Synthesis of Polycitrin A and 3,4-Bis(4-hydroxyphenyl)pyrrole Derivatives Related to Polycitone A

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Dedicated to Professor Siegfried Hünig on the occasion of his 85th birthday

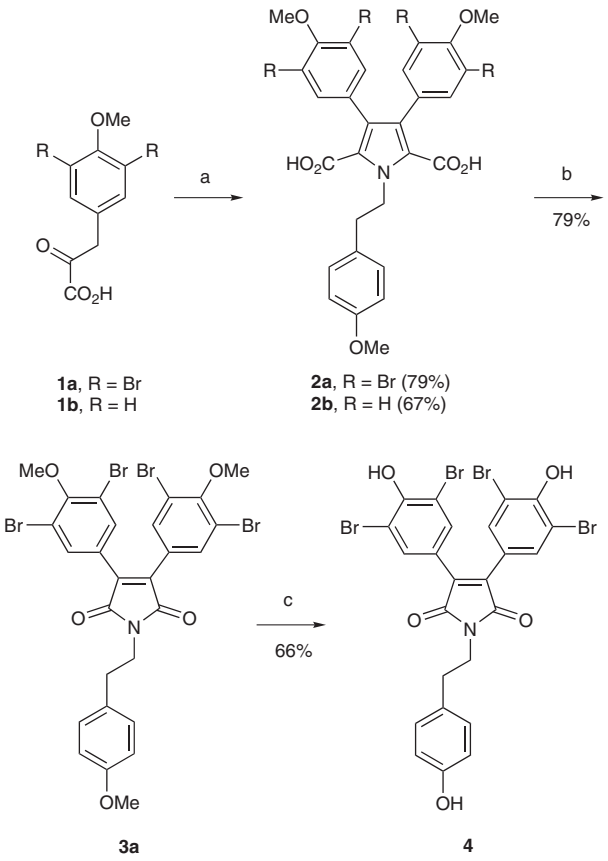
Abstract: The oxidative condensation of 3-arylpyruvic acids with arylethylamines to give 3,4-diarylpyrrole-2,5-dicarboxylic acids was used for an efficient synthesis of polycitrin A (**4**). Investigation of the bromine-mediated degradation of acid **2b** to maleimide **3b** suggested that 2,5-dibromopyrrole (**5**) and 5,5-dimethoxy-3-pyrroline-2-one (**6**) are intermediates in this process. The debromo analogue of polycitone A (**10**) was prepared in two steps from pyrrole dicarboxylic acid diester **7**.

Key words: biomimetic synthesis, bromination, marine alkaloids, pyrroles, polycitrins, polycitones

Polycitrins and polycitones constitute a group of highly brominated marine alkaloids that have been isolated by Kashman et al.[1,2] from ascidians of the genus *Polycitor*. Polycitone A is a potent general inhibitor of retroviral transcriptase and cellular DNA polymerases,[3] and its pentamethyl ether inhibits the growth of SV40 transformed fibroblast cells.[1]

In our previous synthesis, polycitrin A (**4**) was obtained from 3-(4-methoxyphenyl)pyruvic acid in six steps and 26% overall yield.[4] Key steps were the oxidative degradation of a pyrrole-2,5-dicarboxylic acid with sodium hypochlorite and the conversion of the resulting maleimide into the corresponding anhydride (prepolycitrin A), followed by reaction of the latter with tyramine. A maleic anhydride intermediate was also used by Becalli[5] in his convergent synthesis of polycitrin B.

In this publication we describe a considerably shorter route to polycitrin A (**4**) (Scheme 1). It starts from 3-(3,4-dibromo-4-methoxyphenyl)pyruvic acid (**1a**), which can be prepared from 3,4-dibromo-4-methoxybenzaldehyde and *N*-acetylglycine under standard Erlenmeyer conditions.[6] Oxidative dimerization of the sodium enolate of arylpyruvate **1a** with 0.5 equivalent iodine and subsequent one-pot pyrrole formation[4] with 2-(4-methoxyphenyl)ethylamine afforded pyrrole dicarboxylic acid **2a** in 79% yield. Treatment of the latter with bromine in refluxing aqueous MeOH yielded the desired maleimide **3a**. After removal of the *O*-methyl groups with BBr_3, polycitrin A (**4**) was obtained from keto acid **1a** in three steps and in 43% overall yield, thus representing a considerable improvement over our earlier synthesis.



Scheme 1 *Reagents and conditions*: (a) NaH (or *n*-BuLi, 2 equiv), THF, then I_2 (0.5 equiv), 4-$MeOC_6H_4CH_2CH_2NH_2$, 4 Å MS; (b) Br_2, MeOH-H_2O, reflux; (c) BBr_3.

