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Total Synthesis of Natural and Unnatural Lamellarins with Saturated and Unsaturated D-Rings

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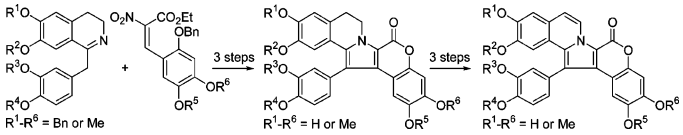

Twenty-eight natural and unnatural lamellarins with either a saturated or an unsaturated D-ring were synthesized according to our developed synthetic route. The key step involved the Michael addition/ring closure (Mi−RC) of the benzyldihydroisoquinoline and α-nitrocinnamate derivatives, which provided the 2-carboethoxypyrrole intermediates in moderate to good yields (up to 78% yield). Subsequent hydrogenolysis/lactonization furnished lamellarins with a saturated D-ring in excellent yields (up to 93% yield). DDQ oxidation of the saturated lamellarin acetates led directly to the corresponding unsaturated analogues in 54−95% yield. In addition, only two steps in our developed strategy require column chromatography.

Introduction

Lamellarins exhibit a wide array of potentially therapeutically useful biological activities. Their advancement as drug candidates for treatment of some forms of cancer and AIDS has become increasingly significant due to their multidrug resistance (MDR) reversal in some cancer cell lines and inhibition against HIV-1 integrase.[1] Since the first isolation in 1985, over 30 members belonging to this class of compounds have been isolated from ascidians and mollusks, and new lamellarins are continually identified and reported.[2] The structure of most lamellarins is generally pentacyclic in nature (**1**) and contains polyoxygenated aromatics on their periphery (Figure 1). Significant differences in lamellarin structure occur at the D-ring; for instance, some feature a 2-pyrrolodihydroisoquinoline lactone (**2** and **3**) or 2-pyrroloisoquinoline lactone (**4**) as their core. A small number of lamellarins (**5** and **6**) possess an "open

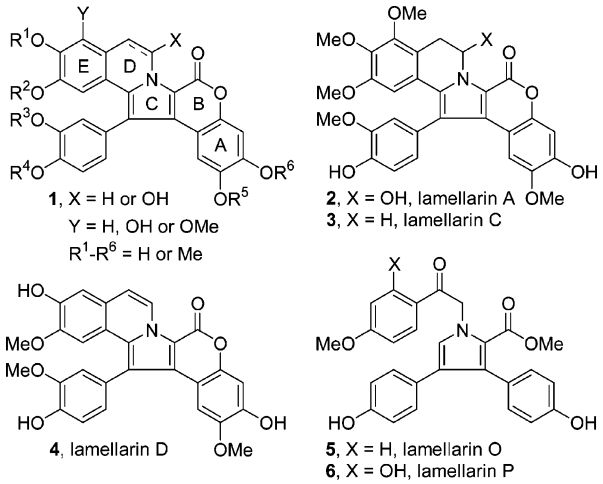

FIGURE 1. General structure (**1**) and some representative members of lamellarins (**2**−**6**).

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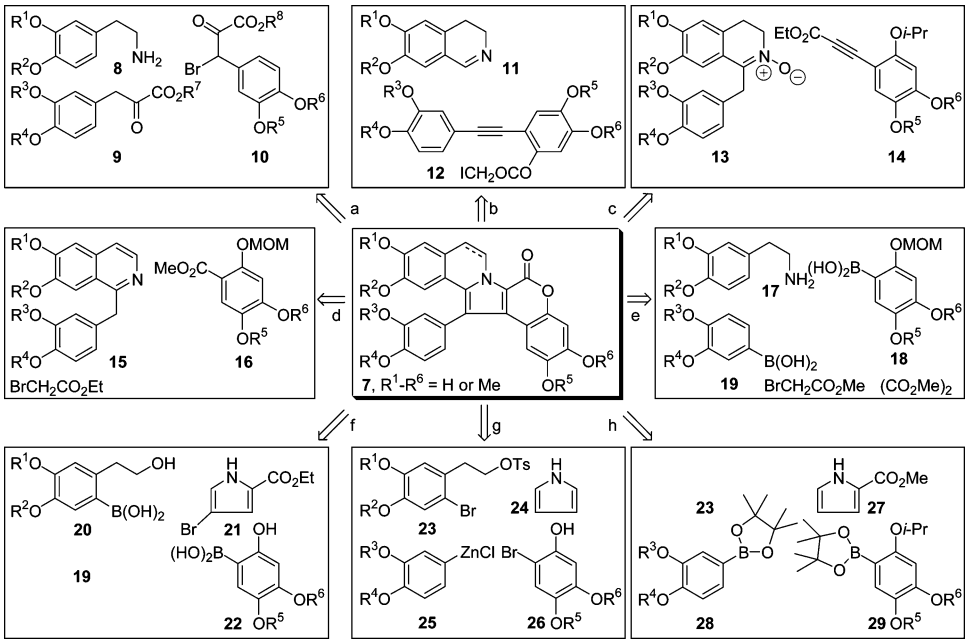
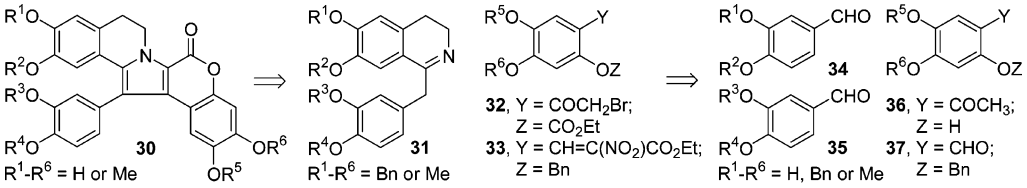
SCHEME 1. Several Retrosynthetic Analyses for the Lamellarin Framework[a]



[a] Route a = Steglich; b and g = Banwell; c = Guitián; d and e = Ishibashi; f = Handy; h = Álvarez.

SCHEME 2. Our Retrosynthetic Analysis for the Lamellarin Framework



structure" where the pyrrole and dihydroisoquinoline moieties are not fused.

