Synthesis of the Indolo[2,3-*a*]carbazole Natural Products Staurosporinone and Arcyriaflavin B

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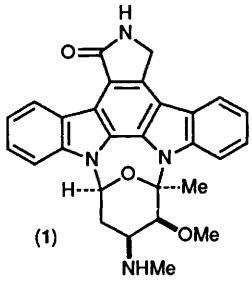
Flexible synthetic routes involving double nitrene insertions are described leading to the indolo[2,3-*a*]carbazole systems present in a growing group of natural products. The methods are exemplified by the total synthesis of two members of this group staurosporinone (**9**; R = H) and arcyriaflavin B (**2**).

Since the first isolation and characterisation of the hypotensive antibiotic staurosporine (**1**) produced by *Streptomyces staurosporeus*[1] many more examples of the natural occurrence of derivatives of the hitherto rare indolo[2,3-*a*]carbazole have been reported.[2,3] These unusual structures have prompted considerable interest in approaches to their synthesis[2,4] because of their wide variety of biological activity. Following our preliminary report of a portion of our work[4] we now give full details of a versatile general synthesis of substituted indolo[2,3-*a*]carbazoles which is applicable to both symmetrical and unsymmetrical substitution patterns. The methods are here exemplified by the synthesis of the naturally occurring aglycone of (**1**), staurosporinone (**9**; R = H) and of arcyriaflavin B (**2**), a pigment of the slime mould *Arcyria denudata*.[2]



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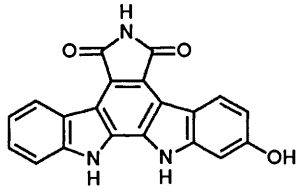

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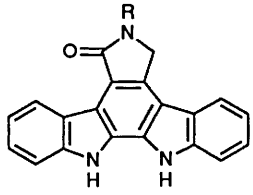

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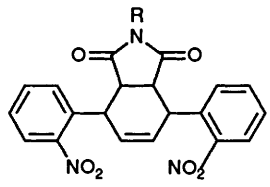
Results and Discussion

The initial approaches were directed to the synthesis of a protected staurosporinone (**9**) whose lactam *N*-protecting group R could either be removed to produce staurosporinone itself (**9**; R = H), or be retained to furnish a useful intermediate for ultimate bis-*N*-glycosylation to an immediate precursor of staurosporine (**1**). In the latter case conditions for the removal of R would have to be compatible with the preservation of the *N*-glycoside linkages. To this end, a Diels–Alder reaction between *N*-benzylmaleimide and (*E,E*)-1,4-bis(2-nitrophenyl)buta-1,4-diene gave the adduct (**3**; R = benzyl) which was dehydrogenated to the substituted terphenyl imide (**4**; R = benzyl) by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). On a preparative scale it proved more convenient to employ dimethyl acetylenedicarboxylate as the dienophile, aromatize the adduct (**5**) with palladium, convert this species into the terphenyl anhydride (**6**); and treat this anhydride with benzylamine to furnish (**4**; R = benzyl). This procedure was obviously more versatile in that treatment of the anhydride (**6**) with suitable primary amines would generate a range of *N*-protected imides of type (**4**).



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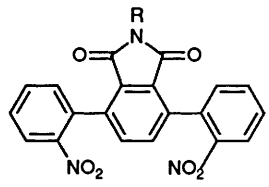

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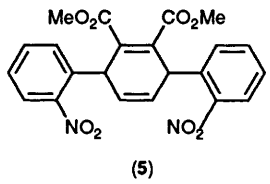

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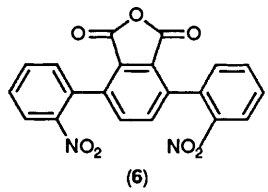
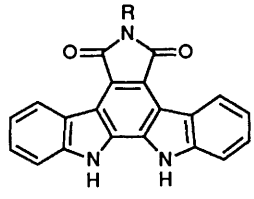


(6)

Deoxygenation of the two nitro groups of (**4**; R = benzyl) with triphenylphosphine gave in good yield the desired indolocarbazole imide (**7**; R = benzyl), formed by insertion of the two resulting nitrene systems into the two C–H bonds of the central benzene ring.[5] A minor by-product was found to be the phenanthridine (**8**) formed by insertion of one of the nitrenes



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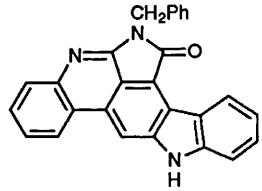

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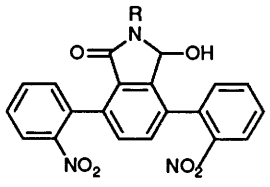
into one of the carbonyl groups of the imide ring. Initially t-butylbenzene was used as solvent but we found that collidine was a much better general medium in this process, especially for precursors of low solubility. The use of triethyl phosphite in this reaction largely gave mixtures of the mono- and di-*N*-ethylated products. Reduction of the imide ring of (**7**; R = benzyl) to the corresponding lactam proved surprisingly difficult. Eventually

