Total Syntheses of the Slime Mold Alkaloid Arcyriacyanin A**

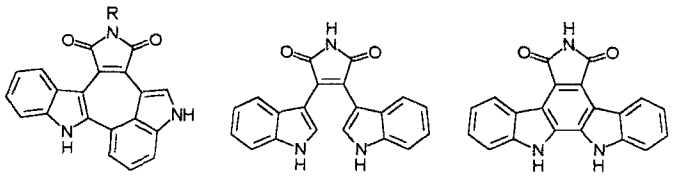
Michael Brenner, Guido Mayer, Andreas Terpin, and Wolfgang Steglich*

Abstract: Arcyriacyanin A (**1**) has been synthesized by three different routes. In the first synthesis the bisbromomagnesium salt of 2,4'-biindole (**5**) was treated with dibromomaleimide (**6**) to yield arcyriacyanin A (**1**). The second approach used an intramolecular Heck reaction for the cyclization of a 4-(triflyloxy)arcyriarubin **8** to *N*-methylarcyriacyanin A (**2**). Thirdly, compound **2** was obtained by a domino Heck reaction between 3-bromo-4-[1-(*tert*-butoxycarbonyl)indol-3-yl]-1-methylmaleimide (**9**) and 4-bromoindole (**10**). The *N*-methyl derivative **2** could be transformed into arcyriacyanin A (**1**) by standard methods.

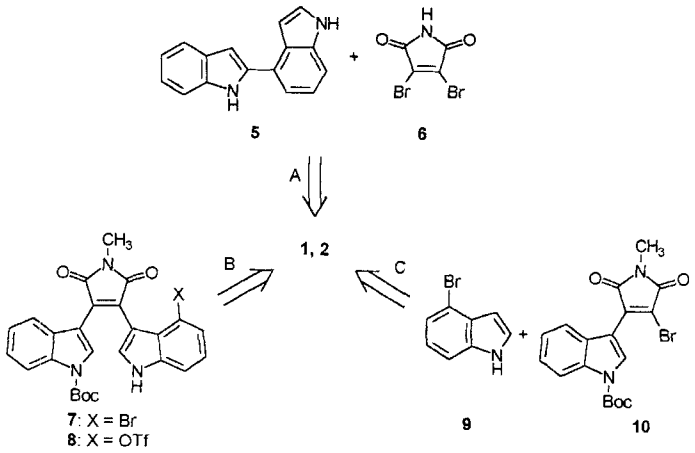
Keywords
alkaloids · Heck reactions · heterocycles · indoles · total syntheses

Introduction

Arcyriacyanin A (**1**) is a modified bisindoylmaleimide alkaloid isolated from the yellowish sporangia of the slime mold *Arcyria obvelata* (= *A. nutans*, Myxomycetes).[1] Its structure can be formally derived from arcyriarubin A (**3**) by connecting the two indole units at C(2) and C(4'). Arcyriacyanin A (**1**) is isomeric to arcyriaflavin A (**4**) for which several syntheses have been developed.[2] The unique structure of arcyriacyanin A (**1**) and its structural relationship to several protein kinase C inhibitors[2a] prompted us to study the synthesis of this compound.



Three strategies for the synthesis of arcyriacyanin A (**1**) can be envisaged (Scheme 1). The application of our general method for the synthesis of bisindolylmaleimides[3] should allow the synthesis of **1** in one step by reaction of the bisbromomagnesium salt from 2,4-biindole (**5**) with 3,4-dibromomaleimide (**6**) (Synthesis A). A second entry to the arcyriacyanin system involves the formation of the C(2)–C(4') bond from a suitably 4-substituted bisindolylmaleimide (e.g., **7** or **8**, Synthesis B). Finally, a one-pot formation of *N*-methylarcyriacyanin A (**2**) from the protected 3-bromo-4-indolylmaleimide **9** and 4-bromoindole (**10**) by a domino Heck reaction is considered (Synthesis C).



Scheme 1. Strategies for the synthesis of **1** and **2**.

Results and Discussion

Synthesis A: The 2,4'-biindole (**5**) needed for this approach was obtained by Stille coupling[4] of stannylindole (**12**)[5] with 1-tosyl-4-bromoindole[6] (**13**) followed by removal of the *N*-protecting groups from the coupling product **14** by alkaline hydrolysis (Scheme 2). The stannyl derivative **12** was itself prepared from 1-(*tert*-butoxycarbonyl)indole (**11**)[6] by metalation with lithium diisopropylamide (LDA)[7] and subsequent reaction with chlorotrimethylstannane.[8] After conversion into its bisbromomagnesium salt, biindole **5** was treated with 3,4-dibromomaleimide[9] (**6**) in refluxing toluene to yield arcyriacyanin A (**1**).

