Modular Total Synthesis of Lamellarin G Trimethyl Ether

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Abstract: A modular synthesis of the lamellarin G trimethyl ether has been developed based on the application of several reaction sequences which include Friedel–Crafts acylation, esterification, haloarylation, and oxidative cyclization. The formation of pyrrolo [2,1-*a*]isoquinoline core, the key step for the successful completion of lamellarin G trimethyl ether synthesis, is comfortably accomplished through the haloarylation of 3-bromo-4-(3,4-dimethoxybenzoyl)-6,7-dimethoxy-chroman-2-one which has resulted in exclusive *endo* product.

Key words: lamellarins, Friedel–Crafts acylation, esterification, bromoarylation, oxidative cyclization

Lamellarin G belongs to a group of marine natural products that contain 5-oxa-6b-aza-dibenzo[*a*,*i*]fluoren-6-one skeleton. Lamellarins were isolated from the prosobranch mollusk *Lamellaria sp.* and the ascidians.[1] The first four lamellarins were isolated by Faulkner et al. in 1985 and were named lamellarins A, B, C, and D (Figure 1).

The structure of lamellarin A was determined by X ray crystallographic analysis and the structures of the remaining compounds were derived from spectroscopic data.[2] At present 35 lamellarins have so far been isolated and identified.[2,3] Interestingly, some of these lamellarins have been found to exhibit potent biological activities,[4] such as cytotoxicity to a wide range of cancer cell lines, cell division inhibition, immunomodulatory activity, and a recently discovered multidrug resistant (MDR) reversal[5] and HIV-1 integrase inhibition.[6]

In view of these interesting biological activities and the difficulty in obtaining large quantities of the lamellarins from their natural sources, they have garnered a considerable amount of synthetic interest. A number of elegant studies directed towards the total synthesis of lamellarins have been employed. The notable strategies involve highly functionalized precursors which assembled into the pyrrole core by means of an intramolecular ylide cycloaddition,[6] an azadiene Diels–Alder cycloaddition,[6c] or an oxidative dimerization.[7] One unifying feature of all these syntheses is that they form the key pyrrole core late in the synthesis,[8] due to the difficulty in functionalizing pyrrole in a regiocontrolled fashion. There have been other strategies starting with an intact pyrrole core as reported by Banwell and coworkers whose strategy involved functionalization of pyrrole ester by tandem intramolecular

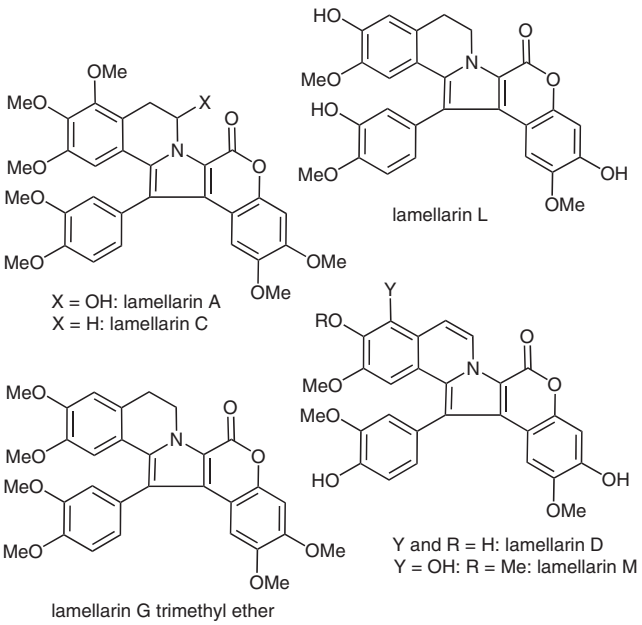

Figure 1 Members of the lamellarin family of natural products

Heck reaction.[9a] Simpler members of the lamellarins (O, P) have also been prepared independently by Banwell and Wong using Stille and Suzuki cross-coupling methods.[9b] Recently, lamellarin G trimethyl ether has been prepared by Iwao and coworkers,[10] Handy et al.,[11] and Ruchirawat et al.[12a] More recently, large number of methods for the total synthesis of lamellarin G have been reported by employing various methodologies.[12,13]

Our approach to the synthesis of lamellarin skeleton is based on the formation of pyrrole ring in the final step of the synthesis, which may be extended for the synthesis of several analogues in a shortest route (see Scheme 1 for the retrosynthesis). As depicted in Scheme 2, this strategy focuses on the Friedel–Craft's acylation, esterification, intramolecular bromoarylation of alkene and oxidative cyclisation reactions.

