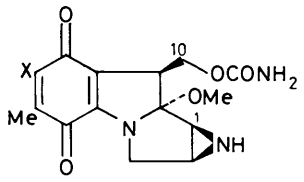
Structurally Modified Antitumour Agents. Part 2.[1] Total Synthesis of a Cyclopropamitosene[2]

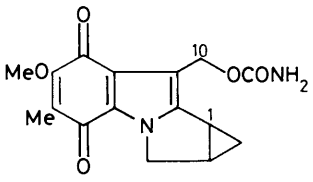
Graham B. Jones and Christopher J. Moody *
Department of Chemistry, Imperial College of Science, Technology and Medicine, London SW7 2AY

The total synthesis of the cyclopropapyrroloindolequinone (**2**), the cyclopropane analogue of the biologically active aziridinomitosene derived from *N*-methylmitomycin A, is described. The synthesis starts from commercially available 4-methylsalicylic acid, which is converted into 2-benzyloxy-3-methoxy-4-methylbenzaldehyde (**17**), the key step being the selective *ortho*-formylation of the hydroxy ester(**12**) to introduce, after Baeyer-Villiger oxidation, the second oxygen substituent. The benzaldehyde (**17**) was converted into the 4,5,6-trisubstituted indole-2-ester (**19**) using the high yielding nitrene cyclisation method, subsequent functional group transformations giving the tosylhydrazone (**23**). Decomposition of the sodium salt of the tosylhydrazone resulted in intramolecular cycloaddition to give the tetracyclic cyclopropapyrroloindole (**24**) in excellent yield. The synthesis was completed by formylation, oxidation to the quinone, and elaboration of the side chain.

Although they were first isolated over 30 years ago, the mitomycins, for example mitomycins A and C (**1**; X = OMe and NH_2 respectively) are still of immense interest and importance because of their potent antitumour action. Indeed a search of the *Chemical Abstracts* database reveals that over 2 000 papers on mitomycins have been published during the last 20 years, with new work currently being published at the rate of about 250 papers per year. As discussed in detail in the preceding paper,[1] much of this recent work has been concerned with the molecular basis for the antitumour action of the mitomycins, in particular their interaction with DNA, although not surprisingly there have also been a large number of synthetic studies carried out.[3] Our own work in this area is designed to focus attention of the role of C-10 of the mitomycins in the alkylation of DNA, by the preparation of compounds in which the electrophilicity at C-1 is much reduced by replacing the readily opened aziridine ring by a less reactive cyclopropane. In the previous paper,[1] we reported the details of our initial studies on the synthesis of the previously unknown cyclopropapyrroloindole ring system, and we now report full details of the total synthesis of the cyclopropapyrroloindolequinone (**2**), the cyclopropane analogue of the aziridinomitosene derived from *N*-methylmitomycin A.



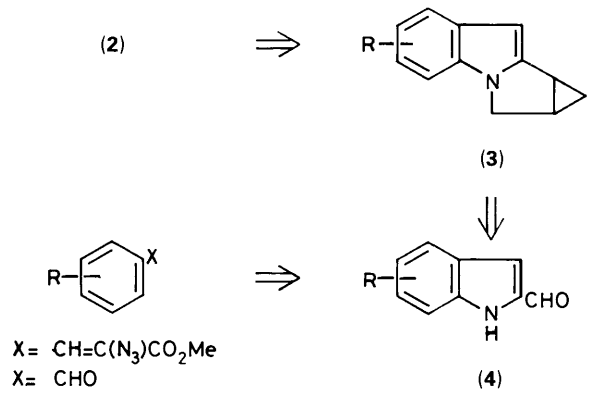
(**1**)



(**2**)

Results and Discussion

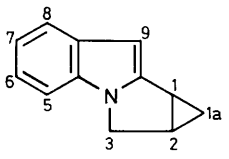
Since our initial studies had already established that the C-10 carbon atom could be introduced by Vilsmeier formylation of the cyclopropapyrroloindole system at position 9,† the synthesis of the cyclopropamitosene (**2**) therefore required a suitably substituted cyclopropapyrroloindole (**3**) (Scheme 1). Our overall strategy involved the formation of the tetracyclic cyclopropapyrroloindole (**3**) from a suitable indole-2-carbaldehyde (**4**) using our previously developed intramolecular cycloaddition, and based on experience in the synthesis of polysubstituted indoles,[4] we expected that the required indole (**4**) could be readily prepared from a relatively simple benzaldehyde using a nitrene cyclisation reaction (Scheme 1), obviating the need for an additional nitrogen substituent on the benzene ring.



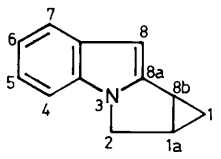
Scheme 1.

The initial problem was therefore the synthesis of an appropriately substituted benzaldehyde for conversion into the

† In the Discussion the numbering of the cyclopropapyrroloindole system (**A**) follows that proposed in ref. 1. However in the Experimental section the IUPAC approved name and numbering (**B**) is used for the compounds described.

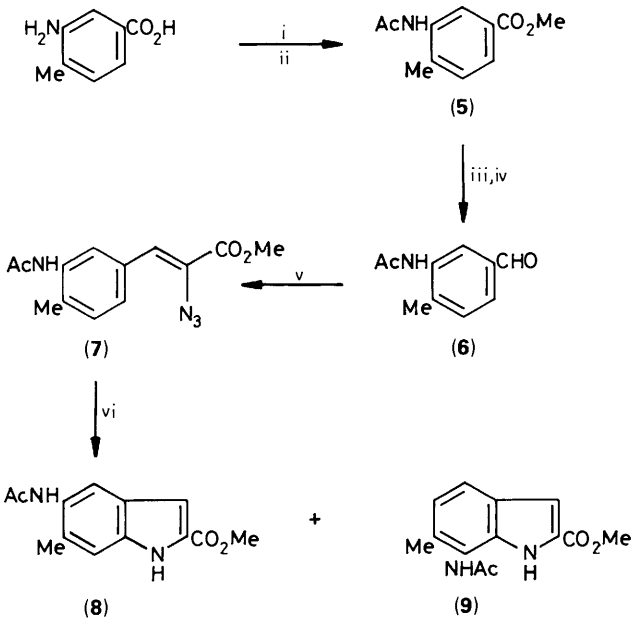


(**A**)



(**B**)

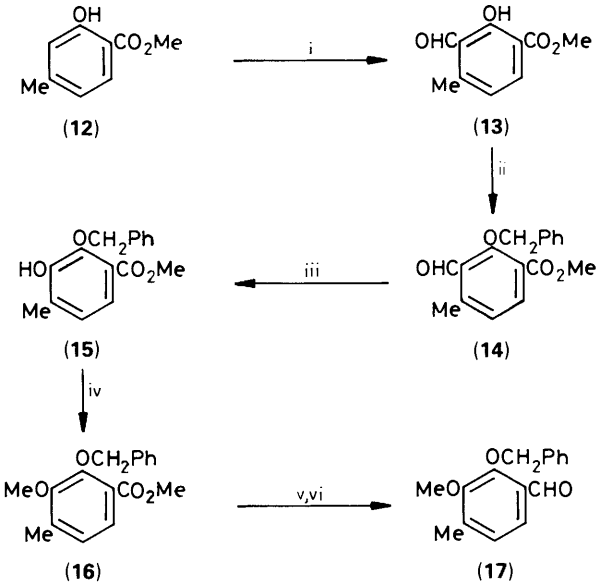
required polysubstituted indole, on the assumption that the 1,4-quinone unit could be introduced late on in the synthesis by oxidation of a suitable aniline or phenol. Initial attempts centred on commercially available 3-amino-4-methylbenzoic acid as the starting material since an additional amino substituent for subsequent oxidation to the quinone could be introduced by nitration at the indole stage at C-4 (indole numbering).[3a] This acid was converted into the corresponding acetamidobenzaldehyde (**6**) by esterification, acetylation, reduction of the ester to the benzyl alcohol, and reoxidation (Scheme 2). This route was abandoned, however, when the derived azide (**7**) gave an inseparable 1:1 mixture of both possible indoles (**8**) and (**9**) on heating in boiling xylene.



