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Demethylation of 2,4-dimethoxyquinolines: the synthesis of atanine

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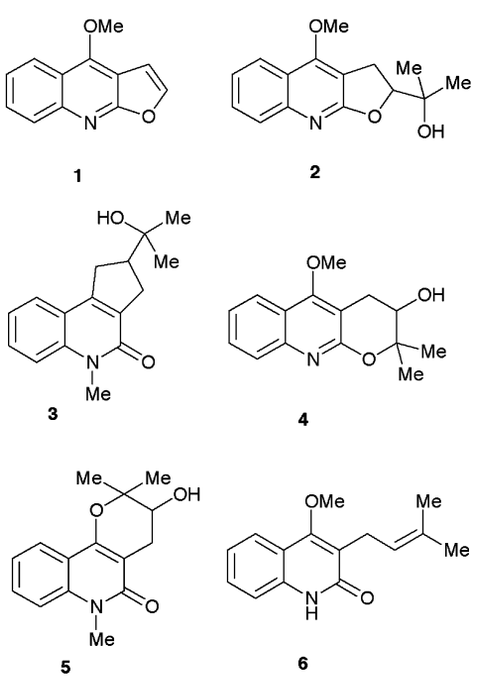
The synthesis of the quinoline alkaloid atanine **6**, by selective demethylation of the 2,4-dimethoxyquinoline **11** is presented. An alternative demethylation utilising a thiolate anion leads to the regioisomeric 4-hydroxyquinoline **13**.

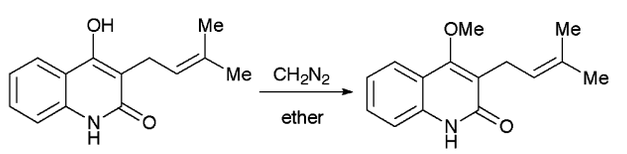
Introduction

The *Rutaceae* family of plants is the source of over 500 alkaloids containing the quinoline ring system.[1,2] The pharmacological properties of this class of compound have received only limited investigation. Nevertheless, a wide range of medicinal properties have already been identified including anti-protozoal,[3] anti-bacterial,[4] anti-fungal[5] and anti-viral[6] activities. Among the compounds isolated from *Rutaceae*, a range of structural types is identifiable. These include the furanoquinolines such as dictamine **1**, the dihydrofuranoquinolines such as platydesmine **2**, the isomeric dihydrofuranoquinolines such as araliopsine **3**, the dihydropyranoquinolines such as geibalansine **4**, the isomeric dihydropyranoquinolines such as ψ-ribalinine **5** and the simple 2,4-dioxygenated quinolines such as atanine **6** (Fig. 1). Atanine was first isolated in 1968[7] although it had been postulated to be a plausible biosynthetic intermediate of the quinoline alkaloids prior to its isolation. Since 1968, it has been found in many members of the Rutaceae family and its biosynthetic involvement has been demonstrated.[8] Our interest in this area was triggered by the discovery of atanine in *Evodia rutaecarpa* and the demonstration of its anthelmintic activity particularly against *Schistosoma mansoni*.[9] As a consequence, we required quantities of atanine and structurally related compounds for testing against a range of parasites. The first synthesis of atanine was reported by Grundon in 1966 and involved treatment of 4-hydroxyquinoline **7** with diazomethane to give atanine **6** in 80% yield (Scheme 1).[10] This approach has recently been used by Boyd *et al.* in an investigation into the absolute configuration of several of the alkaloids referred to above.[11] In 1973, Grundon *et al.* published an alternative synthesis of atanine which avoided diazomethane and involved ortholithiation of 2,4-dimethoxyquinoline **8**, alkylation with prenyl bromide and selective demethylation at the 4-position using dry HCl gas in di-isopropyl ether (Scheme 2).[12] This latter approach appeared ideal for our purposes.



