Alkaloids from Marine Organisms, Part 5[+]

Biomimetic Total Synthesis of Lamellarin L by Coupling of Two Different Arylpyruvic Acid Units

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Dedicated to Professor Gerhard Höfle on the occasion of his 60th birthday

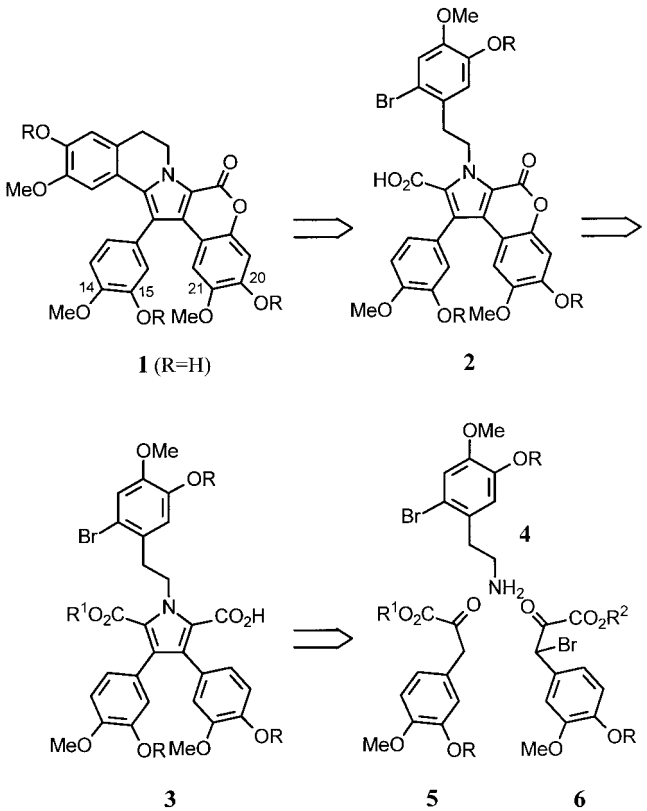
Abstract: Reaction of the ethyl 3-arylpyruvate **5a** with the methyl 2-bromo-3-arylpyruvate **6b** in the presence of the 2-arylethylamine **4** afforded the pyrrole derivative **10**, which could be transformed into lamellarin L (**1**) in five steps. The synthesis proceeds with 38% overall yield and mimics the probable biosynthesis of these marine alkaloids.

Keywords: biomimetic synthesis · lamellarins · marine alkaloids · natural products · pyrrole ring

Introduction

A variety of alkaloids with the hexacyclic lamellarin system have been isolated from prosobranch mollusks[1] and ascidians.[2] Some of these compounds inhibit the growth of several tumor cell lines[1, 2b, 3] and revert the P-glycoprotein mediated multidrug resistance (MDR) of tumor cells at very low concentrations.[3, 4] Consequently, these natural products possess a considerable potential for the development of antitumor drugs as well as nontoxic modulators of the MDR phenotype.[4, 5]

The unique structures and biological activities of the lamellarins have attracted the attention of synthetic chemists. Our synthesis of lamellarin G trimethyl ether[6] followed closely the proposed biosynthesis. Banwell et al.[7] obtained lamellarin K by an elegant intramolecular ylide cycloaddition, whereas Ishibashi's group[8] used a isoquinolinium intermediate in their synthesis of lamellarin D and H. Recently, Boger et al.[9] applied an azadiene Diels–Alder strategy for the synthesis of related marine alkaloids.[10] The key step in our biomimetic lamellarin synthesis[6] is the oxidative dimerization of an arylpyruvic acid and condensation of the resulting 1,4-dicarbonyl compound with a suitable 2-arylethylamine. This reaction leads to lamellarins which carry identical substituents at C-14/C-20 and C-15/C-21, respectively. To obtain nonsymmetrical compounds such as lamellarin L (**1**)[11] two different arylpyruvic acid esters have to be coupled. This is revealed by the retrosynthetic analysis depicted in Scheme 1.



Scheme 1. Retrosynthesis of lamellarin L (**1**).

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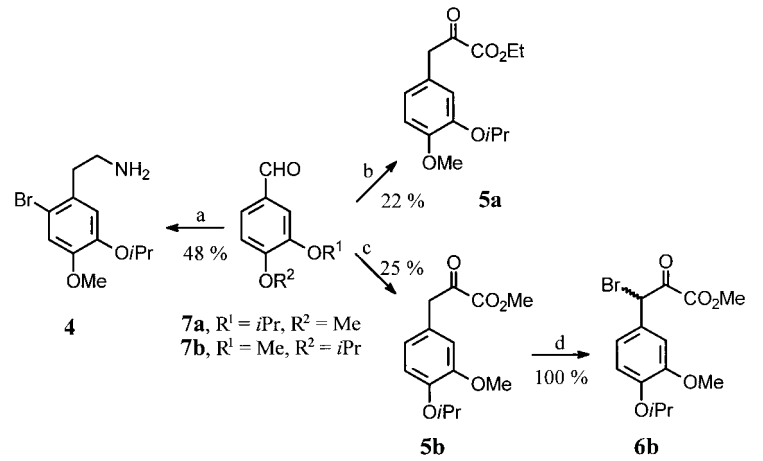
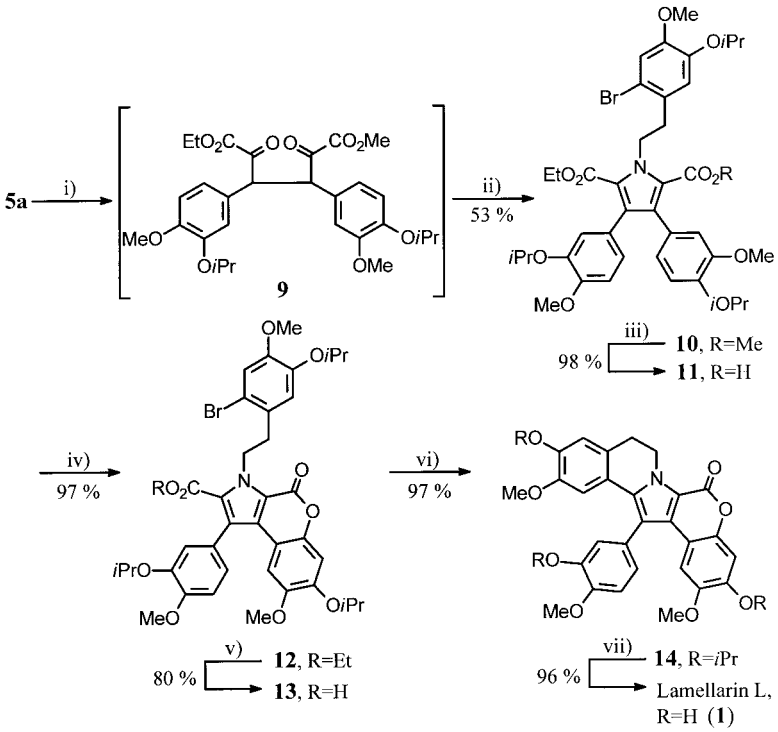
Results and Discussion

In the actual synthesis of lamellarin L (**1**) the ester groups R^1 and R^2 were differentiated as methyl and ethyl,[12] and the phenolic OH groups were protected by isopropyl residues.[13] The starting materials **4**, **5a**, and **6b** were easily available by standard methods (Scheme 2).

