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Total Syntheses of Lamellarin D and H. The First Synthesis of Lamellarin-Class Marine Alkaloids

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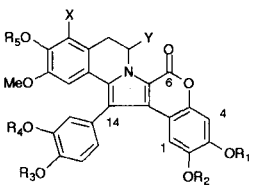
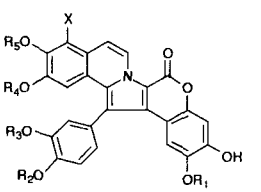
Abstract: Total syntheses of marine polyaromatic alkaloids, lamellarin D (**1**) and H (**2**), are described. The pentacyclic lamellarin ring system was constructed by *N*-ylide mediated pyrrole ring formation and subsequent lactonization of **4** obtained by an assembly of known benzylisoquinoline **5**, benzoate **6** and ethyl bromoacetate. © 1997 Elsevier Science Ltd.

INTRODUCTION

The polycyclic aromatic marine alkaloids, lamellarin A~D, were first isolated from the prosobranch mollusc *Lamellaria* sp. by Faulkner and co-workers[1] in 1985. Later on, in 1988, four additional members, lamellarin E~H, were isolated from the ascidian *Didemnum cartaceum* by Fenical and co-workers.[2] More recently, further six new alkaloids, lamellarin I~N, along with lamellarin A~D were also isolated from the ascidian *Didemnum* sp. by Australian researchers.[3] These isolation studies suggested that lamellarin A~D, obtained from *Lamellaria* sp., were most likely sequestered from the ascidian in the diet of this mollusc.[2,3]



lamellarin	R_1	R_2	R_3	R_4	R_5	X	Y
A	H	Me	H	Me	Me	OMe	OH
C	H	Me	H	Me	Me	OMe	H
E	H	Me	Me	H	Me	OH	H
F	H	Me	Me	Me	Me	OH	H
G	Me	H	Me	H	H	H	H
I	H	Me	Me	Me	Me	OMe	H
J	H	Me	Me	Me	H	H	H
K	H	Me	H	Me	Me	OH	H
L	H	Me	Me	H	H	H	H



lamellarin	R_1	R_2	R_3	R_4	R_5	X
B	Me	H	Me	Me	Me	OMe
D (1)	Me	H	Me	Me	H	H
H (2)	H	H	H	H	H	H
M	Me	H	Me	Me	Me	OH
N	Me	Me	H	Me	H	H

Fig. 1. Lamellarin-Class Alkaloids

The structures of lamellarin-class alkaloids have been characterized as the oxygenated pentacyclic heterocycle (6*H*-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-*a*] isoquinolin-6-one system) possessing an additional aromatic ring at C-14. This aromatic ring is rotationally highly restricted (>600 kcal/mol : MM2 calculation) and exists in essentially orthogonal to the plane of pentacyclic ring.[1] Thus, these molecules should exist as chiral form due to the atropisomerism. Interestingly, however, all natural products so far isolated were racemic.

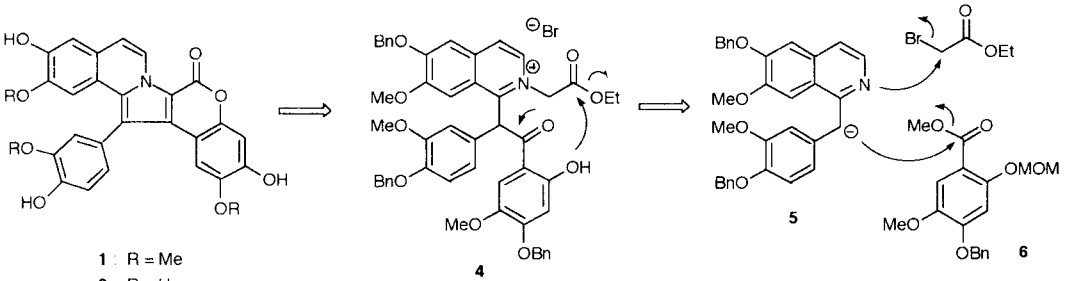
A biological activity of lamellarin A~D was initially tested by Faulkner's group,[1] and lamellarin D and C were shown to inhibit cell division of sea urchin egg at concentration of 19 μg/mL (lamellarin D, 78% inhibition; lamellarin C, 15% inhibition). Recently, lamellarins I, K and L have found to exhibit comparable and significant cytotoxicity against P388 and A549 cell lines, respectively, in culture ($IC_{50} \approx 0.25$ μg/mL against each cell line) and lamellarins K and L have also found to possess moderate immunomodulatory activity (for lamellarins K and L, LcV:MLR 147 and 98, respectively).[3]

Due to the fascinating novel structures and biological activities, we had started synthetic studies for lamellarin-class alkaloids. In this paper, we describe the first total syntheses of lamellarin D and H, based upon practically useful synthetic route.

RESULTS AND DISCUSSIONS

Synthetic Plan

Our retro-synthetic analysis of lamellarin D is shown in **Scheme 1**. We envisaged that the lamellarin ring system (6*H*[1]benzopyrano[4',3';4'5]pyrrolo[2,1-*a*]isoquinolin-6-one) could be constructed by the *N*-ylide-mediated pyrrole ring formation[4] of quaternary ammonium salt **4**, and subsequent lactonization. The key intermediate **4** should be assembled by condensation of known benzylisoquinoline **5**[5a] with benzoate **6**, followed by quaterization of isoquinoline nitrogen with ethyl bromoacetate.



Scheme 1

Model Study

Prior to the synthesis of lamellarin D and H, a model experiment for construction of the lamellarin framework was performed using a commercially available benzylisoquinoline **7** and a simple benzoate **8** (**Scheme 2**).

