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Aryl radical cyclisation onto pyrroles

Carmen Escolano and Keith Jones*

School of Chemical and Pharmaceutical Sciences, Kingston University, Penrhyn Road, Kingston-upon-Thames, Surrey KT1 2EE, UK

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Abstract—The intramolecular cyclisation of aryl radicals onto a pyrrole is studied. The cyclisation allows the synthesis of either the spiropyrrolidinyloxindole or the pyrrolo[3,2-*c*]quinoline skeleton depending on the nature of the protecting group at the *N*-pyrrole atom. The regiochemistry of the cyclisation is not affected by the substituents on the benzene ring. Some limitations on the utility of tosylmethylisocyanide in pyrrole synthesis are also reported. © 2002 Elsevier Science Ltd. All rights reserved.

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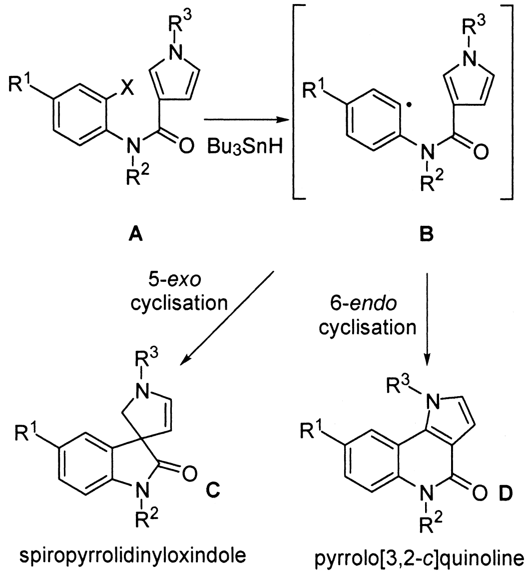
1. Introduction

Intramolecular aryl radical cyclisation reactions have been used by organic chemists in the synthesis of polycyclic natural products.[1] In particular, the intramolecular addition of aryl radicals to multiple bonds is well documented in the literature[2] and the addition of aryl radicals to benzene rings followed by rearomatisation has also been reported.[3] In contrast, there are only a few reports dealing with the intramolecular addition of aryl radicals to heterocyclic rings. For example, Motherwell in the context of the synthesis of heterobiaryls via intramolecular free radical *ipso* substitution reactions has reported some [1,7] addition of aryl radicals onto quinoline, thiophene and pyridine derivatives.[4] Tsuge[5] has reported the intramolecular addition of aryl radical to the C-2 of the indole nucleus leading to dihydroindoles. The only previous examples of intramolecular addition of aryl radical to pyrroles under reductive conditions are due to Muchowski and deal exclusively with the addition of aryl radicals to the C-2 of the pyrrole nucleus.[6]

In this paper we wish to report in full our studies concerning the intramolecular addition of aryl radicals onto a pyrrole in which the linking chain is attached to the C-3 position.[7] Using the radical precursors with the general structure **A** shown in Scheme 1, aryl radical cyclisations were studied. The cyclisation of compounds with the general structure **A** is interesting in the context of natural product synthesis because depending on the position at which the aryl radicals adds onto the pyrrole nucleus, alkaloids with the spiropyrrolidinyloxindole **C** or pyrrolo[3,2-*c*]quinoline **D** nucleus could be accessed. These ring systems are found in a wide range of biologically-active alkaloids such as spirotryprostatin A and B,[8] (+)-elacomine,[9] (−)-horsfiline,[10] potent gastric (H/K) ATPase inhibitors,[11] martinelline and martinellic acid (Fig. 1).[12]



Scheme 1.

2. Results and discussion

2.1. Preparation of radical precursors

Our interest in targets such as the natural products shown in Fig. 1, led us to develop the general synthetic sequence shown in Scheme 2 in order to prepare the radical precursors with the general structure **A**. Reaction of 2-bromo-4-methoxyaniline,[13] **1a**, with acryloyl chloride in dichloromethane and Hünig's base[14] gave the *N*-arylacrylamide **2a** in 93% yield. Reaction of methyl 4-amino-3-iodobenzoate,[15] **1b**, with an excess of acryloyl chloride gave **2b** in

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Keywords: radicals; cyclisation; pyrroles; regioselection; natural products.

* Corresponding author. Tel.: +44-20-8547-8450; fax: +44-20-8547-7562; e-mail: keith.jones@kingston.ac.uk

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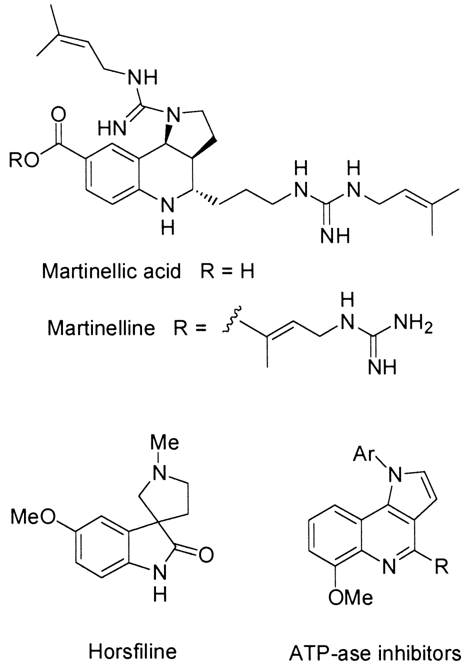
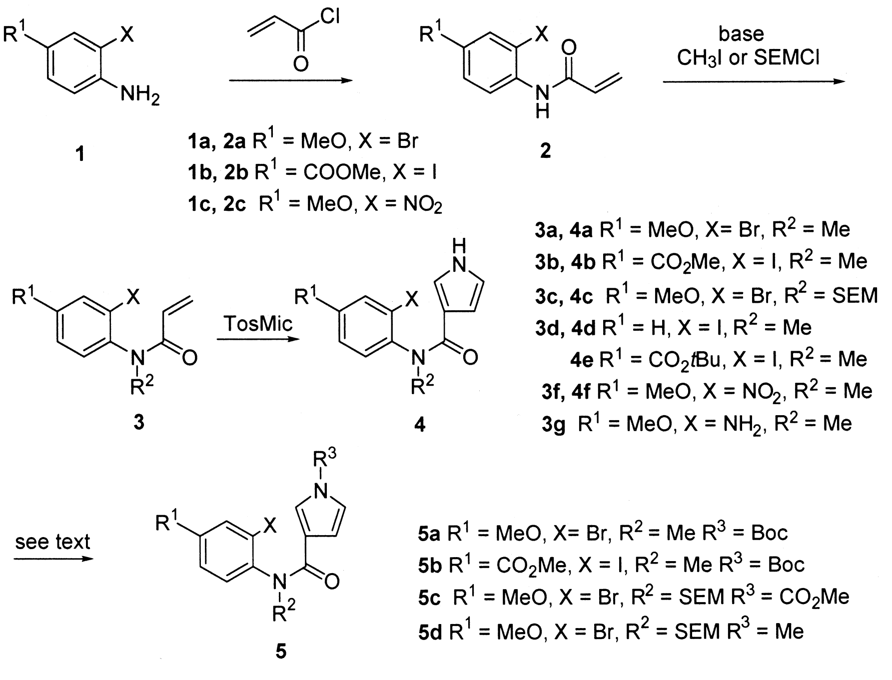


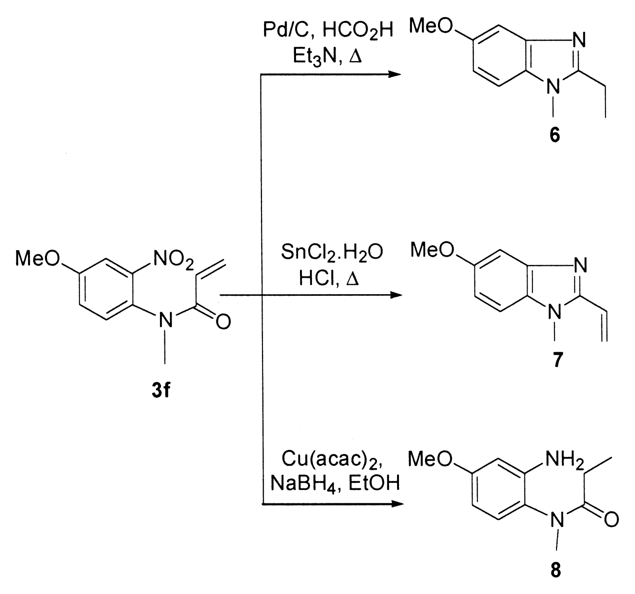
Figure 1.

86% yield. Previous studies by our group had shown that a tertiary amide is required in order to attain the correct conformation around the amide bond for cyclisation to occur.[16] Thus, **2a**,**b** were methylated (NaH, CH$_3$I) to give tertiary amides **3a**,**b** in very good yields. Alternatively, **2a** was alkylated with 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl) to give **3c** in 92% yield. The change in the shift of the H-6′ proton (from $\delta_H \sim 8$ in **2** to $\delta_H \sim 7$ in **3**) clearly demonstrates the switch in conformation upon *N*-alkylation. Reaction of **3a** and **3c** with tosylmethylisocyanide (TosMIC) using NaH as a base in ether/DMSO[17] gave the pyrrole-3-carboxamides **4a**[18] and **4c** in 60 and 57% yield, respectively. These results are in good agreement with our previous results in which the reaction of **3d** with TosMIC gave **4d** in 57% yield.[8b] However, reaction of **3b** with TosMIC using the same experimental conditions as above gave polymeric mixtures. When the reaction was conducted in THF as a solvent and using potassium *tert*-butoxide as a base the desired pyrrolo-3-carboxamide **4b**, was formed but in a very low yield together with the resulting transesterification product **4e** and starting material. Finally, **4b** was obtained in 26% yield when the *N*-methylamidobenzoate **3b** was reacted with TosMIC in THF using NaHMDS[19] as base. These results indicate that *N*-arylacrylamide substrates carrying electron-withdrawing substituents on the aryl ring are poor substrates for pyrrole formation via the TosMIC reaction. As this process is basically a two-stage process with initial (reversible) Michael addition followed by cyclisation to the pyrrole (irreversible), it appears that increasing the Michael acceptor ability of the acrylamide compromises the ability of the intermediate to cyclise presumably by enhanced stabilisation of the intermediate enolate. Electron-donating substituents decrease the stability of the intermediate accelerating the cyclisation reaction and leading to higher yields of pyrrole.

In order to further check this hypothesis, preparation of **3g**, an *o*-aminoacetanilide, was attempted. If, as postulated, the success in the pyrrole formation reaction using TosMIC was related to the Michael acceptor ability of the α,β-unsaturated alkene involved, **3g** would give the corresponding pyrrole derivative in good yield. Thus, nitro-derivative **3f** was prepared in 79% overall yield by reaction of 4-methoxy-2-nitroaniline, **1c**, with acryloyl chloride in dichloromethane to give **2c**, followed by methylation (NaH, CH$_3$I). As expected, reaction of **3f** with TosMIC using NaH as a base in DMSO/ether led to polymeric mixtures in which the pyrrole derivative could not be detected. Reaction of **3f** with



Scheme 2.



Scheme 3.

