The regioselective synthesis of aryl pyrroles

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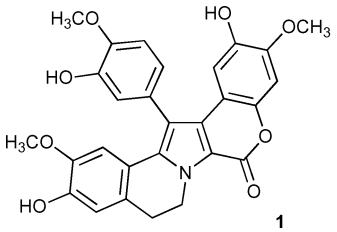
Received 31st March 2006, Accepted 28th April 2006
First published as an Advance Article on the web 19th May 2006
DOI: 10.1039/b604692d

Pyrrole is a unique aromatic molecule as it can readily undergo substitution at all five positions but obtaining the desired regioisomer can prove difficult to control. We now report our results on the regioselective arylation of pyrrole, utilizing selective halogenation and the Suzuki–Miyaura reaction to prepare C4-, C5- and C3-aryl derivatives. We have applied this methodology to the synthesis of lamellarin O dimethyl ether, an intermediate in the synthesis of lukinol A.

Introduction

The aryl pyrrole moiety is a common structural motif in natural product chemistry with structural diversity ranging from large polycyclic compounds such as the lamellarins[1] (**1** = lamellarin G), to much simpler derivatives such as pyrrolnitrin (**2**),[2] which has made these molecules popular synthetic targets.[3]



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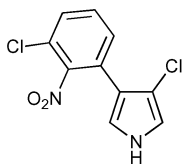

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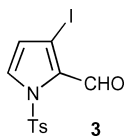
Palladium mediated cross coupling chemistry has proved invaluable for the synthesis of compounds of this type and a review covering this chemistry is currently in print.[4] One problem that is associated with the arylation of pyrroles is the selective formation of monoaryl derivatives. The use of the Suzuki–Miyaura reaction in particular has played a key role in the formation of the compounds in question. However, the scope of the chemistry is limited to the regioselective introduction of a halide onto the pyrrole core. Particularly when an electron withdrawing group is installed at C2 of the pyrrole, such as an ester or formyl group, selective halogenation at C3 or C5 is not possible.[5] Ghosez *et al.* overcame this problem for the synthesis of 2-formyl-3-iodopyrrole (**3**) by the construction of the pyrrole ring with the iodide in place.[6] However, this method suffered from low yields and requires numerous steps. It would be advantageous to be able to introduce a halogen regioselectively on the pyrrole core.



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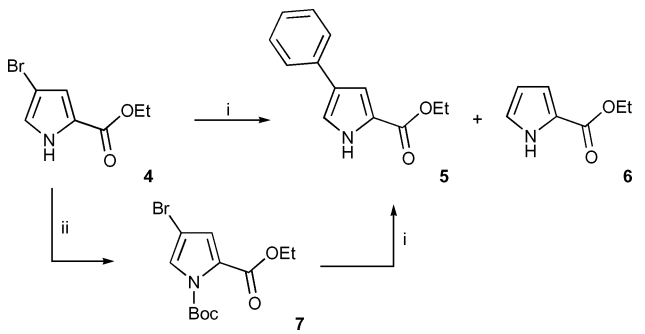
This paper overcomes this problem by the use of a removable blocking group to selectively direct halogenation at the desired position and can be removed after the coupling reaction. Introduction of a chlorine atom at the most reactive position of the pyrrole would then allow substitution at the next most reactive position with bromine or iodine that react preferentially in palladium mediated cross-coupling reactions. After the appropriate cross-coupling reaction the chloride can then be removed under reductive conditions.

Results and discussion

While the C4 bromopyrrole derivative (**4**) has been reported to undergo Suzuki–Miyaura coupling to give **5**, it is not without its problems and results in a large percentage of dehydrohalogenation (**6**) (Scheme 1). Handy *et al.* reported that pyrrole **4** is not a good coupling partner, however, conversion to the *N*-Boc derivative **7** does facilitate the desired coupling with concomitant deprotection.[7] From our previous experience with the Suzuki–Miyaura reaction on pyrrole derivatives we observed subtle differences with the electronic effects.[8] As the pyrrole is electron rich it is prone to dehydrohalogenation.[9] Therefore, the role of the Boc group is not to protect nitrogen but to reduce the electron density of the pyrrole. We found that this problem can be overcome by the use of the corresponding iodide and the accelerated ligandless conditions of Novak *et al*.[10]



Scheme 1 *Reaction conditions (ref. 7):* i) $Pd(PPh_3)_4$, phenyl boronic acid, $Na_2CO_{3(aq)}$, DMF, 110 °C; ii) $(Boc)_2O$.

