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Utility of Polymer-Supported Reagents in the Total Synthesis of Lamellarins

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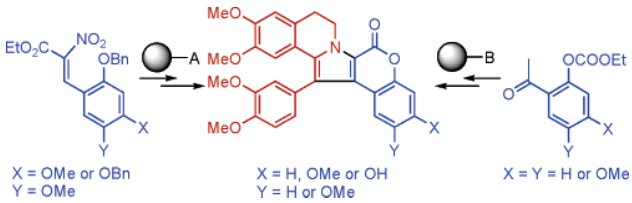

Four solid-supported reagents have been utilized in the multistep synthesis of lamellarins. The use of Amberlyst A-26 Br_3^- and polymer bound pyridine hydrobromide perbromide (PVPHP) for keto α-bromination of the less studied ortho-substituted acetophenone derivatives selectively furnished the corresponding monobromination products (phenacyl bromide derivatives), which were used directly in condensation reactions with benzyldihydroisoquinoline mediated by Amberlyst A-26 $NaCO_3^-$. The 2*H*-pyrrole carbonates subsequently underwent intramolecular Friedel−Crafts transacylation followed by lactonization to provide the lamellarin skeleton. Alternatively, Amberlyst A-26 $NaCO_3^-$ effectively served as base in condensation reaction of benzyldihydroisoquinoline with α-nitrocinnamate derivatives to provide the corresponding 2-ethoxycarbonyl pyrroles, which smoothly underwent O-debenzylation reaction followed by lactonization to furnish the lamellarin skeleton. The novel Amberlyst-15 mediated lactonization reactions effectively combined the otherwise two separate steps into a single transformation.

Introduction

As part of our research program on the synthesis of bioactive natural alkaloids, we have been involved with the synthesis of lamellarins (**1**), a group of marine natural products, which have been found to exhibit a wide array of interesting biological activities. Since the first isolation in 1985 by Faulkner,[1] more than 35 structurally related lamellarins have been reported.[2] A number of lamellarins have been found to be cytotoxic to a wide range of cancer cell lines.[3] More importantly, some members of this class of marine natural products are nontoxic inhibitors of the *p*-glycoprotein possibly responsible for acquired multidrug-resistance (MDR) in various cancer cell lines.[4] In addition, lamellarins K and L exhibit immunomodulatory effects.[5] More recently, there have been reports of lamellarin α-20 sulfate as a selective inhibitor of HIV-1 integrase both in vitro and in vivo.[6] Other modes of action of lamellarins, as well as the development of lamellarin

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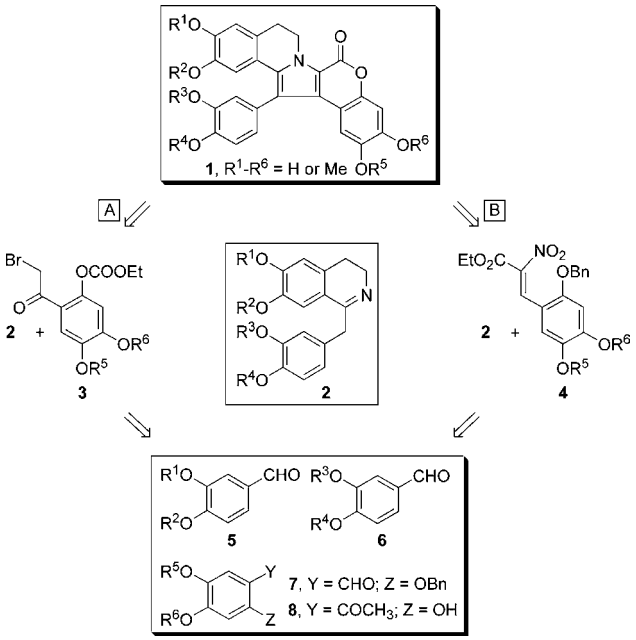
D as a novel potent inhibitor of topoisomerase I are under extensive investigation.[7]

To establish a more comprehensive structure−activity relationship (SAR) and to investigate further the mechanism(s) of action, relatively large quantities of lamellarins are required. However, because the natural sources of lamellarins, some species of ascidians, sponges, and molluscs, provide these compounds in only minute quantities, total synthesis is a vital alternative in providing these compounds for detailed biological evaluations. A number of research groups worldwide have reported elegant strategies for total syntheses of lamellarins over the past 8 years.[5,8] Recently, our research group has reported some developments of their synthesis either via (1) lithium−bromine exchange/intramolecular lactonization of the 2-bromopyrrole carbonate intermediate derived from the condensation of benzyldihydroisoquinoline **2** with phenacyl bromide carbonate **3** (pathway A in Scheme 1) or (2) Michael addition/ring closure (Mi-RC) reaction between **2** and the α-nitrocinnamate derivative **4** (pathway B) as the key step.[9] The basic units for both approaches are the simple and easily prepared benzadehyde derivatives (**5**−**7**) and acetophenone **8**.

Solid-phase chemistry has played a major role in revolutionizing different areas of chemistry, especially combinatorial synthesis. While solid-phase synthesis has proved efficient for building up compound libraries, monitoring the reaction progress and determining the compound loading on the polymer still requires some specialized analytical equipment and techniques, such as single-bead IR, solid-state NMR, or cleavage of the compound from the polymer. Thus, the use of polymer-supported materials as reagents, instead of as anchors for substrates, is an attractive alternative and has been developed to circumvent those limitations encountered in "traditional" solid-phase synthesis. This line of chemistry has resulted in the development of a number of useful polymer-supported reagents which are finding increasing utility in organic synthesis.[10] Recently, the solid-phase synthesis of lamellarins has been reported.[11]

SCHEME 1. Retrosynthetic Analysis of Lamellarin Skeleton 1



We have now applied four polymer-supported reagents (bromine on polymer support (Amberlyst A-26 Br_3^--form and PVPHP), carbonate on polymer support (Amberlyst A-26 $NaCO_3^-$-form), and Amberlyst 15) for both synthetic pathways A and B shown in Scheme 1.

