Vinyl Azides in Heterocyclic Synthesis. Part 8.[1] Synthesis of the Naturally Occurring Phosphodiesterase Inhibitors PDE-I and PDE-II

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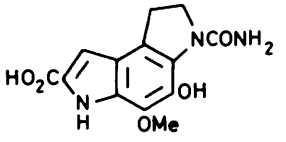
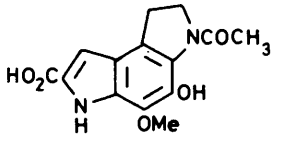
The synthesis of the naturally occurring pyrrolo[3,2-*e*]indole phosphodiesterase inhibitors PDE-I (**1**) and PDE-II (**2**) from isovanillin is described. The route involves the construction of both pyrrole rings by vinylnitrene cyclisations, the key cyclisation substrates being the azidoacrylates (**5**) and (**11**), prepared from the aldehydes (**4**) and (**10**) respectively. The tricyclic intermediate (**12**) is converted into both PDE-I and PDE-II by selective reduction, followed by carbamoylation or acetylation respectively, and deprotection.

The naturally occurring pyrrolo[3,2-*e*]indoles (**1**) and (**2**), known as PDE-I and PDE-II respectively, were isolated from *Streptomyces* MD769-C6 and exhibit inhibitory activity towards cyclic adenosine-3′,5′-monophosphate phosphodiesterase.[2] The structures, assigned by n.m.r. spectroscopy, were confirmed by *X*-ray crystallography,[3] and by syntheses by classical routes.[4,5] Pyrrolo-indoles very closely related to PDE-I and PDE-II also make up the central and right-hand units of the antibiotic CC-1065 (**3**),[6] which because of its very potent antitumour activity has been the subject of considerable synthetic effort.[7] We now report the full details of a new route to pyrrolo[3,2-*e*]indoles, and the synthesis of the natural products PDE-I (**1**) and PDE-II (**2**).[8]



(**1**)



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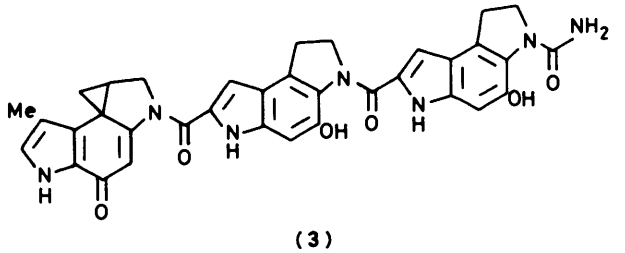
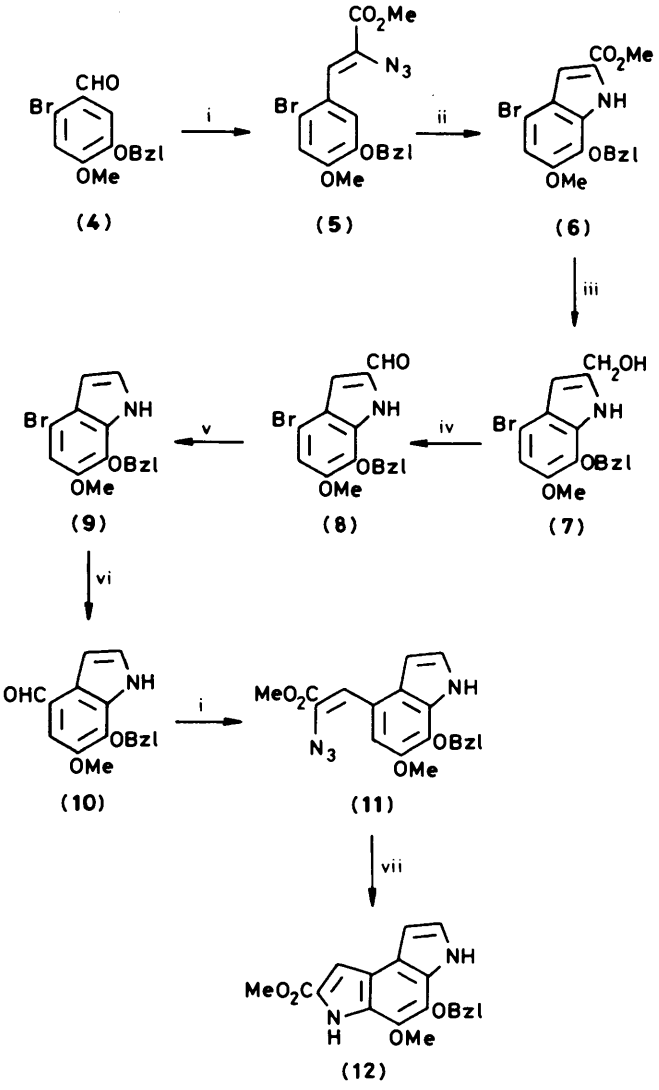


(**3**)