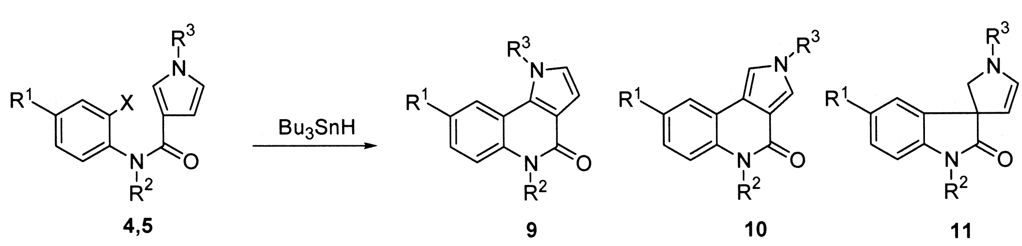
TosMIC using potassium *tert*-butoxide and THF as a solvent, gave the pyrrolecarboxamide **4f** in a low 20% yield. The use of NaHMDS did not improve the yield. Next, we decided to carry out the reduction of the nitro group of **3f** previous to the pyrrole formation. However, all our attempts to carry out the conversion of **3f** in **3g** were fruitless (Scheme 3). Treatment of **3f** with palladium on carbon and formic acid in triethylamine[20] gave the benzimidazole derivative **6** in 80% yield, as a result of the reduction of the nitro group, attack of the newly formed amine onto the amide carbonyl and reduction of the double bond in the side chain. In a similar manner, reaction of **3f** with $SnCl_2 \cdot H_2O$[21] furnished the benzimidazole **7** in 70% yield. Lastly, **3f** was reduced with copper(II)acetylacetonate and sodium borohydride at room temperature.[22] Compound **8** was isolated in 60% yield. Although the nitro group was reduced and no benzimidazole ring was obtained, the double bond in the side chain was reduced thus precluding us from studying the pyrrole ring formation. It is well known that reductive cyclisation of *o*-nitroacetanilides using Fe,[23] Sn[24] or hydrogen[25] leads to benzimidazoles, but to our knowledge the examples reported in this paper are the first involving acrylamide derivatives.

With the pyrrole derivatives **4a–c** in hand, substitution on the pyrrole nitrogen was explored in order to give substrates with differing electronic/steric properties. Reaction of **4a**, **4b** with di-*t*-butyl dicarbonate, triethylamine and catalytic dimethylaminopyridine at low temperature led to *N*-Boc protected pyrroles **5a**, **5b** in very good yields. Two different N-protecting groups were tested on pyrrole **4c**. On the one hand, reaction of **4c** with KH followed by treatment with methyl chloroformate gave the methoxycarbonyl derivative **5c** in 80% yield, and on the other, methylation (NaH, CH_3I) of **4c** furnished the *N*-methyl substituted pyrrole **5d** in 72% yield.

2.2. Radical cyclisations

The radical cyclisation precursors **4a**, **4c**, **5a** and **5b** were subjected to standard reductive radical cyclisation conditions [tributyltin hydride (0.02 M) in refluxing toluene with a sub-stoichiometric amount of AIBN] (Scheme 4, Table 1).

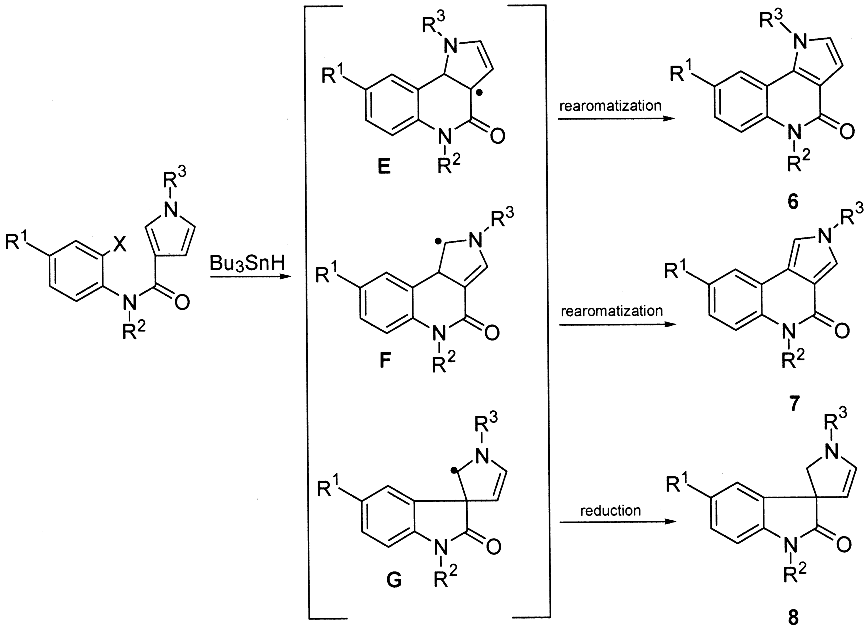
Cyclisation of the *N*-unsubstituted pyrroles **4a** and **4c** gave a mixture (ca. 2:1) of regioisomeric pyrroloquinolines **9a–10a** and **9b–10b**, respectively. Considering the reductive conditions involved in the cyclisation, the obtention of the oxidized aromatic derivatives **9** and **10** rather than the dehydroaromatic derivatives is surprising. However, oxidation during Bu_3SnH mediated radical reactions has been well documented.[26] The 6-*endo* products **9a** and **9b** were obtained as the major products in 37 and 34% yield, together with the 6-*exo* products **10a** and **10b** (15 and 18% yield). The structures of these isomeric pyrroloquinolines were determined by proton NMR chemical shifts and comparison with those for a previously synthesised pyrrolo[3,4-*c*]quinoline, prepared by an unambiguous route. The ^1H NMR



Scheme 4.

Table 1. Radical cyclisation reactions of compounds **4** and **5** (Scheme 4)

Radical precursor	Substituents	**9**, yield (%)	**10**, yield (%)	**11**, yield (%)
4a	R^1=MeO, X=Br, R^2=Me, R^3=H	**9a**, 37	**10a**, 15	
4c	R^1=MeO, X=Br, R^2=SEM, R^3=H	**9b**, 34	**10b**, 18	
5a	R^1=MeO, X=Br, R^2=Me, R^3=Boc	**9c**, 18	**10c**, 1	**11c**, 31
5b	R^1=CO_2Me, X=I, R^2=Me, R^3=Boc	**9d**, 13	**10d**, 5	**11d**, 26
5c	R^1=MeO, X=Br, R^2=SEM, R^3=CO_2Me	**9e**, 15		**11e**, 32
5d	R^1=MeO, X=Br, R^2=SEM, R^3=Me	**9f**, 43		



Scheme 5.

spectrum of **9a**, **9b**, **10a** and **10b** showed resonances for only five aromatic protons. In particular, the electronic effect of the pyrrolic nitrogen in the shift of protons H-9 and H-3 in the cyclised derivatives was taken into account to resolve the regioisomeric question. In compounds **9a** and **9b** H-9 appears as a doublet at δ_H 7.57 and 7.70 and in **10a** and **10b** at δ_H 7.37 and 7.41 indicating a deshielding effect due to the proximity of the pyrrolic nitrogen. In the same manner, H-3 in **9a** (δ_H 6.78) and **9b** (δ_H 6.96) is shielded compared to H-3 in compounds **10a** (δ_H 7.23) and **10b** (δ_H 7.35). No products arising from 5-*exo* cyclisation were detected and in both examples it is interesting to note that the major product, the pyrrolo[3,2-*c*]quinoline skeleton, arises from the more stable radical intermediate **E** (Scheme 5).

In contrast to this result, cyclisation of the N-*t*-Boc derivative **5a** gave a major product that proved to be the spiropyrrolidinyl oxindole **11c** in 31% yield, resulting from 5-*exo* cyclisation (via radical **G**).

The ^{1}H and ^{13}C of **11c** showed the presence of two rotamers in a ratio 1:1. In the ^{1}H NMR of **11c** two doublets at δ_H 4.73 and 4.80 (J=3.8 Hz) and a doublet at δ_H 6.97 (J=3.8 Hz) were assigned as the enaminic protons H-4 and H-3, respectively. In the ^{13}C NMR methylene peaks appeared at δ_C 54.8 and 55.8 and the quaternary spiro-carbon at δ_C 57.6 and 58.7. The two other products showed resonances for five protons in the aromatic zone. Both products result from the 6-*endo* and 6-*exo* cyclisation of the aryl radical generated upon the pyrrole ring. The major product **9c** (18% yield), contained the pyrrolo[3,2-*c*]quinoline skeleton. Traces of **10c** could be isolated. As before the difference in the ^{1}H NMR signals due to H-9 (**9c**, d, δ_H 8.26 and **10c**, d, δ_H 7.20) and H-3 (**9c**, d, δ_H 6.85, and **10c**, d, δ_H 7.98) indicates the electronic effect of the pyrrolic nitrogen.

In a similar manner, cyclisation of **5b** under the standard conditions furnished a mixture of three products. As before, the major product, **11d** (26% yield) showed the presence of two rotamers in a ratio 1:1. The presence of two enaminic protons H-4 (2d, δ_H 4.64 and 4.70) and H-3 (2d, δ_H 6.82 and 6.97) in the ^{1}H NMR and the methylene carbon (δ_C 54.7 and 55.3) and quaternary spiro-carbon (δ_C 57.0 and 58.2) in the ^{13}C was observed. Together with the spiropyrrolidinyl derivative, **11d**, products arising from the 6-*endo*, **9d** (13%) and 6-*exo* **10d** (5%) cyclisation were isolated. As was observed before, an effect of the pyrrolic nitrogen in the shift of H-9 (**9d**, d, δ_H 9.28 and **10d**, d, δ_H 8.55) and H-3 (**9d**, d, δ_H 6.91 and **10d**, d, δ_H 7.25) was observed in both compounds.

It is noteworthy that when the radical cyclisation of **5b** was conducted using tris(trimethylsilylsilane) as a radical mediator the reaction time increased from 1 to 4 h and only the two products resulting from the 6-*endo*, **9d** and 6-*exo*, **10d** cyclisation were isolated in low yield, 17 and 14%, respectively. The spiropyrrolidinyloxindole **11d** was not observed possibly due to the slower rate of hydrogen atom transfer from TTMSS providing tentative evidence for the possibility of compounds **9** and **10** arising by rearrangement of **11**.

In order to investigate whether the regiochemistry of this radical cyclisation arises from a steric effect of the bulky *N*-*t*-Boc group, we decided to prepare and cyclise a radical precursor in which the nitrogen was substituted with a methoxycarbonyl group. Cyclisation of **5c** under the standard radical conditions furnished two products, the spiropyrrolidinyloxindole **11e**, 32% yield and the pyrrolo[3,2-*c*]quinoline derivative **9e**, 15% yield. As before, the presence of enaminic protons in the ^{1}H spectrum and methylenic (δ_C 55.2 and 55.4) and quaternary spiro-carbon signals in the ^{13}C NMR (δ_C 57.0 and 58.2) indicates the formation of the spiropyrrolidinyloxindole derivative. Thus it appears as though an electronic affect is operating and leading to the regioselectivity.

Finally, we examined the effect that an electron-donating group, on the pyrrole nitrogen, can have on the radical cyclisation reaction. Reaction of **5d** with Bu_3SnH in the standard conditions furnished **9f** in 43% yield as the only identified compound, no products arising from the 5-*exo* or 6-*exo* cyclisation were detected. The structure of **9f** was confirmed by an independent synthesis. Thus, methylation of the already cyclised product **9b** was carried out. Deprotonation of **9b** with potassium hydride followed by reaction with MeI gave a product with identical analytical characteristics to the one obtained from the radical cyclisation of **5d**.

Interestingly, the NCH_2O protons in **4c**, **5c** and **5d** appear as two doublets (J=10 Hz) owing to the chiral axis created by the $N-C_{aryl}$ bond.

In conclusion, a series of radical precursors with the general structure **4** and **5**, have been prepared from *p*-substituted acetanilides by formation of the pyrrolic nucleus using the TosMIC reaction. Limitations in this reaction were found when the benzene ring is substituted by an electron-withdrawing group. On the other hand, benzimidazole derivatives were obtained when the reductive cyclisation of *o*-nitroacetanilide **3f** was attempted. Finally, we have shown that the regiochemistry of cyclisation of aryl radicals onto pyrroles attached through an amide at the 3-position (general structure **A** in Scheme 1) is governed by the nature of the *N*-substituent on the pyrrole. Pyrroles substituted with an electron-donating group (methyl) on nitrogen give exclusively the pyrrolo[3,2-*c*]quinoline product arising from 6-*endo* cyclisation. Pyrroles substituted on nitrogen with an electron-withdrawing group (carbamate), give rise to the spiropyrrolodinyloxindole as the major product via a 5-*exo* cyclisation. The regiochemistry is not affected by the substituents on the benzene ring. According to these observations, changing the substituent on the pyrrole will allow controlled formation of either the spiropyrrolidinyloxindole or pyrrolo[3,2-*c*]quinoline nucleus from a common intermediate.

