, 3-isopropoxy-4-methoxyphenethylamine[23] (3.04 g, 15.0 mmol, 3 equiv.) dissolved in ~2 mL of ethanol was added dropwise to the flask over 10 min. The reaction was then allowed to warm to rt and continued stirring for another 6 h, until complete consumption of starting material was indicated by the TLC analysis. Upon reaction completion, the solvent was removed under reduced pressure, and the resultant residue was subjected to purification using SiO_2-gel column chromatography to arrive at the desired aziridine-2- carboxylate, **5** as a pale yellow oil (1.23 g, 80% yield); R_f = 0.8 (50% EtOAc + pet. ether). IR (neat): ν_{max}1746, 1644, 1606, 1513, 1454, 1416, 1384, 1262, 1234, 1186, 1110, 1029, 985 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.78 (d, J = 8 Hz, 1H), 6.74 (d, J = 1.6 Hz, 1H), 6.72 (dd, J_1 = 1.6 Hz, J_2 = 8 Hz, 1H), 4.49 (sept, J = 6 Hz, 1H), 4.24-4.10 (m, 2H), 3.82 (s, 3H), 2.90-2.79 (m, 2H), 2.54 (t, J = 7.2 Hz, 2H), 2.12 (dd, J_1 = 1.2 Hz, J_2 = 3.2 Hz, 1H), 1.95 (dd, J_1 = 3.2 Hz, J_2 = 6.4 Hz, 1H), 1.50 (dd, J_1 = 1.2 Hz, J_2 = 6.4 Hz, 1H), 1.34 (d, J = 6 Hz, 6H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 149.0, 147.2, 132.0, 121.2, 116.9, 112.2, 71.5, 62.6, 61.1, 56.0, 37.6, 35.6, 34.4, 22.2, 22.1, 14.2. HRMS (ESI) m/z calcd for $C_{17}H_{26}NO_4$ $(M+H)^+$: 308.1856; found: 308.1841.

1) General procedure for the preparation of β-bromo-β-nitrostyrene: To a cold solution of *β*-nitrostyrene (2.5 mmol, 1 equiv.) in DCM at 0 °C, pyridine (0.4 mL, 5 mmol, 2 equiv.) was added followed by pyridinium tribromide (0.8 g, 2.5 mmol, 1 equiv.) in two portions. The reaction was then allowed to warm to rt over the next 3-12 h until complete consumption of starting material. Upon reaction completion, water was added followed by extraction with DCM. Drying of the organic phase over Na_2SO_4 followed by removal of the solvent under reduced pressure gave a crude residue which was purified by column chromatography to access *β*-bromo-*β*-nitrostyrene.

(Z)-4-(2-bromo-2-nitrovinyl)-1,2-diisopropoxybenzene (6a): Following general procedure 1, using (*E*)-1,2-diisopropoxy-4-(2-nitrovinyl)benzene (0.66 g, 2.5 mmol), **6a** was obtained as yellow solid (0.61 g, 71% yield); R_f = 0.8; (15% EtOAc + pet. ether); mp 78-80 °C. IR (neat): ν_{max} 1590, 1503, 1300, 1267, 1174, 1138, 1106, 1010, 997 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$):*δ* 8.6 (s, 1H), 7.64 (d, J = 2 Hz, 1H), 7.49 (dd, J_1 = 2 Hz, J_2 = 8.8 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 4.63 (sept, J = 6 Hz, 1H), 4.48 (sept, J = 6 Hz, 1H), 1.39 (d, J = 6 Hz, 6H), 1.36 (d, J = 6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 153.2, 148.4, 136.6, 127.4, 125.2, 122.5, 120.1, 115.4, 72.9, 71.7, 22.1 (2C), 22.0 (2C). HRMS (ESI) m/z calcd for $C_{14}H_{19}BrNO_4$ $(M+H)^+$: 344.0492; found: 344.0484.

(Z)-4-(2-bromo-2-nitrovinyl)-2-isopropoxy-1-methoxybenzene (6b): Following general procedure 1, using (*E*)-2-isopropoxy-1-methoxy-4-(2-nitrovinyl) benzene[4] (0.59 g, 2.5 mmol), **6b** was obtained as a yellow solid (0.76 g, 97% yield); R_f = 0.7; (20% EtOAc + pet. ether); mp 95-96 °C. IR (neat): ν_{max} 1642, 1586, 1527, 1510, 1302, 1263, 1140, 1017, 963, 931 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.62 (s, 1H), 7.63 (d, J = 2 Hz, 1H), 7.49 (dd, J_1 = 2 Hz, J_2 = 8.4 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 4.58 (sept, J = 6 Hz, 1H), 3.94 (s, 3H), 1.41 (d, J = 6 Hz, 6H), ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 153.9, 147.2, 136.7, 127.1, 125.2, 122.4, 116.8, 111.6, 71.8, 56.1, 21.9 (2C). HRMS (ESI) m/z calcd for $C_{12}H_{15}BrNO_4$ $(M+H)^+$: 316.0179; found: 316.0173.

(Z)-4-(2-bromo-2-nitrovinyl)-1-isopropoxy-2-methoxybenzene (6c): Following general procedure 1 using (*E*)-1-isopropoxy-2-methoxy-4-(2-nitrovinyl)benzene (0.59 g, 2.5 mmol), **21b** was obtained as yellow solid (0.66 g, 83% yield); R_f = 0.7; (20% EtOAc + pet. ether); mp 73-75°C. IR (neat): ν_{max}1586, 1529, 1468, 1303, 1268, 1144, 1106, 1031, 945 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$):δ 8.63 (s, 1H), 7.60 (d, J = 2 Hz, 1H), 7.49 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 6.96 (d, J = 8.8 Hz, 1H), 4.68 (sept, J = 6 Hz, 1H), 3.92 (s, 3H), 1.43 (d, J = 6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.3, 149.8, 136.7, 126.9, 125.0, 122.2, 113.6, 113.5, 71.3, 56.1, 21.9 (2C). HRMS (ESI) m/z calcd for $C_{12}H_{15}BrNO_4$ $(M+H)^+$: 316.0179; found: 316.0171.