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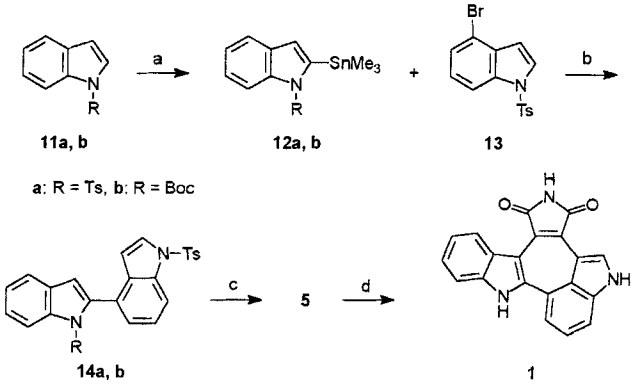


Scheme 2. a) **11a** or **11b**, LDA, THF, −78 °C, 2 h, then Me_3SnCl, −78 °C → RT, NH_4Cl, 46% (**12a**) or 76% (**12b**); b) 1-tosyl-4-bromoindole (**13**), toluene, 80 °C, $Pd(PPh_3)_4$, 20 h, 46% (**14a**) or 75% (**14b**); c) ethanol, 80 °C, 20% NaOH, 3h, 50% from **14a** or 68% from **14b**; d) THF, RT, 2 equiv EtMgBr, then toluene, 110 °C, 3,4-dibromomaleimide (**6**), 2 h, 41%.

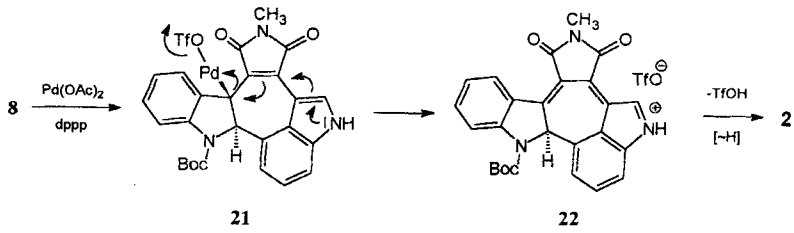
Aqueous workup and purification by gel chromatography afforded the alkaloid in 41% yield. The synthetic product was identical with natural arcyriacyanin A (**1**) in its IR, MS, ^1H and ^{13}C NMR spectra, and by direct TLC comparison.

Synthesis B: In our second approach we tried to mimic the possible biosynthesis of arcyriacyanin A (**1**) through an intramolecular Heck reaction.[10, 11] As suitable candidate for this cyclization we originally considered the 4-bromoarcyriarubin derivative **7**. Unfortunately, this compound could not be prepared in the usual way from the bromomagnesium salt of 4-bromoindole (**9**) and bromo(indolyl)maleimide **10** due to reductive loss of the aromatic bromine atom. We therefore turned to the corresponding triflate[12] **8** whose synthesis is part of Scheme 3.

The 4-(tetrahydropyranyloxy)indole (**17**) required for the coupling step was prepared in analogy to the 6-substituted compound.[3] Diazotation of 2-amino-6-nitrotoluene (**15**) produced the corresponding phenol,[13] which was converted to the THP derivative **16**.[14] Pyrrolidine-catalyzed reaction of **16** with dimethylformamide dimethyl acetal generated an enamine, which was hydrogenated without any further purification to yield the desired indole **17**.[15] Coupling of the bromomagnesium salt of **17** with the Boc-protected bromo(indolyl)maleimide[3] **10** in THF afforded the bisindolylmaleimide **18** in 57% yield. Cleavage of the THP protecting group with Amberlite® 15 in refluxing methanol[16] gave the hydroxy compound **19** in 83% yield. Conversion of **19** into its triflyl derivative **8** ensued with *N*-phenyltriflimide[17] and DMAP in 92% yield.

The Heck cyclization of **8** took place in DMF with catalytic amounts of palladium(II) acetate and 1,3-bis(diphenylphosphino)propane (dppp),[18] and a large excess of triethylamine. After 18 h at 110 °C the reaction mixture was worked up and purified by gel chromatography to yield 81% of *N*-methylarcyriacyanin A (**2**). Interestingly, the *N*-Boc protecting group was lost under these conditions. The *N*-methyl derivative **2** could readily be converted to arcyriacyanin A (**1**) by alkaline hydrolysis, acidic workup, and reaction of the resulting anhydride **20** with hexamethyldisilazane.[19]

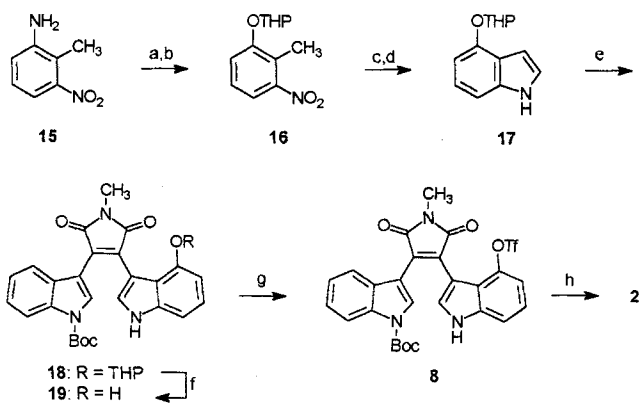
The Heck coupling proceeded with excellent yield despite the unfavorable steric conditions for reductive *syn* elimination in the primary cyclization intermediate **21** (Scheme 4). We propose



