Formal Synthesis of the Antitumour Antibiotic CC-1065

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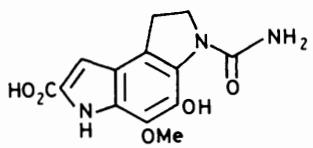
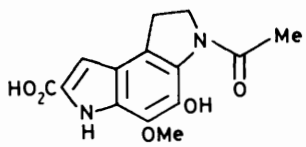
A formal total synthesis of the potent antitumour antibiotic CC-1065 (**1**) is described; both the cyclopropapyrroloindole (**2**) and the 'dimeric' pyrroloindole (**3**) are synthesized by routes involving vinyl azide chemistry. The cyclopropapyrroloindole (**2**) is prepared from 5-benzyloxy-2-bromoacetophenone (Schemes 3—5), the key steps being the formation of both indoles by decomposition of the azides (**9**) and (**13**). The dimer (**3**) is prepared by coupling the monomeric pyrroloindoles (**25**) and (**27**), followed by functional group transformations (Scheme 7).

The antibiotic CC-1065 (**1**), isolated from *Streptomyces zelensis* in 1978 by workers at the Upjohn Company,[1,2] is one of the most potent antitumour agents known.[3–5] On treatment with alkali, CC-1065 (**1**) is degraded into two fragments, the cyclopropapyrroloindole (**2**), variously referred to as the left-hand- or A-unit or as CPI, and the 'dimeric' pyrroloindole (B/C-unit) (**3**) (Scheme 1).[6] The dimer (**3**) is also known as PDE-I dimer because of its relationship to the naturally occurring phosphodiesterase inhibitors PDE-I (**4**) and PDE-II (**5**). Since the alkaline fragmentation is also the obvious retrosynthetic disconnection for CC-1065 (**1**), and because of the potent biological activity of the antibiotic, the pyrroloindoles CPI(**2**), PDE-I (**4**), and PDE-II (**5**) have been the subject of intense synthetic effort.[7–34]

Our own work in this area has centred on the use of vinyl azide chemistry to construct the pyrrole/indole rings, and has resulted in the successful total synthesis of the pyrroloindoles PDE-I (**4**) and PDE-II (**5**),[32] the cyclopropapyrroloindole CPI (**2**),[33] and PDE-I dimer (**3**).[34] We now report the full details of this work which constitutes a formal total synthesis of CC-1065 (**1**), in which, interestingly, *all* six ring nitrogen atoms are derived, ultimately, from sodium azide.



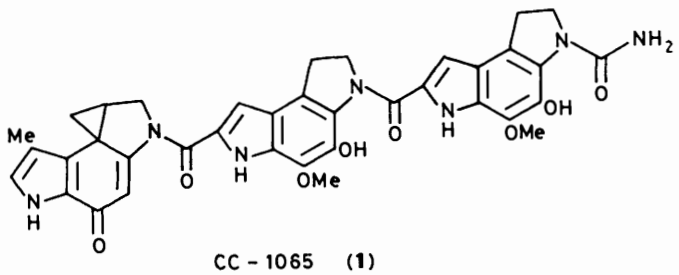
PDE - I (**4**)



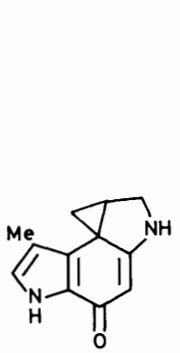
PDE - II (**5**)

Results and Discussion

Synthesis of the Left-hand Cyclopropapyrroloindole Unit.— The basis of our synthetic approach to the pyrroloindoles PDE-I (**4**) and PDE-II (**5**) was the thermal decomposition of azidocinnamates, readily prepared from aromatic aldehydes. In

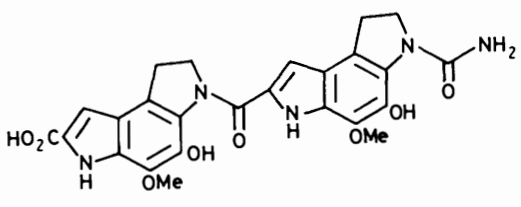


CC - 1065 (**1**)



CPI (**2**)

+

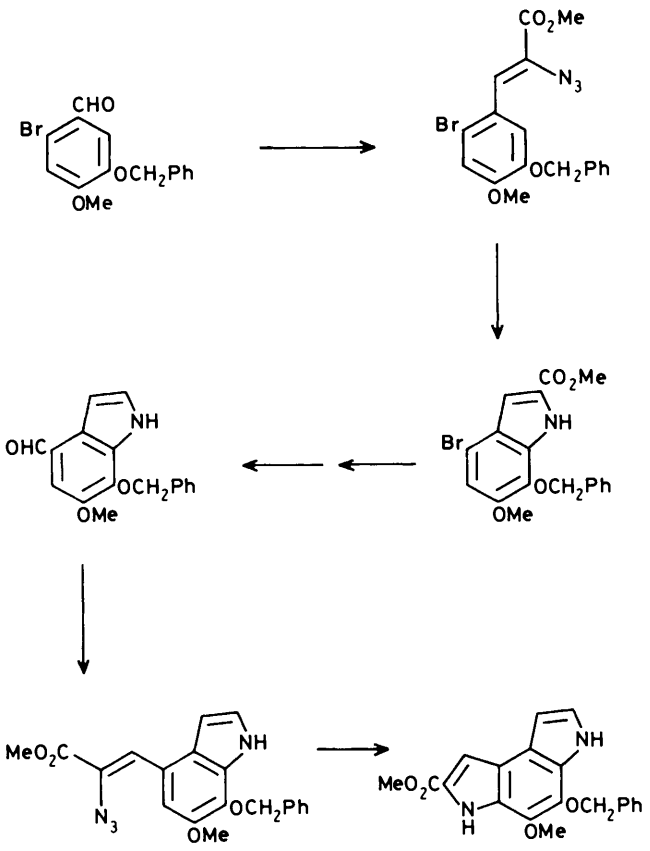


PDE - I Dimer (**3**)

Scheme 1.

this way, both pyrrole rings were quickly and efficiently built up, as outlined in Scheme 2.

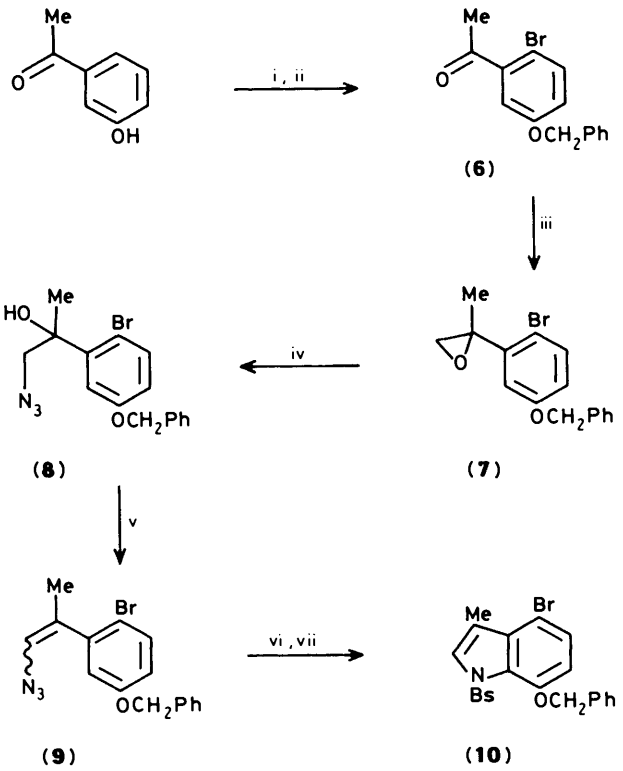
However, the synthesis of the cyclopropapyrroloindole fragment requires the fusion of two β-substituted pyrroles onto a benzene ring, and in contrast to the above formation of 2-substituted indoles from azidocinnamates of the type $ArCH=C(N_3)CO_2Me$, the corresponding formation of 3-substituted



Scheme 2.

indoles from azidostyrenes, $ArCR=CHN_3$, is much less well established.[35,36] Although the latter azides cannot be prepared in one step from ketones, they can be prepared indirectly.

The starting material for our synthesis was 5-benzyloxy-2-bromoacetophenone (**6**), easily prepared on a large scale from commercially available 3-hydroxyacetophenone by benzylation (96%) and bromination (86%). The first vinyl azide group was introduced *via* the epoxide (**7**) and the azido alcohol (**8**). Thus treatment of the ketone (**6**) with dimethyl(oxo)sulphoniomethanide in dimethyl sulphoxide (DMSO) gave the epoxide (**7**) (94%), which was ring opened by treatment with a mixture of sodium azide and lithium chloride in dimethylformamide (DMF) to give the stable azido alcohol (**8**) (72%). The presence of lithium chloride is essential for the successful ring opening of the epoxide (**7**) by the azide ion. No reaction was observed with sodium azide alone, and in the presence of caesium carbonate the yield of azido alcohol (**8**) was only 17%. The successful reaction presumably involves *in situ* formation of lithium azide because similar results could be otherwise obtained by using pre-prepared lithium azide. The dehydration of the alcohol (**8**) to the required vinyl azide (**9**) was attempted under several sets of conditions, the most successful of which used thionyl chloride in pyridine. The vinyl azide (**9**) was formed (73%) as an unstable oil, which darkened rapidly, and was therefore thermolysed



