



Practical Synthesis of Indolopyrrolocarbazoles

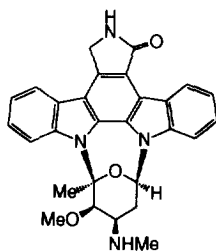
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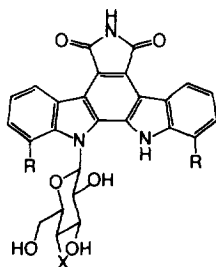
Abstract: A practical method for the synthesis of an indolo[2,3-a]pyrrolo[3,4-c]carbazole ring system is described. The method involves two key processes: a coupling reaction between indole and substituted methylmaleimide portions using lithium hexamethyldisilazide (LiHMDS) as a base, and the oxidative cyclization of bisindolylmaleimide with palladium (II) chloride. We applied this method to the synthesis of arcyriflavin B (5), C (6) and D (7). Copyright © 1996 Elsevier Science Ltd

Introduction

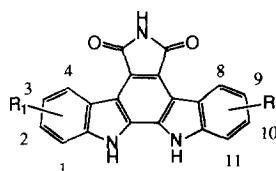
Recently, many compounds containing an indolopyrrolocarbazole ring system have been reported^{1,2} to inhibit protein kinase C³ or topoisomerases⁴. Representative examples of such compounds are staurosporine (1)^a, rebeccamycin (2)^{2b} and arcyriflavins (4-7)^{2c} (Fig. 1).



staurosporine (1)



rebeccamycin (2) R=Cl, X=OMe
ED-110 (3) R=OH, X=OH



arcyriflavin A (4) R₁=R₂=H
arcyriflavin B (5) R₁=2-OH, R₂=H
arcyriflavin C (6) R₁=2-OH, R₂=10-OH
arcyriflavin D (7) R₁=2-OH, R₂=9-OH
BE-13793C (8) R₁=1-OH, R₂=11-OH

Fig. 1

During a search for new antitumor agents targeting topoisomerases, the topoisomerase I inhibitor, BE-13793 C (8)^{2d} was isolated from the culture broth of a *Streptovercillium* species in our laboratory. BE-13793 C, which has two hydroxyl groups at the C-1 and C-11 positions, showed potent antitumor activity in mice inoculated with

ascitic tumor cells. Through studies on the modification of BE-13793 C, we found that ED-110 (**3**)^{2c}, a 13-N- β -D-glucopyranosyl derivative of BE-13793 C, showed greater antineoplastic activity in leukemia and solid tumors in mice. These results suggested to us that it would be worthwhile to further investigate extensive analogues of indolopyrrolocarbazole to find superior antitumor agents. However, no practical methods for the synthesis of indolopyrrolocarbazole derivatives had been developed. A number of synthetic approaches to the construction of the indolo[2,3-a]pyrrolo[3,4-c]carbazole ring system have been reported^{5,6,7}. These methods are summarized in Fig. 2, with the utilization of double Fisher indolization (A)⁵, the Diels-Alder reaction (B)⁶ or the oxidative cyclization of the bisindolylmaleimide (C)⁷ as a key step.

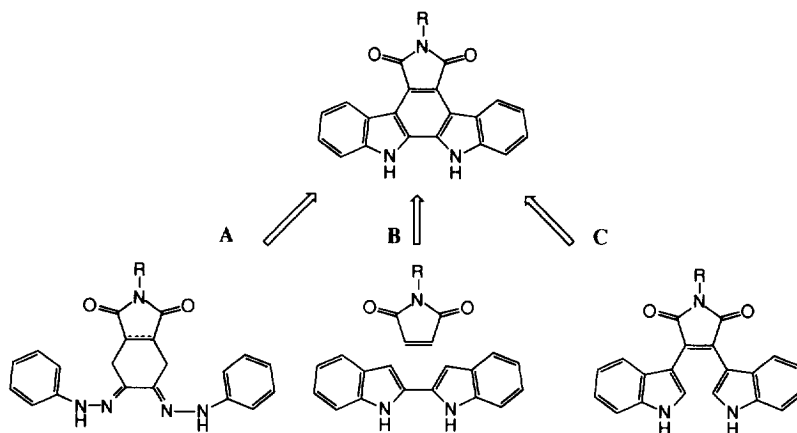
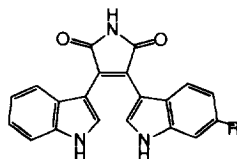


Fig. 2

Route A is likely to be suitable for the synthesis of a symmetric indolopyrrolocarbazole, but the synthesis of the asymmetric substituted bisphenylhydrazone reportedly resulted in a low yield^{5a}. In route B, the Diels-Alder reaction between 2, 2'-bisindole and maleimide moiety was reported to result in a low yield⁶. Route C may be better than route A or B to synthesize both symmetric and asymmetric indolocarbazoles: W. Steglich *et al.* reported^{7c} the synthesis of the bisindolylmaleimides arcyriarubin A (**9**) and B (**10**)^{2c} (Fig. 3) by the reaction of indolylmagnesiumbromide with 2,3-dibromo-N-methylmaleimide **15**, and several groups have reported the cyclization of a bisindolyl compound⁷.



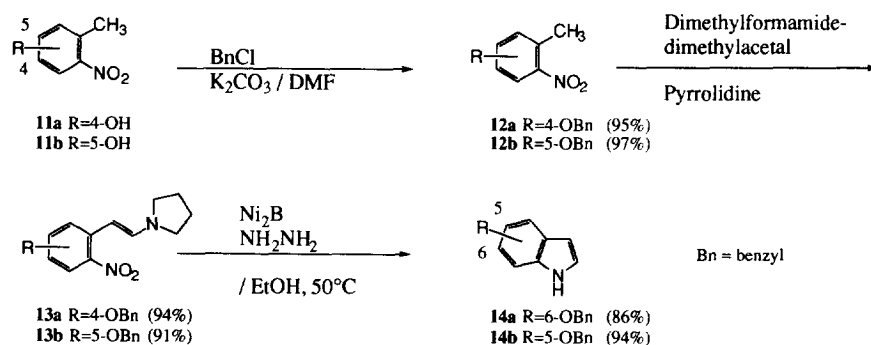
arcyriarubin A (**9**) R = H
arcyriarubin B (**10**) R = OH

Fig. 3

However, a more than twofold excess of the indole compound was required to complete this indole Grignard reaction. We report a practical method of indolopyrrolocarbazole synthesis involving bisindolylmaleimides, in which only one equivalent of the indole compound is used, and describe the synthesis of arcyriflavin B, C and D by this method.