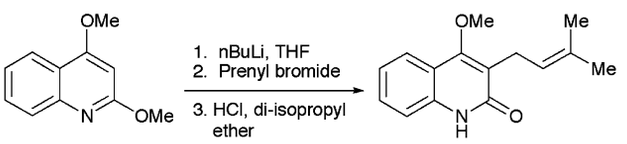
1 **2** **3** **4** **5** **6**

Fig. 1 Representative quinoline alkaloids.



7 **6**

Scheme 1



8 **6**

Scheme 2

Results and discussion

Reaction of aniline with malonic acid in an excess of phosphorus oxychloride at reflux to give 2,4-dichloroquinoline **9** was first reported by Ziegler and Gelfert.[13] Although a reaction time of 24 to 40 hours has been reported, we found that the best yield of **9** (48%) was obtained after only 5 hours at reflux (Scheme 3). Reaction of 2,4-dichloroquinoline **9** with sodium methoxide at reflux for 24 hours gave 2,4-dimethoxyquinoline **8** in 70% yield along with some 12% of 4-chloro-2-methoxyquinoline **10**. Substitution at C-2 is known to be favoured kinetically and the second substitution is slowed considerably by the methoxy group at C-2 making bis-substitution difficult to drive to completion.[14] Ortho-lithiation of **8** using *n*-butyllithium at 0 °C and addition of excess prenyl bromide gave the desired 3-alkylated quinoline **11** in 88% yield. However, reaction with dry HCl in di-isopropyl ether failed to give any

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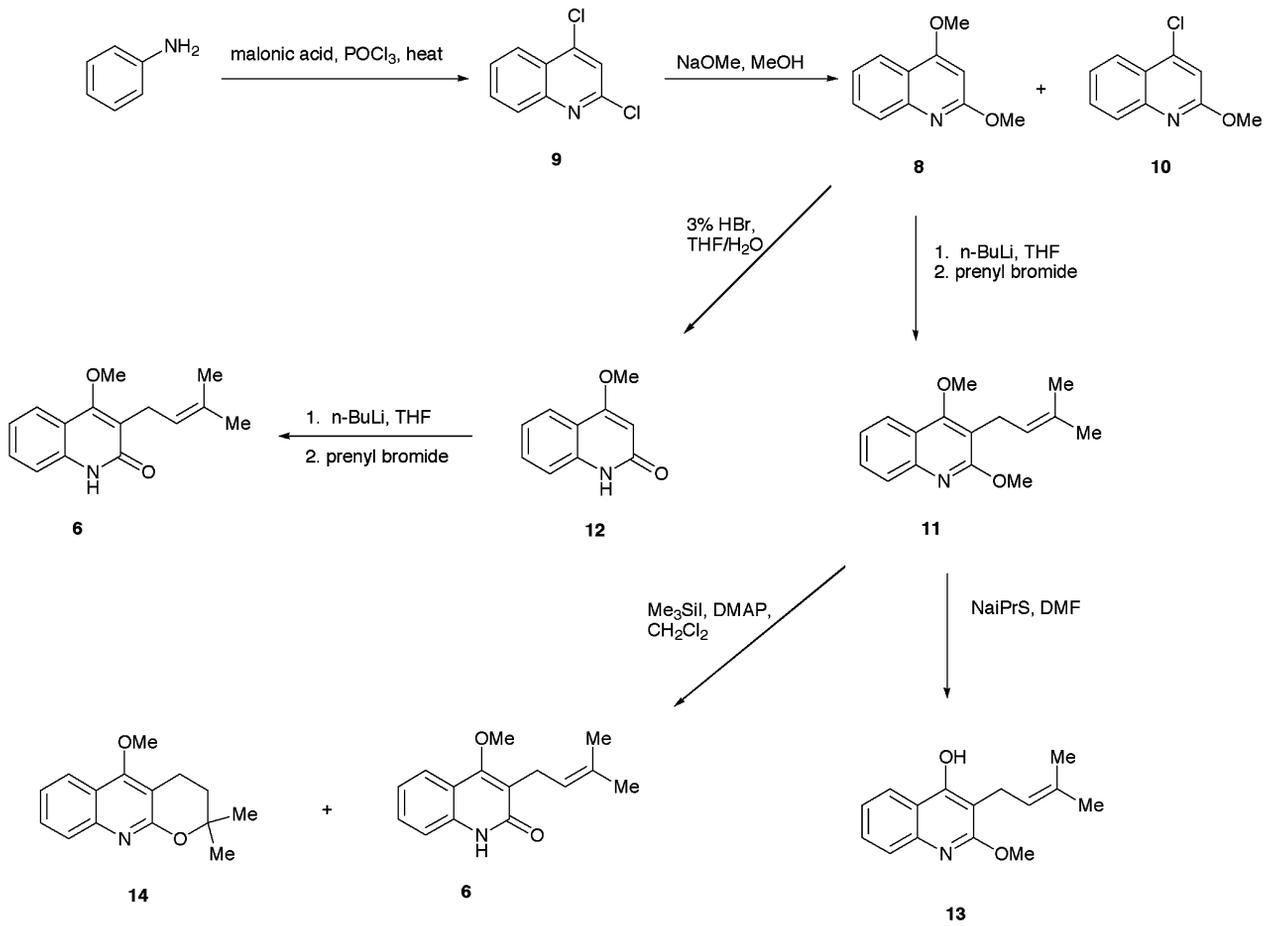