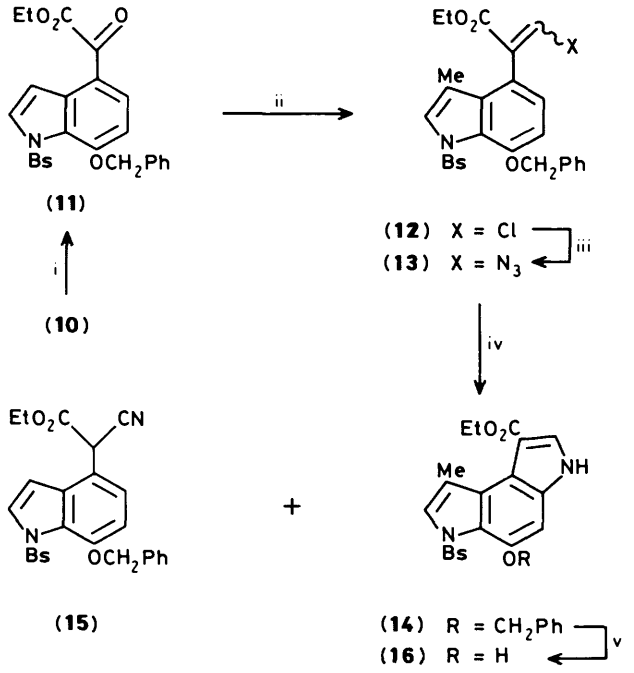
Scheme 3. *Reagents*: i, $PhCH_2Cl$, K_2CO_3, DMF; ii, Br_2, NaOAc, AcOH; iii, $Me_2S^+(O)CH_2^-$, DMSO, iv, NaN_3–LiCl, DMF; v, $SOCl_2$–pyridine; vi, mesitylene, reflux; vii, NaH, THF, $PhSO_2Cl$ (BsCl)

immediately. Heating the azide in boiling mesitylene (166 °C), followed by evaporation of the solvent and treatment of the crude product with sodium hydride and benzenesulphonyl chloride in tetrahydrofuran (THF), gave the indole (**10**) (53% over 2 steps) (Scheme 3).

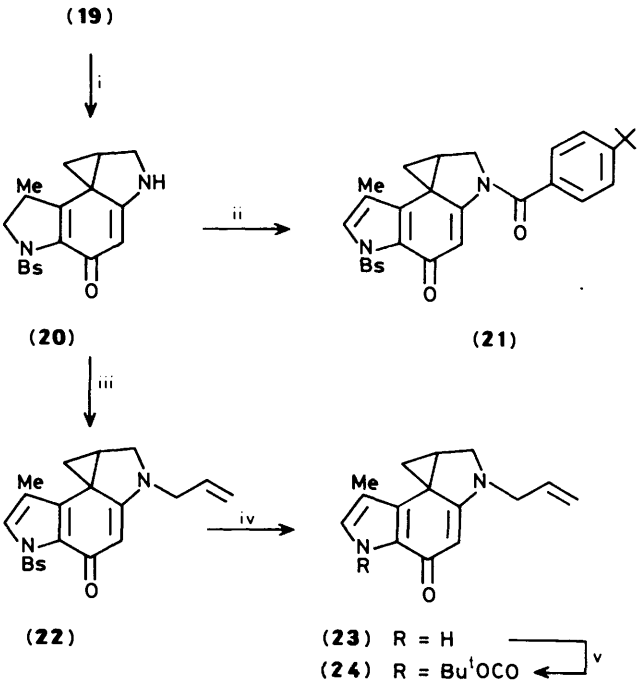
The second vinyl azide group was prepared *via* the glyoxylate (**11**) and the vinyl chloride (**12**) (Scheme 4). The bromoindole (**10**) underwent halogen–metal exchange with butyl-lithium in 1,2-dimethoxyethane (DME), and the resulting aryl-lithium was quenched with diethyl oxalate to give the indole glyoxylate (**11**) (79%). This oxo ester underwent Wittig reaction with chloromethylenetriphenylphosphorane to give the vinyl chloride (**12**) as an *E*/*Z*-mixture (*ca.* 1.6:1) in 81% yield, which on treatment with sodium azide in aqueous DMF[37] gave the vinyl azide (**13**) (89%; *E*/*Z* ratio *ca.* 1.6:1), the substrate for the second cyclisation. Heating the azide (**13**) in mesitylene resulted in cyclisation to the required indole (**14**) (43%), together with the nitrile (**15**) (*ca.* 50%). This nitrile is formed by a competing decomposition of the azide (**13**) involving a ready 1,2-hydrogen shift.[35] Hydrogenolysis of the benzyl ether in (**14**) gave the key intermediate, the known pyrroloindole (**16**).[12,29]

The key pyrroloindole (**16**) was converted into the protected cyclopropapyrroloindole (**19**) and hence CPI (**2**) itself using the conditions developed by Magnus and co-workers[12,29] for the same transformations, and these are summarised in Scheme 5.

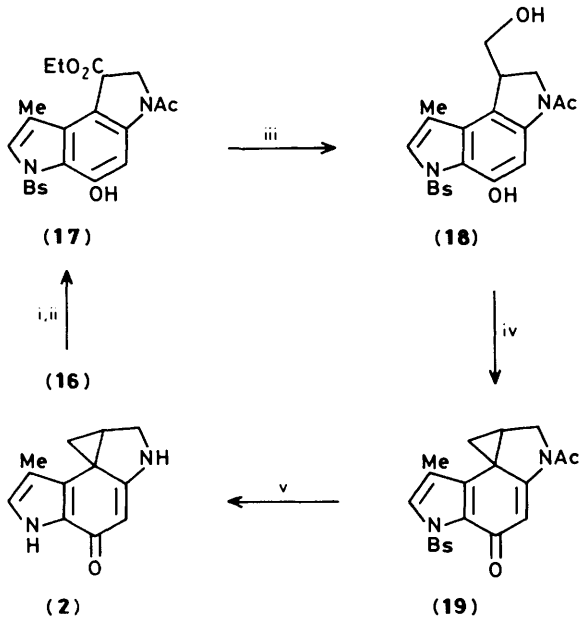
At this stage, with a total synthesis of CC-1065 in mind, it was of interest to investigate potential coupling reactions of the cyclopropapyrroloindole system. The diprotected compound (**19**) was deacetylated by brief treatment with sodium methoxide in methanol as described by Magnus and co-workers[29] to give the NH compound (**20**). This could then be acylated or alkylated using 4-t-butylbenzoyl chloride or allyl bromide to give the derivatives (**21**) and (**22**), respectively. The benzene-



Scheme 4. *Reagents:* i, BuLi, DME, then $(CO_2Et)_2$; ii, $Ph_3P{=}CHCl$, THF; iii, NaN_3, DMF, H_2O; iv, mesitylene, reflux; v, H_2, Pd–C, EtOAc, AcOH, 140 p.s.i.



Scheme 6. *Reagents:* i, NaOMe, MeOH, 15 min; ii, NaH, DMF, 4-$Bu^tC_6H_4COCl$; iii, NaH, THF, allyl bromide; iv, NaOMe, MeOH, 18 h; v, di-t-butyl dicarbonate, MeCN, THF, DMAP



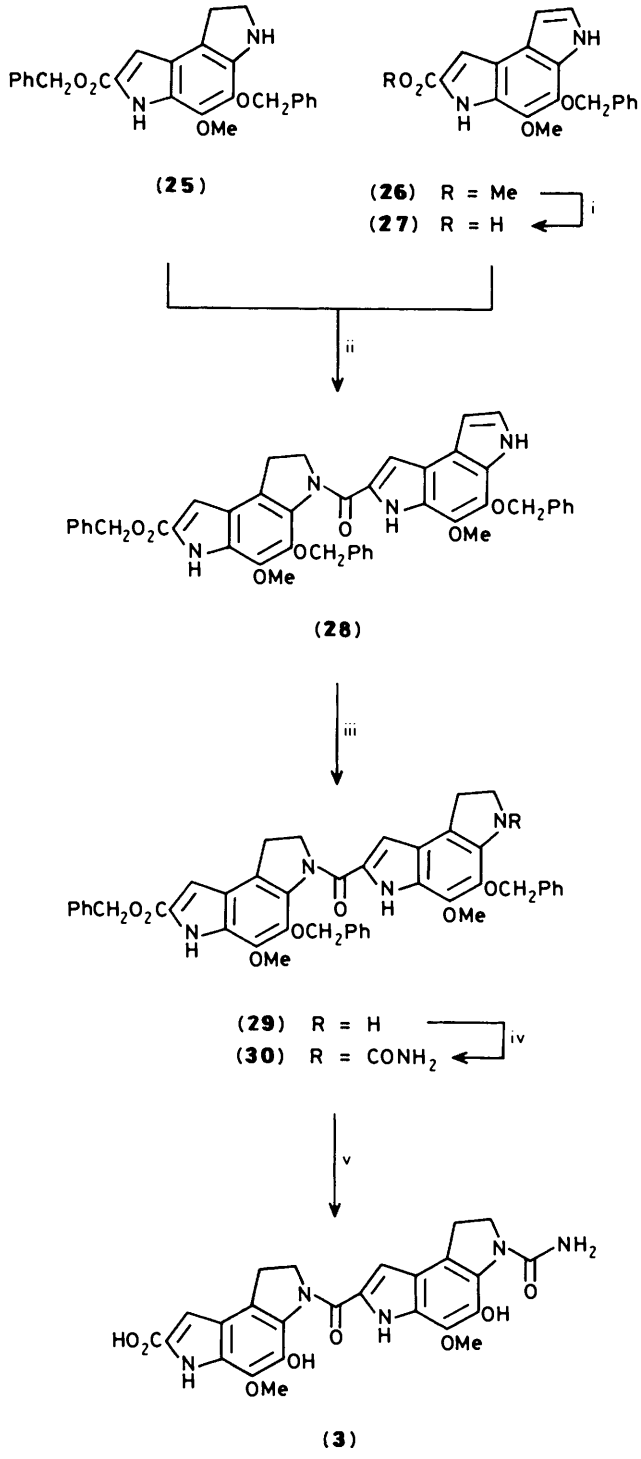
Scheme 5. *Reagents:* i, Et_3SiH, TFA; ii, Ac_2O; iii, $LiAlH_4$, THF; iv, Ph_3P, $EtO_2CN{=}NCO_2Et$, THF; v, NaOMe, MeOH, 18 h

sulphonyl group of (**22**) could easily be removed and the resulting compound (**23**) reprotected with a t-butoxycarbonyl group (Scheme 6).

