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An Improved Synthesis of the Indolequinone Anticancer Agent EO9

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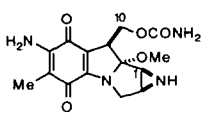
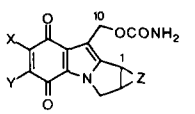
Abstract: *An improved synthesis of the indolequinone anticancer agent EO9, 5-aziridinyl-3-hydroxymethyl-2-(3-hydroxyprop-1-enyl)-1-methylindole-4,7-dione 3 is described.*

INTRODUCTION

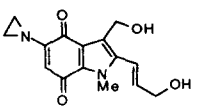
Mitomycin C (MMC) **1**, a clinically useful antitumour agent, is the archetypical quinone bioreductive agent.[1-3] The fact that MMC and related mitosenes, such as aziridinomitosenes **2** and the indolequinone **3**, designated EO9,[4,5] require reductive activation to form electrophilic species toxic to cells is well known, and the drugs presumably act as substrates for one or more of the reductases present in most cells. Bioreductive drugs are assuming increasing importance since they are highly effective against hypoxic tumour cells.[6-13] In this respect, the indolequinone EO9 **3** is proving particularly interesting; it is an excellent substrate for the 2-electron reductase DT-diaphorase,[14-20] and is showing promising results in biological and clinical evaluation.[21-27] The quinone EO9 **3** was first synthesised by Speckamp and co-workers by a multi-step route involving at least 20 steps.[4,5] In view of the potential of EO9 as an anticancer drug, and because of our own interest in indolequinones, in particular the cyclopropamitosenes **4**,[28-31] we have developed an improved synthesis of this important compound, the details of which are reported herein. An alternative synthesis of EO9 has also been devised by the Kyowa Hakko Kogyo Company, although no details have been published.[32]



1 mitomycin C (MMC)



2 Z = NR aziridinomitosene
4 Z = CR_2 cyclopropamitosene

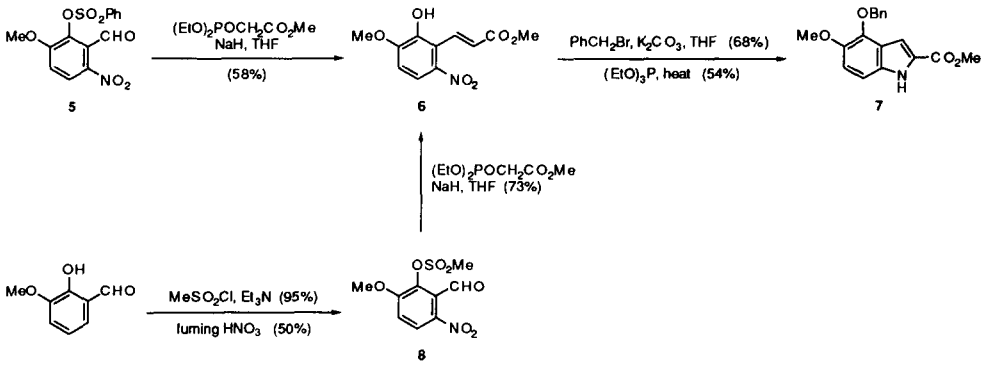


3 EO9

RESULTS AND DISCUSSION

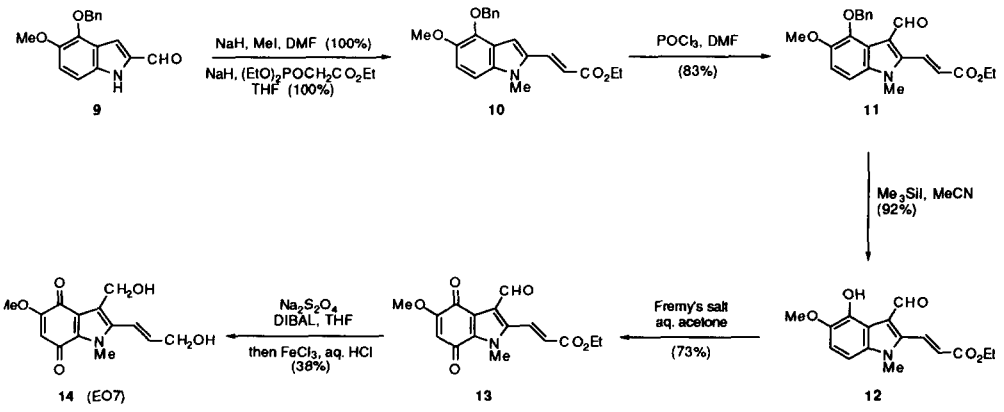
The immediate precursor to EO9 **3** is the corresponding 5-methoxyindolequinone **14**, a compound known as EO7, which is simply converted into EO9 by reaction with aziridine.[4] The key intermediate in our synthesis of EO7 is 4-benzyloxy-5-methoxyindole-2-carbaldehyde **9**, obtained from the corresponding ester **7**, itself readily prepared from *ortho*-vanillin in 3 steps as previously described.[30] However, the previous

