Facile synthesis of the key intermediate of EO 9 *via* the formation of the indole skeleton using the Nenitzescu reaction

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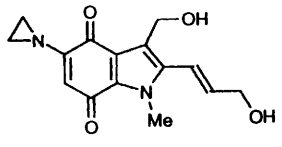
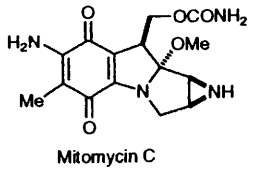
A Nenitzescu reaction has been used to prepare the indole skeleton **6** having all the functional groups necessary for its conversion into **10a**, a key intermediate in a short synthesis of the indolequinone EO 9.

EO 9 is a novel and fully synthetic bioreductive alkylating indolequinone, the structure and function of which are similar to mitomycin C.[1] These features coupled with its excellent activity against various experimental hypoxic tumours in mice, have led to EO 9 being tested in clinical trials by the European Organization for Research and Treatment of Cancer (EORTC).[2] However, since the reported synthesis of EO 9 is a 21-step process (6% overall yield)[1] involving repeated



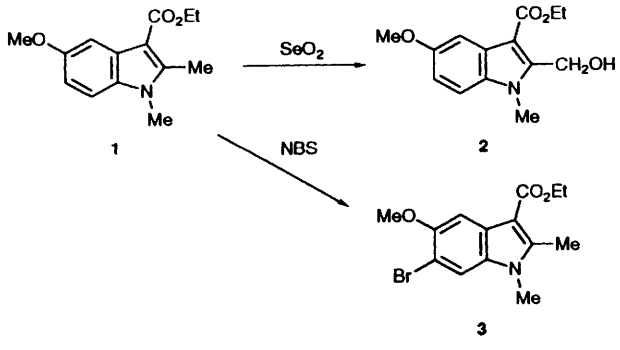
EO9



Mitomycin C

chromatographic purifications, use of an unstable intermediate and hazardous reagents, an improved method has been sought in order to speed clinical trials and the further development of the product's potential.† A feasibility study of the efficient synthesis of the EO 9 skeleton, suggested that a strategy based on the construction and subsequent conversion of a suitably pre-functionalized indole would be preferable to the established method which relies on functionalization including the introduction of a side chain prior to the formation of the indole skeleton. We report herein the facile synthesis of an advanced EO 9 intermediate involving the one-step preparation of a pre-functionalized indole using the Nenitzescu reaction.

Attempted preparation of an indole-2-carbaldehyde suitable for successive side-chain elongation, by oxidation with SeO_2[3] of the commercially available 2-methylindole **1** (Scheme 1)



1 2 3

Scheme 1

afforded only a little of the corresponding alcohol **2**, whilst radically initiated bromination proceeded selectively at C-6 to afford mainly **3**. In view of these disappointing results we decided to treat the benzoquinone **4** with the enamine **5a**‡ in AcOH at room temperature§ to afford, by a Nenitzescu reaction,[4] 2-(methoxymethyl)indole **6a** (22%) after purification by column chromatography (Scheme 2).¶ Since the low yield of product, which required careful chromatographic separation for isolation, and fell further (by *ca.* 50%) upon scale-up (molar scale), we attempted to optimize the reaction using compounds **4** and **5b** under other conditions.‖ As shown in Table 1, EtOAc and a slight excess (3.5 equiv.) of AcOH was effective as the reaction solvent to yield **6b** in good yield. The best results (53–54%) were obtained when 3–5 equiv. of **4** was treated with **5b** in EtOAc–AcOH at 50 °C (entries 6 and 7). Purification was also simplified by the addition of aqueous $Na_2S_2O_4$ to the reaction mixture to convert unchanged benzoquinone into the sodium salts of hydroquinone with adjustment of the pH to 7.5 using aqueous NaOH, and precipitation of the crude crystalline product from the reaction mixture. Subsequently, the aqueous mixture was extracted (EtOAc) and the resulting residual product short column chromatographed. Recrystallization of the combined material afforded pure **6b**.