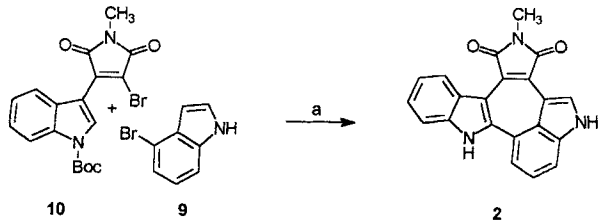
Scheme 4. Mechanism of the last step in Scheme 3.

that this reaction occurs by a base-catalyzed fragmentation as indicated by the arrows. The stable indolylmaleimide **2** is then obtained from **22** by rearrangement and cleavage of the urethane group.

Synthesis C: The key step in the third approach to arcyriacyanin A (**1**) is a domino Heck reaction between bromo(indolyl)maleimide **10** and 4-bromoindole (**9**) (Scheme 5). The reaction took place in acetonitrile under standard conditions. By means of this simple procedure *N*-methylarcyriacyanin A (**2**) was obtained in up to 33% yield after chromatographic purification. Its structure was confirmed by detailed NMR experiments [COSY, NOESY, DEPT, HETCOR, COLOCS ($^3J_{CH} = 7$ Hz)].



Scheme 3. a) KNO_2, aq. H_2SO_4, then 100 °C, 80%; b) EtOAc, dihydropyran, cat. HCl, RT, 72 h, 82%; c) 3 equiv $(MeO)_2NCH(OMe)_2$, 3 equiv pyrrolidine, 110 °C, 3 h; d) EtOAc, H_2, Pd/C (10% C), 3.5 bar, RT, 3 h, 60%; e) THF, 2 equiv **17**, 2 equiv EtMgBr, 45 °C, 30 min, then 1 equiv **10**, 65 °C, 3 h, 57%; f) MeOH, Amberlite® 15, 65 °C, 30 min, 83%; g) CH_2Cl_2, 2 equiv $PhN(SO_2CF_3)_2$, 2 equiv DMAP, 0 °C → RT, 4 h, 92%; h) 0.12% $Pd(OAc)_2$, 0.14% dppp, excess NEt_3, DMF, 110 °C, 18 h, 81%.



Scheme 5. a) $Pd(OAc)_2$, PPh_3, NEt_3, CH_3CN, 80 °C, 3 h, 10 to 30%.

Experimental Procedure

General techniques: Melting points (uncorrected) were determined on a Büchi SMP20 melting point apparatus or a Reichert Thermovar hot-stage microscope. All nonaqueous reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF) was distilled from potassium/benzophenone, and dichloromethane from Sicapent®. Other solvents were purchased at absolute quality and stored over molecular sieves. All reactions were monitored by thin-layer chromatography on silica gel $60\,F_{254}$ plates, E. Merck, and the spots were detected with UV light. Silica gel 60, E. Merck, particle size 0.040–0.063 mm, was used for flash chromatography and Sephadex® LH-20, Pharmacia, for gel chromatography.

1-*tert*-Butoxycarbonyl-2-(trimethylstannyl)indole (12): *n*BuLi (8.2 mL of a 1.6 M solution in hexanes, 13.1 mmol) was added dropwise to diisopropylamine (2 mL, 14.1 mmol) in THF (20 mL) at −70 °C, and the mixture was stirred for 1 h. A solution of 1-(*tert*-butoxycarbonyl)indole (**11b**) (2.72 g, 12.5 mmol) in THF (10 mL) was then added slowly, whereby the temperature was kept below −60 °C. The solution was stirred for 2 h at −70 °C, then warmed to −45 °C, and finally cooled back to −70 °C. A solution of chlorotrimethylstannane (2.50 g, 12.5 mmol) in THF (10 mL) was added, and the mixture was allowed to warm to room temperature overnight. Hydrolysis with ice/water (20 mL) and 20% aqueous citric acid (2 mL) yielded a solution, which was concentrated in vacuo and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was purified by chromatography on silica gel (elution with petroleum ether, $R_f = 0.25$; followed by petroleum ether/CH_2Cl_2 = 5:1, $R_f = 0.67$) to yield **12** as colorless crystals (3.28 g, 69%), M.p. 63 °C; ^{1}H NMR (90 MHz, CCl_4): δ = 7.74–7.90 (m, 1H), 7.32–7.47 (m, 1H), 6.94–7.22 (m, 2H), 6.63 (s, 1H), 1.65 (s, 9H), 0.27 (s, 9H); IR (KBr): $\tilde{\nu}$ = 2980 (CH), 1710 cm^{-1} (C=O); UV/VIS (MeOH): λ_{max} (lgε) = 296 (3.58), 270 (4.21), 232 (4.37), 204 nm (4.18); $C_{16}H_{23}NO_2Sn$ (380.05): calcd C 50.57, H 6.10, N 3.69; found C 50.51, H 6.20, N 3.77.

