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A Modular Synthesis of the Lamellarins: Total Synthesis of Lamellarin G Trimethyl Ether

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A modular synthesis of the lamellarin family of natural products has been developed that is based on the application of three iterative halogenation/cross-coupling reaction sequences. The ability to halogenate the pyrrole core in a regioselective fashion, even in the presence of highly electron-rich aryl substituents, has been established. The compatibility of Suzuki coupling conditions with free alcohols and phenols in the boronic acids has been employed to reduce the number of protection/deprotection steps. Indeed, the presence of a free phenol on boronic acid **3** has been determined to be critical for the successful final coupling in route to lamellarin G trimethyl ether, since protected versions fail to undergo coupling.

Introduction

The lamellarins are a growing family of at least 35 related marine natural products,[1] the first members of which were isolated in 1985 by Faulkner and co-workers (Figure 1).[2] In addition to their interesting structure, members of the lamellarin family have been reported as exhibiting a number of potentially valuable biological activities. For example, virtually all of the lamellarins have been found to be cytotoxic to a wide range of cancer cell lines. The most potent of these compounds (lamellarin D, K, and M) exhibit cytotoxicity values in the mid-to-high nanomolar range (38−110 nM).[3a] Interestingly, multidrug-resistant cell lines are also affected by the lamellarins, which appear to be not only cytotoxic agents but also single-digit micromolar inhibitors of the *p*-glycoprotein responsible for the MDR effect.[3] Lamellarin K and L have also been observed to have immunomodulatory effects in the micromolar range.[4] More recently, Faulkner and co-workers reported that lamellarin α-20 sulfate is a selective inhibitor of HIV integrase both in vitro and in vivo.[5] Unlike most other natural product integrase inhibitors, inhibition was not completely regulated by the core domain but also partially by the N- and/or C-terminal domains (IC_{50} for disintegration for the catalytic core 64 μM, for the intact enzyme 7 μM) indicating that some form of unique multisite binding might be responsible for this inhibition.

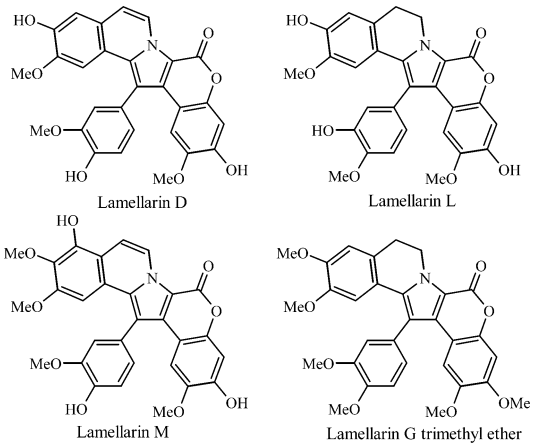

FIGURE 1. Members of the lamellarin family of natural products.

In light of these interesting biological activities and the difficulty in obtaining large quantities of the lamellarins from their natural source, they have garnered a considerable amount of synthetic interest. A number of elegant strategies have been employed in which highly functionalized precursors are assembled into the pyrrole core by means of an intramolecular ylide cycloaddition,[6] an

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(3) (a) Quesada, A. R.; Gravalos, M. D. G.; Puentes, J. L. F. *Brit. J. Cancer* **1996**, *74*, 677−682. (b) Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54−62.

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(5) Reddy, M. V. R.; Rao, M. R.; Rhodes, D.; Hansen, M. S. T.; Rubins, K.; Bushman, F. D.; Venkateswarlu, Y.; Faulkner, D. J. *J. Med. Chem.* **1999**, *42*, 1901−1907. Ridley, C. P.; Reddy, M. V. R.; Rocha, G.; Bushman, F. D.; Faulkner, D. J. *Bioorg. Med. Chem.* **2002**, *10*, 3285−3290.