The 2-arylethylamine **4** was obtained in three steps from *O*-isopropylisovanillin (**7a**).[13] Henry reaction of **7a** with nitromethane[14] gave the (*E*)-β-nitrostyrene in 80% yield, which was smoothly reduced with $LiBH_4$/ trimethylsilyl chloride (TMSCl).[15] The resulting amine was brominated in glacial acetic acid[16] to afford the hydrobromide of **4** in 81% yield (Scheme 2, path a). The arylpyruvates **5a** and **5b** were obtained from the corresponding benzaldehydes **7a** and **7b** by Erlenmeyer azlactone synthesis[17] and subsequent esterification with ethanol/TMSCl[18] (Scheme 2, path b) or diazomethane (Scheme 2, path c). The benzylic position of **5b** was brominated by irradiation with *N*-bromosuccinimide in CCl_4 providing crude **6b** in quantitative yield. The bromopyruvate **6b** was used for the pyrrole condensation step without further purification.



Scheme 2. Syntheses of the building blocks **4**, **5a**, and **6b**. **4:** a) i) **7a**, $MeNO_2$, NH_4OAc, 80%; ii) $LiBH_4$, TMSCl, 74%; iii) Br_2, AcOH, 81%; **5a:** b) i) **7a**, *N*-acetylglycine, NaOAc, Ac_2O, 42%; ii) aq. NaOH, 65%; iii) EtOH, TMSCl, 79%; **6b**: c) i) **7b**, *N*-acetylglycine, NaOAc, Ac_2O, 45%; ii) aq NaOH, 69%; iii) CH_2N_2, 82%; d) NBS, *hv*, 100%.



Scheme 3. Synthesis of lamellarin L (**1**). i) NaH, -12 to $-5\,^\circ C$, then **6b**, -5 to $25\,^\circ C$, CH_2Cl_2; ii) **4**, molecular sieves (4 Å), 5 h reflux; iii) NaCN (50 equiv), DMPU, 1 h, $115\,^\circ C$; iv) $Pb(OAc)_4$ (1.1 equiv), PhH, reflux; v) 40% aq. KOH, 3 h, $150\,^\circ C$, then cat *p*-TsOH, toluene, 30 min, $120\,^\circ C$; vi) $Pd(OAc)_2$ (1 equiv), PPh_3 (2 equiv), CH_3CN/NEt_3 (3:1), 80 min, $150\,^\circ C$; vii) $AlCl_3$ (7.5 equiv), 0 to $25\,^\circ C$, CH_2Cl_2, 4 h.

The key intermediate **10** was obtained in a one-pot procedure by deprotonation of ethyl ester **5a** with sodium hydride and coupling of the resulting enolate with one equivalent of bromide **6b**. The 1,4-diketo compound **9** thus formed was directly converted into the pyrrole **10** by adding the amine **4** at ambient temperature, and the resulting mixture was refluxed in the presence of molecular sieves (4 Å). The yield of pyrrole **10** was 53% after purification of the reaction mixture by column chromatography. When the coupling between **5a** and **6b** was performed with the lithium instead of the sodium enolate, the formation of a mixture of coupling products was observed due to bromine exchange between the two coupling partners (Scheme 3).

The pyrrole **10** bears all atoms and functional groups required for the construction of the lamellarin skeleton. To obtain the monocarboxylic acid **11** the methyl ester group of **10** had to be cleaved leaving the ethyl ester group intact. This was cleanly accomplished by heating of **10** in a suspension of NaCN in 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one (DMPU).[12] Subsequent reaction of the carboxylic acid **11** with lead(IV) acetate[6, 19] in refluxing benzene furnished the lactone **12** in 97% yield. As reported before,[6] this reaction forms exclusively the desired regioisomer by attack of the carboxy radical at the *ortho* position which carries no adjacent alkoxy substituent. For completion of the lamellarin framework, the ethyl ester group had to be cleaved. This was achieved by heating **12** with 40% aqueous KOH, and removal

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of the ethanol by distillation. As monitored by TLC, the lactone ring was also opened under these conditions, but was easily reinstalled by heating the crude reaction product with a catalytic amount of *p*-TsOH in toluene. This two-step reaction sequence afforded the desired carboxylic acid **13** in high yield. The Pd(0)-catalyzed Heck cyclization of bromide **13** was carried out in acetonitrile/triethylamine in a pressure tube at 150 °C. The conversion was complete within 80 min, providing lamellarin L triisopropyl ether (**14**) in 97 % yield after column chromatography. The cyclization proceeds with concomitant decarboxylation,[6] a reaction type, hitherto not observed in Heck reactions. Treatment of **14** with $AlCl_3$ in dichloromethane removed the isopropyl protecting groups[7, 20] and afforded lamellarin L (**1**) in almost quantitative yield. The spectroscopic data (UV, IR, ^{1}H NMR, ^{13}C NMR, MS) of synthetic **1** agreed in all respects with those reported for the natural product.[11]

The first total synthesis of lamellarin L was thus completed in six steps with an overall yield of 38 % (from compounds **4, 5a**, and **6b**). The use of our biomimetic approach for the synthesis of other lamellarins is under active investigation.