Scheme 3

atanine **6**. A range of conditions was investigated without success. The reaction was repeated (in $CDCl_3$) in an NMR tube. After a very short period, the alkene proton at δ5.22 disappeared strongly suggesting that the fastest reaction was addition of HCl to the double bond of the sidechain. Reaction with various dilute mineral acids gave complex mixtures of products from which no atanine could be isolated.

At this point we chose to explore an alternative strategy in which 2,4-dimethoxyquinoline **8** was selectively demethylated to give **12** followed by ortholithiation and alkylation to give atanine **6** (Scheme 3). Treatment of **8** with dry HCl in di-isopropyl ether at reflux for 4 hours led to no reaction and starting material was isolated. The lack of nucleophilicity of the chloride ion was felt to be the problem and so we used HBr instead. Treatment of **8** with 48% HBr led to double demethylation but reaction with 3% HBr in a 1 : 1 mixture of THF and water at reflux for 3 hours gave 54% of **12** along with some 40% of starting material **8**. Reaction of **12** with 2 equivalents of *n*-butyllithium at −78 °C followed by addition of prenyl bromide gave atanine **6** but in only 3% yield along with starting material and decomposition products. The use of prenyl triflate in place of prenyl bromide led to similar results. Clearly this was not a viable method for the synthesis of atanine and analogues and so we turned our attention back to the selective demethylation of **11**.

Boron tribromide is well known to demethylate aromatic methyl ethers and being a Lewis acid should avoid problems of addition to the double bond in the sidechain. Treatment of **11** with boron tribromide gave an intractable red solid that could not be characterised. This appeared to confirm the sensitivity of the side chain to acid. A non-acidic approach was investigated using thiolate ion, which is known to cleave aryl methyl ethers in solvents such as DMF.[15] Treatment of **11** with sodium isopropyl thiolate in DMF at reflux, gave **13** in 38% yield after chromatography (Scheme 3). The structure of **13** was assigned on the basis that the spectral data differed from the published data for atanine and that a correlation between the O–H proton at δ11.5 and the C-5 proton at δ7.98 was observed in the NOESY spectrum. Presumably, this reaction proceeds *via* an S_N2 process and favours 4-demethylation as the leaving group from this site of attack is more stable owing to greater charge delocalisation. On the basis of this result, trimethylsilyl iodide (TMSI) was explored as we felt the first step in the reaction of TMSI with quinoline **11** would be silylation of the nitrogen in a manner similar to protonation. In order to prevent addition of a proton (from any HI either in the reagent or generated in the reaction) to the double bond, one equivalent of pyridine was added along with the TMSI. To our delight stirring **11** with TMSI and pyridine in dry dichloromethane at −78 °C to room temperature gave a 2 : 1 mixture (as determined by ^{1}H NMR) of atanine **6** and pyranoquinoline **14**[16] formed by protonation of the sidechain double bond and subsequent cyclisation onto the 2-quinolone oxygen. The reaction was repeated using the stronger base 4-(dimethylamino)pyridine (DMAP) and atanine **6** was obtained in 62% yield after recrystallisation. The spectroscopic data of the synthetic material matched that of the material isolated from *Evodia* fruits.[9]