Both NMR and X-ray crystallography revealed that the aromatic group on the pyrrole is orthogonal to the rest of the relatively planar pentacyclic system.[2d,3] Such molecular arrangement has been implicated in a plausible mode of their anticancer action in which the orthogonal aromatic ring serves as a "hook" while the remaining part of the lamellarin skeleton intercalates into DNA.[1a,4] Recently, topoisomerase I has been identified as a leading molecular target for lamellarin D.[5] Moreover, when a number of O-sulfated analogues of lamellarin α were studied, selective inhibition against HIV-1 integrase could be established from different patterns of oxygenation on the periphery of these lamellarin derivatives.[6]

Because of the minute amount of lamellarins from natural sources and the need to establish a more comprehensive structure−activity relationship (SAR), total synthesis of lamellarins is an attractive alternative to provide sufficient quantity of compounds for detailed biological evaluations as both potential anticancer and anti-HIV agents.[7] Thus far, detailed synthetic and biological investigations of lamellarin D and its structural analogues as potential anticancer agents have been extensively performed and reported.[5] However, the lack of comprehensive SAR for other lamellarins in various cancer cell lines has prompted us to reinvestigate the synthesis of other members of natural as well as some unnatural analogues in the lamellarin family. Since the early 1990s, a number of convergent and flexible strategies for the synthesis of lamellarin skeleton **7** have been developed as shown retrosynthetically in Scheme 1. Despite the relatively large number of strategies, they fall into two categories of (1) forming the pyrrole as the key step (routes a−e) from intermediates **8**−**19** and (2) elaborating the

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pre-existing pyrrole (routes f−h) using intermediates **20**−**29**.[1a,3a,5f,8] In addition, other synthetic approaches toward the "open structure" lamellarins have been developed.[1a]

Our synthetic route for the lamellarin framework (**30**) has focused on the pyrrole formation as the key step. A condensation reaction between an appropriately substituted benzyldihydroisoquioline unit (**31**) and a derivative of either phenacyl bromide (**32**) or α-nitrocinnamate (**33**) under basic conditions furnishes the desired pyrrole core (Scheme 2).[9] The lamellarin framework **30** could be analyzed to consist of two benzaldehyde derivatives (**34** and **35**) as their benzyldihydroisoquinoline synthon **31** and either acetophenone **36** or another benzaldehyde **37** as the other aryl group of the aromatic lactone. This synthetic approach developed in our laboratory has now been employed in preparing differently substituted natural and unnatural lamellarins having either a saturated or an unsaturated D-ring.

Results and Discussion

Structural analysis of the naturally occurring lamellarins revealed that the benzyldihydroisoquinoline unit shares the common benzaldehyde derivatives **38**−**41**, while the aryl group of the aromatic lactone except that in lamellarin G commonly arose from the benzaldehyde **42** derivable from **38** as shown in Figure 2.[10] The aryl group of the aromatic lactone in lamellarin G and its trimethyl ether had their origin in benzaldehydes **43** and **44**, respectively. Our developed strategy focused on the synthesis of lamellarins containing the dihydroisoquinoline moiety to provide lamellarins that contain a saturated D-ring. It is expected, however, that those lamellarins containing an unsaturated D-ring could arise from oxidation of the corresponding saturated analogues.

Synthesis of Lamellarins Containing a Saturated D-Ring. Following our developed synthesis, the natural lamellarins containing a saturated D-ring were prepared accordingly. Preparation of the required benzyldihydroisoquinoline derivatives (**31**) followed the preparative procedures well documented

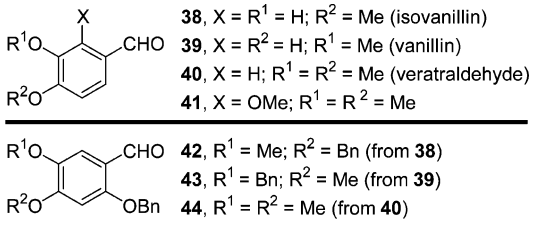

FIGURE 2. Structures of the benzaldehyde derivatives as basic building blocks.

in the literature.[11] As shown in Scheme 3, the key intermediate β-nitrostyrenes (**46**−**49**) underwent LAH reduction or $NaBH_4$ reduction followed by reaction with $NaNO_2$ in acetic acid to provide the appropriately substituted aryl ethylamines (**50**−**53**) and arylacetic acids (**56** and **57**), respectively. Subsequent amide formation between aryl ethylamines (**50**−**54**) and acid chlorides derived from aryl acetic acids (**55**−**57**) followed by Bischler−Napieralski reaction of these amides furnished the desired benzyldihydroisoquinoline derivatives (**58**−**69**). The overall reaction sequences proceeded in moderate to good yields over eight steps as the longest linear sequence from the commercially available vanillin (**38**), isovanillin (**39**), and 2,3,4-trimethoxybenzaldehyde (**41**). It should be noted that some benzyldihydroisoquinolines were prepared using either commercially available aryl ethylamine **54** (homoveratrylamine) or aryl acetic acid **55** (homoveratric acid).

All starting materials used to prepare benzyldihydroisoquinoline derivatives except 2,3,4-trimethoxybenzaldehyde were also employed for preparing four α-nitrocinnamates.[11] Depending on the structures of these α-nitrocinnamates, the reaction sequence generally involved O-benzylation of the phenolic group in vanillin or isovanillin, Baeyer−Villiger oxidation followed by KOH-mediated hydrolysis, O-benzylation of the resulting phenolic group, Vilsmeier aromatic formylation, and Knoevenagel reaction of the benzaldehyde moiety to the desired α-nitrocinnamate. The overall reaction sequences proceeded smoothly, giving **70**−**73** up to 66% yield over 1−5 steps (Scheme 4). It should be noted that the final Knoevenagel reaction of vanillin-derived α-nitrocinnamate **72** was not effective and required the use of $TiCl_4$.

With both benzyldihydroisoquinoline and α-nitrocinnamate derivatives in hand, we then performed a detailed investigation to optimize the base-mediated Michael addition/ring closure (Mi−RC) reaction sequence. We reported earlier that Mi−RC could be best carried out in refluxing anhydrous acetonitrile using $NaHCO_3$ as base.[9c,d] A number of other reaction conditions were examined, and the results are summarized in Table 1.

First, the reaction was modeled using nitrostyrene[12] as the Michael acceptor (entries 1−4). No reaction occurred at room temperature in anhydrous acetonitrile; refluxing facilitated reaction, albeit not leading to the desired product. The ^1H NMR analysis of the crude reaction mixture revealed that the starting material nitrostyrene was completely consumed, but the reaction proceeded to give only an inseparable mixture of unidentifiable products. We then turned to a more powerful Michael acceptor **72**, which is structurally more relevant as an appropriate synthon for lamellarins (see below). Sodium bicarbonate is the base of choice for this reaction (entries 5−16). Interestingly, when Et_3N

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(10) Exceptions to this analysis are lamellarins H, S, Z, *β*, *γ*, and *ϕ*, which contain at least one catechol moiety as a peripheral aromatic group, and lamellarins O, P, Q, and R, which contain the "open structure".

(11) For individual steps, see ref 9c and references cited therein (refs 14−24).