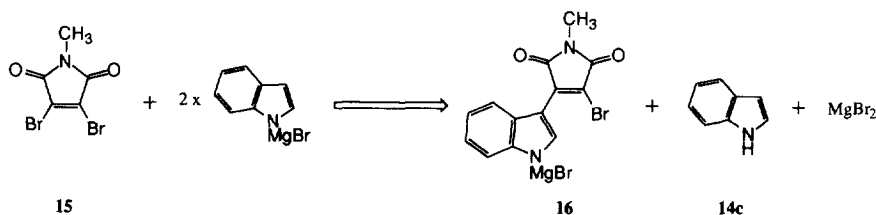
Results and Discussions

Indole compounds with a benzyloxy group substitute, **14a** and **14b**, were prepared from commercially available nitrophenol **11a** and **11b** according to the known procedure⁸ with partial modifications as shown in Scheme 1.



Scheme 1

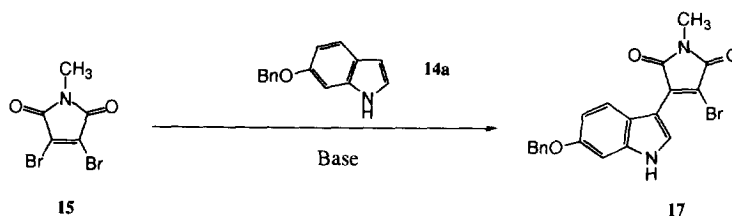
The coupling conditions between 2,3-dibromo-N-methylmaleimide **15**⁹ and the indole segments were studied precisely. The indolylation condition reported by W. Steglich requires a twofold excess of the indole portion to obtain a high yield because the monoindolylmaleimide reacts with the other indolylmagnesiumbromide as shown in Scheme 2.



Scheme 2

We then examined several bases other than the Grignard reagent. As shown in Table 1, LiHMDS was the most effective base for this reaction. A coupling reaction between 6-benzyloxyindole **14a** and 2,3-dibromo-N-methyl-

maleimide **15** proceeded smoothly due to the use of a twofold excess of LiHMDS in tetrahydrofuran (THF) at a low temperature to afford monoindolyl compound **17** in a 93% yield. These results suggest that only one equivalent of the indole is sufficient for indolylation when either LiHMDS or LDA is used as a base, because an excess anion like disilazide or diisopylamide does not act as a nucleophile at all.



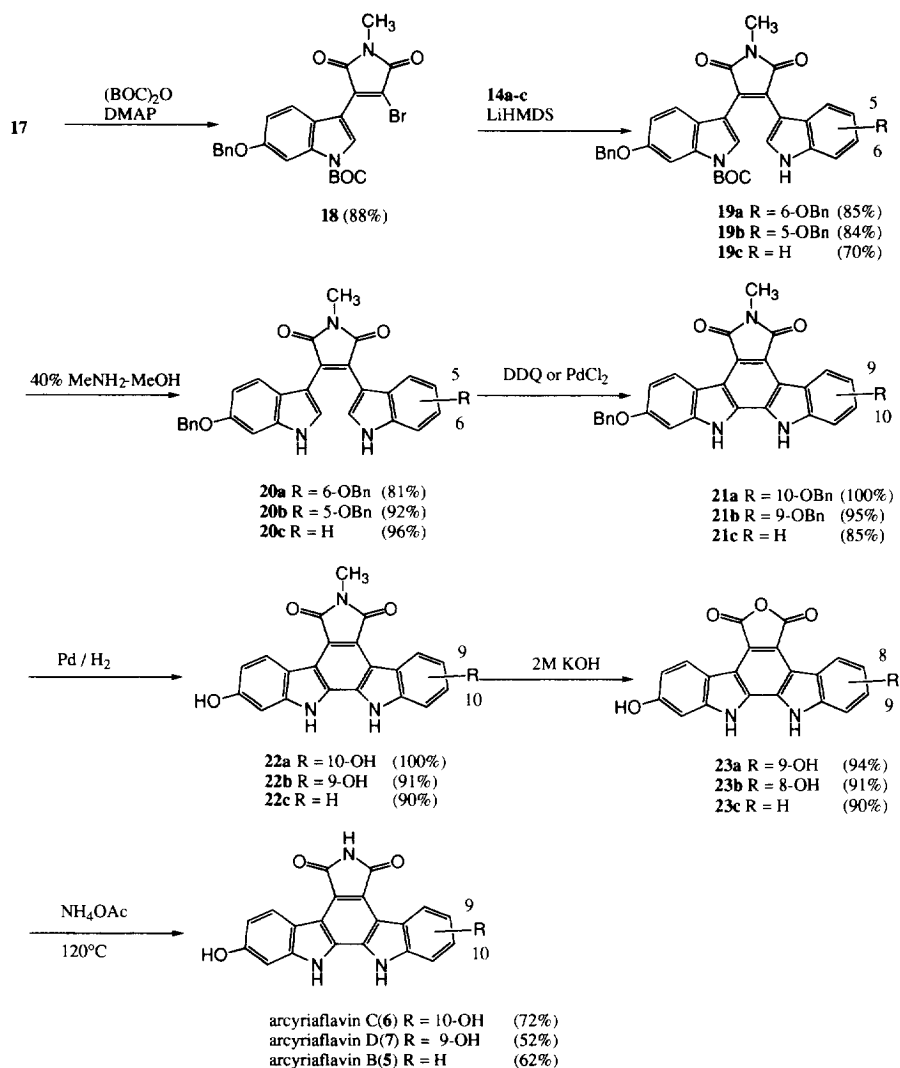
Scheme 3

Table 1 Coupling reaction between **15** and **14a** under several conditions

Indole(equiv)	Base ^{a)} (equiv)	Solvent	Temp.(°C)	Time(min)	Yield(%)
2.2	EtMgBr (2.2-2.4)	Toluene	rt	30	82-93
1.2	EtMgBr (2.4)	THF	0	30	30
1.0	nBuLi (2.4)	THF	0	-	trace
1.0	LDA (2.4)	THF	0	80	76
1.0	LiHMDS (2.1)	THF	0	30	93
1.0	NaHMDS(2.2)	THF	0	10	52
1.0	KHMDS (2.1)	THF	0	10	6

a) LDA (Lithium diisopropylamide), NaHMDS (sodium hexamethyldisilazide), KHMDS (potassium hexamethyldisilazide)