***Gram Scale Synthesis of Ethyl 4-(3,4-diisopropoxyphenyl)-1-(3-isopropoxy-4-methoxypheneth-yl)-1H-pyrrole-2-carboxylate (7)*:** As per our reported procedure, in an oven-dried seal tube, under nitrogen atmosphere, **6a** [(*Z*)-4-(2-bromo-2-nitrovinyl)-1,2-diisopropoxybenzene] (1 g, 2.9 mmol, 1 equiv.) was taken. After that **5** [ethyl 1-(3-isopropoxy-4-methoxyphenethyl)aziridine-2-carboxylate] (0.89 g, 2.9 mmol, 1 equiv.) dissolved in toluene (2 mL) was added. The reaction was then sealed while maintaining the N_2 atmosphere and then stirred in a preheated oil bath at 150°C for 6 h, until complete consumption of starting materials was indicated upon reaction monitoring. After reaction completion, the solvent was removed under reduced pressure and the crude residue was subjected to purification using SiO_2-gel flash column chromatography to access **7** as pale yellow oil (1.3 g, 85% yield); R_f = 0.3; (10% EtOAc + pet. ether). IR (neat): ν_{max} 1638, 1514, 1505, 1470, 1454, 1384, 1371, 1261, 1245, 1136, 1092, 1024, 988 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, J = 2 Hz, 1H), 6.98 (d, J = 2 Hz, 1H), 6.95 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.79 (d, J = 2.0 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 6.69 (dd, J_1 = 2 Hz, J_2 = 8.2 Hz, 1H), 6.59 (d, J = 2.0 Hz, 1H), 4.54-4.37 (m, 5H), 4.32 (q, J = 7.2 Hz, 2H), 3.81 (s, 3H), 2.98 (t, J = 7.2 Hz, 2H), 1.39 (t, J = 7.2 Hz, 3H), 1.34 (d, J = 6 Hz, 6H), 1.33 (d, J

= 6 Hz, 6H), 1.27 (d, *J* = 6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 161.1, 149.3, 149.2, 147.8, 147.2, 131.0, 128.7, 125.3, 123.7, 122.1, 121.5, 118.8, 118.6, 116.9, 115.7, 115.1, 112.1, 72.4, 72.3, 71.6, 59.9, 56.0, 51.2, 37.7, 22.33 (2C), 22.28 (2C), 22.1 (2C), 14.5. HRMS (ESI) m/z calcd for $C_{31}H_{42}NO_6$ $(M+H)^+$: 524.3007; found: 524.3002.

4-(3,4-diisopropoxyphenyl)-1-(3-isopropoxy-4-methoxyphenethyl)-1H-pyrrole-2-carboxylic acid (8): To a solution of **7** (0.9 g, 1.7 mmol, 1 equiv.) in ethanol : water (3:1, 25 mL), crushed NaOH pellets (0.34 g, 8.5 mmol, 5 equiv.) were added at rt and the reaction was then allowed to reflux for 5 h, until completion of the saponification process was indicated by TLC analysis. The reaction was worked up by removing the volatiles under reduced pressure and the resultant residue was neutralized with 1N HCl. The aqueous phase was subjected to extraction with EtOAc (4 × 30 mL). Drying of the organic phase over Na_2SO_4 and then removal of solvent under reduced pressure gave a crude residue which was subjected to SiO_2-gel column chromatography to access pure acid **8** as a white solid (0.79 g, 92% yield); R_f = 0.5 (30% EtOAc + pet. ether); mp 96-97 °C. IR (neat): ν_{max}1660, 1565, 1548, 1514, 1479, 1463, 1402, 1380, 1264, 1235, 1184, 1141, 1113, 1028, 994 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.32 (d, *J* = 2 Hz, 1H), 6.99 (d, *J* = 2 Hz, 1H), 6.96 (dd, J_1 = 2 Hz, J_2 = 8 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 2 Hz, 1H), 6.80 (d, *J* = 8 Hz, 1H), 6.70 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 6.65 (d, *J* = 2 Hz, 1H), 4.54-4.43 (m, 5H), 3.82 (s, 3H), 3.02 (t, *J* = 7.2 Hz, 2H), 1.36 (d, *J* = 6 Hz, 6H), 1.34 (d, *J* = 6 Hz, 6H), 1.31 (d, *J* = 6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 165.8, 149.4, 149.2, 147.9, 147.3, 130.8, 128.2, 126.8, 124.2, 121.3, 121.0, 118.8, 118.6, 117.2, 116.7, 115.6, 112.1, 72.4, 72.3, 71.5, 56.0, 51.6, 37.7, 22.32 (2C), 22.28 (2C), 22.1 (2C). HRMS (ESI) m/z calcd for $C_{29}H_{38}NO_6$ $(M+H)^+$: 496.2694; found: 496.2687.

2) General procedure for the pyrrole-2-carboxylic acid-phenol coupling: To a solution of pyrrole-2-carboxylic acid (1 equiv.) and phenol (1 equiv.) in dichloromethane (5

mL/mmol), EDC.HCl (1.1 equiv.) and DMAP (1.1 equiv.) were added sequentially at rt and the reaction was allowed to stir at rt for 12 h until complete consumption of starting materials was indicated by TLC analysis. The reaction was worked up by removing the solvent under reduced pressure and subjection of the resultant residue to SiO_2-gel flash column chromatography to access the phenyl tethered pyrrole-2-carboxylates.

3,4-diisopropoxyphenyl 4-(3,4-diisopropoxyphenyl)-1-(3-isopropoxy-4-methoxyphenethyl)-1H-pyrrole-2-carboxylate (10a): Following the general procedure 2, using **8** (0.3 g, 0.6 mmol, 1 equiv.) and **9a** [3,4-diisopropoxyphenol] (0.13 g, 0.6 mmol, 1 equiv.), **10a** was obtained as a pale yellow oil (0.38 g, 91% yield); R_f = 0.6 (20% EtOAc + pet. ether). IR (neat): ν_{max}1714, 1605, 1561, 1505, 1472, 1384, 1261, 1109, 1065, 1046, 988 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 7.37 (d, J = 2 Hz, 1H), 7.02 (d, J = 2 Hz, 1H), 6.98 (dd, J_1 = 2 Hz, J_2 = 8.4 Hz, 1H), 6.95 (d, J = 8.8 Hz, 1H), 6.90-6.88 (m, 2H), 6.79-6.77 (m, 2H), 6.74 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.69 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 6.60 (d, J = 2 Hz, 1H), 4.55-4.48 (m, 3H), 4.46-4.36 (m, 4H), 3.81 (s, 3H), 3.01 (t, J = 7.2 Hz, 2H), 1.37-1.33 (m, 24H), 1.26 (d, J = 6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 149.9, 149.4, 149.2, 147.9, 147.2, 146.5, 145.0, 130.7, 128.3, 126.5, 124.2, 121.6, 121.1, 119.2, 118.8, 118.6, 116.8, 116.4, 115.7, 114.1, 112.0, 111.2, 73.1, 72.4 (2C), 72.0, 71.5, 56.0, 51.4, 37.7, 22.34 (2C), 22.31 (2C), 22.30 (2C), 22.2 (2C), 22.1 (2C). HRMS (ESI) m/z calcd for $C_{41}H_{54}NO_8$ $(M+H)^+$: 688.3844; found: 688.3822.