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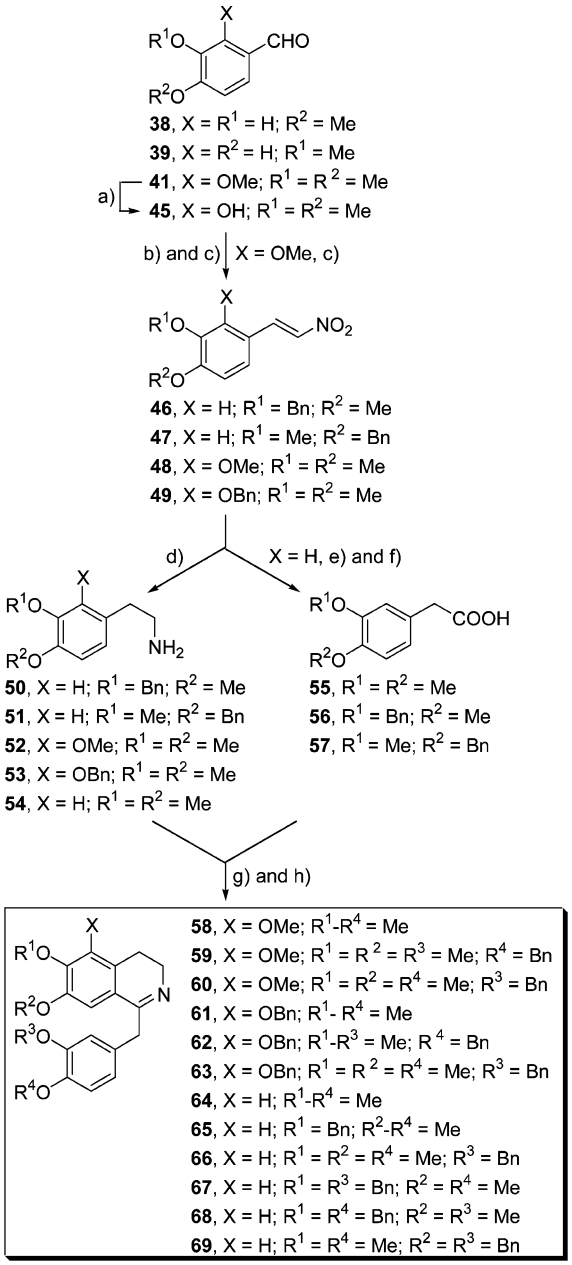
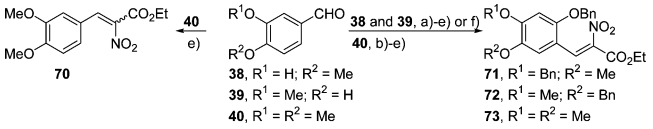
SCHEME 3. Synthesis of Dihydroisoquinoline Derivatives 58−69[a]



[a] Reagents and conditions: (a) $AlCl_3$, PhH, 87%; (b) K_2CO_3, BnBr, acetone, reflux, 6 h, 86%−93%; (c) $MeNO_2$, $(NH_3CH_2)_2$·COOH, AcOH, rt, 16−24 h, 80% (**46**), 96% (**47**), 80% (**48**), 84% (**49**); (d) LAH, THF, rt, 24 h, 93% (**50**), 96% (**51**), 83% (**52**), 95% (**53**); (e) $NaBH_4$, EtOH, rt, 55%−62%; (f) $NaNO_2$, AcOH, DMSO, rt, 60% (**56**), 72% (**57**); (g) (i) **55**−**57**, $(COCl)_2$, DMF (cat.), DCM, rt, 2 h, (ii) **50**−**54**, Na_2CO_3, DCM, H_2O, rt, 2 h, 51−98% (over two steps); (h) $POCl_3$, DMF, rt, 3 h, 94% (**58**), 98% (**59**), 93% (**60**), 78% (**61**), 80% (**62**), 66% (**63**), 98% (**64**), 84% (**65**), 93% (**66**), 94% (**67**), 98% (**68**), 92% (**69**).

was used as base (entry 14), the oxidized product **74** was formed in 20% yield instead of the expected product **75** (Figure 3). However, in a separate experiment **75** could not be converted into **74** using Et_3N as base in acetonitrile while exposing the reaction to oxygen in air, indicating that there might be some transient oxidizing species in the reaction mixture of entry 14 before workup. Among the solvents employed for the optimization of nitroolefin **70**, ethanol gave the best result, furnishing

SCHEME 4. Synthesis of α-Nitrocinnamate Derivatives 70−73[a]



[a] Reagents and conditions: (a) K_2CO_3, BnBr, acetone, reflux, 6 h, 86%−93%; (b) (i) *m*-CPBA, DCM, reflux, 18 h, (ii) KOH, MeOH, rt, 18 h, 86%−99% (over two steps); (c) K_2CO_3, BnBr, acetone, reflux, 6 h, 67%−80%; (d) $POCl_3$, DMF, 3 h, 97%−99%; (e) $O_2NCH_2CO_2Et$, Et_2NH·HCl, toluene, reflux, 48 h, 66% (**70**), 67% (**71**), 55% (**73**); (f) $TiCl_4$, DIPEA, DCM, rt, 2 h, 40% (**72**).

the desired product **75** in 68% yield (entry 12), which is slightly better than acetonitrile (60% yield; entry 8). However, Mi−RC of nitroolefin **71**, under similar reaction conditions, was best performed in anhydrous acetonitrile, which provided the corresponding product **76** in 63% yield, while only 16% yield was obtained from the reaction using ethanol as solvent (entries 17 and 18). Thus, with different substrates, acetonitrile appears superior to ethanol for the Mi−RC. It should be noted that use of anhydrous solvents is crucial as the presence of water in wet solvents could lead to the corresponding benzaldehyde **38** or **40** as a result of the reverse Knoevenagel reaction. In addition, use of 50% aqueous NaOH in the presence of $BnMe_3NCl$ as a phase-transfer reagent also provided the product **75** in moderate yield (entry 15). Interestingly, when *n*-Bu_4NBr was heated to its melting point at 105 °C and was subsequently used as solvent for this reaction in the form of molten salt,[13] the Mi−RC proceeded smoothly to give the product **75** in 61% yield (entry 16).

The reason for employing α-nitrocinnamate **70** for this optimization was 2-fold. First, it is readily available in one step from veratraldehyde. More importantly, we anticipated that if the Mi−RC using **70** was successful, the lactone ring could be formed via $Pb(OAc)_4$-mediated oxidative lactonization as previously reported by Steglich.[3] After 2-carboethoxypyrrole **75** was obtained, saponification using KOH in refluxing EtOH/H_2O was performed. Unfortunately, the corresponding acid **77** was unexpectedly labile and decarboxylated to 2*H*-pyrrole derivative **78** via acid-mediated decarboxylation even upon neutralization and acidification of the crude mixture or upon dissolving in $CDCl_3$, which apparently contained a minute amount of acid (Scheme 5). Lamellarin G trimethyl ether **79** was not detected even in the crude ^1H NMR. Various attempts to obtain such an elusive acid either in crude or in pure form were not successful. Use of a crude unneutralized mixture presumably containing the corresponding carboxylate in the subsequent $Pb(OAc)_4$-mediated oxidative lactonization gave only the decarboxylated product perhaps due to acetic acid present in $Pb(OAc)_4$.