Protection of the resulting indole **17** with the BOC group proceeded smoothly due to the use of di-*tert*-butyl dicarbonate ((BOC)₂O) with a catalytic amount of 4-(dimethylamino)pyridine (DMAP) to give a key intermediate **18** in an 88% yield. Indoles **14a-c** were reacted with compound **18** to obtain the corresponding bisindolyl compounds **19a-c** in satisfactory yields. W. Steglich *et al.* reported the deprotection of BOC groups of bisindolylmaleimides under thermal conditions at 180°C, but we found that the BOC groups of **19a-c** cleaved under mild conditions with methylamine¹⁰ at room temperature to afford the corresponding bisindolylmaleimides **20a-c**. Cyclization of **20a** and **20c** using DDQ led to the corresponding cyclized products **21a** and **21c**. In contrast, the cyclization of **20b** with DDQ yielded only a trace amount of the desired product **21b**. The cyclization of arcyriarubin A (**9**) with palladium (II) acetate in acetic acid was recently reported by C. H. Hill *et al.*¹¹. We tried applying this reaction condition to the cyclization of **20b**; however, it was unsuccessful because of the lability of the compound **20b** under acidic conditions. Cyclization was then carried out under neutral conditions using palladium (II) chloride in DMF to provide compound **21b** in a 95% yield. After removal of the benzyl groups in **21a-c** by hydrogenation over a palladium catalyst, the resulting **22a-c** were converted to **23a-c** by treatment with aqueous KOH. Following ammonolysis of compounds **23a-c** yielded arcyriaflavin C, D and B in good yields. The analytical data of the synthetic samples were identical to the reported data^{2c} of the natural products with the exception of arcyriaflavin D^{1c}, for which reported data were unavailable.



Scheme 4

Summary

We developed a new practical method for the synthesis of indolo[2,3-a]pyrrolo[3,4-c]carbazole ring systems. The new method, which involves indoloylation with LiHMDS and oxidative cyclization by palladium (II) chloride, made it possible to synthesize various kinds of indolo[2,3-a]pyrrolo[3,4-c]carbazole compounds differing in the substitution at the benzene ring. We were able to synthesize arcyriaflavin B (5), C (6) and D (7), showing the advantage of this new method.

Experimental

¹H NMR were recorded on a Varian VXR-300 or Jeol JNM-EX 400 instrument. Infrared spectra were recorded on a Horiba FT-200 spectrometer. High-resolution mass spectra (HRMS) were recorded on a Jeol JMS-SX 102A instrument, and ultraviolet spectra (UV) were recorded on a Shimadzu UV-2200 spectrophotometer. Melting points were determined on a Yanako Model MP-S3 melting point apparatus and are uncorrected.

Preparation of indoles

4-Benzyloxy-2-nitrotoluene (12a): A stirred mixture of 4-methyl-3-nitrophenol **11a** (495 g, 3.23 mol), potassium carbonate (450 g, 3.23 mol) and benzyl chloride (453 g, 3.55 mol) in 3.26 L of *N,N*-dimethylformamide (DMF) was heated at 100 °C for 4 h. The reaction mixture was poured into water and then extracted with ethyl acetate. The organic phase was washed with 1M NaOH, 2% aqueous NaCl and saturated brine, dried over Na₂SO₄ and concentrated in vacuo. The residue was recrystallized from ethyl acetate-hexane to afford **12a** (745 g, 3.06 mol) as colorless prisms (95%), mp 48-50 °C: IR(KBr) ν_{\max} 1535, 1523, 1519, 1508, 1496, 1344, 1232, 1014 cm⁻¹; ¹H NMR (300MHz, CDCl₃) δ 7.60 (1H, d, J = 2.7Hz), 7.32-7.45 (5H, m), 7.23 (1H, d, J = 8.5Hz), 7.12 (1H, dd, J = 2.7, 8.5Hz), 5.10 (2H, s), 2.52 (3H, s); HRMS(FAB) calcd for C₁₄H₁₃NO₃, 243.0895, found 243.0903.

5-Benzyloxy-2-nitrotoluene (12b): A stirred mixture of 3-methyl-4-nitrophenol **11b** (53.7 g, 350 mmol), potassium carbonate (48.5 g, 350 mmol) and benzyl chloride (48.8 g, 385 mmol) in 300 mL of DMF was heated at 100 °C for 1 h. The reaction mixture was poured into water and then extracted with ethyl acetate. The organic phase was washed with 1M NaOH, 2% aqueous NaCl and saturated brine, dried over Na₂SO₄ and concentrated in vacuo. The residue was recrystallized from ethyl acetate-hexane to afford **12b**(83.0 g, 341 mmol) as colorless prisms (97%), mp 71-72 °C: IR(KBr) ν_{\max} 1602, 1506, 1336, 1253, 1076 cm⁻¹; ¹H NMR (300MHz, CDCl₃) δ 8.07 (1H, d, J = 9.7Hz), 7.36-7.42 (5H, m), 6.86-6.89 (2H, m), 5.13 (2H, s), 2.13 (3H, s); HRMS(FAB) calcd for C₁₄H₁₃NO₃, 243.0895, found 243.0900.

(E)-4-Benzyloxy-2-nitro- β -pyrrolidinostyrene (13a): A stirred mixture of **12a** (753 g, 3.09 mol), *N,N*-dimethylformamide dimethylacetal (1230 mL, 9.27 mol) and pyrrolidine (773 mL, 9.27 mmol) was heated at 110 °C for 11 h under nitrogen and allowed to cool to room temperature. Ethanol was added to the reaction mixture, yielding **13a** (947 g, 2.92 mol) as dark red crystals (94%), mp 108-110 °C: IR(KBr) ν_{\max} 1614, 1558, 1508, 1396, 1369, 1332, 1296, 1274, 1008 cm⁻¹; ¹H NMR (300MHz, CDCl₃) δ 7.50 (1H, d, J = 3.1Hz), 7.29-7.45 (6H, m), 7.10 (1H, d, J = 13.5Hz), 7.04 (1H, dd, J = 3.1, 8.9Hz), 5.84 (1H, d, J = 13.5Hz), 5.05 (2H, s), 3.30 (4H, m), 1.94 (4H, m); HRMS(FAB) calcd for C₁₉H₂₀N₂O₃, 324.1417, found 324.1475.