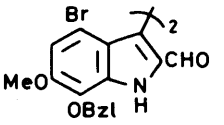
Results and Discussion

The overall strategy (Scheme 1) involves, as key steps, the formation of both pyrrole rings by vinylnitrene cyclisations. The precursors are azidoacrylate derivatives readily prepared from aromatic aldehydes, and we have already illustrated the use of similar intermediates in the total synthesis of the bacterial coenzyme methoxatin.[9] Our starting material was the known[10] 5-benzyloxy-2-bromo-4-methoxybenzaldehyde (**4**) easily prepared on a large scale from isovanillin by benzylation and bromination; by increasing the amount of bromine and increasing the reaction time we were able to improve significantly the literature yield (77% overall, lit.,[10] 20%). Condensation of the aldehyde (**4**) with methyl azidoacetate gave the azidocinnamate (**5**), the substrate for the first vinylnitrene cyclisation. Heating the azide (**5**) in refluxing xylene for 1 h resulted in loss of nitrogen and cyclisation in essentially quantitative yield to the indole-2-carboxylate (**6**). Although this material could be purified, it was more convenient to reduce it directly with lithium aluminium hydride to the alcohol (**7**) in 93% over the two steps. Oxidation of the alcohol (**7**) with freshly prepared manganese dioxide in refluxing dichloromethane for 45 min



Scheme 1. [Bzl = CH_2Ph] *Reagents:* i, $MeO_2CCH_2N_3$, NaOMe, MeOH; ii, xylene, reflux; iii, $LiAlH_4$, ether, reflux; iv, MnO_2, CH_2Cl_2, reflux; v, $Rh(Ph_3P)_2(CO)Cl$ (0.06 equiv.), dppp (0.12 equiv.), mesitylene, reflux; vi, Bu^{t}Li, THF, −78 °C then DMF; vii, toluene, reflux

gave the corresponding aldehyde (**8**) in 84% yield. Interestingly, if the oxidation reaction was allowed to run for longer periods, or if the isolated aldehyde was re-subjected to the oxidation conditions, another product, which is tentatively assigned structure (**13**), was obtained. Decarbonylation of the aldehyde

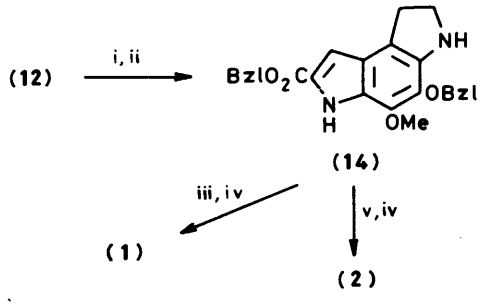


(**13**)

(**8**) by treatment with a catalytic amount of $Rh(Ph_3P)_2(CO)Cl$ and 1,3-bis(diphenylphosphino)propane (dppp) in refluxing mesitylene[11] gave the indole (**9**) in 70% yield. Originally it had been intended to remove the unwanted ester group by hydrolysis and decarboxylation, but as has been reported with other indole-2-carboxylic acids,[11] we found that decarboxylation was unsatisfactory, and hence the alternative decarbonylation approach was employed. The problem is clearly due to the instability of the indole (**9**) under the decarboxylation conditions (refluxing in quinoline or glycerol or a mixture of acetic acid and hydrochloric acid).

In order to introduce the new azidoacrylate side chain, it was necessary to convert the bromoindole (**9**) into the corresponding aldehyde. This was achieved by lithiation with an excess of t-butyl-lithium in tetrahydrofuran (THF) at −78 °C *without* protection of the indole nitrogen, followed by quenching with dimethylformamide (DMF), to give the aldehyde (**10**) in 72% yield. Condensation of the aldehyde (**10**) with methyl azidoacetate gave the azide (**11**) (71%), the substrate for the second vinylnitrene cyclisation. Thermolysis of the azide (**11**) in refluxing toluene resulted in cyclisation to the key intermediate, the tricyclic pyrroloindole (**12**) in excellent (97%) yield (Scheme 1). The lower boiling solvent was used for this cyclisation since, when the azide (**11**) was heated in xylene, another product was formed by rearrangement of the pyrroloindole (**12**). The nature of this rearrangement will be discussed elsewhere.

The conversion of the pyrroloindole (**12**) into PDE-I and PDE-II was achieved as shown in Scheme 2. The methyl ester



Scheme 2. [Bzl = CH_2Ph] *Reagents:* i, $PhCH_2OH$, $PhCH_2ONa$, benzene, reflux; ii, $NaBH_3CN$, AcOH, room temp.; iii, Me_3SiNCO, benzene, room temp.; iv, H_2 (4 atm), Pd–C, MeOH; v, Ac_2O, pyridine, room temp.

was first transesterified by reaction with benzyl alcohol and sodium benzyloxide. This not only increased the solubility but also meant that both the carboxylic acid and phenol groups could be released by hydrogenolysis in the final step. The resulting pyrroloindole benzyl ester underwent selective reduction of the more electron rich indole double bond on treatment with sodium cyanoborohydride in acetic acid[12] to give the pyrroloindole (**14**) [63% from (**12**)]. Carbamoylation of the pyrroloindole (**14**) was most conveniently carried out by reaction with trimethylsilyl isocyanate,[13] sodium cyanate in acetic acid[5] being much less satisfactory. Hydrogenolysis of the benzyl groups gave PDE-I (**1**) in 65% yield from the pyrroloindole (**14**). Similarly, PDE-II (**2**) was obtained from the pyrroloindole (**14**) in 84% yield by acetylation with acetic anhydride in pyridine and hydrogenolysis. The spectra of synthetic PDE-I and PDE-II were identical to those reported in the literature.[2]

Experimental

For general points see ref. 14.

