An aryl radical cyclisation approach to highly substituted oxindoles related to mitomycins

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Dedicated to Professor Otto Meth-Cohn to mark the occasion of his 65th birthday

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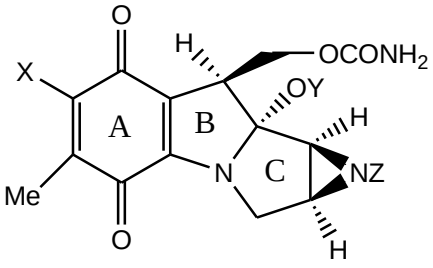
Abstract

Aryl radical cyclisation of anilides 14 and 25 leads to highly substituted oxindoles 15 and 26 respectively in excellent yields. Oxindole 26 possesses the correct substitution pattern for the A-ring of mitomycin A.

Introduction

The mitomycins are a family of molecules that exhibit potent antibiotic and cytotoxic properties, with mitomycin C being used clinically in the treatment of adenocarcinomas of the stomach, pancreas and the colon. It is also used for the treatment of a range of other carcinomas[1].



	X	Y	Z
Mitomycin A	OMe	Me	H
Mitomycin B	OMe	H	Me
Mitomycin C	NH_2	Me	H
Porfiromycin	NH_2	Me	Me

Figure 1

Since the isolation of mitomycins A and B by Hata in 1956[2], mitomycin C by Wakaki in 1958[3] (Fig. 1) and a range of structurally related mitomycins in more recent years,[4] there has been a great deal of interest in their synthesis.[5] However, owing to the synthetic challenges associated with these molecules, namely the dense functionality, chemical lability, and the stereochemical problems there have been only two successful syntheses to date. The first of these by Kishi[6] involved the formation of an eight-membered ring system by an intramolecular Michael reaction followed by a mercuric chloride trans-annular cyclisation to give the B and C rings. The second by Fukuyama[7] took advantage of the fact that isomitomycins can be readily converted to the mitomycins and these were therefore his primary synthetic target.

Our own interest in the mitomycin family of molecules has centred upon the use of oxindoles as pivotal intermediates from which the C-ring can be constructed. This strategy was first proposed by Raphael[8] who attempted (unsuccessfully) to add an acetylenic anion onto the carbonyl carbon of an oxindole to form the C-ring. Our approach relies upon nucleophilic attack on the carbonyl of an oxindole. We have reported two strategies. One involved the intermolecular addition of an organolithium to the carbonyl of an oxindole followed by a Mitsunobu cyclisation to construct the C-ring[9] (Figure 2).

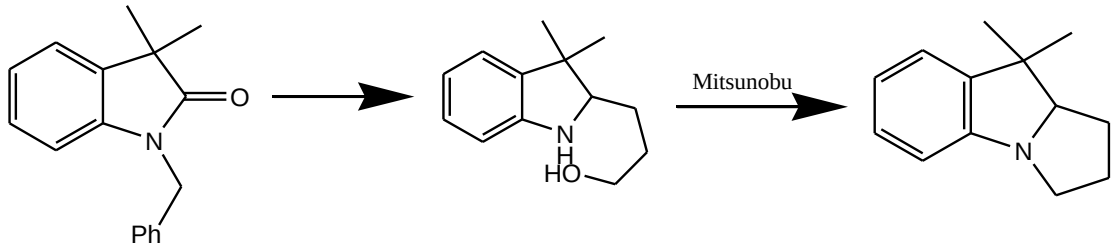


Figure 2

The second involved intramolecular addition of alkyl- and vinyllithiums to the carbonyl of an oxindole[10] (Fig. 3). Both these approaches proved successful for the formation of the pyrrolo[1,2-*a*] indolenine ring system, the core ring system found in the mitomycins.

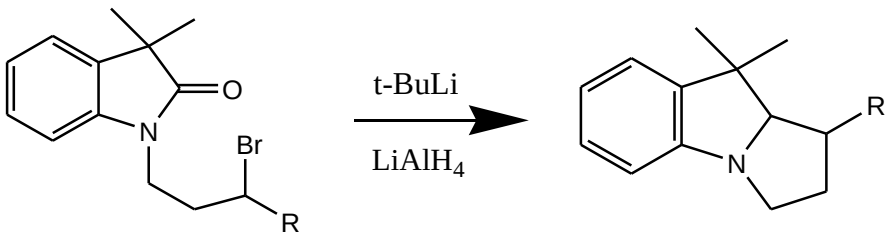
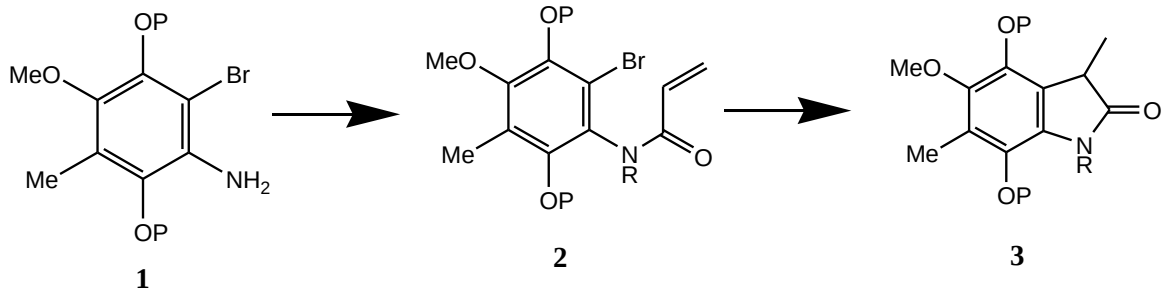