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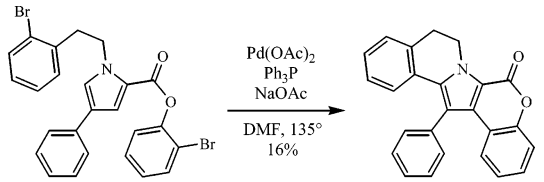
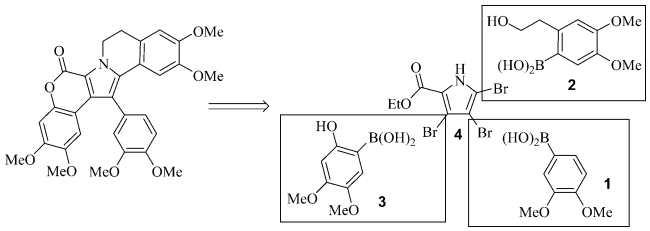
SCHEME 1. Banwell Approach to the Lamellarin Skeleton



SCHEME 2. Retrosynthesis for the Modular Approach to the Lamellarins



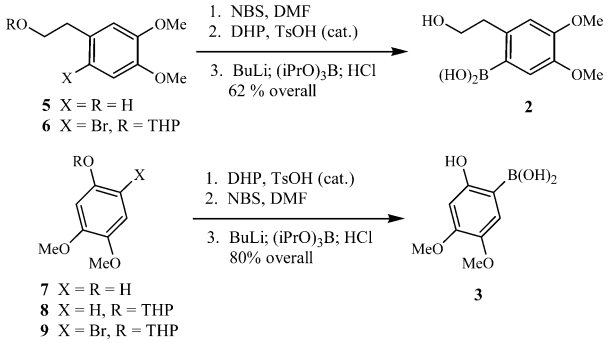
azadiene Diels−Alder cycloaddition,[3b] or an oxidative dimerization.[7] One unifying feature of all of these syntheses is that they form the pyrrole core late in the synthesis,[8] doubtless due to the difficulty in functionalizing pyrrole in a regiocontrolled fashion. At the same time, there are potential advantages, particularly from the standpoint of analogue preparation, to starting with an intact pyrrole core.

A few examples employing the functionalization of an intact pyrrole core have appeared. Of particular note is the approach of Banwell and co-workers. They have used a simple pyrrole ester as their starting point and then functionalized this core using an unusual tandem intramolecular Heck reaction (Scheme 1).[9] Although the yield of the tandem Heck reaction was quite modest (16%), it is an interesting alternative approach to the traditional methods for pyrrole synthesis. Simpler members of the lamellarins (O and P) have also been prepared independently by Banwell and Wong using Stille and Suzuki cross-coupling methods.[10] More recently, lamellarin G trimethyl ether has been prepared by Iwao and co-workers.[11] Starting from a symmetric bis-trifloxy pyrrole, two sequential Suzuki coupling reactions were employed to desymmetrize the molecule and eventually lead to the intact lamellarin framework.

Results and Discussion

Our approach to the synthesis of the lamellarin skeleton likewise chooses to elaborate on a preexisting pyrrole core. As seen in Scheme 2, this strategy focuses on the use of sequential halogenation/cross-coupling reactions.

SCHEME 3. Boronic Acid Subunit Syntheses



In this manner, the complete regiocontrol required for the preparation of differentially substituted triaryl pyrrole esters (as found in the more complex members of the lamellarin family) can be obtained. At the same time, the use of a robust cross-coupling method ensures the maximum amount of flexibility and functional group tolerance.

Such an approach raises three main questions. The first question is simply whether the pyrrole ester nucleus can be halogenated in a regiocontrolled manner. The literature contains remarkably few examples of the selective halogenation of pyrrole esters, beyond the selective preparation of 4-halopyrrole carboxylates.[12] Indeed, only a single report exists indicating that 4-arylpyrrole-2-carboxylates can be halogenated selectively at the C5 position (pyrrole numbering).[13] The second question is whether halogenation will occur selectively on the pyrrole ring of the mono- and diarylated intermediates as opposed to the electron-rich aryl substituents. The final question is whether boronic acids such as **2** and **3**, with free hydroxyl groups, can be successfully employed in the necessary Suzuki couplings, thereby avoiding additional protection/deprotection sequences throughout the synthesis.