Results and Discussion

As shown in Scheme 1, both approaches share a common intermediate in benzyldihydroisoquinoline (**2**) whose synthesis is well documented.[12] We first investigated the polymer-supported bromination of ortho-substituted acetophenones **9a** and **9b** to the corresponding phenacyl bromides **10a** and **10b** (Scheme 2). Some examples of α-bromination of acetophenone derivatives using polymer support have been reported.[13] However, in those cases, the substrates usually contained substituents on the aromatic at positions other than at the ortho-position. Compounds **9a** and **9b** which carry a carbonate group at the ortho position of acetophenone ring system appeared more prone to the undesired α,α-

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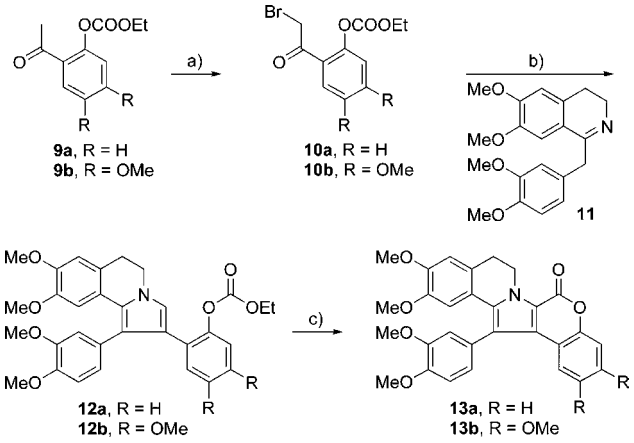
SCHEME 2. Polymer-Supported Synthesis of Lamellarins 13a and 13b[a]



[a] Reagents and conditions: (a) Amberlyst A-26 Br_3^--form and PVPHP, Table 1 (see also Supporting Information); (b) Amberlyst A-26 $NaCO_3^-$-form, Table 2; (c) Amberlyst 15, Table 3.

TABLE 1. Keto α-Bromination[a] of Acetophenone Carbonate Derivatives (9a and 9b)

entry	R	brominating agent[b]	solvent[c]	time (h)	ratio (mono:di)	yield (%)[d]
1	H	A	DCM	18	14:1	96
2	H	B	DCM	18	5:1	83
3	H	B	CH_3CN	18	3.5:1	85
4	H	B	hexane	18	2:1	66
5	H	B	toluene	18	8:1	92
6[e]	H	B	THF	18	100:0	
7[f]	H	C	DCM	18	6.5:1	87
8[g]	H	C	toluene	18		0
9	H	C	toluene	72	33:1	98
10	H	C	toluene	120	25:1	97
11	OMe	A	DCM	18	10:1	90
12	OMe	B	toluene	18	5:1	85
13	OMe	C	DCM	18	4.6:1	86
14	OMe	C	toluene	72	7:1	88

[a] Unless otherwise noted, the reactions were performed at 0 °C to room temperature. [b] A = $BnNMe_3Br_3$; B = Amberlyst A-26 Br_3^--form; C = PVPHP. [c] DCM = dichloromethane; THF = tetrahydrofuran. [d] Yield of monobromination was determined by ^{1}H NMR of the crude material. Isolated and estimated yields (^{1}H NMR) were comparable. The crude mixture contained only monobromination and dibromination products and could be used in the subsequent step without further purification. [e] There were some unidentifiable inseparable contaminants with the monobromination product. [f] The reaction was performed at room temperature. [g] The reaction was not complete; virtually only starting material was observed by ^{1}H NMR.

dibromination when performed in solution phase.[9b] Thus, use of appropriate brominating agents and reaction conditions for selective α-monobromination of ortho-substituted acetophenones **9a** and **9b** was required.

When $BnNMe_3Br_3$ was employed as the brominating agent in dichloromethane (DCM), slow addition and a low effective concentration of bromine at low-temperature played an important role in minimizing the amount of dibromination. As shown in Table 1, the best ratio[14] achieved for **10a** was 14:1 (entry 1) and for **10b** was 10:1 (entry 11) with complete conversion.

We then explored the use of polymer-bound brominating agent, Amberlyst A-26 Br_3^--form and PVPHP. After some experimentation, we found that both polymer-supported brominating agents gave the best selectivity for monobromination product when toluene was used as the solvent and the reaction was performed at low temperature with slow warming to room temperature. The best ratio for monobromination product **10a** was 33:1 with the use of PVPHP when performed in toluene for 3 days (entry 9). For the more activated acetophenone derivative **9b**, which is expected to be more prone to dibromination, the best ratio of 7:1 was obtained when PVPHP was employed in toluene under similar reaction conditions (entry 14). We reasoned that toluene, a relatively nonpolar solvent, would provide better selectivity for monobromination due to less effective enolization of the monobromination product.[13f–h]

TABLE 2. Base-Mediated Condensation[a] of 11 with 10a and 10b

entry	R	base[b]	equivalent	time (h)	yield[c] (%)
1	H	A	1.2	18	72
2	H	B	1.2	48	Trace
3	H	B	2.4	48	0
4	H	C	6.0	18	0
5	H	C[d]	1.1	24	49
6	OMe	A	1.2	18	60
7	OMe	C[d]	1.1	20	60

[a] Unless otherwise noted, the reactions were performed in refluxing CH_3CN. [b] A = $NaHCO_3$; B = Ambersep 900 OH; C = Amberlyst A-26 $NaCO_3^-$. [c] Isolated yields of the desired pyrrole carbonate **12a** and **12b** over two steps after subjecting the crude material to the carbonation reaction using Et_3N, EtOCOCl, and DMAP in DCM. [d] The material was dried under vacuum for 6 h prior to use.