preparation of the indole-2-ester **7** involves an azide intermediate and, although we have carried out the reaction on a 5-10g scale without incident, we sought an alternative preparation of the indole. 2-Benzenesulfonyloxy-3-methoxy-6-nitrobenzaldehyde **5** is readily available in 2 steps from *ortho*-vanillin,[33,34] and proved a useful starting material. Thus Wadsworth-Emmons olefination of the aldehyde **5** using excess phosphonoacetate and excess base gave the cinnamate **6**, in which, fortuitously, the benzenesulfonyl group had been removed under the basic conditions. Benzylation of the free phenol, followed by heating in triethyl phosphite at 156°C resulted in cyclisation to the desired indole **7** (Scheme 1).[35] As an alternative to the benzenesulfonate **5**, the corresponding mesylate **8**, prepared in an analogous manner from *ortho*-vanillin, can also be used (Scheme 1).



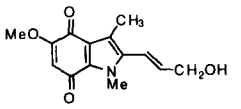
Scheme 1

The ester **7** was converted into the aldehyde **9** as previously described,[30] methylation and olefination of which gave the indole-2-propenoate **10** in quantitative yield (Scheme 2). Vilsmeier-Haack formylation gave the corresponding indole-3-aldehyde **11**, which was smoothly debenzylated by treatment with iodotrimethylsilane. Oxidation of the resulting phenol **12** using Fremy's salt in aqueous acetone gave the quinone **13**. The final reduction of the quinone ester aldehyde **13** to EO7 **14** proved more difficult than expected. Following the original method for a closely related compound,[4] the quinone was pre-reduced to the corresponding hydroquinone with sodium dithionite. Subsequent reduction with DIBAL gave, after reoxidation with iron(III) chloride, EO7 in 38% yield over the 3 steps, together with the over-reduced 3-methylindolequinone **15**.



Scheme 2

Despite several attempts, the yield of EO7 **14** could not be improved; alterations in reaction time or temperature either resulted in more over-reduction or in the formation of partially reduced products such as **16**. Nevertheless the overall route to EO7, and hence EO9, is short being 7 steps from the aldehyde **9** (21.2% overall yield), itself available from *ortho*-vanillin in 5 or 7 steps in 35.6 or 7.9% overall yield respectively, and is easy to carry out.



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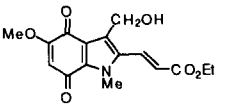

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EXPERIMENTAL

For general experimental details, see ref. 28. Compounds characterised by high resolution mass spectrometry were chromatographically homogeneous. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 250 and 62.9 MHz respectively unless otherwise stated; NMR coupling constants are given in Hz.