Despite the success with simple transformations of the *N*-benzenesulphonyl cyclopropapyrroloindole (**20**) (Scheme 6), the corresponding reactions of the 'free' cyclopropapyrroloindole (**2**) were uniformly unsuccessful. The problem appeared to involve the instability of the anion or dianion generated from compound (**2**). However, we were encouraged by the report that the free cyclopropapyrroloindole (**2**) had been successfully coupled, albeit in poor yield, to PDE-I dimer (**3**), obtained by degradation of CC-1065, by the Upjohn Company.[38] Therefore we attempted no further 'model' coupling reactions on the left-hand unit, and turned our attention to the synthesis of the combined centre and right-hand units, PDE-I dimer (**3**).

Synthesis of PDE-I Dimer (**3**).—The building blocks used for the preparation of PDE-I dimer (**3**) were the monomeric pyrroloindoles (**25**) and (**26**) both of which were key intermediates in our synthesis of PDE-I (**4**) and PDE-II (**5**).[32] Hydrolysis of the methyl ester (**26**) in refluxing aqueous methanolic potassium hydroxide gave the corresponding acid (**27**) in excellent yield. At this stage it was decided to couple the pyrroloindole acid (**27**) with the pyrroloindoline (**25**) *before* the reduction of the unsubstituted pyrrole ring. Since the non-basic indole nitrogen was not expected to interfere in the coupling reaction, this obviates the need for any nitrogen protection that might have been necessary if the reduction step had been carried out first. The indoline (**25**) and the acid (**27**) were successfully coupled using the modified carbodi-imide, 1-cyclohexyl-3-[2-(4-methylmorpholinoethyl]carbodi-imidium toluene-4-sulphonate (CMC) in dichloromethane to give the 'dimer' (**28**) in 63% yield. Selective reduction of the right-hand pyrrole ring of the dimer (**28**) was easily achieved using sodium cyanoborohydride in acetic acid, and carbamoylation of the reduced compound (**29**) with trimethylsilyl isocyanate in 1,2-dichloroethane gave the tribenzyl protected PDE-I dimer (**30**) (Scheme 7). Finally hydrogenolysis of the benzyl groups over palladium–charcoal in DMF gave PDE-I dimer (**3**) in quantitative yield. The structure of this was confirmed by its spectroscopic properties and by comparison using h.p.l.c. with authentic material obtained by degradation of natural CC-1065.

Thus we have synthesized both of the fragments obtained by degradation of CC-1065 (Scheme 1) using vinyl azide chemistry,



Scheme 7. *Reagents:* i, KOH, H_2O, MeOH; ii, CMC, CH_2Cl_2, DMF; iii, $NaBH_3CN$, AcOH; iv, Me_3SiNCO, $ClCH_2CH_2Cl$; v, H_2, Pd–C, DMF

and since the cyclopropapyrroloindole (**2**) has been coupled with natural PDE-I dimer (**3**),[38] our work completes a formal total synthesis of CC-1065 itself.

Experimental

I.r. spectra were recorded in the range 600—4 000 cm^{-1} using Perkin-Elmer 298 or 1710 Fourier Transform spectrophotometers and were calibrated against polystyrene. U.v. spectra were recorded using a Pye Unicam SP1800 spectrophotometer and were calibrated against holmium glass. ^1H N.m.r. spectra were obtained at 60, 90, and 250 MHz using Varian EM360, Perkin-Elmer R32, and Bruker WM250 instruments, respectively, using tetramethylsilane as internal reference. Mass spectra were recorded on a VG Micromass 7070B instrument at 70 eV using a direct insertion probe. Column chromatography was carried out on silica H, type 60, or silica gel (0.063—0.2 mm) (Merck). Solvents were dried by standard procedures, light petroleum refers to the fraction of b.p. 40—60 °C, and ether refers to diethyl ether.

3-Benzyloxyacetophenone.[39,40]—3-Hydroxyacetophenone (95%, 12.2 g, 85 mmol) was dissolved in dry DMF (7.7 ml) under nitrogen. Potassium carbonate (14.5 g, 104 mmol), benzyl chloride (9.9 ml, 85 mmol) and sodium iodide (0.5 g, 4 mol%) were added and the mixture was heated, with stirring, to 80 °C. After 6.5 h at this temperature the mixture was a solid mass. It was then diluted with water and the aqueous mixture extracted with ether. The combined ethereal layers were washed with aqueous potassium hydroxide (5%) and water and dried (Na_2SO_4). Evaporation yielded a brown oil which was purified by flash chromatography on silica (light petroleum) to yield the title compound (18.4 g, 96%), b.p. 220 °C, 15 mmHg (Kugelrohr) (lit.,[40] b.p. 180 °C, 3 mmHg); $\nu_{max.}$(film) 3 066, 3 033, 1 685s, 1 581, 1 497, 1 484, 1 439, 1 357, 1 271, 1 208, and 1 026 cm^{-1}; δ_H(60 MHz; CCl_4) 2.35 (3 H, s, COMe), 4.90 (2 H, s, PhCH_2O), and 6.85—7.60 (9 H, m, ArH).

5-Benzyloxy-2-bromoacetophenone (**6**).—A solution of 3-benzyloxyacetophenone (2.60 g, 11.6 mmol) in glacial acetic acid (8.0 ml) with sodium acetate (1.37 g, 16.7 mmol) was cooled to 0 °C and bromine (0.84 ml, 16.4 mmol) was added slowly with stirring. A calcium chloride guard tube was fitted and the mixture was stirred in the dark, at room temperature, for 24 h. The resulting slurry was diluted with chloroform and washed with aqueous sodium thiosulphate, aqueous potassium carbonate, and water. After the solution had been dried (Na_2SO_4), the solvent was removed under reduced pressure leaving a brown oil. This was purified by dry-column flash chromatography (ether–light petroleum) giving the *title compound* (**6**) (3.03 g, 86%) as a light yellow oil, b.p. 150 °C, 0.6 mmHg (Kugelrohr) (Found: C, 59.3; H, 4.4. $C_{15}H_{13}BrO_2$ requires C, 59.0; H, 4.3%); $\nu_{max.}$(film) 3 066, 3 033, 1 703 (C=O), 1 591, 1 567, 1 497, 1 463, 1 393, 1 355, 1 311, 1 289, 1 241, 1 208, 1 095, 1 009, 873, 813, 739, 697, and 653 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 2.06 (3 H, s, COMe), 5.04 (2 H, s, CH_2Ph), 6.89 (1 H, dd, $J_{4,6}$ 3 Hz, $J_{4,3}$ 8.5 Hz, 4-H), 7.06 (1 H, d, $J_{6,4}$ 3 Hz, 6-H), 7.29—7.41 (5 H, m, Ph), and 7.46 (1 H, d, $J_{3,4}$ 8.5 Hz, 3-H); *m/z* (180 °C) 307/305 (M^+, 53%), 226 (8), 169 (20), 92 (99), 91 (99), 82/80 (100), and 81/79 (41).

2-(5′-Benzyloxy-2′-bromophenyl)-2-methyloxirane (**7**).—Sodium hydride (60% dispersion; 2.44 g, 61 mmol) was washed, under nitrogen, with dry light petroleum and decanted dry, repeating the procedure twice. Solid trimethyl(oxo)sulphonium iodide (13.4 g, 61 mmol) was added followed by dry DMSO (61 ml). A vigorous evolution of hydrogen ensued. After 40 min the reaction had subsided leaving a milky-white mixture. A solution of 5-benzyloxy-2-bromoacetophenone (13.4 g, 44 mmol) in dry DMSO (33 ml) and added over 10 min, with stirring. The mixture was heated to 55 °C for 3 h, cautiously diluted with water, and then extracted with ether. The combined organic layers were washed repeatedly with brine and dried (Na_2SO_4). Evaporation yielded a yellow solid, which was recrystallised from ethanol to give the *title compound* (**7**) (13.2 g, 94%) as a cream crystalline solid, m.p. 78.5—79.5 °C (Found: C, 60.5; H,

4.9; Br, 25.1. $C_{16}H_{15}BrO_2$ requires C, 60.2; H, 4.7; Br, 25.0%); $\nu_{max.}$(Nujol) 3 040, 1 590, 1 410, 1 305, 1 230, and 1 010 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 1.65 (3 H, s, Me), 2.85 (1 H, d, *J* 5.5 Hz, 3-H), 3.02 (1 H, d, *J* 5.5 Hz, 3-H), 5.04 (2 H, s, CH_2Ph), 6.78 (1 H, dd, $J_{4',6'}$ 3 Hz, $J_{4',3'}$ 8.5 Hz, 4'-H), 7.12 (1 H, d, $J_{6,4}$ 3 Hz, 6'-H), and 7.29—7.45 (6 H, m, 3'-H and Ph); *m/z* (FAB) 320/318 (M^-, 46), 229/227 (11), and 91 (100).

In a scaled up experiment, 3-hydroxyacetophenone (103 g) was converted into the oxirane (**7**) (105 g, 45% overall) without purification of the intermediates.