Experimental Section

General: Melting points (uncorrected) were determined on a Reichert Thermovar hot stage microscope. IR spectra were recorded on a Bruker FTIR IFS 48 spectrometer and are presented as: s (strong), m (medium), w (weak), and br. (broad). UV/Vis spectra were obtained on a Perkin–Elmer Lambda 16 instrument. NMR spectra were recorded on Bruker AMX 600 and ARX 300 instruments with the solvent peak as internal reference ($CDCl_3$: $\delta(^1H) = 7.26$, $\delta(^{13}C) = 77.0$; [D$_6$]DMSO: $\delta(^1H) = 2.49$, $\delta(^{13}C) = 39.5$). Mass spectra (MS) and high-resolution mass spectra (HR-MS) were recorded with a Finnigan MAT 95 double focusing spectrometer, equipped with an EI ion source operated at 70 eV. All nonaqueous reactions were carried out under an argon atmosphere in dry solvents, unless otherwise noted. Dichloromethane (CH_2Cl_2) was distilled from Sicapent, and tetrahydrofuran (THF) was distilled from potassium/benzophenone. Other solvents were purchased at absolute quality and stored over molecular sieves (4 Å). All reactions were monitored by thin-layer chromatography (TLC) using E. Merck silica gel plates 60 F_{254}. The spots were detected under UV light (254 and 366 nm). Flash chromatography was conducted on E. Merck silica gel 60, particle size 0.04–0.063 mm.

2-(2-Bromo-5-isopropoxy-4-methoxyphenyl)-1-ethylammonium bromide (4·HBr): 3-Isopropoxy-4-methoxybenzaldehyde (**7a**)[13] (16.12 g, 83 mmol) and ammonium acetate (6.09 g, 79 mmol) in nitromethane (120 mL) were heated at 110 °C for 30 min. The mixture was cooled to 25 °C and kept at −18 °C overnight. The precipitate was filtered off, and washed with water (3 × 60 mL) and ice-cold ethanol (1 × 50 mL). Lyophilization afforded (*E*)-*β*-nitro-3-isopropoxy-4-methoxystyrene (15.67 g, 80 %) as yellow needles. M.p. 83 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.96$ (d, $J = 13.5$ Hz, 1H), 7.51 (d, $J = 13.5$ Hz, 1H), 7.17 (dd, $^3J = 8.4$ Hz, $^4J = 2.1$ Hz, 1H), 7.05 (d, $J = 2.1$ Hz, 1H), 6.92 (d, $J = 8.4$ Hz, 1H), 4.57 (m, $J = 6$ Hz, 1H), 3.92 (s, 3H), 1.40 (d, $J = 6$ Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 154.22$, 147.78, 139.39, 135.06, 124.59, 122.68, 115.0, 111.95, 71.85, 56.05, 21.95; EIMS: *m/z* (%): 237 (75), 195 (100), 148 (65); HRMS: calcd for 237.1001, found 237.1003; elemental analysis (%): calcd for $C_{12}H_{15}NO_4$: C 60.75, H 6.37, N 5.90; found: C 60.89, H 6.31, N 5.86.

TMSCl (50.6 mL, 0.4 mol) was added within 2 min to a vigorously stirred slurry of $LiBH_4$ (4.36 g, 0.2 mol) in dry THF (100 mL). After flushing the vessel several times with argon, a solution of (*E*)-*β*-nitro-3-isopropoxy-4-methoxystyrene (11.86 g, 50 mmol) in dry THF (100 mL) was added dropwise to the mixture within 5 min. The reaction mixture was stirred at ambient temperature for 24 h, then cooled to 0 °C, and carefully quenched with methanol (150 mL). The solvent was removed under reduced pressure, and the residue was treated with 20 % aqueous KOH (150 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL), the combined organic phases were dried (Na_2SO_4), and the solvent was evaporated in vacuo. The resulting brown oil was purified by Kugelrohr distillation (150 °C/11 mbar) to provide 2-(3-isopropoxy-4-methoxyphenyl)-1-ethylamine (7.68 g, 74 %) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta =$ 6.82 (dd, $^3J = 8$ Hz, $^4J = 2$ Hz, 1H), 6.76 (d, $J = 2$ Hz, 1H), 6.75 (d, $J = 8$ Hz, 1H), 4.51 (m, $J = 6$ Hz, 1H), 3.83 (s, 3H), 2.95 (t, $J = 6.9$ Hz, 2H), 2.69 (t, $J = 6.9$ Hz, 2H), 1.89 (br., 2H), 1.36 (d, $J = 6$ Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 148.8$, 147.1, 132.0, 121.1 (CH), 116.6 (CH), 112.0 (CH), 71.3 (CH), 55.9 (CH_3), 43.5 (CH_2), 39.1 (CH_2), 22.0 (CH_3); MS: *m/z* (%): 209 (24), 180 (52), 138 (100); HRMS: calcd for $C_{12}H_{19}NO_2$ 209.1407, found 209.1405.

A solution of bromine (4.07 g, 25.4 mmol) in glacial acetic acid (15 mL) was added at 0 °C through a dropping funnel to a vigorously stirred solution of 2-(3-isopropoxy-4-methoxyphenyl)-1-ethylamine (3.55 g, 17 mmol) in glacial acetic acid (77 mL). The stirring was continued for 30 min at 0 °C, and the solvent was removed on a rotary evaporator at 45 °C. The dark brown oily residue was dried under reduced pressure overnight, diluted with ethyl acetate (250 mL), and stirred for 15 min to yield a colorless precipitate which was filtered and washed with ethyl acetate (3 × 100 mL) to yield the hydrobromide of **4** (5.1 g, 81 %) as a white powder. M.p. 224 °C; ^{1}H NMR ([D$_6$]DMSO, 300 MHz): $\delta = 7.91$ (br. s, 3H), 7.15 (s, 1H), 7.00 (s, 1H), 4.56 (m, $J = 6$ Hz, 1H), 3.76 (s, 3H), 2.92–2.99 (br. m, 4H), 1.25 (d, $J = 6$ Hz, 6H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz): $\delta = 149.9$, 146.5, 128.2, 117.7, 116.3, 113.9, 79.4, 70.8, 56.1, 41.9, 32.9, 22.0; elemental analysis (%): calcd for $C_{12}H_{19}NO_2Br_2$ (369.10): C 39.05, H 5.19, N 3.79; found: C 39.09, H 5.23, N 3.79.