(E)-Methyl 3-(2-hydroxy-3-methoxy-6-nitrophenyl)prop-2-enoate (**6**)
Sodium hydride (0.255 g, 10.6 mmol) was added to dry tetrahydrofuran (10 ml) under a nitrogen atmosphere and the mixture was left to stir for 5 min. Methyl diethyl phosphonoacetate (2.24 g, 10.6 mmol) was added dropwise, the mixture was stirred for 1 h then added to a solution of 2-benzenesulfonyloxy-3-methoxy-6-nitrobenzaldehyde (**5**)[33] (3.27 g, 9.7 mmol) in tetrahydrofuran (30 ml), and the mixture left to stir at room temperature for 2 h. Sodium hydride (0.255 g, 10.6 mmol) was added and the mixture left to stir for a futher 2 h. Ammonium chloride solution (30 ml) was added and the mixture extracted with ethyl acetate (3 x 50 ml), the organic layers were combined and washed with brine (4 x 50 ml), dried over $MgSO_4$ and evaporated under reduced pressure to give a yellow solid. Recrystallisation from ethanol gave the *title compound* (1.42 g, 58 %) as a pale yellow solid, m.p. 123-125°C; ν_{max} ($CHCl_3$)/cm^{-1} 3400br and 1721; δ_H 3.75 (3H, s, CO_2Me), 3.96 (3H, s, OMe), 6.38 (1H, s, OH), 6.66 (1H, d, *J* 16.2), 6.81 (1H, d, *J* 8.9), 7.55 (1H, d, *J* 8.9) and 7.73 (1H, d, *J* 16.2); δ_C (62.9 MHz; CD_3OD : $CDCl_3$) 51.39, 55.96, 109.14, 116.04, 116.70, 124.02, 124.86, 135.96, 142.78, 151.26 and 167.82; *m/z* 253 (M^+, 10%), 221 (20), 207 (100), 176 (30), 77 (40), 51 (55) and 29 (40).

(E)-Methyl 3-(2-benzyloxy-3-methoxy-6-nitrophenyl)prop-2-enoate
Methyl 3-(2-hydroxy-3-methoxy-6-nitrophenyl)prop-2-enoate (**6**) (5.06 g, 20.01 mmol), potassium carbonate (3.04 g, 22.01 mmol), benzyl bromide (3.48 g, 20.01 mmol) and tetrahydrofuran (100 ml) were heated under reflux for 14 h. The reaction mixture was cooled and ammonium chloride solution (100 ml) added. The mixture was extracted with ether (3 x 100 ml), the organic layers were combined and washed with saturated sodium hydrogen carbonate (3 x 100 ml), brine (2 x 100 ml), dried over $MgSO_4$ and evaporated under reduced pressure to give a brown oil. Tritutation with light petroleum gave an orange solid which was recrystallised from diethyl ether to give the *title compound* (4.66 g, 68 %) as a pale yellow solid, m.p. 115-116°C, (Found: C, 63.10; H, 4.93; N, 4.02. $C_{18}H_{17}NO_6$ requires C, 62.97; H, 5.00; N, 4.08 %); ν_{max} ($CHCl_3$)/cm^{-1} 1701; δ_H 3.79 (3H, s, CO_2Me), 3.99 (3H, s, OMe), 4.94 (2H, s, OCH_2), 6.34 (1H, d, *J* 16.1), 6.97 (1H, d, *J* 9.2), 7.34 (5H, m), 7.71 (1H, d, *J* 16.2) and 7.88 (1H, d, *J* 9.2); δ_C 51.73, 56.31, 73.82, 110.90, 121.54, 121.90, 125.76, 126.44, 128.19, 128.30, 128.38, 128.52, 136.02, 141.86, 157.34 and 166.45; *m/z* 343 (M^+, 3%), 266 (5), 91 (100) and 65 (10).

Methyl 4-benzyloxy-5-methoxyindole-2-carboxylate (**7**)
Methyl 3-(2-benzyloxy-3-methoxy-6-nitrophenyl)propenoate (4.4 g, 12.8 mmol) and triethyl phosphite (10.68 g, 64.1 mmol, 11.15 ml) were heated under reflux in an oil bath for 3 h. The reaction mixture was cooled and evaporated under reduced pressure to give a viscous brown oil. Column chromatography (2:1 light petroleum:ether through to 1:1 and finally 1:2), gave the title compound (2.2g, 54%) as a pale yellow solid, identical to a previously prepared sample.[30]