A closer inspection of the bromine-mediated oxidative degradation of pyrrole-2,5-dicarboxylic acids to maleimides revealed the sequence of reactions depicted in Scheme 2. Thus, if a solution of dicarboxylic acid **2b** in refluxing MeOH is slowly treated with bromine, the first species detectable by TLC is the 2,5-dibromopyrrole **5**. It could be isolated in 72% yield if three equivalents of bromine were employed. Compounds of type **5** are unknown and offer interesting synthetic possibilities as reactants in Pd-catalyzed cross-coupling reactions.[7] The isolation of a second intermediate **6** required the addition of sodium methoxide to the reaction mixture in order to avoid acid-catalyzed hydrolysis by liberated HBr. The pyrrolinone **6**

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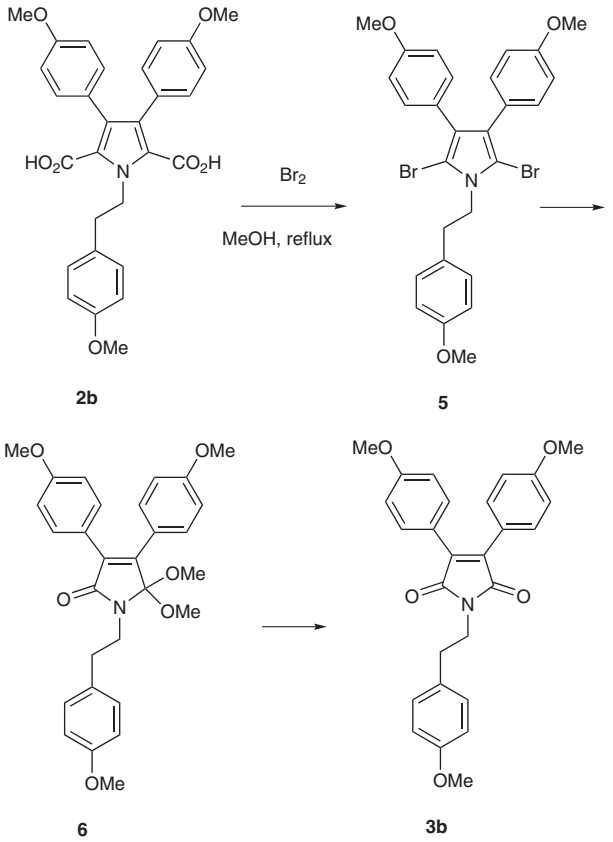
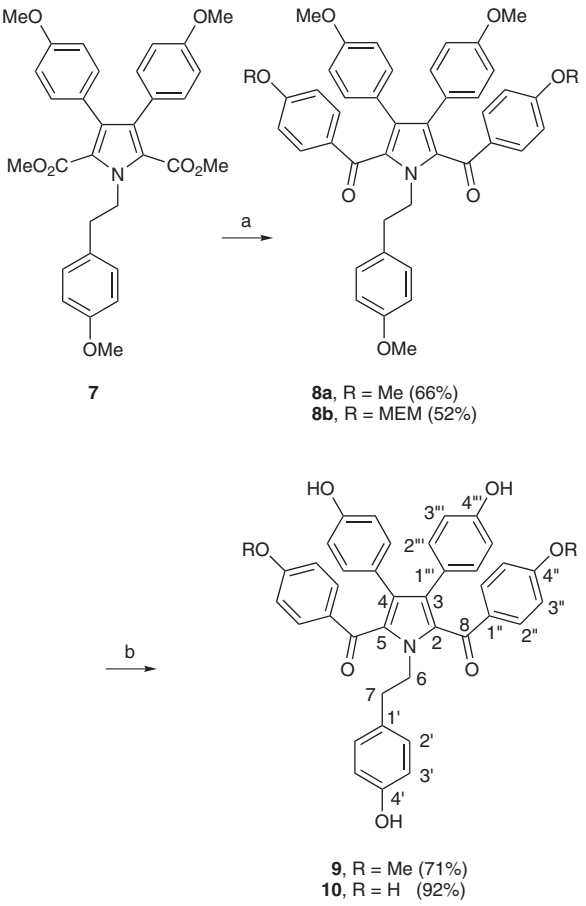
could thus be obtained in 40% yield. 5,5-Dimethoxy-3-pyrrolin-2-ones have been prepared before by electrochemical methoxylation of *N*-alkylpyrroles[8] or rearrangement of chlorinated 3-pyrrolin-2-ones.[9] Treatment of acid **2b** with excess bromine afforded maleimide **3b** in quantitative yield.



Scheme 2 Bromination of pyrrole dicarboxylic acid **2b**.

Pyrrole dicarboxylic acid **2b** could also be used for the synthesis of polydebromopolycitone A (**10**) (Scheme 3).[10] Thus reaction of **2b** with methyl iodide and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) yielded the corresponding dimethyl ester **7** which, upon treatment with a large excess of 4-methoxyphenylmagnesium bromide, afforded diketone **8a** in 66% yield. The use of lesser amounts of the Grignard reagent led to incomplete reaction. Treatment of the permethyl ether **8a** with an excess of BBr_3 yielded dimethyl ether **9** still containing the two *O*-methyl groups at the 4-methoxybenzoyl residues. To avoid this problem, we prepared the 2-methoxyethoxymethyl (MEM) analogue **8b** in the same manner as described for the methyl derivative **8a**. In this case, all of the *O*-protecting groups were smoothly removed with BBr_3 and the previously unreported polydebromo analogue of polycitone A (**10**) was obtained in 92% yield. Based on diacid **2b**, the total yield of **10** was 45%. Attempts to brominate compound **10** so as to generate polycitone A only led to complex mixtures of bromo derivatives.