Lithiation of papaverine (**7**) with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) formed a deep red solution of the corresponding benzyl anion, which on treatment with benzoate **8** afforded a tautomeric mixture[6] of the acylated products in 70% yield. Mondelli and Merlini[6a] have reported for a related 2-substituted quinoline

system that the acetonyl derivative exists as a tautomeric mixture composed of 75% of the enamino-keto form **13b** and 25% of the iminic form **13a** in $CDCl_3$. They also described that the signals of both H-3 and H-4 of **13b** are shifted ca. 0.6 ppm upfield and their coupling constant increases by 1.0 Hz compared with those of **13a** due to the loss of the ring current contribution of the aromatic nucleus (**Fig. 2**). On the contrary, in our case, the major isomer was found to be the iminic form **9a** on the basis of ^1H and ^{13}C NMR spectra of the mixture,

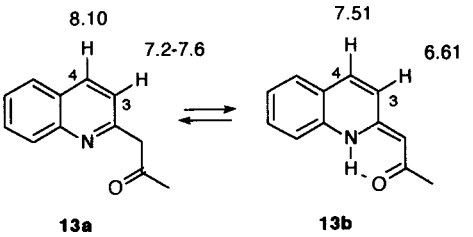
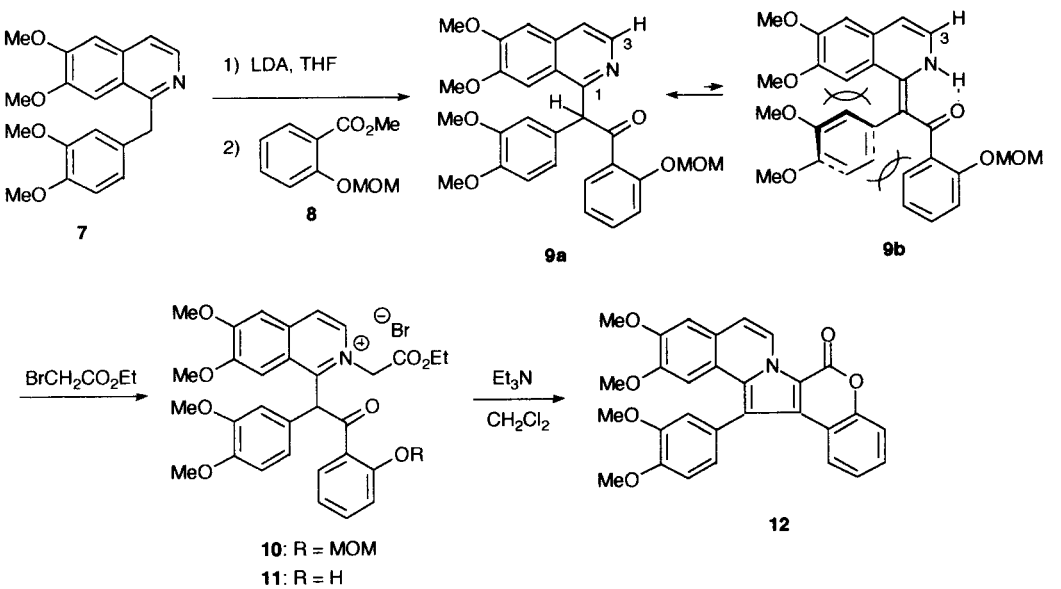


Fig. 2

which clearly indicated the presence of a benzylic methine α to the carbonyl due to the signals at δ_H 6.69 ppm (singlet) and δ_C 99.4 ppm (CH), respectively. The assignment was further supported by the appearance of a correlation peak between the above two signals in the ^1H-^{13}C COSY spectrum. For the minor isomer, the enamino-ketonic structure **9b** was suggested from the minor peaks in the ^1H NMR spectrum, in which a signal due to H-3 of **9b** (δ 7.59 ppm, d, J=6.4 Hz) was observed 0.67 ppm upfield to that of **9a** (δ 8.26 ppm, d, J=5.7 Hz). From the integration intensities of the two signals, the ratio of the tautomers in $CDCl_3$ was determined to be **9a**:**9b**=92:8. The minor formation of **9b** would be due to the steric repulsion between the aromatic nuclei in the resonated planar structure stabilized by the intramolecular hydrogen bonding.



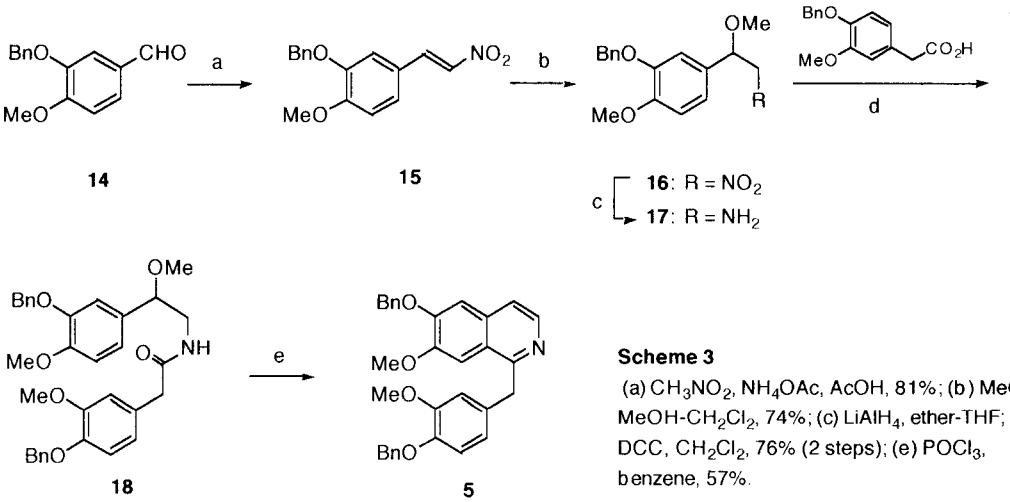
Scheme 2

Heating of the tautomeric mixture together with excess ethyl bromoacetate (10 equiv.) at 70-75 °C gave the corresponding quaternary ammonium salt (**10**). In the reaction, a part of the methoxymethyl (MOM) ether cleaved and the product was obtained as a mixture of **10** and **11**. Without separation, the mixture was exposed in methanolic HCl to effect complete removal of the resisted MOM group. Addition of excess triethylamine to a

CH_2Cl_2 solution of **11** formed a deep purple solution typical for its *N*-ylide,[4] which, on refluxing for 3 hours, underwent dehydrative cyclization with simultaneous aromatization and lactonization to furnish 6*H*[1]benzopyrano[4',3';4'5]pyrrolo[2,1-*a*]isoquinolin-6-one **12** in 33% yield for the three steps.

