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[12] Crystal structure data of **1**: $C_{28}H_{32}N_4O_{10}ClFe_2$, $M = 731.7$, monoclinic, space group $P2_1/n$, $a = 8.224(2)$, $b = 15.710(3)$, $c = 11.738(3)$ Å, $\beta = 101.72(2)°$, $V = 1484.9(6)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.637$ g cm^{-3}, crystal dimensions $0.48 \times 0.21 \times 0.15$ mm, $\lambda(Mo_{K\alpha}) = 0.71073$ Å, $\mu = 11.32$ cm^{-1}, $F(000) = 754$. Of 3598 reflections measured, 3440 were unique ($R_{int} = 0.0284$); $2.6° < \theta < 27.6°$, $h = \pm 10$, $k = 0$–20, $l = 0$–15. Lorentzian polarization and semi-empirical absorption correction (ψ scans) were made. The structure was determined by direct methods (SHELXS-86) and refined by full-matrix least-squares on F^2 (SHELXL-93). The ClO_4 anion was disordered over two sites and refined with 0.5 occupancy, and H-atoms were fixed geometrically. Refinement converged to $R(F)[I > 2\sigma(I)] = 0.0370$ and wR (F^2 on all data) = 0.1012, GOF = 1.037, ΔF map peaks = + 0.418/ − 0.357 e Å^{-3}. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-179-131. Copies of the data can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: Int. code + (1228) 336-033; e-mail: deposit@chemcrys.cam.ac.uk).

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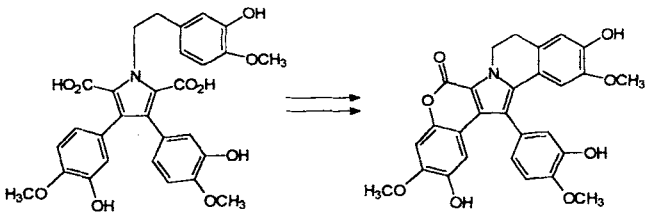
Biomimetic Synthesis of Lamellarin G Trimethyl Ether**

Alexander Heim, Andreas Terpin, and Wolfgang Steglich*

Lamellarin G (**2**) belongs to a group of marine natural products that contain a 5-oxa-6b-aza-dibenzo[*a*,*i*]fluoren-6-one skeleton. Up to now, 16 members of this class of alkaloids are known from ascidians and prosobranch molluscs.[1] Some of

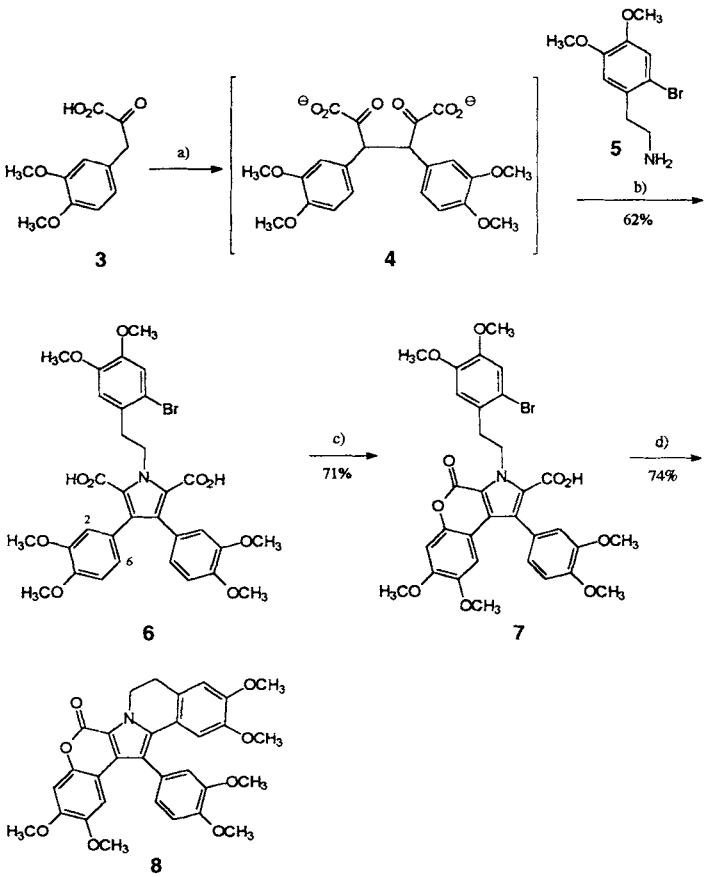


1 **2**

these compounds inhibit cell division [1a] or show cytotoxic and immunomodulatory activity.[1c] However, hitherto, no synthesis of this type of compound has been published.