With these questions in mind, the first stage in the synthesis of the lamellarins was the preparation of the necessary aryl subunits **1**, **2**, and **3** (Scheme 3). Boronic acid **1** is commercially available. Boronic acid **2** was prepared starting with commercially available alcohol **5** via bromination at C6. Protection of the alcohol as a THP ether set the stage for the standard preparation of boronic acids from aryl halides: halogen−metal exchange, quenching with tri(isopropyl)borate, and hydrolysis of the boronic ester with aqueous hydrochloric acid. This final hydrolysis also served to cleave the THP ether, affording boronic acid **2** in sufficient purity to be directly used in the subsequent coupling reactions without further purification, although **2** could also be further purified by recrystalization.

The preparation of boronic acid **3** was more problematic. We wished to prepare this compound with the unprotected *o*-phenol since it was suspected that a protecting group on the oxygen adjacent to the boronic acid might seriously impede the final Suzuki coupling for steric reasons. Further, couplings of simple 2-hydroxyphenylboronic acid have been reported in the literature

(7) (a) Heim, A.; Terpin, A.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 155−156. (b) Peschko, C.; Winklhofer, C.; Steglich, W. *Chem. Eur. J.* **2000**, *6*, 1147−1152.

(8) This same feature is true of synthetic approaches that do not fall into the previous three categories. See: Gupton, J. T.; Clough, S. C.; Miller, R. B.; Lukens, J. R.; Henry, C. A.; Knaters, R. P. F.; Sikorski, J. A. *Tetrahedron* **2003**, *59*, 207−215.

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(10) Banwell, M. G.; Flynn, B. L.; Hamel, E.; Hockless, D. C. R. *Chem. Commun.* **1997**, 207−208. Liu, J.-H.; Yang, Q.-C.; Mak, T. C. W.; Wong, H. N. C. *J. Org.Chem.* **2000**, *65*, 3587−3595.

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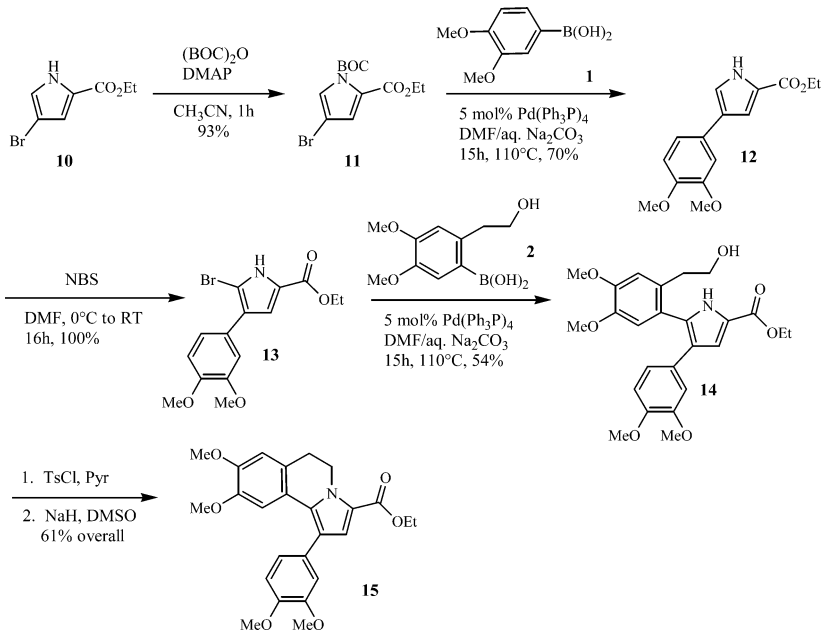
(12) Belanger, P. *Tetrahedron Lett.* **1979**, *27*, 2505−2508.

(13) Balsamini, C.; Bedini, A.; Diamantini, G.; Spadoni, G.; Tontini, A.; Tarzia, G.; Di Fabio, R.; Feriani, A.; Reggiani, A.; Tedesco, G.; Valigi, R. *J. Med. Chem.* **1998**, *41*, 808−820.