Scheme 2. *Reagents*: i, MeOH, H^+; ii, Ac_2O, pyridine, DMAP; iii, $LiAlH_4$, THF; iv, MnO_2, $CHCl_3$; v, $MeO_2CCH_2N_3$, MeONa, MeOH, −15 °C; vi, xylene, reflux

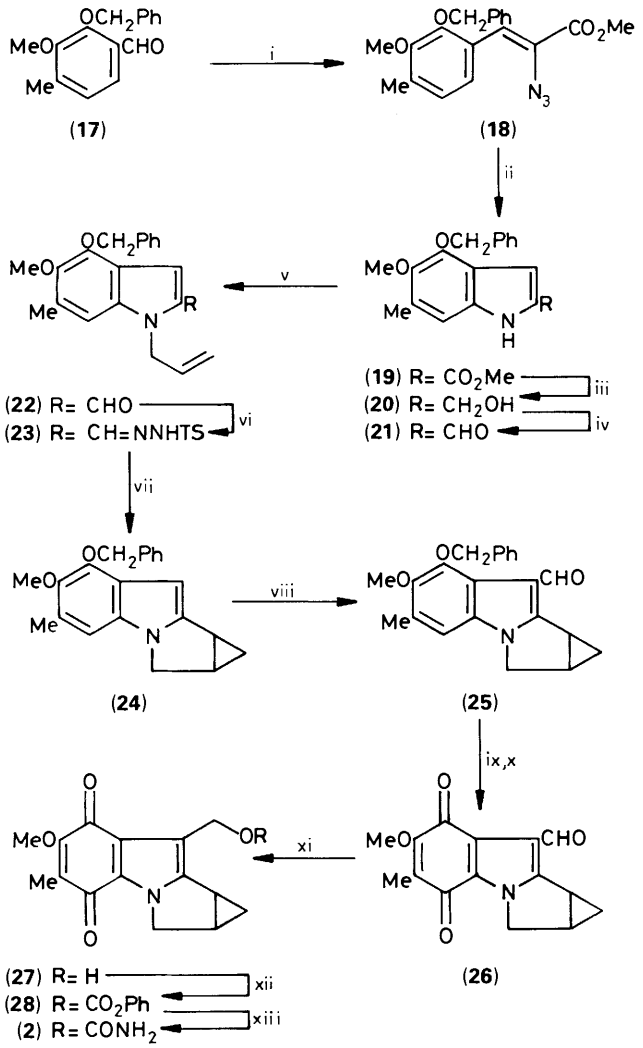
This lack of selectivity in the nitrene cyclisation of an azide derived from a 3,4-disubstituted benzaldehyde indicated that a 2-substituent was required to block the undesired cyclisation. Since this substituent eventually has to be converted into the quinone oxygen, it should be a nitrogen or oxygen function. The only commercially available benzene derivative with the correct substitution pattern was 3-hydroxy-4-methyl-2-nitrobenzoic acid, which was converted without incident into the protected amino ester (**10**). However, this route was not developed any further when problems were encountered in the conversion of the related but simpler amidobenzaldehydes, *e.g.* (**11**) into the 4-substituted indole using the azide route. In a final effort to avoid the problems associated with the *ortho*-amino substituent in the tetra-substituted benzene (**10**), we attempted to convert the amino group into a hydroxy group by diazotisation, or into a 1,4-quinone by direct oxidation with Fremy's salt, both without success.

The route which eventually proved successful used methyl 2-hydroxy-4-methylbenzoate (**12**), prepared by esterification of the commercially available acid, as starting material. Although the 3-oxygen substituent could not be introduced directly by oxidation with benzoyl peroxide,[5] it could be introduced in two steps by formylation followed by a Baeyer-Villiger reaction. Thus the ester (**12**) was formylated using dichloromethyl methyl ether in the presence of titanium(IV) chloride[6] to give the aldehyde (**13**) in 77% yield after crystallisation of the crude product. As expected, the formylation had occurred mainly *ortho*- to the phenol, although the alternative product resulting from *para*-formylation could be isolated (18%) by chromatography of the crystallisation mother liquors. After benzylation of the phenolic OH group which necessitated an inverse addition procedure with the base (NaH) being added to a mixture of the phenol and benzyl bromide (83%), the resulting aldehyde (**14**) was subjected to Baeyer–Villiger oxidation with 3-chloroperbenzoic acid (MCPBA) to give, after acid hydrolysis of the formate ester, the phenol (**15**) in excellent yield (96%). Methylation, followed by conversion of the ester into an aldehyde, then gave the required benzaldehyde (**17**) (Scheme 3).



Scheme 3. *Reagents*: i, Cl_2CHOMe, $TiCl_4$, CH_2Cl_2; ii, $PhCH_2Br$, DMF, NaH; iii, MCPBA then H_3O^+; iv, Me_2SO_4, K_2CO_3, acetone; v, $LiAlH_4$, ether; vi, $BaMnO_4$, CH_2Cl_2

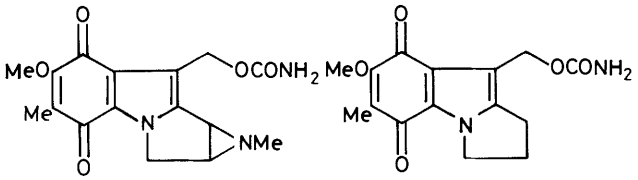
The benzaldehyde (**17**) was condensed with methyl azidoacetate in methanol in the presence of sodium methoxide, and the resulting azidocinnamate (**18**) was decomposed in boiling xylene to give the 4,5,6-trisubstituted indole-2-ester (**19**) (Scheme 4). This high yielding sequence (77% over the 2 steps) highlights the advantages of the nitrene cyclisation route to polysubstituted indoles. The indole ester (**19**) was converted into the corresponding aldehyde (**21**) by lithium aluminium hydride reduction to the alcohol (**20**) followed by reoxidation with barium manganate. The precursor for the key intramolecular cycloaddition reaction, the *N*-allyl tosylhydrazone (**23**) was prepared from the aldehyde (**21**) by *N*-allylation followed by reaction with toluene-*p*-sulphonylhydrazide in methanol. To effect the intramolecular cycloaddition, the tosylhydrazone (**23**) was converted into its sodium salt which was heated in boiling chlorobenzene to give the cyclopropapyrrolo[1,2-*a*] indole (**24**) in 84% yield. Thus the tetracyclic ring system of cyclopropamitosene (**2**) was established directly from an indole in excellent yield, and it remained only to introduce the side chain at C-9 and oxidise the benzene ring to the quinone level.



Scheme 4. *Reagents*: i, $MeO_2CCH_2N_3$, NaOMe, MeOH, −15 °C; ii, xylene, reflux; iii, $LiAlH_4$, ether–THF; iv, $BaMnO_4$, CH_2Cl_2, reflux; v, $H_2C{=}CHCH_2Br$, NaH, DMF; vi, $TsNHNH_2$, MeOH; vii, NaH, THF; PhCl, reflux; viii, NMFA, $POCl_3$, $Cl_2CH_2CH_2Cl$; ix, H_2, Pd-C, EtOAc; x, Fremy's salt, acetone, NaH_2PO_4 buffer; xi, $NaBH_4$, MeOH; $FeCl_3$ work-up; xii, $ClCO_2Ph$, pyridine; xiii, NH_3, CH_2Cl_2

The side chain was introduced by Vilsmeier formylation using *N*-methylformamilide (NMFA) and phosphorus oxychloride in 1,2-dichloroethane and gave the 9-aldehyde (**25**) (63%). The *O*-benzyl group was removed by hydrogenolysis over a palladium-on-carbon catalyst to give the corresponding phenol in excellent yield, with no evidence for any reduction of the cyclopropane ring, and subsequent oxidation with Fremy's salt gave the tetracyclic quinone (**26**). Reduction of the formyl group in the quinone aldehyde (**26**) with sodium borohydride was accompanied by reduction of the quinone unit. However the crude product was re-oxidised to the required quinone alcohol (**27**) simply by incorporating an iron(III) chloride wash during the work-up. Attempted conversion of the alcohol (**27**) into the final carbamate (**2**) in a single step by reaction with trimethysilyl isocyanate[7] resulted, surprisingly, in silylation of the alcohol group. Therefore the urethane group was introduced by a more conventional 2-step procedure involving reaction with phenyl chloroformate, and treatment of the resulting carbonate (**28**) with ammonia, and this gave the required carbamate (**2**).

The cyclopropamitosene (**2**) is an orange crystalline solid whose spectroscopic properties closely resemble those of related aziridinomitosenes derived from natural mitomycins. In particular its u.v. spectrum[$\lambda_{max.}$ 236 (log ε 4.32), 288 (4.06), 343 (3.40), and 465 nm (3.17)] was practically identical with those of the aziridinomitosene (**29**) [$\lambda_{max.}$ 232 (log ε 4.32), 285 (4.16), 346 (3.56), and 430 nm (3.08)], derived by degradation of natural mitomycin B,[8] and the simpler synthetic mitosene (**30**) [$\lambda_{max.}$ 230 (log ε 4.28), 287 (4.16), 345 (3.59), and 460 nm (3.14)][9] establishing that all three compounds share a common chromophore. The biological results on the cyclopropamitosene (**2**), and related compounds will be reported separately.



(**29**) (**30**)

Experimental

For general points see ref. 1.

Methyl 3-Amino-4-methylbenzoate.—3-Amino-4-methylbenzoic acid (5.0 g, 33 mmol) was refluxed in methanol (50 ml) with concentrated sulphuric acid (3 ml) for 3 h and then allowed to cool to room temperature. The solvent was removed under reduced pressure and the residue dissolved in ether (100 ml). The ethereal solution was washed with aqueous sodium hydrogen carbonate (10%; 2 × 50 ml), water (2 × 50 ml), and brine (50 ml), and dried ($MgSO_4$). Removal of solvent under reduced pressure gave a pale yellow residue, which was recrystallised from ethyl acetate–light petroleum to give the title compound (5.34 g, 98%) as colourless crystals, m.p. 104—105 °C (lit.,[10] 115—116 °C); $\nu_{max.}$(Nujol) 3 460, 3 380, 1 705, 1 640, 1 250, and 765 cm^{-1}.