5-Benzyloxy-2-bromo-4-methoxybenzaldehyde (**4**).—Isovanillin (20 g, 0.132 mol) was dissolved in ethanol (120 ml) and potassium hydroxide (8 g, 0.143 mol) added with rapid stirring. Benzyl chloride (16.4 ml, 0.143 mol) was added immediately, and the mixture refluxed for 4.25 h with vigorous stirring. Water was added to dissolve the potassium chloride, and the mixture was extracted with ether. The ether extract was washed with aqueous potassium hydroxide (5%; 2 × 50 ml) and dried ($MgSO_4$), and evaporated under reduced pressure to give 3-benzyloxy-4-methoxybenzaldehyde (31.2 g, 98%) as a light tan solid, m.p. 59—62 °C (lit.,[15] 62—63 °C).

The above compound (24.25 g, 0.1 mol) was dissolved in acetic acid (350 ml) and sodium acetate (12 g) added. Bromine (6 ml) was added slowly to the mixture which was then stirred for 22 h at room temperature. More sodium acetate (12 g) was added, followed by a further amount of bromine (7 ml), and the stirring continued for a further 24 h. More bromine (7 ml) was added and the stirring continued for 20 h. The product was filtered, washed with a little acetic acid, and dried *in vacuo* to give the title compound (**4**) (22.07 g, 69%). Half the solvent was removed at low pressure and the solid produced filtered off. This solid was extracted with chloroform and the extract dried ($MgSO_4$) and concentrated to give a further yield of product (3.2 g, 10%; total 25.27 g, 79%), m.p. 139—143 °C (lit.,[10] 122—123 °C).

Methyl 2-Azido-3-(5-benzyloxy-2-bromo-4-methoxyphenyl)-propenoate (**5**).—Sodium (20.44 g, 0.89 mol) was dissolved in dry methanol under nitrogen and the mixture cooled to −5 °C. A suspension of methyl azidoacetate (100 g, 0.87 mol) and the aldehyde (**4**) (40 g, 0.125 mol) in warm THF (120 ml) was added slowly to the methoxide over 1 h with gentle stirring. The temperature was maintained at −5 °C for 5 h and then raised slowly to 4 °C for 48 h. The product was filtered off and washed with a little cold methanol until the washings were colourless to give the *title compound* (**5**) (36.9 g, 71%) as a pale yellow crystalline solid, m.p. 113—115 °C (Found: C, 51.85; H, 3.8; N, 10.0. $C_{18}H_{16}BrN_3O_4$ requires C, 51.7; H, 3.9; N, 10.05%); $\nu_{max.}$(Nujol) 2 120vs (N_3), 1 700s (C=O), 1 610, 1 590, 1 500s, 1 440, 1 390, 1 365, 1 290, 1 270s, 1 205s, 1 170s, 1 090, 1 045w, 1 030, 960w, 910w, 890, 870, 845, 835, 810, 760s, 750, 735s, and 700 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 3.90 (3 H, s, OMe), 3.91 (3 H, s, OMe), 5.22 (2 H, s, CH_2Ph), 7.08 (1 H, s, ArH), 7.17 (1 H, s, ArH), 7.3—7.5 (5 H, m, Ph), and 7.83 (1 H, s, 3-H); *m/z* 419/417 (M^+, 0.4%), 391/389 (4), 332/330 (3), 300/298 (8), 268/266 (5), and 91 (100).

7-Benzyloxy-4-bromo-6-methoxy-1H-indol-2-ylmethanol (**7**).—The azide (**5**) (27 g, 65 mmol) was dissolved in dry xylene (2 100 ml) under nitrogen. The solution was heated rapidly and refluxed for 1 h. The solvent was removed under reduced pressure to give the indole ester (**6**) which, without further purification, was dissolved in dry ether (250 ml). The mixture was cooled to 0 °C under nitrogen, lithium aluminium hydride (3.5 g, 92 mmol) was slowly added to the stirred mixture and the ether refluxed gently for 4 h. The solution was stirred overnight

at room temperature and then re-cooled to 0 °C. Water (10 ml) was added cautiously followed by aqueous sodium hydroxide (5M; 10 ml). The mixture was filtered through a plug of silica and the precipitate washed well with warm dichloromethane until no more product could be detected in the washings by t.l.c. The solvent was removed under reduced pressure to yield the *title compound* (**7**) (21.8 g, 93%) as a colourless solid, m.p. 152—154 °C (from ether) (Found: C, 56.4; H, 4.3; N, 4.0. $C_{17}H_{16}BrNO_3$ requires C, 56.4; H, 4.45; N, 4.0%); $\lambda_{max.}$(EtOH) 222 (log ε 4.58), 276 (3.99), and 304 nm sh (3.70); $\nu_{max.}$(Nujol) 3 400br (NH), 3 240br (OH), 1 635, 1 625, 1 510s, 1 505sh, 1 430, 1 410, 1 380, 1 340, 1 300w, 1 250s, 1 235, 1 225, 1 210, 1 140s, 1 060, 1 035, 1 020s, 995, 980, 970, 965, 915w, 850w, 830, 820, 795, 750w, 740, and 705 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 3.92 (3 H, s, OMe), 4.68 (2 H, br s, CH_2OH), 5.14 (2 H, s, CH_2Ph), 6.28 (1 H, d, *J* 2 Hz, 3-H), 7.00 (1 H, s, 5-H), 7.30—7.46 (5 H, m, Ph), and 8.26 (1 H, br s, NH); *m/z* 363/361 (M^+, 25%), 272/270 (92), 254/252 (19), 226/224 (8), 192 (6), 163 (10), 145 (12), 133 (11), 130 (10), 117 (6), 102 (7), and 91 (100).

