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Synthesis of the Combined Centre- and Right-hand Section of the Antitumour Agent CC-1065

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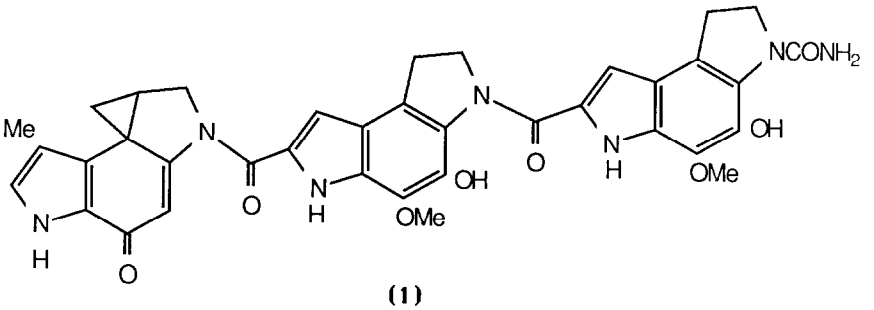
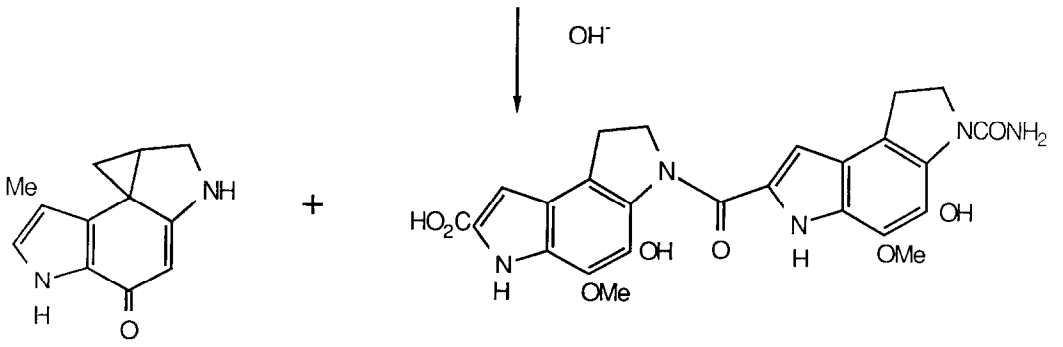
Summary: The complete centre-and right-hand section of the anti-tumour antibiotic CC-1065, known as PDE-I dimer (**3**), has been synthesised by coupling the pyrroloindole (**6**) and pyrroloindoline (**5**), followed by functional group transformations; the synthetic PDE-I dimer (**3**) was identical to material obtained from natural sources, and since natural PDE-I dimer has been converted into CC-1065, this work constitutes a formal total synthesis of the antibiotic.

The antibiotic CC-1065 (**1**) is one of the most potent antitumour agents known[1] and has therefore, not surprisingly, been the subject of considerable synthetic effort.[2-21] Whilst all three separate units have been synthesised, their coupling to give "dimeric" or "trimeric" sections closely related to the natural product has not yet been reported. As part of our own work towards the total synthesis of the antibiotic, we have developed a new route to the



(1)



(2) **(3)**

pyrrolo[3,2-e]indole sub-units of CC-1065 based on vinyl azide chemistry.[13,15] We now report the synthesis of the combined centre- and right-hand section (**3**), a compound known as PDE-I dimer which is obtained, along with the cyclopropapyrroloindole (**2**), by alkaline degradation of the antibiotic.[22]

The building blocks for the preparation of PDE-I dimer (**3**) are the "monomeric" pyrroloindoles (**4**) and (**5**), both of which are key intermediates in our previous synthesis of the phosphodiesterase inhibitors, PDE-I and PDE-II.[13] Hydrolysis of the methyl ester in refluxing aqueous methanolic potassium hydroxide gave the corresponding acid (**6**) in excellent (93%) yield. It was decided to couple the pyrroloindole acid (**6**) with the pyrroloindoline (**5**) prior to reduction of the unsubstituted pyrrole ring, since the non-basic nitrogen was expected not to interfere in the coupling reaction. Thus reaction of acid (**6**) and indoline (**5**) in the presence of 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-4-toluenesulphonate (CMC) in dichloromethane gave the required "dimer" (**7**), m.p. 205-207°C, in 63% yield. Selective reduction of the right-hand pyrrole ring of the dimer (**7**) was readily achieved (61%) using sodium cyanoborohydride in acetic acid. Carbamoylation of the reduced dimer with trimethylsilyl isocyanate gave benzyl protected PDE-I dimer (**8**), m.p. 134-136°C in 71% yield. Finally, hydrogenolysis of the benzyl groups over palladium-on-charcoal in dimethyl formamide (DMF) gave PDE-I dimer (**3**) in quantitative yield, the structure of which was confirmed by its spectroscopic properties,[23] and by comparison with an authentic sample.[24]

The synthetic PDE-I dimer produced by this route was identical to material obtained by degradation of natural CC-1065, and this work taken with the successful coupling of natural PDE-I dimer with an appropriate left-hand fragment,[24] constitutes a formal total synthesis of CC-1065 itself.