Conclusions

In summary, we have clarified the synthesis of atanine **6** *via* ortholithiation–demethylation and have developed the TMSI–DMAP reagent system for the demethylation of such acid-sensitive aryl methyl ethers. We have also been able to synthesise selectively *via* thiolate promoted demethylation the regioisomer **13** of atanine.

Experimental[17]

2,4-Dichloroquinoline 9

Aniline (6.7 g, 72 mmol) and malonic acid (11.7 g, 112 mmol) were heated under reflux in phosphorus oxychloride (60 ml), with stirring, for 5 hours. The mixture was cooled, poured into crushed ice with vigorous stirring and then made alkaline with 5 M sodium hydroxide. Filtration gave the crude product as a brown solid. A four hour continuous (Soxhlet) extraction with hexane followed by evaporation of solvent under reduced pressure yielded a pale yellow powder. Column chromatography (95 : 5 hexane : EtOAc) yielded the pure dichloroquinoline as off-white needles (6.8 g, 48%), mp 66–67 °C(lit.[18] 66 °C); R_f (95 : 5 hexane : EtOAc) 0.51; ν_{max}/cm^{-1}: 1580 (s, C=N); δ_H 8.18 (1H, dd, *J* 8.4, 1.3, H-5), 8.03 (1H, dd, *J* 8.5, 1.0, H-8), 7.79 (1H, ddd, *J* 8.5, 7.0, 1.3, H-7), 7.65, (1H, ddd, *J* 8.4, 7.0, 1.0, H-6), 7.50 (1H, s, H-3); δ_C 149.8 (C-2), 148.1 (C-8a), 144.4 (C-4), 131.5 (C-7), 129.0 (C-8), 127.9 (C-6), 125.2 (C-4a), 124.2 (C-5), 121.9 (C-3); *m*/*z*: 201 (15%, M$^+$ $^{37}Cl_2$), 199 (72, M$^+$ ^{37}Cl ^{35}Cl), 197 (100, M$^+$ $^{35}Cl_2$), 162 (69, M$^+$ − Cl) (Found: M$^+$($^{35}Cl_2$) 196.9792. $C_9H_5{}^{35}Cl_2N$ requires 196.9799).

2,4-Dimethoxyquinoline, 8 and 4-chloro-2-methoxyquinoline 10

2,4-Dichloroquinoline (2.8 g, 14 mmol) was heated under reflux in methanolic sodium methoxide solution (from 2.0 g, 86 mmol Na in 50 ml MeOH) for 24 hours. The reaction mixture was cooled and poured into ice-cold water, and the resulting white precipitate was filtered off. Column chromatography (9 : 1 hexane : EtOAc) yielded the two products 2,4-dimethoxyquinoline, (1.85 g, 70%) and 4-chloro-2-methoxyquinoline, (0.32 g, 12%), both as white needles.