1-*Azido*-2-(5'-*benzyloxy*-2'-*bromophenyl*)*propan*-2-*ol* (**8**).—Oxirane (**7**) (100 mg, 0.3 mmol), sodium azide (120 mg, 1.8 mmol), and caesium carbonate (98 mg, 0.3 mmol) were heated to 80 °C in dry DMF (2 ml). After 24 h, the mixture was diluted with water and extracted with ether. The combined ether layers were washed several times with water to remove any DMF, dried (Na_2SO_4), and evaporated to yield a solid (98 mg) shown by t.l.c. to be a mixture of the starting material and one other compound. Dry-column flash chromatography (ether–light petroleum) gave starting material (45 mg, 45%) as the first fraction followed by the *title compound* (**8**) (18.7 mg, 17%) as a stable colourless oil which solidified on prolonged storage at −10 °C, m.p. 55—55.5 °C (Found: C, 53.2; H, 4.4; N, 11.5; M^+, 361.0430. $C_{16}H_{16}BrN_3O_2$ requires C, 53.1; H, 4.45; N, 11.6%; *M*, 361.0426); $\nu_{max.}$(film) 3 460br, 3 040, 3 020, 2 990, 2 940, 2 110vs, 1 590, 1 570, 1 450, 1 380, 1 310, 1 290, 1 230, and 1 010 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 1.73 (3 H, s, Me), 2.80 (1 H, br s, OH), 3.70 (1 H, d, *J* 12.5 Hz, CH_2N_3), 4.17 (1 H, d, *J* 12.5 Hz, CH_2N_3), 5.06 (2 H, s, CH_2Ph), 6.76 (1 H, dd, $J_{4',6'}$ 3 Hz, $J_{4',3'}$ 8.5 Hz, 4'-H), and 7.3—7.48 (7 H, m, ArH); *m/z* (120 °C) 363/361 (M^+, 0.1%), 307/305 (6.5), 292/290 (0.7), 227 (1.1), and 91 (100).

In an improved procedure, oxirane (**7**) (55.3 g, 173 mmol) was dissolved in dry DMF (135 ml) and lithium chloride (72.0 g, 1.69 mol) and sodium azide (48.0 g, 0.74 mol) were added. The mixture was stirred with a mechanically driven paddle and heated to 60 °C for 18 h. After cooling to ambient temperature, the mixture was diluted with water, extracted with chloroform and the organic layers washed with water, dried (Na_2SO_4), and evaporated under reduced pressure to give a yellow oil. This was chromatographed in four batches (ether–light petroleum) to give the *title compound* (**8**) (44.8 g, 72%) as a colourless oil whose t.l.c. and n.m.r. properties were identical to those described above.

Dehydration of the Azido Alcohol (**8**).—(a) *With* $MeSO_2Cl$–SO_2–*collidine*. Azido alcohol (**8**) (508 mg, 1.4 mmol) was taken up in *sym*-collidine (1.16 ml) and dry DMF and cooled to 0 °C under nitrogen. Methanesulphonyl chloride (0.35 ml, 4.43 mmol) was slowly added followed by a DMF solution of SO_2 (11.4mM; 0.7 ml, 8.0 mmol). The mixture was allowed to warm to room temperature. After 5 min a red precipitate had formed. Water was added dropwise with cooling and this caused the precipitate to redissolve. The reaction mixture was then poured into an excess of water and extracted with dichloromethane. The extracts were washed with cold dilute sulphuric acid, cold dilute sodium hydrogen carbonate, and water, and dried (Na_2SO_4). Evaporation gave a yellow oil which was purified by flash chromatography on silica (light petroleum) to yield a light yellow, unstable oil (179 mg, 37%) which was assigned the structure 1-azido-2-(5'-benzyloxy-2'-bromophenyl)propene (**9**) on the basis of its n.m.r. and i.r. spectra; $\nu_{max.}$(film) 2 110 (N_3) and 1 645 cm^{-1}; δ_H(90 MHz; $CDCl_3$) 1.97 (3 H, s, Me), 5.04 (2 H, s, CH_2Ph), 6.20 (1 H, br s, 1-H), 6.70—6.95 (3 H, m, ArH), and 7.20—7.55 (5 H, m, ArH). The compound darkened rapidly in the presence of air at room temperature and was not characterised further but rather used directly in the next stage.

(b) *With thionyl chloride and pyridine*. Azido alcohol (**8**) (200 mg, 0.55 mol) was dissolved in dry redistilled pyridine (3.7 ml) and cooled to 0 °C. Thionyl chloride (0.12 ml, 1.65 mmol) was slowly added and the reaction stirred at 0 °C for 10 min. The reaction mixture was poured onto crushed ice. When the ice had melted the aqueous mixture was extracted with ether, which was then washed with cold dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and brine, and then dried (Na_2SO_4). After evaporation under reduced pressure, a small amount of light petroleum was added and the solution was loaded onto the top of a very short column (5:1, silica gel/product) which was eluted with light petroleum. The first component was vinyl azide (**9**) (139 mg, 73%) which was a colourless oil with identical spectroscopic properties to those described above.

7-*Benzyloxy*-4-*bromo*-3-*methyl*-1-*phenylsulphonyl*-1H-*indole* (**10**).—The vinyl azide (**9**) (50 mg, 0.145 mmol) was dissolved in dry redistilled mesitylene (2.0 ml) under nitrogen. A reflux condenser was fitted and the flask was lowered into a hot (>200 °C) Wood's metal bath. After refluxing for 1 h the solvent was removed under reduced pressure to give a brown oil, which darkened rapidly in air and was used directly in the next stage.

A suspension of sodium hydride (60% dispersion; 7.5 mg, 0.188 mmol) in dry THF (0.1 ml) was cooled to 0 °C under nitrogen. A solution of the crude product from the above thermolysis, in THF (0.30 ml), was added. Some effervescence was observed and after 5 min at this temperature the cooling bath was removed. Stirring was continued at room temperature for 1 h and under reflux for 15 min. After cooling, benzenesulphonyl chloride (30 μl, 0.235 mmol) was added and the mixture stirred at room temperature for 30 min. After quenching with water (**CARE!** vigorous evolution of hydrogen), the mixture was extracted with ethyl acetate. The organic layers were washed with brine and dried (Na_2SO_4). Evaporation and chromatography (ether and light petroleum) gave a yellow crystalline solid which was recrystallised from ethanol to give the *title compound* (**10**) (35 mg, 53% from the vinyl azide; in other experiments yields ranged from 37—53%) as pale yellow crystals, m.p. 152—153 °C (Found: C, 57.6; H, 3.8; Br, 17.5; N, 3.0; S, 6.6. $C_{22}H_{18}BrNO_3S$ requires C, 57.9; H, 4.0; Br, 17.5; N, 3.1; S, 7.0%); $\nu_{max.}$(Nujol) 2 960, 1 570, 1 480, 1 470, 1 450, 1 355, 1 290, 1 265, 1 230, 1 170, 1 150, 1 125, 1 045, 1 020, 995, 925, and 910 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 2.54 (3 H, d, *J ca.* 1 Hz, Me), 4.94 (2 H, s, CH_2Ph), 6.46 (1 H, d, *J* 8.3 Hz, 6-H), 7.16 (1 H, d, *J* 8.3 Hz, 5-H), 7.18—7.59 (10 H, m, 2 × Ph), and 7.66 (1 H, ~q, 2-H); *m/z* 457/455 (M^+, 8.5%), 366/364 (4.0), 316/314 (11.3), 141 (7.9), and 91 (100).

Ethyl (7-*Benzyloxy*-3-*methyl*-1-*phenylsulphonyl*-1H-*indol*-4-*yl*)*glyoxylate* (**11**).—The bromo indole (**10**) (1.0 g, 2.19 mmol) was dissolved in dry dimethoxyethane (20 ml), under nitrogen, and cooled to −78 °C. Butyl-lithium in hexane (1.6M; 1.8 ml, 2.86 mmol) was slowly added. The mixture was kept at this temperature for 10 min during which time the mixture turned bright yellow. It was then slowly transferred through a double-ended needle into a flask containing a vigorously stirred solution of diethyl oxalate (3.5 ml, 21.9 mmol) in dimethoxyethane (3.5 ml) maintained at approximately −55 °C. After complete transfer of the material, the mixture was left at −55 °C for 1 h and then it was allowed to warm slowly to room temperature. Saturated aqueous ammonium chloride was added and the resulting slurry was extracted with dichloromethane. The organic extracts were washed with water, dried, and the solvent removed under reduced pressure. The resultant yellow solid was triturated with light petroleum containing a few drops of ether to give pure *title compound* (**11**) (830 mg, 79%; in other experiments yields ranged from 67—79%) as pale

yellow crystals, m.p. 153—154.5 °C (from dichloromethane–ether) (Found: C, 65.7; H, 4.8; N, 2.9; S, 6.9. $C_{26}H_{23}NO_6S$ requires C, 65.4; H, 4.85; N, 2.9; S, 6.7%); $\nu_{max.}$(Nujol) 1 740, 1 680, 1 600, 1 550, 1 300, 1 270, 1 245, 1 205, 1 170, 1 145, and 1 015 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 1.39 (3 H, t, *J* 7.1 Hz, CH_2Me), 2.40 (3 H, d, *J* 1.1 Hz, 3-Me), 4.40 (2 H, q, *J* 7.1 Hz, OCH_2Me), 5.04 (2 H, s, CH_2Ph), 6.62 (1 H, d, *J* 8.6 Hz, 6-H), 7.13—7.22 (2 H, m, ArH), 7.26—7.37 (5 H, m, Ph), 7.45—7.60 (3 H, m, ArH), 7.50 (1 H, d, *J* 8.6 Hz, 5-H), and 7.81 (1 H, q, *J* 1.1 Hz, 2-H); *m/z* (180 °C) 477 (M^+, 18%), 404 (32), 376 (8), 337 (12), 264 (10), 263 (12), 135 (11), and 91 (100).