Scheme 3 Synthesis of polydebromopolycitone A (**10**). *Reagents and conditions*: (a) 1. 4-$MeOC_6H_4MgBr$ (20 equiv), THF for **8a**; 2. 4-$MEMOC_6H_4MgBr$ (20 equiv), THF for **8b**; (b) BBr_3, CH_2Cl_2.

In conclusion, the biomimetic condensation of 3-arylpyruvic acids with primary amines to give 3,4-diarylpyrrole-2,5-dicarboxylic acids not only offers easy access to pyrrole alkaloids of the polycitrin and polycitone series, but also to 3,4-disubstituted 2,5-dibromopyrroles and 5,5-dimethoxy-3-pyrrol-2-ones.

Melting points (uncorrected): Büchi SMP 535 apparatus. IR spectra: PerkinElmer FT-IR Spectrum 1000. Abbreviations: s, strong; m, medium; w, weak; br, broad. Mass spectra (EI, 70 eV): Finnigan MAT 90 and Finnigan MAT 95Q. High-resolution mass spectra (EI, 70 eV): Finnigan MAT 95Q. NMR spectra: Bruker ARX 300 and Bruker AMX 600. Spectra were recorded in $CDCl_3$, DMSO-d_6 or acetone-d_6 using the residual solvent peak as an internal standard ($CDCl_3$, $\delta_H = 7.26$ and $\delta_C = 77.10$; DMSO-d_6, $\delta_H = 2.49$ and $\delta_C = 39.5$; acetone-d_6, $\delta_H = 2.04$ and $\delta_C = 29.80$). In the case of compound **9**, the assignment of the NMR signals was established by 2D NMR experiments (COSY, HMQC, HMBC). Elemental analyses were carried out by the Microanalytical Laboratory of the Department of Chemistry, University of Munich. Flash chromatography (FC): Merck Kieselgel 60 (0.040–0.063 mm). TLC: Aluminum-backed silica gel 60 F_{254} (Merck). Solvents for flash chromatography (FC) were distilled before use. THF was distilled under argon from Na/benzophenone. CH_2Cl_2 was distilled under argon from Sicapent (Merck). Anhyd DMF was purchased from Fluka.

3-(3,5-Dibromo-4-methoxyphenyl)pyruvic Acid (1a)

A mixture of 3,5-dibromo-4-methoxybenzaldehyde (18.0 g, 61 mmol), *N*-acetylglycine (8.60 g, 73 mmol), and NaOAc (6.54 g, 80 mmol) in Ac_2O (150 mL) was heated for 7 h at 90 °C. The ensuing mixture was cooled to 0 °C and quenched with H_2O. The crude azlactone was collected by filtration, washed with ice-water (3 ×), and poured into refluxing 5% aq NaOH. The resulting dark-brown solution was cooled to 0 °C and adjusted to pH 2 with concd HCl. The resulting precipitate was recrystallized from MeOH to yield α-acetamino-3,5-dibromo-4-methoxycinnamic acid (5.08 g, 21%) as a colorless solid.

α-Acetamino-3,5-dibromo-4-methoxycinnamic Acid

Mp 242 °C.

Anal. Calcd for $C_{12}H_{11}Br_2NO_4$: C, 36.67; H, 2.82; N, 3.56. Found: C, 36.65; H, 2.48; N, 3.53.

The above cinnamic acid was dissolved in 40% aq NaOH (30 mL) and the resulting solution heated under reflux. TLC was used to monitor the reaction. Once the reaction was complete, the mixture was cooled to 0 °C and adjusted to pH 3 with concd HCl. Extraction of the solution with EtOAc (3 × 100 mL), concentration of the combined extracts under vacuum and purification by FC (CH_2Cl_2–acetone–HCO_2H, 50:5:1) yielded **1a** (1.04 g, 78%) as a colorless solid, mp 163–164 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.78 (s, 3 H), 6.34 (s, 1 H), 8.04 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 60.7 (CH_3), 106.3 (CH), 117.5, 133.1 (CH), 134.7, 143.5, 152.0, 165.9.

HRMS: *m*/*z* calcd for $C_{10}H_8{}^{79}Br_2O_4$: 349.8789; found: 349.8773.

3,4-Bis(3,5-dibromo-4-methoxyphenyl)-1-[2-(4-methoxyphenyl)ethyl]pyrrole-2,5-dicarboxylic Acid (2a)

NaH (53 mg, 2.2 mmol) was added to a solution of keto acid **1a** (352 mg) in anhyd THF (15 mL) at 0 °C. After H_2 evolution had ceased, a solution of I_2 (127 mg, 0.5 mmol) in anhyd THF (5 mL) was added dropwise, and the mixture was stirred for 1 h at r.t. 2-(4-Methoxyphenyl)ethylamine (352 mg, 1.00 mmol) and portions of 4 Å molecular sieves were then added and the stirring continued for 18 h. After removal of the molecular sieves by filtration, the filtrate was diluted with EtOAc (50 mL) and washed several times with 1 M aq $KHSO_4$, H_2O and brine. The organic layer was dried ($MgSO_4$), concentrated, and purified by FC (toluene–HCO_2Et–HCO_2H, 5:4:1) to yield **2a** (325 mg, 79%) as a colorless powder, mp 218–219 °C.