a modified Clemmensen reduction[6] was successful and a fair yield of *N*-benzylstaurosporinone (**9**; R = benzyl) was obtained. A more convenient process involved the prior reduction of the terphenyl imide (**4**; R = benzyl) with sodium borohydride[7] to give the corresponding hydroxy lactam (**10**; R = benzyl); this structural unit also occurs in this natural product group (UCN-01). Further reduction with triethylsilyl hydride–trifluoroacetic acid[8] then produced the dinitro lactam (**11**; R = benzyl). Deoxygenation of this lactam with triphenylphosphine effected the required double insertion to give *N*-benzylstaurosporinone (**9**; R = benzyl). Unfortunately, it then proved impossible by any means to remove the *N*-benzyl protecting group to give staurosporinone (**9**; R = H). Applications of the above methods to precursors containing other *N*-protecting groups including 4-methoxybenzyl, 3,4-dimethoxybenzyl, anisyl, allyl, benzyloxymethyl, and 1-oxy-2-picolyl[9] all failed at some point in the sequence.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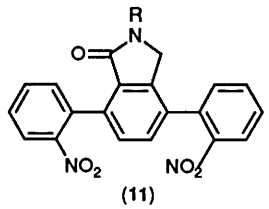
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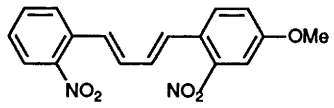
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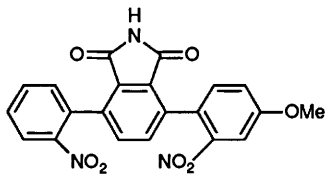
It was then decided to attempt the synthesis without an *N*-protecting group. To this end, prolonged interaction of neat maleimide and (*E*,*E*)-1,4-bis(2-nitrophenyl)buta-1,4-diene gave the adduct (**3**; R = H) converted by treatment with DDQ into the terphenyl imide (**4**; R = H). The latter was more conveniently made by treating the anhydride (**6**) with ammonia. Sequential reduction with borohydride to give (**10**; R = H) followed by triethylsilyl hydride–trifluoroacetic acid treatment produced the lactam (**11**; R = H). Deoxygenation with triphenylphosphine seemed to proceed well but, unfortunately, the staurosporinone produced (**9**; R = H) formed a complex with the generated triphenylphosphine oxide which was so stable that no separation of the two could be achieved. It had been previously noted[10] that such 'complexes are stabilised by strong hydrogen bonds between the phosphoryl oxygen and the proton donor of the substrate.' Accordingly the lactam hydrogen of (**11**; R = H) was removed by treatment with dihydropyran and toluene-*p*-sulphonic acid to yield the protected lactam (**11**; R = tetrahydropyran-2-yl). This underwent smooth deoxygenation with triphenylphosphine to give the protected staurosporinone (**9**; R = tetrahydropyran-2-yl), which was readily convertible to the long-sought staurosporinone (**9**; R = H) by aqueous sulphuric acid treatment.

The starting material for the synthesis of arcyriaflavin B (**2**) was the diene (**12**) obtained by interaction of 2-nitrocinnamaldehyde and the Wittig reagent from 4-methoxy-2-nitrobenzyl bromide (made by an improved procedure from 4-methylphenol). Condensation of (**12**) with neat maleimide and subsequent DDQ dehydrogenation gave the substituted terphenyl (**13**). Triphenylphosphine deoxygenation of (**13**) gave a good yield of *O*-methylarcyriaflavin B (**14**). The low solubility of this highly polar imide complicated the seemingly trivial demethylation step to the free phenol, and most of the standard methods proved ineffectual. It was finally achieved by heating (**14**) with molten pyridine hydrochloride;[11] this gave an excellent yield of arcyriaflavin B, which was identical with the natural product.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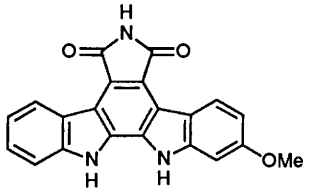
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Experimental

M.p.s were recorded on a Büchi 510 apparatus and are uncorrected. IR spectra were determined on a Perkin-Elmer 297 spectrometer and UV spectra were recorded on a Pye-Unicam SP8-100 instrument. ^{1}H NMR spectra were recorded on Varian EM390A, Bruker WP80, WM250, and WH400 instruments with tetramethylsilane as internal standard. Mass spectra were determined on AEI MS902 and MS30 instruments. Plates coated with Merck Kieselgel 60 F_{254} silica gel were used for analytical and preparative TLC. Merck Kieselgel 60, 70–230 mesh was used for column chromatography.

(E,E)-1,4-*Bis*(2-*nitrophenyl*)*buta*-1,3-*diene*.—Lithium metal (350 mg) was added to dry methanol (75 ml) and a portion of the solution (3 ml) added to further methanol (200 ml), followed successively by 2-nitrocinnamaldehyde (8.85 g) and 2-nitrobenzyltriphenylphosphonium bromide (23.9 g). The remainder of the lithium methoxide solution was then added with stirring over 10 min. (If this sequence was not followed, much 2-nitrocinnamaldehyde dimethyl acetal was formed.) The mixture was stirred at room temperature for 20 min and at 0 °C for 15 min. The resulting crystalline precipitate was filtered off, washed with a little cold methanol, suspended in toluene (75 ml), and stirred with iodine (20 mg) for 48 h. Filtration of the cooled (0 °C) mixture and crystallisation from toluene gave the (*E*,*E*)-diene as yellow needles (11.1 g, 75%), m.p. 195–196 °C (lit.,[12] 219–220 °C). Repeated recrystallisation did not raise the melting point (Found: C, 64.7; H, 4.25; N, 9.5. Calc. for $C_{16}H_{12}N_2O_4$: C, 64.85; H, 4.1; N, 9.45%); λ_{max}(EtOH) 292 and 350 nm (ε 19 500 and 12 000 dm^3 mol^{-1} cm^{-1}); ν_{max}($CHCl_3$) 1 512, 1 348, and 985 cm^{-1}; δ_H($CDCl_3$; 250 MHz) 6.99 (2 H, m, 1-H or 2-H), 7.26 (2 H, m, 2-H or 1-H), 7.41 (2 H, ddd, *J* 1.3, 7.6, and 7.9 Hz, 5′-H), 7.60 (2 H, ddd, *J* 1, 3, 7.6, and 8.1 Hz, 4′-H), 7.74 (2 H, dd, *J* 1.3 and 7.9 Hz, 6′-H), and 7.94 (2 H, dd, *J* 1.2 and 8.2 Hz, 3′-H); *m*/*z* 296 (M^+, 8%), 119 (83), 92 (100), and 91 (60).