With the phenacyl bromide derivatives in hand, we then focused on the subsequent base-mediated formation of the pyrroles by coupling of **11** with phenacyl bromides **10a** and **10b**. Our previously reported conditions for this coupling reaction employed sodium bicarbonate as base and provided the desired pyrrole carbonate **12a** in 72% yield and **12b** in 60% yield (entries 1 and 6, Table 2).[9b] Two polymer-supported bases were explored for this coupling reaction, and the results are summarized in Table 2.

When 1.2 equiv of Ambersep 900 OH was employed, only a trace amount of the desired product, along with some phenacyl bromide carbonate **10a**, could be isolated. A larger excess of Ambersep 900 OH resulted in complete consumption of starting phenacyl bromide carbonate but gave none of the desired product. We then turned to Amberlyst A-26 $NaCO_3^-$-form.[15] After some experimentation, we found that drying the reagent under vacuum was critical. With dried reagent, the desired products **12a** and **12b** were isolated, after column chromatography, in 49% and 60% yields, respectively (entries 5 and 7). When compared with $NaHCO_3$ (method A), the use of Amberlyst

(14) Only reactions in DCM were attempted because $BnNMe_3Br_3$ is not completely soluble in other solvents. Partial optimization was performed for methods of addition (which affect the effective concentration of bromine) and temperatures. Addition of $BnNMe_3Br_3$ either (1) as a solid in batches at 0 °C with slow warming up of the resulting reaction mixture to room temperature following the addition or (2) as a solution in DCM dropwise at room temperature resulted in less selectivity for monobromination product. Between these two sets of reaction conditions, the latter gave slightly better selectivity, providing **10a** and **10b** in about 7:1 and 4:1 ratios, respectively.

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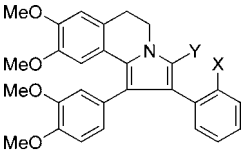

14a, X = OMs, Y = CHO
14b, X = OCOOEt, Y = Br

FIGURE 1. Structure of 2-formylpyrrole **14a** and 2-bromopyrrole **14b**.

TABLE 3. Acid-Mediated Friedel–Crafts Reaction[a] of 12a and 12b

entry	R	acid[b]	equivalent	solvent	*T* (°C)	yield[c] (%)
1	H	$AlCl_3$	1.2	DCM	d	
		A	catalytic	PhMe[e]	110	86[f]
2	H	A	0.5	PhMe[e]	110	90
3	H	B	1.1	THF	110	0[g]
4	H	B	1.5	PhMe	105	—[h]
5	H	B	3	PhMe	105	98
6	H	B	5	PhMe	105	95
7	OMe	A	0.5	PhMe[f]	110	91
8	OMe	B	3	PhMe	105	94

[a] Unless otherwise noted, the reactions were performed for 18 h. [b] A = *p*-TsOH; B = Amberlyst-15. [c] Isolated yields after recrystallization from MeOH/hexane. [d] 0 °C to room temperature. [e] The reactions were performed in refluxing toluene for 1.5 h. [f] Overall yield. [g] All starting material was recovered. [h] A 1:1 mixture of starting material **12a** and the desired product (**13a**) was obtained.

A-26 $NaCO_3^-$-form (method C) as base in the pyrrole formation step could provide the desired pyrrole carbonate products, albeit in slightly lower yields.

The remaining step for the synthesis of lamellarin involves transacylation from the carbonate to the 2-position of 2*H*-pyrrole followed by lactonization. Previously, we reported an anionic approach involving the generation of a carbanion at the 2-position of the pyrrole via either directed remote metalation (DreM) of **12a** and **12b** or lithium–bromine exchange of the corresponding 2-bromopyrrrole carbonate.[9b] In both approaches, the carbonate serves a dual role as the phenoxy protecting group and a masked carbonyl equivalent. With DreM, we encountered some problems of reproducibility, while the bromide route requires an additional step. After careful examination, we noted that the 2-position of the 2*H*-pyrrole appears susceptible to electrophilic attack by Vilsmeier species generating 2-formylpyrrole **14a**[9a] and by *N*-bromosuccinimide yielding 2-bromopyrrole **14b**[9b] as shown in Figure 1.

Thus, the 2-position is sufficiently nucleophilic for an intramolecular electrophilic attack from the acyl group of the carbonate moiety with appropriate acid activation. In other words, the direct acid-mediated intramolecular Friedel–Crafts transacylation from the carbonate carbonyl group to the 2-position of pyrrole and subsequent lactonization of the resulting intermediate could lead to the desired lamellarin skeleton (**13a** and **13b**) in one step. Results of this Friedel–Crafts transacylation/lactonization are summarized in Table 3.