Synthesis of 6-Benzyloxy-1-(4-benzyloxy-3-methoxybenzyl)-7-methoxyisoquinoline (5)

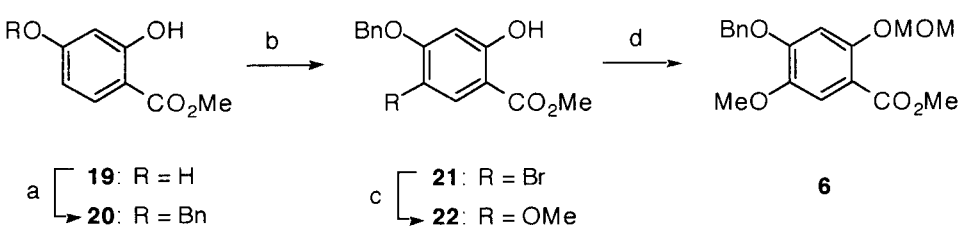
Benzylisoquinoline **5** required for the syntheses of lamellarins was prepared according to a well-known procedure[5] as shown in **Scheme 3**. For large scale preparation we slightly modified the reported procedure[5a] and could somewhat improve the yield of each step.



Scheme 3
(a) CH_3NO_2, NH_4OAc, AcOH, 81%; (b) MeONa, MeOH-CH_2Cl_2, 74%; (c) $LiAlH_4$, ether-THF; (d) DCC, CH_2Cl_2, 76% (2 steps); (e) $POCl_3$, benzene, 57%.

Synthesis of Methyl 4-Benzyloxy-5-methoxy-2-methoxymethoxybenzoate (6)

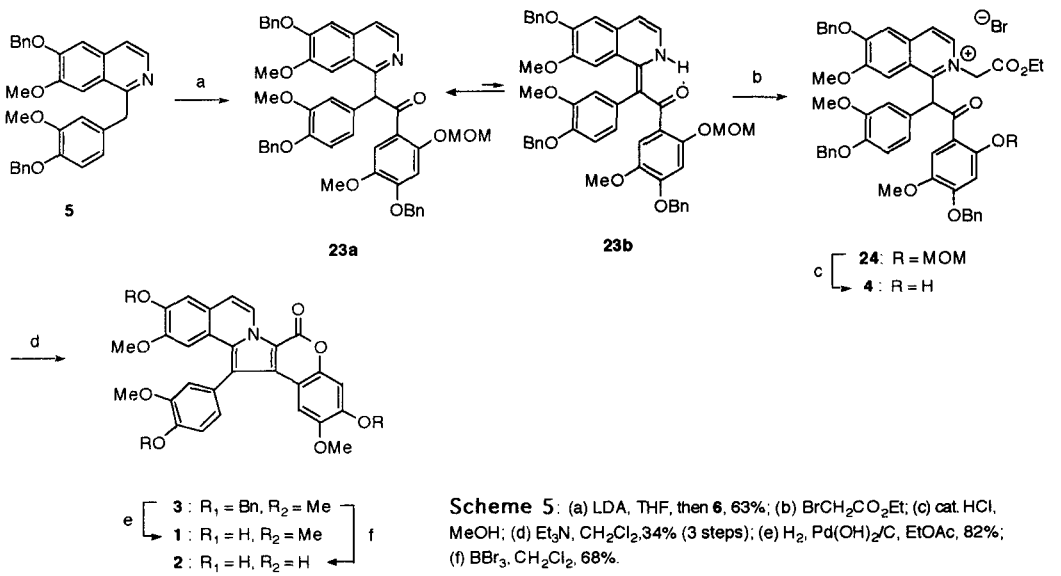
Another synthon, 4-benzyloxy-3-methoxy-6-methoxymethoxybenzoate (**6**) was readily obtained by a four-steps synthesis from methyl 2,4-dihydroxybenzoate (**19**) in 49% overall yield (**Scheme 4**). Monobenzylation of **19** using 1.2 equiv. of benzyl bromide and K_2CO_3 in refluxing acetone gave the 4-*O*-benzylated product **20**,[8] whose bromination took place exclusively at 5-position, giving **21**. Copper(II)-assisted replacement[9] of the bromine atom of **21** with methoxy group followed by protection of the phenolic hydroxyl group of **22** as MOM ether afforded benzoate **6**.



Scheme 4: (a) BnBr, K_2CO_3, acetone, 91%; (b) Br_2, $CHCl_3$, 91%; (c) MeONa, $CuCl_2$, DMF-MeOH, 63%; (d) MOMCl, *t*-BuOK, THF, 94%.

Synthesis of Lamellarin D and H

The synthesis of lamellarins was commenced with the condensation of benzylisoquinoline **5** with benzoate **6** (**Scheme 5**). In order to optimize the reaction, we examined the reaction with variation in base and reaction condition (**Table 1**). For metalation of benzylisoquinoline **5**, LDA was found to be most effective among the three different bases tested (run 1, 5 and 6). We next optimized the amount of LDA by using 1.1, 1.5 or 2.0 equivalent of the base. Surprisingly, the best result was obtained when almost equimolar LDA was used (run 1) and the yield of the products (**23a** and **23b**) lowered with increasing amount of LDA (run 2 and 3), although the major product **23a** is enolizable. Prolonged reaction of the lithium salt with benzoate **6** also decreased the yield of **23a,b** (run 4). In most cases in which the reactions resulted in low yields, a considerable amount of starting **5** and/or **6**, presumably formed *via* a retro reaction of once formed **23a,b** under the basic condition, was recovered from a complex mixture of products.



Scheme 5: (a) LDA, THF, then **6**, 63%; (b) $BrCH_2CO_2Et$; (c) cat. HCl, MeOH; (d) Et_3N, CH_2Cl_2,34% (3 steps); (e) H_2, $Pd(OH)_2/C$, EtOAc, 82%; (f) BBr_3, CH_2Cl_2, 68%.