1-*tert*-Butoxycarbonyl-1′-(4-toluenesulfonyl)-2,4′-biindole (14): A solution of **12** (1.37 g, 3.6 mmol), 4-bromo-1-(4-toluenesulfonyl)indole [6] (**13**, 1.05 g, 3.0 mmol) and tetrakis(triphenylphosphane)palladium(0) (0.42 g, 0.36 mmol) in toluene was heated at 80 °C for 20 h. Solvent evaporation followed by chromatography on silica gel (elution with petroleum ether/CH_2Cl_2 1:1, $R_f = 0.67$) gave the biindole as a colorless solid (1.10 g, 75%), M.p. 71 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.25 (dm, J = 8.0 Hz, 1H), 8.01 (dt, J = 8.0, 1.0 Hz, 1H), 7.79 (dm, J = 8.4 Hz, 2H), 7.56 (d, J = 3.6 Hz, 1H), 7.55 (ddd, J = 7.4, 1.6, 0.7 Hz, 1H), 7.19–7.45 (m, 6H), 6.56 (d, J = 0.8 Hz, 1H), 6.54 (dd, J = 3.7, 0.7 Hz, 1H), 2.34 (s, 3H), 0.85 (s, 9H); IR (KBr): $\tilde{\nu}$ = 3140 (ar. CH), 2975 (aliph. CH), 1730 (C=O), 1595 (ar. CC), 1360 (SO_2N), 1175 cm^{-1} (SO_2N); UV/VIS (MeOH): λ_{max} (lgε) = 288 (4.26), 224 nm (4.53); $C_{28}H_{26}N_2O_4S$ (486.59): calcd C 69.12, H 5.39, N 5.76; found C 69.26, H 5.45, N 5.65.

2,4′-Biindole (5): To a solution of **14** (1.10 g, 2.30 mmol) in ethanol (50 mL) was added 20% aqueous NaOH (20 mL). The mixture was heated to 80 °C, cooled to 20 °C, and neutralized with 20% aqueous citric acid. Following extraction with ethyl acetate (3 × 20 mL), the combined organic layers were washed with water, dried ($MgSO_4$), and concentrated in vacuo. Chromatography of the residue on silica gel (elution with petroleum ether/CH_2Cl_2 1:1, R_f: 0.34) gave 0.35 g (68%) of **5** as colorless crystals, M.p. 197 °C; ^{1}H NMR (400 MHz, [D$_6$]acetone/$CDCl_3$): δ = 10.50 (brs, 1H), 10.40 (brs, 1H), 7.92 (m, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.39–7.49 (m, 3H), 7.19 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 7.10 (dd, J = 8.0, 8.0 Hz, 1H), 7.03 (dd, J = 8.0 8.0 Hz, 1H), 6.94–6.99 (m, 2H); IR (KBr): $\tilde{\nu}$ = 3430 (indole NH), 3380 (indole NH), 3040 (ar. CH), 1600 cm^{-1} (ar. CC); UV/VIS (MeOH): λ_{max} (lgε) = 328 (4.38), 228 nm (4.43); HRMS ($C_{16}H_{12}N_2$): calcd 232.1000; found 232.0992.

2-Methyl-3-nitro-1-(α-tetrahydropyranyloxy)benzene (16): To a solution of 2-methyl-3-nitrophenol [13] (5.3 g, 34.6 mmol) in DMF (60 mL) was added dihydropyran (12.7 mL, 138 mmol) and 37% hydrochloric acid (0.1 mL). After 72 h the reaction mixture was poured into 2% aqueous NaOH (25 mL). The organic layer was washed with 2% aqueous NaOH (2 × 15 mL) and water (2 × 25 mL), dried ($MgSO_4$), and evaporated. Chromatography of the residue on silica gel (elution with petroleum ether/acetone 10:1, R_f = 0.62) yielded 6.7 g (82%) of **16** as a colorless oil. ^{1}H NMR (90 MHz, $CDCl_3$): δ = 7.50–7.03 (m, 3H), 5.41 (s, 1H), 4.00–3.43 (m, 2H), 2.36 (s, 3H), 2.01–1.43 (m, 6H); IR ($CHCl_3$): $\tilde{\nu}$ = 3030 (ar. CH), 2950 (aliph. CH), 1605 (ar. CC), 1525 (ar. NO_2), 1350 (ar. NO_2), 1255 cm^{-1} (ar. C-O-C); $C_{12}H_{15}NO_4$ (237.26): calcd C 60.75, H 6.37, N 5.90; found C 61.06, H 6.44, N 5.65.