Our initial attempt employed $AlCl_3$ as a Lewis acid in DCM to yield a 1:1 mixture of the starting material and the corresponding 2-ethoxycarbonyl pyrrole intermediate **15** (Figure 2). Treatment of such mixture with *p*-TsOH in toluene gave cleanly the desired lamellarin skeleton **13a** in 86% yield (entry 1). The result suggested that the

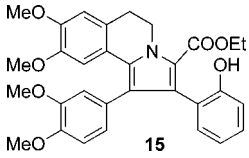

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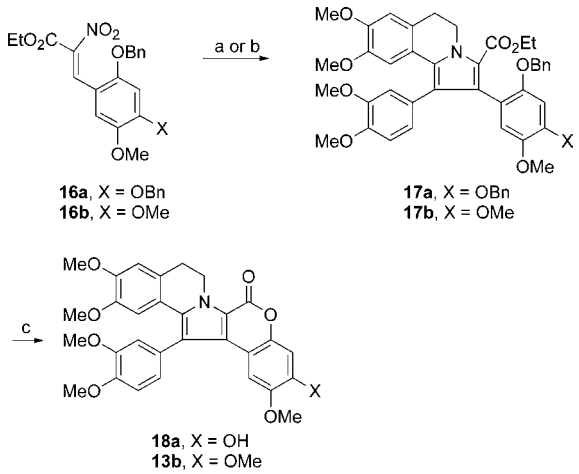
FIGURE 2. Structure of 2-ethoxycarbonyl pyrrole intermediate **15**.

SCHEME 3. Polymer-Supported Synthesis of Lamellarins 18a and 13b via Mi-RC[a]



16a, X = OBn
16b, X = OMe

17a, X = OBn
17b, X = OMe

18a, X = OH
13b, X = OMe

[a] Reagents and conditions: (a) **11**, $NaHCO_3$ (1.2 equiv), CH_3CN, reflux, 50% (**17a**), 60% (**17b**); (b) **11**, Amberlyst A-26 $NaCO_3^-$ (1.1 equiv; dried), CH_3CN, reflux, 44% (**17a**); (c) Amberlyst-15, toluene, 105 °C, 63% (**18a**), 90% (**13b**).

2*H*-pyrrole starting material could directly undergo the Friedel–Crafts transacylation/lactonization to the desired lamellarin when treated with *p*-TsOH. When the reaction was performed using 0.5 equiv of *p*-TsOH in refluxing toluene for 1.5 h, **13a** was obtained in 90% yield (entry 2).

Amberlyst-15 was chosen as a polymer-supported acid to mediate the novel Friedel–Crafts transacylation/lactonization reaction on the basis of its sulfonic acid functionality, analogous to that in *p*-TsOH. When 1.1 equiv of this reagent was employed in refluxing THF, only starting material was recovered. When the reaction was performed in toluene at 105 °C[16] using 1.5 equiv of the polymer-supported acid, a ca. 1:1 mixture of starting material and the desired lamellarin was obtained (entry 4). The reaction went to completion when 3–5 equiv of the acid were employed under similar reaction conditions (entries 5 and 6), providing the desired lamellarin **13a** or **13b** in excellent yields (94–98%).

An alternative route to the lamellarin skeleton involves the base-mediated Michael addition/ring closure (Mi-RC) between **11** and α-nitrocinnamate **16a** or **16b** (Scheme 3).[9c] Similar to the base-mediated pyrrole formation of **11** and **10a** or **10b**, we found that Amberlyst A-26 $NaCO_3^-$-form could serve as the base to mediate Mi-RC when 1.1 equiv of the dried reagent was employed in refluxing acetonitrile. The reaction provided the desired 2-ethoxycarbonyl pyrrole intermediate **17a** in 44% yield,

(16) The temperature was arbitrarily chosen not to exceed 120 °C at which, according to the supplier (Fluka), Amberlyst-15 decomposes.

which is comparable to the 50% yield obtained when the reaction was performed in the presence of $NaHCO_3$.

With the observation that Amberlyst-15 could mediate O-debenzylation,[17] we now envisioned that the lamellarin skeleton could be obtained directly in one step via a novel O-debenzylation/lactonization reaction from a substrate containing an ethoxycarbonyl functionality at the pyrrole C-2 and an *ortho*-benzyloxyaryl substituent at the pyrrole C-3 (**17a** or **17b**). In fact, when compounds **17a** and **17b** were heated with 3 equiv of Amberlyst-15 in toluene at 105 °C, the corresponding lamellarins **18a** and **13b** were obtained in 63%[18] and 90% yields, respectively.

Conclusion

We have significantly improved the total synthesis of the lamellarin skeleton with the use of polymer-supported reagents in the selective monobromination of ortho-substituted acetophenones by the use of Amberlyst A-26 Br_3^--form and PVPHP, the base-mediated pyrrole formation from the condensation of benzyldihydroisoquinoline with either phenacyl bromide or α-nitrocinnamate by Amberlyst A-26 $NaCO_3^-$-form, and the novel acid-mediated lactone formation either via Friedel–Crafts transacylation/lactonization or via O-debenzylation/lactonization by Amberlyst-15. The use of polymer-supported reagents facilitates the synthesis by minimizing both the workup procedure and column chromatography, rendering synthetic approaches more practical. In addition, the use of polymer-supported reagents requires only conventional means for monitoring reaction progress (thin-layer chromatography) and assessing product yields. Lamellarin skeletons such as **13a** could be obtained from acetophenone carbonate derivative **9a** using three polymer-supported reagents in 47% overall yield over three steps as compared to 33% yield over five steps previously reported.[9b] A more structurally complex unnatural lamellarin such as **18a** could be obtained in a similar fashion from α-nitrocinnamate **16a** in 28% yield over two steps.