IR (KBr): 3435 (s, br), 2924 (s), 2854 (m), 1701 (m), 1638 (w), 1512 (m), 1459 (w), 1415 (m), 1376 (w), 1249 (w), 1200 (w), 1170 (w), 1068 (w), 1000 (w), 892 (w), 784 (w), 743 (w), 571 (w) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.98 (t, *J* = 7.6 Hz, 2 H), 3.72 (s, 3 H), 3.75 (s, 6 H), 4.87 (t, *J* = 7.6 Hz, 2 H), 6.86 (d, *J* = 8.6 Hz, 2 H), 7.08 (d, *J* = 8.6 Hz, 2 H), 7.31 (s, 4 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 36.9 (CH_2), 48.3 (CH_2), 55.2 (CH_3), 60.5 (CH_3), 114.1 (CH), 116.1, 124.8, 126.8, 129.9 (CH), 130.1, 133.6, 134.9 (CH), 152.1, 158.2, 161.8.

FAB-MS (*m*NBA): *m*/*z* (%) = 822 (17), 821 (31, [M($^{81}Br_4$)]$^+$), 820 (75), 819 (75), 818 (93), 817 (100, [M($^{79}Br_2{}^{81}Br_2$)]$^+$), 816 (66), 815 (58), 814 (23), 813 (16, [M($^{79}Br_4$)]$^+$), 805 (11), 804 (11), 803 (10), 802 (32), 801 (16), 800 (27), 799 (10), 798 (23), 796 (9), 776 (16), 754 (10), 744 (9), 707 (23), 705 (19).

Polycitrin A Trimethyl Ether (3a)

A solution of Br_2 (0.04 mL, 0.72 mmol) in MeOH (5 mL) was added at 0 °C to a solution of **2a** (195 mg, 0.24 mmol) in MeOH–H_2O (10 mL, 20:1). The resulting mixture was stirred for 18 h at r.t. and then treated with EtOAc (30 mL). The organic phase was washed with sat. aq $NaHCO_3$, H_2O, and brine, then dried ($MgSO_4$) and concentrated under reduced pressure. FC (hexanes–EtOAc, 2:1) afforded **3a** as a light yellow powder (144 mg, 79%); mp 61–63 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.91 (t, *J* = 7.5 Hz, 2 H), 3.80 (s, 3 H), 3.84 (t, *J* = 7.5 Hz, 2 H), 3.94 (s, 6 H), 6.85, 7.14 (d each, *J* = 8.7 Hz, 2 H), 7.62 (s, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.0 (CH_2), 40.5 (CH_2), 55.8 (CH_3), 61.2 (CH_3), 114.6 (CH), 119.1, 126.6, 130.0, 130.2 (CH), 133.9, 134.2 (CH), 156.3, 158.9, 169.7.

EI-MS: *m*/*z* (%) = 763 (1, [M($^{81}Br_4$)]$^+$), 761 (5), 759 (7, [M($^{79}Br_2{}^{81}Br_2$)]$^+$), 757 (5), 755 (1, [M($^{79}Br_4$)]$^+$), 135 (10), 134 (100), 121 (47).

HRMS: *m*/*z* calcd for $C_{27}H_{21}{}^{79}Br_2{}^{81}Br_2NO_5$: 754.8153; found: 754.8124.

Polycitrin A (4)

BBr_3 (0.06 mL, 0.66 mmol) was added to maleimide **3a** (50 mg, 0.066 mmol) in anhyd CH_2Cl_2 (10 mL) at –78 °C. The violet reaction mixture was warmed to r.t. and stirred for 18 h. Aq 2 N NaOH (1 mL) was then added dropwise, and, after a short period of stirring, the solution was acidified with 2 N HCl (5 mL). After addition of EtOAc (30 mL), the organic phase was washed with 1 M aq $KHSO_4$, H_2O, brine, and dried ($MgSO_4$). FC ($CHCl_3$–MeOH, 10:1) afforded polycitrin A (**4**) as an orange solid (33 mg, 70%); mp 180–182 °C. The spectral data for synthetic **4** agreed with those reported for the natural product.[1]

3,4-Bis(4-methoxyphenyl)-1-[2-(4-methoxyphenyl)ethyl]pyrrole-2,5-dicarboxylic Acid (1b)