Compound **7** was prepared by dimethylation of **6b** (86%) and upon DDQ oxidation[7] afforded indole-2-carbaldehyde **8** (86%).** The Horner–Wadsworth–Emmons olefination[8] of **8** exclusively afforded the *E*-olefin **9** (95%), and subsequent introduction of the 4-nitro group (92%) also proceeded smoothly to afford **10a** having the carbon skeleton of EO 9. The structure of **10a** was also confirmed by derivatization into **10b**, the key intermediate of the conventional preparative method. Since compound **10a** is equivalent to the reported key intermediate **10b** for the synthesis of EO 9 it is convertible into the latter in 6 steps.[1]

† *Note added in proof:* Quite recently an improved synthesis of EO has been reported (A. S. Cotterill, C. J. Moody and J. R. A. Roffey, *Tetrahedron*, 1995, **51**, 7223.

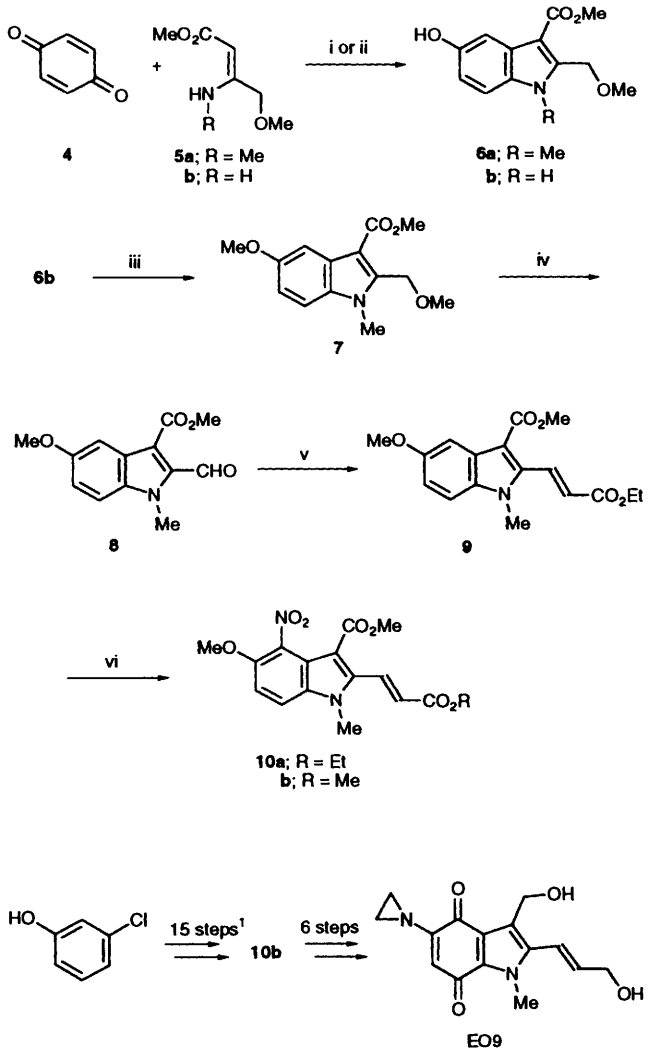
‡ The enamine **5a** was quantitatively prepared from commercially available methyl 4-methoxyacetoacetate and $MeNH_2$. For similar preparations, see ref. 5.

§ Addition of acid to the reaction mixture is effective in improving the yield of product. For reviews on the Nenitzescu reaction, see ref. 6.

¶ All new compounds showed satisfactory spectral data and elemental analyses.

‖ The enamine **5b** was used in these experiments since the 1-methyl group could be introduced during the successive methylation of the 5-*O*-position. Compound **5b** was easily prepared from methyl 4-methoxyacetoacetate and NH_3. See also ref. 5.