Such unsuccessful attempts prompted us to reconsider other approaches, which utilize the benzyloxy group as a masked hydroxy group for lactonization. We have previously reported Amberlyst-15 mediated O-debenzylation/lactonization of **76** as an alternative.[9d] However, side reactions of C-benzylation increased with the number of benzyl groups. In addition, preparation of the appropriately substituted phenacyl bromide carbonates like **32** (with R^5 or R^6 = benzyl) for Friedel−Crafts transacylation/lactonization[9d] proved difficult and thus was not practical or synthetically useful for preparing lamellarins. We then reinvestigated the exhaustive hydrogenolysis/base-

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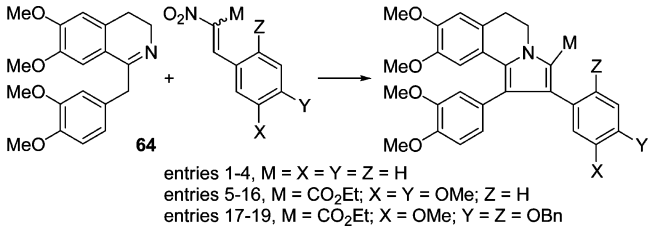
TABLE 1. Reaction Conditions for the Base-Mediated Mi−RC of 64[a]



entry	nitroolefin[b]	base	equiv	additives	solvent[c]	*T* (°C)	time (h)	yield (%)[d]
1	A	none		none	MeOH	rt	18	0[e]
2	A	none		$ZnCl_2$[f]	MeCN	rt	96	0[e]
3[g]	A	$NaHCO_3$	2.2	none	MeCN	rt	18	0[e]
4[g]	A	$NaHCO_3$	2.2	none	MeCN	reflux	18	0[h]
5[g]	B	Na_2CO_3	2.2	none	dioxane	rt	18	0[e]
6[g]	B	LDA	2.0	none	PhMe	rt[i]	18[i]	0[e]
7	B	none		none	MeCN	rt	18	10
8	B	$NaHCO_3$	1.5	none	MeCN	reflux	18	60[j]
9	B	$NaHCO_3$	1.5	none	THF	reflux	18	40[k]
10	B	$NaHCO_3$	1.5	none	PhMe	reflux	18	10[k]
11	B	$NaHCO_3$	1.5	none	dioxane	reflux	18	25[k]
12	B	$NaHCO_3$	1.5	none	EtOH	reflux	18	68[k]
13	B	$NaHCO_3$	1.5	none	DMF	reflux	18	11[k]
14	B	Et_3N	1.5	none	MeCN	reflux	18	20[l]
15	B	50% NaOH	6.0	PTC[m]	pyridine	rt	18	40
16[n]	B	none		none	*n*-Bu_4NBr	105	1	61
17	C	$NaHCO_3$	1.5	none	MeCN	reflux	18	63
18	C	$NaHCO_3$	1.5	none	EtOH	reflux	18	16
19	C	$NaHCO_3$	1.5	none	DCM	reflux	18	43

[a] Unless otherwise noted, free base form of **64** was employed. [b] 1 equiv of nitroolefin was used. A = nitrostyrene; B = **70**; C = **71**. [c] All solvents were dried and distilled according to standard literature procedures prior to use. THF = tetrahydrofuran; DMF = *N*,*N*-dimethylformamide; DCM = dichloromethane. [d] Isolated yields. [e] All nitroolefins were recovered. [f] 0.1 equiv of $ZnCl_2$ was added. [g] Hydrochloride salt of **64** was employed. [h] Nitrostyrene was consumed, but the reaction gave no desired product. [i] Initially, the reaction was at −78 °C and was slowly raised over 3 h to room temperature at which it was stirred for 15 h. [j] Isolated yield and estimated yield by integration of the crude ^{1}H NMR using piperonal as an internal standard were comparable (63% estimated yield). [k] Estimated yield by integration of the crude ^{1}H NMR using piperonal as an internal standard. [l] The reaction gave the corresponding oxidized product **74**. [m] PTR = phase-transfer reagent which is benzyltrimethylammonium chloride (2 equiv used). [n] The reaction was performed at 105 °C at which tetrabutylammonium bromide melts and thus was used as "solvent" in the form of "molten salt".

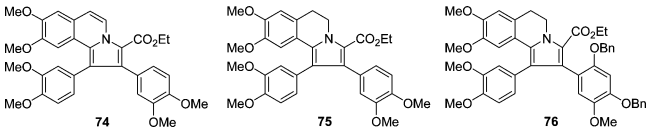
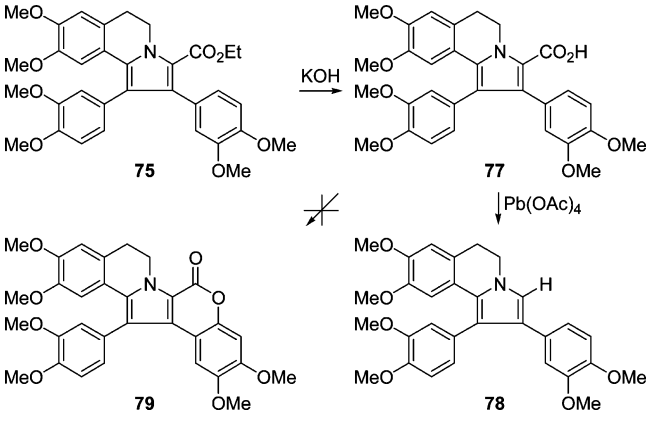


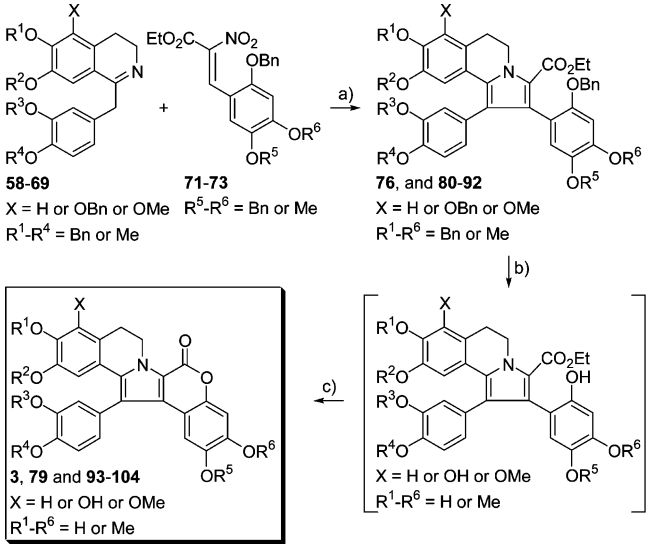
FIGURE 3. Structures of the Mi−RC products.

SCHEME 5. Attempted Synthesis of Lamellarin G Trimethyl Ether 79



mediated lactonization as an alternative.[9c] Thus, α-nitrocinnamate derivatives **71**−**73** were required for the synthesis of lamellarins containing a saturated D-ring **3**, **79**, and **93**−**104** (Scheme 6).