Methyl 3-Acetamido-4-methylbenzoate (**5**).—Methyl 3-amino-4-methylbenzoate (4.0 g, 24.2 mmol) was stirred at room temperature with acetic anhydride (25.0 g, 23 ml, 242 mmol) in pyridine (50 ml) containing a single crystal of 4-dimethylaminopyridine for 2 h. The solution was concentrated under reduced pressure, and the residue was crystallised from dichloromethane–light petroleum to give the *title compound* (**5**) (3.9 g, 78%) as colourless crystals, m.p. 149—151 °C (Found: C, 63.7; H, 6.3; N, 6.9. $C_{11}H_{13}NO_3$ requires C, 63.8; H, 6.3; N, 6.8%); $\nu_{max.}$(Nujol) 3 230, 1 720, 1 645, and 760 cm^{-1}; δ_H(60 MHz; CD_3COCD_3) 8.4 (1 H, s, NH), 8.2 (1 H, s, 2-H), 7.6—7.2 (2 H, m, 5-H, 6-H), 3.8 (3 H, s, OMe), 2.3 (3 H, s, ArMe), and 2.1 (3 H, s, Ac); *m/z* 207 (M^+, 50%), 176 (15), 165 (100), 134 (38), 106 (18), 43 (36), and 28 (80).

3-Acetamido-4-methylbenzyl Alcohol.—Lithium aluminium hydride (0.55 g, 14.5 mmol) was added to a solution of methyl 3-acetamido-4-methylbenzoate (**5**) (1.5 g, 7.25 mmol) in dry THF (20 ml), the mixture being kept at 0 °C throughout addition. The suspension was then stirred at 0 °C for 3 h, before aqueous sodium hydroxide (10%; 5 ml) was added, followed by magnesium sulphate (2.0 g). After being stirred at room temperature for a further 10 min, the mixture was filtered, and the filtrate concentrated under reduced pressure to afford a buff coloured solid. Recrystallisation from ethyl acetate–light petroleum gave the *title compound* (1.093 g, 84%) as colourless crystals, m.p. 180—181 °C (Found: C, 67.0; H, 7.4; N, 7.7. $C_{10}H_{13}NO_2$ requires C, 67.0; H, 7.3; N, 7.8%); $\nu_{max.}$(Nujol) 3 270 and 1 660 cm^{-1}; δ_H (60 MHz; CD_3SOCD_3) 9.2 (1 H, s, NH), 7.21 (1 H, s, 2-H), 7.0 (2 H, s, 5-H, 6-H), 5.1 (1 H, s, OH), 4.3 (2 H, m, CH_2OH), 2.2 (3 H, s, ArMe), and 2.1 (3 H, s, Ac); *m/z* 179 (M^+, 54%), 161 (41), and 137 (100).

3-*Acetamido*-4-*methylbenzaldehyde* (**6**).—Freshly ground manganese dioxide (3.75 g, 43 mmol) was added to a rapidly stirred suspension of 3-acetamido-4-methylbenzyl alcohol (0.5 g, 2.56 mmol) in chloroform (125 ml). The mixture was brought to reflux, at which point all the alcohol went into solution. After 15 min, the mixture was filtered through a pad of Celite, and the filtrate concentrated under reduced pressure to give a tan solid. Recrystallisation of this from ethyl acetate–light petroleum gave the *title compound* (**6**) (0.35 g, 77%) as colourless crystals, m.p. 150—151 °C (Found: C, 67.9; H, 6.3; N, 8.0. $C_{10}H_{11}NO_2$ requires C, 67.8; H, 6.3; N, 7.9%); $\nu_{max.}$(Nujol) 3 265, 1 685, 1 650, and 1 610 cm^{-1}; δ_H(60 MHz; CD_3SOCD_3) 10.1 (1 H, s, CHO), 9.1 (1 H, s, NH), 8.1 (1 H, s, 2-H), 7.6—7.2 (2 H, m, 5-, 6-H), 2.2 (3 H, s, ArMe), and 2.1 (3 H, s, Ac); *m*/*z* 177 (M^+, 49%); 135 (95), 106 (33), 43 (62), and 28 (100).

Methyl 2-*Azido*-3-(3-*acetamido*-4-*methylphenyl*)*propenoate* (**7**).—Sodium metal (0.172 g, 7.5 mmol) was added in portions to dry methanol (5.0 ml). The solution was cooled to −15 °C. A solution of methyl azidoacetate (0.71 g, 6.15 mmol) and 3-acetamido-4-methylbenzaldehyde (**6**) (0.300 g 1.54 mmol) in dry methanol (2 ml) was introduced dropwise by syringe. The mixture was warmed to −5 °C and stirred at this temperature for 5 h; it was then warmed to 4 °C and stirred for 12 h. The mixture was then poured into water (10 ml) and extracted with ether (3 × 30 ml). The combined organic extracts were washed with water (50 ml) and brine (30 ml), dried ($MgSO_4$), and finally evaporated under reduced pressure to give a pale yellow solid. Recrystallisation of this from ethyl acetate–light petroleum gave the *title compound* (**7**) (0.299 g, 71%) as colourless crystals, m.p. 124—125 °C (Found: C, 56.9; H, 5.1; N, 19.7 $C_{13}H_{14}N_4O_3$ requires C, 56.9; H, 5.1; N, 20.4%); $\nu_{max.}$(Nujol 3 280, 2 215, 1 680, and 1 650 cm^{-1}; δ_H(250 MHz; CD_3SOCD_3) 9.39 (1 H, s, NH), 7.93 (1 H, s, Ar 2-H), 7.58 (1 H, d, *J* 10 Hz, Ar 5-H), 7.29 (1 H, d, *J* 10 Hz, Ar 6-H), 6.87 (1 H, s, 3-H), 3.85 (3 H, s, OMe), 2.21 (3 H, s, ArMe), and 2.05 (3 H, s, Ac); *m*/*z* 274 (M^+, 1%), 246 (70), 172 (91), and 28 (100).

Methyl 5-*Acetamido*-6-*methylindole*-2-*carboxylate* (**8**).—Methyl 2-azido-3-(3-acetamido-4-methylphenyl)propenoate (**7**) (0.230 g, 0.84 mmol) was dissolved in dry xylene (100 ml) and the solution refluxed for 3 h under a nitrogen atmosphere. Removal of xylene under reduced pressure afforded an orange solid, which was purified by chromatography to give the *title compound* (**8**) and an equal amount of its isomer methyl 7-acetamido-6-methylindole-2-carboxylate (**9**) as an inseparable 1:1 mixture, isolated as a colourless solid (0.153 g, 74%) (Found: M^+, 246.1007. $C_{13}H_{14}N_2O_3$ requires *M*, 246.1004); $\nu_{max.}$(Nujol) 3 340, 1 685, and 1 650 cm^{-1}; δ_H(250 MHz; CD_3SOCD_3) indole (**8**): 11.77 (s, 1 H, AcN*H*), 9.30 (1 H, s, NH), 7.58 (1 H, s, 5- or 7-H), 7.23 (1 H, s, 5- or 7-H), 7.11 (1 H, s, 3-H), 3.88 (3 H, s, OMe), 2.27 (3 H, s, 6-Me), and 2.14 (3 H, s, Ac); indole (**9**): 11.41 (1 H, s, AcN*H*), 9.21 (1 H, s, NH), 7.43 (1 H, d, *J* 10 Hz, 4- or 5-H), 7.09 (1 H, s, 3-H), 6.96 (1 H, d, *J* 10 Hz, 4- or 5-H), 3.88 (3 H, s, OMe), 2.25 (3 H, s, 6-Me), and 2.09 (3 H, s, Ac); *m*/*z* 246 (M^+, 81%), 214 (15), 204 (18), 177 (18), 172 (100), and 135 (30).

Methyl 3-*Methoxy*-4-*methyl*-2-*nitrobenzoate*.—3-Hydroxy-4-methyl-2-nitrobenzoic acid (4.0 g, 20.3 mmol) was dissolved in butan-2-one (200 ml). Potassium carbonate (60 g, 435 mmol) was added, in portions, and the suspension stirred vigorously. After 30 min, methyl iodide (30 ml, 482 mmol) was added, and the mixture refluxed for 12 h. The mixture was filtered, and the filtrate was evaporated under reduced pressure to give a brown oil. This was dissolved in ethyl acetate (100 ml) and the organic layer was washed with aqueous potassium carbonate (10%; 100 ml), water (3 × 100 ml), and brine (100 ml), and dried ($MgSO_4$). Removal of solvent under reduced pressure gave a yellow solid which was recrystallised from ethyl acetate to give the *title compound* (4.34 g, 95%) as pale yellow crystals, m.p. 35—36 °C (Found: C, 53.6; H, 5.0; N, 6.2. $C_{10}H_{11}NO_5$ requires C, 53.3; H, 4.9; N, 6.2%); $\nu_{max.}$($CHCl_3$) 1 740, 1 560, 1 300, and 1 290 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 7.8 (1 H, d, *J* 8 Hz, 5- or 6-H), 7.4 (1 H, d, *J* 8 Hz, 5- or 6-H), 3.85 (6 H, s, OMe), and 2.4 (3 H, s, ArMe); *m*/*z* 225 (M^+, 100%), 194 (41), 164 (39), 163 (47), 120 (25), and 90 (31).