SCHEME 4. Preparation of the Key Tricyclic Intermediate

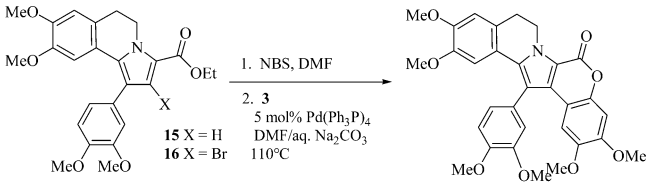


and proceed well.[14] To that end, THP-protected bromide **9** was the target, since we had already established that these ethers were cleaved under the conditions required for the hydrolysis of the boronic ester. Unfortunately, all attempts to protect 2-bromo-3,4-dimethoxyphenol were unsuccessful as even mildly acidic conditions resulted in extensive decomposition. Fortunately, protection of the phenol prior to bromination avoided this acid-catalyzed decomposition. Thus, THP ether **8** could be readily prepared using normal conditions and then carefully brominated in the presence of sodium carbonate to afford bromide **9** in roughly 80% yield overall. The sodium carbonate was required, since bromination in the absence of any base, or even in the presence of a milder base such as sodium bicarbonate, resulted in nearly complete cleavage of the THP ether. With bromide **9** in hand, standard conditions for the preparation of boronic acids afforded highly sensitive boronic acid **3**.

With the necessary subunits in hand, the synthesis itself began with known bromopyrrole ester **10** (prepared in three steps from pyrrole)[12] (Scheme 4). Previous studies indicated that the nitrogen of this pyrrole must be protected prior to the first coupling event to avoid extensive dehalogenation.[15] To that end, bromopyrrole ester **10** was protected as the corresponding *tert*-butyl carbamate to afford **11** in nearly quantitative yield. Coupling with boronic acid **1** proceeded cleanly to afford monoaryl compound **12** in 70% yield. It is worth noting that a modest excess (2−3 equiv) of the boronic acid was required. The use of only 1.2 equiv of the boronic acid afforded 50−60% yields of compound **12** along with some homocoupling of bromide **11**.

With compound **12** in hand, the first significant questions regarding the regioselectivity of halogenation could be addressed. Gratifyingly, treatment of **12** with an equimolar amount of *N*-bromosuccinimide led cleanly to selective halogenation at the C5 position. At this point, the second coupling with boronic acid **2** was then carried out under standard Suzuki coupling conditions. A potential concern with this coupling was the possibility that, given the proximity of the alcohol to the boronic acid, it could hinder either the initial oxidative insertion or, by stabilization, further steps along the catalytic pathway. Fortunately, the coupling proceeded as planned to afford adduct **14** and avoided the need to protect the free hydroxyl group. At this point, the dihydroisoquinoline ring was closed in a two step procedure: formation of the tosylate followed by intramolecular alkylation of the pyrrole nitrogen. The yield over these two steps was 61%.

SCHEME 5. Couplings with Bromide 16 Leading to Lamellarin G Trimethyl Ether



Entry	Equivalents of **3**	Yield
1	2	8%
2	8	20%
3	3, then slow addition of 5 more	46%[a]

[a] 51% of **15** was also recovered.

As expected on the basis of the previous halogenation result, the final halogenation also proceeded cleanly at C3 to afford bromide **16** (Scheme 5). Initial efforts at coupling with boronic acid **3** were only slightly encouraging. Trace amounts of lamellarin G trimethyl ether were observed indicating that both the desired coupling as well as lactonization could occur in the same reaction pot. Nevertheless, the yield of this coupling (8%) was too low for any practical applications of this method. The most significant problem appeared to be the thermal sensitivity of boronic acid **3**. Storage at room temperature for a

(14) For an example, see: Ito, K.; Kashiwagi, R.; Iwasaki, K.; Katsuki, T. *Synlett* **1999**, 1563−1566.

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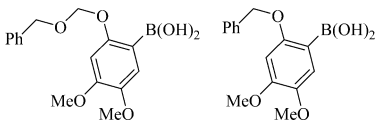

FIGURE 2. Protected versions of boronic acid **3**.

few days was sufficient to cause nearly complete decomposition. Given the high temperatures required for the Suzuki coupling, it seemed likely that even more rapid decomposition of the boronic acid might be responsible for the very modest yield of this reaction. In an effort to confirm this suspicion, couplings were undertaken with both phenyl boronic acid and boronic acid **1** under identical conditions. Interestingly, in both cases the anticipated Suzuki-coupling product was the major product (82% and 56% with phenyl boronic acid and boronic acid **1**, respectively). The hypothesis that decomposition of boronic acid **3** was the limiting factor in the final coupling was further supported by the observation that the use of a larger excess of the boronic acid (8 equiv) led to the isolation of lamellarin G trimethyl ether in 20% yield.