The regioselective halogenation of C4 can be controlled by the use of a strongly electron withdrawing group at C2. Bélanger has reported that the trichloroacetyl derivative **8** undergoes exclusive halogenation at C4 (Scheme 2) while the methyl ester derivative gives an inseparable 1 : 1 mixture of the C4 and C5 halogenated

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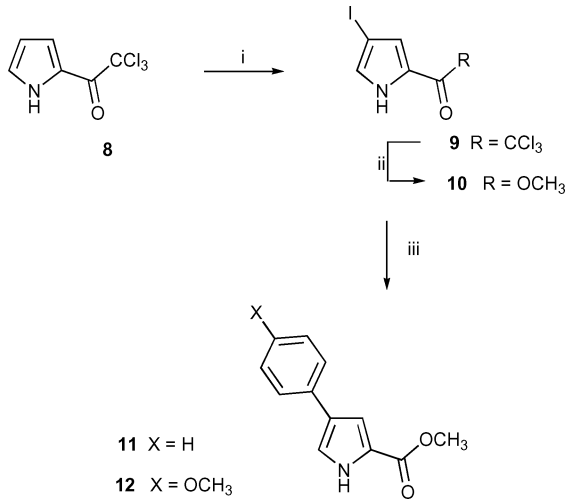
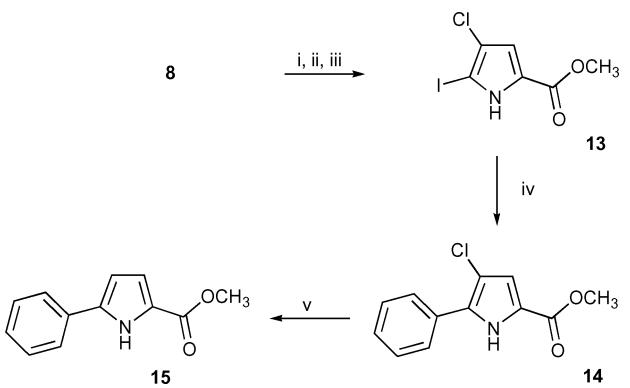


Scheme 2 *Reaction conditions:* i) I_2, AgTFA, $CHCl_3$ 81%; ii) CH_3OH, K_2CO_3 88%; iii) aryl boronic acid, $Pd(OAc)_2$, $K_2CO_{3(aq)}$, acetone, reflux (**11** 83%), (**12** 52%).

derivatives.[5] The trichloroketone can then be converted to the methyl ester by the haloform reaction with alkaline methanol giving the coupling precursor **10** in good yield. The reaction of the iodopyrrole under Suzuki–Miyaura conditions with phenyl boronic acid and tetrakistriphenylphosphine palladium as the catalyst was still problematic as Handy *et al.* had reported for the corresponding bromide.[7] However, the use of phosphine-free conditions as reported by Novak *et al.*[10] gave the C4-arylated pyrrole **11** in 83% yield without resorting to activation of the pyrrole by acylation of the nitrogen. The coupling of electron rich phenyl boronic esters such as 4-methoxyphenyl pinacol borane was also achieved under these so called "ligandless" conditions. With an effective arylation procedure at hand we then sought to selectively arylate C5 and C3 of the pyrrole.

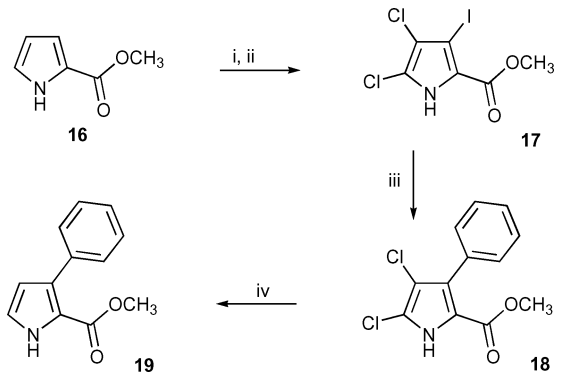
The trichloromethyl ketone **8** was reacted with one equivalent of sulfuryl chloride to give exclusively the C4 chloro derivative[5] followed by conversion to the methyl ester which was then reacted with iodine/silver trifluoroacetate to introduce iodine regioselectively at C5 (Scheme 3). This iodide was then subjected to the Suzuki–Miyaura reaction with phenyl boronic acid to give the 4-chloro-5-phenylpyrrole derivative **14** in 75% yield. The chlorine