***4-isopropoxy-3-methoxyphenyl 4-(3,4-diisopropoxyphenyl)-1-(3-isopropoxy-4-methoxyphenethyl)-1H-pyrrole-2-carboxylate (10b)*:** Following the general procedure 2, using **8** (0.45 g, 0.9 mmol, 1 equiv.) and **9b** [4-isopropoxy-3-methoxyphenol] (0.16 g, 0.9 mmol, 1 equiv.), **10b** was obtained as a pale yellow oil (0.58 g, 97% yield); R_f = 0.7 (30% EtOAc + pet. ether). **IR** (neat): ν_{max}1717, 1559, 1542, 1508, 1265, 1223, 1187, 1136, 1109, 1066, 1047, 989 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$)

7.38 (d, J = 2 Hz, 1H), 7.02 (d, J = 2 Hz, 1H), 6.99 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 6.91-6.88 (m, 2H), 6.78-6.72 (m, 3H), 6.68 (dd, J_1 = 2 Hz, J_2 = 8.2 Hz, 1H), 6.60 (d, J = 2 Hz, 1H), 4.55-4.44 (m, 5H), 4.42-4.36 (m, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.01 (t, J = 7.2 Hz, 2H), 1.38 (d, J = 6 Hz, 6H), 1.36 (d, J = 6 Hz, 6H), 1.40 (d, J = 6 Hz, 6H), 1.26 (d, J = 6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 151.1, 149.4, 149.2, 147.9, 147.2, 145.0, 144.6, 130.7, 128.3, 126.5, 124.3, 121.6, 121.1, 118.8, 118.6, 117.0, 116.5, 116.4, 115.7, 113.4, 112.1, 106.6, 72.4 (2C), 72.2, 71.6, 56.04. 56.0, 51.3, 37.7, 22.33 (2C), 22.29 (2C), 22.2 (2C), 22.1 (2C). HRMS (ESI) m/z calcd for $C_{39}H_{50}NO_8$ $(M+H)^+$: 660.3531; found: 660.3520.

3) General procedure for the cross-dehydrogenative coupling (CDC) reaction: Using the earlier reported procedure,[10,13] an oven-dried schlenk tube was charged with phenyl esters (1 equiv.), $Pd(OAc)_2$ (2 equiv.) and $Cu(OAc)_2$ (6 equiv.) under N_2 atmosphere. Then, dimethylacetamide (3 mL/mmol) followed by K_2CO_3 (2 equiv.) was added maintaining the inert atmosphere and the reaction was allowed to stir at 95 °C for 28-36 h. Upon reaction completion indication by TLC analysis, the reaction was filtered through celite and the celite bed was washed with EtOAc. The filtrates were combined and subjected to solvent removal under reduced pressure to arrive at a crude residue which was purified by SiO_2-gel flash column chromatography to access pentacyclic coumarin fused pyrrolo-dihydroisoquinolines.

14-(3,4-diisopropoxyphenyl)-2,3,11-triisopropoxy-12-methoxy-8,9-dihydro-6H-chromeno[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (11a)*:* Following the general CDC reaction procedure 3, using **10a** (0.25 g, 0.36 mmol), **11a** was obtained as a white solid (0.102 g, 41% yield); R_f = 0.8 (EtOAc). IR (neat): ν_{max}1712, 1649, 1643, 1572, 1536, 1513, 1484, 1416, 1268, 1207, 1109, 1035, 936 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, J = 8.8 Hz, 1H), 7.02-7.00 (m, 2H), 6.92 (s, 1H), 6.76 (s, 1H), 6.72 (s, 1H), 6.71 (s, 1H), 4.87-4.80 (m, 1H), 4.76-4.69 (m, 1H), 4.59-4.40 (m, 4H), 4.00-3.94 (m,

1H), 3.34 (s, 3H), 3.10-3.06 (m, 2H), 1.40-1.28 (m, 24H), 1.14 (d, *J* = 6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 155.7, 150.2, 148.8,148.7, 148.6, 147.3, 146.4, 145.2, 136.0, 129.2, 128.2, 126.4, 123.8, 120.3, 119.5, 119.4, 115.0, 114.7, 113.6, 111.1, 110.8, 109.2, 105.4, 72.8, 72.2, 72.16, 71.9, 71.4, 55.1, 42.5, 28.7, 22.25, 22.23, 22.20, 22.07 (3C), 22.0 (2C), 22.9 (2C). HRMS (ESI) m/z calcd for $C_{41}H_{50}NO_8$ $(M+H)^+$: 684.3531; found: 684.3559.

14-(3,4-diisopropoxyphenyl)-2,11-diisopropoxy-3,12-dimethoxy-8,9-dihydro-6H-chromeno[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (11b)*:* Following the general oxidative coupling procedure 6, using **10b** (0.338 g, 0.5 mmol, 1 equiv.), **11b** was obtained as a white solid (0.141 g, 42% yield); R_f = 0.4 (20% EtOAc + pet. ether). **IR** (neat): ν_{max}1715, 1648, 1541, 1508, 1488, 1456, 1418, 1338, 1269, 1209, 1162, 1110, 1031, 938 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.10 (d, *J* = 8.4 Hz, 1H), 7.04-7.02 (m, 2H), 6.89 (s, 1H), 6.76 (s, 1H), 6.71 (d, *J* = 2.8 Hz, 2H), 4.87-4.81 (m, 1H), 4.75-4.68 (m, 1H), 4.57-4.48 (m, 2H), 4.47-4.41 (m, 1H), 4.00-3.94 (m, 1H), 3.85 (s, 3H), 3.34 (s, 3H), 3.10-3.06 (m, 2H), 1.40 (d, *J* = 6 Hz, 3H), 1.39 (d, *J* = 6 Hz, 3H), 1.37 (d, *J* = 6 Hz, 6H), 1.30 (d, *J* = 6 Hz, 3H), 1.29 (d, *J* = 6 Hz, 3H), 1.16 (d, *J* = 6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 155.7, 150.2, 149.9, 148.73, 148.66, 147.3, 146.1, 143.6, 136.0, 129.2, 128.2, 126.4, 123.8, 120.3, 119.5, 119.4, 114.9, 114.7, 113.6, 110.4, 109.2, 108.2, 100.8, 72.8, 71.9, 71.4, 71.1, 56.1, 55.1, 42.5, 28.7, 22.26, 22.24, 22.20, 22.07 (2C), 22.04, 21.76, 21.74. HRMS (ESI) m/z calcd for $C_{39}H_{46}NO_8$ $(M+H)^+$: 656.3218; found: 656.3206.