Ethyl (3-isopropoxy-4-methoxyphenyl)pyruvate (5a): A mixture of 3-isopropoxy-4-methoxybenzaldehyde (**7a**)[13] (19.11 g, 98.4 mmol), *N*-acetylglycine (13.83 g, 118 mmol), sodium acetate (10.49 g, 128 mmol), and acetic anhydride (47 mL, 492 mmol) was heated at 120 °C for 8 h under stirring. The resulting solution was allowed to cool to 50 °C and then poured into ice water (100 mL). After 20 min of stirring, the precipitate was filtered off, washed with water (3 × 100 mL), and recrystallized from ethanol/water 7:3 to afford 4-(3-isopropoxy-4-methoxybenzylidene)-2-methyloxazol-5(4*H*)-one (11.34 g, 42 %) as a bright yellow powder. M.p. 113 °C; UV/Vis (MeOH): λ_{max} (ε) = 203 (14609), 253 (7563), 367 nm (23080 M^{-1}cm^{-1}); IR (KBr): $\tilde{\nu} = 1780$ (s), 1763 (s), 1659 (s), 1609 (m), 1588 (s), 1514 cm^{-1} (s); ^{1}H NMR ([D$_6$]DMSO, 300 MHz): $\delta = 7.94$ (d, $J = 1.5$ Hz, 1H), 7.75 (dd, $^3J = 8.4$ Hz, $^4J = 1.5$ Hz, 1H), 7.17 (s, 1H), 7.09 (d, $J = 8.4$ Hz, 1H), 4.55 (m, $J = 6$ Hz, 1H), 3.83 (s, 3H), 2.37 (s, 3H), 1.29 (d, $J = 6$ Hz, 6H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz): $\delta = 167.7$, 165.5, 152.8, 146.7, 130.7 (CH), 130.3, 127.2 (CH), 126.1, 118.1 (CH), 112.3 (CH), 70.7 (CH), 55.8 (CH_3), 22.0 (CH_3), 15.6 (CH_3); MS: *m/z* (%): 275 (73), 233 (24), 205 (13), 163 (100), 148 (14); elemental analysis (%): calcd for $C_{15}H_{17}NO_4$ (275.30) C 65.44, H 6.22, N 5.09; found: C 65.39, H 6.13, N 5.05.

The finely ground oxazolone (19.50 g, 71 mmol) was added at 100 °C to a solution of NaOH (80 g) in water (120 mL). After heating the mixture for 70 min at 130 °C, it was cooled to 25 °C on an ice bath, poured into ice water (400 mL), and adjusted to pH 3 with concentrated HCl. The mixture was extracted with ethyl acetate (3 × 100 mL), and the combined organic phases were washed with aqueous $KHSO_4$ (1.1 M, 100 mL) and brine (100 mL), and dried over Na_2SO_4. Evaporation of the solvent and recrystallization of the residue from ethyl acetate yielded (3-isopropoxy-4-methoxyphenyl)pyruvic acid (11.57 g, 65 %) as light yellow needles. M.p. 149 °C; ^{1}H NMR ([D$_6$]DMSO, 300 MHz): $\delta = 13.03$ (br. s, 1H), 8.96 (s, 1H), 7.45 (d, $J = 2$ Hz, 1H), 7.29 (dd, $^3J = 9$ Hz, $^4J = 2$ Hz, 1H), 6.95 (d, $J = 9$ Hz, 1H), 6.36 (s, 1H), 4.48 (m, $J = 6$ Hz, 1H), 3.76 (s, 3H), 1.25 (d, $J = 6$ Hz, 6H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz): $\delta = 166.7$, 149.7, 146.3, 140.2, 130.0, 123.2 (CH), 117.1 (CH), 112.3 (CH), 110.3 (CH), 70.6 (CH), 55.6 (CH_3), 22.1 (CH_3); MS: *m/z* (%): 252 (19), 210 (15), 164 (14), 137 (100); HRMS: calcd for $C_{13}H_{16}O_5$ 252.0998, found 252.0995; elemental analysis (%): calcd for $C_{13}H_{16}O_5$ (252.27) C 61.90, H 6.39; found: C 61.90, H 6.24.

(3-Isopropoxy-4-methoxyphenyl)pyruvic acid (2.22 g, 8.8 mmol) and 1.5 equivalents of TMSCl (1.67 mL, 13.2 mmol) were dissolved in absolute ethanol (26.5 mL) and stirred at 50 °C. After 4.5 h, the solution was poured into ice water (100 mL) and stirred for 5 min. The precipitate was separated, washed with water (2 × 30 mL), and dried in vacuo to afford the ethyl ester **5a** (1.96 g, 79 %) as colorless crystals. M.p. 101 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.48$ (d, $J = 2$ Hz, 1H), 7.28 (dd, $^3J = 8.4$ Hz, $^4J =$ 2.1 Hz, 1H), 6.87 (d, $J = 8.4$ Hz, 1H), 6.47 (s, 1H), 6.35 (s, 1H), 4.57 (m,

$J = 6.1$ Hz, 1H), 4.35 (q, $J = 7$ Hz, 2H), 3.87 (s, 3H), 1.39 (t, $J = 7$ Hz, 3H), 1.38 (d, $J = 6.1$ Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 166.4$, 150.4, 147.0, 137.9, 127.1, 123.6, 117.1, 111.6, 111.0, 71.4, 62.4, 55.9, 22.1, 14.3; MS: *m/z* (%): 280 (54), 238 (16), 164 (100), 137 (99); HRMS: calcd for $C_{15}H_{20}O_5$ 280.1311, found 280.1312; elemental analysis (%): calcd for $C_{15}H_{20}O_5$ (280.32) C 64.27, H 7.19; found: C 64.28, H 7.07.

Methyl 3-bromo-3-(4-isopropoxy-3-methoxyphenyl)pyruvate (6b): The oxazolone was prepared from 4-isopropoxy-3-methoxybenzaldehyde (**7b**) (15.54 g, 80 mmol), *N*-acetylglycine (11.24 g, 96 mmol), sodium acetate (8.53 g, 104 mmol), and acetic anhydride (38 mL, 400 mmol) by the same procedure as described for **5a**. Recrystallization from 70% aqueous ethanol afforded 3-(4-isopropoxy-3-methoxybenzylidene)-2-methyloxazol-5(4*H*)-one (9.88 g, 45%) as a bright yellow powder. M.p. 98 °C; ^{1}H NMR ([D$_6$]DMSO, 300 MHz): $\delta = 7.89$ (d, $J = 1.9$ Hz, 1H), 7.72 (dd, $^3J = 8.5$ Hz, $^4J = 1.9$ Hz, 1H), 7.13 (s, 1H), 7.07 (d, $J = 8.5$ Hz, 1H), 4.69 (m, $J = 6$ Hz, 1H), 3.77 (s, 3H), 2.36 (s, 3H), 1.27 (d, $J = 6$ Hz, 6H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz): $\delta = 167.8$, 165.4, 150.1, 149.5, 130.7 (CH), 130.2, 127.1 (CH), 125.9, 115.3 (CH), 114.1 (CH), 70.4 (CH), 55.7 (CH_3), 22.0 (CH_3), 15.6 (CH_3); MS: *m/z* (%): 275 (23), 233 (27), 163 (100); elemental analysis (%): calcd for $C_{15}H_{17}NO_4$ (275.30) C 65.44, H 6.22, N 5.09; found: C 65.28, H 6.24, N 5.02.