Table 1. Condensation of **5** with **6**.

run	base	equiv.	condition 1[a]	condition 2[b]	yield
1	LDA	1.1	-78 to -15 °C, 1 h	rt, 3.5 h	63%
2	LDA	1.5	-78 to -15 °C, 1.5 h	rt, 3.5 h	51%
3	LDA	2.0	-78 to -15 °C, 1 h	rt, 3.5 h	21%
4	LDA	1.2	-78 to -15 °C, 1 h	rt, 14 h	trace[c]
5	$LiN(TMS)_2$	1.2	-20 °C, 1 h	rt, 3 h	13%
6	*t*-BuOK-BuLi	1.2	-78 °C, 1 h	0 °C, 4 h	0%

[a] reaction conditions on generation of the anion of **5**.
[b] conditions in the reaction of the anion of **5** with **6**.
[c] 68% of **5** was recovered

Construction of the lamellarin framework from a mixture of **23a** and **23b** involves (1) quaterization with haloacetate, (2) removal of the MOM protecting group, and (3) pyrrole ring formation and subsequent lactonization. The three-steps sequence can be operated virtually in a one-pot procedure. The first quaterization required heating of **23a,b** with excess ethyl bromoacetate, however, elevated temperature (run 5) or prolonged reaction period (run 4) caused serious problem in decreasing the yield of **3** due to structural decomposition (**Table 2**). Use of more reactive iodide (run 7) or triflate[10] (run 8) instead of the bromide or acetone as the solvent (run 6) could not improve the yield of **3**. In an optimized condition, compound **3** was obtained in 34% overall yield by heating a mixture of **23a** and **23b** with 20 equivalent of ethyl bromoacetate at 70 °C for 22 hours, followed by exposure to methanolic hydrochloric acid (**24** → **4**), and finally treatment of **4** with excess triethylamine in MeOH at reflux.

Table 2. Construction of the Lamellarin Framework

run	haloacetate	condition	yield of **3**[c]
1	$BrCH_2CO_2Et$	50 °C, 24 h	19%
2	$BrCH_2CO_2Et$	50 °C, 96 h	31%
3	$BrCH_2CO_2Et$	70 °C, 22 h	34%
4	$BrCH_2CO_2Et$	70 °C, 65 h	6%
5	$BrCH_2CO_2Et$	140 °C, 6 h	7%
6	$BrCH_2CO_2Et$	reflux, 96 h[a]	29%
7	ICH_2CO_2Et	65 °C, 24 h	27%
8	$TfOCH_2CO_2Et$	reflux, 7 h[b]	20%

[a] acetone was used as the solvent.
[b] $CHCl_3$ was used as the solvent.
[c] Overall yield from a mixture of **23a** and **23b**.

Finally, the synthesis of lamellarin D (**1**) was accomplished by hydrogenolysis of the benzyl groups of **4** over Parlman catalyst[11] (82% yield). Cleavage of both methyl and benzyl ether linkages in **4** using 6 molar equivalent of boron tribromide afforded lamellarin H (**2**) in 68% yield. The spectroscopic properties (^1H NMR, MS) of both synthetic lamellarin D and H agreed with the data for the natural products.[1,2] In addition, ^1H NMR spectrum of the triacetate of synthetic **1** was completely superimposed on that of natural lamellarin D triacetate.

CONCLUSION

We have accomplished the first total syntheses of lamellarin D and H in five steps each in 18 and 15% total yield, respectively, starting from the condensation between readily accessible benzylisoquinoline **5** and benzoate **6**. Further transformations of the key intermediate **3** to the derivatives of 3-hydroxy and 3,4-dihydroisoquinoline types as well as total syntheses of the other members of lamellarin-class alkaloids are in progress.

EXPERIMENTAL

General. Melting points (mp) were uncorrected. Unless otherwise stated, ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian Gemini 200, a Gemini 300, or an UNITY plus 500 instruments at nearly 200, 300, or 500 MHz, respectively. ^{13}C NMR were recorded on an UNITY plus 500 instrument in $CDCl_3$. EI and FAB mass spectra (MS) were recorded on a JOEL JMS-DX303 spectrometer. IR and UV/Vis spectra were recorded on a JASCO IR-810 spectrometer and a Shimadzu UV-2100 spectrophotometer, respectively. Dry tetrahydrofuran (THF) and ether were distilled from sodium metal/benzophenone ketyl under an atmosphere of dry nitrogen prior to use. Dichloromethane (CH_2Cl_2) and chloroform ($CHCl_3$) used as dry solvents were distilled from phosphrous pentoxide. Dimethylformamide (DMF) was distilled from calcium hydride under reduced pressure. Diisopropylamine was distilled from sodium hydride under an atmosphere of dry argon.

6,7-Dimethoxy-1-[1-(3,4-dimethoxyphenyl)-2-(2-methoxymethoxyphenyl)-2-oxoethyl]isoquinolines (9a and 9b). To a stirred and cooled (-78 °C) solution of LDA, prepared from a 1.6 M hexane solution of BuLi (3.28 mL, 5.25 mmol) and *i*-Pr_2NH (0.69 mL, 5.25 mmol) in dry THF (20 mL), was added as drops a solution of papaverine (7, 1.70 g, 5.00 mmol) in THF (20 mL) under Ar. The resulting deep red solution was stirred at that temperature for 1 h and benzoate **8** dissolved in THF (3 mL) was then injected. The cooling bath was removed and the whole was stirred at rt for 20 h. The mixture was poured into 10% aq. NH_4Cl solution (100 mL) and extracted twice with CH_2Cl_2 (50 mL x 2). After drying (Na_2SO_4) and removing the solvent, the oily residue was chromatographed on silica gel (CH_2Cl_2:acetone=9:1) to give a 92:8 (based on NMR) mixture of tautomeric **9a** and **9b** (1.77 g, 3.53 mmol, 71%) as a yellow amorphous powder. The major isomer **9a**: ^{1}H NMR (500 MHz) δ 2.92 (s, 3H), 3.76 (s, 3H), 3.83 (s, 3H), 3.88 (s, 3H), 3.99 (s, 3H), 4.66 (dd, 2H, J=18.77, 6.87 Hz), 6.68 (s, 1H), 6.80 (d, 1H, J=8.01 Hz), 6.83-6.90 (m, 2H), 7.02-7.06 (m, 2H), 7.03 (s, 1H), 7.33-7.37(m, 1H), 7.35 (d, 1H, J=5.95 Hz), 7.39 (s, 1H), 8.02 (dd, 1H, J=7.78, 1.60 Hz), 8.26 (d, 1H, J=5.49 Hz); ^{13}C NMR δ 55.75 (CH_3), 55.82 (CH_3 x 2), 55.88 (CH_3), 56.05 (CH_3), 62.68 (CH), 94.45 (CH_2), 103.85 (CH), 105.41 (CH), 110.96 (CH), 113.34 (CH), 114.73 (CH), 118.57 (CH), 121.97 (CH x 2), 122.86 (C), 128.39 (C), 130.88 (C), 131.74 (CH_2), 133.36 (CH_2), 133.45 (C), 140.77 (CH), 148.23 (C), 148.89 (C), 149.89 (C), 152.34 (C), 155.83 (C), 157.57 (C), 197.43 (C); IR ($CHCl_3$) ν_{max} 1158, 1205, 1270, 1480, 1508, 1590, 1680, 3010 cm^{-1}. *Anal.* Calcd. for $C_{29}H_{29}NO_7$: C, 69.17; H, 5.81; N, 2.78. Found: C, 68.96; H, 5.92; N, 2.79.