N-*Benzyl*-1,2,3,6-*tetrahydro*-3,6-*bis*(2-*nitrophenyl*)*phthalimide* (**3**; R = benzyl).—A solution of the above diene (1 g) and *N*-benzylmaleimide (1.28 g) in toluene (25 ml) was heated at reflux under nitrogen for 5 days. The mixture was cooled in ice and the solid filtered off and washed with carbon tetrachloride. Crystallisation from toluene gave the *adduct* (**3**; R = benzyl) as

needles (1.35 g, 83%), m.p. 222–223 °C (Found: C, 67.1; H, 4.1; N, 8.7. $C_{27}H_{21}N_3O_6$ requires C, 67.05; H, 4.4; N, 8.7%); λ_{max}(EtOH) 255 nm (ε 11 000 dm^3 mol^{-1} cm^{-1}); ν_{max}($CHCl_3$) 1 775, 1 705, 1 530, and 1 345 cm^{-1}; δ_H($CDCl_3$; 90 MHz) 4.00 (2 H, m, 1- and 2-H, or 3- and 6-H), 4.20 (2 H, m, 3- and 6-H, or 1- and 2-H), 4.47 (2 H, s, CH_2Ph), 6.25 (2 H, s, 4- and 5-H), 7.2–7.6 (11 H, m, aromatic H), and 7.97 (2 H, dd, *J* 2 and 7 Hz, 3′-H); *m/z* 483 (M^+, 2%) 287 (88), 271 (100), and 91 (95).

Dimethyl 3,6-*Dihydro*-3,6-*bis*(2-*nitrophenyl*)*phthalate* (**5**).—A solution of the above diene (10 g) in an excess of dimethyl acetylenedicarboxylate (16.6 ml) was heated at 120 °C under nitrogen for 36 h. The ice-cooled reaction mixture was triturated with carbon tetrachloride. The resulting solid was filtered off, washed with carbon tetrachloride and crystallised from toluene to give the *adduct* (**5**) as pale yellow prisms (11.6 g, 79%), m.p. 178–180 °C (Found: C, 60.0; H, 4.2; N, 6.35. $C_{22}H_{18}N_2O_8$ requires C, 60.25; H, 4.15; N, 6.4%); λ_{max}(EtOH) 244sh and 276sh (ε 11 000 and 6 900 dm^3 mol^{-1} cm^{-1}); ν_{max}($CHCl_3$) 1 728, 1 518, and 1 353 cm^{-1}; δ_H($CDCl_3$; 90 MHz) 3.53 (6 H, s, OCH_3), 5.22 (2 H, s, 3 and 6-H), 5.95 (2 H, s, 4 and 5-H), 7.25–7.75 (6 H, m, 4′, 5′, and 6′-H), and 7.94 (2 H, dd, *J* 2 and 8 Hz, 3′-H); *m/z* 390 ($M^+ - H_2 - NO_2$, 100%).

3,6-*Bis*(2-*nitrophenyl*)*phthalic Anhydride* (**6**).—A solution of the diester (**5**) (8.76 g) in mesitylene (80 ml) was heated under reflux with palladium black (100 mg) for 7 h. The cooled mixture was diluted with dichloromethane (250 ml) and filtered through Celite and Florisil. Evaporation of the solvent and crystallisation from toluene gave *dimethyl* 3,6-*bis*(2-*nitrophenyl*)-*phthalate* (7.1 g, 82%) as prisms, m.p. 172–174 °C (Found: C, 60.25; H, 3.8; N, 6.5. $C_{22}H_{16}N_2O_8$ requires C, 60.55; H, 3.7; N, 6.4%); δ_H($CDCl_3$; 90 MHz) 3.49 (6 H, s, OCH_3), 7.2–7.75 (8 H, m, aromatic H), and 8.13 (2 H, dd, *J* 2 and 7 Hz, 3′-H). This diester (5.2 g) was heated under reflux for 7 h with a solution of sodium hydroxide (2.4 g) in water and methanol (35 ml), the resulting solution diluted with water (300 ml) and acidified with 2M hydrochloric acid. The mixture was extracted with ethyl acetate (3 × 50 ml) and the combined extracts were washed with water and brine, dried ($MgSO_4$), and evaporated to give the crude solid diacid which was heated with acetic anhydride (50 ml) at 100 °C for 3 h. Removal of the solvent under reduced pressure gave the *anhydride* (**6**) (4.3 g, 92%) which crystallised from toluene as prisms, m.p. 256–257 °C; ν_{max}($CHCl_3$) 1 855, 1 775, 1 525, and 1 350 cm^{-1}; δ_H($CDCl_3$; 80 MHz) 7.2–7.9 (8 H, m, aromatic H), and 8.30 (2 H, dd, *J* 2 and 7 Hz, 3′-H); *m/z* 344 ($M^+ - NO_2$, 68%), 298 ($M^+ - 2 - NO_2$, 100), and 270 (42).