At this point, there were two further alternatives for increasing the yield of this final coupling. The first approach was to see if a protecting group on the phenol would serve to stabilize the boronic acid and yet at the same time not impede the coupling by increasing the steric hindrance. In light of the synthetic manipulations required for the preparation of boronic acids such as **3**, ether protecting groups appeared to be the most promising. Both the benzyl and BOM-protected versions of **3** were prepared (Figure 2). They did indeed exhibit much greater thermal and acid stability. Unfortunately, attempts at coupling these boronic acids with bromide **16** or the corresponding iodide resulted only in dehalogenation of **16** and the nearly quantitative recovery of compound **15**. As a result, the steric hindrance of these protected boronic acids appears to be too great for effective coupling to occur without extensive optimization of the reaction conditions.

The other main possibility was to add an excess of boronic acid **3** slowly over time. In this way, any potential thermal decomposition of **3** at the high temperatures required for the coupling could be largely mitigated. In the event, three equivalents of boronic acid **3** were added immediately to the reaction mixture, followed by the slow addition of an additional five equivalents of **3** over the span of 2.5 h. In this way, lamellarin G trimethyl ether was obtained in 46% yield along with 51% of compound **15**. The spectral data and melting point were consistent with that reported in the literature.[7a] Although further optimization is clearly required to make this coupling more efficient, it does support our hypothesis that boronic acid stability is the limiting factor. By applying a greater excess of the boronic acid and more active catalysts (which in turn should enable the use of lower reaction temperatures), the yield of this coupling should be improved even more.

Conclusion

In short, we have completed a modular synthesis of the lamellarin skeleton that employs three sequential and regioselective halogenation/coupling events. This route accesses the complete structure of lamellarin G trimethyl ether in 11 steps and 9% overall yield. Future efforts will focus on improving the yield of the final coupling step and in exploring regioselective couplings on polyhalogenated pyrrole esters. These efforts will be reported in due course.

Experimental Section

4-Bromopyrrole-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Ethyl Ester (11). To a solution of 2.81 g (13.1 mmol) of 4-bromo-1*H*-pyrrole-2-carboxylic acid ethyl ester in 25 mL of anhydrous acetonitrile was successively added 160 mg (1.31 mmol) of DMAP and 3.71 g (17.0 mmol) of di-*tert*-butyl dicarbonate. The reaction was stirred at room temperature for 1 h. To the mixture was added 80 mL of diethyl ether and 40 mL of 1 M aqueous $KHSO_4$. The organic layer was separated and washed sequentially with aqueous $KHSO_4$, water, saturated aqueous $NaHCO_3$, and brine and then dried with anhydrous magnesium sulfate. The solvent was removed in vacuo. The resulting residue was purified by chromatography on silica gel, using 20:80 EtOAc−hexane, to afford 3.87 g (93.0%) of **11** as a yellow oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.28 (s, 1H), 6.76 (s, 1H), 4.28 (q, 2H, J = 7.2), 1.55 (s, 9H), 1.32 (t, 3H, J = 7.2); ^{13}C NMR (90 MHz, $CDCl_3$) δ 159.8, 147.1, 125.9, 125.3, 121.9, 98.7, 85.5, 61.2, 27.7, 14.1; IR (neat) 3440 (w, br), 3139 (w), 2982 (m), 1757 (s), 1729 (s), 1458 (w), 1397 (m), 1371 (m), 1304 (s), 1153 (s), 1072 (m), 922 (w), 845 (w), 774 (w) cm^{-1}; HRMS (electrospray) calcd for $C_{12}H_{16}BrNO_4$ + Na 340.0160, found 340.0158.