11,12-Dimethoxy-14-(3,4-dimethoxyphenyl)-6*H*[1]benzopyrano[4',3';4,5]pyrrolo[2,1-a]isoquinoline-6-one (12). A mixture of **9** (154 mg, 0.309 mmol) and ethyl bromoacetate (517 mg, 3.10 mmol) was heated at 70-75 °C for 20 h under Ar. The mixture was dissolved in a minimum amount of CH_2Cl_2 (2 mL) and poured into dry ether (15 mL). The precipitated solid was collected and washed with dry ether to give 219 mg of a mixture of the salts **10** and **11**.

The crude salts were dissolved in MeOH (10 mL) containing one drop of conc. HCl and the solution was heated under reflux for 30 min. The mixture was concentrated *in vacuo* to give crude **11**.

The crude product was dissolved in dry $CHCl_3$ (5 mL) and Et_3N (0.250 mL, 1.79 mmol) was added. The resulting deep purple solution was allowed to stand at rt for 1.5 days and then heated under reflux for 30 min, at which time the purple color disappeared. The mixture was then concentrated and the residue was chromatographed on silica gel to give crude **12** (88 mg). Recrystallization from CH_2Cl_2-hexane (1:1) gave pure **12** as fine needles,

mp 254-256 °C: ^{1}H NMR (300 MHz) δ 3.47 (s, 3H), 3.87 (s, 3H), 3.99 (s, 3H), 4.03 (s, 3H), 7.03-7.20 (m, 6H), 7.26-7.46 (m, 4H), 9.28 (d, 1H, J=7.4 Hz); EI-MS *m/z* (relative intensity) 482 ([M+1]$^+$, 32.6), 481 (M$^+$, 100). Anal. Calcd. for $C_{29}H_{23}NO_6$: C, 72.34; H, 4.81; N, 2.91. Found: C, 71.59; H, 4.82; N, 2.93.

1-(3-Benzyloxy-4-methoxyphenyl)-2-nitroethene (15). A solution of *O*-benzylisovanillin (**14**, 30.00 g, 0.1238 mol), nitromethane (16.8 mL, 0.310 mol) and NH_4OAc (10.50 g, 0.1362 mol) in AcOH (100 mL) was heated under reflux for 2 h. The yellow crystals appeared on cooling the solution were collected and washed with cold EtOH (10 mL x 2), giving **15** (26.50 g) as yellow plates, mp 129-130 °C (lit.[5b] mp 125-127 °C). The mother liquid was poured into water (350 mL) and the gummy precipitates were recrystallized from EtOH, giving a second crop (2.20 g). Total yield, 28.70 g (0.1006 mol), 81%. ^{1}H NMR (300 MHz) δ 3.95 (s, 3H), 5.18 (s, 2H), 6.94 (d, 1H, J=8.1 Hz), 7.03 (s, 1H), 7.18 (d, 1H, J=8.1 Hz), 7.25-7.47 (m, 5H), 7.91 (d, 1H, J=14.7 Hz). *Anal.* Calcd. for $C_{16}H_{17}NO_4$: C, 67.36; H, 5.29; N, 4.90. Found: C, 67.22; H, 5.37; N, 4.85.

1-Methoxy-1-(3-benzyloxy-4-methoxyphenyl)-2-nitroethane (16). A fine suspension was prepared by adding dry methanol (200 mL) to a vigorously stirred solution of **15** (25.00 g, 0.08763 mol) in dry CH_2Cl_2 (200 mL). A cold methanolic solution of NaOMe, prepared by dissolving Na (2.42 g, 0.1052 mol) in dry MeOH (102 mL), was added in one portion to the suspension at rt and the whole was stirred for 5 min before being quenched with AcOH (7.15 mL, 0.125 mol). *It should benoted that prolonged reaction results in formation of polymeric substances and the yield of* ***16*** *is extremely decreased.* After concentration of the mixture *in vacuo*, the residue was taken up in ether (200 mL) and washed with water (100 mL). The aqueous layer was extracted twice with ether (80 mL x 2). The combined ethereal extracts were dried (Na_2SO_4) and concentrated. The gummy residue was dissolved in ether and stored in a refrigerator for a few days. The yellow crystals thus formed were collected and washed with cold ether to give the addition product **16** (17.35 g, 54.67 mmol, 62%) as pale yellow crystals: ^{1}H NMR (200 MHz) δ 3.17 (s, 3H), 3.89 (s, 3H), 4.30, (dd, 1H, J=12.5, 3.4 Hz), 4.52 (dd, 1H, J=12.4, 9.9 Hz), 4.83 (dd, 1H, J=9.9, 3.4 Hz), 5.16 (s, 2H), 6.88-6.80 (m, 3H), 7.25-7.48 (m, 5H). An analytically pure sample was obtained by recrystallization from MeOH: slightly yellow needles; mp 102-103 °C (lit.[5a] mp 100-102 °C). *Anal.* Calcd. for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.04; N, 4.41. Found: C, 64.45; H, 6.01; N, 4.39.