Accordingly, 4-(3,4-dimethoxy-phenyl)-4-oxo-but-2-enoic acid (**3**), was synthesized from veratrole and maleic anhydride under Friedel–Crafts conditions.[14,15] Compound **3** on esterification with **4** resulted in 4-(3,4-dimethoxy-phenyl)-4-oxo-but-2-enoic acid-3,4-dimethoxy-phenyl ester (**5**) following the previously reported procedure.[16,17] The ester **5** on bromo arylation resulted in 3-bromo-4-(3,4-dimethoxy-benzoyl)-6,7-dimethoxy-chroman-2-one (**6**) following the intramolecular haloarylation methodology used for aryl cinnamates.[18,19] Upon coupling of **6** with 6,7-

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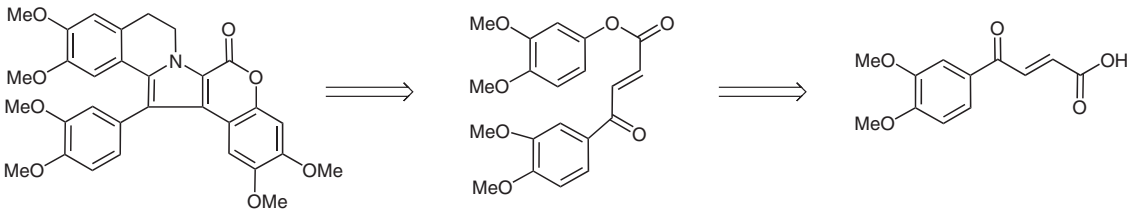
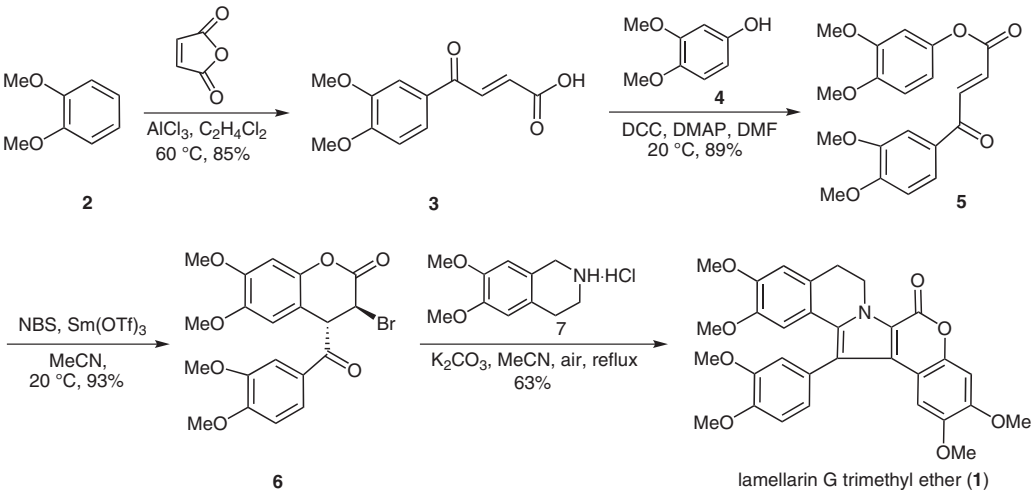


Scheme 1 Retrosynthesis of lamellarin G trimethyl ether



Scheme 2 Synthesis of lamellarin G trimethyl ether

dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (**7**) in the presence of K_2CO_3 in acetonitrile gave the expected final product lamellarin G trimethyl ether **1** in 63% yield (Scheme 2).[20,21] The spectral data and the melting point were consistent with those reported in the literature.[7a,10–12]