4) General procedure for the BCl_3 mediated deisopropylation: To a cold solution of pentacyclic isopropylated phenyl ether (1 equiv.) in DCM (3 mL/0.1 mmol of the substrate) at -78°C, BCl_3 (1M solution in DCM, 10 equiv.) was added dropwise over 5 min. and after stirring at the same temperature for almost 20 min., the reaction was allowed to warm to rt and stirred for another 3 h until the formation of a prominent new

spot was indicated by TLC analysis. The reaction was worked up by quenching it with MeOH followed by removal of the volatiles under reduced pressure. To the resultant residue, H_2O was added and extracted with EtOAc. Drying of the organic phase over Na_2SO_4 and then removal of the solvent under reduced pressure gave a crude residue that was subjected to SiO_2-gel flash column to access the deisopropylated compounds.

Lamellarin S*:* Exhaustive deisopropylation on **11a** (0.025 g, 0.036 mmol) using general procedure 4, afforded lamellarin S as a white solid (0.016 mg, 92% yield); R_f = 0.3 (80% EtOAc + pet. ether) with NMR spectral data similar to those reported in the literature.[16] IR (neat): ν_{max}2928, 2855, 1677, 1278, 1196, 1049, 955 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 6.98 (d, J = 8 Hz, 1H), 6.87 (d, J = 2 Hz, 1H), 6.83 (s, 1H), 6.77 (dd, J_1 = 1.6 Hz, J_2 = 8 Hz, 1H), 6.75 (s, 1H), 6.70 (s, 1H), 6.62 (s, 1H), 4.70-4.54 (m, 2H), 3.38 (s, 3H), 3.00 (t, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, MeOD-d_4) δ 157.6, 148.1, 147.46, 147.41, 147.3, 146.73, 146.7, 143.4, 138.6, 129.9, 128.7, 128.1, 123.7, 120.2, 119.0, 117.5, 116.4, 115.8, 113.8, 111.3, 110.4, 109.8, 104.2, 55.6, 43.5, 29.3.

Lamellarin Z*:* Exhaustive deisopropylation on **11b** (0.025 g, 0.01 mmol) using general procedure 4, afforded lamellarin Z as a white solid (0.016 g, 89% yield); R_f = 0.6 (80% EtOAc + pet. ether) which was spectroscopically found to be in good agreement with the earlier reported data.[17] IR (neat): ν_{max} 2889, 2839, 1654, 1560, 1542, 1523, 1458, 1377, 1363, 1340, 1276, 1205, 1188, 1161, 1117, 1080, 1042, 1026, 964 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.34 (s, 1H), 9.12 (s, 1H), 9.08 (s, 1H), 8.92 (s, 1H), 7.00 (s, 1H), 6.93 (d, J = 8 Hz, 1H), 6.76 (d, J = 2 Hz, 1H), 6.72 (s, 1H), 6.70 (s, 1 H), 6.69 (dd, J_1 = 8 Hz, J_2 = 2 Hz, 1H), 6.55 (s, 1H), 4.71-4.65 (m, 1H), 4.55-4.49 (m, 1H), 3.80 (s, 3H), 3.29 (s, 3H), 3.01-2.97 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.3, 147.8, 146.9, 146.1, 145.9, 145.3, 144.6, 142.8, 136.0, 127.1, 126.9, 125.4, 121.5, 118.1, 117.7, 116.6, 115.2, 114.7, 112.5, 110.2, 109.3, 108.4, 100.7, 55.8, 54.6, 41.9, 27.5. HRMS (ESI) m/z calcd for $C_{27}H_{21}NO_8$ $(M+H)^+$: 488.1340; found: 488.1333.

***Ethyl 1-(3-isopropoxy-4-methoxyphenethyl)-4-(3-isopropoxy-4-methoxyphenyl)-1H-pyrrole-2-carboxylate (12)*:** As per the procedure described for synthesis of pyrrole-2-carboxylate **7**, using **5** [ethyl 1-(3-isopropoxy-4-methoxyphenethyl)aziridine-2-carboxylate] (0.68 g, 2.2 mmol, 1 equiv.) and **6b** [(*Z*)-4-(2-bromo-2-nitrovinyl)-2-isopropoxy-1-methoxybenzene] (0.7 g, 2.2 mmol, 1 equiv.) with a reaction time of 5 h, **12** was obtained after flash column chromatography as pale yellow oil (0.91 g, 83% yield); R_f = 0.6; (20% EtOAc + pet. ether). **IR** (neat): ν_{max}1716, 1698, 1556, 1538, 1519, 1505, 1454, 1433, 1417, 1395, 1372, 1360, 1337, 1249, 1137, 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, J = 2 Hz, 1H), 6.97-6.95 (m, 2H), 6.83 (d, J = 8.4 Hz, 1H), 6.79-6.77 (m, 2H), 6.69 (dd, J_1 = 2 Hz, J_2 = 8 Hz, 1H), 6.60 (d, J = 2 Hz, 1H), 4.56 (sept, J = 6.0 Hz, 1H), 4.49 (t, J = 6.8 Hz, 2H), 4.41 (sept, J = 6.0 Hz, 1H), 4.32 (q, J = 7.2 Hz, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 2.98 (t, J = 6.8 Hz, 2H), 1.39 (t, J = 7.2 Hz, 3H), 1.37 (d, J = 6 Hz, 6H), 1.27 (d, J = 6 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 161.1, 149.2 (2C), 147.4, 147.2, 131.0, 127.6, 125.3, 123.7, 122.1, 121.5, 118.0, 116.9, 115.1, 113.7, 112.4, 112.0, 71.6, 71.5, 60.0, 56.1, 56.0, 51.3, 37.7, 22.2 (2C), 22.1 (2C), 14.5. **HRMS** (ESI) m/z calcd for $C_{29}H_{38}NO_6$ $(M+H)^+$: 496.2694; found: 496.2689.