1-Amino-2-(3-benzyloxy-4-methoxyphenyl)-2-methoxyethane (17). To an ice-cooled and stirred suspension of $LiAlH_4$ (4.622 g, 0.1218 mol) in dry ether (150 mL) was added dropwise a solution of **16** (9.662 g, 30.45 mmol) in dry THF (60 mL) over a period of 1.5 h under Ar and the whole was heated under reflux for 3.5 h. After cooling, the excess reagent was decomposed by successive addition of a water-saturated ether (ca. 200 mL), water (8 mL) and a saturated solution of potassium sodium tartrate (8 mL). The gel which formed was removed by filtration. The filtrate was dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel (AcOEt:Et_3N=95:5~90:10) to give the crude amine **17** (8.45 g) as a colorless viscous oil: ^{1}H NMR (200 MHz) δ 1.51 (br, 2H), 2.74 (dd, 1H, J=13.2, 4.7 Hz), 2.85 (dd, 1H, 13.2, 7.3 Hz), 3.18 (s, 3H), 3.89 (s, 3H), 4.01 (dd, 1H, J=7.3, 4.7 Hz), 5.17 (s, 2H), 6.78-6.90 (m, 3H), 7.23-7.47 (m, 6H). This was used for the next step without further purifications.

1-(3-Benzyloxy-4-methoxyphenylacetyl)amino-2-(3-benzyloxy-4-methoxyphenyl)-2-methoxyethane (18). To an ice-cooled and stirred solution of DCC (6.54 g, 31.69 mmol) in dry CH_2Cl_2 (100 mL) was added 4-

benzyloxy-3-methoxyphenylacetic acid[7] (7.85 g, 28.81 mmol) in one portion. After the mixture had been stirred at 0 °C for 25 min, a solution of the crude amine **17** (8.16 g) in dry CH_2Cl_2 (50 mL) was added in one portion and the whole was stirred overnight at rt. The precipitated *N,N'*-dicyclohexylurea was then filtered off and the filtrate was concentrated. Recrystallization from EtOH gave **18** (5.95 g) as fine needles, mp. 104-105 °C (lit.[5a] mp 96.5-98.5 °C). A scond crop (6.82 g) was obtained from the mother liquid after chromatography on silica gel (hexane:AcOEt:Et_3N=75:25:1). Total yield, 12.78 g, 76% yield for the two steps. ^1H NMR (300 MHz) δ 3.05-3.27 (m, 4H), 3.46-3.60 (m, 3H), 3.87 (s x 2, 6H), 4.02-4.09 (m, 1H), 5.12 (s, 2H), 5.15 (s, 2H), 5.73 (br, 1H), 6.64-6.85 (m, 6H), 7.25-7.46 (m, 10H). *Anal.* Calcd. for $C_{33}H_{35}NO_6$: C, 73.18; H, 6.51; N, 2.59. Found: C, 72.88; H, 6.65; N, 2.65.

6-Benzyloxy-1-(3-benzyloxy-4-methoxybenzyl)-7-methoxyisoquinoline (5). A solution of **18** (1.51 g, 2.79 mmol) and $POCl_3$ (2.60 mL, 27.88 mmol) in dry benzene (10 mL) was heated under gentle reflux for 2.5 h. The excess reagent was decomposed by carefully adding water followed by 5% aq. NH_4OH solution (70 mL) and the mixture was extracted twice with CH_2Cl_2 (50 mL x 2). The organic extracts were combined, dried (Na_2SO_4), and concentrated. The gummy residue was chromatographed on silica gel (CH_2Cl_2:acetone=9:1) to give the benzylisoquinoline **5** (786 mg, 1.59 mmol, 57%) as brown crystals: ^1H NMR (300 MHz) δ 3.77 (s, 3H), 3.86 (s, 3H), 4.51 (s, 2H), 5.09 (s, 2H), 5.27 (s, 2H), 6.75-6.83 (m, 3H), 7.07 (s, 1H), 7.26-7.49 (m, 12H), 8.33 (d, 1H, J=5.6 Hz). An analytically pure sample was obtained by recrystallization from toluene, mp 150-151 °C (lit.[5a], mp 146-147 °C). *Anal.* Calcd. for $C_{32}H_{29}NO_4$: C, 78.19; H, 5.94; N, 2.85. Found: C, 78.31; H, 6.02; N, 2.80.

Methyl 4-benzyloxy-2-hydroxybenzoate (20). A mixture of methyl 2,4-dihydroxybenzoate (10.00 g, 0.0595 mol) and anhydrous K_2CO_3 (9.00 g, 0.0654 mol) in dry acetone (300 mL) was stirred at rt for 1 h. Benzyl bromide (7.80 mL, 0.0654 mol) was then added and the whole was heated under reflux for 3.5 h. After cooling, the mixture was filtered and the filtrate was concentrated. The oily residue was taken up in CH_2Cl_2 (200 mL) and washed with water (100 mL). The aqueous layer was back-extracted with CH_2Cl_2 (100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The crystalline residue was triturated with hot MeOH (100 mL) to give **20** (13.50 g) as white needles, mp 99-100 °C (lit.[8] mp 93-95 °C) . The filtrate was concentrated and the residue was recrystallized from MeOH (30 mL) to give a second crop (0.49 g). Total yield, 13.99 g (0.05420 mol), 91%. ^1H NMR (300 MHz) δ 3.91 (s, 3H), 5.08 (s, 2H), 6.49-6.55 (m, 2H), 7.26-7.45 (m, 5H), 7.75 (dd, J=0.9, 8.3 Hz, 1H), 10.96 (s, 1H). *Anal.* Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.62; H, 5.49.