In a separate experiment, the product from the azide thermolysis was purified by crystallisation to give *methyl 7-benzyloxy-4-bromo-6-methoxy-1H-indole-2-carboxylate* (**6**), m.p. 135—140 °C (Found: C, 55.3; H, 4.2; N, 3.45. $C_{18}H_{16}BrNO_4$ requires C, 55.4; H, 4.1; N, 3.6%); $\lambda_{max.}$(EtOH) 246 (log ε 4.38) and 311 nm (4.18); $\nu_{max.}$(Nujol) 3 420sh, 3 310br, 3 030w, 2 950, 2 840w, 1 700s, 1 630, 1 570w, 1 550, 1 510, 1 440, 1 420, 1 350, 1 315, 1 260vs, 1 205, 1 180w, 1 130, 1 060, 1 000, 930w, 910, 830, 770, 750, 730, and 700 cm^{-1}; δ (250 MHz; $CDCl_3$) 3.90 (3 H, s, OMe), 3.94 (3 H, s, OMe), 5.17 (2 H, s, CH_2Ph), 7.09 (1 H, s, 5-H), 7.11 (1 H, d, *J* 2 Hz, 3-H), 7.30—7.43 (5 H, m, Ph), and 8.70 (1 H, br s, NH); *m/z* 391/389 (M^+, 15%), 298/296 (18), 266/264 (5), 175 (41), 159 (35), 120 (62), 106 (73), and 91 (100).

7-Benzyloxy-4-bromo-6-methoxy-1H-indole-2-carbaldehyde (**8**).—The alcohol (**7**) (10 g, 27.6 mmol) was dried *in vacuo* and then dissolved in dry dichloromethane (500 ml) with gentle heating. Finely ground, freshly prepared manganese dioxide (36 g, 15 equiv.) was added slowly to the mixture which was then brought to reflux. After 45 min, t.l.c. showed that no starting material remained. The warm mixture was filtered through a pad of coarse silica and the MnO_2 washed well with hot dichloromethane. The solvent was removed under reduced pressure to give the *title compound* (**8**) (8.4 g, 84%) as a beige solid, m.p. 147—148 °C (from ether–light petroleum) (Found: C, 56.85; H, 3.9; N, 3.7. $C_{17}H_{14}BrNO_3$ requires C, 56.7; H, 3.9; N, 3.9%); $\lambda_{max.}$(EtOH) 254 (log ε 4.29), and 323 nm (4.24); $\nu_{max.}$(Nujol) 3 345br (NH), 1 665vs (conj. C=O), 1 625s, 1 570w, 1 540, 1 510, 1 430w, 1 370, 1 325s, 1 315sh, 1 250s, 1 225, 1 145s, 1 060w, 995w, 980w, 960w, 830, 820, 790, 760, 730, and 700 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 3.96 (3 H, s, OMe), 5.15 (2 H, s, CH_2Ph), 7.11 (1 H, s, 5-H), 7.14 (1 H, d, *J* 2.4 Hz, 3-H), 7.3—7.55 (5 H, m, Ph), 8.84 (1 H, br s, NH), and 9.70 (1 H, s, CHO); δ_C (62.9 MHz; $CDCl_3$) 57.47, 75.36, 110.80, 113.57, 114.66. 124.63, 128.31, 128.40, 128.55, 132.71, 133.61, 136.17, 137.25, 150.61, and 180.86; *m/z* 361/359 (M^+, 4.1%), 333/331 (2.2), 280 (1.0), 270/268 (9.1), 242/240 (1.8), 161 (9.9), 146 (4.8), 133 (6.3), and 91 (100).

When the aldehyde (**8**) was stirred at room temperature with MnO_2 for prolonged periods it gave the *7,7′-dibenzyloxy-4,4′-dibromo-2,2′-diformyl-6,6′-dimethoxy-3,3′-bi-indole* (**13**), m.p. 228.5—229 °C (from ether–light petroleum) (Found: C, 56.7; H, 3.9; N, 4.1. $C_{34}H_{26}Br_2N_2O_6$ requires C, 56.8; H, 3.65; N, 3.9%); $\lambda_{max.}$(EtOH) 258 (log ε 4.52), and 329 nm (4.45); $\nu_{max.}$(Nujol) 3 250br (NH), 3 085w, 3 065w, 1 660s, 1 655s, 1 645s, 1 625s, 1 563, 1 520, 1 505, 1 430, 1 380w, 1 365, 1 335 , 1 310s, 1 265s, 1 250, 1 220, 1 200, 1 195, 1 135, 1 120, 1 083, 1 008, 965, 910w, 832, 815w, 790, 750, 740, and 700 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 3.97 (3 H, s, OMe), 5.23 (2 H, s, CH_2Ph), 7.08 (1 H, s, 5-H), 7.30—7.45 (5 H, m, Ph), 8.90 (1 H, br s, NH), and 9.37 (1 H, s, CHO); δ_C (62.9 MHz; $CDCl_3$), 57.34, 76.50, 111.04, 114.88, 117.41, 124.12, 128.59, 132.15, 133.55, 135.86, 137.12, 150.52, 180.90; *m/z* 720 (M^+, 1.4%), 718 (2.7), 716 (1.2), 627 (4.0), 538 (2.0), 467 (1.8), 457 (1.8), 439 (2.0), 377 (11.3), 376 (12.8), 347 (2.6), 265 (3.9), 103 (6.2), and 91 (100)