Biogenetically, compounds like lamellarin G (**2**) can be derived from 3,4-diaryl-1-(2-arylethyl)-2,5-pyrrole dicarboxylic acids (e. g. **1**) by two consecutive oxidative cyclizations. Since compounds of type **1** can be easily obtained from 3-arylpyruvic acids,[2, 3] we tried to use a suitable pyrrole dicarboxylic acid for the synthesis of lamellarin G trimethyl ether (**8**). The key step in our one-pot synthesis is the oxidative coupling of two molecules of 3-(3,4-dimethoxyphenyl)pyruvic acid (**3**) to give the 1,4-diketone **4**, which was not isolated but allowed to react directly with the 2-phenylethylamine **5** to form the pyrrole dicarboxylic acid **6** in 62% yield (Scheme 1).

Treatment of **6** in refluxing ethyl acetate with one equivalent of lead(IV) acetate afforded lactone **7** in 71% yield.[4] Interestingly, only one regioisomer was obtained, which showed two singlets for the coumarin protons at $\delta = 6.38$ and 6.61 in the ^{1}H NMR spectrum in accord with the proposed structure. In addi-



Scheme 1. Synthesis of lamellarin G trimethyl ether (**8**): a) 1. −70 °C, 2 equiv *n*BuLi; 2. 0.5 equiv I_2, −70 °C → RT. b) Molecular sieves (4 Å) 12 h, RT. c) EtOAc, 1 equiv $Pb(OAc)_4$, reflux. d) CH_3CN, PPh_3, NEt_3, $Pd(OAc)_2$.

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tion, one of the methoxy resonances was shifted upfield to $\delta = 3.28$ as a result of shielding of the methoxy group by the neighboring phenyl ring.[1b] This group occupies a nearly orthogonal position, which would also explain the absence of dilactone formation after closure of the first lactone ring.

In the final synthetic step an intramolecular Pd-catalyzed Heck reaction was applied for the formation of the isoquinoline ring. This reaction afforded lamellarin G trimethyl ether (**8**) in 74% yield. To our knowledge, this is the first example of a Heck reaction in which after oxidative addition, the Pd^{II} intermediate fragments by elimination of CO_2. This method delivers the cyclization product **8** in higher yields than the conventional Heck reaction with the free pyrrole obtained by decarboxylation of **7**.

This short sequence (three steps) affords lamellarin G trimethyl ether (**8**) in 33% overall yield. Application of our method to the synthesis of other lamellarins, especially to those with unsymmetrically substituted aryl groups, is in progress. Since lamellarins of type **2** are easily dehydrogenated to the corresponding dihydroisoquinoline derivatives[1c] by action of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), compounds of the latter type can also be obtained by our procedure.