(E)-5-Benzyloxy-2-nitro- β -pyrrolidinostyrene (13b): A stirred mixture of **12b** (80 g, 329 mmol), *N,N*-dimethylformamide dimethylacetal (55.5 g, 465 mmol) and pyrrolidine (28 g, 393 mmol) was heated at 110 °C for 14 h under nitrogen and allowed to cool to room temperature. Ethanol was added to the reaction mixture, yielding **13b** (97.1 g, 299 mmol) as dark red crystals (91%), mp 89-91 °C: IR(KBr) ν_{\max} 1616, 1592, 1384, 1234, 1068 cm⁻¹; ¹H NMR (300MHz, CDCl₃) δ 7.96 (1H, d, J = 9.2Hz), 7.34-7.45 (5H, m), 7.18 (1H, d, J =

13.4Hz), 6.93 (1H, d, $J = 2.6$ Hz), 6.56 (1H, dd, $J = 2.6, 9.2$ Hz), 6.04 (1H, d, $J = 13.4$ Hz), 5.12 (2H, s), 3.31-3.36 (4H, m), 1.93-2.01 (4H, m); HRMS(FAB) calcd for $C_{19}H_{20}N_2O_3$ 324.1474, found 324.1461.

6-Benzylxyindole (14a): A stirred mixture of compound **13a** (945 g, 2.91 mol) and hydrazine monohydrate (641 g, 12.8 mol) in ethanol (2.9 L) was heated at 80 °C for 1 h, then allowed to cool to room temperature. The mixture was added slowly to a stirred suspension of nickel boride (prepared from 6.40 mol of nickel acetate) in 6 L of ethanol at 50 °C. After an additional 1 h, hydrazine monohydrate (464 g, 9.2 mol) was added and the mixture was stirred for 1 h. After cooling, the mixture was filtered through a Celite pad and the filtrate was evaporated in vacuo. The resulting colorless residue was diluted with ethyl acetate and the organic phase was successively washed with 2M HCl, aqueous $NaHCO_3$ and saturated brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was passed through a short column of Florisil® (2 Kg), eluting with dichloromethane-hexane (1:1). The resulting solution was concentrated in vacuo and the residue was recrystallized from hexane to afford **14a** (566 g, 2.54 mol) as a colorless crystalline powder (86%), mp 116-117 °C: IR(KBr) ν_{max} 3390, 1716, 1683, 1540, 1508, 1456, 1166, 1093 cm^{-1} ; 1H NMR (300MHz, $CDCl_3$) δ 7.99 (1H, NH, br s), 7.52 (1H, d, $J = 8.4$ Hz), 7.30-7.48 (5H, m), 7.10 (1H, dd, $J = 2.4, 3.9$ Hz), 6.95 (1H, d, $J = 2.4$ Hz), 6.88 (1H, dd, $J = 2.4, 8.4$ Hz), 6.48 (1H, m), 5.12 (2H, s); HRMS(FAB) calcd for $C_{15}H_{13}NO$ 223.0997, found 223.1008.

5-Benzylxyindole (14b): A stirred mixture of compound **13b** (314.4 g, 0.97 mol) and hydrazine monohydrate (106.9 g, 2.13 mol) in ethanol (1.0 L) was heated at 80 °C for 0.5 h and allowed to cool to room temperature. The mixture was added slowly to a stirred suspension of nickel boride (prepared from 2.13 mol of nickel acetate) in 1.8 L of ethanol at 50 °C. After an additional 1 h, hydrazine monohydrate (50 g, 0.99 mol) was added and the mixture was stirred for 2 h. After cooling, the mixture was filtered through Celite pad and the filtrate was evaporated in vacuo. The resulting colorless residue was dissolved in ethyl acetate and the organic phase was successively washed with 2M HCl, aqueous $NaHCO_3$ and saturated brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was passed through a short column of Florisil® (1 Kg), eluting with chloroform. The resulting solution was concentrated in vacuo and the residue was recrystallized from chloroform-hexane to afford **14b** (202.4 g, 0.91 mol) as a colorless crystalline powder (94%), mp 109-111 °C: IR(KBr) ν_{max} 3315, 1697, 1646, 1540, 1508, 1457, 1224, 1151 cm^{-1} ; 1H NMR (300MHz, $CDCl_3$) δ 8.07 (1H, NH, br s), 7.32-7.50 (5H, m), 7.29 (1H, d, $J = 8.4$ Hz), 7.19 (2H, m), 6.95 (1H, dd, $J = 2.4, 8.4$ Hz), 6.48 (1H, m), 5.11 (2H, s); HRMS(FAB) calcd for $C_{15}H_{13}NO$ 223.0997, found 223.1002.

Preparation of Arcyriaflavins

4-Bromo-2,5-dihydro-3-(6-benzylxy-1H-indol-3-yl)-1-methyl-1H-pyrrole-2,5-dione (17): In an N_2 atmosphere, 2.7 L of LiHMDS (1 M in THF) at -20 °C was added to a solution of 6-benzylxyindole **14a** (284 g, 1.27 mol) in THF (3 L) and stirred for 45 min. A solution of 2,3-dibromo- N-methylmaleimide **15** (340 g, 1.26 mol) in THF (3 L) was then added by drip over 1 h, followed by stirring for 15 min at 0 °C. The reaction mixture was poured into 0.2 M aqueous hydrochloric acid, and this mixture was extracted with ethyl acetate. The organic phase was successively washed with aqueous $NaHCO_3$, H_2O and saturated brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was recrystallized from methanol to afford **17** (482 g, 1.17 mol)

as an orange crystalline powder (93%), mp 140 °C (decompose): IR(KBr) ν_{\max} 3330, 3318, 1762, 1701, 1606, 1511, 1450, 1165 cm^{-1} ; $^1\text{H NMR}$ (300MHz, CDCl_3) δ 8.60 (1H, br s), 7.96 (1H, d, $J = 8.1\text{Hz}$), 7.94 (1H, d, $J = 2.5\text{Hz}$), 7.33-7.47 (5H, m), 7.00 (1H, dd, $J = 2.5, 8.8\text{Hz}$), 6.97 (1H, d, $J = 2.5\text{Hz}$), 5.13 (2H, s), 3.16 (3H, s); HRMS(FAB) calcd for $\text{C}_{20}\text{H}_{15}\text{N}_2\text{O}_3\text{Br}$ 410.0266, found 410.0292.