Experimental Section

A. General Procedure for Keto α-Bromination of Acetophenone Carbonates. To a stirred solution of acetophenone carbonate derivatives (**9a** or **9b**; 1 equiv) in solvent (10 mL/mmol) and at the temperature indicated in Table 1 was added the brominating agent (1.05 equiv of A, B, or C as indicated in Table 1). In case of $BnNMe_3Br_3$ (brominating agent A), its solution in DCM was added very slowly via a dropping funnel to the reaction mixture at 0 °C. The mixture was allowed to stir at the given temperature for, typically, 18 h (or otherwise as noted in Table 1). At that time, if polymer-supported reagent was employed, the reaction was filtered, the polymer washed with DCM and EtOAc, and the resulting mixture concentrated under reduced pressure. The mixture was then analyzed for the ratio of monobromination product to dibromination product and used in the next step without further purification. If $BnNMe_3Br_3$ was used, after 18 h, water was added and the two phases were separated. The organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was analyzed for the ratio of monobromination product to dibromination product and purified (see Table 1 for yields). It should be noted that **10a** was recrystallized from MeOH/hexanes to give a 12:1 mixture of mono- and dibromination product while column chromatography on silica gave **10a** as a mixture with hydrolyzed product. **10b** was purified by column chromatography on silica.

2-(2-Bromoacetyl)phenyl Ethyl Carbonate (10a) (as a 12:1 inseparable mixture of monobromination and dibromination product). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.41 (t, 3H, J = 7.0 Hz), 4.35 (q, 2H, J = 7.0 Hz), 4.46 (s, 2H), 6.80 (s, 1H, dibromination product, COC*H*Br_2), 7.31 (d, 1H, J = 8.0 Hz), 7.39 (t, 1H, J = 8.0 Hz), 7.61 (t, 1H, J = 8.0 Hz), 7.86 (d, 1H, J = 8.0 Hz), 7.95 (d, 1H, J = 7.2 Hz, dibromination product). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 34.1, 42.0 (dibromination product), 65.4, 65.6 (dibromination product), 123.3, 123.4 (dibromination product), 126.3, 126.4 (dibromination product), 127.7, 130.6, 131.1 (dibromination product), 134.1, 134.3 (dibromination product), 134.5 (dibromination product), 149.6, 152.7, 190.7.

2-(2-Bromoacetyl)-4,5-dimethoxyphenyl Ethyl Carbonate (10b). IR (KBr): ν_{max} 3014, 2959, 1759, 1685, 1605, 1521, 1466, 1426, 1404, 1364, 1249, 1131, 1056, 1029 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.39 (t, 3H, J = 7.0 Hz), 3.90 (s, 3H), 3.91 (s, 3H), 4.34 (q, 2H, J = 7.0 Hz), 4.41 (s, 2H), 6.74 (s, 1H), 7.37 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2, 34.7, 56.2, 56.4, 65.4, 106.1, 111.8, 118.9, 145.2, 146.8, 152.8, 153.8, 188.8. LRMS (EI) *m/z* (rel intensity) 348 (M^+ + 2, 9), 346 (M^+, 9), 304 (4), 302 (4), 277 (4), 276 (33), 275 (4), 274 (34), 209 (17), 195 (7), 194 (8), 182 (14), 181 (100), 125 (10). FAB-HRMS calcd for $C_{13}H_{16}BrO_6$ (M + H^+) 347.0130, found 347.0126.

B. General Procedure for Pyrrole Formation from 11 with Phenacyl Bromide Carbonates. To a stirred solution of **11** (1.2 equiv) in acetonitrile (10 mL/mmol of **11**) at room temperature was added the base (equivalent as indicated in Table 2) and phenacyl bromide carbonate (**10a** or **10b**; 1 equiv). The resulting mixture was heated at reflux for the amount of time indicated in Table 2. At that time, if polymer-supported reagent was employed, the reaction was filtered, the polymer washed with DCM and EtOAc, and the resulting mixture concentrated under reduced pressure. If $NaHCO_3$ was used, water was added and the two phases were separated. The organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue (from either polymer-supported reaction or $NaHCO_3$ reaction) was dissolved in DCM, and to the mixture were added Et_3N, ethyl chloroformate (1.2 equiv each based on the amount of **10a** or **10b**), and DMAP (ca. 0.1 equiv) at room temperature for 18 h. The residue was purified by column chromatography to furnish the desired product **12a** or **12b** (see Table 2 for yields).

2-[1-(3,4-Dimethoxyphenyl)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-2-yl]phenyl Ethyl Carbonate (12a). mp (MeOH) 174–175 °C. IR (Nujol): ν_{max} 2924, 2855, 1761, 1464, 1329, 1251, 1224 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, 3H, J = 7.0 Hz), 3.03 (apparent t, 2H, J = 6.4 Hz), 3.41 (s, 3H), 3.64 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 4.07 (apparent t, 2H, J = 6.4 Hz), 4.18 (q, 2H, J = 7.0 Hz), 6.70 (s, 1H), 6.80 (s, 1H), 6.80 (d, 1H, J = 8.0 Hz), 6.84 (s, 2H), 6.90 (dd, 1H, J = 8.1, 1.8 Hz), 6.96 (dd, 1H, J = 8.1, 1.8 Hz), 7.00 (ddd, 1H, J = 8.1, 8.1, 1.8 Hz), 7.13 (dd, 1H, J = 8.1, 1.8 Hz), 7.15 (ddd, 1H, J = 8.1, 8.1, 1.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 29.4, 44.7, 55.2, 55.6, 55.75, 55.79, 64.3, 107.5, 110.9, 111.1, 114.3, 118.1, 119.5, 119.7, 121.6, 122.2, 122.9, 123.9, 125.4, 125.6, 126.7, 128.6, 128.7, 132.1, 146.8, 147.27, 147.34, 148.5, 148.7, 153.2. LRMS (EI) *m/z* (rel intensity) 530 (M + H^+, 25), 529 (M^+, 100), 514 (14), 483 (11), 456 (6), 350 (3), 213 (4), 133 (5). FAB-HRMS calcd for $C_{31}H_{32}NO_7$ (M + H^+) 530.2179, found 530.2178. Anal. Calcd for $C_{31}H_{31}NO_7$: C, 70.30; H, 5.90; N, 2.64. Found: C, 70.21; H, 5.88; N, 2.94.