2,4-Dimethoxyquinoline. Mp 78–80 °C (lit.[19] 81–82 °C); R_f (9 : 1 hexane : EtOAc) 0.48; ν_{max}/cm^{-1}: 1640, 1580 (s, C=C, C=N); δ_H 8.04 (1H, dd, *J* 8.2, 1.5, H-5), 7.78 (1H, dd, *J* 8.5, 1.2, H-8), 7.60 (1H, ddd, *J* 8.5, 7.0, 1.5, H-7), 7.33 (1H, ddd, *J* 8.2, 7.0, 1.2, H-6), 6.21(1H, s, H-3), 4.05 (3H, s, 2-OMe), 3.97 (3H, s, 4-OMe); δ_C 163.9 (C-4), 163.84 (C-2), 147.1 (C-8aC, 130.0 (C-7), 126.9 (C-8), 123.3 (C-6), 121.8 (C-5), 119.3 (C-4a), 90.7 (C-3), 55.7 (4-OMe), 53.4 (2-OMe); *m*/*z* 189 (100%, M$^+$), 188 (93, M$^+$ − H) (Found: M$^+$ 189.0797. $C_{11}H_{11}NO_2$ requires 189.0790).

4-Chloro-2-methoxyquinoline. Mp 70–72 °C (lit.[20] 70–71 °C); R_f (9 : 1 hexane : EtOAc) 0.61; ν_{max}/cm^{-1}: 1610, 1580 (s, C=N and C=C); δ_H 8.10 (1H, dd, *J* 8.2, 1.3, H-5), 7.86 (1H, dd, *J* 8.0, 1.2, H-8), 7.67 (1H, ddd, *J* 8.0, 7.0, 1.3, H-7), 7.46 (1H, ddd, *J* 8.2, 7.0, 1.2, H-6), 7.03 (1H, s, H-3), 4.06 (3H, s, –OCH$_3$); δ_C 161.9 (C-2), 147.0 (C-8a), 143.7 (C-4), 130.5 (C-7), 127.6 (C-8), 124.8 (C-6), 124.1 (C-5), 123.3 (C-4a), 112.9 (C-3), 53.8 (OCH$_3$); *m*/*z* 195 (33%, M$^+$ ^{37}Cl), 193 (100, M$^+$ ^{35}Cl), 192 (67, M$^+$ ^{35}Cl–H), 163 (33, M$^+$–CH$_2$O) (Found M$^+$: 193.0298. $C_{10}H_8{}^{35}ClNO$ requires 193.0294).

2,4-Dimethoxy-3-(3-methylbut-2-enyl)quinoline 11

2,4-Dimethoxyquinoline (2.0 g, 11 mmol) in dry THF (10 ml) was cooled to 0 °C under argon and *n*-butyllithium (6.2 ml of a 2.5 M solution in hexane) was added dropwise, with stirring. The mixture was stirred at 0 °C under argon for 30 minutes, then 1-bromo-3-methylbut-2-ene (2.8 g, 19 mmol) was added dropwise over 5 minutes. The mixture was stirred at 0 °C for 30 minutes and then allowed to warm to room temperature with stirring for a further hour. The reaction mixture was poured into water and extracted with ether (4 × 30 ml) to give the crude product as a yellow–brown oil. Column chromatography (4 : 1 hexane : EtOAc) yielded the pure product as a yellow–brown oil (2.4 g, 88%); R_f (4 : 1 hexane : EtOAc) 0.57; ν_{max}/cm^{-1}: 3070 (s, C–H), 1620, 1605, 1575 (s, C=C and C=N); δ_H 7.92 (1H, ddd, *J* 8.2, 1.5, 0.5, H-5), 7.82 (1H, ddd, *J* 8.5, 1.2, 0.5, H-8), 7.56 (1H, ddd, *J* 8.5, 6.9, 1.5, H-7), 7.35 (1H, ddd, *J* 8.2, 6.9, 1.2, H-6), 5.22 (1H, br t, *J* 6.9, C=C*H*), 4.08 (3H, s, 2-OMe), 3.95 (3H, s, 4-OMe), 3.45 (2H, d, *J* 6.9, C*H*$_2$), 1.81 (3H, d, *J* 0.7, =CC*H*$_3$), 1.69 (3H, d, *J* 1.2, =CC*H*$_3$); δ_C 162.5 (C-4), 161.6 (C-2), 146.1 (C-8a), 132.3 (=*C*Me$_2$), 128.9, 127.3, (C-7, C-8) 123.6, 121.9, 121.8, (C-5, C-6 and =CH), 121.2 (C-3), 116.9 (C-4a), 62.3 (OMe), 53.8 (OMe), 25.8 (CH$_3$), 23.3 (CH$_2$), 18.0 (CH$_3$); *m*/*z* 257 (100%, M$^+$), 242 (82, M$^+$ − Me), 202 (52, M$^+$ − Me$_2$C=CH) (Found: M$^+$ 257.1417. $C_{16}H_{19}NO_2$ requires 257.1416).