Mechanistically, the reaction proceeds via N-alkylation of isoquinoline (**7**) with the bromo derivative (**6**) to give N-alkylated product **A**. Then compound **A** undergoes intramolecular aldol-type condensation to give dihydro-derivative **B**, which sequentially undergoes aromatization under air or atmospheric oxygen to furnish the desired molecule **1**. On the other hand, isoquinoline can also react with ketone to give enamine (X), which upon intramolecular C-alkylation followed by aromatization would expect the formation of undesired product (Y). However, no formation of Y was observed under the reaction conditions. The possible reaction mechanism is depicted in Scheme 3.

In conclusion, we have completed a short synthesis of the lamellarin skeleton that employs four sequential steps involving Friedel–Crafts acylation, esterification, haloarylation, and oxidative cyclization. This route accesses the complete structure of lamellarin G trimethyl ether in four steps with 44% overall yields. Future efforts will focus on the use of various arenes in the first step to obtain other lamellarin cores. These efforts will be reported in due course.

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References and Notes

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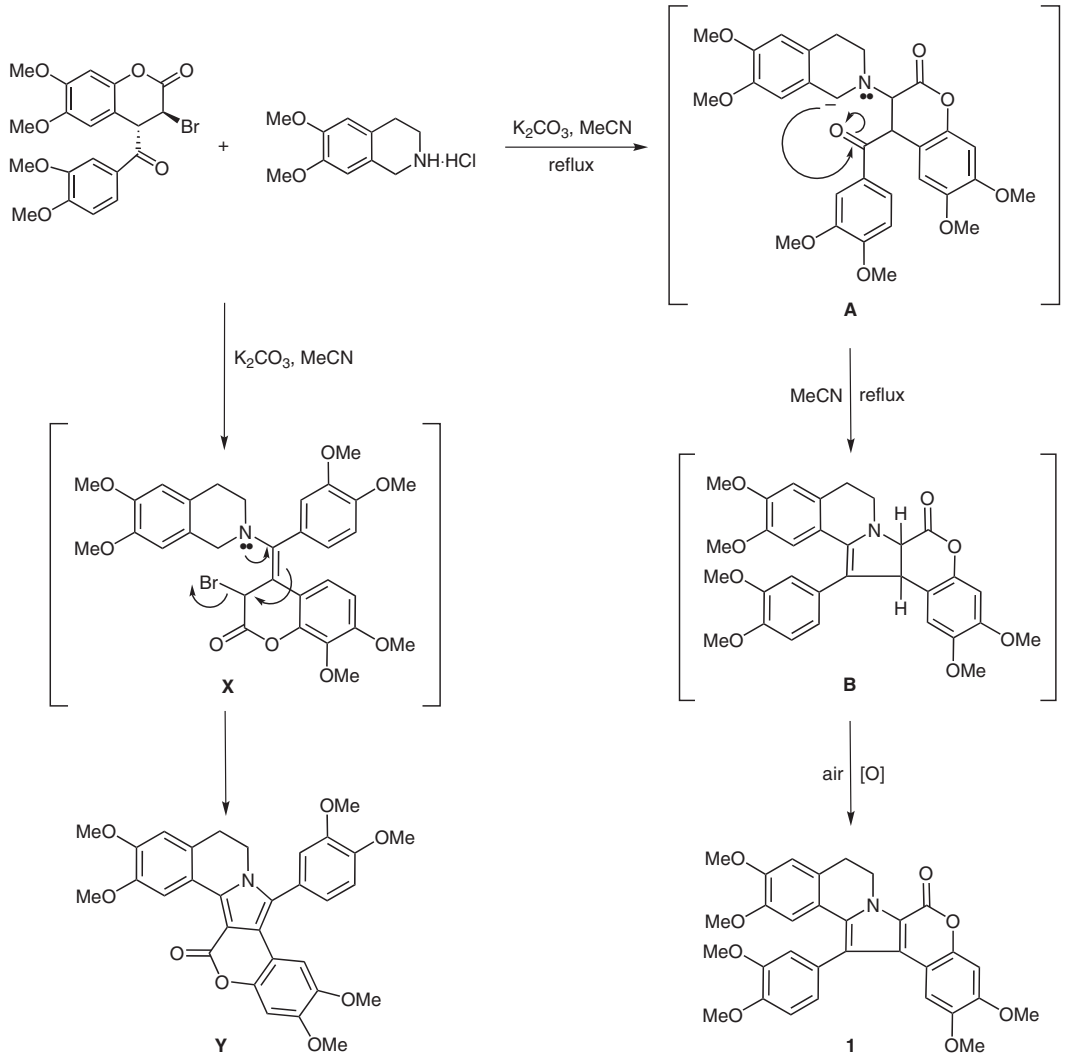