Ethyl 2-(7-*Benzyloxy*-3-*methyl*-1-*phenylsulphonyl*-1H-*indol*-4-*yl*)-3-*chloropropenoate* (**12**).—A finely ground powder of (chloromethyl)triphenylphosphonium chloride (550 mg, 1.58 mmol) was suspended in dry THF (3.5 ml) under nitrogen and cooled to −78 °C. Phenyl-lithium in cyclohexane–ether (70:30) (1.7M; 0.86 ml, 1.46 mmol) was added slowly and the solution gained a slight red colouration. After 4.75 h at this temperature the cloudy mixture had turned from red to yellow. The mixture was then transferred through a wide bore, double-ended needle into a flask containing a stirred solution of the indole glyoxylate (**11**) (500 mg, 1.05 mmol) in THF (3.5 ml) maintained at −78 °C. The mixture was stirred at −78 °C for 2 h and at 4 °C overnight. It was then diluted with a few drops of water and the THF evaporated under reduced pressure. The residue was triturated with ether and the solution was decanted from the solid triphenylphosphine. The solution was then washed with water, dried (Na_2SO_4), and the crude product presorbed on silica and chromatographed (ether–light petroleum, 50:50). This yielded the *title compound* (**12**) (431 mg, 81%), an approximately 1.6:1 mixture of *E*- and *Z*-isomers by high field ^1H n.m.r., as an unstable pale green oil (Found: M^+, 509.1064. $C_{27}H_{24}{}^{35}ClNO_5S$ requires *M*, 509.1064); $\nu_{max.}$($CHCl_3$) 1 715s, 1 615, 1 575, 1 500, 1 450, 1 375, 1 290, 1 170, 1 135, and 1 095 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 1.21 (3 H, t, *J* 6.75 Hz, *Z* $MeCH_2$), 1.27 (3 H, br t, *J* 6.75 Hz, *E* $MeCH_2$), 2.13 (3 H, d, *J* 1.1 Hz, *E* 3-Me), 2.24 (3 H, d, *J* 1.1 Hz, *Z* 3-Me), 4.235 and 4.24 (2 H, 2 × q, *J* 6.75 Hz, *E* $MeCH_2$ conformational isomers), 4.25 (2 H, q, *J* 6.75 Hz, *Z* $MeCH_2$), 4.97 (2 H, br s, CH_2Ph), 6.55 (1 H, s, ClCH=C), 6.60 (1 H, d, *J* 8.25 Hz, *Z* indole 6-H), 6.69 (1 H, d, *J* 8.25 Hz, *E* indole 6-H), 6.82 (1 H, d, *J* 8.25 Hz, *E* indole 5-H), 6.90 (1 H, d, *J* 8.25 Hz, *Z* indole 5-H), 7.20—7.50 (7 H, m, 2 × Ph), 7.52—7.61 (3 H, m, 2 × Ph), 7.62 (1 H, q, *J* 1.1 Hz, *E* indole 2-H), 7.64 (1 H, q, *J* 1.1 Hz, *Z* indole 2-H), and 7.67 (1 H, s, *E* ClCH=C); *m/z* (150 °C) 511 (M^+, ^{37}Cl, 3%), 509 (M^+, ^{35}Cl, 6%), 420 (1), 418 (3), 377 (14), 370 (4), 368 (10), 236 (27), and 91 (100).

Ethyl 3-*Azido*-2-(7-*benzyloxy*-3-*methyl*-1-*phenylsulphonyl*-1H-*indol*-4-*yl*)*propenoate* (**13**).—The vinyl chloride (**12**) (431 mg, 0.85 mmol) was dissolved in DMF–H_2O (94:6 v/v; 2.0 ml) and sodium azide (431 mg, 6.63 mmol) was added. After stirring, in the dark, for 3 h at room temperature ether was added until the solution was clear and the inorganic salts completely precipitated. These were filtered off and the filtrate washed with brine (× 3) and dried (Na_2SO_4). After evaporation the resulting oil was purified by dry-flash column chromatography (ethyl acetate–ether–light petroleum) giving the *title compound* (**13**) in approximately 1.6:1 *E*/*Z* isomeric ratio (392 mg, 89%) as a pale yellow glass going dark in the light (Found: $M^+ - N_2$, 488.1399. $C_{27}H_{24}N_2O_5S$ *M*, requires 488.1406); $\nu_{max.}$(Nujol) 2 110s, 1 700br, 1 605, 1 290, 1 220, and 1 020 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 1.21 (3 H, t, *J* 6.75 Hz, *Z* $MeCH_2$), 1.24 (3 H, t, *J* 6.75 Hz, *E* $MeCH_2$), 2.17 (3 H, br s, *E* 3-Me), 2.21 (3 H, br s, *Z* 3-Me), 4.20 (2 H, q, *J* 6.75 Hz, *E* $MeCH_2$), 4.21 (2 H, q, *J* 6.75 Hz, *Z* $MeCH_2$), 4.97 (2 H, br s, CH_2Ph), 6.58 (1 H, d, *J* 8.25 Hz, *Z* indole 6-H), 6.66 (1 H, d, *J* 8.25 Hz, *E* indole 6-H), 6.74 (1 H, s, *Z* N_3CH=C), 6.78 (1 H, d, *J* 8.25 Hz, *E* indole 5-H), 6.83 (1 H, d, *J* 8.25 Hz, *Z* indole 5-H), 7.21—7.63 (11 H, m, 2 × Ph and indole 2-H), and 7.73 (1 H, s, *E* N_3CH=C); *m/z* (150 °C) 488 ($M^+ - N_2$, 8%), 348 (6), 347 (6) 275 (3), 185 (4), 142 (3), 141 (3), and 91 (100).

Ethyl 5-*Benzyloxy*-3,6-*dihydro*-8-*methyl*-6-*phenylsulphonyl*-*pyrrolo*[3,2-e]*indole*-1-*carboxylate* (**14**).—A solution containing the vinyl azide (**13**) (155 mg, 0.30 mmol) in dry mesitylene (36 ml) was rapidly brought to reflux, under nitrogen, using a Wood's metal bath. After 15 min the solution was allowed to cool and the solvent was removed under reduced pressure. The resulting viscous brown oil was chromatographed (ether–light petroleum) to give the *title compound* (**14**) (61 mg, 42%; in other experiments yields were in the range 37—43%) as a stable crystalline solid, m.p. 216—216.5 °C (decomp.) [from ether–light petroleum (b.p. 60—80 °C)] (Found: C, 66.3; H, 4.9; N, 5.7. $C_{27}H_{24}N_2O_5S$ requires C, 66.4; H, 4.95; N, 5.7%); $\nu_{max.}$(Nujol) 3 230br (NH), 1 665, 1 615, 1 350, 1 300, 1 170, and 1 030 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 1.39 (3 H, t, *J* 7.3 Hz, $MeCH_2O$), 2.50 (3 H, d, *J* 1 Hz, 2-Me), 4.36 (2 H, q, *J* 7.3 Hz, $MeCH_2O$), 4.90 (2 H, s, CH_2Ph), 6.51 (1 H, s, 4-H), 7.08—7.18 (2 H, m, PhH), 7.22—7.36 (5 H, m, Ph), 7.38—7.48 (1 H, br s, 2-H), 7.54—7.63 (3 H, m, Ph), 7.73 (1 H, q, *J* 1 Hz, 7-H), and 8.49 (1 H br s, NH); *m/z* (250 °C) 488 (M^+, 1%), 398 (2), 397 (2), 347 (1), 295 (2), 257 (4), 255 (2), 235 (2), 233 (2), 225 (3), 211 (4), 149 (23), 141 (18), 101 (21), 91 (22), and 85 (100), together with *ethyl* 2-(7-*benzyloxy*-3-*methyl*-1-*phenylsulphonyl*-1H-*indol*-4-*yl*)-2-*cyanoacetate* (**15**) (79 mg, 54%) as a brown oil, which resisted further purification. The structure was assigned on the basis of its spectroscopic properties (Found: M^+, 488.1409. $C_{27}H_{24}N_2O_5S$ requires *M*, 488.1406); $\nu_{max.}$(film) 2 930, 2 260w, 1 745, 1 615, 1 575, 1 505, 1 450, 1 360, 1 340, 1 295, 1 230, 1 170, 1 130, and 1 030 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 1.27 (3 H, t, *J* 7.5 Hz, $MeCH_2O$), 2.50 (3 H, d, *J* 1 Hz, 3-Me), 4.24 (2 H, m, prochiral $MeCH_2O$), 4.94 (1 H, d, *J* 12.5 Hz, CH_2Ph), 4.99 (1 H, d, *J* 12.5 Hz, CH_2Ph), 5.36 (1 H, s, $ArCH(CN)CO_2Et$), 6.66 (1 H, d, *J* 8.4 Hz, indole 6-H), 7.19—7.60 (11 H, m, 2 × Ph and indole 5-H), and 7.71 (1 H, q, *J* 1 Hz, indole 2-H); *m/z* (260 °C) 488 (M^+, 7%), 462 (1), 347 (7), and 91 (100).

Ethyl 3,6-*Dihydro*-5-*hydroxy*-8-*methyl*-6-*phenylsulphonyl*-*pyrrolo*[3,2-e]*indole*-1-*carboxylate* (**16**).—The 5-benzyloxypyrroloindole (**14**) (842 mg, 1.73 mmol) was suspended in ethyl acetate–acetic acid (2:1; 75 ml) and palladium–carbon (10%; 490 mg) and concentrated hydrochloric acid (2 drops) were added. The mixture was subjected to ultrasound for 25 min and then stirred vigorously under an atmosphere of hydrogen (140 p.s.i.) for 7 days. The catalyst was filtered off and washed with chloroform. The catalyst was placed, with the filter paper, in a Soxhlet thimble and continuously extracted overnight with chloroform. The chloroform washings, extract, and filtered reaction solution were combined and evaporated to give the title compound (**16**) (660 mg, 96%) as a fawn solid, m.p. 156—158 °C (from dichloromethane–light petroleum) (lit.,[29] 160—162 °C); δ_H(250 MHz; $CDCl_3$) 1.35 (3 H, t, *J* 7 Hz, $MeCH_2O$), 2.37 (3 H, s, 8-Me), 4.31 (2 H, q, *J* 7 Hz, $MeCH_2O$), 6.88 (1 H, s, 4-H), 7.27—7.50 (4 H, m, PhH), 7.61 (1 H, d, *J* 3 Hz, 2-H), 7.72—7.77 (2 H, m, Ph and 7-H), 8.54 (1 H, br s, NH), and 8.97 (1 H, s, OH).