Methyl 4-benzyloxy-5-bromo-2-hydroxybenzoate (21). To a cooled (ice-water) solution of **20** (6.63 g, 0.0257 mol) in $CHCl_3$ (70 mL) was added dropwise a solution of bromine (1.46 mL, 0.0283 mol) in $CHCl_3$ (20 mL) over 1 h. After stirring 30 min at rt, the mixture was washed with water (50 mL), dried (Na_2SO_4), and concentrated. The crystalline residue was triturated with MeOH to give **21** (7.91 g, 0.0235 mol, 91%) as white needles, mp 141-142 °C: ^1H NMR (200 MHz) δ 3.93 (s, 3H), 5.17 (s, 2H), 6.53 (s, 1H), 7.26-7.58 (m, 5H), 8.01 (s, 1H), 10.91 (s, 1H). *Anal.* Calcd for $C_{15}H_{13}BrO_4$: C, 53.43; H, 3.88. Found: C, 53.41; H, 3.86.

Methyl 4-benzyloxy-2-hydroxy-5-methoxybenzoate (22). A methanolic solution of NaOMe (3.96 mmol) was prepared by dissolving clean cut Na (0.91 g) in dry MeOH (18 mL). After removal of ca. 1/3 of the MeOH, a mixture of **21** (3.11 g, 9.20 mmol) and anhydrous $CuCl_2$ (0.50 g, 3.69 mmol) dissolved in dry DMF (9.2 mL) was added to the NaOMe solution in one portion. After heating the mixture at 110-115 °C for 1 h, the reaction was quenched by adding water (20 mL) followed by 6*M* aq. HCl solution (9.2 mL). The mixture was extracted twice with EtOAc (15 mL x 2) , washed twice with water (10 mL x 2), died ($MgSO_4$), and concentrated. The crystalline residue was recrystallized from CH_2Cl_2-hexane (1:1) to give **22** (0.88 g) as white needles, mp 131-132 °C. The mother liquid was concentrated and the residue was recrystallized from *i*-Pr_2O to give a second crop (0.79 g). Total yield, 1.67 g (5.79 mmol), 63%. ^{1}H NMR (200 MHz) δ 3.85 (s, 3H), 3.92 (s, 3H), 5.17 (s, 2H), 6.51 (S, 1H), 7.24 (s, 1H), 7.30-7.48 (m, 6H). *Anal.* Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.32; H, 5.63.

Methyl 4-benzyloxy-5-methoxy-2-methoxymethoxybenzoate (6). To a cooled (ice-water) and vigorously stirred solution of phenol **22** (9.18 g, 0.0318 mol) in dry THF (250 mL) was added dropwise a solution of *t*-BuOK (4.42 g, 0.0394 mol) in THF (40 mL). After stirring 30 min, chloromethyl methyl ether (3.16 mL, 0.0416 mol) was added in one portion. After stirring additional 4 h at rt, the mixture was poured into a mixture of 2*M* aq. NH_4OH (100 mL) and 10% aq. NH_4Cl (100 mL) solutions, extracted with ether (200 mL x 2), washed with brine (100 mL), dried (Na_2SO_4), and concentrated. Recrystallization of the residue from *i*-Pr_2O gave **6** (7.18 g) as white needles, mp 61-62 °C. A second crop (2.80 g) was obtained from the mother liquid after purification by chromatography on silica gel (hexane:CH_2Cl_2=1:1). Total yield, 9.98 g (0.0300 mol), 94%. ^{1}H NMR (200 MHz) δ 3.46 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 5.10 (s, 2H), 5.19 (s, 2H), 6.80 (s, 1H), 7.27-7.48 (m, 6H). *Anal.* Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.06. Found: C, 64.96; H, 6.06.

6-Benzyloxy-1-[1-(3-benzyloxy-4-methoxyphenyl)-2-(4-benzyloxy-5-methoxy-2-methoxymethoxyphenyl)-2-oxoethyl]-7-methoxyisoquinolines (23a and 23b). To a solution of LDA, prepared from *i*-Pr_2NH (0.873 mL, 6.23 mmol) and 1.15*M* hexane solution of BuLi (3.89 mL, 4.48 mmol) in THF (20 mL), a solution of benzylisoquinoline **5** (2.00 g, 4.07 mmol) in dry THF (36 mL) was added dropwise over a period of 30 min at -78 °C under Ar. The resulting deep red solution was gradually warmed up to -15 °C over 15 min and kept that temperature for 1 h. The reaction mixture was again cooled to -78 °C and a solution of benzoate **6** (1.62 g, 4.88 mmol) in THF (10 mL) was added dropwise. The cooling bath was removed and the mixture was allowed to stand at rt (32 °C) for 3.5 h, at which time the color of the solution turned to yellow. The reaction was then quenched by adding 10% aq. NH_4Cl solution (50 mL) and the mixture was extracted twice with EtOAc (100 mL x 2). After drying (Na_2SO_4) and removing the solvent, the crude product was purified by repeated chromatography on silica gel (hexane:EtOAc=1:1~2:1) to give a tautomeric mixture of **23a** and **23b** (2.03 g, 2.56 mmol, 63%) as a yellow amorphous powder, which gradually solidified on standing in a freezer for several weeks. Trituration of the solid with hot EtOH gave pure **23a** as white crystals, mp 166-168 °C: ^{1}H NMR (300 MHz) δ 2.66 (s, 3H), 3.76 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 4.28 (d, J=7.2 Hz, 1H), 4.31 (d, J=7.2 Hz, 1H), 5.10 (s, 2H), 5.11 (s, 2H), 5.26 (s, 2H), 6.61 (s, 1H), 6.65 (s, 1H), 6.74-6.85 (m, 3H), 7.06 (s, 1H), 7.21-7.50 (m, 18H), 7.18 (s, 1H), 8.22 (d, J=5.7, 1H); IR (KBr) ν_{max} 988, 1020, 1135, 1150, 1213, 1230, 1262, 1383, 1410, 1455, 1503, 1596, 1680, 2940 cm^{-1}. A mixture of **15a** and **15b**: EI-MS *m z* 791 (M^+), 745, 730, 505, 491, 400, 91 (base); UV/Vis λ_{nm} (log ε) 240.6 (4.82), 272.0 (4.37), 315.1 (sh., 4.22), 327.4 (4.28). *Anal.* Calcd. for $C_{49}H_{45}NO_9$: C, 74.33; H, 5.72; N, 1.77. Found: C, 74.32; H, 5.83; N, 1.78.