Scheme 3 A plausible reaction mechanism

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(15) **4-(3,4-Dimethoxyphenyl)-4-oxobut-2-enoic acid (3)** To a solution of veratrole (0.5 g, 3.6 mmol) and maleic

anhydride (0.354 g, 3.6 mmol) in anhyd DCE (20 mL) was added anhyd $AlCl_3$ powder (1.042 g, 7.8 mmol) in two portions. The reaction mixture was stirred for 1 h under reflux conditions. The reaction was hydrolyzed by adding 2.08 mL of H_2O with vigorous stirring at 0 °C, followed by neutralization with concd HCl (0.416 mL). The resulting mixture was extracted with EtOAc and purified by column chromatography on SiO_2 to afford 0.72 g (85%) of an acid as yellow solid; mp 178–179 °C (lit.[13a] mp 178 °C, no range given). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (dd, *J* = 12.4, 15.2 Hz, 1 H), 7.48 (m, 2 H), 6.88 (dd, *J* = 4.1, 8.2 Hz, 1 H), 6.67 (dd, *J* = 6.2, 15.8 Hz, 1 H), 3.88 (s, 6 H). ^{13}C NMR (50 MHz, $CDCl_3$ + DMSO): δ = 186.4, 166.1, 150.4, 144.2, 135.3, 130.7, 127.7, 121.6, 114.4, 114.1, 38.8, 37.9. IR (neat): 3327, 2925, 2854, 2676, 2361, 1739, 1701, 1654, 1587, 1516, 1461, 1428, 1286, 1169, 1215, 1025, 938, 898, 766, 670, 612, 583 cm^{-1}. ESI-MS: *m/z* = 261 [M$^+$ + 2 + 23], 232, 218, 146, 124, 105. Anal. Calcd for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12. Found: C, 61.02; H, 5.14.

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(17) **Experimental Procedure – 4-(3,4-Dimethoxyphenyl)-4-oxobut-2-enoic Acid 3,4-Dimethoxyphenyl Ester (5)**
To a stirred solution of acid **3** (0.3 g, 1.27 mmol) in anhyd DMF (10 mL) was added DMAP (15.5 mg, 0.127 mmol) and 3,4-dimethoxy phenol (**4**, 0.19 g, 1.27 mmol). Afterwards, DCC (0.28 g, 1.37 mmol) was added to the above reaction mixture at 0 °C and stirred for 5 min at 0 °C and then 3 h at 20 °C. Precipitated urea was filtered off and the filtrate was washed with 0.5 N HCl, followed by sat. $NaHCO_3$ solution, and then dried over Na_2SO_4. The solvent was removed by evaporation, and the resulting crude reaction mixture was purified by column chromatography on SiO_2 to give 0.42 g (83%) of ester. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.62 (d, *J* = 8.6 Hz, 3 H), 6.40 (d, *J* = 2.3 Hz, 3 H), 6.28 (dd, *J* = 3.1, 8.5 Hz, 2 H), 3.73 (d, *J* = 7.8 Hz, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.7, 173.6, 162.9, 156.6, 151.1, 149.7, 147.0, 123.3, 114.2, 114.1, 112.5, 110.1, 109.9, 105.8, 100.7, 99.9, 56.5, 56.0, 55.7, 54.1. IR (neat): 3274, 2933, 2854, 1754, 1690, 1647, 1606, 1512, 1442, 1287, 1223, 1161, 1124, 1026, 953, 834, 803, 763, 720, 626 cm^{-1}. ESI-MS: *m/z* = 372 [M$^+$]. Anal. Calcd for $C_{20}H_{20}O_7$: C, 64.51; H, 5.41. Found: C, 64.54; H, 5.44.