3. Experimental

3.1. General details

All reactions were carried out under argon and solutions dried with magnesium sulphate. Where necessary, solvents and reagents were dried and purified according to recommended procedures.[27] Column chromatography was carried out using the flash chromatography technique. Thin layer chromatography analysis was performed using silica gel 60 F-254 plates. Components were visualised by UV, iodine or potassium permanganate. IR spectra were recorded on a Perkin–Elmer Paragon 1000 Infrared spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM 300 spectrometer operating at 300 MHz for proton and 75 MHz for carbon using $CDCl_3$ as solvent and residual protic solvent was used as internal reference, unless otherwise stated. COSY and HETCOR experiments spectra were recorded on a Bruker AM500. Chemical shifts (δ_H and δ_C) values are reported as parts per million (ppm). The multiplicity of an ^1H NMR signal is designated by one of the following abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, br=broad and m=multiplet. Coupling constants were reported in Hz. GC–MS was carried out on a HP5890 instrument. High-resolution mass spectrometry was performed at the Mass Spectrometry Centre, Chemistry Department, King's College London. Microanalysis was performed at University College London, Chemistry Department, Microanalytical Laboratory.

3.1.1. *N*-(2-Bromo-4-methoxyphenyl)acrylamide, 2a. To a solution of **1a** (14.3 g, 70.8 mmol) and *N*,*N'*-diisopropylethylamine (7.1 mL, 77.8 mmol) in ether (100 mL) at 0°C, acryloyl chloride (6.2 mL, 77.8 mmol) was slowly added. The mixture was allowed to warm to room temperature and stirring was continued for 4 h after which hydrochloric acid (3 M, 50 mL) was added. The organic layer was washed with water (3×50 mL) and dried. Chromatography (SiO_2, hexane/EtOAc 1:1) gave **2a** as a light purple solid (10.5 g, 93%), mp 116–117°C (EtOAc) [lit.[28] 120–121°C] (Found: C, 47.03; H, 3.95; N, 5.45. $C_{10}H_{10}BrNO_2$ requires C, 46.90; H, 3.94; N, 5.47%); ν_{max} (cm^{-1}) 3264 (w, N–H), 1659 (s, amide C=O); δ_H (300 MHz; $CDCl_3$) 3.67 (3H, s, OCH_3), 5.66 (1H, d, J=10 Hz, C(O)CH=CH*Htrans*), 6.21 (1H, dd, J=16.9, 10 Hz, C(O)C*Hgem*=CH_2), 6.36 (1H, dd, J=16.9, 1.4 Hz, C(O)CH=CH*Hcis*), 6.75 (1H, dd, J=9.0, 2.6 Hz, H-5′), 6.97 (1H, d, J=2.6 Hz, H-3′), 7.60 (br s, 1H, NH), 8.07 (1H, d, J=9 Hz, H-6′); δ_C ($CDCl_3$) 55.6 (OCH_3), 113.7 (CH), 114.9 (C), 117.6 (CH), 123.7 (CH), 127.7 (CH_2), 128.8 (C), 131.1 (CH), 156.6 (C), 163.4 (amide C=O); *m*/*z* 257/255 (11%, M^+), 201/199 (22), 176 (73, M^+-Br), 106 (17), 55 (100, $C_3H_3O^+$).

3.1.2. Methyl 3-iodo-4-acrylamidobenzoate, 2b. A solution of **1b** (5 g, 18.0 mmol) and acryloyl chloride (2.1 mL, 27.0 mmol) in dichloromethane (50 mL) was heated for 3 h under reflux. After cooling to room temperature, the mixture was washed successively with saturated aqueous sodium hydrogen carbonate (2×25 mL) and water (2×25 mL). The organic layer was dried and evaporated under reduced pressure. Recrystallisation (EtOAc/hexane 5:1) gave the title compound, **2b** as white crystals (3.6 g, 86%); ν_{max} (cm^{-1}) 3267 (m, N–H), 2948 (m, C–H), 1712 (s, ester C=O), 1664 (s, amide C=O); δ_H (300 MHz; $CDCl_3$) 3.83 (3H, s, OCH_3), 5.80 (1H, dd, J=10, 1 Hz, C(O)CH=CH*Htrans*), 6.24 (1H, dd, J=16.9, 10 Hz, C(O)C*Hgem*=CH_2), 6.41 (1H, dd, J=16.9, 1 Hz, C(O)CH=CH*Hcis*), 7.72 (1H, br s, NH), 7.94 (1H, dd, J=8.6, 1.9 Hz, H-5′), 8.38 (1H, d, J=1.9 Hz, H-3′), 8.43 (1H, d, J=8.6 Hz, H-6′); δ_C ($CDCl_3$) 52.3 (CH_3), 88.5 (C-2′), 120.2 (CH), 127.1 (C), 128.9 (CH_2), 130.8 (CH), 131.0 (CH), 140.2 (CH), 141.8 (C), 163.4 (amide C=O), 165.1 (ester C=O); *m*/*z* (EI) 331 (5%, M^+), 300 (2.5, M^+-CH_3O), 276 (7), 246 (20), 204 (90, M^+-I), 149 (5), 118 (8), 90 (13), 56 (100) (Found: M^+, 330.9707. $C_{11}H_{10}INO_3$ requires *M*, 330.9698).

3.1.3. *N*-(2-Bromo-4-methoxyphenyl)-*N*-methylacrylamide, 3a. A solution of **2a** (6.6 g, 25.8 mmol) in dry THF (43 mL) was added to a stirred suspension of sodium hydride (1.2 g of 60% dispersion in mineral oil, 30.7 mmol) in THF (70 mL). The mixture was stirred for 1 h after which methyl iodide (4.5 mL, 72.3 mmol) was added and the solution stirred overnight. Water (50 mL) was added to quench the reaction. The solvent was evaporated in vacuo and the residue was dissolved in ether (150 mL). The organic layer was washed with water (3×50 mL), dried and evaporated under reduced pressure. Chromatography (SiO_2, hexane/EtOAc 1:1) gave the title compound, **3a** as a light purple solid (5.1 g, 82%) mp 125–126°C (EtOAc); (Found: C, 48.86; H, 4.23; N, 5.08. $C_{11}H_{12}BrNO_2$ requires C, 48.91; H, 4.48; N, 5.19); ν_{max} (cm^{-1}) 2930 (s, C–H), 1661 (s, C=O); δ_H (300 MHz; $CDCl_3$) 3.08 (3H, s, NCH_3), 3.68 (3H, s, OCH_3), 5.34 (1H, dd, *J*=10.3, 1.4 Hz, C(O)CH=CH*Htrans*), 5.75 (1H, dd, *J*=16.7, 10.3 Hz, C(O)C*Hgem*=CH_2), 6.20 (1H, dd, *J*=16.7, 1.4 Hz, C(O)CH=CH*Hcis*), 6.74 (1H, dd, *J*=8.8, 2.8 Hz, H-5′), 7.02 (1H, d, *J*=8.8 Hz, H-6′), 7.03 (1H, d, *J*=2.8 Hz, H-3′); δ_C ($CDCl_3$) 36.1 (NCH_3), 55.7 (OCH_3), 114.5 (CH), 118.6 (CH), 123.8 (C), 127.7 (CH_2), 127.8 (CH), 130.3 (CH), 134.8 (C), 159.7 (C), 165.9 (C=O); *m*/*z* 190 (100, M^+-Br), 175 (6.5), 120 (6).

3.1.4. Methyl 3-iodo-4-*N*-methylacrylamidobenzoate, 3b. A solution of **2b** (3.2 g, 9.6 mmol) in dry THF (16 mL) was added to a stirred suspension of sodium hydride (460 mg of 60% dispersion in mineral oil, 11.6 mmol) in THF (26 mL). The mixture was stirred for 1 h after which methyl iodide (1.6 mL, 26.8 mmol) was added and the solution stirred overnight. Water (10 mL) was added to quench the reaction. The solvent was evaporated in vacuo and the residue was dissolved in diethyl ether (100 mL). The organic layer was washed with water (3×30 mL), dried and evaporated under reduced pressure. Chromatography (SiO_2, hexane/EtOAc 4:1) gave the title compound, **3b** as a white solid (2.6 g, 80%), mp 106–107°C (EtOAc) (Found: C, 42.19; H, 3.47; N; 3.91. $C_{12}H_{12}IO_3N$ requires C, 41.76; H, 3.50; N, 4.06%); ν_{max} (cm^{-1}) 2951 (w, C–H), 1724 (s, ester C=O), 1666 (s, amide C=O), 1621 (s, C=C); δ_H (300 MHz; $CDCl_3$) 3.19 (3H, s, NCH_3), 3.88 (3H, s, OCH_3), 5.46 (1H, dd, *J*=10.3, 1.8 Hz, C(O)CH=CH*Htrans*), 5.72 (1H, dd, *J*=16.6, 10.3 Hz, C(O)C*Hgem*=CH_2), 6.34 (1H, dd, *J*=16.6, 1.8 Hz, C(O)CH=CH*Hcis*), 7.25 (1H, d, *J*=8.1 Hz, H-6′), 8.02 (1H, dd, *J*=8.1, 1.8 Hz, H-5′), 8.52 (1H, d, *J*=1.8 Hz, H-3′); δ_C ($CDCl_3$) 35.5 (NCH_3), 52.2 (OCH_3), 99.1 (C-2′), 127.3 (CH), 128.3 (CH_2), 128.9 (CH), 130.6 (CH), 131.0 (C), 140.8 (CH), 148.8 (C), 164.1 and 164.4 (amide and ester C=O); *m*/*z* (EI) 346 (12%, M^+), 314 (13, M^+-CH_3O), 291 (19, $M^+-C_3H_3O$), 260 (28), 218 (100, M^+-I), 133 (41), 105 (31), 90 (10), 69 (27), 56 (100) (Found: M^+, 344.9863. $C_{12}H_{12}IO_3N$ requires *M*, 344.9856).

3.1.5. *N*-(2-Bromo-4-methoxyphenyl)-*N*-(2-trimethylsilyl-ethoxymethyl)acrylamide, 3c. A solution of **2a** (3.7 g, 14.5 mmol) in THF (10 mL) was added carefully to a suspension of potassium hydride (1.9 g, 14.5 mmol). The mixture was stirred for 1 h after which 2-(trimethylsilyl)-ethoxymethyl chloride (5 g, 28.9 mmol) was added and the suspension was stirred overnight. Water (20 mL) was added slowly to quench the reaction. The solvent was evaporated in vacuo and the residue was dissolved in ethyl ether (150 mL). The organic layer was washed with water (2×50 mL), dried and evaporated under reduced pressure. Chromatography (SiO_2, EtOAc/hexane 2:1) gave the title compound, **3c** as a brown oil (5.1 g, 92%) (Found: C, 49.63; H, 6.14; N, 3.61. $C_{16}H_{24}BrNO_3Si$ requires C, 49.74; H, 6.26; N, 3.63%); ν_{max} (cm^{-1}) 2923 (s, N–H), 2854 (s, C–H), 1678 (s, amide C=O), 1249 (s, Si–Me); δ_H (300 MHz; $CDCl_3$) −0.07 (9H, s, $Si(CH_3)_3$), 0.79–0.95 (2H, m, C*H*$_2$Si$(CH_3)_3$), 3.54–3.69 (m, 2H, OCH_2), 3.73 (3H, s, OCH_3), 4.48 (1H, s, *J*=10.2 Hz, NCH*HO*), 5.48 (1H, dd, *J*=10.3, 1.8 Hz, CH=CH*trans*), 5.53 (1H, d, *J*=10.2 Hz, NCH*HO*), 5.83 (1H, dd, *J*=16.6, 10.3 Hz, CH*gem*=CH_2), 6.34 (1H, dd, *J*=16.6, 1.8 Hz, CH=CH*cis*), 6.82 (1H, dd, *J*=9, 2.9 Hz, H-5′), 7.10 (1H, d, *J*=9 Hz, H-6′), 7.11 (1H, d, *J*=2.9 Hz, H-3′); δ_C ($CDCl_3$) −1.5 ($Si(CH_3)_3$), 18.0 (CH_2Si), 55.5 (OCH_3), 66.2 (OCH_2), 76.3 (NCH_2), 114 (CH), 118.3 (CH), 124.0 (C), 127.7 (CH), 128.9 (CH_2), 131.7 (CH), 132.0 (C), 159.7 (C), 166.3 (amide C=O); *m*/*z* (EI) 387/385 (0.5%, M^+), 248 (100), 216 (25), 214 (29), 73 (45, $SiMe_3^+$), 55 (20) (Found: M^++Na, 408.0607. $C_{16}H_{25}{}^{79}BrNO_3$ requires *M*+Na, 408.0587).