Methyl 2-*Amino*-3-*methoxy*-4-*methylbenzoate*.—Palladium-on-carbon catalyst (10%; 0.080 g), was added to a solution of methyl 3-methoxy-4-methyl-2-nitrobenzoate (1.00 g, 4.44 mmol) in ethyl acetate (80 ml). The mixture was hydrogenated (140 p.s.i.) for 12 h, after which the suspension was filtered, and the filtrate evaporated under reduced pressure to give a brown solid. Recrystallisation of this from ethyl acetate gave the *title compound* (0.796 g, 92%) as colourless crystals, m.p. 84—85 °C (Found: C, 61.6; H, 6.8; N, 7.0. $C_{10}H_{13}NO_3$ requires C 61.5; H, 6.7; N, 7.2%); $\nu_{max.}$(Nujol) 3 471, 3 372, 1 688, 1 621, 1 434, and 774; δ_H (60 MHz; $CDCl_3$) 7.6 (1 H, d, *J* 10 Hz, 5- or 6-H), 6.5 (1 H, d, *J* 10 Hz, 5- or 6-H), 5.8 (2 H, br s, NH_2), 3.8 (3 H, s, OMe), 3.7 (3 H, s, OMe), and 2.3 (3 H, s, ArMe); *m*/*z* 195 (M^+, 100%), 180 (69), 164 (15), 148 (85), 135 (20), 120 (34), and 65 (15).

Methyl 2-*Acetamido*-3-*methoxy*-4-*methylbenzoate* (**10**).—Acetic anhydride (5 ml, 53 mmol) was added to a stirred solution of methyl 2-amino-3-methoxy-4-methylbenzoate (0.365 g, 1.872 mmol) in pyridine (10 ml). The mixture was stirred at 40 °C for 2 h, then evaporated under reduced pressure to give a brown oil, which was dissolved in ethyl acetate (100 ml). The organic layer was washed with water (100 ml), aqueous copper sulphate (2M; 3 × 100 ml), water (100 ml), and brine (100 ml). The organic layers were dried ($MgSO_4$) and then evaporated under reduced pressure to give a yellow oil, which was purified by column chromatography to give the *title compound* (**10**) (0.191 g, 43%) as colourless crystals, m.p. 119—120 °C (Found: C, 60.9; H, 6.4; N, 5.9. $C_{12}H_{15}NO_4$ requires C, 60.8; H, 6.4; N, 5.9%); $\nu_{max.}$(Nujol) 1 729, 1 658, 1 378, and 1 065 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 8.3 (1 H, s, NH), 7.4 (1 H, d, *J* 8 Hz, 5- or 6-H), 6.9 (1 H, d *J* 8 Hz, 5- or 6-H), 3.8 (3 H, s, OMe), 3.7 (3 H, s, OMe), 2.3 (3 H, s, ArMe), and 2.2 (3 H, s, Ac); *m*/*z* 237 (M^+, 50%), 206 (55), 195 (79), 180 (100), 174 (20), 148 (66), 135 (25), 43 (29), and 28 (28).

2-(*Benzyloxycarbonyl*)*aminobenzyl Alcohol*.—Benzyl chloroformate (0.75 g, 4.4 mmol) and aqueous sodium carbonate (4M; 5 ml) were added simultaneously to a stirred solution of 2-aminobenzyl alcohol (0.480 g, 3.9 mmol) and aqueous sodium carbonate (4M; 10 ml) in THF (2 ml). The mixture was stirred at 0 °C for 30 min, after which the THF was removed under reduced pressure. The residue was dissolved in ethyl acetate and the organic layer washed with water, dried ($MgSO_4$), and evaporated to give a yellow solid. Purification by column chromatography gave the *title compound* (0.842 g, 84%) as a colourless solid, m.p. 70—71 °C (Found: M^+, 257.1046. $C_{15}H_{15}NO_3$ requires M, 257.1052); $\nu_{max.}$(Nujol) 3 480, 3 337, 1 715, 1 593, 1 514, and 757 cm^{-1}; δ_H (90 MHz; CD_3COCD_3) 8.6 (1 H, s, br, NH), 8.0 (1 H, d, *J* 9 Hz, ArH), 7.6—7.0 (9 H, m, ArH), 5.2 (2 H, s, PhCH_2), and 4.7 (2 H, s, CH_2OH); *m*/*z* 257 (M^+, 1%), 225 (4), 216 (2), 194 (2), 107 (53), 91 (100), and 79 (38).

2-(*Benzyloxycarbonyl*)*aminobenzaldehyde* (**11**).—Freshly ground manganese dioxide (2.0 g, 20 mmol) was added to a solution of 2-(benzyloxycarbonyl)aminobenzyl alcohol (0.500 g, 2.0 mmol) in dry dichloromethane (30 ml), and the suspension stirred at room temperature for 1 h. The mixture was filtered, and the filtrate evaporated under reduced pressure to give the *title compound* (**11**) (0.449 g, 88%) as colourless crystals, m.p. 59—60 °C (Found: M^+, 255.0884. $C_{15}H_{13}NO_3$ requires *M*, 255.0895); $\nu_{max.}$(Nujol) 3 276, 1 725, 1 670, 1 610, 1 590, 1 533,

1 209, 1 040, and 758 cm^{-1}; δ_H(90) MHz; $CDCl_3$) 9.8 (1 H, s, CHO), 8.4 (1 H, d, *J* 9 Hz, ArH), 7.6—7.1 (9 H, m, ArH), and 5.25 (2 H, s, PhCH_2); *m/z* 255 (M^+, 13%) and 91 (100).

Condensation of 2-(*Benzyloxycarbonyl*)*aminobenzaldehyde with Methyl Azidoacetate.*—Sodium metal (0.170 g, 7.4 mmol) was added in portions to dry methanol (10 ml), and the solution was cooled to −15 °C. A solution of methyl azidoacetate (0.851 g, 7.4 mmol) and 2-(benzyloxycarbonyl)aminobenzaldehyde (**11**) (0.377 g, 1.48 mmol) in dry methanol (10 ml) was introduced dropwise by syringe. The mixture was warmed to −10 °C and stirred for 5 h; it was then warmed to 4 °C and stirred for a further 12 h. After this the mixture was poured into water (20 ml) and extracted with ether (3 × 100 ml). The combined organic extracts were washed with water (2 × 100 ml) and brine (100 ml), dried ($MgSO_4$), and evaporated under reduced pressure to give a yellow oil. This was purified by column chromatography to give *methyl* 3-(2-*aminophenyl*)-2-*azidopropenoate* (0.219 g, 68%) as a yellow solid, m.p. 84—87 °C (Found M^+, 218.0806. $C_{10}H_{10}N_4O_2$ requires *M*, 218.0804); $\nu_{max.}$(film) 3 378, 2 125, 1 1713, 1 605, 1 571, and 1 489 cm^{-1}; δ_H(90 MHz; $CDCl_3$) 7.4—6.7 (5 H, m, ArH, =CH), 3.8 (3 H, s, OMe), and 3.6 (2 H, s, br, NH_2); *m/z* 218 (M^+, 3%), 190 (6), 175 (1), 158 (5), 131 (14), 108 (100), 79 (88), and 77 (46).

Methyl 2-*Hydroxy*-4-*methylbenzoate* (**12**).—Concentrated sulphuric acid (30 ml) was added cautiously to a solution of 4-methylsalicylic acid (50 g, 0.329 mol) in methanol (500 ml). The mixture was refluxed for 12 h. On cooling, the mixture was neutralised ($NaHCO_3$) and concentrated under reduced pressure. The residue was extracted with ethyl acetate (2 × 500 ml), and the combined extracts were washed with water (2 × 250 ml), aqueous sodium hydrogen carbonate (2 × 250 ml), water (2 × 100 ml), and brine (200 ml). The organic layer was dried ($MgSO_4$) and then concentrated under reduced pres-sure to give a dark tan oil. Trituration of this with hexane gave the title compound (**12**) (52.97 g, 97%) as colourless needles, m.p. 25 °C (lit.,[11] m.p. 28 °C) (Found: C, 64.95; H, 6.0. Calc for $C_9H_{10}O_3$: C, 65.05; H, 6.1%); $\nu_{max.}$(film) 3 195, 1 680, 1 440, 1 340, 1 300, 1 260, and 1 220 cm^{-1}; δ_H(60 MHz; $CDCl_3$) 10.6 (1 H, s, OH), 7.6 (1 H, d, *J* 10 Hz, ArH), 6.7 (1 H, s, ArH), 6.6 (1 H, d, *J* 10 Hz, ArH), 3.9 (3 H, s, OMe), and 2.3 (3 H, s, ArMe).