2-Methanesulfonyloxy-3-methoxybenzaldehyde
Methanesulfonyl chloride (17.9 g, 156 mmol, 12.1 ml) was added to a solution of *ortho*-vanillin (20 g, 131.4 mmol) in dichloromethane (300 ml) at 0°C. The mixture was left to stir for 5 min, then triethylamine (33.4 g, 330 mmol, 46 ml) was added dropwise and the temperature maintained between 0-5°C. The mixture was stirred for a futher 30 min and the precipitate was filtered off. The filtrate was washed with water (200 ml), HCl (1M; 3 x 200 ml), saturated sodium hydrogen carbonate (2 x 200 ml), brine (200 ml), dried over $MgSO_4$ and evaporated under reduced pressure to give the *title compound* (28.65 g, 95 %) as an off white solid, m.p. 79-80°C, (Found: C, 47.16; H, 4.26. $C_9H_{10}O_5S$ requires C, 46.95; H, 4.38%); ν_{max} ($CHCl_3$)/cm^{-1} 1701; δ_H 3.36 (3H, s, SO_2Me), 3.95 (3H, s, OMe), 7.28 (1H, dd, *J* 9.2, 1.7), 7.37 (1H, t, *J* 9.3), 7.51 (1H, dd, *J* 9.2, 1.6) and 10.35 (1H, s, CHO); δ_C 39.29, 56.37, 116.29, 120.09, 127.99, 131.07, 141.09, 152.02 and 188.34; *m/z* 230 (M^+, 30%), 151 (100), 108 (32), 93 (30), 65 (30), 52 (33) and 41 (20).

2-Methanesulfonyloxy-3-methoxy-6-nitrobenzaldehyde (**8**)
2-Methanesulfonyloxy-3-methoxybenzaldehyde (25 g, 107.5 mmol) was added portion wise to fuming nitric acid (675 ml) maintaining the temperature between 5-15°C. The mixture was stirred for a further 10 min, then poured onto ice (*ca.* 2 kg) and the precipitate was collected by filtration and recrystallised from methanol to give the *title compound* (14.82 g, 50 %) as a pale yellow solid, m.p. 143-144°C, (Found C, 39.36; H, 3.02; N, 5.02 $C_9H_9NO_7S$ requires C, 39.28; H, 3.3; N, 5.09%); ν_{max} ($CHCl_3$)/cm^{-1} 1719; δ_H 3.34 (3H, s, SO_2Me), 4.06 (3H, s, OMe), 7.21 (1H, d, *J* 9.2), 8.20 (1H, d, *J* 8.1) and 10.28 (1H, s, CHO); δ_C 44.05, 62.11, 119.54, 130.10, 136.18, 140.93, 141.34, 163.28 and 192.04; *m/z* 275 (M^+, 10%), 196 (20), 123 (100), 79 (70), 51 (80) and 30 (50).

(E)-Methyl 3-(2-hydroxy-3-methoxy-6-nitrophenyl)prop-2-enoate (**6**) - *Alternative method*
Sodium hydride (0.645 g, 27.27 mmol) was added to dry tetrahydrofuran (40 ml) under a nitrogen atmosphere and the mixture was left to stir for 5 min. Methyl diethyl phosphonoacetate (5.73 g, 27.27 mmol) was added dropwise, the mixture was stirred for 1 h then added to a solution of 2-methanesulfonyloxy-3-methoxy-6-nitrobenzaldehyde (**8**) (5 g, 18.18 mmol) in tetrahydrofuran (70 ml), and the mixture left to stir at room temperature for 2 h. Sodium hydride (0.654 g, 27.27 mmol) was added and the mixture left to stir for a further 2 h. Ammonium chloride solution (50 ml) was added and the mixture extracted with ethyl acetate (3 x 100 ml), the organic layers were combined and washed with brine (4 x 100 ml), dried $MgSO_4$ and evaporated under reduced pressure to give a yellow solid. Recrystallisation from ethanol gave the *title compound* (3.34 g, 73 %) as a pale yellow solid, identical with the previously prepared sample.

4-Benzyloxy-5-methoxy-1-methylindole-2-carbaldehyde
To a solution of light petroleum washed sodium hydride (60% dispersion; 0.160 g) in *N,N*-dimethylformamide (10 ml) was added 4-benzyloxy-5-methoxyindole-2-carbaldehyde (**9**) (1.03 g, 3.66 mmol) in *N,N*-dimethylformamide (20 ml). The resulting suspension was stirred at room temperature for 50 min after which time methyl iodide (0.25 ml, 4.02 mmol) was added and the mixture stirred for a further 1 h. The reaction was quenched by the addition of water and the mixture extracted with ether (4 x 30 ml). The combined organic extracts were washed with brine (6 x 30 ml), water (30 ml) and dried ($MgSO_4$). Evaporation of the solvent gave a yellow oil which was purified by filtration through a short plug of silica (eluant: ether:light petroleum, 50:50) to give the *title compound* as a yellow solid (1.09 g) in quantitative yield,