4-Bromo-2,5-dihydro-3-[6-benzyloxy-1-(tert-butyloxycarbonyl)-1H-indol-3-yl]-1-methyl-1H-pyrrole-2,5-dione (18): Di-tert-butyl dicarbonate (637 mg, 2.91 mmol) and catalytic amount of DMAP (3 mg, 0.02 mmol) were added to a solution of **17** (1.0 g, 2.42 mmol) in THF (200 mL) and the mixture was stirred for 1 h at 20 °C. After removal of the solvent in vacuo, the yellow residue was recrystallized with hexane-ethyl acetate to obtain **18** (1.18 g, 2.31 mmol) as a yellow crystalline powder (96%), mp 156-159 °C: IR(KBr) ν_{\max} 1740, 1714, 1614, 1527, 1487, 1443, 1373, 1227, 1153 cm^{-1} ; $^1\text{H NMR}$ (300MHz, CDCl_3) δ 8.10 (1H, s), 7.91 (1H, d, $J = 2.3\text{Hz}$), 7.73 (1H, d, $J = 8.9\text{Hz}$), 7.34-7.50 (5H, m), 7.03 (1H, dd, $J = 2.3, 8.5\text{Hz}$), 5.16 (2H, s), 3.18 (3H, s), 1.68 (9H, s); HRMS(FAB) calcd for $\text{C}_{25}\text{H}_{23}\text{N}_2\text{O}_5\text{Br}$ 510.0791, found 510.0771.

General procedure for the preparation of compounds 19a-c: In an N_2 atmosphere, LiHMDS (1 M in THF, 2.1-2.4 equiv) at -20 °C was added to a solution of 1.0 equiv of the appropriate indole (0.05 M) in THF and stirred for 30-45 min. A solution of **18** (0.1 M) in THF was then added by drip over 30-60 min, followed by stirring for 15 min at 0 °C. The reaction mixture was poured into 0.2 M aqueous hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic phase was successively washed with aqueous NaHCO_3 , H_2O and saturated brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was recrystallized to obtain the bisindolylmaleimides **19a-c**.

2,5-Dihydro-3-[6-benzyloxy-1-(tert-butyloxycarbonyl)-1H-indol-3-yl]-4-(6-benzyloxy-1H-indol-3-yl)-1-methyl-1H-pyrrole-2,5-dione (19a): From 6-benzyloxyindole **14a** (218 mg, 0.98 mmol), LiHMDS (2.35 mL, 2.35 mmol) and **18** (500 mg, 0.98 mmol), **19a** (580 mg, 0.89 mmol) was obtained after recrystallized from toluene-hexane as an orange crystalline powder (91%), mp 124-128 °C: IR(KBr) ν_{\max} 1740, 1701, 1646, 1623, 1543, 1445, 1155 cm^{-1} ; $^1\text{H NMR}$ (300MHz, CDCl_3) δ 8.41 (1H, br s), 7.97 (1H, s), 7.84 (1H, br s), 7.68 (1H, br s), 7.16-7.43 (10H, m), 6.98 (1H, d, $J = 9.2\text{Hz}$), 6.85 (1H, br s), 6.74 (1H, d, $J = 9.2\text{Hz}$), 6.54 (1H, d, $J = 9.2\text{Hz}$), 5.05 (2H, s), 5.02 (2H, s), 3.19 (3H, s), 1.67 (9H, s); HRMS(FAB) calcd for $\text{C}_{40}\text{H}_{35}\text{N}_3\text{O}_6$ 653.2526, found 653.2556.

2,5-Dihydro-3-[6-benzyloxy-1-(tert-butyloxycarbonyl)-1H-indol-3-yl]-4-(5-benzyloxy-1H-indol-3-yl)-1-methyl-1H-pyrrole-2,5-dione (19b): From 5-benzyloxyindole **14b** (4.47 g, 20 mmol), LiHMDS (48 mL, 48 mmol) and **18** (10.23 g, 20 mmol), **19b** (11.02 g, 17 mmol) was obtained after recrystallized from ethyl acetate-hexane as an orange crystalline powder (84%), mp 195-198 °C: IR(KBr) ν_{\max} 3357, 1733, 1695, 1646, 1623, 1438, 1220, 1155 cm^{-1} ; $^1\text{H NMR}$ (300MHz, CDCl_3) δ 8.56 (1H, br s), 7.98 (1H, d, $J = 2.9\text{Hz}$), 7.86 (1H, s), 7.83 (1H, br s), 7.18-7.41 (11H, m), 6.96 (1H, d, $J = 8.9\text{Hz}$), 6.78 (1H, dd, $J = 2.5, 8.9\text{Hz}$), 6.65 (1H, dd, $J = 2.5, 8.9\text{Hz}$), 6.44 (1H, d, $J = 8.9\text{Hz}$), 4.97 (2H, s), 4.21 (2H, s), 3.20 (3H, s), 1.56 (9H, s); HRMS(FAB) calcd for $\text{C}_{40}\text{H}_{35}\text{N}_3\text{O}_6$ 653.2525, found 653.2513.

2,5-Dihydro-3-[6-benzyloxy-1-(tert-butyloxycarbonyl)-1H-indol-3-yl]-4-(1H-indol-3-yl)-1-methyl-1H-pyrrole-2,5-dione (19c): From indole **14c** (4.57 g, 39.0 mmol), LiHMDS (9.36 mL, 9.36 mmol) and **18** (20.0 g, 39.0 mmol), **19c** (14.8 g, 27.1 mmol) was obtained after chromatography (hexane/ethyl acetate (3:1-2:1)) and recrystallized from ether-hexane as a yellow crystalline powder (70%), mp 122-126 °C: IR(KBr) ν_{\max} 3361, 1736, 1701, 1616, 1541, 1443, 1387, 1363, 1155 cm^{-1} ; $^1\text{H NMR}$ (300MHz, CDCl_3) δ 8.54 (1H, br s), 7.96 (1H, s), 7.84(1H, br d), 7.78 (1H, d, $J = 3.1\text{Hz}$), 7.28-7.42 (6H, m), 7.07-7.14 (2H, m), 6.84 (1H, ddd, $J = 1.4, 6.7, 8.1\text{Hz}$), 6.72 (1H, d, $J = 8.4\text{Hz}$), 6.49(1H, dd, $J = 2.2, 8.4\text{Hz}$), 5.03 (2H, s), 3.20 (3H, s), 1.66 (9H, s); HRMS(FAB) calcd for $\text{C}_{33}\text{H}_{29}\text{N}_3\text{O}_5$ 547.2107, found 547.2116.

General procedure for the preparation of compounds 20a-c: 40% methylamine in methanol was added to compounds **19a-c** and the reaction mixtures were stirred for 0.5-2 h at room temperature. The solvents were removed in vacuo and the residues were purified to afford the deprotected compounds **20a-c**.