Methyl 3-*Formyl*-2-*hydroxy*-4-*methylbenzoate* (**13**).—Titanium tetrachloride (11 ml, 100 mmol) was added, over 5 min to a stirred solution of methyl 2-hydroxy-4-methylbenzoate (**12**) (8.3 g, 50 mmol) in dichloromethane (100 ml) at 0 °C. Dichloromethyl methyl ether (6.90 ml, 60 mmol) was then added dropwise at 0 °C and the mixture stirred at the same temperature for 22 h. The resulting slurry was poured into water (150 ml) extracted with dichloromethane (3 × 200 ml). The combined extracts were washed with water (2 × 100 ml) and brine (100 ml), dried ($MgSO_4$), and evaporated under reduced pressure. Recrystallisation of the residue from ether gave the *title compound* (**13**) (7.47 g, 77%) as colourless crystals, m.p. 80—81 °C (Found: C, 61.8; H, 5.1. $C_{10}H_{10}O_4$ requires C, 61.9; H, 5.2%); $\nu_{max.}$(CCl_4) 1 676, 1 620, 1 450, and 1 210 cm^{-1}; δ_H(60 MHz; $CDCl_3$) 11.8 (1 H, s, OH), 10.7 (1 H, s, CHO), 7.8 (1 H, d, *J* 10 Hz, ArH), 6.6 (1 H, d, *J* 10 Hz, ArH), 4.0 (3 H, s, OMe), and 2.6 (3 H, s, ArMe); *m/z* 194 (M^+, 46%), 166 (82), 163 (16), 161 (21), 134 (100), 106 (27), and 77 (22). Concentration of the mother liquors, followed by column chromatography gave the *title compound* (1.75 g, 18%), as colourless crystals, m.p. 71—72 °C (Found: C, 61.7; H, 5.1. $C_{10}H_{10}O_4$ requires C, 61.9; H, 5.2%); $\nu_{max.}$(CCl_4) 1 690, 1 675, 1 450, and 1 150 cm^{-1}; δ_H(90 MHz; $CDCl_3$) 11.0 (1 H, s, OH), 9.9 (1 H, s, CHO), 8.1 (1 H, s, ArH), 6.7 (1 H, s, ArH), 3.9 (3 H, s, OMe), and 2.6 (3 H, s, ArMe); *m/z* 194 (M^+, 65%), 162 (100), 134 (21), 106 (26), and 77 (14).

Methyl 2-*Benzyloxy*-3-*formyl*-4-*methylbenzoate* (**14**).—Sodium hydride (50%; 1.8 g, 37.5 mmol) was added, in portions, to a stirred solution of methyl 3-formyl-2-hydroxy-4-methylbenzoate (**13**) (5.03 g, 25.9 mmol) and benzyl bromide (4.2 ml, 35.3 mmol) in DMF (480 ml). After 1 h, the mixture was poured into ice (100 g) and extracted with ethyl acetate (3 × 200 ml). The combined organic extracts were washed with water (2 × 100 ml), and brine (100 ml), dried ($MgSO_4$), and evaporated under reduced pressure. Chromatography of the residue gave the *title compound* (**14**) (6.1 g, 83%) as a colourless solid, m.p. 29—31 °C (Found: M^+, 284.1055. $C_{17}H_{16}O_4$ requires *M*, 284.1049); $\nu_{max.}$(Nujol) 1 736, 1 697, and 1 139 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 12.5 (1 H, s, CHO), 7.98 (1 H, d, *J* 10 Hz, 5- or 6-H), 7.4—7.2 (5 H, m, ArH), 7.09 (1 H, d, *J* 10 Hz, 5- or 6-H), 5.09 (2 H, s, CH_2), 3.90 (3 H, s, OMe), and 2.61 (3 H, s, ArMe); *m/z* 284 (M^+, 2%), 252 (3), 194 (14), 166 (28), 150 (22), 134 (36), 91 (100), 85 (32), 71 (50), 57 (77), and 43 (53).

Methyl 2-*Benzyloxy*-3-*hydroxy*-4-*methylbenzoate* (**15**).—Methyl 2-benzyloxy-3-formyl-4-methylbenzoate (**14**) (6.00, 21.1 mmol) was added to a stirred solution of *m*-chloroperoxybenzoic acid (85%; 7.0 g, 34.5 mmol) in dichloromethane (150 ml). The mixture was stirred at 4 °C for 12 h; the precipitated acid was filtered off, and the filtrate evaporated. The residue was dissolved in ethyl acetate (150 ml) and the solution washed with water (50 ml) and brine (50 ml), dried ($MgSO_4$), and evaporated to give a pale yellow oil. This was immediately dissolved in methanol (150 ml) and treated with hydrochloric acid (6M; 150 ml). The mixture was stirred at 25 °C for 3 h. Water (60 ml) was added, and the resulting suspension evaporated. The residue was extracted with chloroform (2 × 200 ml), and the combined extracts were washed with aqueous sodium hydrogen carbonate (2 × 100 ml), water (100 ml), and brine (50 ml), dried ($MgSO_4$), and evaporated under reduced pressure to give the *title compound* (**15**) (5.5 g, 96%) as a colourless oil (Found: C, 70.4; H, 5.8. $C_{16}H_{16}O_4$ requires C, 70.6; H, 5.8%); $\nu_{max.}$(Nujol) 3 507, 1 724, 1 279, 1 207, and 1 053 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 7.38—7.21 (6 H, m, ArH), 6.81 (1 H, d, *J* 9 Hz, 5- or 6-H), 5.88 (1 H, s, OH), 4.90 (2 H, s, CH_2), 3.78 (3 H, s, OMe), and 2.19 (3 H, s, ArMe), *m/z* 272 (M^+, 8%), 150 (3), 121 (3), and 91 (100).

Methyl 2-*Benzyloxy*-3-*methoxy*-4-*methylbenzoate* (**16**).—Potassium carbonate (17 g, 123 mmol) and dimethyl sulphate (7.6 g, 60.3 mmol) were added to a stirred solution of methyl 2-benzyloxy-3-hydroxy-4-methylbenzoate (**15**) (5.5 g, 20.2 mmol) in dry acetone (200 ml). After 6 h, the mixture was filtered and the filtrate concentrated under reduced pressure. The residue was dissolved in chloroform (100 ml) and the solution washed with water (100 ml) and brine (100 ml), and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by chromatography of the residue gave the *title compound* (**16**) (4.1 g, 71%) as a colourless oil (Found: M^+, 286.1210. $C_{17}H_{18}O_4$ requires *M*, 286.1205); $\nu_{max.}$(film) 1 729, 1 279, and 1 063 cm^{-1}; δ_H(270 MHz; $CDCl_3$) 7.60—7.32 (6 H, m, ArH), 6.99 (1 H, d, *J* 10 Hz, 5- or 6-H), 5.10 (2 H, s, CH_2), 3.88 (3 H, s, OMe), 3.86 (3 H, s, OMe), and 2.36 (3 H, s, ArMe); *m/z* 286 (M^+, 15%), 255 (2), 164 (15), and 91 (100).

2-*Benzyloxy*-3-*methoxy*-4-*methylbenzyl Alcohol.*—Lithium aluminium hydride (0.478 g, 12.6 mmol) was added, in portions, to a stirred solution of methyl 2-benzyloxy-3-methoxy-4-methylbenzoate (**16**) (3.6 g 12.6 mmol) in dry ether (100 ml). The mixture was stirred for 1 h; water (*ca.* 5 ml) was added dropwise (**CAUTION**). The mixture was filtered through a pad of Celite, and the filtrate dried ($MgSO_4$). The solvent was removed under reduced pressure to give the *title compound* (2.98 g, 92%) as a beige solid, m.p. 35 °C (Found: C,74.1; H, 7.0. $C_{16}H_{18}O_3$ requires C, 74.4; H, 7.0%); $\nu_{max.}$(film) 3 377, 1 456, 1 416, 1 277,

1 078, and 1 019 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 7.5—7.3 (5 H, m, ArH), 6.95 (2 H, 2 × d, *J* 11 Hz, 5-H, 6-H), 5.10 (2 H, s, PhCH_2), 4.53 (2 H, m, CH_2OH), 3.88 (3 H, s, OMe), and 2.30 (3 H, s, ArMe); OH not observed; *m/z* 258 (M^+, 5%), 150 (70), 107 (31), 91 (100), and 79 (31).