4-(3,4-Dimethoxyphenyl)-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester (12). To a solution of 187.4 mg (0.60 mmol) of **11**, 328 mg (1.80 mmol) of 3,4-dimethoxyphenyl boronic acid (**1**), and 34.7 mg (0.03 mmol) of tetrakis(triphenylphosphine)-palladium(0) in 10 mL of DMF was added 3.0 mL of 2 M aqueous Na_2CO_3. The reaction mixture was stirred at 110 °C for 15 h. The reaction was quenched with 20 mL of water and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water and brine and dried with anhydrous magnesium sulfate. The solvent was removed in vacuo. The resulting residue was chromatographed on silica gel, using 10:90 acetone−benzene, to afford 116 mg (70.0%) of **12** as a white solid: mp 136.3−137.5 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.13 (br s, 1H), 7.14 (m, 2H), 7.05 (m, 2H), 6.87 (d, 1H, J = 8.3 Hz), 4.34 (q, 2H, J = 7.1 Hz), 3.94 (s, 3H), 3.92 (s, 3H), 1.38 (t, 3H, J = 7.1); ^{13}C NMR (90 MHz, $CDCl_3$) δ 161.2, 149.1, 147.7, 127.7, 126.7, 123.5, 119.0, 117.5, 112.2, 111.5, 108.9, 60.5, 55.9, 55.8, 14.4; IR (neat) 3281 (s), 2989 (w), 1682 (s), 1487 (m), 1405 (m), 1294 (m), 1253 (m), 1230 (s), 1213 (s), 1180 (m), 1136 (m), 1022 (m), 833 (w), 765 (m); HRMS (electrospray) calcd for $C_{15}H_{17}NO_4$ + Na 298.1055, found 298.1059.

5-Bromo-4-(3,4-dimethoxyphenyl)-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester (13). A solution of 170 mg (0.616 mmol) of **12** in 5 mL of DMF was chilled to 0 °C. To this solution was added portionwise 110 mg (0.616 mmol) of NBS. The reaction was allowed to warm to room temperature overnight. The reaction was quenched with 20 mL of water and extracted with EtOAc (3 × 15 mL). The combined organic layers were separated, washed sequentially with saturated aqueous $Na_2S_2O_3$, water, and brine, and concentrated in vacuo to afford 218 mg (100%) of **13** as a white solid: mp (Et_2O) 123.4−125.0 °C; ^{1}H NMR (360 Hz, $CDCl_3$) δ 9.20 (br s, 1H), 7.11 (m, 2H), 7.02 (s, 1H), 6.90 (d, 1H, J = 8.6), 4.38 (q, 2H, J = 8.6), 3.89 (s, 3H), 3.86 (s, 3H), 1.36 (t, 3H, J = 8.8); ^{13}C NMR (360 Hz, $CDCl_3$) δ 160.9, 148.7, 148.0, 126.5, 125.2, 123.5, 120.0, 115.3, 111.1, 111.0, 103.2, 60.9, 55.8, 55.7, 14.4; IR (neat) 3248 (s), 2930 (w), 1708 (s), 1524 (m), 1477 (m), 1433 (m), 1381 (m), 1246 (s), 1204 (m), 1140 (m), 1026 (m), 764 (m); HRMS (electrospray) calcd for $C_{15}H_{16}BrNO_4$ + Na 376.0160, found 376.0179.

4-(3,4-Dimethoxyphenyl)-5-[2-(2-hydroxyethyl)-4,5-dimethoxyphenyl]-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester (14). To a solution of 57 mg (0.16 mmol) of **13**, 43.6 mg (0.19 mmol) of **2**, and 9.2 mg (0.08 mmol) of tetrakis(triphenylphosphine)palladium(0) in 20 mL of DMF was added 0.7 mL of 2 M aqueous Na_2CO_3. The reaction mixture was stirred at 110 °C for 15 h. After being cooled to room temperature, the reaction was quenched with 10 mL of water and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with water and brine, dried with magnesium sulfate, and concentrated in vacuo. The resulting residue was chromatographed on silica gel using 40:60 EtOAc−hexane to give 39.6 mg (54.4%) of **14** as a white solid: mp 171.3−172.4 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 11.1 (br, s, 1H), 7.06 (s, 1H), 6.76−6.70 (m, 4H), 6.61 (s, 1H), 4.25 (q, 2H, J = 7.2), 3.87 (m, 5H), 3.79 (s, 3H), 3.64 (s, 3H), 3.52 (s, 3H), 2.77 (t, 2H, J = 7.2), 1.31 (t, 3H, J = 7.2); ^{13}C NMR (90 MHz, $CDCl_3$) δ 161.6, 149.0, 148.4, 147.1, 147.0, 132.2, 130.4, 128.2, 124.7, 123.7, 121.5, 120.0, 114.6, 114.1, 112.2, 111.1, 111.0, 63.6, 60.2, 55.8, 55.7, 55.6, 55.5, 35.0, 14.4; IR (neat) 3500 (w, br), 3273 (w), 2930 (w), 1702 (s), 1523 (s), 1467 (s), 1440 (m), 1243 (s), 1210 (s), 1140 (m), 1027 (m), 857 (w), 764 (w); HRMS (electrospray) calcd for $C_{25}H_{29}NO_7$ + Na 478.1842, found 478.1837.