m.p. 44-45°C, (Found: C, 73.23; H, 5.90; N, 4.89. $C_{18}H_{17}NO_3$ requires C, 73.20; H, 5.80; N, 4.74%); ν_{max}/cm^{-1} 1663; δ_H 3.84 and 3.96 (each 3 H, s, OMe,NMe), 7.04 (1 H, dd, *J* 8.9 and 0.9, 7-H), 5.20 (2 H, s, OCH_2Ph), 7.20 (1 H, d, *J* 0.9, 3-H), 7.20 (1 H, d, *J* 8.9, 6-H), 7.38 (3 H, m, Ar-H), 7.51 (2 H, m, Ar-H) and 9.72 (1 H, s, CHO); δ_C 31.70 (NMe), 58.51 (OMe), 75.18 (OCH_2Ph), 105.42, 114.67, 118.07, 122.18, 128.02, 128.11, 128.42, 135.82, 137.80, 138.05, 142.10, 145.09 and 182.80 (CHO); *m/z* 295 (M^+, 14%), 267 (23), 204 (64), 148 (27), 133 (49), 91 (100), 77 (36), 69 (67), 65 (27), 63 (21) and 45 (37).

(E)-Ethyl 3-(4-benzyloxy-5-methoxy-1-methyl-2-indolyl)prop-2-enoate (**10**)

To a suspension of light petroleum washed sodium hydride (60% dispersion; 0.080 g) in tetrahydrofuran (10 ml) was added dropwise triethyl phosphonoacetate (0.50 ml, 2.72 mmol) and the resulting mixture was stirred at room temperature for 50 min. 4-Benzyloxy-5-methoxy-1-methylindole-2-carbaldehyde (0.430 g, 1.47 mmol) in tetrahydrofuran (20 ml) was added slowly and the mixture stirred at room temperature for a further 1 h. Water (10 ml) was added and the mixture extracted with dichloromethane (3 x 40 ml). The combined organic extracts were washed with water (40 ml) and dried ($MgSO_4$). Evaporation of the solvent gave a yellow oil which was purified by filtration through a short plug of silica (eluant: ether:light petroleum, 50:50) to give the *title compound* as a bright yellow oil (0.542 g) in quantitative yield, (Found: C, 72.18; H, 6.43; N, 3.87. $C_{22}H_{23}NO_4$ requires C, 72.31 H, 6.34; N, 3.83%); λ_{max}/nm 213 (log ε 4.37), 260 (4.11), 345 (4.42) and 355 sh (4.34); ν_{max}/cm^{-1} 3005, 1703 and 1631; δ_H 1.36 (3 H, t, *J* 7.1, CH_2CH_3), 3.78 and 3.81 (each 3 H, s, NMe,OMe), 4.29 (2 H, q, *J* 7.1, CH_2CH_3), 5.24 (2 H, s, OCH_2Ph), 6.46 (1 H, d, *J* 15.8, 2-H), 6.96 (1 H, s, indole 3-H), 7.02 (2 H, m, 6,7-H), 7.37 (3 H, m, Ar-H), 7.52 (3 H, m, Ar-H) and 7.74 (1 H, d, *J* 15.8, 3-H); δ_C 14.32 (CH_2CH_3), 30.23 (NMe), 58.35 (OMe), 60.55 (CH_2CH_3), 75.04 (OCH_2Ph), 100.67 (C-2), 104.82, 113.91, 118.15, 122.84, 127.85, 128.05, 128.33, 132.46 (C-3), 135.07, 136.31, 137.99, 140.87, 145.20 and 167.03; *m/z* 365 (M^+, 47%), 275 (45), 274 (100), 200 (36) and 91 (40).