A solution of 3-(4-methoxyphenyl)pyruvic acid[11] (4.86 g, 25 mmol) in anhyd THF (400 mL) was treated with a 2.5 M solution of *n*-BuLi in hexane (20 mL, 50 mmol) at –78 °C. The mixture was stirred for 20 min at –78 °C and then treated dropwise with a solution of I_2 (3.17 g, 12.5 mmol) in anhyd THF (50 mL). After completion of the addition, the cold-bath was removed and the mixture stirred for 1 h at r.t. 2-(4-Methoxyphenyl)ethylamine (11.34 g, 75 mmol) and 4 Å molecular sieves (5 g) were then added, and the stirring was continued for 18 h. The mixture was filtered, the filtrate acidified with aq 1 M $KHSO_4$, and extracted with EtOAc (3 × 200 mL). The combined extracts were washed with H_2O (300 mL) and brine (300 mL), then dried (Na_2SO_4), and concentrated under reduced pressure. Recrystallization of the residue from MeOH yielded **1b** (4.23 g, 67%) as a colorless powder; mp 223–224 °C; R_f 0.54 (benzene–HCO_2Et–HCO_2H, 5:4:1).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.97 (t, *J* = 7.2 Hz, 2 H), 3.66 (s, 6 H), 3.71 (s, 3 H), 4.74 (t, *J* = 7.2 Hz, 2 H), 6.70 (d, *J* = 8.8 Hz, 4 H), 6.86 (d, *J* = 8.8 Hz, 2 H), 6.90 (d, *J* = 8.8 Hz, 4 H), 7.10 (d, *J* = 8.8 Hz, 2 H), 12.61 (br, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 37.1 (CH_2), 48.2 (CH_2), 55.0 (CH_3), 55.2 (CH_3), 112.8 (CH), 114.1 (CH), 124.5, 127.0, 129.5, 129.7 (CH), 130.4, 131.6 (CH), 157.8, 158.1, 162.7.

EI-MS: *m*/*z* (%) = 501 (5, [M]$^+$), 457 (10, [M – CO_2]$^+$), 413 (94, [M – 2 × CO_2]$^+$), 292 (100, [M – 2 × CO_2 – $CH_2C_6H_4OCH_3$]$^+$), 279 (11, [M – 2 × CO_2 – $C_2H_3C_6H_4OCH_3$]$^+$), 121 (14, [$CH_2C_6H_4OCH_3$]$^+$).

HRMS: *m*/*z* calcd for $C_{29}H_{27}NO_7$: 501.1788; found: 501.1796.

Anal. Calcd for $C_{29}H_{27}NO_7$: C, 69.45; H, 5.43; N, 2.79. Found: C, 69.45; H, 5.54; N, 2.70.

2,5-Dibromo-3,4-bis(4-methoxyphenyl)-1-[2-(4-methoxyphenyl)ethyl]pyrrole (5)

A solution of Br_2 (0.2 mL, 0.64 g, 2 equiv) in anhyd MeOH (20 mL) was added dropwise to a refluxing solution of dicarboxylic acid **2b** in anhyd MeOH (100 mL). The mixture was cooled to r.t. and partitioned between H_2O (350 mL) and EtOAc (200 mL). The aq phase was extracted with EtOAc (2 × 100 mL), and the combined organic

phases were dried ($MgSO_4$) and concentrated under reduced pressure. FC (Et_2O–hexanes, 1:1) yielded **5** (0.41 g, 36%) as a colorless solid together with varying amounts of pyrrolinone **6** and maleimide **3b**; mp 158–160 °C. Compound **5** decomposes at r.t. within a few days and must be kept in a refrigerator.

IR (KBr): 3436 (m, br), 2953 (w), 2832 (w), 1612 (m), 1575 (w), 1536 (s), 1512 (s), 1500 (m), 1466 (w), 1453 (w), 1377 (w), 1350 (m), 1287 (w), 1248 (s), 1176 (m), 1108 (w), 1034 (s), 836 (m), 794 (w), 740 (w), 608 (w), 526 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.00 (t, *J* = 8.1 Hz, 2 H), 3.78 (s, 6 H), 3.82 (s, 3 H), 4.28 (t, *J* = 8.1 Hz, 2 H), 6.78 (d, *J* = 8.7 Hz, 4 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 7.07 (d, *J* = 8.6 Hz, 2 H), 7.18 (d, *J* = 8.7 Hz, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.2 (CH_2), 50.0 (CH_2), 55.5 (CH_3), 55.7 (CH_3), 101.8, 113.8 (CH), 114.5 (CH), 124.6, 126.8, 130.2, 130.4 (CH), 131.7 (CH), 158.6, 159.9.

EI-MS: *m*/*z* (%) = 574 (14), 573 (52, $[M(^{81}Br_2)]^+$), 572 (29), 571 (100, $[M(^{79}Br^{81}Br)]^+$), 570 (15), 569 (50, $[M(^{79}Br_2)]^+$), 493 (11), 492 (38), 491 (18), 490 (37), 489 (6), 412 (21), 411 (68), 371 (15), 369 (15), 135 (39).

HRMS: *m*/*z* calcd for $C_{27}H_{25}{}^{79}Br_2NO_5$: 569.0201; found: 569.0174; *m*/*z* calcd for $C_{27}H_{25}{}^{79}Br^{81}BrNO_5$: 571.0181; found: 571.0153; *m*/*z* calcd for $C_{27}H_{25}{}^{81}Br_2NO_5$: 573.0160; found: 573.0157.

5,5-Dimethoxy-3,4-bis(4-methoxyphenyl)-1-[2-(4-methoxyphenyl)ethyl]-1,5-dihydropyrrol-2-one (6)

NaOMe [2 g, 30% solution (w/w) in MeOH] was added to **2b** (1 g, 1.98 mmol) in anhyd MeOH (100 mL). The mixture was heated at reflux and a solution of Br_2 (0.31 mL, 0.96 g, 3 equiv) in anhyd MeOH (20 mL) was then added dropwise. The Br_2 was immediately decolorized, and the solution slowly developed a blue-green fluorescence. After completion of the Br_2 addition, the mixture was cooled to r.t. and partitioned between H_2O (350 mL) and EtOAc (200 mL). The aqueous layer was extracted with EtOAc (2 × 100 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. FC (Et_2O–hexanes, 1:1) afforded **6** (0.39 g, 40%) as a colorless solid exhibiting a greenish fluorescence.