2,5-Dihydro-3,4-bis-(6-benzyloxy-1H-indol-3-yl)-1-methyl-1H-pyrrole-2,5-dione (20a): From **19a** (496 g, 0.76 mol) and methylamine (2.5 L), **20a** (340 g, 0.61 mol) was obtained after recrystallization from ethyl acetate-methanol-hexane as a red crystalline powder (81%), mp 243-245 °C: IR(KBr) ν_{\max} 3419, 3350, 1759, 1697, 1533, 1454, 1383, 1292, 1167 cm^{-1} ; $^1\text{H NMR}$ (300MHz, DMSO) δ 11.48 (2H, s), 7.62 (2H, s), 7.28-7.45 (10H, m), 6.95 (2H, d, $J = 1.2\text{Hz}$), 6.70(2H, d, $J = 8.7\text{Hz}$), 6.39 (2H, dd, $J = 1.2, 8.7\text{Hz}$), 5.04 (4H, s), 3.03 (3H, s); HRMS(FAB) calcd for $\text{C}_{35}\text{H}_{27}\text{N}_3\text{O}_4$ 553.2002, found 553.1982.

2,5-Dihydro-3-(5-benzyloxy-1H-indol-3-yl)-4-(6-benzyloxy-1H-indol-3-yl)-1-methyl-1H-pyrrole-2,5-dione (20b): From **19b** (65 mg, 0.10 mmol) and methylamine (1 mL), **20b** (51 mg, 0.092 mmol) was obtained as a red crystalline powder after washing with methanol (92%), mp 241-244 °C: IR(KBr) ν_{\max} 3356, 1701, 1541, 1456, 1387, 1257, 1163 cm^{-1} ; $^1\text{H NMR}$ (300MHz, DMSO) δ 11.61 (1H, s), 11.47 (1H, s), 7.87 (1H, d, $J = 2.7\text{Hz}$), 7.47 (1H, d, $J = 2.8\text{Hz}$), 7.10-7.39 (11H, m), 6.96 (1H, d, $J = 2.3\text{Hz}$), 6.92 (1H, d, $J = 8.5\text{Hz}$), 6.63(1H, dd, $J = 2.8, 9.0\text{Hz}$), 6.49 (1H, dd, $J = 2.4, 8.5\text{Hz}$), 6.14 (1H, d, $J = 2.3\text{Hz}$), 4.95 (2H, s), 4.08 (2H, s), 3.03 (3H, s); HRMS(FAB) calcd for $\text{C}_{35}\text{H}_{27}\text{N}_3\text{O}_4$ 553.2002, found 553.1999.

2,5-Dihydro-3-(6-benzyloxy-1H-indol-3-yl)-4-(1H-indol-3-yl)-1-methyl-1H-pyrrole-2,5-dione (20c): From **19c** (23 g, 4.19 mmol) and methylamine (250 mL), **20c** (18 g, 4.03 mmol) was obtained after chromatography (hexane-ethyl acetate (2:1)) as a red crystalline powder (96%), mp 129-133 °C: IR(KBr) ν_{\max} 3392, 3351, 1693, 1539, 1456, 1387, 1244, 1161 cm^{-1} ; $^1\text{H NMR}$ (300MHz, CDCl_3) δ 8.51 (1H, br s), 8.36 (1H, br s), 7.73 (1H, d, $J = 3.1\text{Hz}$), 7.65 (1H, d, $J = 2.6\text{Hz}$), 7.26-7.47 (6H, m), 7.10 (1H, m), 7.02 (1H, d, $J = 8.3\text{Hz}$), 6.84-6.89 (2H, m), 6.79(1H, ddd, $J = 1.0, 6.8, 7.8\text{Hz}$), 6.49 (1H, dd, $J = 2.3, 9.0\text{Hz}$), 5.01 (2H, s), 3.18 (3H, s); HRMS(FAB) calcd for $\text{C}_{28}\text{H}_{21}\text{N}_3\text{O}_3$ 447.1583, found 447.1575.

2,10-Dibenzyloxy-12,13-dihydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-6-methyl-5,7-(6H)-dione (21a): DDQ (456 mg, 44.4 mmol) was added to a solution of **20a** (1.01 g, 1.82 mmol) in toluene (50 mL), followed by refluxing for 40 min. After cooling, the precipitate was filtered off and washed with methanol. The filtrate was recrystallized from DMSO-dichloromethane-methanol to obtain **21a** (981 mg, 1.78 mmol) as yellow prisms (98%), mp >300 °C: IR(KBr) ν_{\max} 3257, 1740, 1675, 1620, 1571, 1402, 1246, 1178

cm^{-1} ; $^1\text{H NMR}$ (300MHz, DMSO) δ 11.46 (2H, s), 8.79 (2H, s), 7.53 (4H, d, $J = 8.5\text{Hz}$), 7.35-7.44 (8H, m), 7.02 (2H, dd, $J = 0.8, 8.5\text{Hz}$), 5.25 (4H, s), 3.03 (3H, s); HRMS(FAB) calcd for $\text{C}_{35}\text{H}_{25}\text{N}_3\text{O}_4$ 551.1845, found 551.1829.

2,9-Dibenzyloxy-12,13-dihydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-6-methyl-5,7(6H)-dione (21b): Palladium chloride (59 mg, 0.33 mmol) was added to a solution of **20b** (36.5 mg, 0.066 mmol) in DMF (4mL), followed by stirring at 105 °C for 40 min. After cooling, the reaction mixture was poured into 0.2 N aqueous hydrochloric acid and extracted with ethyl acetate. The organic layer was successively washed with aqueous NaHCO_3 , H_2O and saturated brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography on silica gel (chloroform-ethyl acetate (10:1)) to yield **21b** (34.4 mg, 0.062 mmol) as a yellow crystalline powder (95%), mp 239-242 °C; IR(KBr) ν_{max} 3319, 1743, 1684, 1622, 1548, 1379, 1178 cm^{-1} ; $^1\text{H NMR}$ (300MHz, DMSO) δ 11.54 (1H, s), 11.45 (1H, s), 8.81 (1H, d, $J = 8.8\text{Hz}$), 8.64 (1H, d, $J = 2.3\text{Hz}$), 7.69 (1H, d, $J = 8.7\text{Hz}$), 7.55 (4H, t, $J = 6.7\text{Hz}$), 7.32-7.46 (7H, m), 7.25 (1H, d, $J = 8.8\text{Hz}$), 7.04 (1H, d, $J = 8.8\text{Hz}$), 5.26 (2H, s), 5.22 (2H, s), 3.15 (3H, s); HRMS(FAB) calcd for $\text{C}_{35}\text{H}_{25}\text{N}_3\text{O}_4$ 551.1845, found 551.1855.