Experimental Section

6: *n*BuLi (3.56 mL of a 2.5 M solution in hexane, 2.0 equiv) was added dropwise to a stirred solution 3-(3,4-dimethoxyphenyl)pyruvic acid (**3**) (1.0 g, 4.46 mmol) in dry THF (80 mL) at −78 °C. After the mixture had been stirred for 20 min, a solution of iodine (0.56 g, 2.23 mmol, 0.5 equiv) in THF (20 mL) was added dropwise. The reaction mixture was allowed to warm up to room temperature, stirred for another hour, and then 2-(2-bromo-4,5-dimethoxyphenyl)ethylammonium bromide [6] (**5**) (1.0 g, 2.93 mmol) was added and the resulting solution was stirred for 12 h over molecular sieves (4 Å). The cloudy solution was quenched with 2 M NaOH. The layers were separated, the aqueous phase was washed with ethyl acetate (3 × 30 mL), acidified with concentrated HCl to pH 4, and extracted with ethyl acetate (3 × 30 cm^3). The combined organic layers were dried (Na_2SO_4), filtered, and the organic solvent was removed in vacuo to give 1.9 g of crude material, which was recrystallized from methanol to yield **6** as a yellowish powder (1.39 g, 62%). M.p. 201 °C; UV/Vis (CH_3OH): λ_{max} (qualitative, nm) = 208, 288; ^1H NMR (300.13 MHz, [D$_6$]DMSO): δ = 10.77 (s, br., 2H), 7.06 (s, 1H), 6.74 (d, ^3J = 7.9 Hz, 2H), 6.61 (s, 1H), 6.51 (m, 4H), 4.89 (t, ^3J = 6.5 Hz, 2H), 3.73 (s, 3H), 3.69 (s, 3H), 3.67 (s, 6H), 3.51 (s, 6H), 3.06 (t, ^3J = 6.7 Hz, 2H); ^{13}C NMR (75.47 MHz, [D$_6$]DMSO): δ = 162.66 (2 COOH), 148.56 (C-OCH_3), 148.37 (C-OCH_3), 147.50 (2 C-OCH_3), 147.44 (2 C-OCH_3), 129.48 (2 quart. C), 129.26 (quart. C), 127.18 (2 quart. C), 124.77 (2 quart. C), 122.80 (2 CH), 115.71 (quart. C), 114.84 (2 CH), 113.82 (CH), 113.75 (CH), 110.88 (2 CH), 56.08 (OCH_3), 55.52 (OCH_3), 55.47 (2 OCH_3), 55.34 (2 OCH_3), 45.88 (N-CH_2), 37.57 (CH_2); IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3412 (m, br.), 2998 (w), 2937 (m, br.), 1714 (s), 1671 (m), 1350 (m), 1510 (m, br.), 1465 (m), 1440 (m), 1426 (m), 1385 (w), 1347 (m), 1256 (s), 1231 (m), 1218 (w), 1192 (m), 1165 (w), 1028 (m); MS (EI, 70 eV) *m/z* (%) = 671 (0.63) [M^+(^{81}Br)], 669 (0.59) [M^+(^{79}Br)], 627 (2) [M^+(^{81}Br) − CO_2], 625 (2) [M^+(^{79}Br) − CO_2], 583 (10) [M^+(^{81}Br) − 2 CO_2], 581 (10) [M^+(^{79}Br) − 2 CO_2], 503 (29) [583 − Br], 502 (100) [581 − Br]; elemental analysis calcd for $C_{32}H_{32}NO_{10}Br$ (670.51): C 57.32, H 4.81, N 2.08, Br 11.91; found C 57.16, H 4.88, N 2.09, Br 11.88.

7: **6** (130 mg, 0.19 mmol) was heated to reflux with lead(IV) acetate (84.2 mg, 0.19 mmol) in ethyl acetate (40 mL) for 1 h, and the solution turned to light yellow. The reaction was monitored by TLC. In the case of incomplete conversion, further $Pb(OAc)_4$ was added and the reaction time was prolonged until the reaction had reached completion. The reaction mixture was allowed to cool to room temperature, filtered, washed with 20% citric acid, and dried (Na_2SO_4). The solvent was removed and the crude product was recrystallized from methanol to yield **7** (90 mg, 71%) as a yellow powder. M.p. 297 °C; UV/Vis (CH_3OH): λ_{max} (qualitative, nm) = 206, 288, 326; ^1H NMR (600.13 MHz, [D$_6$]DMSO): δ = 12.42 (s, br, 1H), 7.06 (d, ^3J = 8.1 Hz, 1H), 7.03 (s, 2H), 6.85 (s, 1H), 6.83 (d, ^3J = 8.1 Hz, 1H), 6.61 (s, 1H), 6.38 (s, 1H), 5.08 (t, ^3J = 6.4 Hz, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.71 (s, 3H), 3.71 (s, 3H), 3.57 (s, 3H), 3.28 (s, 3H), 3.11 (d, 2H); ^{13}C NMR (150.92 [D$_6$]DMSO): δ = 174.66 (COOH), 161.64 (-COO-), 154.35 (*C*-OCO), 149.18 (*C*-OCH_3), 148.75 (*C*-OCH_3), 148.60 (*C*-OCH_3), 148.52 (*C*-OCH_3), 148.26 (*C*-OCH_3), 145.68 (*C*-OCH_3), 145.41 (quart. C), 131.12 (quart C), 128.86 (quart. C), 126.54 (quart. C), 123.45 (CH), 122.58 (CH), 116.78 (quart. C), 115.66 (quart. C), 114.14 (quart. C), 114.04 (CH), 114.00 (CH), 111.96 (CH), 109.07 (quart. C), 104.49 (CH), 100.95 (CH), 56.09 (OCH_3), 56.05 (OCH_3), 55.86 (OCH_3), 55.74 (OCH_3), 55.46 (OCH_3), 55.00 (OCH_3), 46.14 (N-CH_2), 37.09 (CH_2); IR (KBr): $\tilde{\nu}$ = 3434 cm^{-1} (m, br.), 2940 (w, br.), 1719 (s), 1665 (w), 1539 (m), 1510 (s), 1491 (m), 1464 (m), 1445 (m), 1406 (m), 1384 (w), 1258 (s), 1242 (m), 1221 (s), 1191 (m), 1158 (m), 1038 (m), 1025 (m); MS: (EI, 70 eV) *m/z* (%): 669 (37) [M^+(^{81}Br)], 668 (13) [M^+(^{79}Br) + 1], 667 (38) [M^+(^{79}Br)], 625 (18) [M^+(^{81}Br) − CO_2], 624 (5) [M^+(^{79}Br) + 1 − CO_2], 623 (15) [M^+(^{79}Br) − CO_2], 589 (20) [M^+(^{79}Br) + 1 − Br], 588 (13) [M^+(^{79}Br) + 1 − Br], 545 (22) [589 − CO_2], 544 (60) [588 − CO_2], 543 (59) [M$^+$(^{79}Br) − Br, − CO_2], 518 (33), 517 (100) [545 − CO], 394 (18) [545 − $C_9H_{11}O_2$]; high-resolution MS: calcd for $C_{32}H_{30}NO_{10}Br$: 667.1053; found: 667.1028.