N-*Benzyl*-3,6-*bis*(2-*nitrophenyl*)*phthalimide* (**4**; R = benzyl).—*Method* 1. A solution of DDQ (4.4 g) and the tetrahydrophthalimide (**3**; R = benzyl) (4.3 g) in t-butylbenzene (60 ml) was heated at reflux under nitrogen for 16 h. The solvent was evaporated and the residual solid extracted with dichloromethane (8 × 20 ml) and the solvent evaporated again. The residue was triturated with hot ethanol and then cooled and filtered. The solid crystallised from toluene to give the *phthalimide* (**4**; R = benzyl) (4.3 g, 79%) as needles, m.p. 242–244 °C (Found: C, 67.55; H, 3.75; N, 8.7. $C_{27}H_{17}N_3O_6$ requires C, 67.6; H, 3.5; N, 8.75%) λ_{max}(EtOH) 296 and 328 nm (ε 6 500 and 39 800 dm^3 mol^{-1} cm^{-1}); ν_{max}($CHCl_3$) 1 772, 1 713, 1 520, and 1 352 cm^{-1}; δ_H($CDCl_3$; 90 MHz) 4.62 (2 H, s, CH_2Ph), 7.13 (5 H, s, Ph), 7.3–7.8 (8 H, m, aromatic H), and 8.12 (2 H, dd, *J* 2 and 6 Hz, 3′-H); *m/z* 479 (M^+, 11%), 433 (40), and 91 (100).

Method 2. A solution of the phthalic anhydride (**6**) (975 mg) and benzylamine (0.3 ml) in toluene (50 ml) was heated under reflux for 30 min. Evaporation and work-up of the residue as above gave the phthalimide (**4**; R = benzyl) (943 mg, 79%).

6-*Benzyl*-12,13-*dihydro*-6H-*indolo*[2,3-a]*pyrrolo*[3,4-c]*carbazole*-5,7-*dione* (**7**; R = benzyl) *and* 6-*Benzyl*-12H-*indolo*[3,2-j]-*pyrrolo*[2,3,4-g,h]*phenanthridin*-7(6H)-*one* (**8**).—A solution of the *N*-benzylphthalimide (**4**; 479 mg) and triphenylphosphine (1.3 g) in t-butylbenzene or collidine (20 ml) was heated at reflux under nitrogen for 20 h. The solvent was removed under reduced pressure and the residue chromatographed on silica gel using toluene–acetone (9:1) as eluant to yield the *indolocarbazole* (**7**; R = benzyl) (352 mg, 85%), m.p. >280 °C (Found: C, 78.0; H, 4.2; N, 9.65. $C_{27}H_{17}N_3O_2$ requires C, 78.05; H, 4.1; N, 10.1%) λ_{max}(EtOH) 224, 272sh, 282, 304sh, 316, and 402 nm (ε 24 000, 10 700, 15 800, 15 900, 23 400, and 2 300 dm^3 mol^{-1} cm^{-1}); ν_{max}($CHCl_3$) 3 270, 1 750, 1 695, and 1 565 cm^{-1}; δ_H([$^2H_6$]DMSO; 250 MHz) 4.91 (2 H, s, CH_2Ph), 7.26–7.45 (7 H, m, 3- and 9-H and Ph), 7.56 (2 H, ddd, *J* 1.2, 7.2, and 8.2 Hz, 2- and 10-H), 7.80 (2 H, d, *J* 8.2 Hz, 1- and 11-H), 8.08 (2 H, s, NH), and 9.98 (2 H, d, *J* 7.9 Hz, 4- and 8-H); *m/z* 415 (M^+, 100%) and 91 (21). Also obtained from this reaction was the *phenanthridine* (**8**) (44 mg, 11%) (Found: M^+, 399.1399. $C_{27}H_{17}N_3O$ requires *M*, 399.1372); λ_{max}(EtOH) 218, 234, 257, 275, 384sh, 311, 360, and 415 nm (ε 16 200, 13 500, 6 000, 5 600, 4 200, 740, 6 800, and 2 600 dm^3 mol^{-1} cm^{-1}); ν_{max}($CHCl_3$) 3 420, 1 700, and 1 660 cm^{-1}; δ_H([$^2H_6$]DMSO; 90 MHz) 5.30 (2 H, s, CH_2Ph), 7.0–7.7 (10 H, m, aromatic H), 8.3 (2 H, m, 1-H and aromatic H), 8.53 (1 H, s, 13-H), 9.35 (1 H, d, *J* 8 Hz, 8-H), and 12.0 (1 H, s, NH); *m/z* 399 (M^+, 36%), 282 (59), 254 (67), and 91 (100).

6-*Benzyl*-12,13-*dihydro*-7H-*indolo*[2,3-a]*pyrrolo*[3,4-c]*carbazol*-5(6H)-*one* (**9**; R = benzyl).—A solution of the indolocarbazole (**7**; R = benzyl) (104 mg) in hot ethanol (5 ml) was treated with zinc amalgam (200 mg) and the mixture heated under reflux while hydrochloric acid (6M; 1 ml) was added dropwise. After 30 min the process was repeated with further zinc amalgam (100 mg) and acid (6M; 1 ml) and the mixture heated under reflux for a further 30 min. The mixture was diluted with water, extracted with ethyl acetate and the extract washed (water then brine), dried ($MgSO_4$), and evaporated to give N-*benzylstaurosporinone* (**9**; R = benzyl) as a pale yellow solid (71 mg, 71%), m.p. >280 °C (Found: M^+, 401.1532. $C_{27}H_{19}N_3O$ requires *M*, 401.1528); λ_{max}(MeOH) 235, 268sh, 293, 334, 344, and 361 nm (ε 43 100, 50 100, 86 100, 20 100, 16 300, and 11 000 dm^3 mol^{-1} cm^{-1}); ν_{max}($CHCl_3$) 3 280, 1 665, 1 590, 1 405, 1 325, 1 160, and 1 120 cm^{-1}; δ_H([$^2H_6$]DMSO; 100 MHz) 4.99 (2 H, s, CH_2Ph or 7-H), 5.05 (2 H, s, 7-H or CH_2Ph), 7.2–7.9 (6 H, m, aromatic H), 8.05 (1 H, d, 8-H), 9.34 (1 H, d, *J* 7 Hz, 4-H), 11.47 (1 H, s, 12-H or 13-H), and 11.64 (1 H, s, 13-H or 12-H); *m/z* 401 (M^+, 94%), 310 (44), 196 (52), 179 (75), and 91 (100). An alternative preparation for this lactam is given below.