SCHEME 6. Synthesis of Lamellarins with a Saturated D-Ring 3, 79, and 93−104[a]



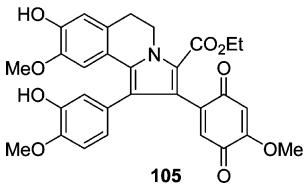
[a] Reagents and conditions: (a) $NaHCO_3$, anhydrous CH_3CN, reflux, 18 h, 57%−78% (see Table 2); (b) H_2, Pd/C, rt, 18−24 h; (c) NaH, THF, 0 C to rt, 4 h, 60%−93% (over two steps; see Table 2).

Table 2 summarizes the results of this Mi−RC/hydrogenolysis/lactonization strategy. Mi−RC reaction sequence was equally effective for all lamellarins regardless of the imines and

TABLE 2. Synthesis of Lamellarins 3, 79, and 93−104 with a Saturated D-Ring

entry	nitrocinnamate	imine	Mi−RC (%)[a]	H/L (%)[b]	lamellarin[c]	overall yield (%)[d]
1	**71**	**58**	**80** (74)	89	**93** (I)	66
2	**71**	**59**	**81** (63)	91	**3** (C)	57
3	**71**	**60**	**82** (57)	86	**94** (T)	49
4	**71**	**61**	**83** (70)	91	**95** (F)	64
5	**71**	**62**	**84** (70)	93	**96** (K)	65
6	**71**	**63**	**85** (62)	90	**97** (E)	56
7	**71**	**64**	**76** (63)	82	**98** (dihydro η)	52
8	**73**	**64**	**86** (61)	85	**79** (G-triMe)	52
9	**71**	**65**	**87** (62)	93	**99** (J)	58
10	**71**	**66**	**88** (78)	91	**100** (U)	71
11	**71**	**67**	**89** (70)	87	**101** (L)	61
12	**72**	**67**	**90** (75)	60	**102** (G)	45
13	**71**	**68**	**91** (61)	83	**103** (χ)	51
14	**71**	**69**	**92** (75)	85	**104** (Y)	64

[a] Numbers in parentheses are isolated yields. [b] H/L = hydrogenolysis/lactonization. The crude product from hydrogenolysis was used in the next step (base-mediated lactonization) without further purification. The yields are over two steps. [c] Letters in parentheses represent the literature-assigned common names for naturally occurring lamellarins with saturated D-ring. Unnatural lamellarins are dihydrolamellarin η (dihydro η; **98**) and lamellarin G trimethyl ether (G-triMe; **79**). [d] Isolated yields over three steps with two purifications.



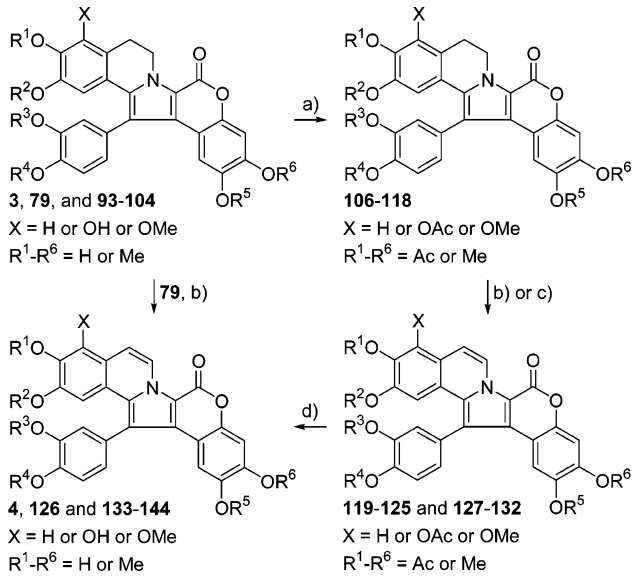
105

FIGURE 4. Structure of the proposed quinone byproduct **105**.

α-nitrocinnamate derivatives, giving the desired 2-carboethoxy pyrroles (**76** and **80**−**92**) in good yields (57−78% yield). Subsequent exhaustive hydrogenolysis followed by NaH-mediated lactonization of the corresponding unmasked phenol proceeded smoothly and gave the desired lamellarins **3**, **79**, and **93**−**104** in good to excellent yields (60−93% yield). It should be noted that the yield for this two-step reaction for lamellarin G was noticeably lower than those for others; this result could be due to the ease of forming the corresponding unisolable quinone **105** from an intermediate of the hydrogenolysis under basic conditions (Figure 4). Overall, naturally occurring lamellarins C, E, F, G, I, J, K, L, T, U, Y, and χ as well as unnatural lamellarins (**3**, **79**, and **93**−**104**) were obtained in moderate to good yields (45−71% yield) in three steps with two purifications.

Synthesis of Lamellarins Containing an Unsaturated D-Ring. With lamellarins containing a saturated D-ring in hand, we next turned our attention to those containing an unsaturated D-ring. We envisioned that oxidation of the lamellarins **3**, **79**, and **93**−**104** with an appropriate oxidizing agent would provide the corresponding lamellarins containing an unsaturated D-ring. It should be noted that direct DDQ oxidation of lamellarin **98** containing an unprotected hydroxy group was expectedly unsuccessful and gave only polar mixtures of unidentifiable compounds. In addition, direct DDQ oxidation of **76** and **86**, which contain one or two benzyl groups, gave the corresponding products in low yields (20% and 25% yields, respectively), and the subsequent Amberlyst-15 mediated O-debenzylation/lactonization of such products also suffered from the side reactions of C-benzylation. Thus, the free hydroxy groups in each lamellarin were first converted into their acetates **106**−**118** (Scheme 7) upon treating with acetyl chloride in the presence of Et_3N and catalytic amount of DMAP.[14]

SCHEME 7. Synthesis of Lamellarins with an Unsaturated D-Ring 4, 126, and 133−144[a]



[a] Reagents and conditions: (a) AcCl, DMAP (cat.), Et_3N, DCM, rt, 4 h, 87%−100%; (b) DDQ (2.5 equiv), DCM, rt, 18 h, 86%−99% (see Table 3); (c) DDQ (2.5 equiv), DCM or DCE, reflux, 18−72 h, 67−93% (see Table 3); (d) (i) 5% KOH in EtOH, rt, 5−10 min, (ii) 2 N HCl, 72%−100% (see Table 3).

Upon treatment with DDQ in DCM at room temperature, the acetates of lamellarins C, T, U, and I, and that of dihydrolamellarin η proceeded to give the corresponding acetates of lamellarins B, W, α, ζ, and η, respectively. However, for those lamellarins whose aryl group of the dihydroisoquinoline contains an acetate (lamellarins K, L, E, F, G, J, Y, and η), refluxing the reaction mixture either in DCM or in DCE normally for 18 h was necessary for the reaction to proceed to completion. It is

(14) It has been reported that the triacetates of lamellarin K and L were oxidized to the corresponding triacetates of lamellarin M and N using DDQ in refluxing ethanol. (For experimental details of DDQ oxidation in EtOH, see: Carroll, A. R.; Bowden, B. F.; Coll, J. C. *Aust. J. Chem.* **1993**, *46*, 489−501.) However, in our hand, such reaction conditions did not furnish the desired products, as the triacetates of lamellarin K and L were not soluble in ethanol even at elevated temperature.