2-Benzyloxy-3-methoxy-4-methylbenzaldehyde (**17**).—Barium manganate (5.9 g, 23.0 mmol) was added, in portions to a well stirred solution of 2-benzyloxy-3-methoxy-4-methylbenzyl alcohol (2.97 g, 11.5 mmol) in dry dichloromethane (250 ml). The suspension was stirred vigorously for 40 min and then filtered through a pad of Celite. The filtrate was dried ($MgSO_4$), and evaporated under reduced pressure and the residue was purified by chromatography to give the *title compound* (**17**) (2.15 g, 73%) as a colourless oil (Found: C, 74.7; H, 6.3. $C_{16}H_{16}O_3$ requires C, 75.0; H, 6.3%); $\nu_{max.}$(film) 1 682, 1 460, 1 270, and 1 075 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 10.19 (1 H, s, CHO), 7.47 (1 H, d, *J* 7.9 Hz, 5- or 6-H), 7.38 (5 H, m, ArH), 7.03 (1 H, d, *J* 7.9 Hz, 5- or 6-H), 5.18 (2 H, s, PhCH_2), 3.91 (3 H, s, OMe), and 2.38 (3 H, s, ArMe); *m/z* 256 (M^+, 7%), 227 (4), 164 (7), 105 (6), and 91 (100).

Methyl 2-Azido-3-(1-benzyloxy-2-methoxy-3-methylphenyl)-propenoate (**18**).—Sodium metal (0.622 g, 26.5 mmol) was added to dry methanol (12 ml) and the solution cooled to −15 °C. A solution of methyl azidoacetate (3.06 g, 26.5 mmol) and 2-benzyloxy-3-methoxy-4-methylbenzaldehyde (**17**) (1.7 g, 6.6 mmol) in dry methanol (5 ml) was added dropwise by a syringe. The mixture was stirred at −10 °C for 3 h and then at 4 °C for 12 h. Water (5 ml) was cautiously added to the mixture, which was then extracted with ether (2 × 50 ml). The combined extracts were washed with water (50 ml) and brine (25 ml), dried ($MgSO_4$), and evaporated under reduced pressure to give a pale yellow residue. This was recrystallised from ether to afford the *title compound* (**18**) (1.86 g, 80%) as pale yellow crystals, m.p. 59—61 °C (Found: C, 64.4; H, 5.4; N, 11.6. $C_{19}H_{19}N_3O_4$ requires C, 64.6; H, 5.4; N, 11.9%); $\nu_{max.}$($CHCl_3$) 2 120, 1 720, 1 290, and 1 095 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 7.91 (1 H, d, *J* 8 Hz, ArH), 7.43 (5 H, m, ArH), 7.29 (1 H, s, =CH), 7.00 (1 H, d, *J* 8 Hz, ArH), 5.05 (2 H, s, PhCH_2), 3.85 (6 H, 2 × s, OMe), and 2.26 (3 H, s, ArMe); *m/z* 244 (M^+ −109, 20%), 196 (51), 164 (69), 136 (65), and 91 (100).

Methyl 4-Benzyloxy-5-methoxy-6-methylindole-2-carboxylate (**19**).—Methyl 2-azido-3-(1-benzyloxy-2-methoxy-3-methylphenyl)propenoate (**18**) (1.8 g 5.1 mmol) was dissolved in dry xylene (300 ml) in a 500-ml round-bottomed flask, and the flask lowered into a Wood's metal bath at 250 °C. The solution was refluxed for 1 h and then evaporated under reduced pressure to give a pale tan residue. Recrystallisation of this from ether gave the *title compound* (**19**) (1.59 g, 96%) as a pale yellow solid, m.p. 151—152 °C (Found: C,70.1; H, 5.8; N, 4.3. $C_{19}H_{19}NO_4$ requires C, 70.1; H, 5.9; N, 4.3%); $\nu_{max.}$(CCl_4) 3 350, 1 715, 1 550, 1 260, and 1 220 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 8.75 (1 H, s br, NH), 7.57—7.30 (5 H, m, ArH), 7.24 (1 H, s, 3-H), 6.94 (1 H, s, 7-H), 5.26 (2 H, s, CH_2), 3.93 (3 H, s, OMe), 3.87 (3 H, s, OMe), and 2.41 (3 H, s, 6-Me); *m/z* 325 (M^+, 16%), 242 (15), and 91 (100).

4-Benzyloxy-5-methoxy-6-methylindol-2-ylmethanol (**20**).—Lithium aluminium hydride (0.184 g, 4.9 mmol) was added to a stirred solution of methyl 4-benzyloxy-5-methoxy-6-methylindole-2-carboxylate (**19**) (1.58 g, 4.86 mmol) in dry ether (200 ml) and tetrahydrofuran (10 ml). The suspension was stirred for 2 h; water (*ca.* 3 ml) was added (**CAUTION**). The precipitate was rapidly filtered off, and the filtrate dried ($MgSO_4$) and evaporated under reduced pressure to give the *title compound* (**20**) (1.43 g, 99%) as a colourless solid, m.p. 60—62 °C (Found: C, 72.4; H; 6.5; N, 4.6. $C_{18}H_{19}NO_3$ requires C, 72.7; H, 6.4; N, 4.7%); $\nu_{max.}$(film) 3 305, 1 627, 1 586, 1 458, 1 124, 911, and 842 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 8.20 (1 H, s, NH), 7.59—7.31 (5 H, m, ArH), 6.85 (1 H, s, 7-H), 6.40 (1 H, s, 3-H), 5.22 (2 H, s, PhCH_2), 4.73 (2 H, s, CH_2OH), 3.88 (3 H, s, OMe), 2.39 (3 H, s, 6-Me), and 2.03 (1 H, s, OH); *m/z* 297 (M^+, 32%), 267 (9), 206 (100), and 91 (94).

4-Benzyloxy-5-methoxy-6-methylindole-2-carbaldehyde (**21**).—Barium manganate (8.7 g, 34 mmol) was added, in portions, to a stirred solution of 4-benzyloxy-5-methoxy-4-methylindol-2-ylmethanol (**20**) (1.0 g 3.37 mmol) in dry dichloromethane (100 ml). The suspension was then heated to reflux for 2 h. The mixture was filtered and the residue washed with hot dichloromethane (500 ml). The combined filtrate and washings were evaporated to give a red oil which was purified by column chromatography to give the *title compound* (**21**) (0.606 g, 61%) as a colourless oil (Found: C, 73.0, H, 5.95; N, 4.7. $C_{18}H_{17}NO_3$ requires C, 73.2; H, 5.8; N, 4.7%): $\nu_{max.}$(CCl_4) 3 480, 1 680, and 1 150 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 9.73 (1 H, s, CHO), 8.40 (1 H, s, br, NH), 7.55—7.33 (5 H, m, ArH), 7.22 (1 H, s, 3-H), 6.96 (1 H, s, 7-H), 5.28 (2 H, s, CH_2), 3.98 (3 H, s, OMe), and 2.42 (3 H, s, 6-Me); *m/z* 295 (M^+, 18%), 267 (12), 204 (41), 184 (43), and 91 (100).

1-Allyl-4-benzyloxy-5-methoxy-6-methylindole-2-carbaldehyde (**22**).—To a flask charged with sodium hydride (50%; 0.133 g, 2.77 mmol) was added dry light petroleum (5 ml). The mixture was stirred for 1 min, after which the petroleum was removed by a syringe, and the flask contents dried *in vacuo*. 4-Benzyloxy-5-methoxy-6-methylindole-2-carbaldehyde (**21**) (0.680, 2.31 mmol) in DMF (60 ml) was added dropwise, and the mixture was stirred at room temperature for 30 min. Allyl bromide (0.335 g, 2.77 mmol) was added, and the mixture was stirred at room temperature. After 1 h, water (30 ml) was cautiously added, and the mixture was extracted with ether (3 × 100 ml). The combined ethereal extracts were washed with water (2 × 150 ml) and brine (100 ml), dried ($MgSO_4$), and evaporated to give the *title compound* (**22**) (0.619 g, 80%) as a colourless oil (Found: C, 75.3; H, 6.6; N, 4.2. $C_{21}H_{21}NO_3$ requires C, 75.2; H, 6.3; N, 4.1%); $\nu_{max.}$(CCl_4) 1 680, 1 470, 1 240, and 700 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 9.76 (1 H, s, CHO), 7.52 (2 H, d, *J* 8 Hz, ArH), 7.44—7.32 (3 H, m, ArH), 7.23 (1 H, s, 3-H), 6.89 (1 H, s, 7-H), 5.96 (1 H, m, CH_2CH=CH_2), 5.28 (2 H, s, CH_2O), 5.12 (3 H, m, CH_2CH=CH_2 and CH_2CH=C*H*H), 4.90 (1 H, d, *J* 18 Hz, CH_2CH=CH*H*), 3.89 (3 H, s, OMe), and 2.42 (3 H, s, 6-Me); *m/z* 335 (M^+, 35%), 307 (15), 244 (100), 184 (20), and 91 (57).