4-(α-Tetrahydropyranyloxy)indole (17): To a stirred solution of **16** (7.5 g, 31.6 mmol) in DMF (60 mL) was added dimethylformamide dimethyl acetal (12.6 mL, 94.8 mmol) and pyrrolidine (2.6 mL, 31.6 mmol). The mixture was stirred at 110 °C for 22 h, cooled to 0 °C, poured into water and extracted with ether (4 × 50 mL). The combined organic layers were washed with water, dried ($MgSO_4$), and evaporated. The residue was taken up in ethyl acetate (100 mL), supplemented with 10% Pd on activated carbon (750 mg), and hydrogenated for 3 h at 3.5 bar. The resulting solution was filtered over Celite® and evaporated. Chromatography of the residue on silica gel (elution with petroleum ether/acetone 10:1, R_f = 0.22; then CH_2Cl_2, R_f = 0.56) gave **17** as a white solid (4.1 g, 60%), M.p. 128–131 °C; ^{1}H NMR (90 MHz, $CDCl_3$): δ = 8.10 (brs, 1H, NH), 7.17–6.53 (m, 5H), 5.58 (m, 1H), 4.13–3.80 (m, 1H), 3.70–3.40 (m, 1H), 2.20–1.40 (m, 6H); IR (KBr): $\tilde{\nu}$ = 3280 (NH), 2950 (aliphat. CH), 1620 (ar. CC), 1510, 1345, 1245 (ar. C–OC), 1205, 1025 cm^{-1}; $C_{13}H_{15}NO_2$ (217.27): calcd C 71.87, H 6.96, N 6.45; found C 71.57, H 7.19, N 6.46.

2-(1-*tert*-Butoxycarbonyl-1*H*-indol-3-yl)-3-[4-(α-tetrahydropyranyloxy)-1*H*-indol-3-yl]-1-methyl-2,5-dioxo-2,5-dihydropyrrole (18): To a Grignard solution formed from Mg turnings (240 mg, 10 mmol) and ethyl bromide (0.9 mL, 12 mmol) in THF (20 mL) under argon was added **17** (2.20 g, 10.0 mmol) dissolved in THF (100 mL). After 30 min of stirring at 45 °C, a solution of **10** (2.25 g, 5 mmol) in THF (50 mL) was added dropwise. The reaction mixture was refluxed for 3 h, cooled to 0 °C and quenched with ice/water (30 mL) and 20% aqueous citric acid (5 mL). After removal of the THF under reduced pressure, the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with water (2 × 25 mL), dried ($MgSO_4$), and evaporated. Chromatography on silica gel (elution with CH_2Cl_2, R_f = 0.22) gave **18** as an orange oil (1.55 g, 57%), which crystallized from methanol; M.p. 185 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.50 (brs, 1H, NH), 8.16 (s, 1H), 8.12 (d, J = 8.5 Hz, 1H), 7.12 (ddd, J = 8.5, 8.4, 1.9 Hz, 1H), 7.07 (dd, J = 8.0, 8.0 Hz, 1H), 6.88–6.58 (m, 5H), 5.54 and 5.47 (each brs, together 1H), 4.05–3.39 (m, 2H, OCH_2), 3.17 (s, 3H, N–CH_3), 1.85–1.55 (m, 6H), 1.70 (s, 9H, Boc); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.90, 171.39, 150.01, 149.18, 137.99, 135.50, 133.41, 129.46, 129.22, 127.15, 125.13, 124.49, 124.03, 122.69, 121.86, 117.40, 114.97, 110.25, 105.21, 104.87, 104.29, 95.81, 84.48, 61.58, 30.10, 28.12 (3C), 25.10, 24.15 (N–CH_3), 18.38; IR (KBr): $\tilde{\nu}$ = 3360 (NH), 3120 (ar. CH), 2960 (aliph. CH), 1735 (C=O), 1690 (C=O), 1610 (ar. CC), 1540, 1450, 1385, 1370 (C(CH_3)$_3$), 1350 (C–O), 1300 (C–O), 1255 (C–O), 1235 (C–O), 1150 (C–O), 1110 (C–O), 1060, 1035 cm^{-1}; UV/VIS (MeOH): λ_{max} (lgε) = 448 (3.67), 378 (3.66), 292 (3.70), 222 nm (4.87); MS (FAB, m-NBA): m/z (%): 542 (13) [M+1$^+$], 541(19) [M^+], 459 (19), 458 (66), 402 (43), 401 (51), 358 (45), 357 (61); HRMS ($C_{31}H_{31}N_3O_6$): calcd 541.2213; found 541.2212.