** Chromatographic purification using alumina could be prevented by washing of the reaction mixture with saturated aqueous $NaHCO_3$ following crystallization.



Scheme 2 *Reagents and conditions* (*Yield*): i (for **5a**), AcOH (22%); ii (for **5b**), AcOH, EtOAc, 50 °C (49%); iii, Bu^{t}OK, MeI, DMF (86%); iv, DDQ, CH_2Cl_2–H_2O (86%); v, $(EtO)_2POCH_2CO_2Et$, LiBr, NEt_3, THF (95%); vi, HNO_3–AcOH (92%)

Table 1 Nenitzescu reaction of compounds **4** and **5b**

Entry[a]	**4** (equiv.)[b]	Solvent[c]	Yield of **6b** (%)[d]
1	2	MeOH	21
2	2	MeOH–AcOH	38
3	2	Acetone–AcOH	44
4	2	EtOH–AcOH	45
5	2	EtOAc–AcOH	46
6	3	EtOAc–AcOH	53
7	5	EtOAc–AcOH	54

[a] Reactions at 50 °C with 1 mmol of **5b** and 2.2 cm^3 of solvent. [b] Based on **5b**. [c] 3.5 Equiv. of AcOH was used (based on **5b**). [d] Determined by HPLC.

In summary, compound **10b** was earlier available only by a 15-step preparation (19% overall yield), while **10a** is now available in only five steps (34% overall yield). The large-scale preparation of **10a** is also now practicable in the absence of chromatographic separation and low-temperature conditions; kilogram amounts have been so obtained by this method in an overall yield similar to that stated above.

Experimental

Methyl 5-hydroxy-2-methoxymethylindole-3-carboxylate 6b

To a solution of 1,4-benzoquinone **4** (642 g, 6.00 mol) in EtOAc (3.96 dm^3) and AcOH (396 cm^3) was added dropwise methyl 3-amino-4-methoxybut-2-enoate **5b** (287 g, 1.98 mol). The mixture was stirred at 50 °C for 16 h after which a solution of $Na_2S_2O_4$ (1.03 kg, 5.98 mol) in water (3.96 dm^3) was added dropwise to it and stirring continued for 2 h at room temperature. The mixture was adjusted to pH 7.5 with aqueous NaOH (10 mol dm^{-3}) after which the precipitated crystals were filtered off and washed with EtOAc to afford the crude product (181 g). The filtrate was collected and the aqueous layer extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated on a rotary evaporator. The paste obtained was purified by column chromatography (2.87 kg of alumina, EtOAc as an eluent) followed by trituration to afford the crude product. The combined crude products were recrystallized from EtOAc to afford **6b** (228 g, 49%), mp 160 °C (decomp.) (Found: C, 61.1; H, 5.8; N, 5.8. Calc. for $C_{12}H_{15}NO_4$: C, 61.27; H, 5.57; N, 5.95%); ν_{max}(KBr)/cm^{-1} 3340, 3310, 1664, 1479, 1464, 1233 and 1170; δ_H(300 MHz, [$^2H_6$]-DMSO 3.39 (s, 3 H, 2-CH_2OCH_3), 3.81 (s, 3 H, 3-CO_2CH_3), 4.91 (s, 2 H, 2-CH_2), 6.78 (dd, *J* 2.4, 8.6, 1 H, 6-H), 7.25 (d, *J* 8.6, 1 H, 7-H), 7.34 (d, *J* 2.4, 1 H, 4-H), 8.97 (s, 1 H, 5-OH) and 11.74 (s, 1 H, 1-NH); *m*/*z* (EI) 235 (M^+).

Details of the experimental procedures for compounds **7**, **8**, **9**, **10a** and **10b** together with spectral results are given in a Supplementary publication (SUP No. 57114 (3 pages)].* For details of the scheme, see Instructions for Authors (1995), *J. Chem. Soc., Perkin Trans. 1*, 1995, issue 1.

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