Figure 3

The use of aryl radical cyclisations to generate a range of simple oxindoles has previously been reported.[11] An essential requirement of this synthetic plan is the availability of oxindoles carrying the correct A-ring substitution pattern. This provides a severe test of the radical cyclisation chemistry and we now wish to disclose in detail the successful conclusion of our efforts in this area.[12] The methodology relies upon the generation of a suitable aniline 1, reaction of this to form an anilide 2 and subsequent radical cyclisation to form an oxindole 3 (Scheme 1). In order to eliminate the problems inherent in handling quinone ring systems we chose to use a protected bis-phenol, which offers the opportunity for deprotection and oxidation to the required quinone at a later stage.



Scheme 1

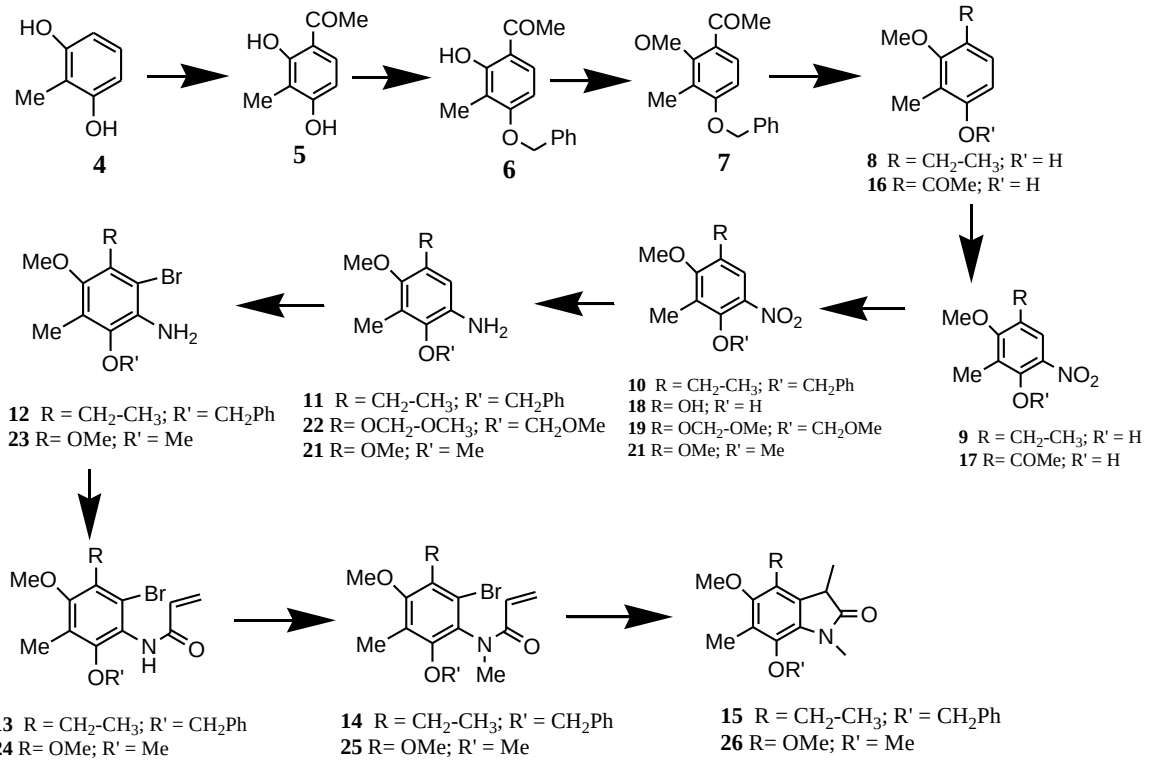
Results and Discussion

Following the procedure reported by Raphael,[8] the tetrasubstituted benzene 7 (scheme 2) was obtained from 2-methylresorcinol 4 in three steps. Friedel-Crafts acylation of 4 to give 5 was followed by selective benzylation of the non-hydrogen bonded hydroxyl of 5 to give 6 and the remaining hydroxyl was protected as the methyl ether in an overall yield for the three steps of 69% after recrystallisation. Catalytic hydrogenation in ethanol over palladium on carbon to remove the benzyl ether gave 8 in 99% yield, in which not only debenzylation but reduction of the benzylic ketone had occurred. However, this provided a suitable substrate to test our synthetic sequence and subsequently the final radical cyclisation.

Nitration of 8 was achieved regiospecifically using concentrated nitric acid in glacial acetic acid to give 9 in 86% yield. Benzylation of 9 was simply achieved by treatment with potassium carbonate and benzyl bromide in acetone at reflux to give 10 in 93% yield. Attempts to introduce bromine into the last remaining site of the aryl ring proved problematic. Bromine in dichloromethane gave rise to benzylic bromination at the ethyl

group. Bromination in acetic acid with and without iron catalysis also failed to give any of the desired product. It seemed likely that further activation of the aromatic ring would be necessary. Clearly the deactivating effect of the nitro group is sufficient to prevent the expected aromatic substitution reaction. To this end the nitro group was reduced using Bellamy's procedure[13] with tin (II) chloride in ethanol to give 11 in quantitative yield.[14] Treatment of 11 with bromine in acetic acid gave 12 in 54% yield, however the yield of this reaction was improved to 92% by the use of pyridinium hydrobromide perbromide[15] as the source of bromine.