Hydrolysis of the oxazolone (9.88 g, 35.9 mmol) by the same procedure as described for **5a**, and recrystallization of the product from ethyl acetate afforded (4-isopropoxy-3-methoxyphenyl)pyruvic acid (6.24 g, 69%) as light yellow needles. M.p. 144–146 °C; ^{1}H NMR ([D$_6$]DMSO, 300 MHz): $\delta = 8.97$ (br. s, 1H), 7.43 (d, $J = 1.8$ Hz, 1H), 7.27 (dd, $^3J = 8.7$ Hz, $^4J = 1.8$ Hz, 1H), 6.94 (d, $J = 8.7$ Hz, 1H), 6.38 (s, 1H), 4.56 (m, $J = 6$ Hz, 1H), 3.74 (s, 3H), 1.25 (d, $J = 6$ Hz, 6H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz): $\delta = 166.7$, 149.6, 146.4, 140.4, 128.3, 128.7 (CH), 115.2 (CH), 113.6 (CH), 110.3 (CH), 70.3 (CH), 55.6 (CH_3), 22.2 (CH_3); MS: *m/z* (%): 252 (21), 210 (20), 164 (11), 137 (100); elemental analysis (%): calcd for $C_{13}H_{16}O_5$ (252.27) C 61.90, H 6.39; found: C 61.84, H 6.52.

The finely powdered (4-isopropoxy-3-methoxyphenyl)pyruvic acid (3.10 g, 12.3 mmol) was suspended in ethyl acetate (400 mL) and cooled in an ice bath. Under vigorous stirring, the mixture was treated with 3 mL portions of a freshly prepared ethereal solution of diazomethane until all particles had dissolved and TLC control showed complete conversion. After stirring for an additional 1 h at 0 °C, the solvent was removed in vacuo. The oily residue was subjected to flash chromatography on silica gel (petroleum ether/Et_2O 1:1) to yield methyl (4-isopropoxy-3-methoxyphenyl)pyruvate (**5b**) (2.69 g, 82%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.45$ (d, $J = 2$ Hz, 1H), 7.23 (dd, $^3J = 8.4$ Hz, $^4J = 2$ Hz, 1H), 6.87 (d, $J = 8.4$ Hz, 1H), 6.48 (s, 1H), 6.36 (s, 1H), 4.54 (m, $J = 6$ Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 1.37 (d, $J = 6$ Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 166.77$, 149.90, 147.44, 137.60, 127.22, 123.31, 114.90, 113.39, 111.47, 71.18, 55.83, 53.06, 22.00; MS: *m/z* (%): 266 (29), 224 (14), 193 (38), 164 (77), 151 (100), 137 (70); HRMS: calcd for $C_{14}H_{18}O_5$ 266.1154, found 266.1145.

A vigorously stirred mixture of methyl ester **5b** (2.69 g, 10.12 mmol), *N*-bromosuccinimide (NBS) (1.89 g, 10.63 mmol), and CCl_4 (180 mL) was irradiated at 12 °C with a halogen lamp (500 W). After 45 min, the mixture was filtered, and the solvent evaporated under reduced pressure to afford the crude bromopyruvate **6b** as a dark yellow oil in quantitative yield. Due to its tendency for decomposition, **6b** was used for the next step without further purification. An analytically pure sample was prepared by flash chromatography on silica gel (petroleum ether/ethyl acetate 2:1) and could be stored at −18 °C for several days. IR (KBr): $\tilde{\nu} = 3462$ (w), 2978 (s), 2836 (w), 1738 (s), 1601 (m), 1512 (s), 1466 (m), 1423 (m), 1385 (m), 1374 (m), 1263 (s), 1140 (s), 1110 (s), 1059 (s), 1035 (s), 953 (m), 858 (w), 811 (w), 776 (w), 719 (w), 678 (w), 565 cm^{-1} (w); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 6.96$–7.00 (br., 2H), 6.84 (d, $J = 9$ Hz, 1H), 6.21 (s, 1H), 4.55 (m, $J = 6$ Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 1.37 (d, $J = 6$ Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 183.48$, 160.52, 150.43, 148.81, 124.79, 122.48, 114.54, 113.05, 71.27, 56.06, 53.52, 50.24, 21.99.

Ethyl 1-[2-(2-bromo-5-isopropoxy-4-methoxyphenyl)ethyl]-3-(3-isopropoxy-4-methoxyphenyl)-4-(4-isopropoxy-3-methoxyphenyl)-5-methoxycarbonyl-1*H*-pyrrole-2-carboxylate (10): A solution of **5a** (448 mg, 1.6 mmol) in dry CH_2Cl_2 (30 mL) was cooled to −12 °C. After addition of sodium hydride (42.2 mg, 1.76 mmol), the stirred mixture was allowed to warm to −5 °C. After 5 min, a cold solution (−5 °C) of **6b** (552 mg, 1.6 mmol) in CH_2Cl_2 (10 mL) was added by a syringe within 1 min. After the mixture had been stirred for 20 min at −5 °C, the cooling bath was removed, and the reaction mixture allowed to warm to room temperature. Then, **4** (692 mg, 2.4 mmol), freshly generated from the hydrobromide with saturated aqueous Na_2CO_3 in CH_2Cl_2 (20 mL), and molecular sieves (4 Å, 2 g) were added. The mixture was refluxed for 5 h and then stirred at 25 °C overnight. After filtration and evaporation of the solvent, the residue was dissolved in Et_2O (30 mL), and then washed with aqueous $KHSO_4$ (1.1 M, 1 × 20 mL), water (1 × 20 mL), and brine (20 mL). After drying (Na_2SO_4), the solvent was evaporated, and the residue purified by flash chromatography on silica gel (CH_2Cl_2/acetone 50:1) to yield **10** (675 mg, 53%) as a light yellow foam. UV/Vis (MeOH): λ_{max} (ε) = 204 (79349), 284 nm (20425 M^{-1}cm^{-1}); IR (KBr): $\tilde{\nu} = 3435$ (m), 2976 (s), 2934 (m), 2836 (w), 1717 (s), 1603 (w), 1582 (w), 1529 (m), 1499 (m), 1466 (m), 1442 (m), 1405 (w), 1385 (m), 1372 (m), 1348 (m), 1300 (m), 1258 (s), 1212 (s), 1163 (s), 1137 (m), 1111 (s), 1049 (m), 1027 (m), 955 (w), 906 (w), 859 (w), 831 (w), 808 (w), 772 cm^{-1} (w); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 6.98$ (s, 1H), 6.71 (d, $J = 8.3$ Hz, 1H), 6.69 (d, $J = 8$ Hz, 1H), 6.68 (s, 1H), 6.61 (dd, $^3J = 8.3$ Hz, $^4J = 2$ Hz, 1H), 6.52 (d, $J = 2$ Hz, 1H), 6.52 (dd, $^3J = 8.3$ Hz, $^4J = 1.9$ Hz, 1H), 6.49 (d, $J = 2$ Hz, 1H), 4.96 (t, $J = 6.8$ Hz, 2H), 4.44 (m, $J = 6.2$ Hz, 1H), 4.43 (m, $J = 6.2$ Hz, 1H), 4.22 (m, $J = 6.2$ Hz, 1H), 4.02 (q, $J = 7.1$ Hz, 2H), 3.80 (s, 2 × 3H), 3.60 (s, 3H), 3.56 (s, 3H), 3.15 (t, $J = 6.9$ Hz, 2H), 1.33 (d, $J = 6$ Hz, 6H), 1.32 (d, $J = 6$ Hz, 6H), 1.16 (d, $J = 6.1$ Hz, 6H), 0.95 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 162.1$, 161.6, 149.6, 149.1, 146.8, 146.1, 145.9, 130.4, 130.3, 129.7, 127.2, 124.5, 124.0, 123.5, 122.8, 118.7, 117.8, 115.9, 114.8, 114.6, 110.9, 71.6, 71.2, 60.5, 56.2, 55.9, 55.7, 51.4, 46.3, 37.8, 22.1, 21.8, 13.6; MS: *m/z* (%): 797 (45), 795 (41), 716 (100), 674 (31), 632 (12); HRMS: calcd for $C_{41}H_{50}NO_{10}{}^{79}Br$ 795.2618, found 795.2586.