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(19) **3-Bromo-4-(3,4-Dimethoxybenzoyl)-6,7-dimethoxychroman-2-one (6)**
The ester (0.2 g, 0.53 mmol) was treated with NBS (0.1 g, 0.59 mmol) and $Sm(OTf)_3$ (0.032 g, 0.053 mmol) in MeCN at 20 °C to produce 0.22 g (93%) of **6**, as an exclusively *endo*-cyclized product. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.23 (s, 1 H), 7.18 (s, 1 H), 6.83 (s, 1 H), 6.54 (s, 2 H), 6.05 (s, 1 H), 5.09 (s, 1 H), 3.80 (m, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.6, 166.5, 149.9, 146.5, 143.7, 135.7, 116.8, 114.9, 106.9, 103.6, 100.6, 99.7, 95.5, 94.6, 56.8, 56.7, 56.5, 56.2, 56.0. IR (neat): 3422, 2925, 2853, 2361, 1713, 1657, 1593, 1507, 1455, 1406, 1204, 1035, 977, 846, 798, 760, 666, 593 cm^{-1}. ESI-MS: *m/z* = 450 [M$^+$], 490 [M$^+$ + 39], 423, 403, 375, 336, 306, 285, 258, 229, 208, 142. Anal. Calcd for $C_{20}H_{19}BrO_7$: C, 53.23; H, 4.24. Found: C, 53.26; H, 4.22.

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(21) **13-(3,4-Dimethoxy-phenyl)-2,3,10,11-tetramethoxy-7,8-dihydro-5-oxa-6b-aza-dibenzo[*a*,*i*]fluoren-6-one (Lamellarin G Trimethyl Ether, 1)**
The bromide **6** (0.05 g, 0.11 mmol) was added to 6,7-dimethoxy-1,2,3,4-tetrahydro isoquinoline (0.51 g, 2.22 mmol) and K_2CO_3 (0.10 g, 0.73 mmol) in MeCN (3 mL) with continuous stirring under aerobic conditions. The mixture was stirred under reflux for 2 h, and then the reaction mixture was quenched with H_2O and extracted with EtOAc (3 × 10 mL) and purified by column chromatography on SiO_2 to afford 0.038 g (63%) of lamellarin G trimethyl ether as white solid; mp 238–239 °C (lit.[11] mp 239.1–240 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.05 (m, 3 H), 6.88 (s, 1 H), 6.75 (s, 1 H), 6.69 (s, 1 H), 6.64 (s, 1 H), 4.78 (m, 2 H), 3.92 (s, 3 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.84 (s, 3 H), 3.46 (s, 3 H), 3.34 (s, 3 H), 3.10 (t, *J* = 6.6 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.4, 149.7, 148.9, 148.8, 148.6, 147.2, 146.1, 145.5, 135.8, 128.0, 127.9, 126.7, 123.7, 120.1, 114.7, 114.0, 113.6, 111.8, 111.1, 110.2, 108.6, 104.4, 100.3, 56.2, 56.1, 56.0, 55.8, 55.4, 55.0, 42.4, 28.5. IR (neat): 3420, 2930, 1705, 1512, 1488, 1460, 1438, 1415, 1270, 1240, 1214, 1166, 1045, 752 cm^{-1}. ESI-MS: *m/z* = 543 [M$^+$]. Anal. Calcd for $C_{31}H_{29}NO_8$: C, 68.50; H, 5.38; N, 2.58. Found: C, 68.48; H, 5.36; N, 2.54.