2-(1-*tert*-Butoxycarbonyl-1*H*-indol-3-yl)-3-[4-hydroxy-1*H*-indol-3-yl]-1-methyl-2,5-dihydro-2,5-dioxopyrrole (19): To a solution of **18** (540 mg, 1 mmol) in methanol (40 mL) was added Amberlite® 15 (150 mg). After refluxing for 30 min the dark red solution was cooled and filtered. The filtrate was concentrated in vacuo and the residue purified by chromatography on silica gel (elution with petroleum ether/EtOAc 3:1, R_f = 0.27) to yield **19** as a dark red microcrystalline solid (0.48 g, 83%), M.p. 110 °C; ^{1}H NMR (300 MHz, CDCl_3): δ = 8.60 (brs, 1H, NH), 8.18 (s, 1H), 8.15 (s, 1H), 8.14 (d, J = 8.8 Hz, 1H), 7.17 (ddd, J = 7.9, 7.7, 1.2 Hz, 1H), 7.16 (dd, J = 7.9, 7.9 Hz, 1H), 6.95 (s, 1H, OH), 6.95 (d, J = 7.0 Hz, 1H), 6.82 (dd, J = 7.9, 7.9 Hz, 1H), 6.75 (ddd, J = 8.5, 7.6, 1.2 Hz, 1H), 6.49 (d, J = 8.0 Hz, 1H), 3.16 (s, 3H, NCH_3), 1.68 (s, 9H, Boc); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.29, 170.25, 150.59, 149.03, 138.47, 135.80, 131.14, 129.82, 129.53, 126.85, 125.40, 124.68, 124.51, 122.81, 122.21, 115.88, 115.19, 110.00, 109.86, 104.81, 103.96, 84.66, 28.10 (3C), 24.46 (N–CH_3); IR (KBr): $\tilde{\nu}$ = 3391 (NH and OH), 2970 (aliphat. CH), 2945, 1739 (C=O), 1690 (C=O), 1453, 1371, 1152, 739 cm^{-1}; UV/VIS (MeOH): λ_{max} (lgε) = 475 (3.60), 381 (3.33), 340 (2.83), 291 (3.93), 219 nm (4.65); MS (FAB, m-NBA): m/z (%): 458 (15) [M+1$^+$], 457 (19) [M^+], 402 (8), 401 (10), 358 (10), 357 (12); HRMS ($C_{26}H_{23}N_3O_5$): calcd 457.1634; found 457.1611.

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2-(1-*tert*-Butoxycarbonyl-1*H*-indol-3-yl)-3-[4-(α-trifluoromethanesulfonyloxy)-1*H*-indol-3-yl]-1-methyl-2,5-dihydro-2,5-dioxopyrrole (8): To a solution of **19** (46 mg, 0.1 mmol) in dichloromethane (15 mL) at 0 °C were added *N*-phenyltriflimide (71 mg, 0.2 mmol) and 4-(dimethylamino)pyridine (24 mg, 0.2 mmol). After the mixture had been stirred for 4 h at 20 °C the reaction was completed. The solvent was evaporated, and the residue purified by chromatography on silica gel (elution with petroleum ether/EtOAc 2:1, $R_f = 0.29$). Yield 54 mg (92%) of **8** as an orange solid, M.p. 130 °C; ^{1}H NMR (300 MHz, [D$_6$]acetone): $\delta = 11.26$ (brs, 1H, NH), 8.18 (s, 1H), 8.13 (d, $J = 8.4$ Hz, 1H), 7.69 (d, $J = 2.9$ Hz, 1H), 7.61 (d, $J = 7.7$ Hz, 1H), 7.21 (dd, $J = 8.1$, 8.1 Hz, 1H), 7.17 (ddd, $J = 7.8$, 7.6, 1.1 Hz, 1H), 6.94 (d, $J = 7.9$ Hz, 1H), 6.85 (d, $J = 7.4$ Hz, 1H), 6.76 (ddd, $J = 7.6$, 7.6, 1.1 Hz, 1H), 3.16 (s, 3H, N–CH$_3$), 1.67 (s, 9H, Boc); ^{13}C NMR (75 MHz, [D$_6$]acetone): $\delta = 171.80$, 171.50, 149.76, 142.99, 139.92, 136.07, 131.54, 130.97, 130.44, 130.15, 128.19, 125.23, 123.43, 123.08, 122.69, 120.30, 119.39 (q, $J = 320.2$ Hz, CF$_3$), 115,62, 113.58 (2C), 111.36, 104.43, 85.22, 28.08 (3C, Boc), 24.36 (N–CH$_3$); IR (KBr): $\tilde{\nu} = 3391$ (NH), 2985 (aliphat. CH), 1743 (C=O), 1706 (C=O), 1545, 1452, 1420, 1388, 1372, 1354, 1214 (CF$_3$), 1152 cm^{-1} (SO$_2$OR); UV/VIS (MeOH): λ_{max} (lg ε) = 522 (2.18), 425 (3.78), 386 (3.62), 332 (3.46), 284 (3.93), 221 nm (4.60); MS (70 eV, EI, 185 °C): *m/z* (%): 589 (3) [M^+], 533 (3), 489 (5), 356 (13), 340 (3), 339 (4), 299 (4), 271 (2); HRMS ($C_{27}H_{22}F_3N_3O_7S$): calcd 589.1131; found 589.1118; $C_{27}H_{22}F_3N_3O_7S + 0.75\ CH_3OH$: calcd C 54.56, H 4.12, N 6.88; found C 54.95, H 4.58, N 6.97.

