Studies on the Synthesis of the Antitumour Agent CC-1065. Synthesis of the Cyclopropapyrroloindole Portion

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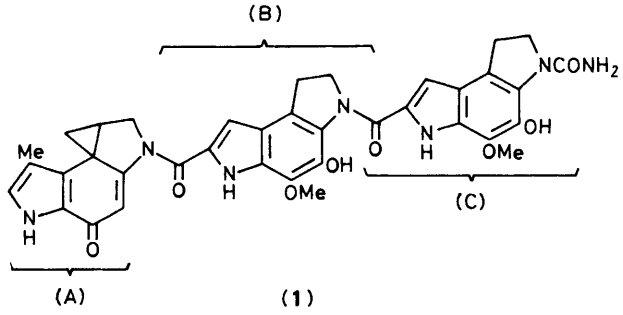
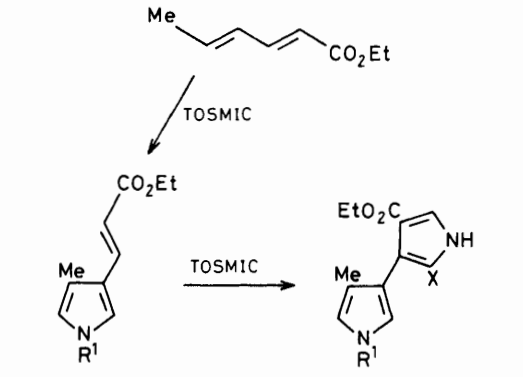
Using a regioselective Mannich reaction the 3,3'-bipyrrole (**4**) is converted into the acid chloride (**10**), which is transformed into the tricyclic phenol (**11**); selective reduction of (**11**) using triethylsilane in trifluoroacetic acid gives (**12**), which is converted by further reduction into (**14**), which by the intramolecular Mitsunobo reaction gives the cyclopropapyrroloindole (**17**).

The potent cytotoxic agent CC-1065 (**1**) has been the subject of recent structural[1] and synthetic[2] efforts. Our own research in this area has focussed upon constructing the rare 3,3'-bipyrrole system using the van Leusen[3]–Schöllkopf[4] reaction, and subsequently, the construction of the central aromatic ring[5] (Scheme 1).

Here we report the completion of this strategy, resulting in a concise synthesis of the (A) portion of CC-1065. The two pyrrole rings in (**4**) should be readily differentiated with respect to electrophilic substitution, since the *N*-phenylsulphonyl group retards substitution in the α-position.[6] In the event, treatment of (**4**) with $Me_2H_2N^+Cl^-$–CH_2O–H_2O–MeOH at 50 °C for 7 h gave the Mannich product (**5**), which was directly converted into the methiodide (**6**), 84% overall yield from (**4**). In contrast to this regiospecific Mannich reaction, acetylation of (**4**) gave a mixture. The methiodide (**6**) was converted into the nitrile (**7**), 66%, m.p. 160–170 °C. Methanolysis (MeOH–HCl) of (**7**) gave [(**8**), > 95%], with



(**1**)



(2) R^1 = H
(3) R^1 = SO_2Ph
unless stated otherwise

(4) X = H
(5) X = CH_2NMe_2
(6) X = $CH_2\overset{+}{N}Me_3I^-$
(7) X = CH_2CN
(8) X = CH_2CO_2Me
(9) X = CH_2CO_2H
(10) X = CH_2COCl

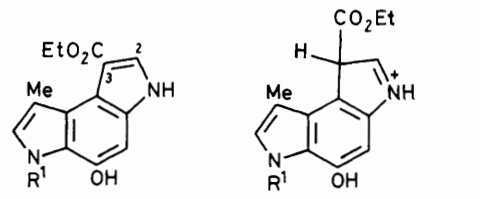
Scheme 1. TOSMIC = Tosylmethyl isocyanide.