The conversion of the hexasubstituted aromatic 12 into the oxindole 15 proved straightforward. Aniline 12 was treated with acryloyl chloride in ether to give anilide 13 in 96% yield. In order that the molecule adopts the correct orientation for cyclisation, substitution of the amide nitrogen is essential.[16] Anilide 13 was therefore alkylated on nitrogen using methyl iodide in the presence of potassium hydride in THF to give 14 in 90% yield. Cyclisation of 14 using tributyltin hydride, at a concentration of 0.012 M in toluene at reflux with AIBN as initiator gave the desired oxindole 15 in 76% yield after column chromatography.



Scheme 2

Having established that the radical cyclisation of an anilide bearing a highly functionalised aromatic ring was feasible and proceeded in good yield, attention was turned to the synthesis of an anilide system more closely resembling that required for the A ring of the mitomycins. Once again the quinone functionality was protected with the intention of unmasking it at a later stage in the synthesis. Owing to their ease of removal, methoxymethyl (MOM) ethers were the first choice of protecting group.

Careful hydrogenolysis of 7 with continuous monitoring enabled us to isolate 16 in 84% yield after two hours with no trace of reduction of the ketone. This was nitrated using concentrated nitric acid in glacial acetic acid to give 17 in 74% yield after recrystallisation from ethanol. Baeyer-Villiger oxidation of 17 in dichloromethane with mCPBA gave the dihydroquinone 18[8] in 78% yield which was converted to its bismethoxymethyl ether derivative 19[8] in 78% yield by treatment with *N*,*N*-diisopropylethylamine and chloromethyl methyl ether in dichloromethane. Reduction of the nitro group was then attempted. Unfortunately using the conditions previously used for 10, namely stannous chloride in ethanol resulted in cleavage of the MOM ethers to give 18 in near quantitative yield. However, the desired transformation to give 20 was achieved quantitatively by catalytic hydrogenation in ethyl acetate using palladium on carbon as catalyst. Bromination was attempted using pyridinium hydrobromide perbromide in acetic acid as for 12 but no identifiable products were isolated. Clearly, acidic conditions had to be avoided and the reaction was repeated in dichloromethane containing *N*,*N*-diisopropylethylamine. Once again none of the desired product was isolated. In order to alleviate the potential problem of oxidative decomposition of the aromatic ring due to its high nucleophilicity, bromination of the nitro aromatic 18 was investigated. Once again under a variety of conditions none of the desired product was obtained.

These results forced a reconsideration of the protection protocol, and the use of methyl ether protecting groups was chosen since oxidation to the quinone required for the A ring of the mitomycins has been reported previously.[17] Protection of 18 was achieved in nearly quantitative yield using potassium carbonate and dimethylsulfate in acetone to give 21.[14] The nitro group of 21 was reduced by catalytic hydrogenation in ethyl acetate using palladium on carbon catalyst to give 22 in 93% yield.[14] Bromination was straightforward using pyridinium hydrobromide perbromide in dichloromethane and pyridine to give 23 in 70% yield. Acylation with acryloyl chloride gave 24 in 95% yield followed by *N*-methylation using sodium hydride and methyl iodide to give 25 in 95% yield. The radical cyclisation of 25 proceeded smoothly to give the oxindole 26 in 97% yield after chromatography.

In summary, we have demonstrated the feasibility of constructing an oxindole containing all the functionality required for ring-A of the mitomycins using an aryl radical cyclisation.

Experimental Section

General Procedures. NMR spectra were recorded on a Bruker AM360 or AM250 spectrometer at 360 MHz and 250 MHz respectively using $CDCl_3$ as solvent with $SiMe_4$ as an internal standard, unless otherwise stated. *J*-values are given in Hz. IR spectra were recorded on a Perkin-Elmer 983G infrared spectrometer, using nujol mulls or carbon tetrachloride solutions unless otherwise stated. Mass spectral data were recorded on a Jeol AX505W with complement data system. Samples were ionised electronically at 70eV with typical accelerating voltage of 6 kV. Melting points were determined using a Kofler hot plate apparatus and are uncorrected. All column chromatography was carried out using the flash chromatography technique, using Merck 60 (230-400 mesh) silica gel. Analytical TLC was carried out on Merck plastic backed TLC plates, coated with silica gel 60 F-254. Plates were visualised using ultraviolet light, unless otherwise stated. Eluting solvent systems are stated where appropriate. All dry reactions were performed in an inert argon atmosphere using a vacuum-argon manifold for the exclusion of water. Stirring was by internal magnetic bead. All syringes, needles and glassware were pre-dried at 110°C and cooled in an anhydrous atmosphere before use. Diethyl ether, tetrahydrofuran (THF), and toluene were pre-dried over sodium wire and refluxed over sodium under argon with benzophenone as an indicator in the reaction vessel. Dichloromethane was refluxed under argon, over CaH_2 and distilled directly into the reaction vessel.