1-Allyl-4-benzyloxy-5-methoxy-6-methylindole-2-carbaldehyde Tosylhydrazone (**23**).—1-Allyl-4-benzyloxy-5-methoxy-6-ethylindole-2-carbaldehyde (**22**) (0.520 g, 1.55 mmol) was added to a stirred solution of toluene-*p*-sulphonylhydrazide (0.346 g, 1.86 mmol) in methanol (10 ml). The mixture was stirred at room temperature for 4 h, after which it was evaporated under reduced pressure and the residue purified by chromatography, eluting with ether, to give the *title compound* (**23**) (0.600 g, 77%) as a pale beige solid, m.p. 49—51 °C (Found: C, 66.5; H, 5.7; N, 7.8. $C_{28}H_{29}N_3O_4S$ requires C, 66.8; H, 5.8; N, 8.3%); $\nu_{max.}$(CCl_4) 3 192, 1 610, 1 459, 1 360, 1 165, and 1 061 cm^{-1}; δ_H(250 MHz; CD_3COCD_3) 10.05 (1 H, s, br, NH), 8.00 (1 H, s, CH=N), 7.81 (2 H, d, *J* 9 Hz, ArH), 7.55—7.31 (7 H, m, ArH), 6.96 (1 H, s, 3-H), 6.80 (1 H, s, 7-H), 5.86 (1 H, m, C*H*=CH_2), 5.23 (2 H, s, CH_2O), 5.11—4.81 (4 H, m, CH_2CH=CH_2 + CH_2CH=C*HH*), 3.79 (3 H, s, OMe), 2.37 (3 H, s, ArMe), and 2.34 (3 H, s, ArMe); *m/z* 503 (M^+, 0.2%), 475 (10), 384 (16), 320 (56), 229 (77), 278 (82), and 91 (100).

7-Benzyloxy-6-methoxy-5-methyl-1,1a,2a,8b-tetrahydrocyclopropa[3,4]pyrrolo[1,2-a]indole (**24**).—Sodium hydride (50%;

0.067 g, 1.402 mmol) was added to a stirred solution of the tosylhydrazone (**23**) (0.470 g, 0.934 mmol) in dry THF (15 ml). After 15 min, the solution was filtered, and the filtrate evaporated. The residue was dissolved in dry chlorobenzene (200 ml), and the solution refluxed for 30 min. The solvent was evaporated, and the residue purified by chromatography to give the *title compound* (**24**) (0.250 g, 84%) as a colourless oil (Found: M^+, 319.1578. $C_{21}H_{21}NO_2$ requires M, 319.1572); $\nu_{max.}(CCl_4)$ 1 480, 1 460, 1 420, 1 240, 1 080, and 1 040 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 7.58 (2 H, d, J 7 Hz, ArH), 7.44—7.28 (3 H, m, ArH), 6.70 (1 H, s, 8-H), 6.23 (1 H, s, 4-H), 5.24 (2 H, s, CH_2O), 4.04 (2 H, m, 2-CH_2), 3.97 (3 H, s, OMe), 2.38 (3 H, s, 5-Me), 2.43—2.30 (2 H, m, 1a-H, 8b-H), 1.27 (1 H, m, 1-C*H*H), and 0.63 (1 H, m, 1-CH*H*); m/z 319 (M^+, 20%), 306 (5), 228 (70), and 91 (47).

7-*Benzyloxy*-6-*methoxy*-5-*methyl*-1,1a,2,8b-*tetrahydrocyclopropa*[3,4]*pyrrolo*[1,2-a]*indole*-8-*carbaldehyde* (**25**).—*N*-Methylformanilide (0.054 g, 0.395 mmol) and phosphorus oxychloride (0.061 g, 0.395 mmol) were stirred under a calcium oxide drying tube for 15 min. The resulting precipitate was cooled to 0 °C, and 1,2-dichloroethane (4 ml) was added. Cyclopropa[3,4]pyrrolo[1,2-*a*]indole (**24**) (0.105 g, 0.329 mmol) was added, and the mixture stirred at room temperature for 3 h. Sodium acetate (1M; 1 ml) was added, and the mixture was extracted with ethyl acetate (2 × 20 ml). The combined extracts were washed with water (2 × 50 ml) and brine (20 ml), dried ($MgSO_4$), and evaporated. Purification of the residue by column chromatography gave the *title compound* (**25**) (0.072 g, 63%) as a colourless solid, m.p. 110—111 °C (Found: C, 75.8; H, 6.2; N, 4.1. $C_{22}H_{21}NO_3$ requires C, 76.1; H, 6.1; N, 4.0%); $\nu_{max.}(CCl_4)$ 1 655, 1 460, 1 420, and 1 120 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 10.29 (1 H, s, CHO), 7.52 (2 Hd, J 7.5 Hz, ArH), 7.38 (3 H, m, ArH), 6.78 (1 H, s, 4-H), 5.18 (2 H, s, CH_2O), 4.10 (2 H, m, 2-CH_2), 3.90 (3 H, s, OMe), 2.99 (1 H, m, 8b-H), 2.47 (1 H, m, 1a-H), 2.39 (3 H, s, 5-Me), 1.48 (1 H, m, 1-C*H*H), and 0.70 (1 H, m, 1-CH*H*); m/z 347 (M^+, 34%), 319 (12), 256 (100), 241 (27), and 91 (8).

7-*Hydroxy*-6-*methoxy*-5-*methyl*-1,1a,2,8b-*tetrahydrocyclopropa*[3,4]*pyrrolo*[1,2-a]*indole*-8-*carbaldehyde*.—To a solution of the cyclopropa[3,4]pyrrolo[1,2a-*a*]indole (**25**) (0.053 g, 0.153 mmol) in ethyl acetate (25 ml) was added 10% palladium on carbon catalyst (0.006 g, 0.0056 mmol), and the mixture stirred under an atmosphere of hydrogen. After 14 h, the suspension was filtered and the filtrate evaporated under reduced pressure to give a yellow oil. Purification of this using column chromatography gave the *title compound* (0.037 g, 95%) as a colourless oil (Found: M^+, 257.1058. $C_{15}H_{15}NO_3$ requires M, 257.1052); $\nu_{max.}(CCl_4)$ 1 615, 1 480, 1 460, 1 390, and 1 360 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 10.68 (1 H, s, CHO), 9.58 (1 H, s, OH), 6.41 (1 H, s, 4-H), 4.08 (2 H, m, 2-CH_2), 3.89 (3 H, s, OMe), 2.72 (1 H, m, 8b-H), 2.54 (1 H, m, 1a-H), 2.32 (3 H, s, 5-Me), 1.5 (1 H, m, 1-C*H*H), and 0.79 (1 H, m, 1-CH*H*); m/z 257 (M^+, 94%) and 242 (100).

8-*Formyl*-6-*methoxy*-5-*methyl*-1,1a,2,8b-*tetrahydrocyclopropa*[3,4]*pyrrolo*[1,2-a]*indole*-4,7-*dione* (**26**).—Potassium nitrosodisulphonate (0.103 g, 0.383 mmol) in water (5 ml) was added to a stirred solution of 7-hydroxy-6-methoxy-5-methyl-1,1a,2,8b-tetrahydrocyclopropa[3,4]pyrrolo[1,2-*a*]indole-8-carbaldehyde (0.035 g, 0.136 mmol) in acetone (10 ml). The mixture was buffered with aqueous sodium dihydrogen phosphate (0.1M; 5 ml). After the mixture had been stirred at room temperature for 2 h, the resulting red solid was filtered off and recrystallised from ethyl acetate–light petroleum to give the *title compound* (**26**) (0.034 g, 92%) as red crystals, m.p. 184—185 °C (Found; M^+, 271.0845. $C_{15}H_{13}NO_4$ requires M, 271.0845); $\nu_{max.}(CCl_4)$ 1 680, 1 660, 1 640, 1 520, and 1 110 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 10.34 (1 H, s, CHO), 4.31 (2 H, m, 2-CH_2), 4.03 (3 H, s, OMe), 2.84 (1 H, m, 8b-H), 2.46 (1 H, m, 1a-H), 1.95 (3 H, s, 5-Me), 1.45 (1 H, m, 1-C*H*H), and 0.61 (1 H, m, 1-CH*H*); m/z 273 (M^+ + 2 H, 10%), 272 (M^+ + H, 17), 271 (M^+, 100), 270 (48), 256 (22), 242 (13), 228 (11), 200 (19), and 214 (8).

8-*Hydroxymethyl*-6-*methoxy*-5-*methyl*-1,1a,2,8b-*tetrahydrocyclopropa*[3,4]*pyrrolo*[1,2-a-]*indole*-5,8-*dione* (**27**).—Sodium borohydride (0.020 g, 0.526 mmol) was added to a stirred solution of the cyclopropa[3,4]pyrrolo[1,2-*a*]indole (**26**) (0.024 g, 0.0886 mmol) in methanol (25 ml). After 2 h, acetone (1 ml) was added, followed by aqueous iron(III) chloride (1 M; 0.5 ml) in hydrochloric acid (0.1M; 0.5 ml). The mixture was immediately transferred to a separating funnel, and extracted with dichloromethane. The combined extracts were washed with water (5 × 20 ml), and brine (30 ml), dried ($MgSO_4$), and evaporated under reduced pressure to give the *title compound* (**27**) (0.024 g, 99%) as red needles, m.p. 174—175 °C (Found: C, 65.8; H, 5.8; N, 4.9. $C_{15}H_{15}NO_4$ requires C, 65.9; H, 5.5; N, 5.1%); $\nu_{max.}(CCl_4)$ 3 442, 1 640, 1 600, and 1 100 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 4.75 (1 H, s, OH), 4.68 (2 H, m, CH_2OH; changes to 2 H, d, J 5 Hz on addition of D_2O), 4.26 (2 H, m, 2-CH_2), 3.97 (3 H, s, OMe), 2.35 (2 H, m, 1a-H, 8b-H), 1.94 (3 H, s, 5-Me), 1.30 (1 H, m, 1-C*H*H), and 0.55 (1 H, m, 1-CH*H*); m/z 275 (M^+ + H_2, 18%), 274 (M^+ + H, 10), 273 (M^+, 51), 272 (46), 258 (24), 257 (21), 94 (100), and 57 (53).

