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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=CHN₃, 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



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



b; $X = N_3 \leftarrow$ Scheme 1. (Bzl = CH₂Ph, Bs = SO₂Ph). *Reagents:* i, Me₂S⁺(O)CH₂⁻, DMSO, 55 °C; ii, NaN₃-LiCl, DMF, 60 °C; iii, SOCl₂, pyridine, 0 °C; iv, mesitylene, reflux; v, NaH, THF, then PhSO₂Cl; vi, BuⁿLi, DME, then (EtO₂C)₂; vii, Ph₃P=CHCl, THF; viii, NaN₃, DMF, H₂O; ix, H₂,

(12) R = H

i)

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 DMF¹⁷ 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 Gallagher⁵ 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)CO₂Et (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.

 $\mathbf{a}; \mathbf{X} = \mathbf{Cl}$

viii

Pd-C, EtOH, 120 p.s.i.; x, see ref. 5.