4-Methoxy-1*H*-quinolin-2-one 12

2,4-Dimethoxyquinoline (2.0 g, 11 mmol) was dissolved in 3% HBr in a 1 : 1 mixture of H_2O–THF (100 ml). The solution was heated under reflux for 3 hours, then cooled and neutralised with aqueous $NaHCO_3$. The THF was removed under reduced pressure, precipitating a white solid, which was filtered and dried under suction. TLC (4 : 1 hexane : EtOAc) showed the presence of starting material and a polar material (baseline). A 5 hour Soxhlet extraction with hexane separated these two compounds. The starting material was extracted into the reaction flask leaving the product as cream needles in the thimble (1.0 g, 54%), mp 249–252 °C (lit.[21] 250–253 °C); ν_{max}/cm^{-1}: 3100 (w, N–H), 1674 (s, C=O), 1634, 1607 (s, C=C); δ_H 7.90 (1H, dd, *J* 8.1, 1.1, H-5), 7.52 (1H, dd, *J* 8.1, 1.1, H-7), 7.40 (1H, dd, *J* 8.1, 1.1, H-8), 7.20 (1H, dd, *J* 8.1, 1.1, H-6), 6.03 (1H, s, H-3), 3.99 (3H, s, OMe); δ_C 166.3 (C-2), 165.0 (C-4), 138.4 (C-8a), 131.2 (C-7), 122.8 (C-8), 122.2 (C-6), 116.1 (C-5), 115.6 (C-4a), 96.0 (C-3), 56.0 (O-Me); *m*/*z* 175 (100%, M$^+$), 132 (63, M$^+$ − CONH), 76 (28, $C_6H_4^+$) (Found M$^+$: 175.0629. $C_{10}H_9NO_2$ requires 175.0633).

4-Hydroxy-2-methoxy 3-(3-methylbut-2-enyl)quinoline 13

Sodium hydride (0.67 g of a 60% mineral oil dispersion, washed with hexane, 17 mmol) was suspended in dimethylformamide (10 ml). 2-Propanethiol (0.51 g, 6.7 mmol) was added and the mixture was stirred for 10 minutes. Then a solution of 2,4-dimethoxy-3-(3-methylbut-2-enyl)quinoline (0.7 g, 2.7 mmol) in DMF (10 ml) was added, and the mixture heated under reflux for 4 hours. After cooling and neutralisation with 2 M HCl the solution was extracted with ether (4 × 50 ml), the combined ether extracts were dried over $MgSO_4$, and the solvent removed *in vacuo* to give a brown oil. Column chromatography (4 : 1 hexane:ethyl acetate) followed by recrystallisation (ethanol) yielded the pure product (0.25 g, 38%) as off-white needles, mp 154–155 °C (lit.[22] 137–138 °C); R_f (4 : 1 hexane : EtOAc) 0.30; ν_{max}/cm^{-1}: 3200–3000 (br, O–H), 1627, 1580 (s, C=C, C=N); δ_H 7.98 (1H, dd, *J* 8.2, 1.3, H-5), 7.75 (1H, dd, *J* 8.2, 1.2, H-8), 7.56 (1H, ddd, *J* 8.3, 6.9, 1.3, H-7), 7.32 (1H, ddd, *J* 8.2, 6.9, 1.2, H-6), 5.38 (1H, tq, *J* 7.3, 1.2, C*H*=), 4.06 (3H, s, OCH$_3$), 3.51 (2H, d, *J* 7.3, C*H*$_2$CH=), 1.86 (3H, s, CH=CC*H*$_3$), 1.81 (3H, d, *J* 1.2, CH=CC*H*$_3$), OH not observed in $CDCl_3$; NOESY (d_6 DMSO) correlation between the OH proton at δ11.5 ppm and the C-5 proton at δ7.98 ppm; δ_C 161.4 (C-2), 145.0 (C-8a), 137.0 (=*C*(CH$_3$)$_2$), 129.3, 126.5, 123.2, 121.6, 121.1 (C-5,-6,-7,-8 and =*C*H), 119.0 (C-4a), 105.2 (C-3), 53.9 (OMe), 25.9 (CH$_3$), 23.0 (CH$_2$), 18.0 (CH$_3$), no signal observed for C4; *m*/*z* 243 (26%, M$^+$), 228 (12, M$^+$ − CH$_3$), 188 (5% M$^+$ − CH=C(CH$_3$)$_2$), 83 (100) (Found: M$^+$ 243.1246. $C_{15}H_{17}NO_2$ requires 243.1259).