7-Benzyloxy-4-bromo-6-methoxy-1H-indole (**9**).—$Rh(PPh_3P)_2CO(Cl)$ (443 mg, 0.64 mmol) was suspended in dry mesitylene (30 ml) and warmed to 80 °C under nitrogen. After 10 min 1,3-bis(diphenylphosphino)propane (528 mg, 1.28 mmol) was added and a yellow precipitate formed. After a further 10 min, 7-benzyloxy-4-bromo-6-methoxy-1*H*-indole-2-carbaldehyde (**8**) (2.88 g, 8.0 mmol) was added and the flask plunged into a woods metal bath at 190 °C. Vigorous reflux was maintained for 1.3 h after which t.l.c. showed that no starting material was present. The mesitylene was removed under reduced pressure and the crude product purified by flash chromatography to give the *title compound* (**9**) (1.87 g, 70%) as a colourless oil which crystallised with time, m.p. 82—84 °C (from dichloromethane–light petroleum) (Found: C, 58.0; H, 4.2; N, 4.2. $C_{16}H_{14}BrNO_2$ requires C, 57.85; H, 4.25; N, 4.2%); $\lambda_{max.}$(EtOH) 275 (log ε 3.89) and 302sh nm (3.54); $\nu_{max.}$(Nujol) 3 400br (NH), 1 635, 1 508, 1 465, 1 412, 1 380, 1 345, 1 330, 1 295, 1 250w, 1 220s, 1 135, 1 090s, 1 080w, 990, 960w, 915w, 885, 820, 770, 740, 730, 700, and 670 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 3.93 (3 H, s, OMe), 5.15 (2 H, s, CH_2Ph), 6.42 (1 H, dd, $J_{1,3}$ 2.6 Hz, $J_{3,2}$ 3.4 Hz, 3-H), 7.035 (1 H, dd, $J_{2,3}$ 3.4 Hz, $J_{2,1}$ 2.5 Hz, 2-H), 7.04 (1 H, s, 5-H), 7.28—7.45 (5 H, m, Ph), and 8.02 (1 H, br s, NH); *m/z* 333/331 (M^+, 22.4), 242/240 (51), 228/226 (10.7), 148 (5.8), 133 (32.9), 118 (15.3), 105 (5.2), and 91 (100).

7-Benzyloxy-6-methoxy-1H-indole-4-carbaldehyde (**10**).—7-Benzyloxy-4-bromo-6-methoxy-1*H*-indole (**9**) (506 mg, 1.5 mmol), previously dried *in vacuo* over phosphorus pentaoxide, was dissolved in dry THF (10 ml) under nitrogen. The solution was cooled to −78 °C and t-butyl-lithium (1.8M in hexane; 5 ml, 9 mmol) added slowly with rapid stirring. The resulting yellow solution was stirred at −78 °C for 1 h after which time it had become orange. Dry DMF (4 ml) was added slowly and the mixture stirred for a further 1 h at −78 °C; a yellow precipitate formed. Saturated aqueous ammonium chloride was added and the mixture allowed to warm to room temperature; it was then stirred for 2 h. The mixture was extracted with ether, and the organic layer was washed with water and dried (Na_2SO_4). Purification of the residue by column chromatography gave the *title compound* (**10**) (308 mg, 72%) as a yellow crystalline solid, m.p. 117—119 °C (Found: C, 72.4; H, 5.45, N, 5.1. $C_{17}H_{15}NO_3$ requires C, 72.6; H, 5.4; N, 5.0%); $\lambda_{max.}$(EtOH) 237 (log ε 4.28), 315 (3.88), and 366 nm (3.96); $\nu_{max.}$(Nujol) 3 300br (NH), 3 100, 1 650vs (C=O), 1 620, 1 560vs, 1 520, 1 500, 1 450, 1 430w, 1 410, 1 395w, 1 360s, 1 310s, 1 240s, 1 220, 1 195w, 1 140vs, 1 100, 1 060w, 1 020, 955s, 905, 855, 850, 785s, 770, 755s, 725, and 695 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 4.02 (3 H, s, OMe), 5.34 (2 H, s, CH_2Ph), 7.15 (1 H, dd, $J_{3,2}$ 3.2 Hz, $J_{3,1}$ 2.2 Hz, 3-H), 7.23 (1 H, dd, $J_{2,3}$ 3.2 Hz, $J_{2,1}$ 2.5 Hz, 2-H), 7.32—7.45 (5 H, m, Ph), 7.40 (1 H, s, 5-H), 8.22 (1 H, br s, NH), and 10.17 (1 H, s, CHO); *m/z* 281 (M^+, 14%), 252 (1.2), 190 (16), and 91 (100).