approximately 20% ester exchange of the β-ethylester. A solution of the diester (**8**), in dry pyridine heated at reflux, was treated with lithium iodide,[7] and the carboxylic acid (**9**) was isolated after chromatographic purification in 91% yield. The acid (**9**) was converted into the acid chloride (**10**) by treatment with oxalyl chloride–CH_2Cl_2–pyridine at 10 °C, and immediately exposed to $SnCl_4$–CH_2Cl_2 at −78 °C to give the tricyclic phenol (**11**), 71%, m.p. 160–162 °C [^{1}H n.m.r. δ ($CDCl_3$) 8.96 (1H, s), 8.66 (1H, br. s), 7.90–7.72 (2H, m), 7.58 (1H, d, *J* 3 Hz), 7.51–7.25 (5H, m), 6.85 (1H, s), 4.32 (2H, q, *J* 7 Hz), 2.37 (3H, s), 1.33 (3H, t, *J* 7 Hz)].

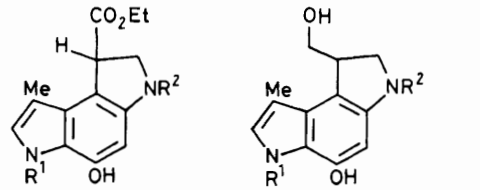
The stage was now set for the crucial reduction of the 2,3-double bond in the pyrroloindole (**11**). We reasoned that this reduction could be accomplished in a regiospecific manner, since exposure of (**11**) to strong acid should lead to C-3 protonation, and the resulting iminium ion (**11a**) would be reduced to (**12**). While (**11**) was inert to Zn–AcOH and $NaCNBH_3$–H^+, treatment with trifluoroacetic acid–$HSiEt_3$ (ionic hydrogenation)[8] gave (**12**), 80%, which was directly acetylated (Ac_2O) to give (**13**), 61% from (**11**). Reduction of (**13**) with $LiAlH_4$–tetrahydrofuran (THF) at 0 °C selectively gave the alcohol (**14**), 85%, with no trace of amide reduction or removal of the *N*-phenylsulphonyl group.

Wierenga[2] has converted (**15**) into (**16**) using CBr_4–Ph_3P–MeCN, followed by Pr^i_2NEt. Application of this procedure to (**14**) gave a complex mixture, whereas, treatment of (**14**) with $EtO_2CN{=}NCO_2Et$–THF–PPh_3 at 20 °C (intramolecular Mitsunobo reaction)[9] resulted in clean conversion into the spirocyclopropane (**17**), > 60%, not yet optimized. Treatment of (**17**) with NaOMe–MeOH at 20 °C rapidly (5 min) gave (**18**), which on prolonged exposure (18 h) to the above conditions, gave the unprotected cyclopropapyrroloindole (A) portion (**19**) [^{1}H n.m.r. ($CDCl_3$, 360 MHz) δ 9.00 (1H, br.), 6.70 (1H, d, *J* 2 Hz), 5.51 (1H, s), 4.56 (1H, br. s), 3.79 (1H, ddd, *J*'s 10, 5, and 2 Hz), 3.63 (1H, d, *J* 10 Hz), 2.95 (1H, m), 2.00 (3H, s), 1.86 (1H, dd, *J*'s 8 and 4 Hz), and 1.20 (1H, t, *J* 4 Hz); identical to the n.m.r. spectrum of an authentic sample, kindly supplied by Dr. Martha Warpehoski, The Upjohn Company].

We are currently adapting this type of stategy for the synthesis of the (B)/(C) portion of CC-1065,[10] and examining alternative ways of converting (**3**) into (**11**). The 3,3′-bipyrrole

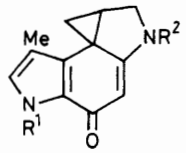


(11) (11a)



(12) R^2 = H
(13) R^2 = Ac

(14) R^2 = Ac
(15) R^1 = H, R^2 = $MeSO_2$



(16) R^1 = H, R^2 = $MeSO_2$
(17) R^2 = Ac
(18) R^2 = H
(19) R^1 = H, R^2 = H

route to CC-1065 could allow ready access to many of its structural analogues for biological evaluation.

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