3.1.6. *N*-(2-Bromo-4-methoxyphenyl)-*N*-methyl-1*H*-3-pyrrolecarboxamide, 4a. A solution of **3a** (3 g, 11.1 mmol) and TosMIC (2.2 g, 11.1 mmol) in THF (42 mL) was added slowly to a stirred solution of potassium *tert*-butoxide (2.5 g, 22.2 mmol) in THF (120 mL) at 0°C. Stirring was continued for 3 h after which water (10 mL) was carefully added. The solvent was evaporated in vacuo and the product was extracted with diethyl ether. The organic layer was dried and evaporated under reduced pressure. Chromatography (SiO_2, EtOAc) gave the title compound, **4a** as a white solid (2.06 g, 60%), mp 186–187°C (hexane/EtOAc 1:2) (Found: C, 50.29; H, 4.22; N, 8.84. $C_{13}H_{13}BrN_2O_2$ requires C, 50.50; H, 4.24; N, 9.06%); ν_{max} (cm^{-1}) 3234 (w, N–H), 2996 (w, C–H), 1605 (s, amide C=O); δ_H (300 MHz; $CDCl_3$) 3.22 (3H, s, NCH_3), 3.75 (3H, s, OCH_3), 5.73 (1H, br s, H-4), 6.42 (1H, br s, H-5), 6.54 (1H, br s, H-2), 6.79 (1H, dd, *J*=8.7, 2.8 Hz, H-5′), 7.10 (1H, d, *J*=2.8 Hz, H-3′), 7.12 (1H, d, *J*=8.7 Hz, H-6′), 8.80 (1H, br s, NH); δ_C ($CDCl_3$) 37.2 (NCH_3), 55.7 (OCH_3), 110.0 (CH), 114.4 (CH), 117.6 (CH), 118.5 (CH), 119.1 (C), 122.6 (CH), 124.2 (C), 130.8 (CH), 136.8 (C), 159.4 (C), 165.4 (amide C=O); *m*/*z* 135 (1%), 120 (4), 107 (2.6), 94 (100), 77 (5), 66 (38).

Note: if the addition of the TosMIC and amide is not done slowly enough **12** is isolated: mp 93–94°C (EtOAc) (Found: C, 49.63; H, 4.35; N, 7.08. $C_{24}H_{25}Br_2N_3O_4$ requires C, 49.76; H, 4.35; N, 7.25%); ν_{max} (cm^{-1}) 3254 (w, N–H), 2930 (w, C–H), 1605 (w, amide C=O); δ_H (400 MHz; $CDCl_3$) 2.18 (2H, m, CH_2CO), 2.71 (2H, 2m, CH_2pyr), 3.20 (3H, s, N′CH_3), 3.34 (3H, s, N″CH_3), 3.88 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 5.73 (1H, 2 br s, H-4 rotamers), 6.23 (1H, 2 br s, H-2 rotamers), 6.91 (1H, m, ArH), 6.92 (1H, dd, *J*=8.8, 2.8 Hz, H-5′), 7.10 (1H, dd, *J*=8.8, 2.8 Hz, H-5″), 7.23 (3H, m, ArH), 9.31 (1H, br s, NH); δ_C ($CDCl_3$) HETCOR 22.2 (CH_2pyr), 34.0 (CH_2CO), 35.8 (N′CH_3), 36.9 (N″CH_3), 55.5 (OCH_3), 107.0 (C-4), 114.1 and 114.1 (CH), 114.5 (CH), 118.0 (C), 118.2 and 118.2 (CH), 118.5 (CH), 121.2 (C-2), 123.2 (C), 123.9 (C), 129.7 (CH), 130.6 (CH), 131.2 (C), 134.5 (C), 136.6 (C), 159.2 (C), 159.5 (C), 165.6 (amide N′C=O), 173.2 (amide N″C=O); *m*/*z* 217 (46%), 215 (47), 202 (98), 200 (100), 174 (12), 172 (12.5), 121 (1.7), 120 (2).

3.1.7. *N*-(2-Bromo-4-methoxyphenyl)-*N*-(2-trimethylsilyl-ethoxymethyl)-1*H*-3-pyrrolecarboxamide, 4c. A solution of **3c** (4 g, 10.3 mmol) and TosMIC (2.0 g, 10.3 mmol) in THF (40 mL) was added slowly to a stirred solution of potassium *tert*-butoxide (2.3 g, 20.6 mmol) in THF (115 mL) at 0°C. Stirring was continued for 1 h after which water (50 mL) was carefully added. The solvent was evaporated in vacuo and the product was extracted with ethyl acetate (3×150 mL). The organic layer was dried and evaporated under reduced pressure. Chromatography (SiO_2, hexane/EtOAc 4:3) gave the title compound, **4c** as a pale solid (2.5 g, 57%), mp 111.5–111.8°C (EtOAc) (Found: C, 50.99; H, 5.83; N, 6.48. $C_{18}H_{25}BrN_2O_3Si$ requires C, 50.82; H, 5.92; N, 6.59%); ν_{max} (cm^{-1}) 3264 (w, N–H), 2952 (w, C–H), 1614 (s, amide C=O), 1249 (m, Si–Me); δ_H (300 MHz; $CDCl_3$) −0.07 (9H, s, $Si(CH_3)_3$), 0.93 and 0.97 (2H, 2dd, J=6.8, 4.3 Hz, $CH_2Si(CH_3)_3$), 3.75 (m, 2H, OCH_2), 3.83 (3H, s, OCH_3), 4.59 (1H, d, J=10 Hz, NCH*H*O), 5.76 (1H, d, J=10 Hz, NCH*H*O), 5.82 (1H, s, H-4), 6.48 (1H, s, H-5), 6.57 (1H, s, H-2), 6.89 (1H, dd, J=8.7, 2.8 Hz, H-5′), 7.18 (1H, d, J=2.8 Hz, H-3′), 7.24 (1H, d, J=8.7 Hz, H-6′), 9.08 (1H, br s, NH); δ_C ($CDCl_3$) −1.4 ($Si(CH_3)_3$), 18.2 (CH_2Si), 55.7 (OCH_3), 66.3 (OCH_2), 77.3 (NCH_2), 109.9 (CH), 114.1 (CH), 118.1 (CH), 118.5 (CH), 123.6 (CH), 124.5 (C), 132.4 (CH), 134.1 (C), 159.7 (C-4′), 166.3 (amide C=O); *m/z* (EI) 215 (7), 200 (6), 124 (9), 94 (100), 73 (51, $SiMe_3^+$) (Found: M^++Na, 447.0716. $C_{18}H_{25}{}^{79}BrN_2O_3Si$ requires *M*+Na, 447.0703).

3.1.8. Methyl 3-iodo-4-(*N*-methyl-1*H*-3-pyrrolecarbamoyl) benzoate, 4b.

A solution of **3b** (1.9 g, 5.7 mmol) and TosMIC (1.2 g, 6.0 mmol) in THF (6 mL) was added slowly to a stirred solution of sodium hydride (289 mg of 60% dispersion in mineral oil, 7.2 mmol) and 1,1,1,3,3,3-hexamethyldisilazane (1.2 mL, 5.8 mmol) in THF (3 mL). After 3 h the reaction mixture was evaporated in vacuo and the residue was dissolved in ethyl acetate (150 mL) and washed with saturated aqueous ammonium chloride (2×50 mL). The organic layer was dried and evaporated under reduced pressure. Chromatography (SiO_2, EtOAc) gave the title compound, **4b** as a white solid (562 mg, 26%) mp 98–99°C (hexane/EtOAc 1:4) (Found: C, 44.33; H, 3.53; N, 7.03. $C_{14}H_{13}IN_2O_3$ requires C, 43.77; H, 3.41; N, 7.29%); ν_{max} (cm^{-1}) 3253 (m, N–H), 2951 (m, C–H), 1728 (s, ester and amide C=O); δ_H (300 MHz; $CDCl_3$) 3.34 (3H, s, NCH_3), 3.97 (3H, s, OCH_3), 5.70 (1H, br s, H-4), 6.48 (1H, br s, H-5), 6.69 (1H, br s, H-2), 7.37 (1H, d, J=8.1 Hz, H-6′), 8.05 (1H, dd, J=8.1, 1.8 Hz, H-5′), 8.59 (1H, s, H-3′), 9.75 (1H, br s, NH); δ_C ($CDCl_3$) 37.1 (NCH_3), 52.5 (OCH_3), 99.4 (C-2′), 109.3 (CH), 118.1 (CH), 123.1 (CH), 129.5 (C), 130.7 (2×CH), 141.1 (CH), 151.2 (C), 164.8 (amide C=O), 165.6 (ester C=O); *m/z* 291 (64%), 257 (100, M^+−I), 94 (93) (Found: M^++H, 385.0049. $C_{14}H_{13}IN_2O_3$ requires *M*+H, 385.0058).

3.1.9. *tert*-Butyl 3-iodo-4-(*N*-methyl-1*H*-3-pyrrolecarbamoyl) benzoate, 4e.

A solution of **3b** (50 mg, 0.14 mmol) and TosMIC (27 mg, 0.14 mmol) in THF (3 mL) was added slowly to a stirred solution of potassium *tert*-butoxide (31 mg, 0.28 mmol) in THF (1 mL). After 30 min water (5 mL) was added and the suspension was extracted with ether (3×10 mL). The organic layer was dried and evaporated under reduced pressure. Chromatography (SiO_2, EtOAc) gave as first eluate starting material (5 mg, 10%). The second eluate gave a mixture of the *tert*-butyl ester **4e** (12 mg, 19%) and the methyl ester **4b** (5 mg, 9%).

Compound **4e**: δ_H (300 MHz; $CDCl_3$) 1.56 (9H, s, $C(CH_3)_3$), 3.27 (3H, s, NCH_3), 5.73 (1H, br s, H-4), 6.45 (1H, br s, H-5), 6.61 (1H, br s, H-2), 7.28 (1H, d, J=8.1 Hz, H-6′), 7.93 (1H, dd, J=8.1, 1.9 Hz, H-5′), 8.45 (1H, d, J=1.9 Hz, H-3′), 8.99 (1H, br s, NH); δ_C ($CDCl_3$) 28.8 ($C(CH_3)_3$), 37.1 (NCH_3), 82.1 ($C(CH_3)_3$), 99.4 (C-2′), 109.8 (CH), 117.8 (CH), 122.9 (CH), 129.4 (C), 130.6 (2×CH), 132.6 (C), 141.0 (CH), 150.9 (C), 163.5 (amide C=O), 164.9 (ester C=O).

3.1.10. *N*-(4-Methoxy-2-nitrophenyl)acrylamide, 2c.