2-*Benzyl*-3-*hydroxy*-4,7-*bis*(2-*nitrophenyl*)*isoindol*-1-*one* (**10**; R = benzyl).—Sodium borohydride (143 mg) was added in one portion to a solution of the phthalimide (**4**; R = benzyl) (600 mg) in THF (10 ml) and ethanol (2 ml). To the stirred mixture hydrochloric acid (2M) was added at a rate of two drops every 5 min until the effervescence ceased (*ca.* 1 h). The mixture was diluted with water, acidified with HCl, and extracted with ethyl acetate, and the extract was then washed (water then brine), dried ($MgSO_4$), and evaporated to give the isoindolone (**10**; R = benzyl) as a foam (587 mg, 98%). A sample crystallised from aqueous ethanol as plates, m.p. 177–178 °C (Found: C, 67.2; H, 3.85; N, 8.55. $C_{27}H_{19}N_3O_6$ requires C, 67.35; H, 4.0; N, 8.75%); λ_{max}(EtOH) 220 and 288 nm (ε 44 000 and 9 200 dm^3 mol^{-1} cm^{-1}); ν_{max}($CHCl_3$) 3 480, 1 720, 1 530, and 1 365 cm^{-1}; δ_H($CDCl_3$; 90 MHz) 2.55 (1 H, br s, OH), 4.25 (1 H, d, *J* 15 Hz, C*H*HPh), 4.90 (1 H, d, *J* 15 Hz, CH*H*Ph), 5.50 (1 H, br d, *J* 10 Hz, C*H*OH), 7.28 (5 H, s, Ph), 7.40 (2 H, s, 5- and 6-H), 7.35–7.80 (6 H, m, aromatic H), and 8.0–8.3 (2 H, m, 3′-H).

2-Benzyl-4,7-bis(2-nitrophenyl)isoindol-1-one (**11**; R = benzyl).—Triethylsilane (0.48 ml) was added in one portion to a stirred solution of the isoindolone (**10**; R = benzyl) (960 mg) in trifluoroacetic acid (5 ml). After 30 min ethyl acetate (50 ml) was added and the solution washed repeatedly with saturated aqueous sodium hydrogen carbonate. The washings were further extracted with ethyl acetate. The combined extracts were washed (water then brine), dried ($MgSO_4$), and evaporated. The solid residue was crystallised from methanol to give the isoindolone (**11**; R = benzyl) (620 mg, 73%) as octahedra, m.p. 178–179 °C (Found: C, 69.6; H, 4.35; N, 9.2. $C_{27}H_{19}N_3O_5$ requires C, 69.65; H, 4.1; N, 9.05%); λ_{max}(EtOH) 236 nm (ε 29 500 dm^3 mol^{-1} cm^{-1}); ν_{max}($CHCl_3$) 1 690, 1 520, and 1 355 cm^{-1}; δ_H($CDCl_3$; 90 MHz) 4.05 (2 H, s, 3-H), 4.65 (2 H, s, CH_2Ph), 7.30 (5 H, s, Ph), 7.46 (2 H, s, 5- and 6-H), 7.4–7.8 (6 H, m, aromatic H), 8.10 (1 H, dd, *J* 3 and 7 Hz, 3′- or 3″-H), and 8.30 (1 H, dd, *J* 3 and 7 Hz, 3″- or 3′-H); *m/z* 465 (M^+, 1%), 419 (16), and 91 (100).

Deoxygenation of this isoindolone (100 mg) with triphenylphosphine (338 mg) in refluxing collidine (3 ml) for 42 h, followed by work-up and chromatography on silica gel using dichloromethane–acetone (20:1) gave the indolocarbazole lactam (**9**; R = benzyl) (58 mg, 67%) identical with the compound prepared as above.

3,6-Bis(2-nitrophenyl)phthalimide (**4**; R = H).—The anhydride (**6**) (2.5 g) was suspended in aqueous ammonia (*d* 0.880; 25 ml) and the mixture stirred at room temperature for 6 h. Toluene (25 ml) was then added and the mixture carefully heated to reflux for 15 h. Addition of water (100 ml) and acidification with hydrochloric acid was followed by extraction with ethyl acetate. The extract was washed (water then brine), dried ($MgSO_4$), and evaporated to give the *phthalimide* (**4**; R = H) (2.2 g, 88%) which crystallised from ethanol as plates, m.p. 261–262 °C (Found: C, 61.7; H, 3.0; N, 10.7. $C_{20}H_{11}N_3O_6$ requires C, 61.7; H, 2.85; N, 10.8%); λ_{max}(EtOH) 223 and 295sh nm (ε 49 200 and 7 000 dm^3 mol^{-1} cm^{-1}); ν_{max}($CHCl_3$) 3 425, 1 780, 1 740, 1 522, and 1 351 cm^{-1}; δ_H([$^2H_6$]DMSO; 90 MHz) 7.80 (2 H, s, 4- and 5-H), 7.45–7.95 (6 H, m, aromatic H), 8.23 (2 H, dd, *J* 2 and 7 Hz, 3′-H), and 11.35 (1 H, br s, NH); *m/z* 343 (M^+ − NO_2, 100%), 295 (51), 239 (55), and 212 (52).

