Initial Studies on the Synthesis of the Antitumour Agent CC-1065: 3,4-Disubstituted Pyrroles and 3,3′-Bipyrroles

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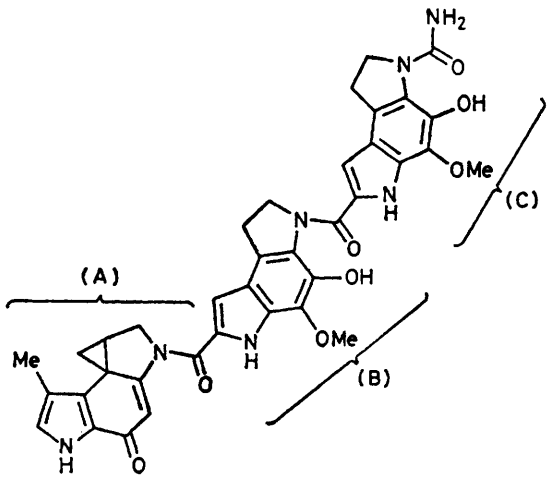
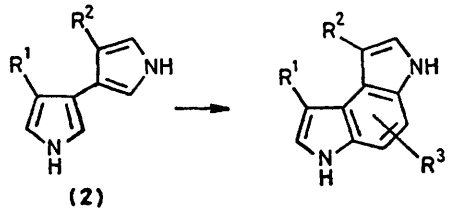
A three-step synthesis of functionalized, differentiated 3,3′-bipyrroles using ethyl sorbate and *p*-tolylsulphonylmethyl isocyanide is described.

The potent cytotoxic agent CC-1065 has the unusual tri-indole structure (**1**). It is more active than actinomycin, vinblastine, or maytansine, and is believed to bind in a nonintercalative manner to the major groove of the DNA double helix.[1]

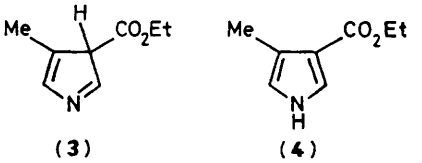


(1) CC-1065



(2)

Scheme 1

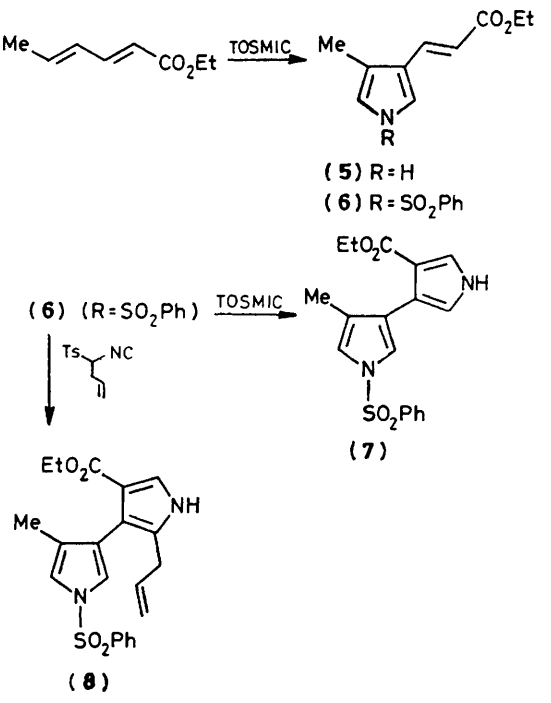


(3) (4)

Recently the cyclopropapyrroloindole (A) portion has been synthesized,[2] and the other identical components (B) and (C) have also been made.[3]

We wished to develop a method that was flexible enough to provide a variety of substitution patterns, allowing simple analogues of (**1**) to be obtained, and we concentrated on methods in which the pyrrole unit was synthesised first, with subsequent formation of the benzenoid portion (Scheme 1) rather than methods starting with the indole component.

Here we report a route to the rare 3,3′-bipyrroles of the general type (**2**).[4] Treatment of ethyl crotonate with *p*-tolylsulphonylmethyl isocyanide (TOSMIC)–NaH–Me_2SO,[5] gave, initially, two compounds (**3**) and (**4**). The imine (**3**) was slowly converted into (**4**) on prolonged (15 h) exposure to the above strongly basic conditions. Extension of this procedure to ethyl sorbate (TOSMIC–NaH–Me_2SO–ether; 20 °C; 3 h) gave the 3,4-disubstituted pyrrole (**5**) (80%), m.p. 88—89 °C (from EtOH); δ ($CDCl_3$) 1.32 (3H, t, *J* 7 Hz), 2.23 (3H, s), 4.26 (2H, q, *J* 7 Hz), 6.13 (1H, d, *J* 18 Hz), 6.58 (2H, br. s), 7.05 (1H, br. s), and 7.73 (1H, d, *J* 18 Hz). In principle, the second pyrrole could be added directly to (**5**), but efforts to do this were unsuccessful, presumably because of the reduced electrophilicity of the α,β-unsaturated ester (vinylogous β-aminoacrylate). Treatment of (**5**) with NaH–tetrahydrofuran (THF)–$PhSO_2Cl$ gave (**6**) (90%), m.p. 101—104 °C (from EtOH). When (**6**) was treated with TOSMIC–$HN(SiMe_3)_2$–NaH–THF at 0 °C for 10 min the 3,3′-bipyrrole (**7**) (85%), m.p. 138—139 °C; δ ($CDCl_3$) 1.2 (3H, t, *J* 7 Hz), 1.9 (3H, s), 4.12 (2H, q, *J* 7 Hz), 6.53 (1H, t, *J* 2 Hz), 6.95 (1H, t, *J* 2 Hz), 7.24 (2H, m), 7.5 (3H, m), and 7.9 (2H, m), was formed. Also, treatment of (**6**) with the methylene-*C*-allyl derivative of TOSMIC gave the 3,3′-bipyrrole (**8**).



Ts = tosyl.

In summary, the sequential pyrrole annulation of ethyl sorbate provides a very short route to functionalized 3,3′-bipyrroles, where the two pyrroles are readily differentiated.

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References

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