4-Methoxy-3-(3-methylbut-2-enyl)-1*H*-quinolin-2-one (atanine) 6

2,4-Dimethoxy-3-(3-methylbut-2-enyl)quinoline (0.50 g, 2.0 mmol) and 4-dimethylaminopyridine (0.24 g, 2.0 mmol) were dissolved in dry dichloromethane (30 ml) and cooled to −78 °C under argon. Iodotrimethylsilane (0.40 g, 2.0 mmol) was added dropwise, and the mixture stirred at −78 °C for 2 hours. Then the flask was left to warm to room temperature, with stirring,

for a further 40 hours. The solution obtained was washed with 1 M aqueous sodium thiosulfate (2 × 30 ml), and then dried ($MgSO_4$) and the solvent removed under reduced pressure. A brown oil was obtained which crystallised overnight to give a pale brown solid. Recrystallisation (EtOH) gave the title compound as off-white needles (0.3 g, 62%), mp 130–132 °C (lit.[12] 132–134 °C) (Found: C, 72.44, H, 6.87, N, 5.69. $C_{15}H_{17}NO_2.0.3H_2O$ requires C, 72.44, H, 7.13, N, 5.63%); ν_{max}/ cm^{-1} 3250 (w, N–H), 1653 (s, C=O), 1568 (m, C=C); δ_H 12.11 (1H, br s, NH/OH), 7.76 (1H, dd, *J* 8.1, 1.2, H-5), 7.47 (1H, ddd, *J* 8.2, 7.0, 1.2, H-7), 7.42 (1H, dd, *J* 8.2, 1.2, H-8), 7.22 (1H, ddd, *J* 8.1, 7.0, 1.2, H-6), 5.32 (1H, t, *J* 6.9, C*H*=CMe_2), 3.95 (3H, s, OMe), 3.45 (2H, d, *J* 6.9, CH_2–CH=CMe_2), 1.86 (3H, s, CH_3), 1.71 (3H, s, CH_3); δ_C 165.9 (C-2), 162.1 (C-4), 137.6, 132.5 (C-8a, C=*C*Me_2), 130.0 (CH), 122.8 (CH), 122.6, 122.2 (CH), 121.6 (CH), 117.2, 116.1 (CH), 61.8 (OCH_3), 25.8 (CH=C(*C*H_3)$_2$), 23.5 (*C*′H_2), 18.1 (CH=C(*C*H_3)$_2$); *m*/*z* 243 (89%, M^+), 228 (39, M^+–OMe), 188 (100, $C_{11}H_{10}NO_2^+$) (Found: M^+ 243.1252. $C_{15}H_{17}NO_2$ requires 243.1259).

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