2-[1-(3,4-Dimethoxyphenyl)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-2-yl]-4,5-dimethoxyphenyl Ethyl Carbonate (12b). IR ($CHCl_3$): ν_{max} 3014, 2830,

(17) Amberlyst-15 mediated debenzylation is currently under investigation in our laboratory, and the results will be reported in due course.

(18) Some product of benzylation of the aromatic ring ortho to the hydroxy group was formed in 10% yield.

1748, 1696, 1615, 1522, 1035 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.27 (t, 3H, J = 7.0 Hz), 3.05 (apparent t, 2H, J = 6.4 Hz), 3.40 (s, 3H), 3.42 (s, 3H), 3.69 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 4.08 (apparent t, 2H, J = 6.4 Hz), 4.21 (q, 2H, J = 7.0 Hz), 6.43 (s, 1H), 6.67 (s, 1H), 6.70 (s, 1H), 6.77 (s, 1H), 6.85 (d, 1H, J = 1.2 Hz), 6.86 (s, 1H), 6.87−6.91 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2, 29.4, 44.7, 55.2, 55.5, 55.8 (2 carbons), 55.85, 55.91, 64.4, 105.4, 107.4, 111.0, 111.2, 111.8, 113.9, 114.2, 118.0, 119.4, 120.1, 122.1, 123.2, 123.9, 125.5, 129.0, 141.7, 146.1, 146.7, 147.0, 147.3, 147.4, 148.7, 153.6. LRMS (EI) *m/z* (rel intensity) 590 (M + H^+, 34), 589 (M^+, 100), 543 (61), 529 (14), 516 (19), 500 (13), 485 (12), 338 (10), 181 (19), 165 (15). FAB-HRMS calcd for $C_{33}H_{36}NO_9$ (M + H^+) 590.2390, found 590.2387.

C. General Procedure for the Acid-Mediated Friedel−Crafts Transacylation/Lactonization. 2*H*-Pyrrole carbonate (**12a** or **12b**; 1 equiv) was dissolved in solvent (40 mL/mmol) as indicated in Table 3, at room temperature. An acid (equiv as indicated in Table 3) was then added, and the resulting mixture was stirred at temperature and for the amount of time indicated in Table 3. If polymer-supported reagent was employed, the reaction was filtered, the polymer washed with DCM and EtOAc, and the crude concentrated under reduced pressure. If *p*-TsOH was used, the reaction was neutralized by Et_3N. The resulting mixture was concentrated under reduced pressure. The crude material was purified by recrystallization from MeOH/hexanes to furnish the desired lamellarins **13a** or **13b** (see Table 3 for yields).

14-(3,4-Dimethoxyphenyl)-11,12-dimethoxy-8,9-dihydro-6*H*-chromeno[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (13a). mp (MeOH) 244−245 °C. IR (Nujol): ν_{max} 3028, 1696, 1515, 1485, 1432, 1339 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.12 (apparent t, 2H, J = 7.0 Hz), 3.37 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 3.99 (s, 3H), 4.82 (apparent t, 2H, J = 7.0 Hz), 6.65 (s, 1H), 6.76 (s, 1H), 6.97−7.07 (m, 4H), 7.22−7.39 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.7, 42.5, 55.2, 55.9, 56.1 (two carbons), 108.8, 110.0, 112.1, 113.9, 114.5, 115.8, 117.1, 118.3, 120.0, 123.4, 123.7, 126.6, 127.3, 127.5, 127.9, 136.1, 147.5, 149.0, 149.9, 151.3, 155.2. LRMS (EI) *m/z* (rel intensity) 484 (M + H^+, 30), 483 (M^+, 100), 469 (4), 468 (13), 226 (19), 189 (10), 141 (3), 139 (12). FAB-HRMS calcd for $C_{27}H_{26}NO_5$ (M + H^+) 484.1760, found 484.1760. Anal. Calcd for $C_{27}H_{25}NO_5$: C, 72.02; H, 5.21; N, 2.90. Found: C, 71.60; H, 5.23; N, 2.71.

14-(3,4-Dimethoxyphenyl)-2,3,11,12-tetramethoxy-8,9-dihydro-6*H*-chromeno[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (13b; Lamellarin G Trimethyl Ether). mp (MeOH) 245−246 °C (lit.[8e] mp 235 °C (no range given), lit.[8l] mp 239.1−240.7 °C). IR (Nujol): ν_{max} 3025, 1699, 1522, 1485, 1444, 1425, 1342, 1250 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.09 (apparent t, 2H, J = 6.6 Hz), 3.35 (s, 3H), 3.45 (s, 3H), 3.82 (s, 3H), 3.86 (s, 6H), 3.94 (s, 3H), 4.75 (apparent t, 2H, J = 6.6 Hz), 6.64 (s, 1H), 6.69 (s, 1H), 6.74 (s, 1H), 6.84 (s, 1H), 7.05−7.15 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.6, 42.3, 55.1, 55.4, 55.85, 55.88, 56.09, 56.13, 100.3, 104.3, 108.5, 110.1, 110.8, 111.7, 113.6, 113.8, 114.7, 119.9, 123.5, 126.6, 127.9, 128.0, 135.8, 145.3, 145.9, 147.3, 148.6, 148.7, 148.8, 149.6, 155.4. LRMS (EI) *m/z* (rel intensity) 543 (M^+, 100), 528 (6), 496 (7), 470 (3), 454 (4), 440 (3), 271 (20), 248 (6), 227 (11). These spectroscopic data are identical to those reported previously.[8e,f]

