Photocyclization of Pyrrole Analogues of Stilbene: an Expedient Approach to Anti-tumour Agent CC-1065

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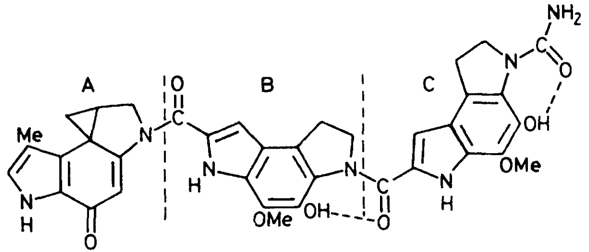
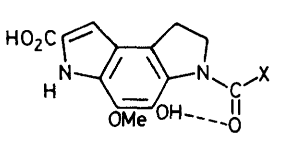
Described are the preliminary results of a photochemical cyclization based approach to CC-1065; readily available heterocycles are converted into pyrrole analogues of stilbene which are cyclized to give the tricyclic ring structure necessary for CC-1065 and its analogues.

The dipeptide CC-1065 (**1**) is an antitumour antibiotic exhibiting significantly higher cytoxicity than actinomycin, vinblastine, or maytansine, and is thought to bind nonintercalatively to DNA.[1] Because of its unusual structure and potent activity, a great deal of research activity has recently been directed towards a total synthesis of CC-1065.[2] Interestingly, unit B (similar to unit C) is like the biologically important phosphodiesterase inhibitors PDE-I and PDE-II, which have been synthesized by a classical route.[3] We describe here the preliminary results of our photochemical strategy aimed at a flexible, rapid synthesis of CC-1065 and its analogues.

To test the feasibility of our photocyclization based approach we prepared the model compound (**5**) as follows. The known iodide (**2**)[4] was converted into the phosphonium salt (**3**) in very good yield (PPh_3, MeCN, reflux, 92%). Wittig reaction of (**3**) with *N*-methylpyrrole-2-carbaldehyde [Bu^{t}OK, dimethylformamide (DMF), 85%] gave the light sensitive 1,2-dipyrrol-2-ylethene (**4**) as a mixture of *cis* and *trans*



(**1**)



X = NH_2 = PDE I

X = Me = PDE II

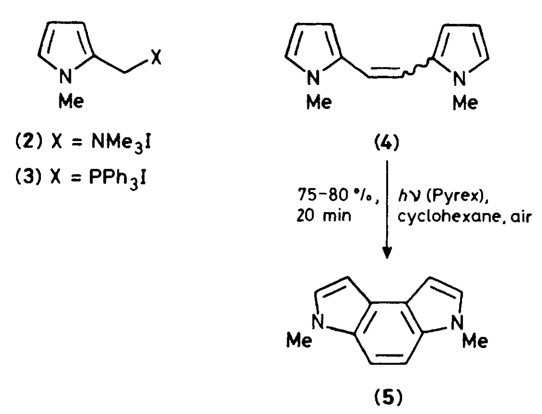
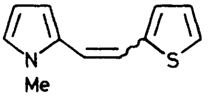
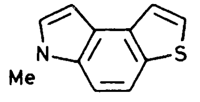
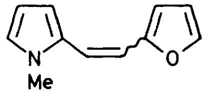
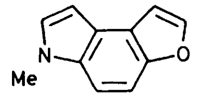
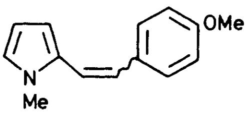
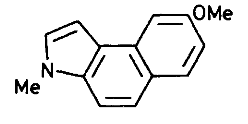


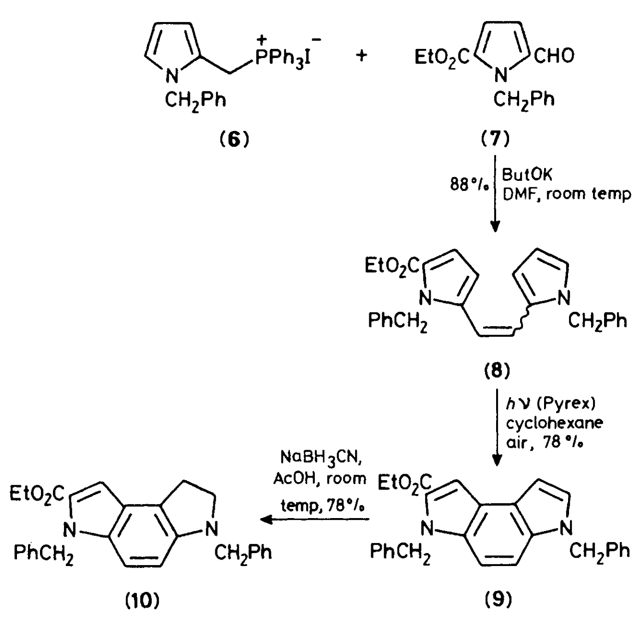
Table 1

Wittig product	Yield %	Photocyclization product	Yield %
	88		59
	90		38
	84		72

isomers, which readily underwent oxidative photocyclization to the pyrroloindole (**5**).†

We were particularly pleased with this result as pyrroles and indoles are known to be very succeptible to photochemical oxidations,[5] and indeed when the photolysis was allowed to continue longer, highly polar water soluble side products started to form. Since little is known about the photocyclization of pyrrole analogues of stilbene[6] we examined the cyclization of some related systems, which were prepared using the appropriate aldehyde by the Wittig procedure described above (Table 1). These cyclization products serve as models for non-pyrrolo analogues of CC-1065, illustrating the flexibility of the photocyclization route.

We then proceeded to prepare a dideoxy-analogue of the PDE type units. The phosphonium salt (**6**) was prepared in good overall yield from *N*-benzylpyrrole as follows: i, 37% aq. HCHO, Me_2NH_2Cl, 83%; ii, MeI, EtOH, 5 °C, 94%; iii, PPh_3, MeCN, reflux, 99%. Benzylation of ethyl 5-formylpyrrole-2-carboxylate[7] ($PhCH_2Br$, DMF, K_2CO_3, 100 °C, 96%) gave the required aldehyde (**7**). Wittig olefination afforded the olefin (**8**) as a mixture of isomers, which upon irradiation cyclized to (**9**). Selective reduction of the more electron rich side was accomplished[8] using the mild procedure of Gribble and Hoffman to give the tricyclic PDE-type unit, (**10**). Using this photocyclization approach we are at present carrying out the synthesis of the oxygenated units of CC-1065.[9]



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9 Part of this work was presented at the 186th Am. Chem. Soc. National Meeting, 1st September, 1983, Washington, D.C., U.S.A.

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† These cyclizations were carried out in dilute solutions (1 mmol/l). All new compounds were characterized spectroscopically (250 Hz ^1H n.m.r., mass, and i.r.).