4-Ethyl-3-methoxy-2-methylphenol (8). A solution of the methyl ether 7 (55.9 g, 207 mmol) in ethanol (500 ml) was treated with palladium on carbon catalyst (5% Pd, 1.5 g) and the mixture was rapidly stirred in an atmosphere of hydrogen for three days. Filtration through celite and removal of solvents at reduced pressure gave 8 (33.9 g, 99%) as a white crystalline solid requiring no further purification. mp 132 °C; (Found: C, 72.36; H, 8.41. $C_{10}H_{14}O_2$ requires C, 72.25; H, 8.48%); ν_{max} (CCl_4)/cm^{-1} 3587, 2950-3050, 1614; δ_H (360 MHz), 1.18 (3H, t, *J* 7.5, $CH_2\underline{CH_3}$), 2.17 (3H, s, Ar-<u>Me</u>), 2.59 (2H, q, *J* 7.5, $\underline{CH_2}CH_3$), 3.71 (3H, s, O-Me), 5.25 (1H, br.s, OH), 6.50 (1H, d, *J* 8.2, H-6), 6.87 (1H, d, *J* 8.2, H-5); m/z (EI) 166 (75), 151 (100%). Found: M^+, 166.0950. $C_{10}H_{14}O_2$ requires: M^+, 166.0994.

4-Ethyl-3-methoxy-2-methyl-6-nitrophenol (9). A solution of phenol 8 (32.0 g, 192 mmol) in acetic acid (100 ml) was treated with a solution of concentrated nitric acid (12 ml) in acetic acid (25 ml). Initially 5 ml of this solution was added and the reaction mixture was warmed to 40 °C. After 15 minutes the remaining nitric acid solution was slowly added. The reaction was stirred for a further 1 hour, then poured into water (500 ml), extracted with diethyl ether (3 x 300 ml), washed with brine (3 x 20 ml) and dried with magnesium sulfate. The ethereal solution was then treated with charcoal, filtered and the solvents removed at reduced pressure to leave a brown crystalline solid. This was recrystallised from hot ethanol and the mother liquor concentrated and purified by

chromatography on silica using petroleum spirit (40 – 60 °C) - ethyl acetate (10 : 1) as eluent to give nitrophenol 9 (34.8 g, 86%) as a brown crystalline solid. mp 34 °C; (Found: C, 56.76; H, 5.99; N, 6.64. $C_{10}H_{13}O_4N$ requires: C, 56.86; H, 6.20; N, 6.63%); ν_{max} (CCl_4)/cm^{-1} 3200, 3000-2800, 1615, 1591; δ_H (360 MHz), 1.19 (3H, t, *J* 7.5, $CH_2\underline{CH_3}$), 2.18 (3H, s, Ar-<u>Me</u>), 2.58 (2H, q, *J* 7.5, $\underline{CH_2}CH_3$), 3.76 (3H, s, OMe), 7.75 (1H, s, H-5), 10.91 (1H, s, OH); m/z (EI) ; 211 (75), 196 (100%). Found: M^+, 211.0834. $C_{10}H_{13}O_4N$ requires: M^+, 211.0844.

2-Benzyloxy-5-ethyl-4-methoxy-3-methylnitrobenzene (10). A stirred mixture of potassium carbonate (5.0 g, 36 mmol) and nitrophenol 9 (1.0 g, 4.7 mmol) in acetone (30 ml) was treated with benzyl bromide (0.89 g, 5.2 mmol). The reaction mixture was heated at reflux overnight, cooled, filtered through celite, and the solvents and excess benzyl bromide were removed at reduced pressure. The crude product was purified by column chromatography on silica using petroleum (40 – 60 °C) - ethyl acetate (12 : 1) as eluent to give 10 (1.32 g, 93%) as a pale yellow crystalline solid. mp 42 °C; ν_{max} (CCl_4)/cm^{-1} 3200-2800, 1615, 1600, 1569; δ_H (360 MHz), 1.24 (3H, t, *J* 7.5, $CH_2\underline{CH_3}$), 2.25 (3H, s, Ar-<u>Me</u>), 2.68 (2H, q, *J* 7.5, $\underline{CH_2}CH_3$), 3.75 (3H, s, OMe), 4.97 (2H, s, benzylic CH_2), 7.40 (3H, m, Ar-H), 7.49 (2H, m, Ar-H), 7.64 (1H, s, H-6); m/z (EI) 301 (10), 255 (10), 91 (100%). Found: M^+, 301.1303. $C_{17}H_{19}O_4N$ requires: M^+, 301.1314.

2-Benzyloxy-5-ethyl-3-methoxy-2-methylaniline (11). A mixture of 10 (5.0 g, 16 mmol) and tin (II) chloride (14.9 g, 78 mmol) were heated at reflux in ethanol for 1 hour. The solution was then cooled, poured into ice, basified with sodium bicarbonate, then extracted with ethyl acetate (3 x 40 ml). The combined organic extracts were washed with brine, treated with charcoal, filtered, dried with magnesium sulfate, and the solvent was removed at reduced pressure to give 11 (4.29 g, 99%) as a clear viscous oil. ν_{max} (CCl_4)/cm^{-1} 3439, 3354, 3200-2800, 1600; δ_H (360 MHz), 1.18 (3H, t, *J* 7.6, $CH_2\underline{CH_3}$), 2.25 (3H, s, Ar<u>Me</u>), 2.56 (2H, q, *J* 7.6, $\underline{CH_2}CH_3$), 3.64 (3H, s, OMe), 4.80 (2H, s, benzylic-CH_2), 6.42 (1H, s, H-6), 7.25 -7.50 (5H, m, Ar-H); m/z (EI) 271 (20), 256 (30), 91 (100%). Found: M^+, 271.1583. $C_{17}H_{21}O_2N$ requires: M^+, 271.1572.