D. General Procedure for the Knoevenagel Reaction. A round-bottomed flask equipped with a Dean−Stark apparatus was charged with the appropriately substituted aldehyde (1 equiv), $Et_2NH{\cdot}HCl$ (1.5 equiv), ethyl nitroacetate (1.25 equiv), and toluene (12 mL/mmol of aldehyde) at room temperature. The mixture was refluxed under argon for 48 h. Toluene was removed, and water and CH_2Cl_2 were added. Two phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product, which was recrystallized from MeOH to furnish the desired product **16a** (67%) or **16b** (55%) as yellow-orange solids.

Ethyl 3-(2,4-Bisbenzyloxy-5-methoxyphenyl)-2-nitroacrylate (16a). mp (MeOH) 103−104 °C (lit.[9c] mp 104−105 °C). IR (KBr): ν_{max} 2938, 1754, 1714, 1608, 1573, 1522, 1268, 1225 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.34 (t, 3H, J = 7.2 Hz), 3.79 (s, 3H), 4.34 (q, 2H, J = 7.2 Hz), 5.00 (s, 2H), 5.12 (s, 2H), 6.50 (s, 1H), 6.83 (s, 1H), 7.27−7.36 (m, 10 H), 7.99 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 56.2, 62.5, 70.9, 71.6, 100.4, 110.3, 110.5, 127.1 (2 carbons), 127.4, 128.2, 128.66, 128.70 (2 carbons), 135.8, 136.0, 137.9, 144.2, 152.9, 153.8, 159.9. LRMS (EI) *m/z* (rel intensity) 464 (M + H^+, 7), 463 (M^+, 40), 326 (28), 236 (29), 181 (36), 91 (100). HR-MS (FAB) calcd for $C_{26}H_{26}NO_7$ (M + H^+) 464.1709, found 464.1699. Anal. Calcd for $C_{26}H_{25}NO_7$: C, 67.38; H, 5.44; N, 3.02. Found: C, 67.51; H, 5.62; N, 2.98. These spectroscopic data are identical to those reported previously.[9c]

Ethyl 3-(2-Benzyloxy-4,5-dimethoxyphenyl)-2-nitroacrylate (16b). mp (MeOH) 132−133 °C. IR (KBr): ν_{max} 2924, 1733, 1707, 1609, 1576, 1524, 1466, 1440, 1275, 1226, 1044 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.35 (t, 3H, J = 7.0 Hz), 3.78 (s, 3H), 3.86 (s, 3H), 4.35 (q, 2H, J = 7.0 Hz), 5.15 (s, 2H), 6.52 (s, 1H), 6.82 (s, 1H), 7.41 (m, 5H), 8.03 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 56.0, 56.1, 62.5, 71.7, 98.2, 109.8, 109.9, 127.2, 127.4, 128.2, 128.7, 136.0, 137.8, 143.7, 153.9, 154.1, 159.9. LRMS (EI) *m/z* (rel intensity) 388 (M + H^+, 2), 387 (M^+, 9), 251 (12), 250 (74), 222 (16), 91 (100), 65 (11). FAB-HRMS calcd for $C_{20}H_{22}NO_7$ (M + H^+) 388.1397, found 388.1396. Anal. Calcd for $C_{20}H_{21}NO_7$: C, 62.01; H, 5.46; N, 3.62. Found: C, 61.98; H, 5.41; N, 3.72.

E. General Procedure for Pyrrole Formation from 11 with α-Nitrocinnamates (Mi-RC). To a stirred solution of **11** (1.2 equiv) in acetonitrile (10 mL/mmol of **11**) at room temperature was added the base (1.1 equiv) and α-nitrocinnamate (**16a** or **16b**; 1 equiv). The resulting mixture was heated to reflux for 18 h. At that time, if polymer-supported reagent was employed, the reaction was filtered, the polymer washed with DCM and EtOAc, and the resulting mixture concentrated under reduced pressure. If $NaHCO_3$ was used, water was added and the two phases were separated. The organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to furnish the desired product **17a** (50%, using $NaHCO_3$; 44%, using Amberlyst A-26 $NaCO_3^-$) or **17b** (60%).