3,11-Bis(benzyloxy)-2,12-dimethoxy-14-(4-benzyloxy-3-methoxyphenyl)-6*H*[1]benzopyrano-[4',3';4,5]pyrrolo[2,1-a]isoquinolin-6-one (3). A mixture of **23a** and **23b** (212 mg, 0.268 mmol) was heated with ethyl bromoacetate (0.80 mL, 7.21 mmol) at 50 °C for 4 days under Ar. After removal of the excess bromoacetate *in vacuo*, the crude product was dissolved in MeOH (5 mL) containing trace of conc. HCl (100 mL) and the solution was heated under reflux for 2 h, whereupon Et_3N (0.50 mL) was added. The resulting deep purple solution was refluxed for additional 3 h, at which time the purple color disappeared and pale yellow crystals appeared. Filtration of the crystals followed by washings with MeOH gave **3** (63.8 mg, 0.0829 mmol, 31%) as fine needles. An analytically pure sample was obtained by recrystallization from $CHCl_3$-ether (1:3), mp 217-218 °C: ^{1}H NMR (200 MHz) δ 3.36 (s, 3H), 3.39 (s, 3H), 3.90 (s, 3H), 5.17 (s, 2H), 5.24 (s, 2H), 5.32 (s, 2H), 6.72 (s, 1H), 6.93 (s, 1H), 6.96 (d, J=7.42 Hz, 1H), 7.07-7.20 (m, 5H), 7.25-7.54 (m, 15H), 9.17 (d, J=7.42 Hz, 1H); EI-MS *m/z* 769 (M^+), 745, 655, 368, 278, 220, 157, 91, 70, 57, 43 (base). *Anal.* Calcd. for $C_{49}H_{39}NO_8$: C, 76.45; H, 5.10; N, 1.82. Found: C, 75.88; H, 5.15, N, 1.82.

Lamellarin D (1). Compound **3** (68.0 mg, 0.0883 mmol) was hydrogenated over 20% $Pd(OH)_2$-C (36 mg) in AcOEt (40 mL) at atmospheric pressure at rt. After the reaction had completed (ca. 100 min), the mixture was filtered and the filtrate was concentrated. The residual pale yellow solid (48.3 mg) was triturated with AcOEt to give **1** (36.2 mg, 0.0725 mmol, 82%) as pale yellow crystals, mp not determined (over 300 °C): ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.36 (s, 3H), 3.39 (s, 3H), 3.78 (s, 3H), 6.71 (s, 1H), 6.86 (s, 1H), 7.00 (dd, J=8, 1.8 Hz, 1H), 7.09-7.19 (m, 5H), 9.88 (d, J=7.4 Hz, 1H), 9.35 (s, 1H, D_2O exchangeable), 9.83 (br s, 1H, D_2O exchangeable), 9.94 (br s, 1H, D_2O exchangeable); EI-MS *m/z* (relative intensity) 499 (M^+, 22), 192 (9), 138 (8), 91 (16), 57 (11), 55 (11), 43 (100). HR-MS calcd. for $C_{34}H_{27}NO_{11}$ 499.1267, found 499.1297. Triacetate of lamellarin D, white crystals [mp not determined (over 300 °C), lit.[3] mp 288-289 °C]: ^{1}H NMR (300 MHz) δ 2.33 (s, 3H), 2.35 (s, 3H), 2.37 (s, 3H), 3.46 (s x 2, 6H), 3.84 (s, 3H), 6.81 (s, 1H), 7.06 (d, J=7.4 Hz, 1H), 7.15 (s, 1H), 7.217 (d, 1H, J=1.7 Hz), 7.223 (s, 1H), 7.24-7.26 (m, 1H), 7.30 (d, 1H, J=8.0 Hz), 7.40 (s, 1H), 9.24 (d, 1H, J=7.4 Hz); EI-MS m/z (relative intensity) 625 (M^+, 11), 582 (17), 541 (18), 499 (16), 147 (10), 91 (15), 44 (100).

Lamellarin H (2). To a solution of **3** (154.2 mg, 0.200 mmol) in dry CH_2Cl_2 (5 mL) was added as drops BBr_3 (114 μL, 1.20 mmol) at -78 °C. The mixture was allowed to stand at rt overnight and then quenched with 2*M* aq. NH_4OH solution. After the aqueous phase had been made acidic (pH 4) with 4*M* aq. HCl solution, the CH_2Cl_2 was removed *in vacuo*. The residue was extracted twice with EtOAc (30 mL x 2), dried (Na_2SO_4), and concentrated. The crude product was purified by chromatography on silica gel (EtOAc:MeOH=95:5), giving **2** (62.6 mg, 0.137 mmol, 68%) as a pale yellow amorphous powder: FAB-MS (glycerin) *m/z* 456 $[M+H]^+$. Hexaacetate of **2**, mp 235-238 °C (decomp., EtOAc-pentane, lit.[2] amorphous solid): ^{1}H NMR (200 MHz) δ 2.25 (s, 3H), 2.26 (s, 3H), 2.298 (s, 3H), 2.303 (s, 3H), 2.32 (s, 3H), 2.37 (2, 3H), 7.09 (s, 1H), 7.13 (d, 1H, J=7.4 Hz), 7.31 (s, 1H), 7.39 (d, 1H, J=1.8 Hz), 7.41 (d, 1H, J=1.8 Hz), 7.42 (s, 1H), 7.44 (s, 1H), 7.57 (s, 1H), 9.31 (d, 1H, J=7.4 Hz). EI-MS *m/z* (relative intensity) 709 (M^+, 2.9), 667 (2.5), 625 (3.5), 602 (2.3), 566 (3.5), 564 (4.0), 541 (2.7),486 (24.5), 455 (5.7), 354 (9.9), 278 (8.7), 256 (3.7), 212 (3.1), 117 (4.9). HR-MS calcd for $C_{37}H_{27}NO_{14}$ 709.1431, found 709.1398.

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