(E)-Ethyl 3-(4-benzyloxy-3-formyl-5-methoxy-1-methyl-2-indolyl)prop-2-enoate (**11**)

A solution of phosphorus oxychloride (0.275 ml, 2.96 mmol) in *N,N*-dimethylformamide (10 ml) was stirred at room temperature for 30 min. (*E*)-Ethyl 3-(4-benzyloxy-5-methoxy-1-methyl-2-indolyl)prop-2-enoate (**10**) (0.540 g, 1.48 mmol) in *N,N*-dimethylformamide (20 ml) was added slowly and the resulting mixture stirred at room temperature for 1 h. Aqueous sodium acetate (1 M, 20 ml) was added and after stirring for 10 min the mixture was extracted with ethyl acetate (4 x 30 ml). The combined organic extracts were washed with brine (6 x 30 ml), water (30 ml) and dried ($MgSO_4$). Evaporation of the solvent gave a yellow oil which was purified by chromatography (ethyl acetate) to give the *title compound* (0.480 g, 83%). Recrystallisation gave bright yellow plates, m.p. 144-145°C (ethyl acetate), (Found: C, 70.20; H, 5.94; N, 3.45. $C_{23}H_{23}NO_5$ requires C, 70.21 H, 5.89; N, 3.56%); λ_{max}/nm 215 (log ε 4.21), 239 (4.16), 254 (4.14), 277 sh (4.04), 346 (4.03) and 361 (4.03); ν_{max}/cm^{-1} 1705 and 1640; δ_H 1.28 (3 H, t, *J* 7.1, CH_2CH_3), 3.71 and 3.86 (each 3 H, s, NMe,OMe), 4.22 (2 H, q, *J* 7.1, CH_2CH_3), 5.11 (2 H, s, CH_2Ph), 6.63 (1 H, d, *J* 16.5, 2-H), 6.99 (2 H, AB, *J* 9.0, 6,7-H), 7.18-7.38 (5 H, m, Ar-H), 8.11 (1 H, d, *J* 16.5, 3-H) and 10.53 (1 H, s, CHO); δ_C 14.22 (CH_2CH_3), 31.88 (NMe), 57.54 (OMe), 60.93 (CH_2CH_3), 74.93 (CH_2Ph), 105.82, 113.16, 116.60, 121.98, 125.73, 128.30, 128.42, 128.47, 132.35, 135.05, 137.10, 138.60, 141.33, 147.88, 166.30 (CO_2Et) and 187.65 (CHO); *m/z* (393, M^+, 3.9%), 230 (89), 215 (51), 186 (30), 91 (100) and 65 (29).

Ethyl 3-(3-formyl-4-hydroxy-5-methoxy-1-methyl-2-indolyl)prop-2-enoate (**12**)

To a solution of (*E*)-ethyl 3-(4-benzyloxy-3-formyl-5-methoxy-1-methyl-2-indolyl)prop-2-enoate (**11**) (0.480 g, 1.22 mmol) in anhydrous acetonitrile (50 ml) was added dropwise trimethylsilyl iodide (0.21 ml, 1.46 mmol) and the resultant dark green solution left to stir at room temperature for 10 min. Methanol (10 ml) was added and after stirring for a further 10 min the mixture was extracted with dichloromethane (3 x 30 ml). Evaporation of the solvent gave an orange residue which was purified by chromatography (ethyl acetate:dichloromethane, 50:50) to give the *title compound* (0.340 g, 92%). Recrystallisation afforded orange-red needles, m.p. 162°C (ethyl acetate) (Found: C, 63.82; H, 5.37; N, 4.34. $C_{16}H_{17}NO_5$ requires C, 63.36

H, 5.65; N, 4.62%); λ_{max}/nm 217 (log ε 4.42), 235 sh (4.35), 260 (4.39), 306 (4.27) and 259 (4.14); ν_{max}/cm^{-1} 3400 br, 1708 and 1639; δ_H 1.39 (3 H, t, *J* 7.1, CH_2CH_3), 3.77 and 3.95 (each 3 H, s, NMe,OMe), 4.35 (2 H, q, *J* 7.1, CH_2CH_3), 6.45 (1 H, d, *J* 16.0, 2-H), 6.76 (1 H, d, *J* 16.0, 3-H), 9.72 (1 H, s, CHO) and 11.13 (1 H, br s, OH); δ_C 14.17 (CH_2CH_3), 31.44 (NMe), 57.48 (OMe), 61.40 (CH_2CH_3), 100.03 (C-2), 114.19 (C-3), 115.84, 117.09, 129.00, 129.30, 134.76, 141.43, 142.89, 145.00, 164.87 (C-1) and 185.21 (CHO); *m/z* 303 (M^+, 11%), 230 (100) and 215 (30).