2-Benzyloxy-6-bromo-5-ethyl-4-methoxy-3-methylaniline (12). A stirred solution of 11 (4.07 g, 15.0 mmol) in acetic acid (100 ml) was treated with a solution of pyridinium hydrobromide perbromide (5.79 g, 18.1 mmol) in acetic acid (10 ml). The reaction was stirred in the dark for 1 hour at room temperature, quenched with sodium thiosulfate solution (50 ml) and the acetic acid was removed at reduced pressure. The resultant residue was diluted with dichloromethane, washed with water (3 x 30 ml), dried over magnesium sulfate, and the solvent was removed at reduced pressure. The crude product was purified by column chromatography on silica using petroleum spirit (40 – 60 °C) - ethyl acetate (9:1) as eluent to give 12 (4.75 g, 90%) as a red/brown oil. ν_{max} (CCl_4)/cm^{-1} 3400, 3200-3000, 1610; δ_H (360 MHz), 1.18 (3H, t, *J* 7.5, $CH_2\underline{CH_3}$), 2.19 (3H, s, Ar-<u>Me</u>), 2.78 (2H, q,

J 7.5, $\underline{CH_2}CH_3$), 3.67 (3H, s, OMe), 3.95 (2H, br.s, NH_2), 4.82 (2H, s, benzylic CH_2), 7.40 (3H, m, Ar-H), 7.49 (2H, m, Ar-H); m/z (EI) 351/349 (30), 260/258 (100%). Found: M^+, 351.0659/349.0684. $C_{17}H_{20}O_2BrN$ requires: M^+, 351.0658/349.0677.

***N*-(2-Benzyloxy-6-bromo-5-ethyl-4-methoxy-3-methylphenyl)propenamide (13).** Acryloyl chloride (240 mg, 2.85 mmol) was slowly added to a stirred solution of 12 (2.0 g, 5.70 mmol) in THF (100 ml). When addition was complete the reaction was heated at reflux for 2 hours, it was then cooled to room temperature, the THF was removed at reduced pressure and the residue was diluted with diethyl ether (50 ml). The ether solution was washed with HCl (1M) (3 x 50 ml), with saturated sodium bicarbonate solution (3 x 20 ml), with water (2 x 10 ml) and then dried with magnesium sulfate. The crude produce was purified by chromatography on silica using petroleum spirit (40 – 60 °C) - ethyl acetate (4 : 1) as eluent and recrystallised from ethyl acetate to give 13 (1.10 g, 94%) as a white crystalline solid. mp 163 °C; (Found: C, 59.19; H, 5.36; N, 3.40. $C_{20}H_{22}O_3BrN$ requires: C, 59.41; H, 5.48; N, 3.46.); ν_{max} (CCl_4)/cm^{-1} 3200-3000, 1614, 1642; δ_H (360 MHz), 1.17 (3H, t, *J* 7.4, $CH_2\underline{CH_3}$), 2.18 (3H, s, Ar-$\underline{Me}$), 2.80 (2H, q, *J* 7.4, $\underline{CH_2}CH_3$), 3.73 (3H, s, O$\underline{Me}$), 4.78 (2H, br.s, benzyl-CH_2), 5.70 (1H, br. d, *J* 9.0, H-3), 6.15 (1H, m. H-2), 6.40 (1H, br. d, *J* 14.0, H-3), 7.21 (1H, br.s, NH), 7.34 (5H, s, Ar-H); m/z (EI) 405/403 (20), 149 (100%). Found: M^+, 405.0729/403.0828. $C_{20}H_{22}O_3BrN$ requires: M^+, 405.0763/403.0783.

***N*-(2-Benzyloxy-4-bromo-5-ethyl-4-methoxy-3-methylphenyl)-*N*-methylpropenamide (14).** Potassium hydride (33% w/w, 179 mg, 1.36 mmol) was pre-washed with petrol (3 x 5 ml) and the washings discarded. The potassium hydride was suspended in THF (50 ml) and was then treated with a solution of 13 (0.50g, 1.23mmol) in THF (10 ml). When hydrogen evolution had ceased MeI (0.87 g, 6.15 mmol) was added and the reaction stirred at room temperature for 3 hours. The unreacted potassium hydride was cautiously destroyed with water and the THF was removed at reduced pressure. The organic residue was then diluted with diethyl ether (100 ml), washed with water (3 x 20 ml) and dried over magnesium sulfate. Solvent was removed at reduced pressure and the resultant oil purified by chromatography on silica using petroleum spirit (40 – 60 °C) - ethyl acetate (10:1) as eluent to give 14 (0.46 g, 90%) as a clear oil. ν_{max} (CCl_4)/cm^{-1} 3200-2800, 1656, 1616; δ_H (360 MHz), 1.19 (3H, t, *J* 7.4, $CH_2\underline{CH_3}$), 2.22 (3H, s, Ar-$\underline{Me}$), 2.84 (2H, q, *J* 7.4, $\underline{CH_2}CH_3$), 3.25 (3H, s, N-$\underline{Me}$), 3.79 (3H, s, Ar-O$\underline{Me}$), 4.75 (2H, s,benzylic-CH_2), 5.56 (1H, dd, *J* 10.3, 2.0, H-3), 6.04 (1H, dd, *J* 6.7, 10.3, H-2), 6.45 (1H, dd, *J* 6.7, 2.0, H-3), 7.37 (5H, m, Ar-H); m/z (EI) 418/420 (20), 338 (40), 91 (100%). Found: M^++H, 420.0961/418.0981. $C_{21}H_{24}O_3BrN$ requires: M^++H, 420.0998/418.1018.

