Synthesis of the Left-hand Unit of the Antitumour Agent CC-1065

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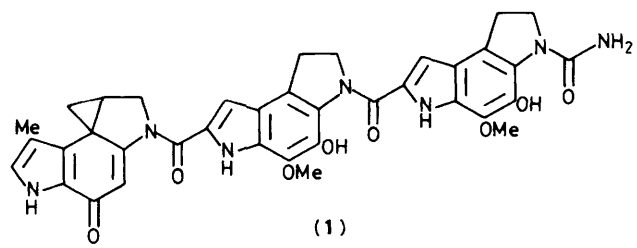
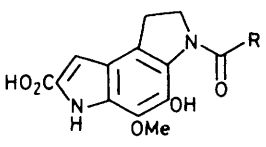
The cyclopropapyrroloindole (**3**), the left-hand unit of the antitumour agent CC-1065 (**1**), has been synthesised from 3-hydroxyacetophenone by a route which involves construction of both pyrrole rings by thermolysis of vinyl azides.

The potent antitumour antibiotic CC-1065 (**1**) has been the subject of considerable synthetic efforts,[1—11] and recently we have reported the synthesis of the naturally occurring phosphodiesterase inhibitors PDE-I (**2a**) and PDE-II (**2b**), the pyrroloindole structures of which are closely related to the central and right-hand units of CC-1065.[12] The key steps in our synthesis of PDE-I and PDE-II were the construction of both pyrrole rings by decomposition of vinyl azide derivatives, and we now report the use of a related strategy in the synthesis of the left-hand cyclopropapyrroloindole unit (**3**) of the antibiotic.[1,5,10]

The synthesis of the pyrroloindole (**3**) requires the initial fusion of two β-substituted pyrroles onto a benzene ring, in contrast to the synthesis of PDE-I and PDE-II which required the fusion of two α-substituted pyrroles,[12] and therefore a slightly different approach was adopted. However, although the formation of indole-2-carboxylates by the thermal decomposition of azidocinnamates, $ArCH{=}C(N_3)CO_2R$, readily prepared by condensation of methyl or ethyl azidoacetate with benzaldehydes, is well described by us[12,13] and others,[14] the corresponding formation of 3-substituted indoles from azidostyrenes, $ArCR{=}CHN_3$, is much less well established.[15,16] Although the latter azides cannot be prepared in one step from ketones, they can be prepared indirectly. Our starting material was 5-benzyloxy-2-bromoacetophenone (**4**), easily prepared on a large scale from 3-hydroxyacetophenone in two steps (83%). Reaction of the ketone (**4**) with dimethyl sulphoxonium methylide in dimethyl sulphoxide (DMSO) gave the epoxide (**5**) (94%), which was ring opened by treatment with a mixture of sodium azide and lithium chloride in dimethylformamide (DMF) to give the azidoalcohol (**6**) (72%). Dehydration of the alcohol (**6**) with thionyl chloride in pyridine gave the required vinyl azide (**7**)† as an oil (73%), which on thermolysis in mesitylene, followed by evaporation of the solvent and reaction of the crude 7-benzyloxy-4-bromo-3-methylindole with sodium hydride and benzenesulphonyl



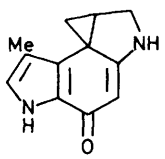
(**1**)



(**2**)

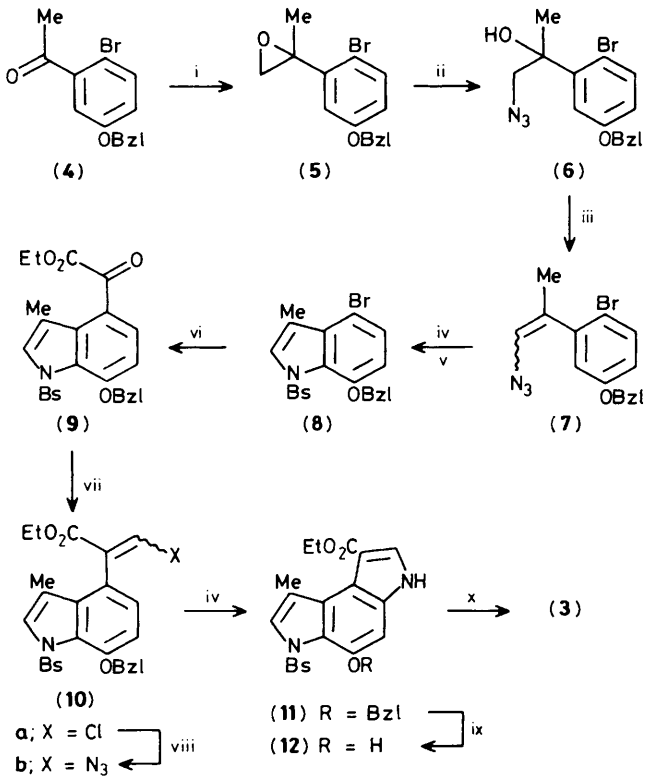
a; R = NH_2

b; R = Me



(**3**)

† The vinyl azide is a mixture of *E*- and *Z*-isomers, both of which can cyclise *via* the common azirine intermediate (*cf.* ref. 15).



Scheme 1. (Bzl = CH_2Ph, Bs = SO_2Ph). *Reagents:* i, $Me_2S^+(O)CH_2^-$, DMSO, 55 °C; ii, NaN_3–LiCl, DMF, 60 °C; iii, $SOCl_2$, pyridine, 0 °C; iv, mesitylene, reflux; v, NaH, THF, then $PhSO_2Cl$; vi, Bu^nLi, DME, then $(EtO_2C)_2$; vii, $Ph_3P{=}CHCl$, THF; viii, NaN_3, DMF, H_2O; ix, H_2, Pd–C, EtOH, 120 p.s.i.; x, see ref. 5.

chloride in tetrahydrofuran (THF) gave the protected indole (**8**), m.p. 151—152.5 °C [44% from (**7**)] (Scheme 1).

The bromoindole (**8**) underwent halogen–metal exchange with n-butyl-lithium in 1,2-dimethoxyethane (DME), and the resulting organolithium was quenched with diethyl oxalate to give the indole (**9**), m.p. 153—154.5 °C (79%). Reaction of the keto-ester (**9**) with chloromethylenetriphenylphosphorane gave the vinyl chloride (**10a**) (75%), which on treatment with sodium azide in aqueous DMF[17] gave the vinyl azide (**10b**)† (94%), the substrate for the second cyclisation reaction. Heating the azide (**10b**) in mesitylene for 30 minutes resulted in cyclisation to the indole (**11**), m.p. 216—216.5 °C (43%),‡ hydrogenolysis of which gave the key intermediate, the pyrroloindole (**12**), m.p. 156—158 °C (lit.,[5] 160—162 °C) (Scheme 1). Selective reduction of the ester-bearing double bond, *N*-acetylation, reduction of the ester group, dehydration to form the fused cyclopropane, and deprotection using the conditions described by Magnus and Gallagher[5] gave the cyclopropapyrrolindole (**3**), the left-hand unit of CC-1065, the high-field ^1H n.m.r. spectrum of which was identical to that reported in the literature.[5]

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‡ The remaining material (*ca.* 40%) from this thermolysis was the nitrile, IndCH(CN)CO_2Et (Ind = 1-benzenesulphonyl-7-benzyloxy-3-methylindol-4-yl), formed by a competing decomposition of the azide (**10b**) (*cf.* ref. 15) which involves a ready 1,2-hydrogen shift.