***1-(3-isopropoxy-4-methoxyphenethyl)-4-(3-isopropoxy-4-methoxyphenyl)-1H-pyrrole-2-carboxylic acid (13)*:** Applying the saponification procedure described for accessing acid **8**, hydrolysis of **12** (0.37 g, 0.75 mmol, 1 equiv.) in EtOH : H_2O (3:1, 15 mL) using crushed NaOH pellets (0.15 g, 3.75 mmol, 5 equiv.) with reaction time of 5 h, afforded the pure acid **13** was obtained as a white solid (0.317 g, 91% yield); R_f = 0.6 (40% EtOAc + pet. ether); mp 124-126 °C. IR (neat): ν_{max} 1649, 1555, 1519, 1460, 1433, 1396, 1372, 1337, 1252, 1232, 1188, 1137, 1108, 1064, 1026, 991 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 2 Hz, 1H), 6.98-6.96 (m, 2H), 6.87-6.85 (m, 2H), 6.80 (d, J = 8 Hz, 1H), 6.70 (dd, J_1 = 1.6 Hz, J_2 = 8.2 Hz, 1H), 6.66 (d, J = 2 Hz, 1H), 4.59-

4.43 (m, 4H), 3.86 (s, 3H), 3.83 (s, 3H), 3.03 (t, J = 7.2 Hz, 2H), 1.39 (d, J = 6 Hz, 6H), 1.31 (d, J = 6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 149.3, 149.2, 147.5, 147.3, 130.8, 127.3, 126.8, 124.3, 121.3, 120.9, 118.0, 117.2, 116.6, 113.6, 112.4, 112.1, 71.6, 71.4, 56.1, 56.0, 51.6, 37.8, 22.2 (2C), 22.1 (2C). HRMS (ESI) m/z calcd for $C_{27}H_{34}NO_6$ $(M+H)^+$: 468.2381; found: 468.2376.

4-isopropoxy-3-methoxyphenyl 1-(3-isopropoxy-4-methoxyphenethyl)-4-(3-isopropoxy-4-methoxyphenyl)-1H-pyrrole-2-carboxylate (14a)**:**Following the general procedure 2, using acid **13** (0.29 g, 0.62 mmol, 1 equiv.) and **9b** [4-isopropoxy-3-methoxyphenol] (0.114 g, 0.62 mmol, 1 equiv.), **14a** was obtained as a pale yellow oil (0.337 g, 86% yield); R_f = 0.4 (20% EtOAc + pet. ether). IR (neat): ν_{max}1717, 1603, 1509, 1467, 1445, 1419, 1384, 1261, 1224, 1187, 1138, 1110, 1068, 1048, 803 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 7.38 (d, J = 1.6 Hz, 1H), 7.02-6.99 (m, 2H), 6.93 (d, J = 8.8 Hz, 1H), 6.91 (d, J = 1.6 Hz, 1H), 6.86 (d, J = 8.8 Hz, 1H), 6.79-6.73 (m, 3H), 6.69 (dd, J_1 = 2 Hz, J_2 = 8.2 Hz, 1H), 6.61 (d, J = 2 Hz, 1H), 4.60-4.46 (m, 4H), 4.45-4.36 (m, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.80 (s, 3H), 3.02 (t, J = 7.2 Hz, 2H), 1.39 (d, J = 6 Hz, 6H), 1.38 (d, J = 6 Hz, 6H), 1.27 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 151.1, 149.3, 149.2, 147.4, 147.2, 145.0, 144.6, 130.7, 127.3, 126.4, 124.3, 121.6, 121.1, 118.1, 116.9, 116.4, 116.3, 113.6, 113.4, 112.4, 112.0, 106.6, 72.1, 71.6, 71.5, 56.1, 56.0, 55.98, 51.3, 37.7, 22.19 (2C), 22.16 (2C), 22.1 (2C). HRMS (ESI) m/z calcd for $C_{37}H_{46}NO_8$ $(M+H)^+$: 632.3218; found: 632.3211.

3-isopropoxy-4-methoxyphenyl 1-(3-isopropoxy-4-methoxyphenethyl)-4-(3-isopropoxy-4-methoxyphenyl)-1H-pyrrole-2-carboxylate (14b)**:** Following the general procedure 2, using acid **13** (0.54 g, 1.156 mmol, 1 equiv.) and **9c** [3-isopropoxy-4-methoxyphenol] (0.21 g, 1.156 mmol, 1 equiv.), **14b** was obtained as a pale yellow oil (0.68 g, 93% yield); R_f = 0.7 (20% EtOAc + pet. ether). IR (neat): ν_{max}1717, 1604, 1509, 1465, 1386, 1225, 1185, 1110, 1068, 1048, 1030, 990 cm^{-1}; ^{1}H

NMR (400 MHz, $CDCl_3$) 7.38 (d, J = 2 Hz, 1H), 7.02-6.99 (m, 2H), 6.91-6.89 (m, 2H), 6.86 (d, J = 8.8 Hz, 1H), 6.79-6.75 (m, 3H), 6.69 (dd, J_1 = 2 Hz, J_2 = 8 Hz, 1H), 6.62 (d, J = 2 Hz, 1H), 4.61-4.50 (m, 4H), 4.43-4.37 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.81 (s, 3H), 3.01 (t, J = 7.2 Hz, 2H), 1.40 (d, J = 6 Hz, 6H), 1.39 (d, J = 6 Hz, 6H), 1.27 (d, J = 6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 149.3, 149.2, 148.0, 147.8, 147.4, 147.2, 144.1, 130.7, 127.3, 126.4, 124.3, 121.6, 121.1, 118.0, 116.9, 116.3, 113.7, 113.6, 112.4, 112.0 (2C), 109.7, 71.6, 71.5 (2C), 56.4, 56.1, 56.0, 51.4, 37.7, 22.2 (2C), 22.1 (2C), 22.0 (2C). HRMS (ESI) m/z calcd for $C_{37}H_{46}NO_8$ $(M+H)^+$: 632.3218; found: 632.3214.

2,11-diisopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-3,12-dimethoxy-8,9-dihydro-6H-chromeno[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (15a): Following the general CDC reaction procedure 3, using **14a** (0.182 g, 0.28 mmol), **15a** was obtained as a white solid (0.071 g, 39% yield); R_f = 0.5 (30% EtOAc + pet. ether). IR (neat): ν_{max}2981, 2897, 1704, 1618, 1483, 1453, 1418, 1268, 1240, 1209, 1162, 1111, 1030 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08-7.03 (m, 3H), 6.90 (s, 1H), 6.76 (s, 1H), 6.73 (s, 1H), 6.65 (s, 1H), 4.86-4.79 (m, 1H), 4.78-4.71 (m, 1H), 4.58-4.47 (m, 2H), 3.98-3.94 (m, 1H), 3.93 (s, 3H), 3.86 (s, 3H), 3.34 (s, 3H), 3.09 (t, J = 6.8 Hz, 2H), 1.38 (d, J = 6 Hz, 3H), 1.37 (d, J = 6 Hz, 3H), 1.34 (d, J = 6 Hz, 3H), 1.32 (d, J = 6 Hz, 3H), 1.17 (d, J = 6 Hz, 3H), 1.16 (d, J = 6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 150.0, 149.8, 148.7, 148.2, 147.3, 146.1, 143.7, 136.0, 128.4, 128.1, 126.4, 123.4, 120.2, 117.4, 114.8, 114.7, 113.6, 112.7, 110.3, 109.1, 107.9, 100.8, 71.4, 71.2 (2C), 56.3, 56.1, 55.1, 42.5, 28.7, 22.1 (2C), 22.0, 21.9, 21.83, 21.79. HRMS (ESI) m/z calcd for $C_{37}H_{42}NO_8$ $(M+H)^+$: 628.2905; found: 628.2892.