(E)-Ethyl 3-(3-formyl-5-methoxy-1-methyl-4,7-dioxo-2-indolyl)prop-2-enoate (**13**)
A mixture of (*E*)-ethyl 3-(3-formyl-4-hydroxy-5-methoxy-1-methyl-2-indolyl)prop-2-enoate (**12**) (0.117 g, 0.386 mmol), potassium dinitrosodisulfonate (0.210 g, 0.772 mmol), sodium dihydrogen phosphate buffer (0.167 M, 15 ml), water (15 ml) and acetone (15 ml) were stirred at room temperature for 16 h. The mixture was extracted with dichloromethane (3 x 30 ml) and the combined organic extracts were dried (Na_2SO_4) and evaporated. The orange/brown residue was chromatographed (ethyl acetate:dichloromethane, 50:50) to give the *title compound* (0.089 g, 73%) as orange needles, m.p. 187-190°C (dichloromethane-ethyl acetate) (Found: C, 60.12; H, 4.83; N, 4.39. $C_{16}H_{15}NO_6$ requires C, 60.57, H, 4.77; N, 4.41%); λ_{max}/nm 211 (log ε 4.09), 221 (4.09), 295 (4.32), 309 sh (4.19) and 434 (2.94); ν_{max}/cm^{-1} 1719, 1682, 1645 and 1607; δ_H 1.34 (3 H, t, *J* 7.1, CH_2CH_3), 3.88 and 4.11 (each 3 H, s, NMe,OMe), 4.28 (2 H, q, *J* 7.1, CH_2CH_3), 5.79 (1 H, s, 6-H), 6.95 (1 H, d, *J* 16.5, 2-H), 8.12 (1 H, d, *J* 16.5, 3-H) and 10.59 (1 H, s, CHO); δ_C 14.15 (CH_2CH_3), 34.09 (NMe), 56.77 (OMe), 61.15 (CH_2CH_3), 107.37 (C-1), 122.50, 123.17, 127.39, 128.96, 130.93, 177.23, 178.71 and 187.05 (CHO); *m/z* 318 (M+H, 3%), 245 (17) and 244 (100).

(E)-Ethyl 3-(3-formyl-4,7-dihydroxy-5-methoxy-1-methyl-2-indolyl)prop-2-enoate
A mixture of (*E*)-ethyl 3-(3-formyl-5-methoxy-1-methyl-4,7-dioxo-2-indolyl)prop-2-enoate (**13**) (0.030 g, 0.095 mmol) and aqueous sodium dithionite (0.9M, 1.3 ml) in chloroform:ethanol (3:1, 1.0 ml) was stirred vigorously at room temperature for 30 min. The mixture was extracted with dichloromethane and the combined organic extracts were washed with brine (30 ml) and dried (Na_2SO_4). Evaporation of the solvent gave the hydroquinone as a bronze coloured solid which was used without further purification (Found: M^+, 319.1056. $C_{16}H_{17}NO_6$ requires M, 319.1056); ν_{max}/cm^{-1} 3400 br, 2380, 1715 and 1643; δ_H 1.35 (3 H, t, *J* 7.1, CH_2CH_3), 3.91 and 4.08 (each 3 H, s, NMe,OMe), 4.30 (2 H, q, *J* 7.1, CH_2CH_3), 5.85 (1 H, s, 6-H), 6.32 (1 H, d, *J* 16.7, 2-H), 8.14 (1 H, d, *J* 16.7, 3-H) and 10.62 (1 H, s, CHO); *m/z* 319 (M^+, 23%), 246 (100), 244 (43), 231 (36), 232 (29), 216 (20), 91 (20), 69 (23) and 55 (21).