Ethyl 3-*Acetyl*-1,2,3,6-*tetrahydro*-5-*hydroxy*-8-*methyl*-6-*phenylsulphonylpyrrolo*[3,2-e]*indole*-1-*carboxylate* (**17**).—The pyrroloindole (**16**) (247 mg, 0.62 mmol) was suspended in distilled triethylsilane (2.0 ml) under nitrogen. Trifluoroacetic acid (2.0 ml) was added and the mixture stirred overnight at room temperature. The excess of reagents were removed under reduced pressure and acetic anhydride (2 ml) was added. After

3 h the excess of acetic anhydride was evaporated off and the resultant oil chromatographed (methanol–ether) yielding the title compound (**17**) (181 mg, 66%, lit.,[29] 66%) as a grey microcrystalline solid, m.p. 205—208 °C (from ethyl acetate–dichloromethane) (lit.,[29] 206—208 °C); $\nu_{max.}$($CHCl_3$) 3 379br, 3 007, 1 734, 1 653, 1 616, 1 586, 1 499, 1 448, 1 407, 1 374, 1 360, 1 313, 1 187, 1 169, 1 142, and 1 090 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 1.04 (3 H, t, *J* 7 Hz, *Me*CH_2O), 2.23 (6 H, s, NAc and 8-Me), 3.98—4.40 (5 H, m, 1- and 2-H), 7.17 (1 H, br s, 7-H), 7.37—7.57 (3 H, m, PhH), 7.72—7.79 (2 H, m, PhH), 7.94 (1 H, br s, 4-H), and 8.86 (1 H, s, OH); *m/z* (220 °C) 442 (M^+, 46%), 384 (5), 369 (48), 327 (21), 301 (38), 259 (6), 243 (12), 229 (21), 215 (28), 201 (13), and 187 (100).

3-*Acetyl*-1,2,3,6-*tetrahydro*-5-*hydroxy*-1-*hydroxymethyl*-8-*methyl*-6-*phenylsulphonylpyrrolo*[3,2-e]*indole* (**18**).—The ester (**17**) (37 mg, 0.083 mmol) in dry THF (1 ml) at 0 °C was treated with lithium aluminium hydride (5 mg, 0.133 mmol). After 4 h the reaction was quenched with water (5 μl) followed by sodium hydroxide (15%; 5 μl) and water (15 μl). After a few min magnesium sulphate was added and the mixture was diluted with ethyl acetate. Filtration, evaporation, and chromatography (acetone–ether) of the crude product gave the *title compound* (**18**) (21 mg, 63%, lit.,[29] 85%), as a crystalline solid, m.p. 234—235 °C (Found: C, 60.2; H, 5.1; N, 7.2. $C_{20}H_{20}N_2O_5S$ requires C, 60.0; H, 5.0; N, 7.0%); $\nu_{max.}$($CHCl_3$) 3 370br, 1 650, 1 615, 1 585, 1 440, 1 405, 1 360, 1 310, 1 165, 1 140, and 1 090 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 2.25 (3 H, s), 2.29 (3 H, s), 3.43—3.76 (3 H, m, CH_2OH and 1-H), 3.97—4.20 (2 H, m, 2-H), 7.20 (1 H, br s, 7-H), 7.36—7.63 (4 H, m, PhH), 7.72—7.80 (2 H, m), 7.95 (1 H, s, 4-H), and 8.80 (1 H, br s); *m/z* (220 °C) 400 (M^+, 20%), 369 (35), 327 (17), 260 (9), 236 (5), 229 (28), and 187 (100).

2-*Acetyl*-1,2,8,8a-*tetrahydro*-7-*methyl*-5-*phenylsulphonyl*-*cyclopropa*[c]*pyrrolo*[3,2-e]*indol*-4(5H)-*one* (**19**).—The primary alcohol (**18**) (21 mg, 0.053 mmol) and triphenylphosphine (14 mg, 0.053 mmol) were dissolved in dry THF (1 ml). Diethyl azodicarboxylate (8.4 μl, 0.053 mmol) was added and the mixture was stirred overnight. The mixture was then diluted with a few drops of water and extracted with dichloromethane. The organic layers were washed with water, dried (Na_2SO_4), evaporated, and the residue chromatographed on silica (methanol–ether). This afforded the title compound (**19**) (15 mg, 75%, lit.,[29] 80.2%) as a solid; $\nu_{max.}$($CHCl_3$) 1 675w, 1 630s, 1 380, 1 290, 1 170, and 1 130 cm^{-1}; *m/z* (200 °C) 318 (17%), 275 (10), 242 (6), and 199 (29); *m/z* (FAB, thiodiethanol) 383 (MH^+, 14%).

1,2,8,8a-*Tetrahydro*-7-*methyl*-5-*phenylsulphonylcyclopropa*-[c]*pyrrolo*[3,2-e]*indol*-4(5H)-*one* (**20**).[29]—The *N*-acetyl-cyclopropapyrroloindole (**19**) (6.5 mg, 0.017 mmol) was treated with sodium methoxide–methanol (1M; 0.5 ml) for 15 min at room temperature and then diluted with water. The aqueous mixture was extracted with dichloromethane (× 6). The organic layers were dried (Na_2SO_4) and evaporated to dryness and the residue chromatographed (methanol–triethylamine–ethyl acetate 1:1:18) to give the title compound (**20**) (5.8 mg, 100%) as an off-white amorphous solid; $\nu_{max.}$($CHCl_3$) 3 460, 3 320br, 2 940, 2 880, 1 620, 1 450, 1 275, 1 225, 1 180, and 1 130 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 1.16 (1 H, dd, *J* 4.3 Hz, 8-H), 1.82 (1 H, dd, *J* 4.3 and 7.8 Hz, 8-H), 1.98 (3 H, ~d, *J* 1.1 Hz, 7-Me), 2.94 (1 H, m, 8a-H), 3.57 (1 H, d, *J* 10 Hz, 1-H), 3.72 (1 H, ddd, *J* 1.3, 5.0, and 10 Hz, 1-H), 4.98 (1 H, br s, NH), 5.32 (1 H, s, 3-H), 7.40—7.60 (4 H, m, Ph and 6-H), and 8.00 (2 H, m, *o*-PhH); *m/z* (200 °C) 340 (M^+, 9%), 200 (94), and 199 (100).

1,2,8,8a-*Tetrahydro*-7-*methylcyclopropa*[c]*pyrrolo*[3,2-e]-*indol*-4(5H)-*one* (**2**).—A solution of the *N*-acetyl *N*-phenylsulphonyl protected pyrroloindole (**19**) (10.6 mg, 0.027 mmol) in sodium methoxide–methanol (1M; 1 ml) was stirred for 18 h at room temperature. Work-up and chromatography as above yielded the title compound (**2**) (5.0 mg, 93%, lit.,[29] 75%) as an amorphous white solid; $\lambda_{max.}$(EtOH)[6] 230 (log ε 4.02), 279 (4.22), and 358 nm (3.97); δ_H(250 MHz; $CDCl_3$)[29] 1.19 (1 H, dd, *J* 4.3 Hz, 8-H), 1.86 (1 H, dd, *J* 3.8 and 7.7 Hz, 8-H), 2.00 (3 H, s, 7-Me), 2.95 (1 H, m, 8a-H), 3.63 (1 H, d, *J* 10 Hz, 1-H), 3.80 (1 H, dd, *J* 5 and 10 Hz, 1-H), 4.60 (1 H, br s, NH), 5.51 (1 H, s, 3-H), 6.70 (1 H, br s, 6-H), and 9.20 (1 H, br s, NH); *m/z* (160 °C) 200 (M^+, 100%).

2-(4-*t*-*Butylbenzoyl*)-1,2,8,8a-*tetrahydro*-7-*methyl*-5-*phenyl*-*sulphonylcyclopropa*[c]*pyrrolo*[3,2-e]*indol*-4(5H)-*one* (**21**).—Sodium hydride (60% dispersion; 4 mg, 0.102 mmol) was added to a stirred solution of the phenylsulphonyl-protected cyclopropapyrroloindole (**20**) (5.8 mg, 0.017 mmol) in dry DMF (0.5 ml), at 0 °C. After 10 min at 0 °C the now yellow mixture was allowed to warm to room temperature and 10 min later it was cooled to 0 °C again. A DMF solution of *p*-t-butylbenzoyl chloride (0.08M; 250 μl, 0.020 mmol) was added dropwise. The mixture was stirred at room temperature for 1 h after which time it was quenched by the addition of water. After extracting the aqueous mixture with ethyl acetate, the organic layers were washed with water and brine, dried (Na_2SO_4) and evaporated to give a colourless oil. This was chromatographed (triethylamine–ethyl acetate) giving the *title compound* (**21**) (4.0 mg, 47%) as an amorphous solid (Found: M^+, 500.1760. $C_{29}H_{28}N_2O_4S$ requires *M*, 500.1770); $\nu_{max.}$($CHCl_3$) 2 965, 2 870, 1 633s, 1 381, 1 338, 1 321, 1 188, 1 173, 1 128, and 1 107 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 1.30 (9 H, s, Me_3C), 1.54 (1 H, dd, *J* 4.7 and 5.1 Hz, 8-H), 2.06 (3 H, d, *J* 1 Hz, 7-Me), 2.11 (1 H, dd, *J* 4.7 and 7.5 Hz, 8-H), 2.90—2.97 (1 H, m, 8a-H), 4.05—4.18 (2 H, m, 1-H), 7.33—7.59 (9 H, m, 2′-, 3′-, 5′-, 6′-, 3-, 6-H, and Ph), and 7.98—8.02 (2 H, m, *o*-PhH); *m/z* (180 °C) 500 (M^+, 0.5%), 436 (5), 360 (8), 161 (100), and 130 (77).