A solution of **1c** (3 g, 17.8 mmol) and acryloyl chloride (2.2 mL, 26.7 mmol) in dichloromethane (75 mL) was heated for 3 h under reflux. After cooling to room temperature, the mixture was washed successively with saturated aqueous sodium hydrogen carbonate (3×25 mL) and water (2×25 mL). The organic layer was dried and evaporated under reduced pressure. Chromatography (ethyl acetate/hexane 1:1) gave the title compound **2c**, as orange crystals (3.6 g, 92%), mp 125–127°C (EtOAc) (Found: C, 54.25; H, 4.76; N, 12.32. $C_{10}H_{10}N_2O_4$ requires C, 54.05; H, 4.54; N, 12.61%); ν_{max} (cm^{-1}) 3344 (w, N–H), 2947 (m, C–H), 1691 (s, amide C=O), 1516 (s, $C–NO_2$); δ_H (300 MHz; $CDCl_3$) 3.98 (3H, s, OCH_3), 5.75 (1H, dd, J=10, 1.3 Hz, C(O)CH=CH*Htrans*), 6.23 (1H, dd, J=16.9, 10 Hz, C(O)C*Hgem*=CH_2), 6.35 (1H, dd, J=16.9, 1.3 Hz, C(O)CH=CH*Hcis*), 7.15 (1H, dd, J=9.2, 3 Hz, H-5′), 7.58 (1H, d, J=3 Hz, H-3′), 8.66 (1H, d, J=9.2 Hz, H-6′), 10.25 (br s, 1H, NH); δ_C ($CDCl_3$) 55.9 (OCH_3), 108.6 (CH), 123.4 (CH), 123.7 (CH), 128.5 (CH_2), 131.6 (CH), 137.0 (C), 155.0 (C), 163.8 (C=O); *m/z* (EI) 222 (68.3%, M^+), 168 (100), 153 (24.3), 122 (27.6), 106 (10.6), 56 (100) (Found: M^+, 222.0640. $C_{10}H_{10}N_2O_4$ requires *M*, 222.0640).

3.1.11. *N*-(4-Methoxy-2-nitrophenyl)-*N*-methylacrylamide, 3f.

A solution of **2c** (1 g, 4.5 mmol) in dry THF (12 mL) was added to a stirred suspension of sodium hydride (216 mg of 60% dispersion in mineral oil, 5.4 mmol) in THF (8 mL). The mixture was stirred for 1 h after which methyl iodide (0.8 mL, 12.6 mmol) was added and the solution stirred overnight. Water (10 mL) was added to quench the reaction. The solvent was evaporated in vacuo and the residue was dissolved in ether (60 mL). The organic layer was washed with water (3×20 mL), dried and evaporated under reduced pressure. Chromatography (SiO_2, hexane/ethyl acetate 3:1) gave the title compound **3f**, as a orange solid (914 mg, 86%), mp 125–126°C (Et_2O) (Found: C, 55.67; H, 5.22; N, 11.78. $C_{11}H_{12}N_2O_4$ requires C, 55.93; H, 5.12; N, 11.86%); ν_{max} (cm^{-1}) 2995 (w, C–H), 1665 (s, amide C=O), 1535 (s, $C–NO_2$); δ_H (300 MHz; $CDCl_3$) 3.25 (3H, s, NCH_3), 3.89 (3H, s, OCH_3), 5.48 (1H, dd, J=10.3, 1.6 Hz, C(O)CH=CH*Htrans*), 5.85 (1H, dd, J=16.7, 10.3 Hz, C(O)C*Hgem*=CH_2), 6.31 (1H, dd, J=16.7, 1.6 Hz, C(O)CH=CH*Hcis*), 7.17 (1H, dd, J=8.7, 2.8 Hz, H-5′), 7.27 (1H, d, J=8.7 Hz, H-6′), 7.48 (1H, d, J=2.8 Hz, H-3′); δ_C ($CDCl_3$) 38.7 (NCH_3), 55.8 (OCH_3), 109.8 (CH), 119.8 (CH), 126.8 (CH), 128.1 (CH_2), 128.7 (C), 131.7 (CH), 146.8 (C), 159.3 (C), 165.3 (C=O); *m/z* (EI) 237 (10%, M^++H), 236 (14.2, M^+), 190 (100,

M^+-NO_2), 182 (81), 175 (31), 149 (28), 121 (70), 92 (39), 77 (53) (Found: M^+, 236.0797. $C_{11}H_{12}N_2O_4$ requires *M*, 236.0794).

3.1.12. (4-Methoxy-2-nitrophenyl)-*N*-methyl-1*H*-3-pyrrole-carboxamide, 4f. A solution of **3f** (1.3 g, 5.5 mmol) and TosMIC (1.07 g, 5.5 mmol) in THF (20 mL) was added slowly to a stirred solution of potassium *tert*-butoxide (1.23 g, 11 mmol) in THF (27 mL) at 0°C. Stirring was continued for 1 h after which water (15 mL) was carefully added. The solvent was evaporated in vacuo and the product was extracted with ethyl acetate (2×50 mL). The organic layer was dried and evaporated under reduced pressure. Chromatography (SiO_2, hexane/ethyl acetate 1:4) gave the title compound **4f**, as a pale oil (305 mg, 20%); ν_{max} (cm^{-1}) 1666 (s, amide C═O), 1537 (s, $C-NO_2$); δ_H (300 MHz; $CDCl_3$) 3.32 (3H, br s, NCH_3), 3.83 (3H, s, OCH_3), 5.60 (1H, br s, H-4), 6.43 (1H, br s, H-5), 6.71 (1H, br s, H-2), 7.09 (1H, dd, *J*=8.8, 2.9 Hz, H-5′), 7.26 (1H, dd, *J*=8.8 Hz, H-6′), 7.35 (1H, d, *J*=2.8 Hz, H-3′), 8.22 (1H, br s, NH); δ_C (CD_3OD) 38.6 (NCH_3), 56.8 (OCH_3), 110.2 (CH), 111.4 (CH), 118.3 (C), 119.1 (CH), 121.2 (CH), 124.0 (CH), 132.1 (C), 133.3 (CH), 148.7 (C), 161.0 (C), 168.5 (C═O); *m/z* (EI) 229 (27%, M^+-NO_2), 182 (90), 167 (5), 136 (4), 121 (10), 94 (100) (Found: M^+, 275.0906. $C_{13}H_{13}N_3O_4$ requires *M*, 275.0907).

3.1.13. 2-Ethyl-5-methoxy-1-methyl-1*H*-benzimidazole, 6. A mixture of **3f** (200 mg, 0.84 mmol), 10% palladium on carbon (ca. 10 mg), triethylamine (1 mL, 7.28 mmol) was heated under reflux. While stirring, formic acid (0.26 mL, 7.05 mmol) was added dropwise. The mixture was heated under reflux for 6 h. The reaction mixture was filtered through Celite and the solid was washed with ether (2×20 mL). The organic phase was washed with saturated aqueous sodium bicarbonate (2×10 mL), dried and evaporated in vacuo. Chromatography (SiO_2, ethyl acetate/methanol 19:1) gave the title compound **6**, as yellow solid (129 mg, 80%); ν_{max} (cm^{-1}) 2939 (w, C–H), 1491, 1155; δ_H (300 MHz; $CDCl_3$) 1.35 (3H, t, *J*=7.5 Hz, CH_2CH_3), 2.79 (2H, q, *J*=7.5 Hz, CH_2CH_3), 3.59 (3H, s, NCH_3), 3.76 (3H, s, OCH_3), 6.79 (1H, dd, *J*=8.7, 2.4 Hz, H-6), 7.06 (1H, d, *J*=8.7 Hz, H-7), 7.14 (1H, d, *J*=2.4 Hz, H-4); δ_C ($CDCl_3$) 11.7 (CH_3), 20.8 (CH_2), 29.6 (NCH_3), 55.8 (OCH_3), 101.6 (CH), 109.1 (CH), 111.6 (CH), 130.4 (C), 143.0 (C), 155.9 (C), 156.4 (C); *m/z* (EI) 190 (100%, M^+), 189 (66), 145 (75), 161 (13) (Found: M^+, 190.1106. $C_{11}H_{14}N_2O$ requires *M*, 190.1104).

3.1.14. 5-Methoxy-1-methyl-2-vinyl-1*H*-benzimidazole,[29] **7.** To a solution of **3f** (200 mg, 0.84 mmol) in ethanol (4 mL), concentrated hydrochloric acid (0.9 mL) and $SnCl_2\cdot H_2O$ (758 mg, 3.36 mmol) was added. The suspension was heated under reflux for 4 h. The reaction mixture was basified with NaOH (2 M) and extracted with ethyl acetate (2×20 mL). The organic phase was washed with water (2×15 mL), dried and evaporated under reduced pressure. Chromatography (SiO_2, hexane/ethyl acetate 2:1) gave the title compound **7**, as a colourless oil (115 mg, 70%); ν_{max} (cm^{-1}) 2925 (w, C–H), 1490, 1158; δ_H (300 MHz; $CDCl_3$) 3.67 (3H, s, NCH_3), 3.77 (3H, s, OCH_3), 5.57 (1H, dd, *J*=11.0, 1.5 Hz, CH═CH*trans*), 6.42 (1H, dd, *J*=17.1, 1.5 Hz, CH═CH*cis*), 6.69 (1H, dd, *J*=17.1, 11.0 Hz, CH*gem*═CH_2), 6.83 (1H, dd, *J*=8.8, 2.3 Hz, H-6), 7.09 (1H, d, *J*=8.8 Hz, H-7), 7.15 (1H, d, *J*=2.3 Hz, H-4); δ_C ($CDCl_3$) 29.8 (NCH_3), 55.7 (OCH_3), 101.4 (CH), 109.6 (CH), 112.9 (CH), 122.5 (CH_2), 122.8 (CH), 130.5 (C), 143.5 (C), 150.7 (C), 156.4 (C); *m/z* 188 (100, M^+), 173 (72), 145 (15) (Found: M^+, 188.0949. $C_{11}H_{12}N_2O$ requires *M*, 188.0950).

3.1.15. *N*-(2-Amino-4-methoxyphenyl)-*N*-methylpropionamide, 8. Sodium borohydride (118 mg, 3.12 mmol) was added to a stirred solution of copper(II)acetylacetonate (54.2 mg, 0.20 mmol) in ethanol (18 mL) to give a brown suspension. Stirring was continued until a dark solid precipitated and the opaque solution turned clear. Compound **3f** (236 mg, 1 mmol) was then added very slowly as a solution in ethanol (1 mL). After being stirring for 5 h the reaction mixture was poured into water (5 mL), filtered and concentrated to low volume under reduced pressure. The aqueous phase was extracted with dichloromethane (3×10 mL) and the combined extracts were dried. Chromatography (SiO_2, hexane/ethyl acetate 1:1) gave the title compound **8**, as a light brown solid (125 mg, 60%) mp 145–146°C (EtOAc) (Found: C, 63.60; H, 7.64; N, 13.11. $C_{11}H_{16}N_2O_2$ requires C, 63.44; H, 7.74; N, 13.45%); ν_{max} (cm^{-1}) 3400 (d, N–H), 2937 (C–H), 1631 (s, amide C═O); δ_H (300 MHz; $CDCl_3$) 0.98 (3H, t, *J*=7 Hz, CH_2CH_3), 2.02 (2H, m, CH_2CH_3), 3.07 (3H, s, NCH_3), 3.68 (3H, s, OCH_3), 3.86 (2H, s, NH_2), 6.21 (2H, dd, *J*=8.4, 2.7 Hz, H-5′), 6.25 (1H, d, *J*=2.7 Hz, H-3′), 6.80 (1H, d, *J*=8.4 Hz, H-6′); δ_C ($CDCl_3$) 9.5 (CH_3), 26.7 (CH_2), 35.4 (NCH_3), 55.2 (OCH_3), 101.0 (CH), 104.3 (CH), 122.5 (C), 129.0 (CH), 143.7 (C), 160.1 (C), 175.6 (C═O); *m/z* (EI) 190 (100%, M^+-H_2O), 175 (75), 147 (15) (Found: M^++H, 209.1296. $C_{11}H_{16}N_2O_2$ requires *M*+H, 209.1290).