4,7-Bis(2-nitrophenyl)isoindol-1-one (**11**; R = H).—Sodium borohydride (106 mg) was added in one portion to a solution of the phthalimide (**4**; R = H) (440 mg) in THF (5 ml) and ethanol (1 ml). Hydrochloric acid (2M) was slowly added dropwise until effervescence ceased. The mixture was diluted with water, extracted with ethyl acetate, and the extract washed (water then brine), dried ($MgSO_4$), and evaporated to give the hydroxyisoindolone (**10**; R = H) (440 mg) which was used in the next step without purification. Crystallisation of a sample from methanol gave prisms, m.p. 163–166 °C; δ_H([$^2H_6$]DMSO; 80 MHz) 5.67 (1 H, d, *J* 8 Hz, C*H*OH), 6.10 (1 H, br d, exchanged with D_2O, OH), 7.4–8.0 (8 H, m, aromatic H), 8.15 (2 H, dd, *J* 2 and 7 Hz, 3′-H, and 8.77 (1 H, br s, exchanged with D_2O, NH). To a solution of this product (340 mg) in trifluoroacetic acid (2 ml) was added, with vigorous stirring, triethylsilane (0.21 ml). After 30 min ethyl acetate (25 ml) was added and the solution washed with aqueous sodium hydrogen carbonate and the washings further extracted with ethyl acetate. The combined extracts were washed (water then brine), dried ($MgSO_4$), and evaporated and the residue chromatographed on silica gel using dichloromethane–methanol (19:1) as eluant. Crystallisation from ethanol gave the *isoindolone* (**11**; R = H) (310 mg, 95%) as prisms, m.p. 237–238 °C (Found: C, 63.5; H, 3.55; N, 11.05. $C_{20}H_{13}N_3O_5$ requires C, 64.0; H, 3.5; N, 11.3%); λ_{max}(EtOH) 235sh and 276sh nm (ε 19 200 and 6 100 dm^3 mol^{-1} cm^{-1}); ν_{max}($CHCl_3$) 3 460, 1 705, 1 525, and 1 325 cm^{-1}; δ_H([$^2H_6$]DMSO; 80 MHz) 4.16 (2 H, s, CH_2), 7.4–7.9 (8 H, m, aromatic H), 8.05–8.2 (2 H, m, 3′-H), and 8.53 (1 H, br s, NH); *m/z* 329 (M^+ − NO_2, 100%) and 284 (35).

2-(Tetrahydropyran-2-yl)-4,7-bis(2-nitrophenyl)isoindol-1-one (**11**; R = tetrahydropyran-2-yl).—A solution of the isoindolone (**11**; R = H) (150 mg), dihydropyran (170 mg), and toluene-*p*-sulphonic acid (10 mg) in dichloromethane (5 ml) was stirred at room temperature under nitrogen for 15 h. Water and dichloromethane were added and the organic phase was separated, washed with saturated aqueous sodium hydrogen carbonate and then water, and dried (Na_2SO_4). Evaporation followed by chromatography of the residue on silica gel using ethyl acetate–hexane (1:1) as eluant gave the *isoindolone* (**11**; R = tetrahydropyran-2-yl) as a gum (130 mg, 72%) which crystallised from ethyl acetate as a crystalline powder, m.p. 133–137 °C (Found: M^+, 459.1390. $C_{25}H_{21}N_3O_6$ requires *M*, 459.1350); λ_{max}(EtOH) 228 nm (ε 22 300 dm^3 mol^{-1} cm^{-1}); ν_{max}($CHCl_3$) 1 690, 1 505, and 1 380 cm^{-1}; δ_H($CDCl_3$; 250 MHz) 1.50–1.88 (6 H, m, $CH_2CH_2CH_2$) 3.53–3.85 (2 H, m, OCH_2), 5.28 (2 H, m, CH_2), 6.01 (1 H, br s, OCHN), 7.33–7.75 (8 H, aromatic H), 8.05 (1 H, d, *J* 8 Hz, 3′- or 3″-H), and 8.20 (1 H, d, *J* 8 Hz, 3″- or 3′-H).

6-(Tetrahydropyran-2-yl)-12,13-dihydro-7H-indolo[2,3-a]pyrrolo[3,4-c]carbazole (**9**; R = tetrahydropyran-2-yl).—A solution of the isoindolone (**11**; R = tetrahydropyran-2-yl) (100 mg) and triphenylphosphine (310 mg) in collidine (10 ml) was heated under reflux for 40 h. Evaporation under reduced pressure and flash chromatography of the residue on silica gel using ethyl acetate–hexane (2:1) as eluant gave N-*(tetrahydropyran-2-yl)staurosporinone* (**9**; R = tetrahydropyran-2-yl) as a yellow solid (42 mg, 54%), m.p. 261–268 °C (decomp.) (Found: M^+, 395.1642. $C_{25}H_{21}N_3O_2$ requires *M*, 395.1650); λ_{max}(MeOH) 241, 270sh, 301, 318sh, and 360 nm (ε 27 000, 52 700, 81 200, 16 000, and 12 700 dm^3 mol^{-1} cm^{-1}); ν_{max}($CHCl_3$) 3 340 and 1 685 cm^{-1}; δ_H([$^2H_6$]DMSO; 250 MHz) 1.79–2.05 (6 H, m, $CH_2CH_2CH_2$), 3.70–4.04 (2 H, m, OCH_2), 5.12 (2 H, s, lactam CH_2), 5.58 (1 H, m, OCHN), 7.22–7.70 (6 H, m, aromatic H), 8.12 (1 H, d, *J* 7 Hz, 8-H), 9.43 (1 H, d, *J* 7 Hz, 4-H), 10.69 (1 H, br s, NH), and 10.87 (1 H, br s, NH).