***N*-Methylarcyriacyanin A (2**, 2-methyl-5,9-dihydropyrrolo[3′,4′;6,7]cyclohepta[2,1-*b*;5,4,3-*c*′,*d*′]diindole-1,3-dione):

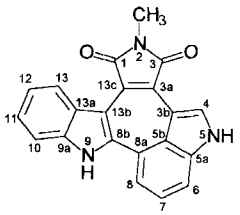
Synthesis B: To a stirred solution of **8** (100 mg, 0.17 mmol) in DMF (30 mL) was added palladium(II) acetate (12 mg, 0.05 mmol, 29 mol%), 1,3-bis-(diphenylphosphino)propane (14 mg, 0.03 mmol, 20 mol%), and triethylamine (2 mL, 14.4 mmol). After being heated to 110 °C and maintained at this temperature for 18 h, the dark blue solution was cooled and poured into water. The aqueous solution was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with water (2 × 25 mL) and brine (25 mL). After drying (MgSO$_4$) the solvent was evaporated and the residue purified as described below. Yield 46 mg (81%) of **2**, dark blue green solid.

Synthesis C: A solution of bromo(indolyl)maleimide **10** (405 mg, 1 mmol), 4-bromoindole (**9**) (196 mg, 1 mmol), triphenylphosphane (120 mg, 0.46 mmol), palladium(II) acetate (100 mg, 0.41 mmol), and triethylamine (2 mL, 14.4 mmol) in acetonitrile (10 mL) was put in a 15 mL pressure tube and heated at 150 °C for 2.5 h. The resulting dark brown solution was filtered through Celite® and concentrated in vacuo. The product **2** could be separated from by-products by gel chromatography (eluent: methanol/chloroform 1:1 or methanol/acetone 4:1). The blue zone with the highest retention time yielded 107 mg (33%) of **2** as a dark blue-green solid. The yields of several experiments varied between 8 and 33%.

2: M.p. 299–302.5 °C; $R_f = 0.64$ (petroleum ether/EtOAc = 1:1); ^{1}H NMR (600 MHz, [D$_6$]DMSO): $\delta = 11.72$ (brs, 1H, NH), 11.55 (brs, 1H, NH), 8.31 (d, $J = 9.0$ Hz, 1H), 7.80 (s, 1H), 7.31 (d, $J = 7.9$ Hz, 1H), 7.10 (d, $J = 6.8$ Hz, 1H), 7.07 (dd, $J = 7.9$, 6.8 Hz, 1H), 7.02 (d, $J = 7.9$ Hz, 1H), 6.97 (dd, $J = 7.9$, 7.9 Hz, 1H), 6.93 (dd, $J = 6.8$, 7.9 Hz, 1H), 2.92 (s, 3H, N–CH$_3$); ^{13}C NMR (150 MHz, [D$_6$]DMSO): see Table 1. The assignment of the ^{1}H and ^{13}C resonances is given in Table 1. IR (KBr): $\tilde{\nu} = 3422$ (NH), 1695 (C=O), 1684 (C=O), 1442, 1387, 738 cm^{-1}; UV/VIS (MeOH): λ_{max} (lg ε) = 630 (3.01), 366 (4.13), 290 (4.00) (sh), 246 (4.54), 226 nm (4.42); MS (FAB, m-NBA): *m/z* (%): 340 (15) [$M+1^+$], 339 (34) [M^+]; HRMS ($C_{21}H_{13}N_3O_2$): calcd 339.1008; found 339.0996; $C_{21}H_{13}N_3O_2 \cdot 0.5\,H_2O$: calcd C 72.41, H 4.05, N 12.06; found C 72.46, H 3.89, N 12.37.

5,9-Dihydro-furo[3′,4′;6,7]cyclohepta[2,1-*b*;5,4,3-*c*′,*d*′]diindole-1,3-dione (20): A suspension of **2** (20 mg, 0.06 mmol) in 10% aqueous KOH (30 mL) was refluxed for 20 min until a light brown, clear solution resulted. On filtration of this solution into a mixture of ethyl acetate (20 mL) and 1.1 M aqueous KHSO$_4$ (80 mL) the organic layer turned green immediately. Concentration of the dried (MgSO$_4$) organic phase gave a crude product, which yielded 15 mg (78%) of **20** as a blue-green solid on gel chromatography (eluent: methanol/chloroform = 1:1). ^{1}H NMR (600 MHz, [D$_6$]acetone/[D$_6$]-DMSO = 9:1): $\delta = 11.78$ (brs, 1H), 11.54 (brs, 1H), 8.35 (d, $J = 7.9$ Hz, 1H), 7.80 (s, 1H), 7.38 (d, $J = 8.4$ Hz, 1H), 7.23 (d, $J = 7.4$ Hz, 1H), 7.11–7.09 (m, 2H), 7.03 (dd, $J = 7.9$, 6.8 Hz, 1H), 6.97 (dd, $J = 7.9$, 7.9 Hz, 1H);

Table 1. Assignment of the ^{13}C and ^{1}H NMR signals for **2**.