Methyl 2-Azido-3-(7-benzyloxy-6-methoxy-1H-indol-4-yl)-propenoate (**11**).—Sodium (710 mg, 31 mmol) was dissolved in dry methanol (15 ml) under nitrogen and the solution cooled to −15 °C. A suspension of methyl azidoacetate (3.47 g, 30.2 mmol) and 7-benzyloxy-6-methoxy-1*H*-indole-4-carbaldehyde (**10**) (1.06 g, 3.8 mmol) in methanol (11 ml) was added slowly to the methoxide over 25 min with gentle stirring. The stirred mixture was kept in the dark at −15 °C for 6.5 h after which the

temperature was raised slowly to 4 °C and stirring continued for a further 15 h. The precipitated product was filtered off, washed with cold methanol, and dried *in vacuo*. The mother liquor was poured into saturated aqueous ammonium chloride and extracted with chloroform. The organic phase was washed with brine, dried (Na_2SO_4) and purified by flash chromatography to give a yellow, light sensitive solid which was combined with the filtered material to give the *title compound* (**11**) (1.01 g, 71%), m.p. 103—105 °C (decomp.) (Found: C, 63.3; H, 4.8. $C_{20}H_{18}N_4O_4$ requires C, 63.5; H, 4.8%); $\lambda_{max.}$(EtOH) 270 (log ε 3.97) and 373 nm sh (3.65); $\nu_{max.}$(Nujol) 3 360br (NH), 2 130vs (N_3), 1 688vs (C=O), 1 625, 1 600w, 1 570w, 1 515, 1 470, 1 440s, 1 340, 1 320s, 1 290s, 1 260, 1 240, 1 220, 1 190w, 1 145, 1 120, 1 095, 1 070, 1 020, 973, 960w, 915w, 885, 840, 775, 760s, and 720 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 3.94 (3 H, s, OMe), 4.01 (3 H, s, OMe), 5.25 (2 H, s, CH_2Ph), 6.59 (1 H, dd, $J_{3,2}$ 3.2 Hz, $J_{3,1}$ 2.2 Hz, 3-H), 7.09 (1 H, dd, $J_{2,3}$ 3.2 Hz, $J_{2,1}$ 2.4 Hz, 2-H), 7.30—7.48 (5 H, m, Ph), 7.35 (1 H, s, 5-H), 7.94 (1 H, s, =CHAr), and 8.06 (1 H, br s, NH); *m/z* 352 ($M^+ - N_2 + 2$, 9%), 350 (18, $M^+ - N_2$), 322 (7), 320 (9), 261 (52), 259 (100, $M^+ - 91$), 227 (46), 201 (11), and 199 (11).

Methyl 4-Benzyloxy-3,6-dihydro-5-methoxypyrrolo[3,2-e]*indole-7-carboxylate* (**12**).—The azide (**11**) (810 mg, 2.1 mmol) was dissolved in dry toluene (250 ml) under nitrogen in a flask protected from light. The stirred solution was heated rapidly and refluxed gently for 1 h. The toluene was removed under reduced pressure and the residue purified by flash chromatography (ether–light petroleum) to give the *title compound* (**12**) (730 mg, 97%) as a light yellow glassy solid, m.p. 57—59 °C (Found: C 68.8; H, 5.1; N, 7.75. $C_{20}H_{18}N_2O_4$ requires C, 68.6; H, 5.2; N, 8.0%); $\lambda_{max.}$(EtOH) 250 (log ε 4.18), and 329 nm (4.37); $\nu_{max.}$(Nujol) 3 360br (NH), 1 690vs (C=O), 1 625w, 1 600w, 1 520s, 1 495w, 1 460, 1 380s, 1 350, 1 290s, 1 270s, 1 200, 1 175, 1 150, 1 075, 1 050, 1 000, 910w, 890, 830, 765s, 740, and 700 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 3.95 (3 H, s, OMe), 4.07 (3 H, s, OMe), 5.29 (2 H, s, CH_2Ph), 6.72 (1 H, dd, $J_{1,2}$ 3.5 Hz, $J_{1,3}$ 2.4 Hz, 1-H), 7.11 (1 H, dd, $J_{2,1}$ 3.5 Hz, $J_{2,3}$ 3.0 Hz, 2-H), 7.34—7.51 (5 H, m, Ph), 7.42 (1 H, d, *J* 2.4 Hz, 8-H), 8.29 (1 H, br s, 3-H), and 9.12 (1 H, br s, 6-H); *m/z* 350 (M^+, 14%), 259 (100), 227 (53), 199 (9), 184 (15), and 149 (5).