***3,11-diisopropoxy-14-(4-isopropoxy-3-methoxyphenyl)-2,12-dimethoxy-8,9-dihydro-6H-chromeno[4',3':4,5]pyrrolo[2,1-a] isoquinolin-6-one (15b)*:** Following the general CDC reaction procedure 3, using **14b** (0.47 g, 0.75 mmol), **15b** was

obtained as a white solid (0.19 g, 40% yield); R_f = 0.4 (30% EtOAc + pet. ether). IR (neat): ν_{max} 2930, 1700, 1508, 1485, 1419, 1281, 1270, 1253, 1192, 1121, 1030, 1015, 930 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.10-7.03 (m, 3H), 6.92 (s, 1H), 6.77 (s, 1H), 6.72 (s, 1H), 6.66 (s, 1H), 4.85-4.72 (m, 2H), 4.63-4.50 (m, 3H), 3.92 (s, 3H), 3.43 (s, 3H), 3.34 (s, 3H), 3.10 (t, J = 6.4 Hz, 2H), 1.41-1.36 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 150.0, 148.6, 148.0, 147.3, 147.0, 146.5, 146.0, 136.0, 128.3, 127.9, 126.3, 123.6, 120.2, 117.8, 114.8, 114.6, 113.6, 112.6, 110.4, 109.1, 104.8, 103.4, 71.36, 71.34, 71.25, 56.3, 55.5, 55.1, 42.4, 28.6, 22.0 (2C), 22.0, 21.9, 21.8 (2C). HRMS (ESI) m/z calcd for $C_{37}H_{42}NO_8$ $(M+H)^+$: 628.2905; found: 628.2894.

***Lamellarin G*:** Deisopropylation on **15a** (0.020 g, 0.03 mmol) using general procedure 4, afforded lamellarin G as a white solid (0.014 g, 88% yield); R_f = 0.6 (70% EtOAc + pet. ether) which was spectroscopically found to be in good agreement with the earlier reported data.[19] IR (neat): ν_{max} 2977, 2931, 1637, 1561, 1542, 1509, 1458, 1439, 1420, 1383, 1260, 1187, 1137, 1109, 1067, 1048, 1032, 988 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.43 (br s, 1H), 9.30, (s, 1H), 8.99 (s, 1H), 7.13 (d, J = 8 Hz, 1H), 7.00 (s, 1H), 6.83 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz 1H), 6.81 (d, J = 2 Hz, 1H), 6.72 (s, 1H), 6.66 (s, 1H), 6.48 (s, 1H), 4.69-4.63 (m, 1H), 4.57-4.51 (m, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.25 (s, 3H), 2.98 (t, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.4, 147.9, 147.7, 147.5, 147.0, 146.0, 144.7, 142.8, 136.1, 127.2 (2C), 126.9, 121.5, 118.0, 117.6, 115.3, 114.4, 113.3, 112.6, 110.1, 109.2, 108.3, 100.8, 55.9, 55.8, 54.6, 42.0, 27.6.

***Lamellarin L*:** Deisopropylation on **15b** (0.030 g, 0.04 mmol) using general procedure 4, afforded lamellarin L as a white solid (0.020 g, 83% yield); R_f = 0.4 (70% EtOAc + pet. ether) which was spectroscopically found to be in good agreement with the earlier reported data.[20] IR (neat): ν_{max} 1685, 1582, 1481, 1431, 1276, 1242, 1231, 1167, 1048 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.78 (s, 1H), 9.53 (s, 1H), 9.40 (s, 1H), 7.15 (d, J = 8.0 Hz, 1H), 6.90-6.87 (m, 2H), 6.79 (s, 1H), 6.74 (s, 1H), 6.67 (s, 1H), 6.65 (s,

1H), 4.65-4.58 (m, 1H), 4.56-4.50 (m, 1H), 3.81 (s, 3H), 3.36 (s, 3H), 3.27 (s, 3H), 2.99 (t, J = 6.8 Hz, 2H) ;^{13}C NMR (100 MHz, DMSO-d_6) δ 154.5, 147.8, 147.7, 147.3, 147.0, 146.2, 145.8, 144.7, 136.0, 127.7, 127.5, 127.4, 121.9, 118.2, 118.0, 115.5, 114.2, 113.6, 112.5, 109.4, 108.9, 105.2, 103.8, 56.2, 55.2, 54.9, 42.2, 27.7. HRMS (ESI) m/z calcd for $C_{28}H_{24}NO_8$ $(M+H)^+$: 502.1496; found: 502.1489.

***3,11-diisopropoxy-14-(4-isopropoxy-3-methoxyphenyl)-2,12-dimethoxy-6H-chromeno[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (16)*:** To the solution of pentacyclic coumarin fused pyrrolo-dihydroisoquinolines **15b** (0.020 g, 0.03 mmol, 1 equiv.) in DCM (1 mL), DDQ (0.017 g, 0.075 mmol, 2.5 equiv.) was added at rt. The reaction was then allowed to stir at room temperature for 12 h until complete consumption of starting material was indicated by TLC analysis. Subjection of the crude reaction mixture to SiO_2-gel flash column chromatography afforded **16** as a white solid (0.019 g, 96% yield); R_f = 0.5 (30% EtOAc + pet. ether). IR (neat): ν_{max}2924, 1693, 1519, 1480, 1434, 1286, 1229, 1180, 1110, 1039, 945, 859 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (d, J = 7.2 Hz, 1H), 7.19 (dd, J_1 = 2 Hz, J_2 = 8 Hz, 1H), 7.17 (s, 1H), 7.15 (d, J = 8 Hz, 1H), 7.13 (d, J = 2 Hz, 1H), 7.10 (s, 1H), 7.03 (d, J = 7.2 Hz, 1H), 6.96 (s, 1H), 6.75 (s, 1H), 4.74-4.67 (m, 1H), 4.63-4.50 (m, 2H), 3.96 (s, 3H), 3.45 (s, 3H), 3.44 (s, 3H), 1.43 (d, J = 6 Hz, 6H), 1.40 (d, J = 6 Hz, 6H), 1.35 (d, J = 6 Hz, 3H), 1.34 (d, J = 6 Hz, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 150.2, 148.5, 148.1, 147.9, 146.6, 146.5, 134.6, 129.6, 128.2, 124.7, 124.1, 123.2, 119.0, 118.0, 112.6, 112.4 (2C), 111.1, 110.3, 109.9, 107.7, 105.6, 105.4, 103.3, 71.4, 71.2, 71.1, 56.4, 55.5, 55.1, 21.9 (2C), 21.85 (2C), 21.79 (2C). HRMS (ESI) m/z calcd for $C_{37}H_{40}NO_8$ $(M+H)^+$: 628.2748; found: 628.2738.