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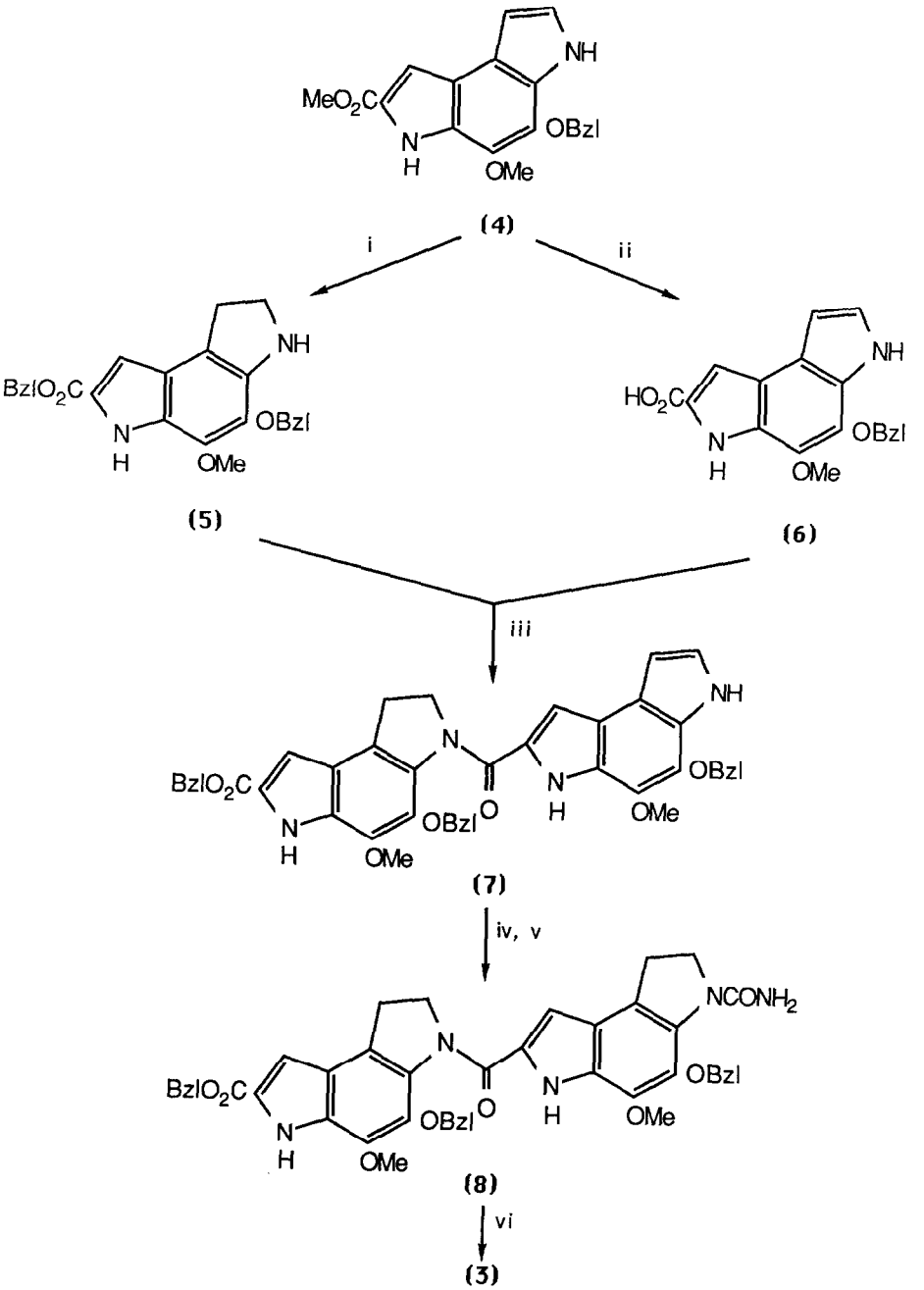

Scheme. [Bzl = CH_2Ph] Reagents: i, ref. 13; ii, KOH, H_2O, MeOH; iii, CMC, CH_2Cl_2, RT; iv, $NaBH_3CN$, AcOH; v, Me_3SiNCO, $ClCH_2CH_2Cl$; vi, H_2, Pd-C, DMF.

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23. PDE-I dimer (**3**), m.p. >300°C, $\lambda_{max.}$(EtOH) 290 (log ε 4.37) and 352 nm (4.52); $\upsilon_{max.}$ (KBr) 3470br, 2930, 2498br, 1707, 1690w, 1636s, 1565w, 1545w, 1490s, 1470, 1414, 1374, 1333, 1314, 1255, 1175, 1148, 1070w, 1048w, 1020, 1000w, 956, 890, 790, 770, 746, and 726 cm^{-1}; δ_H [250 MHz; $(CD_3)_2SO$] 3.12-3.31 (4 H, m, 1-H and 9-H), 3.81 (3 H, s, OMe), 3.85 (3 H, s, OMe), 4.03 (2 H, t, J 8 Hz, 2-H or 10-H), 4.66 (2 H, t, J 7 Hz, 10-H or 2-H), 6.89 (1 H, s, 8-H or 16-H), 6.92 (2 H, s, NH_2), 7.05 (1 H, s, 16-H or 8-H), 10.83 (1 H, s, 4-OH or 12-OH), 11.15 (1 H, br s, NH), 11.35 (1 H, br s, NH), and 12.92 (1 H, s, 12-OH or 4-OH); m/z (FAB, thiodiethanol) 522 (MH^+).
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