Staurosporinone (**9**; R = H).—A solution of *N*-(tetrahydropyran-2-yl)staurosporinone (30 mg) in THF (5 ml) and aqueous sulphuric acid (2M; 4 ml) was heated at 50 °C for 2 h. The resulting suspension was diluted with water and extracted with ethyl acetate. The organic phase was washed (water then brine), dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel using ethyl acetate–hexane (2:1) as eluant, to give staurosporinone (20 mg, 80%) as a pale yellow powder m.p. >310 °C (Found: M^+, 311.1030. Calc. for $C_{20}H_{13}N_3O$: M^+, 311.1058); λ_{max}(MeOH) 235sh, 290, 320, 335, 346, and 358 nm (ε 28 000, 82 000, 12 000, 21 700, 8 100, and 18 200 dm^3 mol^{-1} cm^{-1}); ν_{max}(Nujol) 3 390 and 1 670 cm^{-1}; δ_H([$^2H_6$]-DMSO; 250 MHz) [values reported for the natural product in square brackets] 4.96 (2 H, s, lactam CH_2) [4.98], 7.25 (1 H, t) [7.24], 7.33 (1 H, t) [7.31], 7.42 (1 H, t) [7.44], 7.47 (1 H, t) [7.48], 7.72 (1 H, d, *J* 8 Hz) [7.73, d, *J* 8.1 Hz], 7.78 (1 H, d, *J* 8 Hz) [7.79, d, *J* 8.1 Hz], 8.04 (1 H, d, *J* 8 Hz) [8.05, d, *J* 7.8 Hz], 8.49 (1 H, br s, lactam NH) [8.49], 9.21 (1 H, d, *J* 8 Hz) [9.24, d, *J* 7.9 Hz], 11.35 (1 H, br s, NH) [11.38], and 11.52 (1 H, br s, NH) [11.56].

4-Methoxy-2-nitrobenzyl Bromide.—*p*-Tolyl methanesulphonate[13] (28 g) was dissolved in concentrated sulphuric acid at 0 °C and a mixture of concentrated nitric acid (10 ml) and concentrated sulphuric acid (25 ml) was added dropwise, the temperature being kept below 0 °C. The mixture was stirred at

0 °C for 10 min and then poured onto ice. The precipitated solid was filtered off, washed well with water, and air-dried. The crude product was dissolved in dichloromethane and treated with $MgSO_4$ and charcoal for 1 h. Filtration, evaporation, and crystallisation of the residue from dichloromethane–hexane gave *4-methyl-3-nitrophenyl methanesulphonate* as pale yellow needles (23 g, 66%), m.p. 105–105.5 °C (Found: C, 41.3; H, 3.7; N, 6.2. $C_8H_9NO_5S$ requires C, 41.66; H, 3.9; N, 6.05%); λ_{max}(EtOH) 208, 253, and 290 nm (ε 15 800, 5 100, and 1 900 dm^3 mol^{-1} cm^{-1}); ν_{max}($CHCl_3$) 1 522, 1 380, 1 352, and 1 165 cm^{-1}; δ_H($CDCl_3$; 90 MHz) 2.59 (3 H, s, CH_3Ar), 3.23 (3 H, s, CH_3SO_2), 7.40 (1 H, d, *J* 8 Hz, 5-H), 7.50 (1 H, dd, *J* 2 and 8 Hz, 6-H), and 7.90 (1 H, d, *J* 2 Hz, 2-H); *m/z* 231 (M^+, 36%), 214 (72), 136 (98), 108 (66), 105 (100), and 77 (71). Basic hydrolysis of this product and methylation of the resulting phenol with dimethyl sulphate[14] gave the methyl ether. Treatment of this 4-methyl-3-nitroanisole with *N*-bromosuccinimide in carbon tetrachloride[15] gave 4-methoxy-2-nitrobenzyl bromide which crystallised from hexane, m.p. 63–64 °C (lit.,[15] 62–63 °C).

(E,E)-1-(2-*Nitrophenyl*)-4-(4-*methoxy*-2-*nitrophenyl*)*buta*-1,3-*diene* (**12**).—A solution of the foregoing benzyl bromide (6.15 g) and triphenylphosphine (7.2 g) in toluene (25 ml) was stirred at room temperature for 16 h. The chilled mixture was filtered and the solid washed with cold toluene to give the *phosphonium bromide* (11.46 g, 86%). A sample crystallised from ethanol as yellow prisms, m.p. 241–242 °C (Found: C, 60.95; H, 4.55; N, 2.75. $C_{26}H_{23}BrNO_3P$ requires C, 61.4; H, 4.55; N, 2.75%). The bromide (9.2 g), 2-nitrocinnamaldehyde (3.2 g), potassium carbonate (2.9 g), and a few crystals of 18-crown-6 were added successively to dichloromethane (150 ml) and the mixture stirred at room temperature for 36 h. The mixture was filtered and the solids washed with dichloromethane. Evaporation and chromatography of the residue on silica gel using chloroform as eluant gave the diene as a mixture of geometrical isomers (4.68 g, 80%). This mixture was suspended in toluene and stirred with a crystal of iodine for 16 h. Evaporation and crystallisation from toluene gave the (E,E)-*diene* (**12**) as orange prisms, m.p. 171–172 °C (Found: C, 62.3; H, 4.25; N, 8.4. $C_{17}H_{14}N_2O_5$ requires C, 62.55; H, 4.3; N, 8.6%); λ_{max}(EtOH) 236, 282sh, 306, and 358sh nm (ε 16 600, 19 900, 22 600, and 13 200 dm^3 mol^{-1} cm^{-1}); ν_{max}($CHCl_3$) 2 860, 1 607, 1 516, 1 348, 1 035, and 987 cm^{-1}; δ_H($CDCl_3$; 90 MHz) 3.85 (3 H, s, OCH_3), 6.8–7.8 (10 H, m, olefinic and aromatic H), and 7.92 (1 H, dd, *J* 2 and 8 Hz, 3′-H); *m/z* 326 (M^+, 6%), 189 (50), 146 (60), 134 (47), 132 (53), 119 (63), and 92 (100).