***Lamellarin N*:** BCl_3 mediated deisopropylation on **16** (0.025 g, 0.04 mmol) using general procedure 4, afforded lamellarin N as a white solid (0.017 g, 85% yield); R_f = 0.3 (70% EtOAc + pet. ether) which was spectroscopically found to be in good

agreement with the earlier reported data.[20] IR (neat): 1670, 1588, 1491, 1465, 1256, 1210, 1022, 1012, 955, 860 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.98 (br s, 1H), 9.88 (br s, 1H), 9.42 (s, 1H), 9.01 (d, J = 7.2 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.19 (s, 1H), 7.17 (s, 1H), 7.04-7.01 (m, 2H), 6.87 (s, 1H), 6.76 (s, 1H), 3.87 (s, 3H), 3.40 (s, 3H), 3.39 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.4, 148.6, 148.4, 148.0, 147.9, 147.7, 146.4, 144.6, 133.9, 128.8, 127.4, 124.7, 122.2, 122.1, 118.3, 117.5, 113.7, 112.5, 111.6, 110.6, 108.3, 106.5, 105.7, 105.3, 103.8, 56.2, 55.0, 54.6.

***Gram Scale Synthesis of Ethyl 4-(4-isopropoxy-3-methoxyphenyl)-1-(3-isopropoxy-4-methoxy-phenethyl)-1H-pyrrole-2-carboxylate (17)*:** As per the general procedure 3, using **5** [ethyl 1-(3-isopropoxy-4-methoxyphenethyl)aziridine-2-carboxylate] (1.33 g, 4.36 mmol, 1 equiv.) and **6c** [(*Z*)-4-(2-bromo-2-nitrovinyl)-1-isopropoxy-2-methoxybenzene] (1.37 g, 4.36 mmol, 1 equiv.) with a reaction time of 5 h, **17** was obtained after flash column chromatography as pale yellow oil (1.85 g, 86% yield); R_f = 0.47; (20% EtOAc + pet. ether). IR (neat): ν_{max}1696, 1633, 1513, 1470, 1423, 1383, 1249, 1196, 1137, 1092, 1033, 801 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 2 Hz, 1H), 6.94-6.91 (m, 2H), 6.85 (d, J = 8.8 Hz, 1H), 6.79 (d, J = 2.4 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 6.69 (dd, J_1 = 2 Hz, J_2 = 8 Hz, 1H), 6.59 (d, J = 2 Hz, 1H), 4.53-4.47 (m, 3H), 4.43-4.37 (m, 1H), 4.32 (q, J = 7.2 Hz, 2H), 3.88 (s, 3H), 3.81 (s, 3H), 2.98 (t, J = 6.8 Hz, 2H), 1.39 (t, J =6.8 Hz, 3H), 1.36 (d, J = 6 Hz, 6H), 1.27 (d, J = 6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.1, 150.6, 149.1, 147.2, 145.8, 130.9, 128.2, 125.4, 123.8, 122.1, 121.4, 117.4, 116.8, 116.5, 115.2, 112.0, 109.4, 71.6, 71.5, 60.0, 56.0, 55.97, 51.3, 37.7, 22.1 (2C), 22.0 (2C), 14.5. HRMS (ESI) m/z calcd for $C_{29}H_{38}NO_6$ $(M+H)^+$: 496.2694; found: 496.2689.

***4-(4-isopropoxy-3-methoxyphenyl)-1-(3-isopropoxy-4-methoxyphenethyl)-1H-pyrrole-2-carboxylic acid (18)*:** Applying the saponification procedure described for

accessing acid **8**, hydrolysis of ester **17** (0.55 g, 1.11 mmol, 1 equiv.) in EtOH : H_2O (3:1, 15 mL) using crushed NaOH pellets (0.22 g, 5.55 mmol, 5 equiv.) with reaction time of 5 h furnished the pure acid **18** as a white solid (0.46 g, 90% yield); R_f = 0.5 (50% EtOAc + pet. ether); mp 114-116°C. IR (neat): ν_{max} 1723, 1659, 1564, 1547, 1512, 1478, 1462, 1257, 1235, 1194, 1141, 1112, 1036, 954 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 2 Hz, 1H), 6.95-6.92 (m, 2H), 6.89-6.87 (m, 2H), 6.80 (d, J = 8.0 Hz, 1H), 6.69 (dd, J_1 = 2 Hz, J_2 = 8.4 Hz, 1H), 6.64 (d, J = 2 Hz, 1H), 4.54-4.47 (m, 3H), 4.45-4.42 (m, 1H), 3.89 (s, 3H), 3.82 (s, 3H), 3.02 (t, J = 7.2 Hz, 2H), 1.37 (d, J = 6 Hz, 6H), 1.30 (d, J = 6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 150.7, 149.2, 147.3, 146.0, 130.8, 127.8, 126.9, 124.4, 121.3, 120.9, 117.4, 117.2, 116.6, 116.5, 112.1, 109.4, 71.7, 71.4, 56.0, 55.9, 51.6, 37.7, 22.14 (2C), 22.11 (2C). HRMS (ESI) m/z calcd for $C_{27}H_{34}NO_6$ $(M+H)^+$: 468.2381; found: 468.2376.