Benzyl 4-Benzyloxy-1,2,3,6-tetrahydro-5-methoxypyrrolo[3,2-e]*indole-7-carboxylate* (**14**).—The methyl ester (**12**) (370 mg, 1.1 mmol) was dissolved in dry benzene (2 ml) and sodium benzyloxide (140 mg, 1.1 mmol) added under nitrogen. Benzyl alcohol (1.1 ml, 10.5 mmol) was added and the solution stirred at 80 °C for 0.5 h. The benzene and excess benzyl alcohol were removed under reduced pressure and the solid dissolved in dry acetic acid (10 ml). Sodium cyanoborohydride (662 mg, 10.5 mmol) was added and the mixture stirred at room temperature for 1 h. The crude product was cautiously added to saturated aqueous potassium hydrogen carbonate, extracted with chloroform (3 × 30 ml) and the organic phase dried (Na_2SO_4). Column chromatography (ether–light petroleum) yielded the air-sensitive *indole* (**14**) (285 mg, 63%) as a glassy solid, m.p. 42—44 °C (Found: M^+, 428.1751. $C_{26}H_{24}N_2O_4$ requires *M*, 428.1736); $\lambda_{max.}$(EtOH) 240 (log ε 4.33), 308 (4.28), and 343 nm (3.64); $\nu_{max.}$($CHCl_3$) 3 460s, 3 380w, 2 950, 2 860w, 1 705vs, 1 600, 1 530, 1 505, 1 450, 1 420, 1 250, 1 230br s, 1 220, 1 200, 1 155, 1 130, 1 095, 1 000, and 910 cm^{-1}; δ_H (90 MHz; $CDCl_3$) 3.0—3.3 (2 H, m, 1-H), 3.45—3.75 (2 H, m, 2-H), 4.04 (3 H, s, OMe), 5.15 (2 H, s, CH_2Ph), 5.42 (2 H, s, CH_2Ph), 7.05 (1 H, d, *J* 2 Hz, 8-H); 7.25—7.60 (10 H, m, Ph), and 8.83 (1 H, br s, 6-H); *m/z* 428 (M^+, 22%), 337 (48), 335 (17), 229 (11), and 91 (100).

In a separate experiment, the intermediate compound, *benzyl 4-benzyloxy-3,6-dihydro-5-methoxypyrrolo*[3,2-e]*indole-7-carboxylate* was isolated and purified by chromatography, m.p. 157—160 °C (Found: C, 72.9; H, 5.1; N, 6.6. $C_{26}H_{22}N_2O_4$ requires C, 73.2; H, 5.2; N, 6.6%); $\lambda_{max.}$(EtOH) 253 (log ε 4.20) and 328 nm (4.38); $\nu_{max.}$(Nujol) 3 475s, 3 320s, 1 705sh, 1 700s, 1 590w, 1 510, 1 455, 1 340w, 1 290s, 1 265s, 1 230w, 1 190, 1 175s, 1 160, 1 075, 1 050, 990, 950w, 910w, 835w, 770s, 760, 740, and 705s cm^{-1}; δ_H (250 MHz; $CDCl_3$) 4.08 (3 H, s, OMe), 5.30 (2 H, s, CH_2Ph), 5.42 (2 H, s, CH_2Ph), 6.71 (1 H, dd, $J_{1,3}$ 2 Hz, $J_{1,2}$ 3 Hz, 1-H), 7.10 (1 H, dd, $J_{2,1}$ 3 Hz, $J_{2,3}$ 3 Hz, 2-H), 7.30—7.55 (10 H, m, Ph), 8.30 (1 H, br s, NH), and 9.15 (1 H, br s, NH); *m/z* 426 (M^+, 3.2%), 350 (1.0), 335 (36.6), 259 (7.1), 227 (11.1), 111 (8.8), 97 (14.0), and 91 (100).

3-Carbamoyl-4-hydroxy-5-methoxy-1,2,3,6-tetrahydropyrrolo[3,2-e]*indole-7-carboxylic Acid* (PDE-I) (**1**).—Tetrahydropyrroloindole (**14**) (27 mg, 0.063 mmol) was dissolved in dry benzene (1 ml) under nitrogen and trimethylsilyl isocyanate (0.2 ml, 1.5 mmol) was added. The mixture was stirred at room temperature for 3 days. The precipitated product was filtered off and washed with dry ether. The mother liquor was purified by flash chromatography (ether–light petroleum) to produce a further amount of product which was combined with the filtered material to give *benzyl 4-benzyloxy-3-carbamoyl-5-methoxy-1,2,3,6-tetrahydropyrrolo*[3,2-e]*indole-7-carboxylate* (21.5 mg, 72%), m.p. 160—162 °C (Found: C, 68.7; H, 5.3; N, 9.1. $C_{27}H_{25}N_3O_5$ requires C, 68.8; H, 5.3; N, 8.9%); $\lambda_{max.}$(EtOH) 253 (log ε 4.32), 296sh (3.97), and 307 nm (4.04); $\nu_{max.}$(KBr) 3 430s br, 3 351br, 1 696vs, 1 653vs, 1 583s, 1 526, 1 498w, 1 431br, 1 292, 1 261, 1 214, 1 192w, 1 164, 1 101, 1 015, 970, 906w, 833w, 752, and 696 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 3.07 (2 H, t, *J* 8 Hz, 1-H), 4.06 (3 H, s, OMe), 4.36 (2 H, t, *J* 8 Hz, 2-H), 5.03 (2 H, s, CH_2Ph), 5.40 (2 H, s, CH_2Ph), 5.75 (2 H, br s, NH_2), 7.10 (1 H, d, *J* 2.3 Hz, 8-H), 7.3—7.55 (10 H, m, Ph), and 8.97 (1 H, br s, NH); *m/z* (FAB) 472 (MH^+).