1-(3,4-Dimethoxyphenyl)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylic Acid Ethyl Ester (15). A solution of 260 mg (0.57 mmol) of **14** in 2 mL of chloroform was chilled to 0 °C. To this solution was added 0.14 mL (1.71 mmol) of pyridine. After 10 min, 218 mg (1.14 mmol) of *p*-toluenesulfonyl chloride was added in portions over 30 min. The reaction was allowed to warm to room temperature overnight. To the reaction mixture was added 30 mL of diethyl ether, and the resulting mixture was washed with 1 N HCl and water and dried with magnesium sulfate. The solvent was removed in vacuo, and the residue was chromatographed on silica gel using 40:60 EtOAc−hexane to give 215.2 mg (62.0%) of the tosylate as a white solid: ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.19 (br s, 1H), 7.52 (d, 2H, J = 8.4), 7.22 (m, 3H), 7.08 (d, 1H, J = 2.8), 6.76 (s, 1H), 6.66 (m, 3H), 4.29 (q, 2H, J = 7.2), 3.82 (m, 11H), 3.58 (s, 3H), 2.61 (t, 2H, J = 7.2), 2.40 (s, 3H), 1.35 (t, 3H, J = 7.2); ^{13}C NMR (90 MHz, $CDCl_3$) δ 161.1, 149.2, 148.5, 147.8, 147.3, 144.5, 132.7, 131.4, 129.6 (2 carbons), 128.6, 127.6 (2 carbons), 124.4, 123.8, 122.1, 118.9, 114.1, 113.6, 112.8, 111.1, 110.0, 70.0, 60.4, 55.9, 55.8, 55.7, 55.3, 32.3, 21.5, 14.4 (one aromatic ^{13}C signal unresolved for two carbons); IR (neat) 3290 (m), 2914 (w), 1654 (s), 1522 (s), 1466 (s), 1407 (m), 1315 (m), 1243 (s), 1180 (s), 1016 (m), 952 (m), 764 (w), 713 (w); HRMS (electrospray) calcd for $C_{32}H_{35}NO_9S$ + Na 632.1930, found 632.1938. To a solution of 270 mg (0.44 mmol) of the tosylate in 8 mL of DMSO was added 44 mg (1.10 mmol) of sodium hydride (60% in mineral oil) in portions. The solution was stirred for 2 h before 80 mL of ethyl acetate was added, and then the solution was washed with water and brine and dried with magnesium sulfate. The solvent was removed in vacuo and the residue chromatographed on silica gel (40% ethyl acetate/hexanes) to afford 189.0 mg (98.3%) of **15** as a white solid: mp 147.2−149.0 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.94 (m, 3H), 6.85 (m, 2H), 6.68 (s, 1H), 4.56 (t, 2H, J = 6.5), 4.25 (q, 2H, J = 7.2), 3.84 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 3.39 (s, 3H), 2.97 (t, 2H, J = 6.9), 1.31 (t, 3H, J = 7.7); ^{13}C NMR (90 MHz, $CDCl_3$) δ 161.2, 148.7, 148.1, 147.8, 147.1, 131.3, 129.2, 125.8, 121.5, 121.4, 120.9, 120.4, 119.0, 112.5, 111.1, 110.7, 108.5, 59.7, 55.9, 55.8, 55.8, 55.3, 42.4, 29.0, 14.4; IR (neat) 3400 (w), 2930 (w), 1690 (s), 1549 (w), 1518 (w), 1464 (m), 1435 (m), 1244 (s), 1212 (m), 1142 (m), 1061 (w), 1026 (w), 860 (w), 762 (w), 668 (w); HRMS (electrospray) calcd for $C_{25}H_{27}NO_6$ + Na 460.1736, found 460.1746.