6-*Methoxy*-5-*methyl*-8-*trimethylsiloxymethyl*-1,1a,2,8b-*tetrahydrocyclopropa*[3,4]*pyrrolo*[1,2-a]*indole*-5,8-*dione*.—Trimethylsilyl isocyanate (0.053 g, 0.458 mmol) was added to a stirred solution of the cyclopropa[3,4]pyrrolo[1,2-*a*]indole (**27**) (0.005 g 0.0183 mmol) in dry THF (3 ml). The mixture was stirred for 20 min after which triethylamine (0.0002 g, 0.002 mmol) was added. After 1 h, the mixture was evaporated under reduced pressure and the residue recrystallised from dichloromethane–hexane to give the *title compound* (0.0051 g, 81%) as red crystals, m.p. 114—115 °C (Found: M^+, 344.1316. $C_{18}H_{23}NO_4Si$ −H requires M, 344.1318); $\nu_{max.}(CCl_4)$ 1 660, 1 645, 1 110, and 880 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 4.90 (2 H, AB, J 15 Hz, $SiOCH_2$), 4.23 (2 H, d, J 5 Hz, 2-CH_2), 3.97 (3 H, s, OMe), 2.49 (1 H, m, 8b-H), 2.30 (1 H, m, 1a-H), 1.92 (3 H, s, 5-Me), 1.30 (1 H, m, 1-C*H*H), 0.53 (1 H, m, 1-CH*H*), and 0.18 (9 H, s, $SiMe_3$); m/z 346 (M^+ + H, 9%), 345 (M^+, 29), 344 (100), 314 (12), and 254 (11).

6-*Methoxy*-5-*methyl*-8-*phenoxycarbonyloxymethyl*-1,1a,2,8b-*tetrahydrocyclopropa*[3,4]*pyrrolo*[1,2-a]*indole*-5,8-*dione* (**28**).—Phenyl chloroformate (0.0106 ml, 0.0844 mmol) was added dropwise to a stirred solution of the alcohol (**27**) (0.0144 g, 0.0527 mmol) in dry pyridine (1 ml). The mixture was stirred at 0 °C for 2 h, after which water (2 ml) was added. The mixture extracted with dichloromethane (2 × 15 ml), and the combined extracts were washed with water (3 × 15 ml), and brine (15 ml), dried ($MgSO_4$), and evaporated under reduced pressure to give a bright red residue. This was purified by chromatography to give the *title compound* (**28**) (0.0155 g, 75%) as an orange gummy solid, m.p. 40—45 °C (Found: M^+, 393.1218. $C_{22}H_{19}NO_6$ requires M, 393.1214); $\nu_{max.}(CCl_4)$ 1 763, 1 665, 1 650, 1 580, 1 250, 1 220, and 1 120 cm^{-1}; δ_H(270 MHz; $CDCl_3$) 7.40 (2 H, m, ArH), 7.22 (3 H, m, ArH), 5.47 (2 H, s, $COOCH_2$), 4.28 (2 H, m, 2-CH_2), 4.01 (3 H, s, OMe), 2.53 (1 H, m, 8b-H), 2.37 (1 H, m, 1a-H), 1.92 (3 H, s, 5-Me), 1.30 (1 H, m, 1-C*H*H), and 0.55 (1 H, m, 1-CH*H*); m/z 393 (M^+, 3%), 258 (11), 257 (18), and 256 (100).

8-*Carbamoyloxymethyl*-6-*methoxy*-5-*methyl*-1,1a,2,8b-*tetrahydrocyclopropa*[3,4]*pyrrolo*[1,2-a]*indole*-5,8-*dione* (**2**).—A solution of the dione (**28**) (0.008 g, 0.0204 mmol) in dry

dichloromethane (5 ml) was cooled to −78 °C. Ammonia gas was bubbled into the solution for 30 min after which the contents of the flask were allowed to warm to room temperature. Residual ammonia was removed by heating on a steam-bath after which the solvent was removed under reduced pressure. Recrystallisation of the residue from dichloromethane–hexane gave the *title compound* (**2**) (0.0047 g, 73%) as a red crystalline solid, m.p. 190—191 °C (Found: M^+, *316.1058*. $C_{16}H_{16}N_2O_5$ requires *M*, 316.1059); $\lambda_{max.}$(MeOH) 236 (log ε 4.32), 288 (4.06), 343 (3.40), and 465 nm (3.17); $\nu_{max.}$($CHCl_3$) 3 610, 3 450, 1 730, 1 660, 1 640, and 1 605 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 5.27 (2 H, AB, *J* 12.5 Hz, $COOCH_2$), 4.61 (2 H, br, NH_2), 4.26 (2 H, m, 2-CH_2), 3.99 (3 H, s, OMe), 2.53 (1 H, m, 8b-H), 2.33 (1 H, m, 1a-H), 1.92 (3 H, s, 5-Me), 1.31 (1 H, m, 1-C*H*H), and 0.55 (1 H, m, 1-CH*H*); *m/z* 316 (M^+, 31%), 273 (100), and 256 (47).

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References

1 Part 1, G. B. Jones and C. J. Moody, preceding paper.
2 Preliminary communication, G. B. Jones and C. J. Moody, *J. Chem. Soc., Chem. Commun.*, 1989, 186.
3 For example, see: A. R. MacKenzie, C. J. Moody, and C. W. Rees, *Tetrahedron*, 1986, **42**, 3259; R. E. Bolton, C. J. Moody, C. W. Rees, and G. Tojo, *J. Chem. Soc., Perkin Trans. 1*, 1987, 931.; T. Martin and C. J. Moody, *ibid.*, 1988, 241.
4 For reviews on synthetic work in the mitomycin and mitosene area, see: (*a*) K. Takahoshi and T. Kametani, *Heterocycles*, 1979, **13**, 411; (*b*) R. W. Franck, *Fortschr. Chem. Org. Naturst.*, 1979, 311; (*c*) W. Verboom and D. N. Reinhoudt, *Rec. Trav. Chim. Pays-Bas*, 1986, **105**, 199. For the total synthesis of mitomycins, see: T. Fukuyama, F. Nakatsubo, A. J. Cocuzza, and Y. Kishi, *Tetrahedron Lett.*, 1977, 4295; T. Fukuyama and L. Yang, *J. Am. Chem. Soc.*, 1987, **109**, 7881. For some other approaches, see: J. Rebek, S. H. Shaber, Y.-K. Shue, J.-C. Gehret, and S. Zimmerman, *J. Org. Chem.*, 1984, **49**, 5164; K. J. Shaw, J. R. Luly, and H. Rapoport, *ibid.*, 1985, **50**, 4515; S. Danishefsky, E. M. Berman, M. Ciufolini, S. J. Etheredge, and B. E. Segmuller, *J. Am. Chem. Soc.*, 1985, **107**, 3891; P. A. Wender and C. B. Cooper, *Tetrahedron Lett.*, 1987, **28**, 6125.
5 D. H. R. Barton, P. D. Magnus, and M. J. Pearson, *J. Chem. Soc., Chem. Commun.*, 1969, 550.
6 A. Rieche, H. Gross, and E. Höft, *Org. Synth.*, 1967, **47**, 1.
7 R. G. Neville and J. J. McGee, *Inorg. Synth.*, 1966, **VIII**, 23.
8 J. S. Webb, D. B. Cosulich, J. H. Mowat, J. B. Patrick, R. W. Broschard, W. E. Meyer, R. P. Williams, C. F. Wolf, W. Fulmor, C. Pidacks, and J. E. Lancaster, *J. Am. Chem. Soc.*, 1962, **84**, 3185; J. B. Patrick, R. P. Williams, W. E. Meyer, W. Fulmor, D. B. Cosulich, R. W. Broschard, and J. S. Webb, *ibid.*, 1964, **86**, 1889.
9 G. R. Allen, J. F. Poletto, and M. J. Weiss, *J. Am. Chem. Soc.*, 1964, **86**, 3877.
10 I. Niculescu-Duvaz, M. Ionescu, A. Cambanis, M. Vitan, and V. Feyns, *J. Med. Chem.*, 1968, **11**, 500.
11 R. Anschütz, *Liebigs Ann. Chem.*, 1924, **439**, 8.

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