TABLE 3. Synthesis of Lamellarins 4, 126, and 133−144 with an Unsaturated D-Ring

entry	lamellarin	acetylation (%)[a]	DDQ oxidation (%)[a,b]	deacetylation (%)[a,c]	overall yield (%)[a]
1	**93** (I)	**106** (100)	**119** (92)	**133** (ζ, 97)	89
2	**3** (C)	**107** (95)	**120** (86)	**134** (B, 95)	78
3	**94** (T)	**108** (96)	**121** (99)	**135** (W, 72)	68
4	**95** (F)	**109** (100)	**122** (89)[d]	**136** (ϵ, 100)	89
5[e]	**96** (K)	**110** (92)	**123** (85, 90)	**137** (M, 97)	76, 80
6[e]	**97** (E)	**111** (100)	**124** (71, 86)	**138** (X, 100)	71, 86
7	**98** (dihydro η)	**112** (100)	**125** (89)	**139** (η, 100)	89
8[f]	**79** (G-triMe)		**126** (95)		95
9	**99** (J)	**113** (93)	**127** (81)[d]	**140** (J-DB, 100)	75
10	**100** (U)	**114** (95)	**128** (94)	**141** (α, 100)	89
11[e]	**101** (L)	**115** (87)	**129** (84, 80)	**142** (N, 100)	73, 70
12[e]	**102** (G)	**116** (88)	**130** (93, 83)	**143** (G-DB, 100)	82, 73
13[e]	**103** (χ)	**117** (88)	**131** (62, 67)	**4** (D, 99)	54, 58
14	**104** (Y)	**118** (96)	**132** (80)[d,g]	**144** (Y-DB, 98)	75

[a] Numbers in parentheses are isolated yields. [b] Unless otherwise noted, yields of these reactions were of those performed in DCM. [c] The first letters in parentheses represent the literature-assigned common names for naturally occurring lamellarins with unsaturated D-ring. Unnatural lamellarins are J-DB (**140**), G-DB (**143**), and Y-DB (**144**). [d] These reactions were performed in DCE (dichloroethane). [e] Yields in parentheses for DDQ oxidation were of the reactions performed in refluxing DCM and DCE for 18 h, respectively. The two overall yields were calculated from these two reaction conditions of DDQ oxidation. [f] Because lamellarin G trimethyl ether does not possess any free hydroxy group, acetylation and deacetylation were not performed. The oxidized product **126** is an unnatural lamellarin G-triMe-DB (or permethylated lamellarin H). [g] When DCM was used, there was no reaction either at room temperature or at reflux for up to 72 h. In refluxing DCE, the reaction took 72 h to complete.

interesting to note that lamellarin Y acetate required much longer reaction time (72 h) even when DCE was used as solvent. The final step required removal of the acetate. To our surprise, these aromatic O-acetates were unexpectedly difficult to remove using saturated $NaHCO_3$ solution, a reaction condition typically employed for such removal.[15] After some experimentation, we found that the removal of acetates required 5% KOH in EtOH. It was observed that the best way to prevent other side reactions was to acidify the reaction mixture with 2 N HCl immediately after the acetate was completely dissolved in the ethanol solution (normally 5−10 min).[16] The results of these reaction sequences are summarized in Table 3. Overall, both natural and unnatural lamellarins with an unsaturated D-ring were obtained in moderate to excellent yields (54−95%).

Conclusion

Significant progress has been reported recently in the investigation of the detailed structure−activity relationship of lamellarin D and its analogues; this progress includes the implication of their possible mode(s) of action at the molecular level. More comprehensive SARs for other members of the lamellarin family are necessary for (1) identifying suitable and potential lead compound(s) for further development of drug candidates and (2) developing a better understanding of their anticancer action, especially their ability to reverse multidrug resistance against some cancer cell lines. However, total synthesis of all available members of lamellarins represents a daunting and challenging task, which requires a general synthetic strategy applicable for virtually all lamellarins. Among our developed synthetic approaches for lamellarins, the three-step Mi−RC/exhaustive hydrogenolysis/base-mediated lactonization protocols are the most efficient as they provide 14 natural and unnatural lamellarins with a saturated D-ring in 45−71% yields with only one purification involving column chromatography. In addition, the obtained lamellarins with a saturated D-ring could be converted into the corresponding analogues with an unsaturated D-ring via a convenient and efficient three-step acetylation/DDQ oxidation/deacetylation strategy, which provided the products in 54−95% yields with only one purification involving column chromatography. Over six steps from Mi−RC, lamellarins with an unsaturated D-ring could be obtained in 28−63% yields. Therefore, our synthetic approach offers several advantages over other existing synthetic methods because the synthesis of the benzyldihydroisoquinoline derivatives is well-established. It has been shown that our strategy is general for a wide range of lamellarins with a "fused" skeleton. Moreover, our protecting group strategy is simplified, as only benzyl (for those with a saturated D-ring) and acetate (for those with an unsaturated D-ring) are employed as hydroxy-protecting groups. Out of six chemical steps developed in our laboratory, only two involve the use of column chromatography for purification, while the crude materials either of the benzyldihydroisoquinolines from Bischler−Napieralski reaction for subsequent Mi−RC or of the "free phenols" from exhaustive hydrogenolysis could be used directly in the next step without purification. In addition, all of our synthons and reagents have been shown to possess good chemical stability under reaction conditions employed and upon storage. Overall, 28 natural and unnatural lamellarins with either saturated or unsaturated D-rings were successfully prepared. Biological evaluations of these natural and unnatural lamellarin analogues are underway and will be reported in due course.

Experimental Section

Ethyl 3-(2,5-Dibenzyloxy-4-methoxyphenyl)-2-nitroacrylate (72). To a mixture of 2,5-dibenzyloxy-4-methoxybenzaldehyde (1.00 g, 2.87 mmol), ethyl nitroacetate (0.32 mL, 2.87 mmol), and diisopropylethylamine (1.96 mL, 11.50 mmol) in DCM (25 mL) was added dropwise a solution of titanium tetrachloride (0.55 g, 2.87 mmol) in DCM (6 mL). The mixture was stirred at room temperature for 2 h. The reaction mixture was transferred to a quick column (SiO_2) and eluted with DCM. Solvent was removed under

(15) The aromatic O-acetates were not removed even upon stirring with saturated $NaHCO_3$ in DCM with Bu_4NBr serving as a phase-transfer reagent at room temperature for 18−24 h. Performing such reactions in refluxing DCM or DCE with Bu_4NBr was not effective.