3-Hydroxymethyl-2-[(E)-3-hydroxyprop-2-enyl]-5-methoxy-1-methylindole-4,7-dione (**14**, *EO7*)
To the hydroquinone (**7**) (30 mg, 0.0945 mmol) in tetrahydrofuran (15 ml) at 0°C was added diisobutylaluminium hydride (1.5M solution in toluene, 0.56 ml, 9 eq.) and stirred at 0°C for 100 min. Aqueous iron(III) chloride (0.05M, 0.5 ml) in hydrochloric acid (0.05M, 0.5 ml) was added and stirred for 20 min. The mixture was exhaustively extracted with *n*-butanol and dried (Na_2SO_4). Chromatography (dichloromethane:acetone, 70:30) gave EO7 (10 mg, 38%), together with the further reduced product described below. EO7 was obtained as a dark red solid (Found: M^+, 277.0950. $C_{16}H_{17}NO_6$ requires M, 277.0950); δ_H 3.77 and 3.86 (each 3 H, s, NMe,OMe), 4.35 (2 H, dd, *J* 4.6 and 1.9, 3'-H), 4.63 (2 H, s, CH_2OH), 5.62 (1 H, s, 6-H), 6.09 (1 H, dt, *J* 16.0 and 4.6, 2'-H) and 6.43 (1 H, dt, *J* 16.0 and 1.9, 1'-H); *m/z* 277 (M^+, 17%), 260 (41), 258 (42), 246 (41), 244 (60), 242 (24), 232 (29), 231 (98), 230 (100), 228 (39), 217 (57), 216 (64), 215 (55), 214 (31), 204 (20), 203 (22), 202 (36), 201 (26), 199 (29), 190 (24), 188 (37), 187 (34), 186 (34), 176 (27), 175 (23), 174 (34), 160 (24), 159 (20), 158 (50), 146 (51), 132 (27), 131 (22), 129 (26), 118 (27), 117 (212), 115 (213), 105 (23), 104 (36), 103 (23), 95 (39), 93 (24), 91 (44), 90 (22), 89 (24), 82 (29), 81 (29), 80 (22), 79 (37), 78 (27), 77 (75), 67 (73), 64 (26), 58 (39), 57 (26), 56 (21), 55 (59), 53 (39), 52 (21), 51 (43) and 50 (29).

2-[(E)-3-Hydroxyprop-1-enyl]-5-methoxy-1,3-dimethylindole-4,7-dione (**15**)
The *title compound* was obtained as an orange solid in 20-35% yield (Found: M^+, 261.0994. $C_{16}H_{17}NO_6$ requires M, 261.1001); λ_{max}/nm 222, 279 and 465; ν_{max}/cm^{-1} 3400br, 2927, 2855, 1669 and 1636; δ_H 2.34 (3 H, s, 3-Me), 3.74 and 3.89 (each 3 H, s, NMe,OMe), 4.34 (2 H, dd, *J* 4.9 and 1.7, 3'-H), 5.57 (1 H, s, 6-H), 6.15 (1 H, dt, *J* 16.2 and 4.9, 2'-H) and 6.44 (1 H, dm, *J* 16.2, 1'-H); *m/z* 261 (M^+, 100%), 232 (23), 230 (40), 218 (72), 205 (20), 158 (28), 148 (28), 91 (26), 79 (24), 77 (47), 69 (61), 66 (21), 65 (27), 63 (27), 57 (42), 55 (42), 53 (31), 52 (28), 51 (38), 50 (60), 44 (51), 43 (29), 42 (47), 41 (65), 40 (43), 39 (64), 31 (40), 29 (54), 27 (47) and 20 (31).

Attempts to increase the yield of EO7 by decreasing reaction time and/or temperature resulted in isolation of a partially reduced product, together with those already described; *(E)-Ethyl 3-(3-hydroxymethyl-5-methoxy-1-methyl-4,7-dioxo-2-indolyl)prop-2-enoate* (**16**), obtained as an orange solid (Found: M^+, 319.1056. $C_{16}H_{17}NO_6$ requires M, 319.1056); λ_{max}/nm 212, 294, 315 sh and 448; ν_{max}/cm^{-1} 1706, 1676 and 1654; δ_H 1.35 (3 H, t, *J* 7.1, CH_2CH_3), 3.86 and 4.05 (each 3 H, s, NMe,OMe), 4.29 (2 H, q, *J* 7.1, CH_2CH_3), 4.79 (2 H, d, *J* 7.0, CH_2OH), 5.76 (1 H, s, 6-H), 6.27 (1 H, d, *J* 16.1, 2'-H) and 7.60 (1 H, d, *J* 16.1, 3'-H); *m/z* 319 (M^+, 26%), 302 (43), 291 (24), 274 (28), 273 (69), 245 (58), 244 (100), 231 (26), 230 (71), 229 (27), 218 (23), 217 (31), 216 (31), 202 (43), 132 (21), 77 (20) and 69 (26).

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