Ethyl 1-[2-(2-bromo-5-isopropoxy-4-methoxyphenyl)ethyl]-5-carboxy-3-(3-isopropoxy-4-methoxyphenyl)-4-(4-isopropoxy-3-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (11): Diester **10** (0.40 g, 0.5 mmol) was added to a suspension of finely ground NaCN (1.23 g, 25 mmol) in DMPU (80 mL). The mixture was stirred for 1 h at 115 °C. After cooling to 0 °C, an aqueous solution of $FeSO_4$ (1 M, 100 mL) was added, and the reaction mixture was stirred vigorously in an open vessel until a green–blue color indicated the formation of Berlin blue. After acidification with HCl (2 M), the crude product was extracted with ethyl acetate (3 × 100 mL), and the combined organic layers were washed with water (2 × 100mL) and brine (100 mL). The solution was dried (Na_2SO_4), concentrated, and purified by flash chromatography on silica gel (CH_2Cl_2/acetone 10:1) to yield **11** (365 mg, 94%) and recovered starting material (16 mg, 4%). Compound **11** crystallized from Et_2O/petroleum ether as a colorless solid. M.p. 129 °C; UV/Vis (MeOH): λ_{max} (ε) = 204 (75815), 285 nm (19557 M^{-1}cm^{-1}); IR (KBr): $\tilde{\nu} = 3429$ (m), 2977 (s), 2935 (m), 1715 (s), 1672 (w), 1607 (w), 1582 (w), 1529 (m), 1498 (m), 1466 (m), 1442 (m), 1426 (m), 1406 (w), 1385 (m), 1371 (m), 1346 (m), 1296 (m), 1256 (s), 1213 (s), 1174 (m), 1138 (m), 1111(s), 1028 (w), 956 (w), 859 (w), 792 cm^{-1} (w); ^{1}H NMR ([D$_6$]DMSO, 600 MHz): $\delta = 12.70$ (br., 1H), 7.06 (s, 1H), 6.78 (d, $J = 8.6$ Hz, 1H), 6.73 (d, $J = 8.6$ Hz, 1H), 6.59 (s, 1H), 6.55 (d, $J = 1.9$ Hz, 1H), 6.50–6.53 (m, 2H), 6.42 (d, $J = 1.9$ Hz, 1H), 4.86 (t, $J = 6.3$ Hz, 2H), 4.41 (m, $J = 6$ Hz, 1H), 4.37 (m, $J = 6$ Hz, 1H), 4.18 (m, $J = 6$ Hz, 1H), 3.87 (q, $J = 7$ Hz, 2H), 3.71 (s, 3H), 3.67 (s, 3H), 3.50 (s, 3H), 3.02 (t, $J = 6.3$ Hz, 2H), 1.21 (d, $J = 6$ Hz, 6H), 1.19 (d, $J = 6$ Hz, 6H), 1.04 (d, $J = 6$ Hz, 6H), 0.84 (t, $J = 7$ Hz, 3H); ^{13}C NMR ([D$_6$]DMSO, 150 MHz): $\delta = 162.66$, 161.15, 149.62, 148.93, 148.62, 146.39, 145.57, 145.50, 129.40, 129.05, 127.18, 126.88, 123.36, 122.80, 118.67, 117.44, 115.98, 115.29, 114.18, 114.17, 111.48, 70.77, 70.48, 70.13, 60.24, 55.98, 55.63, 55.38, 45.71, 37.40, 22.14, 22.06, 21.85, 13.48; MS: *m/z* (%): 783 (3), 781 (3), 739 (12), 737 (11), 658 (100), 586 (23), 542 (11), 501 (6), 459 (5); HRMS: calcd for $C_{40}H_{48}NO_{10}{}^{81}Br$ 783.2442, found 783.2462; elemental analysis (%): calcd for $C_{40}H_{48}NO_{10}Br$ (782.73) C 61.38, H 6.18, N 1.79; found C 61.13, H 6.21, N 1.77.