(16) Longer reaction times resulted in much lower yields presumably from base-mediated opening of the lactone and possibly subsequent decarboxylation of the pyrrole-2-carboxylate (Scheme 5) upon acidification of the crude mixture.

reduced pressure to provide a crude product, which was further purified by column chromatography on silica (70% DCM/hexanes) to furnish the desired product **72** as a yellow solid of a 1:1 mixture of cis and trans isomers (0.53 g, 1.15 mmol, 40%). Recrystallization from MeOH gave an analytically pure red crystal as a single isomer. mp (MeOH) 119.5−120 °C. IR (KBr): ν_{max} 1722, 1609, 1526, 1255, 1225, 1208, 1007 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (t, J = 7.4 Hz, 3H), 3.85 (s, 3H), 4.31 (q, J = 7.2 Hz, 2H), 5.00 (s, 2H), 5.12 (s, 2H), 6.50 (s, 1H), 6.82 (s, 1H), 7.39−7.47 (m, 10H), 7.98 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 56.0, 62.4, 71.6, 71.8, 88.6, 110.2, 113.3, 127.2, 127.3, 127.6, 127.9, 128.2, 128.5, 128.7, 136.1, 136.4, 138.0, 142.8, 154.4, 154.7, 159.9. LRMS (EI) *m*/*z* (rel intensity) 463 (M^+, 6), 326 (11), 253 (9), 235 (7), 91 (100), 65 (14). TOF-HRMS calcd for $C_{26}H_{26}NO_7$ ($M + H^+$) 464.1715, found 464.1714. Anal. Calcd for $C_{26}H_{25}NO_7$: C, 67.38; H, 5.44; N, 3.02. Found: C, 67.13; H, 5.57; N, 2.86.

Representative Example for Pyrrole Formation via Mi−RC (Ethyl 1-(3-Benzyloxy-4-methoxyphenyl)-2-(2,4-dibenzyloxy-5-methoxyphenyl)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (88)). To a stirred solution of benzyldihydroisoquinoline **66** (0.50 g, 1.23 mmol) in anhydrous acetonitrile (13 mL) at room temperature were added sodium bicarbonate (0.10 g, 1.23 mmol) and α-nitrocinnamate **71** (0.38 g, 0.82 mmol). The mixture was heated to reflux for 18 h. At that time, the reaction was cooled to room temperature, and sodium bicarbonate was filtered off. Successive washings (3×) with EtOAc followed by concentration under reduced pressure of the combined organic materials furnished crude product, which was further purified by column chromatography on silica (30% EtOAc/hexanes) to provide the desired product 2-carboethoxypyrrole **88** as a sticky gum (0.53 g, 0.64 mmol, 78%). IR (neat): ν_{max} 2933, 2900, 2833, 2091, 1683, 1609, 1531, 1497, 1480, 1454, 1396, 1383, 1333, 1251, 1210, 1173, 1127, 1062, 1022 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.83 (t, J = 8.0 Hz, 3H), 3.05 (apparent t, J = 6.4 Hz, 2H), 3.30 (s, 3H), 3.64 (s, 3H), 3.83 (s, 3H), 3.88 (s, 3H), 3.97 (q, J = 8.0 Hz, 2H), 4.61 (br m, 2H), 4.72 (s, 2H), 4.76 (s, 2H), 5.01 (s, 2H), 6.43 (s, 1H), 6.59 (d, J = 8.0 Hz), 6.76 (s, 3H), 7.02−7.10 (m, 1H), 7.20−7.32 (m, 10H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 29.3, 43.0, 55.3, 56.1, 56.3, 56.8, 59.7, 71.2, 71.6, 72.0, 103.7, 107.4, 109.0, 111.0, 112.0, 116.7, 116.8, 117.2, 119.3, 121.3, 121.9, 123.4, 124.0, 125.9, 126.9, 127.3, 127.4, 127.5, 127.9, 128.4, 128.5, 128.6, 131.1, 137.3, 137.4, 138.1, 144.0, 147.5, 148.2, 148.6, 150.9, 162.2. LRMS (EI) *m*/*z* (rel intensity) 832 ($M + H^+$, 11), 831 (M^+, 15), 741 (15), 651 (11), 650 (12), 91 (100), 65 (33). TOF-HRMS calcd for $C_{52}H_{50}NO_9$ ($M + H^+$) 832.3480, found 832.3466.

Representative Example for Hydrogenolysis/NaH-Mediated Lactonization (14-(3-Hydroxy-4-methoxyphenyl)-3-hydroxy-2,-11,12-trimethoxy-8,9-dihydro-6*H*-chromeno[4′,3′:4,5]pyrrolo-[2,1-*a*]isoquinolin-6-one (100; Lamellarin U)). A high-pressure Paar apparatus was charged with 2-carboethoxypyrrole **88** (0.50 g, 0.60 mmol), EtOAc (10 mL), and palladium on activated charcoal (Pd/C; ca. 0.05 g) at room temperature. The reaction was flushed with hydrogen and kept under hydrogen atmosphere (75 psi). Progress of the reaction was monitored by TLC until all starting material was consumed (20 h). Palladium was filtered off using Celite. After concentration under reduced pressure and removal of trace solvent under vacuum, the crude material (0.34 g, 0.60 mmol) was dissolved in anhydrous THF (60 mL) at room temperature. The reaction mixture was cooled to 0 °C, and NaH (70% dispersion in paraffin; 1.5 equiv/each hydroxy group) was added. The reaction was stirred at 0 °C for 0.5 h, and slowly warmed to room temperature at which the reaction was stirred for 4 h. At that time, a saturated solution of NH_4Cl (15 mL) and EtOAc (25 mL) was added. The two layers were separated, and the aqueous phase was extracted with EtOAc (3 × 25 mL). The aqueous phase was allowed to stir with EtOAc (20 mL) for 6 h to ensure that all lamellarins partitioned into the organic layer. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude product, which was triturated with MeOH to furnish the desired lamellarin U **100** as a white solid (0.28 g, 0.54 mmol, 91% over two steps). A small amount of these products was recrystallized from MeOH for melting point determination. mp (MeOH) 247−250 °C. IR (neat): ν_{max} 3407 (br), 3002, 2936, 2838, 1682, 1584, 1549, 1513, 1485, 1439, 1413, 1339, 1320, 1272, 1246, 1212, 1163, 1143, 1043, 1023 cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.08 (apparent t, J = 6.0 Hz, 2H), 3.24 (s, 3H), 3.38 (s, 3H), 3.76 (s, 3H), 3.81 (s, 3H), 4.52−4.70 (m, 2H), 6.67 (s, 2H), 6.79 (s, 1H), 6.87 (s, 1H), 6.89 (d, J = 6.6 Hz, 1H), 6.97 (s, 1H), 7.14 (d, J = 8.8 Hz, 1H), 9.33 (s, 1H), 9.71 (s, 1H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 28.1, 42.4, 55.0, 55.6, 56.1, 56.6, 104.1, 105.7, 109.1, 109.3, 112.4, 113.0, 114.1, 114.8, 118.3, 119.8, 122.1, 127.4, 127.8, 135.8, 144.9, 146.1, 147.3, 147.5, 148.0, 148.2, 149.4, 154.7. LRMS (EI) *m*/*z* (rel intensity) 516 ($M + H^+$, 43), 515 (M^+, 100), 258 (24). TOF-HRMS calcd for $C_{29}H_{26}NO_8$ ($M + H^+$) 516.1653, found 516.1661. These spectroscopic data are identical to those reported previously.[2g]