IR (KBr): 3435 (s, br), 2998 (w), 2935 (w), 2837 (w), 1702 (s), 1606 (s), 1571 (w), 1514 (s), 1462 (w), 1442 (w), 1421 (m), 1399 (m), 1299 (m), 1249 (s), 1180 (m), 1125 (m), 1111 (m), 1072 (w), 1043 (m), 1031 (m), 984 (w), 838 (m), 786 (w), 601 (w), 576 (w), 536 (w), 412 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.01 (m, 2 H), 3.11 (s, 6 H), 3.50 (m, 2 H), 3.79, 3.81, 3.84 (s each, 3 H), 6.81, 6.86, 6.91, 7.24, 7.43, 7.60 (d each, *J* = 8.8 Hz, 2 H); the d at δ = 7.24 overlapped with the $CDCl_3$ signal.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.2 (CH_2), 40.5 (CH_2), 51.5 [$C(OCH_3)_2$], 55.7 (CH_3), 113.5, 114.4 (3 × CH), 123.1, 123.5, 130.3 (CH), 130.6 (CH), 131.5 (CH), 133.1, 142.4 [*C*$(OCH_3)_2$], 158.6, 160.4, 160.9, 169.6. One signal was obscured.

EI-MS: *m*/*z* (%) = 490 (32), 489 (95, $[M]^+$), 459 (15), 458 (45, $[M - OCH_3]^+$), 369 (16), 368 (72), 356 (22), 355 (100, $[M - CHCH_2C_6H_4OCH_3]^+$), 338 (24), 336 (14), 324 (24), 323 (16), 309 (15), 308 (14), 208 (48), 135 (48), 134 (16), 121 (18), 116 (20).

HRMS: *m*/*z* calcd for $C_{29}H_{31}NO_6$: 489.2160; found: 489.2156.

3,4-Bis(4-methoxyphenyl)-1-[2-(4-methoxyphenyl)ethyl]pyrrole-2,5-dione (3b)

A solution of Br_2 (0.62 mL, 1.92 g, 3 equiv) in anhyd MeOH (30 mL) was added dropwise to a refluxing solution of **2b** (2 g, 3.99 mmol) in anhyd MeOH (200 mL). The progress of the reaction could be followed by the development of the intense yellow color of the product. After completion of the Br_2 addition, the solvent was removed under reduced pressure to yield **3b** (1.73 g, ca. 100%) as yellow crystals; mp 120–124 °C.

IR (KBr): 2865 (w), 2819 (w), 1765 (w), 1697 (s), 1602 (s), 1513 (s), 1454 (w), 1442 (w), 1408 (m), 1352 (w), 1296 (m), 1252 (s), 1177 (s), 1117 (w), 1035 (m), 1023 (m), 845 (m), 835 (m), 789 (m), 532 (m) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.90 (t, *J* = 7.8 Hz, 2 H), 3.76 (s, 3 H), 3.80 (t, *J* = 7.8 Hz, 2 H), 3.81 (s, 6 H), 6.83 (d, *J* = 8.2 Hz, 2 H), 6.86 (d, *J* = 8.7 Hz, 4 H), 7.17 (d, *J* = 8.2 Hz, 2 H), 7.44 (d, *J* = 8.7 Hz, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.8 (CH_2), 40.0 (CH_2), 55.2 (CH_3), 55.3 (CH_3), 113.9 (CH), 114.0 (CH), 121.3, 129.8 (CH), 130.2, 131.4 (CH), 134.0, 158.3, 160, 171.1.

EI-MS: *m*/*z* (%) = 444 (16), 443 (61, $[M]^+$), 322 (11), 310 (16), 309 (100), 223 (11), 134 (17), 133 (14), 121 (27).

UV (MeOH): λ_{max} (ε) = 206 (22134), 228 (23819), 268 (123081), 364 (3880), 406 nm (5180).

HRMS: *m*/*z* calcd for $C_{27}H_{25}NO_5$: 443.1724; found: 443.1734.

3,4-Bis(4-methoxyphenyl)-1-[2-(4-methoxyphenyl)ethyl]pyrrole-2,5-dicarboxylic Acid Dimethyl Ester (7)