2-Bromo-1-(3,4-dimethoxyphenyl)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylic Acid Ethyl Ester (16). A solution of 189 mg (0.43 mmol) of **15** in 5 mL of DMF was chilled to 0 °C. To this solution was added in portions 86 mg (0.48 mmol) of NBS. The reaction was allowed to warm to room temperature overnight. The reaction was poured into 10 mL of water and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate, water, and brine and then dried with anhydrous magnesium sulfate. The solvent was removed in vacuo to afford 221 mg (99.6%) of **16** as a brown solid: mp (toluene) 166.7−168.3 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.93 (m, 2H), 6.88 (s, 1H), 6.69 (s, 1H), 6.56 (s, 1H), 4.60 (t, 2H, J = 7.1), 4.38 (q, 2H, J = 7.2), 3.91 (s, 3H), 3.86 (s, 3H), 3.63 (s, 3H), 3.33 (s, 3H), 3.01 (t, 3H, J = 6.8), 1.41 (t, 3H, J = 7.2); ^{13}C NMR (90 MHz, $CDCl_3$) δ 160.9, 148.9, 148.4, 148.3, 147.2, 131.7, 127.2, 125.7, 123.4, 122.3, 119.9, 114.0, 111.2, 110.6, 108.5, 107.6, 107.5, 60.4, 55.9, 55.8, 55.8, 55.2, 43.3, 28.7, 14.3; IR (neat) 3400 (w, br), 2930 (w), 1698 (s), 1522 (m), 1466 (s), 1438 (m), 1381 (w), 1243 (s), 1207 (m), 1142 (m), 1027 (m), 860 (w), 767 (w); HRMS (electrospray) calcd for $C_{25}H_{26}BrNO_6$ + Na 538.0841, found 538.0828.

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 (Lamellarin G Trimethyl Ether). A solution of 51.6 mg (0.1 mmol) of **16** in 2 mL of DMF was degassed with argon. To this solution was successively added 54.9 mg (0.3 mmol) of **3**, 11.6 mg (0.01 mmol) of tetrakis(triphenylphosphine)-palladium(0), and 95.4 mg (0.9 mmol) of sodium carbonate in 0.5 mL of water. The reaction was heated to 110 °C. To the reaction was added slowly 99.0 mg (0.5 mmol) of **3** in 1 mL of DMF via syringe pump over 2.5 h. The reaction was stopped after 5 h and was poured into 5 mL of water and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over anhydrous magnesium sulfate. The solvent was removed in vacuo. The resulting residue was chromatographed in EtOAc−hexane (50:50) to afford 25.0 mg (46.0%) of lamellarin G trimethyl ether as a white solid and 22.4 mg (51.3%) of **15**: mp 239.1−240.7 °C (lit.[7a] mp 235 °C, no range given); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.08 (m, 3H), 6.88 (s, 1H), 6.74 (s, 1H), 6.69 (s, 1H), 6.64 (s, 1H), 4.77 (m, 2H), 3.93 (s, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 3.44 (s, 3H), 3.34 (s, 3H), 3.10 (t, 2H, J = 6.5); ^{13}C NMR (90 MHz, $CDCl_3$) δ 155.4, 149.7, 148.9, 148.8, 148.6, 147.4, 146.0, 145.4, 135.8, 128.0, 127.9, 126.6, 123.6, 120.0, 114.7, 113.9, 113.6, 111.8, 110.9, 110.2, 108.6, 104.4, 100.3, 56.2, 56.1, 55.9, 55.8, 55.4, 55.1, 42.3, 28.6; IR (neat) 3420 (w, br), 2936 (w), 1703 (s), 1513 (m), 1486 (m), 1463 (m), 1438 (m), 1415 (s), 1270 (s), 1241 (s), 1214 (s), 1166 (s), 1041 (m), 758 (w).

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Supporting Information Available: Experimental procedures for the preparation of boronic acids **2** and **3**. ^{1}H and ^{13}C spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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