2-*Allyl*-1,2,8,8a-*tetrahydro*-7-*methyl*-5-*phenylsulphonylcyclo*-*propa*[c]*pyrrolo*[3,2-e]*indol*-4(5H)-*one* (**22**).—The *N*-acetyl-*N*-phenylsulphonylcyclopropapyrroloindole (**19**) (5.4 mg, 0.014 mmol) was de-acetylated in sodium methoxide as described earlier. Work-up gave the mono-protected compound (**20**) which was used directly without further purification.

The material was dissolved in dry THF (0.3 ml) under nitrogen and cooled to −10 °C. Sodium hydride (60% dispersion; 1.1 mg, 0.028 mmol) was added and after 5 min the now yellow solution was treated with a THF solution of allyl bromide (0.19M; 0.1 ml, 0.019 mmol). After 1.5 h the reaction was quenched with water and the mixture was extracted with ethyl acetate. Drying, evaporation, and chromatography (triethylamine–ethyl acetate) yielded the title compound (**22**) (3.9 mg, 73% for 2 steps) as a pale yellow amorphous solid. The structure was assigned on the basis of its spectroscopic properties; $\nu_{max.}$($CDCl_3$) 2 927, 1 605s, 1 567, 1 451, 1 230, 1 173, 1 130, 777, 684, and 594 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 1.10 (1 H, dd, *J* 4.2 and 4.8 Hz, 8-H), 1.78 (1 H, dd, *J* 4.2 and 7.8 Hz, 8-H), 1.97 (3 H, d, *J* 1 Hz, 7-Me), 2.88 (1 H, ddd, *J* 4.8, 5.2, and 7.8 Hz, 8a-H), 3.48 (1 H, d, *J* 10.5 Hz, 1-H), 3.62—3.69 (3 H, m, 1-H and $NCH_2CH{=}CH_2$), 5.10—5.20 (3 H, m, 3-H and $NCH_2CH{=}CH_2$), 5.60—5.75 (1 H, m, $NCH_2CH{=}CH_2$), 7.44—7.58 (4 H, m, 6-H and Ph), and 8.04—8.10 (2 H, m, *o*-PhH); *m/z* (260 °C) 416 (M^+, 5%), 380 (7), 366 (43), 218 (20), 142 (4), 125 (6), and 110 (12).

2-*Allyl*-5-*t*-*butoxycarbonyl*-1,2,8,8a-*tetrahydro*-7-*methyl* *cyclopropa*[c]*pyrrolo*[3,2-e]*indol*-4(5H)-*one* (**24**).—The diprotected compound (**22**) (8.1 mg, 0.021 mmol) was treated with sodium methoxide–methanol (1M; 1 ml) at room temperature overnight. Water was added and the resulting mixture was extracted with dichloromethane. Drying and evaporation gave

the monoprotected compound (**23**) (5.3 mg) as a pale yellow amorphous solid which was homogeneous by t.l.c. (triethylamine–methanol–ethyl acetate); $\nu_{max.}$(CHCl$_3$) 3 460, 3 300br, 2 962, 1 597s, 1 552, 1 529, 1 243, and 1 112 cm^{-1}; δ_H(250 MHz; CDCl$_3$) 1.11 (1 H, dd, *J* 4.3 and 4.5 Hz, 8-H), 1.80 (1 H, dd, *J* 4.3 and 7.5 Hz, 8-H), 1.98 (3 H, d, *J ca.* 0.8 Hz, 7-Me), 2.87 (1 H, ddd, *J* 4.5, 5.5, and 7.5 Hz, 8a-H), 3.52 (1 H, d, *J* 10.3 Hz, 1-H), 3.71 (1 H, dd, *J* 5.5 and 10.3 Hz, 1-H), 3.74 (2 H, m, NCH_2CH=CH$_2$), 5.18 (1 H, m, NCH$_2$CH=CH_2), 5.24 (1 H, m, NCH$_2$CH=CH_2), 5.34 (1 H, s, 3-H), 5.67—5.83 (1 H, m, NCH$_2$C*H*=CH$_2$), 6.70 (1 H, m, 6-H), and 9.33 (1 H, br s, NH). This was used directly in the next stage without further purification. Thus it was dissolved in dry acetonitrile (0.5 ml) and a THF solution of di-t-butyl dicarbonate (0.069M; 0.4 ml, 0.028 mmol) was added, followed by 4-(dimethylamino)pyridine (0.4 mg, 0.003 mmol). The mixture was stirred for 2 days at room temperature and the reaction followed by t.l.c. The reaction was quenched with water and extracted with dichloromethane. Drying and evaporation gave a yellow solid which was purified by chromatography (triethylamine–methanol–ethyl acetate). This yielded the *title compound* (**24**) (4.8 mg, 66% over 2 steps) as a glass (Found: M^+, 340.1775. $C_{20}H_{24}N_2O_3$ requires *M*, 340.1787); $\nu_{max.}$(CDCl$_3$) 2 965, 1 735, 1 608s, 1 569, 1 455, 1 429, 1 396, 1 370, 1 336, 1 277, 1 234, 1 159, and 1 060 cm^{-1}; δ_H(250 MHz; CDCl$_3$) 1.13 (1 H, dd, *J* 4 and 4.8 Hz, 8-H), 1.60 (9 H, s, Me$_3$C), 1.78 (1 H, dd, *J* 4 and 7.8 Hz, 8-H), 1.92 (3 H, d, *J* 1 Hz, 7-Me), 2.85 (1 H, ddd, *J* 4.8, 5.2, and 7.8 Hz, 8a-H), 3.49 (1 H, d, *J* 10.5 Hz, 1-H), 3.66 (1 H, dd, *J* 5.2 and 10.5 Hz, 1-H), 3.70 (2 H, d, *J* 6.0 Hz, NCH_2CH=CH$_2$), 5.15—5.23 (2 H, m, NCH$_2$CH=CH_2), 5.32 (1 H, s, 3-H), 5.67—5.83 (1 H, m, NCH$_2$C*H*=CH$_2$), and 7.05 (1 H, br, 6-H); *m/z* (200 °C) 340 (M^+, 6%), 240 (100), 225 (5), 199 (8), and 56 (17).

Attempted Removal of the Allyl Protecting Group of Compound (**24**).—The *N*-allyl protected indoline (**24**) (4.8 mg, 0.014 mmol) was dissolved in aqueous ethanol (90% w/w; 1 ml) containing 1,4-diazabicyclo[2.2.2]octane (DABCO) (0.9 mg, 8 μmol). Tris(triphenylphosphine)rhodium(I) chloride (Wilkinson's catalyst) (1.4 mg, 1.5 μmol) was added and the mixture was stirred for 3 days at room temperature. The mixture was poured into water and extracted with dichloromethane. The combined organic layers were washed with water and dried (Na_2SO_4). Evaporation gave a yellow gum which was chromatographed (triethylamine–methanol–ethyl acetate) giving a green yellow glass (3 mg, 89%) which was identified as the product (**23**) arising from removal of the t-butoxycarbonyl protecting group, by comparison of its i.r. and n.m.r. spectra with those of an authentic sample.

4-*Benzyloxy*-3,6-*dihydro*-5-*methoxypyrrolo*[3,2-e]*indole*-7-*carboxylic Acid* (**27**).—Pyrroloindole ester (**26**) (82 mg, 0.23 mmol) was dissolved in methanol (12 ml) and water (0.5 ml) added. A precipitate formed which redissolved in a few seconds. Potassium hydroxide (100 mg, 1.8 mmol) was added and the mixture gently warmed to reflux. The mixture was heated for 1 h after which t.l.c. indicated that there was no starting material present. Hydrochloric acid was added to acidify the solution and the solvent was removed under reduced pressure. The crude mixture was purified by column chromatography (ether–light petroleum, product; R_F 0.32, ether) to yield the *title compound* (**27**) (73 mg, 93%) as a crystalline solid, m.p. 191—192 °C (decomp.) (Found: C, 67.9; H, 4.7; N, 8.2. $C_{19}H_{16}N_2O_4$ requires C, 67.85; H, 4.8; N, 8.3%); $\lambda_{max.}$(EtOH) 244 (log ε 4.22), 315 (4.44); (EtOH–NaOH) 238 (4.24), 308 (4.46); (EtOH–HCl) 249 (4.24) and 322 nm (4.43); $\nu_{max.}$(Nujol) 3 450 (NH), 3 320 (NH), 2 600br (OH), 1 665vs (C=O), 1 530, 1 520, 1 490w, 1 455, 1 430w, 1 380, 1 350, 1 280s, 1 270s, 1 200, 1 180, 1 150, 1 120, 1 090, 1 070, 1 055, 1 030w, 1 010, 980w, 935, 890, 850, 830, 770, 735s, 700, and 665 cm^{-1}; δ_H(250 MHz; CDCl$_3$) 4.08 (3 H, s, OMe), 5.28 (2 H, s, CH$_2$Ph), 6.72 (1 H, dd, $J_{1,2}$ 3 Hz, $J_{1,3}$ 2 Hz, 1-H), 7.11 (1 H, t, $J_{2,1}$ and $J_{2,3}$ 3 Hz, 2-H), 7.29—7.5 (5 H, m, Ph), 7.56 (1 H, d, *J* 2 Hz, 8-H), 8.30 (1 H, br s, 3-H), and 9.23 (1 H, br s, 6-H); *m/z* (200 °C) 336 (M^+, 7%), 292 (16), 262 (11), 245 (40), 227 (20), 201 (100), 184 (10), 173 (7), 158 (18), and 91 (32).