A solution of **2b** (1.50 g, 3.0 mmol) in anhyd DMF (50 mL) was treated with DBU (0.99 mL, 6.57 mmol) at 0 °C. The mixture was maintained for 10 min at 0 °C, then treated with MeI (1.89 mL, 29.9 mmol), and stirred for 18 h at r.t. After the addition of H_2O, the mixture was carefully extracted with Et_2O. For removal of the DMF, the organic phases were washed several times with 1 M aq $KHSO_4$, H_2O, 1 N aq NaOH, and brine. Evaporation of the dried ($MgSO_4$) Et_2O solution yielded **7** (1.49 g, 94%); mp 185–187 °C.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.09 (t, *J* = 7.7 Hz, 2 H), 3.58 (s, 6 H, CO_2CH_3), 3.76 (s, 6 H, OCH_3), 3.79 (s, 3 H, OCH_3), 4.84 (t, *J* = 7.7 Hz, 2 H), 6.71 (d, *J* = 8.9 Hz, 4 H), 6.85 (d. *J* = 8.6 Hz, 2 H), 6.92 (d, *J* = 8.9 Hz, 4 H), 7.19 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.5 (CH_2), 48.8 (CH_2), 51.4 (CH_3), 55.1 (CH_3), 55.3 (CH_3), 112.7 (CH), 113.9 (CH), 124.1, 126.9, 130.1, 130.6 (CH), 130.7, 131.5 (CH), 158.1, 158.4, 162.1.

EI-MS: *m*/*z* (%) = 530 (31, $[M + H]^+$), 529 (100, $[M]^+$), 408 (78), 407 (19), 395 (14), 363 (20), 121 (14).

HRMS: *m*/*z* calcd for $C_{31}H_{31}NO_7$: 529.2101; found: 529.2112.

Anal. Calcd for $C_{31}H_{31}NO_7$: C, 70.31; H, 5.90; N, 2.64. Found: C, 70.33; H, 5.86; N, 2.64.

{5-(4-Methoxybenzoyl)-3,4-bis(4-methoxyphenyl)-1-[2-(4-methoxyphenyl)ethyl]-1*H*-pyrrol-2-yl}-(4-methoxyphenyl)]methanone (8a); Typical Procedure

A solution of diester **7** (0.53 g, 1.00 mmol) in anhyd THF (30 mL) was treated, dropwise at 0 °C, with the Grignard reagent freshly prepared from Mg (0.61 g, 25 mmol) and 4-bromoanisole (2.50 mL, 20 mmol) in anhyd THF (25 mL). The mixture was warmed to r.t., stirred for 18 h at r.t. and then quenched with H_2O (3 mL). After addition of EtOAc (100 mL), the solution was washed with 1 M aq $KHSO_4$, H_2O, and brine, dried ($MgSO_4$), and concentrated. Purification of the residue by FC (Et_2O–hexanes, 1:1) yielded **8a** (0.45 g, 66%) as a beige powder; mp 72–73 °C.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.01 (t, *J* = 7.8 Hz, 2 H), 3.64 (s, 6 H), 3.69 (s, 3 H), 3.74 (s, 6 H), 4.49 (t, *J* = 7.8 Hz, 2 H), 6.48 (d, *J* = 8.8 Hz, 4 H), 6.61 (d, *J* = 9.0 Hz, 4 H), 6.70 (d, *J* = 8.6 Hz, 2 H), 6.79 (d, *J* = 8.8 Hz, 4 H), 7.10 (d, *J* = 8.6 Hz, 2 H), 7.61 (d, *J* = 9.0 Hz, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.3 (CH_2), 48.1 (CH_2), 55.4 (CH_3), 55.5 (CH_3), 55.7 (CH_3), 113.46 (CH), 113.54 (CH), 114.2

(CH), 126.5, 127.6, 130.4 (CH), 130.7, 131.2, 131.8 (CH), 132.3, 132.8 (CH), 158.3, 158.6, 163.6, 189.5.

EI-MS: *m/z* (%) = 682 (15, $[M + H]^+$), 681 (31, $[M]^+$), 560 (11), 548 (37), 547 (100, $[M + H - COC_6H_4OCH_3]^+$), 135 (59), 121 (68).

UV (MeOH): λ_{max} (ε) = 228 (41869), 284 nm (25928).

HRMS: *m/z* calcd for $C_{43}H_{39}NO_7$: 681.2727; found: 681.2692.

Anal. Calcd for $C_{43}H_{39}NO_7$: C, 75.75; H, 5.77; N, 2.05. Found: C, 75.43; H, 5.88; N, 2.02.

{5-[4-(2-Methoxyethoxymethoxy)benzoyl]-3,4-bis(4-methoxyphenyl)-1-[2-(4-methoxyphenyl)ethyl]-1*H*-pyrrol-2-yl}-[4-(2-methoxyethoxymethoxy)phenyl]methanone (8b)

From diester **7** (0.40 g, 0.76 mmol) and the Grignard reagent prepared from 4-(2-methoxyethoxymethoxy)-1-bromobenzene as described above; yield: 0.34 g (52%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.01 (t, *J* = 7.6 Hz, 2 H), 3.34 (s, 6 H), 3.48 (m, 4 H), 3.59 (s, 6 H), 3.66 (s, 3 H), 3.78 (m, 4 H), 4.52 (t, *J* = 7.6 Hz, 2 H), 5.17 (s, 4 H), 6.46 (d, *J* = 8.7 Hz, 4 H), 6.70 (d, *J* = 8.5 Hz, 2 H), 6.75 (d, *J* = 8.7 Hz, 4 H), 6.77 (d, *J* = 8.9 Hz, 4 H), 7.10 (d, *J* = 8.5 Hz, 2 H), 7.58 (d, *J* = 8.9 Hz, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.8 (CH_2), 47.5 (CH_2), 54.8 (CH_3), 54.9 (CH_3), 58.8 (CH_3), 67.6 (CH_2), 71.3 (CH_2), 92.9 (CH_2), 112.9 (CH), 113.7 (CH), 115.0 (CH), 125.9, 127.4, 129.8 (CH), 130.1, 131.3, 131.6, 131.7 (CH), 132.1 (CH), 157.8, 158.1, 160.6, 189.9.