3.1.16. *tert*-Butyl 3-[*N*-(2-bromo-4-methoxyphenyl)-*N*-methyl-carbamoyl]-1*H*-1-pyrrolecarboxylate, 5a. Amide **4a** (2.1 g, 6.79 mmol) was dissolved in THF (280 mL) and cooled to −78°C. Triethylamine (2.2 g, 1.4 mL, 10.2 mmol) was added followed by addition of di-*tert*-butyl dicarbonate (2.2 g, 10.2 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred overnight, while it was allowed to warm to room temperature. The solvent was removed in vacuo, the residue was dissolved in ethyl acetate (150 mL) and washed with water (3×50 mL). The organic layer was dried and evaporated under reduced pressure. Chromatography (SiO_2, EtOAc) gave the title compound, **5a** as a colourless oil (2.5 g, 90%) (Found: C, 52.76; H, 5.32; N, 6.49. $C_{18}H_{21}BrN_2O_4$ requires C, 52.82; H, 5.17; N, 6.84%); ν_{max} (cm^{-1}) 2925 (w, C–H), 1748 (s, carbamate C═O), 1636 (s, amide C═O); δ_H (300 MHz; $CDCl_3$) 1.40 (9H, s, $C(CH_3)_3$), 3.19 (3H, s, NCH_3), 3.70 (3H, s, OCH_3), 5.82 (1H, br s, H-4), 6.76 (1H, br s, H-5), 6.79 (1H, dd, *J*=8.7, 2.7 Hz, H-5′), 6.85 (1H, br s, H-2), 7.08 (1H, d, *J*=2.7 Hz, H-3′), 7.09 (1H, d, *J*=8.7 Hz, H-6′); δ_C ($CDCl_3$) 27.0 ($C(CH_3)$), 36.7 (NCH_3), 55.3 (OCH_3), 83.9 ($C(CH_3)_3$), 112.3 (CH), 114.1 (CH), 118.2 (CH), 118.8 (CH), 121.8 (C), 122.9 (CH), 123.7 (C), 130.3 (CH), 135.6 (C), 147.6 (carbamate C═O), 159.4 (C), 164.1 (amide C═O); *m/z* (EI) 310/308 (1%), 229 (86), 215 (59), 200 (38), 120 (14), 94 (100) (Found: M^++H, 409.0763. $C_{18}H_{21}N_2O_4{}^{79}Br$ requires *M*+H, 409.0758).

3.1.17. *tert*-Butyl 3-[*N*-(2-iodo-4-methoxycarbonylphenyl)-*N*-methylcarbamoyl]-1*H*-1-pyrrolecarboxylate, 5b. Amide **4b** (345 mg, 0.9 mmol) was dissolved in THF (48 mL) and cooled to −78°C. Triethylamine (0.2 mL, 1.3 mmol) was added followed by di-*tert*-butyl dicarbonate (290 mg, 1.3 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred overnight, while it was allowed to warm to room temperature. The solvent was removed in vacuo and the residue was dissolved in ethyl acetate (50 mL), washed with water (3×25 mL). The organic layer was dried and evaporated under reduced pressure. Chromatography (SiO_2, EtOAc) gave the title compound, **5b** as a pale brown oil (361 mg, 83%); ν_{max} (cm^{-1}) 2955 (w, C–H), 1750 (s, carbamate C=O), 1728 (s, amide C=O); δ_H (300 MHz; $CDCl_3$) 1.41 (9H, s, $C(CH_3)_3$), 3.23 (3H, s, NCH_3), 3.83 (3H, s, OCH_3), 5.73 (1H, br s, H-4), 6.85 (2H, br s, H-5 and H-2), 7.28 (1H, d, J=8.1 Hz, H-6′), 7.95 (1H, dd, J=8.1, 1.7 Hz, H-5′), 8.48 (1H, d, J=1.7 Hz, H-3′); δ_C ($CDCl_3$) 27.4 ($C(CH_3)_3$), 36.8 (NCH_3), 52.3 (OCH_3), 84.2 ($C(CH_3)_3$), 99.2 (C-2′), 112.1 (CH), 119.1 (CH), 121.6 (C), 123.3 (CH), 129.3 (CH), 130.6 (CH), 130.8 (C), 140.9 (CH), 147.5 (C), 150.4 (carbamate C=O), 164.6 (C=O), 164.2 (C=O); m/z (EI) 291 (66%), 257 (98), 94 (100) (Found: M^++H, 485.0573. $C_{19}H_{21}IN_2O_5$ requires M+H, 485.0584).

3.1.18. Methyl 3-[*N*-(2-bromo-4-methoxyphenyl)-*N*-(2-trimethylsilylethoxymethyl)carbamoyl-1*H*-1-pyrrolecarboxylate, 5c. A solution of **4c** (230 mg, 0.54 mmol) in THF (8 mL) was added dropwise to a suspension of potassium hydride (93 mg of 35% dispersion in mineral oil, 0.81 mmol) at 0°C. The mixture was stirred for 1 h after which methyl chloroformate (0.08 mL, 0.65 mmol) was added and the suspension stirred overnight. Water (2 mL) was added to quench the reaction. The solvent was evaporated in vacuo and the residue was dissolved in ethyl acetate (10 mL). The organic layer was washed with water (3×10 mL), dried and evaporated under reduced pressure. Chromatography (SiO_2, hexane/ethyl acetate 1:1) gave the title compound, **5c** as a yellow solid (209 mg, 80%), mp 78–81°C (EtOAc) (Found: C, 49.31; H, 5.39; N, 5.68. $C_{20}H_{27}BrN_2O_5Si$ requires C, 49.69; H, 5.63; N, 5.79%); ν_{max} (cm^{-1}) 2954 (w, C–H), 1760 (s, carbamate C=O), 1651 (s, amide C=O), 1279 (s, Si–Me); δ_H (300 MHz; $CDCl_3$) 0.00 (9H, s, $Si(CH_3)_3$), 0.95 (2H, m, $CH_2Si(CH_3)_3$), 3.71 (2H, m, CH_2O), 3.81 (3H, s, OCH_3), 3.89 (3H, s, $COOCH_3$), 4.59 (1H, d, J=10 Hz, NCH*H*O), 5.72 (1H, d, J=10 Hz, NCH*H*O), 5.92 (1H, br s, H-4), 6.89 (1H, dd, J=8.7, 2.8 Hz, H-5′), 6.98 (1H, br s, H-5), 7.02 (1H, br s, H-2), 7.16 (1H, d, J=2.8 Hz, H-3), 7.23 (1H, d, J=8.7 Hz H-6′); δ_C ($CDCl_3$) −1.27 ($Si(CH_3)_3$), 18.1 (CH_2Si), 54.3 ($COOCH_3$), 55.7 (OCH_3), 66.3 (OCH_2), 77.1 (NCH_2), 113.1 (CH), 114.0 (CH), 118.4 (CH), 119.4 (CH), 122.4 (C), 123.8 (CH), 124.3 (C), 132.0 (CH), 133.3 (C), 150.1 (carbamate C=O), 159.9 (C), 164.7 (amide C=O); m/z (EI) 425/423 (3%), 345 (6), 257 (6), 152 (84), 73 (100, $SiMe_3{}^+$) (Found: M^+, 482.0873. $C_{20}H_{27}{}^{79}BrN_2O_5Si$ requires M, 482.0875).

3.1.19. 1-Methyl *N*-(2-bromo-4-methoxyphenyl)-*N*-(2-trimethylsilylethoxymethyl)-1*H*-3-pyrrolecarboxamide, 5d. A solution of **4c** (600 mg, 1.41 mmol) in dry THF (18 mL) was added to a stirred suspension of sodium hydride (85 mg of 60% dispersion in mineral oil, 2.1 mmol) in THF (28 mL). The mixture was stirred for 1 h after which methyl iodide (0.24 mL, 3.9 mmol) was added and the solution stirred overnight. Water (10 mL) was added to quench the reaction. The solvent was evaporated in vacuo and the residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with water (3×20 mL), dried and evaporated under reduced pressure. Chromatography (SiO_2, hexane/EtOAc 5:6) gave the title compound, **5d** as a yellow oil (446 mg, 72%) (Found: C, 51.68; H, 6.21; N, 5.76. $C_{19}H_{27}BrN_2O_3Si$ requires C, 51.93; H, 6.19; N, 6.38%); ν_{max} (cm^{-1}) 2940 (s, C–H), 1636 (s, amide CO), 1261 (s, SiMe); δ_H (300 MHz; $CDCl_3$) 0.0 (9H, s, $Si(CH_3)_3$), 0.94 (2H, m, $CH_2Si(CH_3)_3$), 3.50 (3H, s, NCH_3), 3.71 (3H, s, OCH_2), 3.82 (3H, s, OCH_3), 4.56 (1H, d, J=10 Hz, NCH*H*O), 5.63 (1H, br s, H-4), 5.76 (1H, d, J=10 Hz, NCH*H*O), 6.30 (1H, br s, H-5), 6.55 (1H, br s, H-2), 6.89 (1H, dd, J=8.7, 2.8 Hz, H-5′), 7.18 (1H, d, J=2.8 Hz, H-3′), 7.23 (1H, d, J=8.7 Hz, H-6′); δ_C ($CDCl_3$) −1.1 ($Si(CH_3)_3$), 18.2 (CH_2Si), 36.3 (NCH_3), 55.7 (OCH_3), 66.0 (OCH_2), 77.3 (NCH_2), 110.4 (CH), 114.0 (CH), 118.3 (CH), 118.5 (C), 121.5 (CH), 124.6 (CH), 127.0 (CH), 132.4 (C), 134.1 (C), 159.7 (C), 166.3 (amide C=O); m/z (EI) 359 (12%, M^+−Br), 301 (4), 213 (15), 138 (4), 119 (1), 108 (100), 73 (23, $SiMe_3{}^+$) (Found: M^++Na, 461.0872. $C_{19}H_{27}{}^{79}BrN_2O_3Si$ requires M+Na, 461.0851).

3.1.20. 8-Methoxy-5-methyl-4,5-dihydro-2*H*-pyrrolo[3,4-*c*]-quinolin-4-one, 10a and 8-methoxy-5-methyl-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]quinolin-4-one, 9a. A suspension of **4a** (150 mg, 0.5 mmol) and a sub-stoichiometric amount of AIBN in toluene (32 mL) was heated under reflux. Then, tri-*n*-butyltin hydride (0.1 mL, 0.5 mmol) was added dropwise and the reaction mixture was stirred at this temperature for 1 h. After evaporation of the solvent the residue was chromatographed (SiO_2, EtOAc). The first eluate gave **10a** as a yellow oil (30 mg, 15%); ν_{max} (cm^{-1}) 3156 (w, N–H), 2926 (m, C–H), 1620 (s, tertiary amide C=O); δ_H (300 MHz; $CDCl_3$) 3.82 (3H, s, NCH_3), 3.90 (3H, s, OCH_3), 6.76 (1H, t, J=2.7 Hz, H-1), 7.03 (1H, dd, J=9.2, 2.8 Hz, H-7), 7.30 (1H, t, J=2.7 Hz, H-3), 7.36 (1H, d, J=9.2 Hz, H-6), 7.38 (1H, d, J=2.8 Hz, H-9); δ_H (300 MHz; CD_3OD) 3.68 (3H, s, NCH_3), 3.79 (3H, s, OCH_3), 6.76 (1H, d, J=2.8 Hz, H-1), 6.99 (1H, dd, J=9.2, 2.9 Hz, H-7), 7.23 (1H, d, J=2.8 Hz, H-3), 7.37 (1H, d, J=2.9 Hz, H-9), 7.38 (1H, d, J=9.2 Hz, H-6); δ_C ($CDCl_3$) 29.3 (NCH_3), 55.7 (OCH_3), 102.2 (CH), 106.5 (CH), 114.5 (CH), 116.4 (CH), 119.7 (C), 122.9 (C), 126.0 (CH), 126.6 (C), 130.9 (C), 155.0 (C); m/z (EI) 228 (23.7%, M^+), 213 (9.1, M^+−CH_3), 185 (12.2) (Found: M^+, 228.0898. $C_{13}H_{12}N_2O_2$ requires M, 228.0905). The second eluate gave **9a** as a colourless oil (75 mg, 37%); ν_{max} (cm^{-1}) 3117 (w, N–H), 2910 (w, C–H), 1614 (s, amide C=O); δ_H (300 MHz; CD_3OD) 3.77 (3H, s, NCH_3), 3.90 (3H, s, OCH_3), 6.78 (1H, d, J=3.0 Hz, H-3), 7.12 (1H, dd, J=9.2, 2.8 Hz, H-7), 7.16 (1H, d, J=3.0 Hz, H-2), 7.53 (1H, dd, J=9.2 Hz, H-6), 7.57 (1H, d, J=2.8 Hz, H-9). δ_C (CD_3OD) 29.9 (NCH_3), 56.1 (OCH_3), 104.6 (CH), 106.6 (CH), 115.6 (C), 116.5 (C), 117.0 (CH), 118.3 (CH), 123.8 (CH), 132.6 (C), 135.7 (C), 156.8 (C), 161.9 (amide C=O); m/z (EI) 228 (1%, M^+), 213 (100, M^+−CH_3), 197 (4.5, M^+−OCH_3), 167 (60) (Found: M^++H, 229.0977. $C_{13}H_{12}N_2O_2$ requires M+H, 229.0986).