Ethyl 1-(3,4-Dimethoxyphenyl)-2-(2,4-dibenzyloxy-5-methoxy)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (17a). mp (EtOAc/hexanes) 165−166 °C. IR ($CHCl_3$): ν_{max} 3018, 2935, 1686, 1610, 1482, 1422, 1398, 1335, 1255, 1214, 1176, 1130, 1064, 1027 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.84 (t, 3H, J = 7.0 Hz), 3.07 (apparent t, 2H, J = 6.6 Hz), 3.36 (s, 3H), 3.53 (s, 3H), 3.65 (s, 3H), 3.83 (s, 3H), 3.88 (s, 3H), 4.00 (q, 2H, J = 7.0 Hz), 4.64 (br m, 2H), 4.75 (s, 2H), 5.03 (s, 2H), 6.43 (s, 1H), 6.60 (s, 1H), 6.68 (s, 1H), 6.73 (m, 4H), 7.05−7.15 (m, 2H), 7.20−7.38 (m, 8H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.7, 29.1, 42.7, 55.2, 55.6, 55.8 (2 carbons), 56.4, 59.5, 71.1, 71.6, 102.9, 108.6, 110.5, 110.7, 113.9, 116.0, 118.7, 119.1, 121.0, 121.6, 123.0, 125.8, 126.7, 127.2, 127.3, 127.7, 128.1, 128.2, 128.4, 130.8, 137.0, 137.8, 143.4, 146.9, 147.1, 147.4, 147.8, 148.3, 150.5, 162.0. LRMS (EI) *m/z* (rel intensity) 756 (M + H^+, 4), 755 (M^+, 12), 679 (6), 664 (8), 588 (10), 500 (8), 91 (100), 65 (25). FAB-HRMS calcd for $C_{46}H_{46}NO_9$ (M + H^+) 756.3172, found 756.3177. Anal. Calcd for $C_{46}H_{45}NO_9$: C, 73.10; H, 6.00; N, 1.85. Found: C, 73.31; H, 6.02; N, 1.94.

Ethyl 1-(3,4-Dimethoxyphenyl)-2-(2-benzyloxy-4,5-dimethoxy)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (17b). IR ($CHCl_3$): ν_{max} 3019, 2937, 2837, 1684, 1610, 1583, 1500, 1335, 1215, 1130, 1064, 1026 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.93 (t, 3H, J = 7.0 Hz), 3.08 (apparent t, 2H, J = 6.6 Hz), 3.35 (s, 3H), 3.56 (s, 3H), 3.66 (s, 3H), 3.76 (s, 3H), 3.83 (s, 3H), 3.90 (s, 3H), 4.06 (q,

2H, J = 7.0 Hz), 4.65 (apparent t, 2H, J = 6.6 Hz), 4.84 (s, 2H), 6.45 (s, 1H), 6.61 (s, 1H), 6.72 (apparent s, 2H), 6.74 (apparent s, 3H), 7.13−7.25 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8, 29.1, 42.8, 55.2, 55.7, 55.85 (2 carbons), 55.94, 56.3, 59.5, 72.1, 100.8, 108.8, 110.8, 111.0, 114.2, 115.8, 118.3, 119.2, 121.1, 121.8, 123.2, 125.8, 126.8, 127.4, 128.2, 128.3, 128.6, 130.8, 137.9, 143.0, 147.3, 147.6, 148.0, 148.3, 148.5, 150.8, 161.9. LRMS (EI) *m/z* (rel intensity) 680 (M + H$^+$, 40), 679 (M$^+$, 95), 590 (10), 589 (45), 588 (87), 544 (20), 543 (69), 542 (77), 527 (20), 511 (45), 500 (31), 484 (20), 468 (12), 452 (12), 440 (12), 424 (9), 178 (8), 165 (13), 91 (100), 65 (15). FAB-HRMS calcd for $C_{40}H_{42}NO_9$ (M + H$^+$) 680.2860, found 680.2862.

F. General Procedure for O-Debenzylation/Lactonization. 2-Carboethoxy pyrrole (**17a** or **17b**; 1 equiv) was dissolved in toluene (40 mL/mmol) at room temperature. Amberlyst-15 (3 equiv) was then added, and the resulting mixture was stirred at 105 °C for 18 h. The reaction was filtered, the polymer washed with DCM and EtOAc, and the crude concentrated under reduced pressure. The crude material was purified by recrystallization from MeOH/hexanes to furnish the desired lamellarins **18a** (63%) or **13b** (90%).

14-(3,4-Dimethoxyphenyl)-3-hydroxy-2,11,12-trimethoxy-8,9-dihydro-6*H*-chromeno[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (18a). mp (MeOH/hexanes) 240−241 °C. IR (KBr): ν_{max} 3396 (br), 3000, 2936, 2834, 1676, 1610, 1519, 1485, 1438, 1415, 1339, 1320, 1252, 1246, 1216, 1165, 1045, 862 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.12 (apparent t, 2H, J = 7.0 Hz), 3.37 (s, 3H), 3.49 (s, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 3.97 (s, 3H), 4.74−4.84 (m, 2H), 5.90 (br s, 1H), 6.63 (s, 1H), 6.70 (s, 1H), 6.76 (s, 1H), 6.95 (s, 1H), 7.06−7.10 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.6, 42.3, 55.1, 55.5, 55.9, 56.1, 56.2, 103.3, 103.9, 108.5, 110.1, 110.9, 111.7, 113.6, 113.9, 114.5, 119.9, 123.6, 126.6, 128.0, 128.2, 135.8, 143.3, 145.4, 146.3, 147.3, 148.7, 148.9, 149.6, 155.6. LRMS (EI) *m/z* (rel intensity) 530 (M + H$^+$, 34), 529 (M$^+$, 100), 515 (11), 514 (14), 454 (14), 233 (7), 218 (8), 189 (6), 183 (6), 56 (12). FAB-HRMS calcd for $C_{30}H_{28}NO_8$ (M + H$^+$) 530.1815, found 530.1819. Anal. Calcd for $C_{30}H_{27}NO_8$: C, 68.04; H, 5.14; N, 2.65. Found: C, 67.82; H, 5.29; N, 2.69.

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Supporting Information Available: ^{1}H and ^{13}C NMR of **10a**, **10b**, **12a**, **12b**, **13a**, **16b**, **17a**, **17b**, and **18a** and an extensive table of the α-keto bromination reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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