2-Benzyloxy-12,13-dihydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-6-methyl-5,7(6H)-dione (21c): DDQ (10.1 g, 44.4 mmol) was added to a solution of **20c** (18.0 g, 40.6 mmol) in toluene (1.8 L), followed by stirring at 90 °C for 2 h. After cooling, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was successively washed with aqueous NaHCO_3 , H_2O and saturated brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was washed with methylethylketone to obtain **21c** (15.2 g, 34.5 mmol) as a yellow solid (85%), mp 182-186 °C; IR(KBr) ν_{max} 3340, 3326, 1743, 1689, 1624, 1570, 1456, 1404, 1379, 1338, 1323, 1244, 1174 cm^{-1} ; $^1\text{H NMR}$ (300MHz, DMSO) δ 11.63 (1H, s), 11.56 (1H, s), 8.96 (1H, d, $J = 7.9\text{Hz}$), 8.82 (1H, d, $J = 8.8\text{Hz}$), 7.77 (1H, d, $J = 8.3\text{Hz}$), 7.29-7.58 (8H, m), 7.04 (1H, d, $J = 8.8\text{Hz}$), 5.26 (2H, s), 3.14 (3H, s); HRMS(FAB) calcd for $\text{C}_{28}\text{H}_{19}\text{N}_3\text{O}_3$ 445.1427, found 445.1455

12,13-Dihydro-2,10-dihydroxy-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-6-methyl-5,7(6H)-dione (22a): A catalytic amount of 10% palladium on carbon (1.0 g) was added to a solution of **21a** (30 g, 54.4 mmol) in THF (1.5 L). The mixture was stirred for 10 h in a hydrogen atmosphere. The catalyst was filtered off and washed with THF-methanol. The solvent was removed in vacuo and the residue was recrystallized from acetone-hexane to yield **22a** (18.4 g, 50.0 mmol) as a red crystalline powder (92%), mp >300 °C; IR(KBr) ν_{max} 3401, 3396, 1738, 1676, 1630, 1576, 1437, 1406 cm^{-1} ; $^1\text{H NMR}$ (300MHz, DMSO) δ 11.27 (2H, s), 9.72 (2H, s), 8.70 (2H, d, $J = 8.2\text{Hz}$), 7.05 (2H, d, $J = 1.5\text{Hz}$), 6.78 (2H, dd, $J = 1.5, 8.2\text{Hz}$), 3.13 (3H, s); HRMS(FAB) calcd for $\text{C}_{21}\text{H}_{13}\text{N}_3\text{O}_4$ 371.0906, found 371.0906.

12,13-Dihydro-2,9-dihydroxy-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-6-methyl-5,7(6H)-dione (22b): A catalytic amount of palladium hydroxide on carbon (15 mg) was added to a solution of **21b** (165 mg, 0.30 mmol) in THF (15 mL). The mixture was stirred for 4 h in a hydrogen atmosphere. The catalyst was filtered off and washed with THF-DMF. The solvent was removed in vacuo and the residue was washed with chloroform to yield **22b** (101 mg, 0.27 mmol) as a red crystalline powder (91%), mp >300 °C; IR(KBr)

ν_{\max} 3295, 1734, 1653, 1570, 1558, 1410, 1381 cm^{-1} ; $^1\text{H NMR}$ (300MHz, DMSO) δ 11.36 (1H, s), 11.24 (1H, s), 9.73 (1H, s), 9.18 (1H, s), 8.73 (1H, d, $J = 8.6\text{Hz}$), 8.40 (1H, d, $J = 2.5\text{Hz}$), 7.56 (1H, d, $J = 8.7\text{Hz}$), 7.07 (1H, d, $J = 2.1\text{Hz}$), 7.01 (1H, dd, $J = 2.5, 8.7\text{Hz}$), 6.81 (1H, dd, $J = 2.1, 8.6\text{Hz}$), 3.15 (3H, s); HRMS(FAB) calcd for $\text{C}_{21}\text{H}_{13}\text{N}_3\text{O}_4$ 371.0906, found 371.0905.

12,13-Dihydro-2-hydroxy-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-6-methyl-5,7(6H)-dione (22c): A catalytic amount of 10% palladium on carbon (20 mg) was added to a solution of **21c** (177.2 mg, 0.40 mmol) in THF (15 mL). The mixture was stirred for 1 day in a hydrogen atmosphere. The catalyst was filtered off and washed with THF. The solvent was removed in vacuo and the residue was recrystallized from ethyl acetate-hexane to yield **22c** (128.0 mg, 0.36 mmol) as a red crystalline powder (90%), mp >300 °C: IR(KBr) ν_{\max} 3311, 1733, 1684, 1570, 1558, 1406 cm^{-1} ; $^1\text{H NMR}$ (300MHz, DMSO) δ 11.55 (1H, s), 11.40 (1H, s), 9.76 (1H, s), 8.96 (1H, d, $J = 7.8\text{Hz}$), 8.74 (1H, d, $J = 8.5\text{Hz}$), 7.76 (1H, d, $J = 7.8\text{Hz}$), 7.52 (1H, t, $J = 7.8\text{Hz}$), 7.32 (1H, t, $J = 7.8\text{Hz}$), 7.10 (1H, d, $J = 2.0\text{Hz}$), 6.82 (1H, dd, $J = 2.0, 8.5\text{Hz}$), 3.16 (3H, s); HRMS(FAB) calcd for $\text{C}_{21}\text{H}_{13}\text{N}_3\text{O}_3$ 355.0957, found 355.0972.

General procedure for the preparation of compounds 23a-c: Compounds **22a-c** was dissolved in 2 M aqueous potassium hydroxide at room temperature and the solution was acidified after 0.5-2 h with 2 M HCl. The mixture was extracted with ethyl acetate-MEK (1:1) and the extract was washed with saturated brine, dried over Na_2SO_4 and concentrated. The residual solid was washed with chloroform to obtain compounds **23a-c**.

11,12-Dihydro-2,9-dihydroxy-indolo[2,3-a]carbazole-5,6-dicarboxylic anhydride (23a): From **22a** (110 mg, 0.30 mmol), **23a** (100 mg, 0.28 mmol) was obtained as an orange crystalline powder (94%), mp >300 °C: IR(KBr) ν_{\max} 3415, 1793, 1740, 1626, 1410, 1338, 1267, 1184 cm^{-1} ; $^1\text{H NMR}$ (300MHz, DMSO) δ 11.91 (2H, s), 9.88 (2H, s), 8.55 (2H, d, $J = 8.7\text{Hz}$), 7.10 (2H, d, $J = 1.9\text{Hz}$), 6.86 (2H, dd, $J = 1.9, 8.7\text{Hz}$); HRMS(FAB) calcd for $\text{C}_{20}\text{H}_{10}\text{N}_2\text{O}_5$ 358.0589, found 358.0597.