Representative Example for Acetylation (14-(3-Acetoxy-4-methoxyphenyl)-3-acetoxy-2,11,12-tetramethoxy-8,9-dihydro-6*H*-chromeno[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (114; Lamellarin U Diacetate)). To a mixture of lamellarin U **100** (51.5 mg, 0.10 mmol) in DCM (9 mL) at room temperature were added Et_3N (40 μL, 0.30 mmol), DMAP (30 mg, 0.25 mmol), and acetyl chloride (20 μL, 0.30 mmol). The reaction was monitored by TLC until all starting material was consumed (4 h). At that time, water (10 mL) was added, and the two layers were separated. The aqueous phase was extracted with DCM (3 × 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude product, which was purified by recrystallization (MeOH) to furnish lamellarin U diacetate **114** as a white solid (56.7 mg, 0.095 mmol, 95%). mp (MeOH) >250 °C. IR (neat): ν_{max} 2987, 2939, 2841, 1766, 1717, 1547, 1519, 1484, 1439, 1414, 1369, 1267, 1203, 1131, 1041, 1010 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.30 (s, 3H), 2.31 (s, 3H), 3.03−3.25 (m, 2H), 3.43 (s, 3H), 3.47 (s, 3H), 3.90 (s, 6H), 4.57−4.71 (m, 1H), 4.90−5.02 (m, 1H), 6.63 (s, 1H), 6.75 (d, J = 3.6 Hz, 2H), 7.10 (d, J = 8.8 Hz, 1H), 7.16 (s, 1H), 7.25 (d, J = 2.2 Hz, 1H), 7.33 (dd, J = 8.0, 2.2 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.7, 20.8, 28.8, 42.6, 55.5, 55.8, 56.1, 56.4, 105.6, 108.7, 111.1, 112.0, 113.2, 114.3, 114.5, 116.4, 119.9, 125.7, 126.7, 127.5, 127.9, 129.8, 136.4, 138.9, 140.9, 145.1, 147.7, 149.2, 151.5, 155.3, 168.7, 169.0. TOF-LRMS *m*/*z* (rel intensity) 600 ($M + H^+$, 100). TOF-HRMS calcd for $C_{33}H_{30}NO_{10}$ ($M + H^+$) 600.1864, found 600.1866.

Representative Example for DDQ Oxidation (14-(3-Acetoxy-4-methoxyphenyl)-3-acetoxy-2,11,12-tetramethoxy-6*H*-chromeno-[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (128; Lamellarin α Diacetate)). To a solution of lamellarin U diacetate **114** (20 mg, 0.033 mmol) in DCM (3.5 mL) at room temperature was added DDQ (23 mg, 0.083 mmol). The resulting mixture was stirred at room temperature for 18 h. At that time, water (5 mL) was added, and the two layers were separated. The aqueous phase was extracted with DCM (3 × 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude product, which was purified by column chromatography on silica (1% MeOH/CH_2Cl_2) to furnish lamellarin α diacetate **128** as a white solid (18.5 mg, 0.031 mmol, 94%). mp (EtOAc/hexanes) 193−198 °C. IR (neat): ν_{max} 2938, 2840, 1766, 1706, 1616, 1540, 1512, 1486, 1418, 1369, 1266, 1194, 1139, 1082, 1042 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.25 (s, 6H), 3.41 (s, 3H), 3.46 (s, 3H), 3.86 (s, 3H), 3.90 (s, 3H), 6.71 (s, 1H), 6.97−7.06 (m, 3H), 7.15 (d, J = 8.0 Hz, 1H), 7.19 (s, 1H), 7.25 (d, J = 1.4 Hz, 1H), 7.36 (dd, J = 8.0, 1.4 Hz, 1H), 9.14 (d, J = 7.4 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.4, 20.5, 55.4, 55.7, 56.0, 56.4, 105.3, 106.4, 107.6, 108.4, 110.4, 112.1, 112.9, 113.3, 115.9, 119.1, 123.1, 124.7, 126.1, 128.2, 128.6, 130.2, 134.5, 139.8, 141.1, 145.6, 147.7, 149.6, 150.4, 151.7, 155.0, 168.4, 168.6. LRMS (EI) *m*/*z* (rel intensity) 598 ($M + H^+$, 10), 597 (M^+, 41), 556 (34), 555 (100), 43 (20). TOF-HRMS calcd for $C_{33}H_{28}NO_{10}$ ($M + H^+$) 598.1708, found 598.1717.

Representative Example for Deacetylation Using 5% KOH in EtOH (14-(3-Hydroxy-4-methoxyphenyl)-3-hydroxy-2,11,12-trimethoxy-6*H*-chromeno[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (141; Lamellarin α)). To lamellarin α diacetate **128** (17.9 mg, 0.03 mmol) was added 5% KOH in EtOH (10 mL) at room temperature. The mixture was stirred at room temperature until a clear solution was obtained (5 min). At that time, the reaction was immediately acidified with 2 N HCl. The material was extracted with EtOAc (3 × 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide crude product, which was purified by recrystallization ($MeOH/CH_2Cl_2$) to furnish lamellarin α **141** as a white solid (15.3 mg, 0.03 mmol, 100%). mp ($MeOH/CH_2Cl_2$) >250 °C (lit.[2e] 228−230 °C, >260 °C; lit.[6b,8h] >260 °C). IR (neat): ν_{max} 3405 (br), 2993, 2927, 2851, 1679, 1511, 1453, 1429, 1403, 1268, 1223, 1165, 1084, 1046, 1020 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ 3.36 (s, 6H), 3.85 (s, 6H), 6.74 (s, 1H), 6.85 (s, 1H), 6.98 (d, J = 8.0 Hz, 1H), 7.00 (s, 1H), 7.16 (d, J = 8.0 Hz, 1H), 7.24 (s, 1H), 7.26 (d, J = 7.2 Hz, 1H), 7.37 (s, 1H), 9.00 (d, J = 7.2 Hz, 1H), 9.40 (s, 1H), 9.86 (s, 1H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 54.9, 55.6, 56.0, 56.6, 104.2, 105.4, 106.3, 107.1, 108.6, 111.2, 113.0, 114.2, 118.7, 122.5, 122.6, 124.8, 127.8, 129.2, 134.0, 145.0, 146.8, 148.2, 148.3, 148.5, 149.4, 150.4, 154.7. LRMS (EI) *m*/*z* (rel intensity) 513 (M^+, 5), 91 (100), 65 (20). TOF-HRMS calcd for $C_{29}H_{24}NO_8$ ($M + H^+$) 514.1496, found 514.1451. These spectroscopic data are identical to those reported previously.[2e,6b]

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Supporting Information Available: General methods, detailed characterization, and copies of ^1H and ^{13}C NMR of all new compounds and all lamellarins (compounds **3**, **4**, **70**, **72**, **74**, **75**, and **79**−**144**). This material is available free of charge via the Internet at http://pubs.acs.org.

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