	δC		δC		δH
C(1)/C(3)	170.99	C(8b)	138.92	H(4)	7.80
C(3)/C(1)	170.04	C(9a)	137.85	*N*-H(5)	11.55
C(3a)	129.63	C(10)	111.49	H(6)	7.02
C(3b)	110.55	C(11)	123.05	H(7)	6.93
C(4)	122.76	C(12)	120.92	H(8)	7.10
C(5a)	137.27	C(13)	124.36	*N*H(9)	11.72
C(5b)	130.44	C(13a)	126.60	H(10)	7.31
C(6)	112.36	C(13b)	107.05	H(11)	7.07
C(7)	124.18	C(13c)	126.60	H(12)	6.97
C(8)	114.03	*N*-CH$_3$	23.80	H(13)	8.31
C(8a)	127.37			*N*-CH$_3$	2.92

^{13}C NMR (150 MHz, [D$_6$]acetone/[D$_6$]DMSO = 9:1): $\delta = 165.46$, 165.44, 141.01, 138.92, 138.66, 131.46, 131.05, 129.40, 127.84, 127.36, 125.11, 124.77, 124.51, 124.05, 122.28, 115.59, 113.59, 112.46, 110.83, 106.76; IR (KBr): $\tilde{\nu} = 3345$ (brs), 3181 (m), 3053 (w), 1806 (m), 1743 (s), 1732 (s), 1608 (w), 1587 (w), 1507 (w), 1473 (m), 1444 (s), 1420 (w), 1385 (m), 1263 (m), 1231 (w), 1169 (m), 1024 (m), 999 (m), 736 (s), 618 (w) cm^{-1}; UV/VIS (MeOH): λ_{max} (lg ε) = 618 nm (2.986), 352 (3.944), 246 (4.167); HRMS ($C_{20}H_{10}N_3O_2$): calcd 326.0692; found 326.0678.

Arcyriacyanin A (1):

Synthesis A: To a Grignard solution formed from Mg turnings (49 mg, 2 mmol) and bromoethane (0.15 mL, 2 mmol) in THF (1 mL) was added dropwise a solution of 2,4′-biindole (**5**) (232 mg, 1 mmol) in toluene (30 mL). After the mixture had been stirred for 30 min at room temperature, 2,3-dibromomaleimide (**6**, 255 mg, 1 mmol) in toluene (20 mL) was added. The solution was refluxed for 2 h, hydrolyzed with ice/water and 20% aqueous citric acid (2 mL), and extracted with ethyl acetate (3 × 20 mL). The combined extracts were dried (MgSO$_4$), concentrated, and purified by repeated gel chromatography (eluent: acetone) to give 0.13 g (41%) of **1** as a blue-green solid.

Synthesis B,C: A mixture of hexamethyldisilazane (0.64 mL, 0.3 mmol) and dry methanol (10 μL) was added to the light brown solution of anhydride **20** (15 mg, 0.05 mmol) in DMF (5 mL). After having been stirred for 12 h, the reaction mixture was hydrolyzed with 20% aqueous citric acid (10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried (MgSO$_4$) and evaporated. The crude product was purified by gel chromatography to yield 10 mg (67%) of **1**.

1: M.p. > 300 °C; $R_f = 0.48$ (CH$_2$Cl$_2$/acetone 20:1); ^{1}H NMR (400 MHz, [D$_6$]acetone): $\delta = 10.95$ (brs, 1H), 10.72 (brs, 1H), 9.58 (brs, 1H), 8.46 (d, $J = 8.5$ Hz, 1H), 7.94 (d, $J = 3$ Hz, 1H), 7.31 (d, $J = 8$ Hz, 1H), 7.11–7.05 (m, 3H), 7.00 (dd, $J = 7.0$, 7.0 Hz, 1H), 6.93 (dd, $J = 8.0$, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, [D$_6$]acetone): $\delta = 172.46$, 171.54, 139.75, 138.75, 138.31, 131.70, 131.54, 128.42, 128.01, 125.64, 125.03, 123.93, 123.75, 123.59, 121.74, 114.37, 112.86, 111.97, 111.83, 108.49; IR (KBr): $\tilde{\nu} = 3400$ (NH), 3040 (ar. CH), 1750 (C=O), 1685 (C=O), 1600 cm^{-1} (ar. CC). UV/VIS (MeOH): λ_{max} (lg ε) = 622 (3.13), 360 (4.20), 244 (4.59), 224 nm (4.53); MS (70 eV, EI, 180 °C): *m/z* (%): 325 (100), 254 (14), 253 (9), 163 (7), 127 (14), 43 (25); HRMS ($C_{20}H_{11}N_3O_2$): calcd 325.0851; found 325.0847.

The synthetic compounds proved to be identical to the natural product by direct TLC comparison and based on the IR, NMR, and MS spectra.

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