11,12-Dihydro-2,8-dihydroxy-indolo[2,3-a]carbazole-5,6-dicarboxylic anhydride (23b): From **22b** (17.0 mg, 0.046 mmol), **23b** (15.0 mg, 0.042 mmol) was obtained as an orange crystalline powder (91%), mp >300 °C: IR(KBr) ν_{\max} 3403, 1811, 1747, 1623, 1558, 1408, 1277 cm^{-1} ; $^1\text{H NMR}$ (300MHz, DMSO) δ 11.88 (1H, s), 11.58 (1H, s), 9.88 (1H, s), 9.27 (1H, s), 8.56 (1H, d, $J = 8.5\text{Hz}$), 8.22 (1H, d, $J = 2.8\text{Hz}$), 7.64 (1H, d, $J = 8.8\text{Hz}$), 7.13 (1H, d, $J = 1.7\text{Hz}$), 7.06 (1H, dd, $J = 2.8, 8.8\text{Hz}$), 6.87 (1H, dd, $J = 1.7, 8.5\text{Hz}$); HRMS(FAB) calcd for $\text{C}_{20}\text{H}_{10}\text{N}_2\text{O}_5$ 358.0589, found 358.0606.

11,12-Dihydro-2-hydroxy-indolo[2,3-a]carbazole-5,6-dicarboxylic anhydride (23c): From **22c** (50 mg, 0.14 mmol), **23c** (45 mg, 0.13 mmol) was obtained as an orange crystalline powder (90%), mp > 300 °C: IR(KBr) ν_{\max} 3403, 1811, 1743, 1558, 1406, 1329, 1261, 1165 cm^{-1} ; $^1\text{H NMR}$ (300MHz, DMSO) δ 11.93 (1H, s), 11.78 (1H, s), 9.91 (1H, s), 8.79 (1H, d, $J = 7.8\text{Hz}$), 8.58 (1H, d, $J = 8.5\text{Hz}$), 7.82 (1H, d, $J = 7.8\text{Hz}$), 7.58 (1H, t, $J = 7.8\text{Hz}$), 7.38 (1H, t, $J = 7.8\text{Hz}$), 7.16 (1H, d, $J = 2.1\text{Hz}$), 6.90 (1H, dd, $J = 2.1, 8.5\text{Hz}$); HRMS(FAB) calcd for $\text{C}_{20}\text{H}_{10}\text{N}_2\text{O}_4$ 342.0641, found 342.0626

General procedure for the preparation of arcyriaflavins: Compounds **23a-c** were heated with ammonium acetate for 0.5–2 h at 140 °C (bath temperature). The mixture was cooled and extracted with ethyl acetate-MEK (1:1) after the addition of water. The organic layer was washed with saturated brine, dried over Na₂SO₄ and evaporated in vacuo. The residue was chromatographed on a Sephadex LH-20 with methanol to yield the arcyriaflavins.

Arcyriaflavin B (5): From the compound **23c** (30 mg, 0.084 mmol) and ammonium acetate (720 mg), arcyriaflavin **B (5)** (18 mg, 0.053 mmol) was obtained as a yellow crystalline powder (62%), mp >300 °C: UV(MeOH) 413 (log ε 3.66), 323 (log ε 4.72), 229 (log ε 4.66); IR(KBr) ν_{\max} 3311, 3276, 1773, 1697, 1623, 1405 cm⁻¹; ¹H NMR (300MHz, DMSO) δ 11.60 (1H, s), 11.46 (1H, s), 10.88 (1H, s), 9.75 (1H, s), 8.95 (1H, d, J = 7.8Hz), 8.73 (1H, d, J = 8.7Hz), 7.76 (1H, d, J = 7.8 Hz), 7.51 (1H, t, J = 7.8Hz), 7.31 (1H, t, J = 7.8Hz), 7.10 (1H, d, J = 2.1Hz), 6.82 (1H, dd, J = 2.1, 8.7Hz); HRMS(FAB) calcd for C₂₀H₁₁N₃O₃ 341.0801, found 341.0826.

Arcyriaflavin C (6): From the compound **23a** (50 mg, 0.14 mmol) and ammonium acetate (1.2 g), arcyriaflavin **C (6)** (36 mg, 0.10 mmol) was obtained as a yellow crystalline powder (72%), mp >300 °C: UV(MeOH) 420 (log ε 3.80), 329 (log ε 4.76), 227 (log ε 4.61); IR(KBr) ν_{\max} 3297, 1734, 1697, 1684, 1406 cm⁻¹; ¹H NMR (300MHz, DMSO) δ 11.24 (2H, s), 10.76 (1H, s), 9.68 (2H, s), 8.70 (2H, d, J = 8.5Hz), 7.05(2H, d, J = 2.3Hz), 6.78 (2H, dd, J = 2.3, 8.5Hz); HRMS(FAB) calcd for C₂₀H₁₁N₃O₃ 357.0749, found 357.0746.

Arcyriaflavin D (7): From the compound **23b** (10.0 mg, 0.028 mmol) and ammonium acetate(240 mg), arcyriaflavin **D (7)** (8.2 mg, 0.023 mmol) was obtained as a yellow crystalline powder (52%), mp >300 °C: UV(MeOH) 418 (log ε 3.66), 327 (log ε 4.61), 229 (log ε 4.61); IR(KBr) ν_{\max} 3300, 1734, 1697, 1652, 1570, 1417, 1406, 1219, 1381 cm⁻¹; ¹H NMR (300MHz, DMSO) δ 11.37 (1H, s), 11.25 (1H, s), 10.79 (1H, s), 9.69 (1H, s), 9.14 (1H, s), 8.71 (1H, d, J = 8.5Hz), 8.37 (1H, d, J = 2.2Hz), 7.55 (1H, d, J = 8.5Hz), 7.06 (1H, d, J = 2.2Hz), 7.00 (1H, dd, J = 2.2, 8.5Hz), 6.80 (1H, dd, J = 2.0, 8.5Hz); HRMS(FAB) calcd for C₂₀H₁₁N₃O₄ 357.0750, found 357.0763.

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