7-Benzyloxy-4-ethyl-5-methoxy-1,3,6-trimethylindole-2(3H)one (15). A solution of 14 (100 mg, 0.24 mmol) in toluene (20 ml) was treated with tributyltin hydride (76.5 mg, 0.26 mmol) and a substoichiometric amount of AIBN (5 mg). The reaction was then heated

at reflux for 2 hours. After cooling to room temperature the toluene was removed at reduced pressure and the resultant oil diluted with diethylether (50 ml). The ether solution was washed with ammonia solution (20%, 5 x 20 ml), dried with magnesium sulfate, and the solvent was removed at reduced pressure. The crude oil was purified by chromatography on silica using petroleum spirit (40 – 60 °C) - ethyl acetate (8:1) as eluent to give 15 (61.4 mg, 76%) as a white crystalline solid; mp 113 °C. (Found: C, 74.08; H, 7.66; N, 4.03. $C_{21}H_{25}NO_3$ requires: C, 74.33; H, 7.43; N, 4.13%.); ν_{max} (CCl_4)/cm^{-1} 3200-2800, 1666, 1609; δ_H (360 MHz), 1.22 (3H, t, *J* 7.4, $CH_2\underline{CH_3}$), 1.51 (3H, d, *J* 7.61, CH_3), 2.30 (3H, s, Ar-Me), 2.65 (2H, q, *J* 7.4, $\underline{CH_2}CH_3$), 3.41 (4H, m, N-Me, H-3), 3.74 (3H, s, Ar-OMe), 4.86 (2H, s, benzyl-CH_2), 7.40 (5H, m, Ar-H); m/z (EI) 339 (60), 248 (100 %). Found: M^+, 339.1856. $C_{21}H_{25}NO_3$ requires: M^+, 339.1834.

4-Hydroxy-2-methoxy-3-methylacetophenone (16). A solution of 7 (13.0 g, 48.1 mmol) in ethanol (150 ml) was treated with Pd/C catalyst (10% Pd, 0.50 g). The reaction mixture was rapidly stirred in a hydrogen atmosphere for 2 hours whereupon it was filtered through celite and the solvent was removed at reduced pressure to give 16 (7.7 g, 89% yield) as a white crystalline solid. mp 130 °C, (lit. mp 130-132 °C[8]); ν_{max} (CCl_4)/cm^{-1} 3570, 3200-3000, 1668, 1594; δ_H (360 MHz), 2.17 (3H, s, Ar-Me), 2.59 (3H, s, COMe), 3.74 (3H, s, OMe), 6.69 (1H, d, *J* 8.6, H-5'), 7.48 (1H, d, *J* 8.6, H-6').

4-Hydroxy-2-methoxy-3-methyl-5-nitroacetophenone (17). A stirred solution of phenol 16 (32.0 g, 177 mmol) in acetic acid (100 ml) was treated with nitric acid/acetic acid solution (conc. nitric acid:glacial acetic acid, 1:2, 5 ml). The solution was warmed to 40 °C and after 15 minutes the a further quantity (7 ml) of the nitric acid solution was slowly added over 10 minutes. After 1 hour the reaction was cooled to room temperature, poured into water (200 ml) and extracted with diethyl ether (3 x 300 ml). The ether extracts were washed with brine, dried with magnesium sulfate, treated with charcoal, filtered and the solvent was removed at reduced pressure. The crude product was recrystallised from ethanol to give 17 (29.8 g, 74%) as a yellow crystalline solid, mp 70 °C. (Found: C, 53.26; H, 5.13; N, 6.21. $C_{10}H_{11}NO_5$ requires: C, 53.31; H 4.93; N 6.20.); ν_{max} (CCl_4)/cm^{-1} 3195, 1532, 1617; δ_H (360 MHz), 2.26 (3H, s, Ar-Me), 2.65 (3H, s, COMe), 3.84 (3H, s, OMe), 8.43 (1H, s, Ar-H), 10.98 (1H, s, OH).

2-Methoxy-3-methyl-5-nitro-1,4-hydroquinone (18). Acetophenone 17 (1.00 g, 4.44 mmol) was stirred rapidly in dichloromethane (30 ml) with 3-chloroperoxybenzoic acid (1.53 g, 8.88 mmol) and a catalytic amount of concentrated hydrochloric acid (0.25 ml) for 5 hours. Water (1 ml) was then added and stirring continued for a further hour. The reaction was then basified with sodium hydroxide solution (2 M) until the solution took on a permanent mauve coloration and then stirred for a further hour. After cautious acidification with dilute HCl the aqueous phase was extracted with diethyl ether (4 x 50 ml). The combined ether extracts were dried with magnesium sulfate and solvent was

removed at reduced pressure. The crude produce was purified by chromatography on silica using petroleum (40 - 60 °C) - ethyl acetate (8:1) as eluent to give 18 as a yellow crystalline solid (0.80 g, 90%). mp 135 °C; ν_{max} (CCl_4)/cm^{-1} 3000, 1621, 1535; δ_H (360 MHz), 2.26 (3H, s, Ar-Me), 3.89 (3H, s, OMe), 5.50 (1H, br. s, 1-OH), 7.53 (1H, s, Ar), 10.85 (1H, s, 4-OH); m/z (EI) 199 (100%). Found: M^+, 199.0529. $C_8H_9NO_5$ requires: M^+, 199.0480.