3-[2-(2-Bromo-5-isopropoxy-4-methoxyphenyl)ethyl]-7-isopropoxy-1-(3-isopropoxy-4-methoxyphenyl)-8-methoxy-4-oxo-3*H*-[1]benzopyrano[3,4-*b*]-pyrrole-2-carboxylic acid ethyl ester (12): Lead(IV) acetate (34 mg, 0.077 mmol) was added to a solution of **11** (55 mg, 0.07 mmol) in benzene (2 mL). The mixture was refluxed at 90 °C for 20 min. The color of the mixture turned light yellow, and precipitation occurred. When TLC control indicated incomplete conversion, more $Pb(OAc)_4$ was added in portions of 0.1 equivalent. After cooling to room temperature, the reaction mixture was filtered, diluted with ethyl acetate (10 mL), and washed with 2% aqueous $NaHCO_3$ (1 × 5 mL), water (2 × 5 mL), and brine (1 × 5 mL). Evaporation of the dried (Na_2SO_4) solution yielded **12** (53 mg, 97%) as a

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light-yellow foam, which crystallized from methanol. M.p. 175 °C; UV/Vis (MeOH): λ_{max} (ε) = 202 (33466), 257 nm (10618 M^{-1}cm^{-1}); IR (KBr): $\tilde{\nu}$ = 3438 (w), 2977 (m), 2934 (m), 2836 (w), 1730 (s), 1620 (w), 1537 (m), 1507 (s), 1487 (m), 1467 (m), 1441 (m), 1406 (m), 1385 (m), 1352 (w), 1332 (w), 1305 (m), 1264 (s), 1216 (s), 1197 (m), 1177 (m), 1158 (s), 1138 (m), 1112 (s), 1019 (m), 968 (w), 939 (w), 856 (w), 811 (w), 794 (w), 769 (w), 643 (w), 623 (w), 449 cm^{-1} (w); ^{1}H NMR ([D$_6$]DMSO, 600 MHz): δ = 7.07 (d, J = 2.5 Hz, 1H), 7.06 (d, J = 6 Hz, 1H), 7.02 (s, 1H), 6.81 (s, 1H), 6.80 (dd, ^3J = 5.7 Hz, ^4J = 1.8 Hz, 1H), 6.56 (s, 1H), 6.43 (s, 1H), 5.08 (t, J = 6.4 Hz, 2H), 4.63 (m, J = 6 Hz, 1H), 4.48 (m, J = 6 Hz, 1H), 4.21 (m, J = 6 Hz, 1H), 3.84 (q, J = 7.1 Hz, 2H), 3.78 (s, 3H), 3.69 (s, 3H), 3.28 (s, 3H), 3.07 (t, J = 6.5 Hz, 2H), 1.24 (d, J = 6 Hz, 6H), 1.22 (d, J = 6 Hz, 3H), 1.21 (d, J = 6 Hz, 3H), 1.09 (d, J = 6 Hz, 3H), 1.07 (d, J = 6 Hz, 3H), 0.80 (t, J = 7.1 Hz, 3H); ^{13}C NMR ([D$_6$]DMSO, 150 MHz): δ = 160.10, 154.37, 153.08, 150.02, 149.52, 147.20, 146.61, 146.39, 145.70, 130.33, 128.62, 126.61, 126.17, 123.71, 122.92, 118.11, 117.37, 117.06, 115.81, 114.31, 112.48, 109.19, 104.92, 103.39, 70.73, 70.70, 70.67, 60.70, 55.99, 55.97, 54.98, 46.05, 36.92, 21.93, 21.78, 13.45; MS: *m/z* (%): 781 (100), 779 (93), 739 (6), 737 (5), 700 (83), 658 (56), 616 (45), 543 (18), 501 (13); HRMS: calcd for $C_{40}H_{46}NO_{10}{}^{79}Br$ 779.2306, found 779.2333; elemental analysis (%): calcd for $C_{40}H_{46}NO_{10}Br$ (780.71) C 61.54, H 5.94, N 1.79; found: C 61.39, H 5.90, N 1.76.

3-[2-(2-Bromo-5-isopropoxy-4-methoxyphenyl)ethyl]-7-isopropoxy-1-(3-isopropoxy-4-methoxyphenyl)-8-methoxy-4-oxo-3*H*-[1]benzopyrano[3,4-*b*]-pyrrole-2-carboxylic acid (13): Finely ground **12** (295 mg, 0.38 mmol) was suspended in a freshly prepared, degassed solution of KOH (9.45 g, 168 mmol) in water (14 mL, 777 mmol). The mixture was heated for 3 h at 150 °C and the ethanol was removed by distillation. The reaction mixture was cooled to 0 °C, acidified dropwise with 37% HCl, and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (1 × 20 mL), dried (Na_2SO_4), and concentrated to afford a deep-yellow oil. The residue was lyophilized and dissolved in dry toluene (50 mL). Toluene-*p*-sulfonic acid monohydrate (30 mg) and molecular sieves (4 Å, 0.4 g) were added, and the mixture was refluxed for 30 min. After filtration and evaporation of the solvent, the residue was dissolved in ethyl acetate (20 mL) and washed with aqueous $KHSO_4$ (1.1 M, 1 × 10 mL) and brine (1 × 10 mL). After drying (Na_2SO_4), the solvent was removed in vacuo to afford **13** (0.23 g, 80%) as a light yellow solid. An analytically pure sample was prepared by recrystallization from Et_2O and methanol. M.p. 201 °C; UV/Vis (MeOH): λ_{max} (ε) = 204 (89093), 288 (13598), 333 nm (11019 M^{-1}cm^{-1}); IR (KBr): $\tilde{\nu}$ = 3436 (s), 2977 (m), 2933 (m), 1730 (s), 1622 (m), 1537 (m), 1497 (m), 1466 (m), 1441 (m), 1385 (m), 1260 (s), 1214 (s), 1179 (m), 1158 (m), 1111 (m), 1018 (w), 967 (w), 930 (w), 856 (w), 773 (w), 448 cm^{-1} (w); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.00 (d, J = 8.5 Hz, 1H), 6.94 (d, J = 2 Hz, 1H), 6.93 (s, 1H), 6.90 (d, J = 8.5 Hz, 1H), 6.88 (s, 1H), 6.81 (s, 1H), 6.48 (s, 1H), 5.17 (t, J = 6.5 Hz, 2H), 4.53 (m, J = 5.9 Hz, 2H), 4.40 (m, J = 6.1 Hz, 1H), 3.92 (s, 3H), 3.77 (s, 3H), 3.40 (s, 3H), 3.21 (t, J = 6.5 Hz, 2H), 1.38 (d, J = 6.1 Hz, 6H), 1.33 (dd, J = 6 Hz, 1.7 Hz, 6H), 1.26 (dd, J = 6 Hz, 2.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 193.82, 164.62, 155.13, 150.27, 149.76, 147.55, 147.23, 146.78, 145.83, 129.12, 128.17, 127.27, 126.06, 125.97, 122.87, 118.52, 117.83, 117.66, 116.05, 114.67, 111.89, 109.38, 104.90, 103.22, 71.57, 71.51, 71.32, 56.16, 56.08, 55.46, 47.11, 37.66, 22.00, 21.95, 21.75; MS: *m/z* (%): 754 (21), 753 (59), 752 (21), 751 (54), 711 (6), 709 (4), 672 (17), 630 (17), 588 (22), 544 (11), 502 (15), 379 (44); HRMS: calcd for $C_{38}H_{42}NO_{10}{}^{79}Br$ 751.1992, found 751.1983; elemental analysis (%): calcd for $C_{38}H_{42}NO_{10}Br$ (752.66) C 60.64, H 5.62, N 1.86; found: C 60.75, H 5.50, N 1.82.