8: **7** (30 mg, 0.044 mmol), palladium(II) acetate (9.8 mg, 0.044 mmol), triphenylphosphane (11.5 mg, 0.044 mmol), and triethylamine (1.0 mL) were dissolved in acetonitrile (10.0 mL) and heated to 150 °C in a pressure tube. After 5 h the solution was diluted with EtOAc (50 mL), washed with 20% citric acid, dried (Na_2SO_4), and purified by column chromatography (SiO_2, chloroform) to yield **8** as a white powder (17.7 mg, 74%). M.p. 235 °C; UV/Vis ($CHCl_3$) λ_{max} (qualitative, nm) = 244, 280, 316 (sh); ^1H NMR (399.52 MHz, $CDCl_3$): δ = 7.12 (dd, ^4J = 1.9, ^3J = 8.1 Hz, 1H), 7.08 (d, ^3J = 8.1 Hz, 1H), 7.05 (d, ^3J = 1.9 Hz, 1H), 6.91 (s, 1H), 6.76 (s, 1H), 6.72 (s, 1H), 6.67 (s, 1H), 4.78 (m, 2H), 3.96 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 3.46 (s, 3H), 3.37 (s, 3H), 3.13 (t, ^3J = 6.7 Hz, 2H); ^{13}C NMR (100.58 MHz, $CDCl_3$): δ = 155.54 (-COO-), 149.79 (*C*-OCO), 149.01 (*C*-OCH_3), 148.88 (*C*-OCH_3), 148.83 (*C*-OCH_3), 147.51 (*C*-OCH_3), 146.11 (*C*-OCH_3), 145.52 (*C*-OCH_3), 135.92 (quart. C), 128.17 (quart. C), 128.02 (quart. C), 126.62 (quart. C), 123.62 (CH), 120.06 (quart. C), 114.76 (quart. C), 114.05 (CH), 113.77 (quart. C), 111.93 (CH), 111.02 (CH), 110.31 (quart. C), 108.71 (CH), 104.54 (CH), 100.55 (CH), 56.24 (OCH_3), 56.14 (OCH_3), 56.05 (OCH_3), 55.92 (OCH_3), 55.50 (OCH_3), 55.17 (OCH_3), 42.43 (N-CH_2), 28.71 (CH_2); IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3440 (w, br.), 2980 (w, br.), 1707 (s), 1616 (w), 1610 (w), 1543 (m), 1514 (m), 1487 (m), 1465 (m), 1415 (s), 1339 (w), 1321 (w), 1272 (s), 1241 (s), 1215 (s), 1166 (s), 1152 (m), 1042 (m, br.), 1013 (m); MS: (EI, 70 eV) *m/z* (%) = 544 (30) [M^+ + 1], 543 (100) [M^+]; high-resolution MS calcd for $C_{31}H_{29}NO_8$: 543.1893; found: 543.1897.

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Synthesis and Coordination Chemistry of Fluorine-Containing Cages**

Herbert Plenio,* Ralph Diodone, and Dirk Badura

Following a structural data bank survey in the early 1980s Glusker, Murray-Rust et al.[1a] proposed that in the solid state, covalently bonded fluorine can function as a donor to hard acceptors such as alkali and alkaline earth metal ions.[1] We recently demonstrated that this proposal is correct, since an interaction occurs not just in the solid state, but also in solution and that the contacts between the metal ion and fluorine result

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