The above compound (12 mg, 25 μmol) was dissolved in dry methanol (3 ml) and palladium–charcoal (5%; 50 mg) added. The suspension was hydrogenated at 60 p.s.i. for 1 h. The catalyst was removed by filtration through Celite, and the solvent removed under reduced pressure to yield essentially pure PDE-I (**1**) (7.2 mg, 97%), m.p. 235 °C (decomp.) [lit.,[2] 235 °C (decomp.)]; $\lambda_{max.}$(H_2O) 252 (log ε 4.63), and 308 nm (4.20); (NaOH, 0.04M) 236 (4.48), 251 (4.42), and 337 (4.32); (HCl, 0.01M) 257 (4.57), and 320 nm (4.26); $\nu_{max.}$(KBr) 3 362, 3 209, 2 925, 2 540, 1 670s, 1 637s, 1 569, 1 540, 1 465s, 1 331, 1 291, 1 257, 1 224, 1 180, 1 120, 1 091, 1 043, 1 022, 1 000w, 961, 859, 812, 746, 722, 657, and 605 cm^{-1}; δ_H [250 MHz; $(CD_3)_2SO$)] 3.18 (2 H, t, *J* 8 Hz), 3.75 (3 H, s), 3.99 (2 H, t, *J* 8 Hz), 6.86 (3 H, br s), 11.23 (1 H, br s), and 12.84 (1 H, s); *m/z* (FAB) 292 (MH^+).

3-Acetyl-4-hydroxy-5-methoxy-1,2,3,6-tetrahydropyrrolo[3,2-e]*indole-7-carboxylic Acid* (PDE-II) (**2**).—The tetrahydropyrroloindole (**14**) (16 mg, 0.037 mmol) was dissolved in dry pyridine (1 ml) and freshly distilled acetic anhydride (1 ml) added. The solution was stirred at room temperature overnight. Water (2 ml) was added and the mixture made slightly acidic with dilute hydrochloric acid. After extraction with chloroform (3 × 50 ml) the organic phase was washed with water and then brine and finally dried (Na_2SO_4). Flash chromatography (ether–light petroleum) gave *benzyl 3-acetyl-4-benzyloxy-5-methoxy-1,2,3,6-tetrahydropyrrolo*[3,2-e]*indole-7-carboxylate* (16 mg, 91%) as a colourless foam, m.p. 56—59 °C (Found: M^+, 470.1833. $C_{28}H_{26}N_2O_5$ requires *M*, 470.1842); $\lambda_{max.}$(EtOH) 263 (log ε 4.47), 298sh (4.08), and 308 nm (4.17); $\nu_{max.}$(KBr) 2 930, 1 710s, 1 635s, 1 620, 1 560, 1 497, 1 445, 1 412s, 1 380s, 1 346, 1 310w, 1 287s, 1 257s, 1 208, 1 189w, 1 160s, 1 100, 1 022, 983, 908w, 890w, 815, 753, and 698 cm^{-1}; δ_H (90 MHz; $CDCl_3$) 2.28 (3 H, s, $COCH_3$), 3.08 (2 H, t, *J* 7 Hz, 1-H), 4.12 (3 H, s, OMe), 4.27 (2 H, t, *J* 7 Hz, 2-H), 5.02 (2 H, s, CH_2Ph), 5.45 (2 H, s, CH_2Ph), 7.15 (1 H, d, *J* 2 Hz, 8-H), 7.25—7.60 (10 H, m, Ph), and 9.05 (1

H, br s, NH); *m/z* 470 (M^+, 6%), 379 (5), 337 (24), 261 (5), 229 (3), 149 (6), 91 (40), 71 (37), 57 (56), and 43 (100).

The above compound (26 mg, 55 μmol) was dissolved in ethyl acetate (5 ml). Palladium–charcoal (5%; 50 mg) was added and the mixture was hydrogenated at 60 p.s.i. overnight. The catalyst was filtered off through Celite and washed well with more warm solvent. Concentration gave essentially pure PDE-II (**2**) (15.5 mg, 96%), m.p. 253 °C (decomp.) [lit.,[2] 253 °C (decomp.)]; $\lambda_{max.}$(H_2O) 263 (log ε 4.56), and 309 (4.09); (NaOH, 0.04M) 265 (4.53), and 342 (4.32); (HCl, 0.01M) 265 (4.52), and 321 nm (4.16); $\nu_{max.}$(KBr) 3 286s, 2 926, 1 668s, 1 636, 1 600w, 1 569, 1 521, 1 458, 1 420w, 1 380w, 1 330, 1 289, 1 244, 1 210w, 1 192, 1 175, 1 150w, 1 120w, and 1 097 cm^{-1}; δ_H [250 MHz: $(CD_3)_2SO$] 2.28 (3 H, s, $COCH_3$), 3.20 (2 H, t, *J* 8 Hz, 1-H), 3.77 (3 H, s, OMe), 4.20 (2 H, t, *J* 8 Hz, 2-H), 6.94 (1 H, t, *J* 2 Hz, 8-H), 11.40 (1 H, br s, NH), and 12.18 (1 H, s, OH); *m/z* 290 (M^+, 84%), 272 (7), 248 (67), 247 (12), 233 (22), 230 (100), 215 (31), 204 (8), 202 (14), 187 (17.5), and 43 (80).

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