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Synthesis of the Topoisomerase II Inhibitor BE 10988

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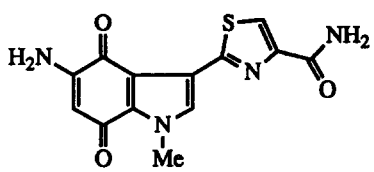
Abstract: The naturally occurring indolequinone BE 10988 **1**, an inhibitor of topoisomerase II, has been synthesised in an overall yield of 28%.

Topoisomerases, DNA modifying enzymes, are becoming increasingly important as biological targets for potential anticancer agents,[1] and in the search for new compounds of this type from culture broths, Japanese workers have recently described the isolation and structure elucidation of BE 10988, a potent inhibitor of topoisomerase II.[2,3] The structure of BE 10988 **1**, which contains a novel thiazole substituted indolequinone, was established by spectroscopic methods and apparently has been confirmed by synthesis,[3] although the details of this synthesis have not yet been published. In view of our own interest in indolequinones and their anticancer properties,[4,5] we decided to investigate a short synthesis of BE 10988, which is reported herein.



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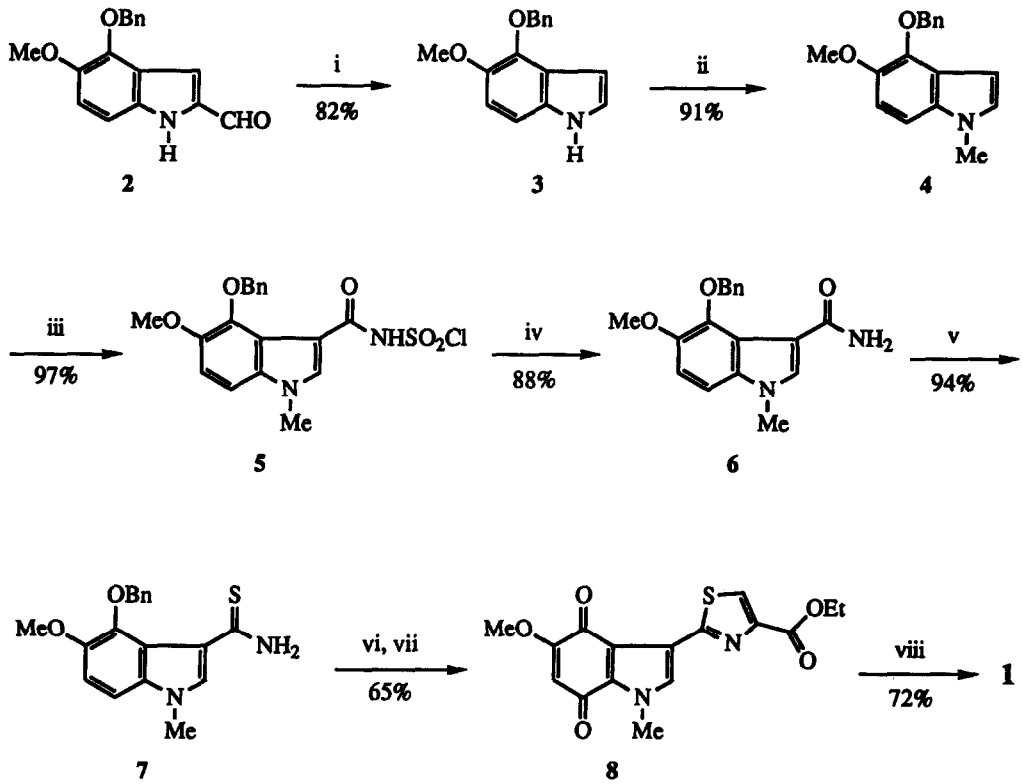
BE 10988

The starting material for the synthesis was the readily available 4-benzyloxy-5-methoxyindole-2-carboxaldehyde **2**, a key intermediate in our work on the synthesis of mitomycin analogues.[5-7] The aldehyde was decarbonylated in high yield using a rhodium catalyst,[8] and the resulting indole **3** methylated under standard conditions. The side chain was introduced into the indole 3-position using the highly electrophilic chlorosulfonyl isocyanate (CSI),[9] which gave the corresponding *N*-chlorosulfonylamide **5** in excellent yield. Attempts to remove the chlorosulfonyl group under the usual reductive hydrolytic conditions (Na_2SO_3 - KOH) were unsuccessful,[10] and therefore a new procedure was developed involving treatment of the chlorosulfonylamide **5** with tri-*n*-butyltin hydride in benzene in the presence of AIBN as radical initiator. This resulted in clean formation of the amide **6**, which was subsequently converted into the corresponding thioamide **7** with Lawesson's reagent (LR). The synthesis was completed by a Hantzsch reaction of the thioamide **7** with ethyl bromopyruvate, resulting not only in formation of the desired thiazole ring, but also, somewhat surprisingly, in debenzylation. The 4-hydroxyindole was oxidised directly to the quinone **8** (65% over 2 steps) with Fremy's salt in buffered acetone solution. Finally, dissolution of **8** in liquid ammonia gave BE 10988 **1**, in an overall yield (from **2**) of 28%, whose spectroscopic properties closely matched those described in the literature.[2,3]



Scheme (Bn = CH_2Ph). *Reagents:* (i) $(Ph_3P)_2RhCO(Cl)$, $Ph_2P(CH_2)_3PPh_2$, mesitylene; (ii) KH, MeI, DMF; (iii) CSI, Et_2O; (iv) Bu_3SnH, AIBN, PhH; (v) LR, PhH; (vi) $BrCH_2COCO_2Et$, EtOH, reflux; (vii) Fremy's salt, acetone, NaH_2PO_4 buffer; (viii) liq. NH_3.

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