2,5-Bis-(methoxymethoxy)-4-methoxy-3-methylnitrobenzene (19). A stirred solution of 18 (2.00 g, 10 mmol) and *N*,*N*-diisopropylethylamine (2.58 g, 20 mmol) in dichloromethane (70 ml) at 0 °C was treated dropwise with a solution of chloromethyl methyl ether (1.62 g, 20 mmol). The reaction was warmed to room temperature and stirred for 30 minutes, it was then washed with water (2 x 10 ml), ice cold HCl (1 M, 2 x 10 ml), with water (2 x 10 ml) and then dried with magnesium sulfate. The crude product was purified by chromatography on silica using petroleum spirit (40 – 60 °C) - ethyl acetate (10:1) as eluent to give 19 (2.24 g, 78%) as a clear viscous oil. ν_{max} (CCl_4)/cm^{-1} 3000-2800, 1524; δ_H (360 MHz), 2.27 (3H, s, Ar-Me), 3.51 (3H, s, O-Me), 3.56 (3H, s, O-Me), 3.89 (3H, s, Ar-OMe), 5.01 (2H, s, CH_2), 5.21 (2H, s, CH_2), 7.55 (1H, s, Ar-H); m/z (EI) ; 287 (100%). Found: M^+, 287.0982. $C_{12}H_{17}NO_7$ requires: M^+, 287.1005.

2,5-Bis(methoxymethoxy)-4-methoxy-3-methylaniline (20). A solution of 19 (50 mg, 0.17 mmol) and palladium on carbon (5% Pd, 10 mg) in ethyl acetate (10 ml) was stirred rapidly in an atmosphere of hydrogen. When the reaction was shown to be complete by tlc analysis the solution was filtered through celite and solvents were removed at reduced pressure. The crude product 20 was isolated as a clear oil (44 mg, 99%). ν_{max} (CCl_4)/cm^{-1} 3500-3400, 1609, 1484; δ_H (360 MHz) 2.16 (3H, s, Ar-Me), 3.48 (3H, s, OMe), 3.58 (3H, s, OMe), 3.71 (3H, s, ArOMe), 4.91 (2H, s, CH_2), 5.12 (2H, s, CH_2), 6.44 (1H, s, ArH); m/z (EI) 257 (100 %), 212 (95). Found: M^+, 257.1267. $C_{12}H_{19}NO_5$ requires M^+, 257.1263.

3-Methyl-2,4,5-trimethoxynitrobenzene (21). A stirred solution of nitrophenol 18 (50 mg, 0.25 mmol) and potassium carbonate (140 mg, 1.0mmol) in acetone was treated with dimethylsulfate (126 mg, 1.00 mmol). After 24 hours the solution was filtered through celite and the acetone was removed at reduced pressure. The residue was dissolved in diethyl ether, washed with water (3 x 20 ml) and dried with magnesium sulfate. After removal of solvent at reduced pressure the crude product was purified by chromatography on silica using petroleum spirit (40 – 60 °C) - ethyl acetate as eluent to give 21 (55 mg, 98%) as a clear viscous oil. ν_{max} (CCl_4)/cm^{-1} 3200-2800, 1612; δ_H (360 MHz), 2.25 (3H, s, ArMe), 3.85 (3H, s, OMe), 3.89 (6H, s, OMe), 7.33 (1H, s, ArH); m/z (EI) 227 (30 %), 212 (10). Found: M^+, 227.0799 $C_{10}H_{13}O_5N$ requires: M^+, 227.0793.

3-Methyl-2,4,5-trimethoxyaniline (22). A solution of 21 (40 mg, 0.17 mmol) and palladium on carbon (5% Pd, 5 mg) in ethyl acetate was rapidly stirred in an atmosphere of hydrogen until all starting material had been consumed as indicated by tlc analysis. The

solution was filtered through celite and the solvent was removed at reduced pressure to give 22 (31 mg, 93%) as a viscous oil, which required no further purification but decomposed slowly. ν_{max} (CCl_4)/cm^{-1} 3400, 3354, 1606; δ_H (360 MHz), 2.27 (3H, s, Ar-Me), 3.25 (2H, br. s, NH_2), 3.41 (6H, s,OMe), 3.68 (3H, s, OMe), 5.90 (1H, s, ArH); m/z (EI) 197 (60), 182 (100%). Found: M^+, 197.1057. $C_{10}H_{15}O_3N$ requires: 197.1051.

6-Bromo-3-methyl-2,4,5-trimethoxyaniline (23). A solution of pyridinium hydrobromide perbromide (327 mg, 1.0 2mmol) in dichloromethane / pyridine (10 ml : 2 ml) was added to a stirred solution of 22 (184 mg, 0.93 mmol) in dichloromethane (50 ml) at 0 °C. The reaction was stirred at 0 °C for 1 hour then warmed to room temperature and stirred for a further 2 hours. Saturated sodium thiosulfate solution (40 ml) was added and stirring was continued for a further 5 minutes. The dichloromethane solution was then washed with water (3 x 30 ml), dried over magnesium sulfate and the solvents were removed at reduced pressure. The crude reaction mixture was purified by chromatography on silica using petroleum spirit (40 – 60 °C) - ethyl acetate (8:1) as eluent to give 23 (0.18 g, 70%) as a yellow viscous oil. ν_{max} (CCl_4)/cm^{-1} 3400, 2900, 1605, 890; δ_H (360 MHz), 2.16 (3H, s, Ar-Me), 3.71 (3H, s, O-Me), 3.76 (3H, s, O-Me), 3.84 (3H, s, O-Me), 4.06 (2H, br. s, NH_2); m/z (EI) ; 275/277 (40), 259/261 (20), 83 (100%). Found: M^+, 275.0139/277.0124. $C_{10}H_{14}NO_3Br$ requires: M^+, 275.0157/277.0138.