8,9-Dihydro-3,11-diisopropoxy-14-(3-isopropoxy-4-methoxyphenyl)-2,12-dimethoxy-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (14): Compound **13** (90 mg, 0.12 mmol), palladium(II) acetate (27 mg, 0.12 mmol), triphenylphosphane (63 mg, 0.24 mmol), and CH_3CN (20 mL) were stirred in an argon-flushed pressure tube to give a fine suspension. After the addition of NEt_3 (7 mL), the tube was sealed and dipped in a hot (150 °C) oil bath. The resulting solution was heated for 80 min, then cooled to ambient temperature, and filtered through Celite. The palladium precipitate remained on the filter and was rinsed with ethyl acetate (3 × 10 mL). The combined solutions were adjusted to pH 5 with aqueous HCl (2 M). The organic layer was separated, and the aqueous layer reextracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with saturated aqueous Na_2CO_3 (1 × 20 mL), water (1 × 20 mL), and brine (1 × 20 mL). After drying (Na_2SO_4) and concentration, the residue was subjected to flash chromatography on silica gel (CH_2Cl_2/acetone 50:1) to yield **14** (73 mg, 97%) as a colorless solid. Compound **14** crystallizes with one molecule of acetone. M.p. 174 °C; UV/Vis (MeOH): λ_{max} (ε) = 204 (60214), 277 (34101), 315 nm (30997 M^{-1}cm^{-1}); IR (KBr): $\tilde{\nu}$ = 3436 (s), 2976 (m), 2934 (m), 1709 (s), 1620 (w), 1577 (w), 1542 (m), 1512 (m), 1483 (s), 1465 (m), 1439 (s), 1417 (s), 1384 (w), 1336 (w), 1270 (s), 1241 (s), 1211 (s), 1177 (s), 1163 (s), 1137 (m), 1111 (s), 1039 (m), 1020 (m), 968 (w), 939 (w), 855 (w), 763 (w); ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.09 (dd, ^3J = 8.1 Hz, ^4J = 1.7 Hz, 1H), 7.07 (d, J = 8.1 Hz, 1H), 7.05 (d, J = 1.4 Hz, 1H), 6.92 (s, 1H), 6.76 (s, 1H), 6.73 (s, 1H), 6.66 (s, 1H), 4.79 (m, 2H), 4.53 (m, J = 6.3 Hz, 3 × 1H), 3.92 (s, 3H), 3.43 (s, 3H), 3.34 (s, 3H), 3.09 (t, J = 6.7 Hz, 2H), 1.38 (d, J = 6.1 Hz, 6H), 1.37 (d, J = 6.1 Hz, 6H), 1.34 (d, J = 6.3 Hz, 3H), 1.33 (d, J = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 155.68, 150.11, 148.74, 148.10, 147.35, 147.08, 146.58, 146.03, 136.01, 128.79, 128.30, 128.05, 126.38, 123.74, 120.29, 117.99, 114.85, 113.70, 112.73, 110.48, 109.23, 104.99, 103.57, 77.21, 71.45, 71.37, 56.35, 55.52, 55.14, 42.48, 28.66, 22.06, 21.93, 21.84; MS: *m/z* (%): 627 (100), 585 (26), 543 (54), 501 (22). HRMS: calcd for $C_{37}H_{41}NO_8$ 627.2832, found 627.2818; elemental analysis (%): calcd for $C_{37}H_{41}NO_8$+C_3H_6O (685.81): C 70.10, H 6.91, N 2.04; found: C 70.07, H 7.08, N 2.26.

Lamellarin L (1): Compound **14** (47 mg, 0.075 mmol) was dissolved in CH_2Cl_2 (20 mL), cooled to 0 °C, and treated with $AlCl_3$ (75 mg, 0.56 mmol). After 10 min, the ice bath was removed and the mixture stirred at ambient temperature for 4 h. Quenching with water (20 mL) was followed by evaporation of the organic solvent under reduced pressure, extraction with ethyl acetate (5 × 10 mL), and removal of the aqueous layer. Aqueous ammonia (1 mL) was added to the combined organic extracts, and after shaking the mixture thoroughly, it was adjusted to pH 4 with HCl (2 M). The organic layer was separated, washed with brine (10 mL), and dried (Na_2SO_4). Evaporation of the solvent yielded lamellarin L (**1**) (36 mg, 96%) as a light-gray, amorphous solid. Subsequent trituration with Et_2O and CH_2Cl_2 afforded a white powder. M.p. 301 °C (Lit.[11]: 285–287 °C); UV/Vis (MeOH): λ_{max} (ε) = 204 (56361), 276 (30059), 314 (26923), 332 nm (25649 M^{-1}cm^{-1}); IR (KBr): $\tilde{\nu}$ = 3430 (s), 2938 (m), 2839 (m), 1689 (s), 1587 (m), 1552 (m), 1515 (m), 1485 (s), 1432 (s), 1407 (s), 1341 (m), 1326 (m), 1275 (s), 1248 (s), 1208 (s), 1159 (s), 1040 (m), 967 (w), 950 (w), 872 (w), 820 (w), 769 (w), 745 (w), 639 (w), 554 (w), 480 cm^{-1} (w); ^{1}H NMR ([D$_6$]DMSO, 600 MHz): δ = 9.62 (s, 1H), 9.39 (s, 1H), 9.25 (s, 1H), 7.15 (d, J = 8 Hz, 1H), 6.89 (dd, ^3J = 8 Hz, ^4J = 2 Hz, 1H), 6.88 (br., 1H), 6.78 (s, 1H), 6.73 (s, 1H), 6.67 (s, 1H), 6.66 (s, 1H), 4.63 (m, 1H), 4.54 (m, 1H), 3.82 (s, 3H), 3.37 (s, 3H), 3.27 (s, 3H), 3.00 (t, J = 8.6 Hz, 2H); ^{13}C NMR ([D$_6$]DMSO, 150 MHz): δ = 154.43, 147.82, 147.68, 147.25, 146.99, 146.14, 145.82, 144.62, 135.94, 127.58, 127.55, 127.37, 121.81, 118.17, 118.04, 115.48, 114.09, 113.66, 112.51, 109.46, 108.86, 105.24, 103.77, 56.23, 55.23, 54.86, 42.12, 27.65; MS: *m/z* (%): 501 (100); HRMS: calcd for $C_{28}H_{23}NO_8$ 501.1424, found 501.1434.[11]

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