***3-isopropoxy-4-methoxyphenyl 4-(4-isopropoxy-3-methoxyphenyl)-1-(3-isopropoxy-4-methoxyphenethyl)-1H-pyrrole-2-carboxylate (19)*:** Following the general procedure 2, using acid **18** (0.50 g, 1.08 mmol, 1 equiv.) and **9c** [3-isopropoxy-4-methoxyphenol] (0.20 g, 1.08 mmol, 1 equiv.), **19** was obtained as a pale yellow oil (0.607 g, 89% yield); R_f = 0.3 (20% EtOAc + pet. ether). IR (neat): ν_{max}1714, 1606, 1512, 1470, 1423, 1384, 1226, 1185, 1137, 1110, 1068, 1048, 987 cm^{-1}; ^1H NMR (400 MHz, DCl_3) 7.40 (d, J = 1.2 Hz, 1H), 6.98-6.96 (m, 2H), 6.92-6.87 (m, 3H), 6.79-6.73 (m, 3H), 6.69 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 6.61 (d, J = 2 Hz, 1H), 4.56-4.49 (m, 4H), 4.42-4.36 (m, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.81 (s, 3H), 3.01 (t, J = 7.2 Hz, 2H), 1.40 (d, J = 6 Hz, 6H), 1.37 (d, J = 6.4 Hz, 6H), 1.26 (d, J = 6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 150.6, 149.1, 147.9, 147.7, 147.0, 145.9, 144.0, 130.6, 127.7, 126.4, 124.2, 121.5, 121.0, 117.4, 116.8, 116.4, 116.3, 113.5, 112.02, 111.99, 109.7, 109.4, 71.6, 71.4 (2C), 56.3, 55.9 (2C), 51.3, 37.6, 22.1(2C), 22.0 (2C), 21.9 (2C). HRMS (ESI) m/z calcd for $C_{37}H_{46}NO_8$ $(M+H)^+$: 632.3218; found: 632.3211

3,11-diisopropoxy-14-(4-isopropoxy-3-methoxyphenyl)-2,12-dimethoxy-8,9-dihydro-6H-chromeno[4',3':4,5]pyrrolo[2,1-a] isoquinolin-6-one (20): Following the general CDC reaction procedure 3, using **19** (0.47 g, 0.75 mmol), pentacyclic lactone **20** was obtained as a white solid (0.19 g, 40% yield); R_f = 0.4 (30% EtOAc + pet. ether). IR (neat): ν_{max} 2930, 1700, 1508, 1485, 1419, 1281, 1270, 1253, 1192, 1121, 1030, 1015, 930 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.10-7.03 (m, 3H), 6.91 (s, 1H), 6.76 (s, 1H), 6.73 (s, 1H), 6.66 (s, 1H), 4.85-4.72 (m, 2H), 4.63-4.50 (m, 3H), 3.81 (s, 3H), 3.42 (s, 3H), 3.33 (s, 3H), 3.09 (t, J = 6.4 Hz, 2H), 1.41-1.36 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 151.3, 148.6, 147.3, 147.0, 146.9, 146.5, 146.0, 136.0, 128.6, 128.2, 126.4, 123.4, 120.2, 116.9, 114.9, 114.65, 114.61, 113.7, 110.4, 109.2, 104.9, 103.5, 71.8, 71.45, 71.36, 56.2, 55.5, 55.1, 42.5, 28.6, 22.1 (2C), 21.94, 21.89, 21.83 (2C). HRMS (ESI) m/z calcd for $C_{37}H_{42}NO_8$ $(M+H)^+$: 628.2905; found: 628.2894.

3,11-diisopropoxy-14-(4-isopropoxy-3-methoxyphenyl)-2,12-dimethoxy-6H-chromeno[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (21): Applying the same oxidation procedure as described for synthesis of **16**, oxidation of **20** (0.020 g, 0.03 mmol, 1 equiv.) using DDQ (0.017 g, 0.075 mmol, 2.5 equiv.) afforded **21** as a white solid (0.019 g, 96% yield); R_f = 0.5 (30% EtOAc + pet. ether). IR (neat): ν_{max}2924, 1693, 1519, 1480, 1434, 1286, 1229, 1180, 1110, 1039, 945, 859 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.22 (d, J = 7.2 Hz, 1H), 7.18-7.17 (m, 3H), 7.12 (s, 1H), 7.09 (s, 1H), 7.02 (d, J = 7.6 Hz, 1H), 6.96 (s, 1H), 6.75 (s, 1H), 4.72-4.67 (m, 1H), 4.66-4.61 (m, 1H), 4.60-4.54 (m, 1H), 3.84 (s, 3H), 3.44 (s, 3H), 3.43 (s, 3H), 1.43 (d, J = 6 Hz, 12H), 1.40 (d, J = 6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 151.4, 150.2, 148.5, 147.9, 147.2, 146.6, 146.5, 134.5, 129.5, 128.8, 124.8, 123.9, 123.2, 119.0, 116.8, 115.0, 112.4, 111.1, 110.4, 110.0, 107.8, 105.7, 105.4, 103.4, 71.8, 71.5, 71.2, 56.2,

55.4, 55.2, 21.9 (3C), 21.88, 21.84, 21.82. HRMS (ESI) m/z calcd for $C_{37}H_{40}NO_8$ $(M+H)^+$: 628.2748; found: 628.2738.

***Lamellarin D*:** BCl_3 mediated deisopropylation on **21** (0.025 g, 0.04 mmol) using general procedure 4, afforded lamellarin D as a white solid (0.020 g, 80% yield); R_f = 0.4 (80% EtOAc + pet. ether) which was spectroscopically found to be in good agreement with the earlier reported data.[7b] IR (neat): 1670, 1598, 1556, 1491, 1499, 1433, 1404, 1359, 1277 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.90 (br s,2H), 9.39 (br s, 1H), 9.02 (d, J = 7.6 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.21 (s, 1H), 7.17 (d, J = 1.6 Hz, 1H), 7.15 (s, 1H), 7.11 (d, J = 8.0 Hz, 1H), 7.03 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H), 6.88 (s, 1H), 6.73 (s, 1H), 3.79 (s, 3H), 3.39 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.4, 148.7, 148.5, 148.4, 147.9, 146.8, 146.4, 144.6, 134.1, 129.0, 125.5, 124.7, 123.8, 122.1, 117.6, 116.4, 115.0, 112.4, 111.5, 110.9, 108.4, 106.4, 105.7, 105.4, 103.8, 56.0, 55.1, 54.5. HRMS (ESI) m/z calcd for $C_{28}H_{21}NO_8$ $(M+H)^+$: 500.1340; found: 500.1335.

Supporting Information

^1H and ^{13}C spectral copies of the synthesized compounds.

Supporting Information File 1:

File Name: Supporting Information

File Format: PDF

Acknowledgements

We are grateful to Dr. Sapna Tripathi Khan for proof reading the manuscript.

Funding

Funding text T. K. gratefully acknowledges the financial support from the Council of Scientific and Industrial Research (CSIR), India (Grant No. 02(0320)/17/EMR-II) as well as Science and Engineering Research Board (SERB), DST, India (Grant No. CRG/2019/002595). V.K is thankful to MHRD for the financial support during his Ph.D. A.S. and D.K. acknowledges the financial support in the form of SRF from DST/CSIR and UGC respectively. All the authors also acknowledge the financial and infrastructural support from IIT Bhubaneswar.

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