***N*-(6-Bromo-3-methyl-2,4,5-trimethoxyphenyl)propenamide (24).** A solution of 23 (84 mg, 0.30 mmol) and *N*,*N*-diisopropylethylamine (78 mg, 0.60 mmol) in THF (10 ml) was treated with acryloyl chloride (27.5 mg, 0.30 mmol). The reaction was stirred for four hours at 50 °C, cooled to room temperature, and the THF was removed at reduced pressure. The residue was diluted with diethyl ether (50 ml) and the ether solution was washed with HCl (1 M, 3 x 10 ml), with saturated sodium bicarbonate solution (3 x 5 ml), with water (2 x 5 ml) and then dried with magnesium sulfate. The crude produce was purified by chromatography on silica using petroleum spirit (40 – 60 °C) - ethyl acetate (1:1) as eluent to give 24 (57 mg, 57%) as a clear oil. ν_{max} (CCl_4)/cm^{-1} 3400, 3000-2800, 1700, 1610; δ_H (360 MHz), 2.16 (3H, s, Ar-Me), 3.65 (3H, s, OMe), 3.84 (3H, s, OMe), 3.85 (3H, s, OMe), 5.77 (1H, br. d, *J* 9.0, H-3), 6.25-6.50 (H, br. m, H-2), 6.45 (1H, d, *J* 16.0, H-3). 7.19 (1H, br. s, N-H); m/z (EI) 331/329 (25), 250 (100%). Found: M^+, 331.0261/329.0266. $C_{13}H_{16}NO_4Br$ requires: M^+, 329.0263 / 331.0244.

***N*-(6-Bromo-3-methyl-2,4,5-trimethoxyphenyl)-*N*-methylpropenamide (25).** Sodium hydride (80% w/w, 6.6 mg, 0.16 mmol) was washed with dry petroleum spirit (3 x 10 ml) to remove the oil. THF (5 ml) was then added and the suspension was treated with 24 (50 mg, 0.15 mmol) in THF (2 ml). The reaction was stirred at room temperature until hydrogen evolution had ceased whereupon methyl iodide (27 mg, 0.19 mmol) was added. The reaction was stirred for a further 4 hours then the THF was blown off with nitrogen. The residue was dissolved in diethyl ether (50 ml) and the ether solution was washed with

water (3 x 10 ml), dried with magnesium sulfate and the solvent was removed at reduced pressure. The crude product was purified by chromatography on silica using petroleum spirit (40 – 60 °) - ethyl acetate (1:1) as eluent to give 25 (49.6 mg, 95%) as a clear viscous oil. ν_{max} (CCl_4)/cm^{-1} 3000-2800, 1665, 1620; δ_H (360 MHz), 2.16 (3H, s, Ar-Me), 3.20 (3H, s, N-Me), 3.65 (3H, s, OMe), 3.84 (3H, s, OMe), 3.87 (3H, s, OMe), 5.50 (1H, dd, *J* 10.1, 1.0, H-3), 5.95 (1H, dd, *J* 17.0, 10.1, H-2), 6.40 (1H, dd, *J* 17.0, 1.0, H-3); m/z (EI) 345/343 (10), 264 (100%). Found: M^+, 343.0399/345.0381 $C_{14}H_{18}NO_4Br$ requires: M^+, 343.0419/345.0400.

4,5,7-Trimethoxy-1,3,6-trimethylindole-2(3H)-one (26). A stirred solution of 25 (45 mg, 0.13 mmol) in toluene (10 ml) was treated with tributyltin hydride (41 mg, 0.14 mmol) and a substoiciometric amount of AIBN (5 mg). The reaction was heated to 100 °C and after 30 minutes more AIBN was added (5 mg). After cooling to room temperature the toluene was removed at reduced pressure and the resultant oil diluted with diethyl ether (50 ml). The ether solution was washed with ammonia solution (20%, 5 x 10 ml), dried with magnesium sulfate, and the solvent was removed at reduced pressure. The crude oil was purified by chromatography on silica using petroleum spirit (40 – 60 °C) - ethyl acetate (2:1) as eluent to give 26 (33 mg, 97%) as a clear viscous oil. ν_{max} (CCl_4)/cm^{-1} 3000-2800, 1700, 1615; δ_H (360 MHz), 1.50 (3H, d, *J* 7.8, 3-Me), 2.25 (3H, s, Ar-Me), 3.43 (3H, s, N-Me), 3,45 (1H, q, *J* 7.8, H-3), 3.74 (3H, s, Ar-OMe) 3.80 (3H, s, Ar-OMe), 3.90 (3H, s, Ar-OMe); m/z (EI) 265 (100), 250 (70%). Found: M^+, 265.1307. $C_{14}H_{19}NO_4$ requires; M^+, 265. 1314.

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