3.1.21. 8-Methoxy-5-(2-trimethylsilylethoxymethyl)-4,5-dihydro-2*H*-pyrrolo[4,3-*c*]quinolin-4-one, 10b and 8-methoxy-5-(2-trimethylsilylethoxymethyl)-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]quinolin-4-one, 9b. A suspension of **4c** (410 mg, 0.96 mmol) and a sub-stoichiometric amount of AIBN in toluene (50 mL) was heated under reflux. Then, tri-*n*-butyltin hydride (0.2 mL, 1.0 mmol) was added dropwise and the reaction mixture was stirred at this temperature for 1 h. After evaporation of the solvent the residue was chromatographed (SiO_2, hexane/EtOAc 2:3) The first eluate gave **10b** as a yellow solid (60 mg, 18%); ν_{max} (cm^{-1}) 3117 (w, N–H), 2910 (w, C–H), 1614 (s, amide C=O), 1228 (w, SiMe); δ_H (300 MHz; $CDCl_3$) −0.07 (9H, s, $Si(CH_3)_3$), 1.00 (2H, t, *J*=8 Hz, $CH_2Si(CH_3)_3$), 3.77 (2H, t, *J*=8 Hz, OCH_2), 3.96 (3H, s, OCH_3), 5.93 (2H, br s, NCH_2O), 6.84 (1H, t, *J*=2.5 Hz, H-1), 7.09 (1H, dd, *J*=9.2, 2.7 Hz, H-7), 7.35 (1H, t, *J*=2.5 Hz, H-3), 7.41 (1H, d, *J*=2.7 Hz, H-9), 7.67 (1H, d, *J*=9.2 Hz, H-6), 10.4 (1H, br s, NH); δ_C ($CDCl_3$) −1.3 ($Si(CH_3)_3$), 18.1 ($CH_2Si(CH_3)_3$), 55.6 (OCH_3), 66.0 (NCH_2), 71.3 (NCH_2O), 102.6 (CH), 106.3 (CH), 114.7 (CH), 117.8 (CH), 119.7 (C), 122.2 (C), 126.4 (CH), 127.5 (C), 130.1 (C), 155.3 (C), 155.8 (C=O); *m/z* (EI) 344 (15%, M^+), 271 (100, M^+-SiMe_3), 228 (62), 197 (25), 73 (35, $SiMe_3^+$) (Found: M^++Na, 367.1454. $C_{18}H_{24}N_2O_3Si$ requires *M*+Na, 367.1458). The second eluate gave **9b** as a colourless solid (112 mg, 34%); mp 169–170°C (isopropanol) (Found: C, 62.76; H, 7.02; N, 8.13. $C_{18}H_{24}N_2O_3Si$ requires C, 62.51; H, 6.89; N, 7.94%); ν_{max} (cm^{-1}) 3195 (w, N–H), 2954 (w, C–H), 1617 (s, amide C=O), 1246 (w, SiMe); δ_H (300 MHz; $CDCl_3$) −0.07 (9H, s, $Si(CH_3)_3$), 1.02 (2H, t, *J*=8.2 Hz, $CH_2Si(CH_3)_3$), 3.82 (2H, t, *J*=8.2 Hz, OCH_2), 3.89 (3H, s, OCH_3), 6.01 (2H, br s, NCH_2O), 6.96 (1H, t, *J*=2.5 Hz, H-3), 7.14 (1H, t, *J*=2.5 Hz, H-2), 7.15 (1H, dd, *J*=9.2, 2.8 Hz, H-7), 7.70 (1H, d, *J*=2.8 Hz, H-9), 7.73 (1H, d, *J*=9.2 Hz, H-6), 11.05 (1H, br s, NH); δ_C ($CDCl_3$) −1.4 ($Si(CH_3)_3$), 18.1 ($CH_2Si(CH_3)_3$), 55.6 (OCH_3), 66.0 (OCH_2), 71.5 (NCH_2), 103.8 (CH), 106.8 (CH), 114.4 (C), 115.3 (C), 115.6 (CH), 118.1 (CH), 122.5 (CH), 131.0 (C), 134.8 (C), 155.2 (C), 160.7 (amide C=O); *m/z* (EI) 344 (19%, M^+), 271 (63.3, M^+-SiMe_3), 228 (39.4), 199.1 (16.7), 167.1 (18), 73 (80, $SiMe_3^+$) (Found: M^+, 344.1542. $C_{18}H_{24}N_2O_3Si$ requires *M*, 344.1556).

3.1.22. *tert*-Butyl 5-methoxy-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,3′-pyrrole]-1′-carboxylate, 11c, *tert*-butyl 8-methoxy-5-methyl-4-oxo-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]quinoline-1-carboxylate, 9c and *tert*-butyl 8-methoxy-5-methyl-4-oxo-4,5-dihydro-2*H*-pyrrolo[4,3-*c*]quinoline-1-carboxylate, 10c. A suspension of **5a** (2.5 g, 6.1 mmol) and a sub-stoichiometric amount of AIBN in toluene (315 mL) was heated under reflux. Then, tri-*n*-butyltin hydride (1.8 mL, 6.7 mmol) was added dropwise and the reaction mixture was stirred at this temperature for 1 h. After evaporation of the solvent the residue was chromatographed (SiO_2, hexane/EtOAc 1:2). The first eluate gave **11c** as a colourless oil (625 mg, 31%); ν_{max} (cm^{-1}) 2974 (w, C–H), 1702 (s, carbamate and amide C=O); δ_H (300 MHz; $CDCl_3$) 1.46 and 1.50 (9H, s, $C(CH_3)_3$), 3.18 (3H, s, NCH_3), 3.77 (3H, s, OCH_3), 3.84 and 3.91 (1H, 2d, *J*=12 Hz, H-1), 4.13 and 4.16 (1H, 2d, *J*=12 Hz, H-1), 4.73 and 4.80 (1H, 2d, *J*=3.8 Hz, H-4), 6.72 (1H, d, *J*=8.2 Hz, H-8), 6.79 (1H, d, *J*=2.7 Hz, H-10), 6.97 (1H, d, *J*=3.8 Hz, H-3), 7.10 (1H, d, *J*=8.7 Hz, H-7); δ_C ($CDCl_3$) 27.3 (NCH_3), 28.3 ($C(CH_3)_3$), 54.8 and 55.8 (CH_2), 55.8 (OCH_3), 57.6 and 58.7 (C), 80.9 and 81.1 ($C(CH_3)_3$), 108.5 (CH), 108.5 (CH), 110.9 (CH), 113.2 and 113.4 (CH), 114.6 (CH), 122.4 (C), 128.8 (CH), 137.4 (C), 150.9 (carbamate C=O), 156.6 (C), 177.8 (amide C=O); *m/z* (EI) 330 (35%, M^+), 274 (33.8, $M^+-C_4H_9$), 257 (16.2, $M^+-C_4H_9O$), 230 (64.8), 202 (37.5), 187 (24.1), 149 (50.1) (Found: M^+, 330.1575. $C_{18}H_{22}N_2O_4$ requires *M*, 330.1579). The second eluate gave **9c** as a colourless oil (360 mg, 18%); ν_{max} (cm^{-1}) 2933 (w, C–H), 1702 (s, carbamate C=O), 1656 (s, amide C=O); δ_H (300 MHz; $CDCl_3$) COSY 1.61 (9H, s, $C(CH_3)_3$), 3.69 (3H, s, NCH_3), 3.89 (3H, s, OCH_3), 6.85 (1H, d, *J*=3.5 Hz, H-3), 7.04 (1H, dd, *J*=9.2, 2.8 Hz, H-7), 7.30 (1H, d, *J*=9.2 Hz, H-6), 7.41 (1H, d, *J*=3.5 Hz, H-2), 8.26 (1H, d, *J*=2.8 Hz, H-9); δ_C ($CDCl_3$) HETCOR 28.2 ($C(CH_3)_3$), 29.7 (NCH_3), 55.5 (OCH_3), 85.4 ($C(CH_3)_3$), 108.4 (C-3), 109.0 (C-9), 115.1 (C), 116.0 (C-6), 116.1 (C-7), 121.0 (C), 126.8 (C-2), 132.8 (C), 134.3 (C), 149.5 (carbamate C=O), 153.9 (C), 158.9 (amide C=O); *m/z* (ES) 329 (26%, $M^+ + 1$), 273 (100, $M^+-C_4H_7$), 229 (100), 213 (25), 199 (14), 183 (14) (Found: M^++H, 329.1510. $C_{18}H_{20}N_2O_4$ requires *M*+H, 329.1501). The third eluate gave **10c** as a yellow oil (20 mg, 1%); ν_{max} (cm^{-1}) 2960 (m, C–H), 1698 (s, amide C=O), 1659 (s, carbamate C=O); δ_H (300 MHz; $CDCl_3$) 1.59 (9H, s, $C(CH_3)_3$), 3.58 (3H, s, NCH_3), 3.81 (3H, s, OCH_3), 6.90 (1H, dd, *J*=9.1, 2.9 Hz, H-7), 7.14 (1H, d, *J*=9.1 Hz, H-6), 7.20 (1H, d, *J*=2.9 Hz, H-9), 7.69 (1H, d, *J*=2.1 Hz, H-1), 7.98 (1H, d, *J*=2.1 Hz, H-3) (Found M^+, 328.1423. $C_{18}H_{20}N_2O_4$ requires *M*, 328.1422).