3-(2-*Nitrophenyl*)-6-(4-*methoxy*-2-*nitrophenyl*)*phthalimide* (**13**).—An intimate mixture of the diene (**12**) (1.63 g) and maleimide (1.92 g) was heated at 120 °C under nitrogen for 24 h with periodic return of sublimed maleimide to the melt. The excess of sublimed maleimide was separated and the residue chromatographed on silica gel using chloroform–methanol (9:1) as eluant. The resulting *adduct* (2.01 g, 95%) crystallised from aqueous acetic acid as prisms, m.p. 238–239 °C (Found: C, 59.6; H, 4.15; N, 10.2%; M^+, 423. $C_{21}H_{17}N_3O_7$ requires C, 59.55; H, 4.05; N, 9.95%; *M*, 423). A solution of the adduct (846 mg) in t-butylbenzene (15 ml) was heated with DDQ (1 g) at 170 °C under nitrogen for 2 h. Evaporation and purification by chromatography on silica gel with dichloromethane–methanol (50:1) as eluant gave the *phthalimide* (**13**) (660 mg, 79%) which crystallised from ethanol as needles, m.p. 232–233 °C (Found: C, 60.05; H, 3.35; N, 10.05. $C_{21}H_{13}N_3O_7$ requires C, 60.15; H, 3.1; N, 10.0%); λ_{max}(EtOH) 222, 229sh, 239sh, and 310 nm (ε 71 200, 69 300, 56 800, and 8 200 dm^3 mol^{-1} cm^{-1}); ν_{max}($CHCl_3$) 3 430, 2 850, 1 778, 1 740, 1 528, and 1 360 cm^{-1}; δ_H($CDCl_3$; 90 MHz) 3.94 (3 H, s, OCH_3), 7.35–7.95 (7 H, m, aromatic H), 7.70 (2 H, s, 4- and 5-H), 8.2 (1 H, dd, *J* 2 and 7 Hz, 3′-H), and 11.30 (1 H, s, exchanged with D_2O, NH); *m/z* 419 (M^+, 1%), 373 (33), 91 (78), and 57 (100).

O-*Methylarcyriaflavin B* (**14**).—A solution of the phthalimide (**13**) (500 mg) and triphenylphosphine (1.57 g) in collidine (10 ml) was heated at reflux under nitrogen for 40 h. Evaporation under reduced pressure and flash chromatography on silica gel using dichloromethane–acetone (6:1) as eluant gave O-*methylarcyriaflavin B* (**14**) (274 mg, 65%) which crystallised slowly from acetone as yellow needles, m.p. >325 °C (Found: M^+, 355.0946. $C_{21}H_{13}N_3O_3$ requires *M*, 355.0957); λ_{max}(EtOH) 231, 254, 272, 280, 323, and 413 nm (ε 52 500, 19 500, 20 400, 24 000, 64 600, and 7 600 dm^3 mol^{-1} cm^{-1}); ν_{max}(KBr) 1 740 and 1 695 cm^{-1}; δ_H([$^2H_6$]DMSO; 400 MHz) 3.92 (3 H, s, OCH_3), 6.97 (1 H, d, *J* 8.6 Hz, 3-H), 7.33 (2 H, m, 3-H and 9- or 10-H), 7.53 (1 H, m, 10- or 9-H), 7.78 (1 H, d, *J* 7.9 Hz, 11-H), 8.82 (1 H, d, *J* 8.5 Hz, 4-H), 8.97 (1 H, d, *J* 7.9 Hz, 8-H), 10.93 (1 H, s, imide NH), 11.64 (1 H, s, NH), and 11.78 (1 H, s, NH).

Arcyriaflavin B (**2**).—An intimate mixture of the methyl ether (**14**) (50 mg) and pyridine hydrochloride (250 mg) was heated at 190 °C in a sealed tube for 2 h. The reaction mixture was treated with water and extracted with ethyl acetate. The extract was washed (water then brine), dried (Na_2SO_4), and evaporated. Preparative layer chromatography of the residue using dichloromethane–acetone (2:1) as eluant gave arcyriaflavin B (**2**) (42 mg, 87%) which crystallised slowly from acetone as yellow needles, m.p. >325 °C, identical in properties with an authentic sample (Found: M^+, 341.0802. $C_{20}H_{11}N_3O_3$ requires *M*, 341.0800); λ_{max}(MeOH) 230, 272, 282, 324, and 415 nm (ε 26 000, 10 200, 11 300, 31 300, and 3 800 dm^3 mol^{-1} cm^{-1}); ν_{max}(KBr) 1 735 and 1 690 cm^{-1}; δ_H($CDCl_3$; 250 MHz) 6.92 (1 H, dd, *J* 2.2 and 8.6 Hz, 3-H), 7.10 (1 H, d, *J* 2.0 Hz, 1-H), 7.34 (1 H, ddd, *J* 1.0, 7.1 and 8.1 Hz, 9-H), 7.52 (1 H, ddd, *J* 1.2, 7.1, and 8.2 Hz, 10-H), 7.67 (1 H, d, *J* 8.2 Hz, 11-H), 8.72 (1 H, s, OH), 8.93 (1 H, d, *J* 8.7 Hz, 4-H), 9.13 (1 H, d, *J* 8.1 Hz, 8-H), 9.74 (1 H, br s, 6-H), and 10.83 (2 H, br s, 12- and 13-H).

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