EI-MS: *m/z* (%) = 830 (26, $[M + H]^+$), 829 (48, $[M]^+$), 696 (23), 695 (51, $[M - C_9H_{10}O]^+$), 135 (31), 121 (26), 89 (52), 59 (100).

HRMS: *m/z* calcd for $C_{49}H_{51}NO_{11}$: 829.3462; found: 829.3465.

3,4-Bis(4-hydroxyphenyl)-1-[2-(4-hydroxyphenyl)ethyl]-2,5-bis(4-methoxybenzoyl)pyrrole (9)

From **8a** (100 mg, 0.15 mmol) and BBr_3 (0.21 mL, 2.20 mmol) as described for polycitrin (**3**). FC (toluene–HCO_2Et–HCO_2H, 5:4:1) afforded dimethyl ether **9** (67 mg, 71%) as a solid; mp 102–103 °C.

^{1}H NMR (600 MHz, acetone-d_6): δ = 2.92 (t, *J* = 8.0 Hz, 2 H, 7-H), 3.78 (s, 6 H, 4″-OCH_3), 4.44 (t, *J* = 8.0 Hz, 2 H, 6-H), 6.47 (d, *J* = 8.6 Hz, 4 H, 3‴/5‴-H), 6.69 (d, *J* = 8.6 Hz, 4 H, 3′/5′-H), 6.76 (d, *J* = 9.0 Hz, 4 H, 3″/5″-H), 6.77 (d, *J* = 8.8 Hz, 4 H, 2‴/6‴-H), 6.96 (d, *J* = 8.6 Hz, 2 H, 2′/6′-H), 7.65 (d, *J* = 9.0 Hz, 4 H, 2″/6″-H).

^{13}C NMR (150 MHz, acetone-d_6): δ = 38.5 (C-7), 48.3 (C-6), 55.8 (4″-OCH_3), 114.1 (C-3″/5″), 115.3 (C-3‴/5‴), 116.1 (C-3′/5′), 126.0 (C-1‴), 128.0 (C-2/5), 129.8 (C-2′/6′), 130.5 (C-1′), 131.8 (C-3/4), 132.1 (C-1″), 132.7 (C-2‴/6‴), 133.0 (C-2″/6″), 156.7 (C-4‴), 156.9 (C-4′), 164.2 (C-4″), 189.3 (C-8).

EI-MS: *m/z* (%) = 640 (18, $[M + H]^+$), 639 (42, $[M]^+$), 532 (20), 520 (39), 519 (100, $[M - C_8H_8O]^+$), 518 (12), 135 (70), 121 (79), 120 (10), 107 (11), 77 (14).

HRMS: *m/z* calcd for $C_{40}H_{33}NO_7$: 639.2257; found: 639.2239.

Anal. Calcd for $C_{43}H_{39}NO_7 \cdot 1.5\ H_2O$: C, 72.06; H, 5.44; N, 2.10. Found: C, 72.48; H, 5.30; N, 2.10.

3,4-Bis(4-hydroxyphenyl)-2,5-bis(4-hydroxybenzoyl)-1-[2-(4-hydroxyphenyl)ethyl]pyrrole (10)

From **8b** (0.22 g, 0.27 mmol) and BBr_3 (0.30 mL, 3.22 mmol) as described for polycitrin (**3**). FC (toluene–HCO_2Et–HCO_2H, 5:4:1) afforded diketone **10** (0.15 g, 92%) as a solid; mp 143–144 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.73 (t, *J* = 7.6 Hz, 2 H), 4.22 (t, *J* = 7.6 Hz, 2 H), 6.37 (d, *J* = 8.6 Hz, 4 H), 6.58 (d, *J* = 8.7 Hz, 4 H), 6.59 (d, *J* = 8.6 Hz, 2 H), 6.66 (d, *J* = 8.6 Hz, 4 H), 6.78 (d, *J* = 8.6 Hz, 2 H), 7.48 (d, *J* = 8.7 Hz, 4 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 37.3 (CH_2), 47.2 (CH_2), 114.6 (CH), 115.1 (CH), 115.5 (CH), 124.3, 126.6, 127.9, 128.7, 129.4 (CH), 131.0, 131.6 (CH), 132.5 (CH), 155.8, 156.2, 162.7, 188.2.

EI-MS: *m/z* (%) = 612 (12, $[M + H]^+$), 611 (24, $[M]^+$), 504 (15), 492 (36), 491 (100, $[M - C_8H_8O]^+$), 490 (15), 384 (11), 372 (17), 371 (65), 370 (16), 265 (10), 264 (59), 121 (70), 120 (11), 107 (44), 94 (23), 93 (10), 77 (10), 65 (11), 46 (29), 45 (26).

HRMS: *m/z* calcd for $C_{38}H_{29}NO_7$: 611.1944; found: 611.1973.

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