3.1.23. *tert*-Butyl 5-methoxycarbonyl-1-methyl-2-oxo-1,2-dihydrospiro[indole-3,3′-pyrrole]-1′-carboxylate, 11d, *tert*-butyl 8-methoxycarbonyl-5-methyl-4-oxo-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]quinoline-1-carboxylate, 9d and *tert*-butyl-8-methoxycarbonyl-5-methyl-4-oxo-4,5-dihydro-2*H*-pyrrolo[4,3-*c*]quinoline-2-carboxylate, 10d. A suspension of **5b** (600 mg, 1.23 mmol) and a sub-stoichiometric amount of AIBN in toluene (63 mL) was heated under reflux. Then, tri-*n*-butyltin hydride (0.36 mL, 1.36 mmol) was added dropwise and the reaction mixture was stirred at this temperature for 1 h. After evaporation of the solvent the residue was chromatographed (SiO_2, ethyl acetate/hexane 1:1). The first eluate gave **11d** as a colourless oil (115 mg, 26%); ν_{max} (cm^{-1}) 2976 (w, C–H), 1704 (s, C=O); δ_H (300 MHz; $CDCl_3$) 1.41 and 1.46 (9H, 2s, $C(CH_3)_3$), 3.19 (3H, s, NCH_3), 3.84 (3H, s, OCH_3), 3.88 (1H, d, *J*=11.5 Hz, H-1), 4.07 and 4.11 (1H, 2d, *J*=11.5 Hz, H-1), 4.64 and 4.70 (1H, 2d, *J*=3.8 Hz, H-4), 6.81 (1H, d, *J*=8.1 Hz, H-7), 6.82 (0.5H, d masked, H-3), 6.97 (0.5H, d, *J*=3.8 Hz, H-3), 7.83 (1H, s, H-10), 7.98 (1H, dd, *J*=8.1, 1.6 Hz, H-8); δ_C ($CDCl_3$) 26.8 (NCH_3), 28.3 ($C(CH_3)_3$), 52.1 (OCH_3), 54.7 and 55.3 (CH_2), 57.07 and 58.24 (C), 81.1 and 81.3 ($C(CH_3)_3$), 107.6 (CH), 107.8 (CH), 125.1 (CH), 125.2 (C), 131.5 (CH), 132.6 (C), 133.9 and 134.1 (CH), 146.8 (C), 150.8 (carbamate C=O), 166.6 (amide C=O), 178.0 (ester C=O); *m/z* (EI) 258 (100%), 241 (12), 230 (23), 199 (32) (Found: M^++H, 359.1607. $C_{19}H_{22}N_2O_5$ requires *M*+H, 359.1610). The second eluate gave **9d** as a colourless oil (57 mg, 13%) ν_{max} (cm^{-1}) 2951 (w, C–H), 1717 (s, ester and carbamate C=O), 1663 (s, amide C=O); δ_H (300 MHz; $CDCl_3$)

COSY 1.70 (9H, s, $C(CH_3)_3$), 3.83 (3H, s, NCH_3), 3.97 (3H, s, OCH_3), 6.91 (1H, d, J=3.5 Hz, H-3), 7.48 (1H, d, J=8.9 Hz, H-6), 7.53 (1H, d, J=3.5 Hz, H-2), 8.13 (1H, dd, J=8.9, 1.9 Hz, H-7), 9.28 (1H, d, J=1.9 Hz, H-9); δ_C ($CDCl_3$) HETCOR 27.7 ($C(CH_3)_3$), 29.9 (NCH_3), 52.2 (OCH_3), 86.3 ($C(CH_3)$), 108.3 (C-3), 114.3 (C), 115.0 (C-6), 120.9 (C), 122.6 (C), 127.5 (C-9), 127.8 (C-2), 129.1 (C-7), 134.3 (C), 141.3 (C), 149.8 (carbamate C═O), 159.8 (amide C═O), 166.7 (ester C═O); m/z (EI) 256 (100%), 225 (51), 197 (13), 168 (25), 167 (3) (Found: M^++H, 357.1450. $C_{19}H_{20}N_2O_5$ requires M+H, 357.1461). The third eluate gave **10d** as a colourless oil (22 mg, 5%) ν_{max} (cm^{-1}) 2920 (w, C–H), 1714 (s, carbamate and ester C═O), 1643 (m, amide C═O); δ_H (300 MHz; $CDCl_3$) 1.70 (9H, s, $C(CH_3)_3$), 3.78 (3H, s, NCH_3), 3.91 (3H, s, OCH_3), 6.83 (1H, s, H-1), 7.25 (1H, s, H-3), 7.40 (1H, d, J=8.9 Hz, H-6), 8.02 (1H, dd, J=8.9, 2 Hz, H-7), 8.55 (1H, d, J=2 Hz, H-9); m/z (EI) 256 (100%), 225 (88), 197 (13), 169 (4), 168 (4), 167 (12) (Found: M^+, 356.1372. $C_{19}H_{20}N_2O_5$ requires M, 356.1369).

A suspension of **5b** (180 mg, 0.41 mmol) and a sub-stoichiometric amount of AIBN in toluene (20 mL) was heated under reflux. Tris(trimethylsilyl)silane (0.12 mL, 0.45 mmol) was added dropwise and the reaction mixture was stirred at this temperature for 4 h. After evaporation of the solvent the residue was chromatographed (SiO_2, hexane/EtOAc 1:2). The first eluate gave **9d** as a colourless oil (22 mg, 17%) and the second eluate gave **10d** as a colourless oil (18 mg, 14%).

3.1.24. Methyl 5-methoxy-1-(2-trimethylsilylethoxymethyl)-2-oxo-1,2-dihydrospiro[indole-3,3′-pyrrole]-1′-carboxylate, 11e and methyl 8-methoxy-5-(2-trimethylsilylethoxymethyl)-4-oxo-4,5-dihydropyrrolo[3,2-*c*]quinoline-1-carboxylate, 9e. A suspension of **5c** (130 mg, 0.27 mmol) and a sub-stoichiometric amount of AIBN in toluene (14 mL) was heated under reflux. Then, tri-*n*-butyltin hydride (0.06 mL, 0.27 mmol) was added dropwise and the reaction mixture was stirred at this temperature for 1 h. After evaporation of the solvent the residue was chromatographed (SiO_2, hexane/EtOAc 1:1). The first eluate gave **11e** as a colourless oil (35 mg, 32%); ν_{max} (cm^{-1}) 2976 (w, C–H), 1713 (s, carbamate C═O), 1651 (m, amide C═O); δ_H (300 MHz; $CDCl_3$) 0.00 (9H, s, $Si(CH_3)_3$), 0.94 (2H, t, J=8 Hz, $CH_2Si(CH_3)_3$), 3.58 (2H, t, J=8 Hz, CH_2O), 3.80 and 3.84 (3H, 2s, $COOCH_3$), 3.82 (3H, s, OCH_3), 3.96 and 4.04 (1H, 2d, J=11 Hz, H-1), 4.24 (1H, t, J=12 Hz, H-1), 4.85 and 4.90 (1H, 2d, J=4 Hz, H-4), 5.14, 5.18 (2H, ABq, J=10.5, 2.6 Hz, NCH_2O), 6.84–7.06 (4H, ArH and H-3); δ_C ($CDCl_3$) −1.43 ($Si(CH_3)_3$), 17.7 (CH_2Si), 53.0 ($COOCH_3$), 55.2 and 55.4 (CH_2), 55.8 (OCH_3), 57.0 and 58.2 (C), 66.1 (OCH_2), 69.8 (NCH_2), 109.5 and 109.7 (CH), 110.4 (CH), 110.5 (CH), 113.8 (CH), 132.6 and 133.4 (CH), 132.8 (C), 134.3 (C), 134.4 (C), 156.8 (C), 178.2 (amide C═O); m/z (EI) 404 (27, M^+), 346 (22), 345 (19), 287 (16), 273 (19), 214 (8), 73 (100, $SiMe_3^+$) (Found: M^+, 404.1778. $C_{20}H_{28}N_2O_5Si$ requires M, 404.1778). The second eluate gave **9e** as a yellow oil (16 mg, 15%); ν_{max} (cm^{-1}) 2940 (w, C–H), 1714 (m, carbamate C═O), 1659 (s, amide C═O); δ_H (300 MHz; $CDCl_3$) −0.07 (9H, s, $Si(CH_3)_3$), 0.98 (2H, t, J=8 Hz, $CH_2Si(CH_3)_3$), 3.75 (2H, m, CH_2O), 3.94 (3H, s, $COOCH_3$), 4.15 (3H, s, OCH_3), 5.88 (2H, br s, NCH_2O), 7.00 (1H, d, J=3.6 Hz, H-3), 7.16 (1H, dd, J=9.3, 2.9 Hz, H-7), 7.60 (1H, d, J=3.6 Hz, H-2), 7.70 (1H, d, J=9.3 Hz, H-7), 8.41 (1H, d, J=2.9 Hz, H-9); δ_C ($CDCl_3$) −1.36 ($Si(CH_3)_3$), 18.1 (CH_2Si), 55.0 ($COOCH_3$), 55.6 (OCH_3), 66.3 (OCH_2), 71.7 (NCH_2), 108.5 (CH), 109.4 (CH), 110.4 (CH), 113.8 (CH), 116.7 (CH), 117.6 (CH), 120.8 (C), 126.7 (CH), 132.2 (C), 151.2 (carbamate C═O), 154.4 (C), 159.7 (amide C═O); m/z (EI) 402 (28, M^+), 344 (38), 329 (72, M^+-SiMe_3), 271 (36), 169 (68), 73 (100, $SiMe_3^+$). (Found: M^+, 402.1599. $C_{20}H_{26}N_2O_5Si$ requires M, 402.1610).

3.1.25. 8-Methoxy-1-methyl-5-(2-trimethylsilylethoxymethyl)-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]quinolin-4-one, 9f. A suspension of **5d** (266 mg, 0.60 mmol) and a sub-stoichiometric amount of AIBN in toluene (32 mL) was heated under reflux. Then, tri-*n*-butyltin hydride (0.13 mL, 0.66 mmol) was added dropwise and the reaction mixture was stirred at this temperature for 1 h. After evaporation of the solvent the residue was chromatographed (SiO_2, hexane/EtOAc 3:4) to give the title compound, **9f** as a yellow solid (93 mg, 43%). ν_{max} (cm^{-1}) 2955 (w, C–H), 1651 (s, amide C═O), 1250 (w, SiMe); δ_H (300 MHz; $CDCl_3$) −0.01 (9H, s, $Si(CH_3)_3$), 0.98 (2H, t, J=8 Hz, $CH_2Si(CH_3)_3$), 3.76 (2H, t, J=8 Hz, CH_2O), 3.95 (3H, s, NCH_3), 4.19 (3H, s, OCH_3), 5.88 (2H, br s, NCH_2O), 6.91 (2H, s, H-2 and H-3), 7.10 (1H, dd, J=9.3, 2.7 Hz, H-7), 7.61 (1H, d, J=2.7 Hz, H-9), 7.73 (1H, d, J=9.3 Hz, H-6); δ_C ($CDCl_3$) −1.3 ($Si(CH_3)_3$), 18.1 (CH_2Si), 38.0 (NCH_3), 55.7 (OCH_3), 65.9 (OCH_2), 71.5 (NCH_2), 105.8 (CH), 105.9 (CH), 113.1 (CH), 116.3 (C), 116.6 (C), 118.0 (CH), 128.6 (CH), 131.5 (C), 132.7 (C), 154.5 (C), 159.9 (amide C═O); m/z (EI) 358 (10%, M^+), 285 (100, M^+-SiMe_3), 257 (10), 242 (76), 211 (25), 119 (10), 169 (10), 73 (50, $SiMe_3^+$) (Found: M^+, 358.1700. $C_{19}H_{26}N_2O_3Si$ requires M, 358.1712).

3.1.26. 8-Methoxy-1-methyl-5-(2-trimethylsilylethoxymethyl)-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]quinolin-4-one, 9f. A solution of **9b** (40 mg, 0.11 mmol) in dry THF (2 mL) was added to a stirred suspension of sodium hydride (7 mg of 60% dispersion in mineral oil, 0.17 mmol) in THF (3 mL). The mixture was stirred for 1 h after which methyl iodide (0.02 mL, 0.30 mmol) was added and the solution stirred overnight. Water (5 mL) was added to quench the reaction. The solvent was evaporated in vacuo and the residue was dissolved in ethyl acetate (15 mL). The organic layer was washed with water (3×10 mL), dried and evaporated under reduced pressure. Chromatography (SiO_2, hexane/EtOAc 3:4) gave **9f** (30 mg, 72%).

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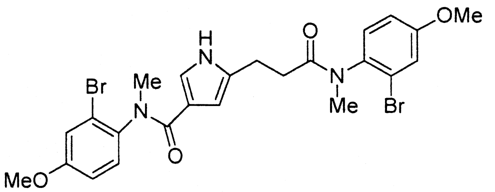

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