Benzyl 4-*Benzyloxy*-3-[(4-*benzyloxy*-3,6-*dihydro*-5-*methoxypyrrolo*[3,2-e]*indol*-7-*yl*)*carbonyl*]-1,2,3,6-*tetrahydro*-5-*methoxypyrrolo*[3,2-e]*indole*-7-*carboxylate* (**28**).—Indoline (**25**) (106 mg, 0.37 mmol) and acid (**27**) (125 mg, 0.37 mmol) were dissolved in dichloromethane (2 ml) and DMF (1 drop). The mixture was cooled to 0 °C under nitrogen and CMC (Aldrich) (95%; 180 mg, 1.1 mol equiv.) was added. The solution was warmed slowly to room temperature and stirred overnight. The mixture was diluted with water (1 ml), extracted with ethyl acetate, washed with brine, and dried (Na_2SO_4). The solvent was removed under reduced pressure and the dark coloured residue was purified by chromatography on silica (ether–light petroleum; product R_F 0.38, ether) to give the *title compound* (**28**) (174 mg, 63%; in other experiments yields ranged from 55—73%) as a yellow crystalline solid, m.p. 205—207 °C (Found: C, 72.3; H, 5.1; N, 7.3. $C_{45}H_{38}N_4O_7$ requires C, 72.4; H, 5.1; N, 7.5%); $\lambda_{max.}$(EtOH) 236 (log ε 4.37), 300sh (4.36), and 339 nm (4.51); $\nu_{max.}$(KBr) 3 440, 3 310, 2 940, 1 687s, 1 610s, 1 580, 1 506s, 1 445, 1 416s, 1 380, 1 320vs, 1 286, 1 260, 1 240, 1 210, 1 195, 1 180, 1 155s, 1 140sh, 1 100, 1 075, 1 050s, 1 025, 1 005w, 980, 950, 910, 890, 870, 840, 815, 775, 755s, 745, and 695s cm^{-1}; δ_H(250 MHz; CDCl$_3$) 3.19 (2 H, t, *J* 7.5 Hz, 1-H), 4.07 (3 H, s, OMe), 4.09 (3 H, s, OMe), 4.49 (2 H, t, *J* 7.5 Hz, 2-H), 5.12 (2 H, s, CH$_2$Ph), 5.31 (2 H, s, CH$_2$Ph), 5.39 (2 H, s, CH$_2$Ph), 6.72 (1 H, t, *J* 3 Hz, 1′-H), 7.10—7.56 (18 H, m, 3 × Ph, 2′-, 8′-, and 8-H), 8.31 (1 H, br s, NH), 9.00 (1 H, br s, NH), and 9.40 (1 H, br s, NH); *m/z* (FAB, thiodiethanol) 747 (MH^+).

Benzyl 4-*Benzyloxy*-3-[(4-*benzyloxy*-1,2,3,6-*tetrahydro*-5-*methoxypyrrolo*[3,2-e]*indol*-7-*yl*)*carbonyl*]-1,2,3,6-*tetrahydro*-5-*methoxypyrrolo*[3,2-e]*indole*-7-*carboxylate* (**29**).—The above dimer (**28**) (106 mg, 0.14 mmol) was dissolved in dry acetic acid (1 ml) under nitrogen and sodium cyanoborohydride (180 mg) added in one portion. The mixture was stirred at room temperature for 1 h, and then added cautiously to saturated aqueous potassium hydrogen carbonate, extracted with chloroform, and dried (Na_2SO_4). The solvent was removed under low pressure and the crude product purified by chromatography on silica (ether–light petroleum; product R_F 0.35, ether) to give the *title compound* (**29**) (65 mg, 61%; in other experiments yields ranged from 61—74%), m.p. 190—191 °C (Found: C, 72.0; H, 5.35; N, 7.4. $C_{45}H_{40}N_4O_7$ requires C, 72.2; H, 5.4; N, 7.5%); $\lambda_{max.}$(EtOH) 236 (log ε 4.51) and 317 nm (4.58); $\nu_{max.}$(KBr) 1 688s, 1 615s, 1 590w, 1 525w, 1 500s, 1 442w, 1 416s, 1 372, 1 330s, 1 314s, 1 288, 1 260, 1 245w, 1 209, 1 187, 1 152, 1 134, 1 107, 1 022, 990w, 974w, 906w, 874w, 840w, 813, 776, 758s, and 695s cm^{-1}; δ_H(250 MHz; CDCl$_3$) 3.15 (2 H, t, *J* 8 Hz, 1-or 1′-H), 3.17 (2 H, t, *J* 8 Hz, 1′-or 1-H), 3.59 (2 H, t, *J* 8 Hz, 2′-H), 4.00 (3 H, s, OMe), 4.05 (3 H, s, OMe), 4.41 (2 H, t, *J* 8 Hz, 2-H), 5.09 (2 H, s, CH$_2$Ph), 5.10 (2 H, s, CH$_2$Ph), 5.37 (2 H, s, CH$_2$Ph), 6.64 (1 H, d, *J* 2 Hz, 8- or 8′-H), 7.09 (1 H, d, *J* 2 Hz, 8′-or 8-H), 7.13—7.54 (15 H, m, 3 × Ph), 8.99 (1 H, br s, NH), and 9.10 (1 H, br s, NH).

Benzyl 4-*Benzyloxy*-3-[(4-*benzyloxy*-3-*carbamoyl*-1,2,3,6-*tetrahydro*-5-*methoxypyrrolo*[3,2-e]*indol*-7-*yl*)*carbonyl*]-1,2,3,6-*tetrahydro*-5-*methoxypyrrolo*[3,2-e]*indole*-7-*carboxylate* (**30**).—The above reduced dimer (**29**) (60 mg, 0.08 mmol) was dissolved in dry dichloroethane (2 ml) with gentle swirling. Trimethylsilylisocyanate (TMS–NCO) (85%; 200 μl) was added and the mixture stirred at room temperature for 12 h. A further

portion of TMS–NCO (85%; 50 μl) was added and stirring continued for a further 4 h. The mixture was preadsorbed directly onto silica and purified by chromatography (EtOAc–light petroleum; product R_F 0.42, EtOAc) to give the *title compound* (**30**) (45 mg, 71%; in other experiments yields ranged from 58—71%), m.p. 134—136 °C (Found: C, 65.9; H, 5.0; N, 8.4. $C_{46}H_{41}N_5O_8 \cdot 2.5H_2O$ requires C, 66.0; H, 5.5; N, 8.4%); $\lambda_{max.}$(EtOH) 246 (log ε 4.43) and 313 nm (4.45); $\nu_{max.}$(KBr) 3 430br, 3 340br, 3 035w, 2 940, 2 895, 2 840w, 1 709s, 1 637s, 1 589s, 1 522, 1 497, 1 445, 1 412vs, 1 367, 1 329s, 1 315, 1 288s, 1 256s, 1 209s, 1 189, 1 150vs, 1 106s, 1019, 971, 907, 875w, 813, 751s, and 696s cm^{-1}; δ_H(250 MHz; $CDCl_3$) 3.11 (2 H, t, *J* 7.5 Hz, 1- or 1′-H), 3.20 (2 H, t, *J* 7.5 Hz, 1′- or 1-H), 4.05 (3 H, s, OMe), 4.07 (3 H, s, OMe), 4.40 (4 H, t, *J* 7.5 Hz, 2′- and 2-H), 5.04 (2 H, s, CH_2Ph), 5.10 (2 H, s, CH_2Ph), 5.40 (2 H, s, CH_2Ph), 6.69 (1 H, d, *J* 2.5 Hz, 8′-H), 7.13 (1 H, d, *J* 2.5 Hz, 8-H), 7.16—7.52 (15 H, m, 2 × Ph), 9.05 (1 H, br s, NH), and 9.24 (1 H, br s, NH); *m/z* (FAB, thiodiethanol) 792 (MH^+, 5.2%), 701 (3.0), 657 (3.2), 568 (3.0), 429 (1.8), and 365 (1.7).

3-[(3-*Carbamoyl*-1,2,3,6-*tetrahydro*-4-*hydroxy*-5-*methoxypyrrolo*[3,2-e]*indol*-7-*yl*)*carbonyl*]-1,2,3,6-*tetrahydro*-4-*hydroxy*-5-*methoxypyrrolo*[3,2-e]*indole*-7-*carboxylic Acid*-[PDE-I Dimer] (**3**).—The above reduced carbamoylated dimer (**30**) (45 mg, 0.06 mmol) was dissolved in dry DMF (2 ml) and palladium–carbon (5%; 2 mg) added. The mixture was stirred at room temperature under an atmosphere of hydrogen (60 p.s.i.) and the reaction followed by h.p.l.c. (5% H_2O in MeOH). After 3.5 h the catalyst was filtered off and the DMF removed by low-pressure distillation to give pure PDE-dimer (**3**) (30 mg, 100%), m.p. > 300 °C; $\lambda_{max.}$(EtOH) 290 (log ε 4.37) and 352 nm (4.52); $\nu_{max.}$(KBr) 3 470br, 2930, 2 498br, 1 707, 1 690w, 1 636s, 1 565w, 1 545w, 1 490s, 1 470, 1 414, 1 374, 1 333, 1 314, 1 255, 1 175, 1 148, 1 070w, 1 048w, 1 020, 1 000w, 956, 890, 790, 770, 746, and 726 cm^{-1}; δ_H[250 MHz; $(CD_3)_2SO$] 3.12—3.31 (4 H, m, 1- and 1′-H), 3.81 (3 H, s, OMe), 3.85 (3 H, s, OMe), 4.03 (2 H, t, *J* 8 Hz, 2′- or 2-H), 4.66 (2 H, t, *J* 7 Hz, 2- or 2′-H), 6.89 (1 H, s, 8- or 8′-H), 6.92 (2 H, s, NH_2), 7.05 (1 H, s, 8′- or 8-H), 10.83 (1 H, s, 4- or 4′-OH), 11.15 (1 H, br s, NH), 11.35 (1 H, br s, NH), and 12.92 (1 H, s, 4′- or 4-OH); *m/z* (FAB, thiodiethanol) 522 (MH^+). This product was compared with an authentic specimen from CC-1 065 by h.p.l.c. analysis on a Rainin Microsorb C_{18} column (5 μm, 150 × 4.6 mm). DMSO solutions (0.4mM; 10 μl) were eluted with 15% water in methanol at a flow rate of 1.5 ml min^{-1}. The two specimens, separately and combined, had identical retention times.

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