Scheme 3 *Reaction conditions:* i) SO_2Cl_2, $CHCl_3$, 83%; ii) CH_3OH, K_2CO_3 88%; iii) I_2, AgTFA, $CHCl_3$, 86%; iv) phenyl boronic acid, $Pd(OAc)_2$, $K_2CO_{3(aq)}$, acetone, reflux 75%; v) 10% Pd/C, CH_3OH, H_2 (40 psi), 82%.

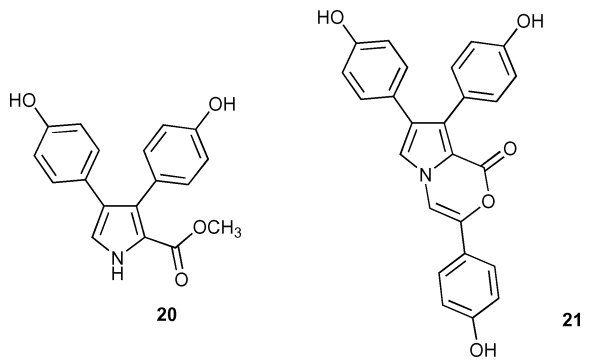
was removed by catalytic hydrogenation with palladium on carbon to give methyl 5-phenylpyrrole-2-carboxylate (**15**) in 82% yield. The position of the phenyl group at C5 is supported by the coupling constant of 3.9 Hz in the ^{1}H NMR spectrum between the protons at C3 and C4 and by comparison with spectral data reported in the literature.[11]

The 3-phenyl derivative was then targeted by first reacting the methyl ester **16** with two equivalents of sulfuryl chloride to give the C4,C5 dichloride in 91% yield (Scheme 4). As both C4 and C5 were substituted the trichloroketone was not required. The iodination of this compound then gave the tetrasubstituted pyrrole derivative **17** ready for Suzuki–Miyaura coupling. The reaction with phenyl boronic acid, again using palladium acetate in acetone, gave the desired product **18** in 94% yield. Characterisation of **18** was difficult due to the lack of distinguishing features in the ^{1}H NMR, however, hydrogenation with palladium on carbon reduced the two remaining halogens and introduced the two hydrogens at C4 and C5 which appeared as apparent triplets at 6.96 and 7.35 ppm in the ^{1}H NMR spectrum and is consistent with spectral data reported for the corresponding ethyl ester.[12]

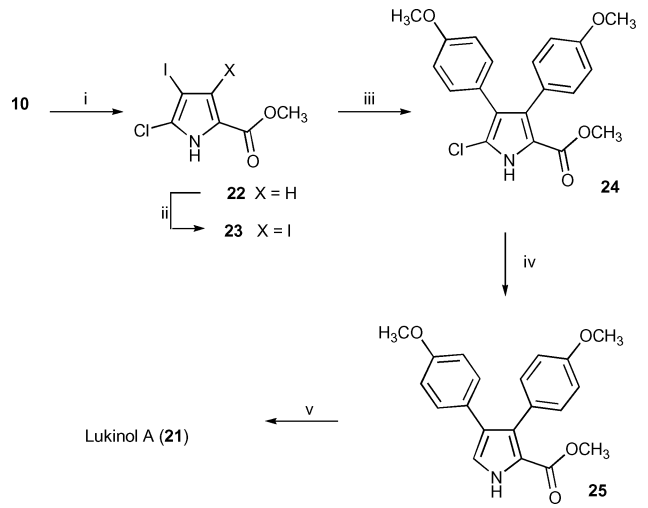


Scheme 4 *Reaction conditions:* i) SO_2Cl_2 (2 eq.), $CHCl_3$, 91%; ii) I_2, AgTFA, $CHCl_3$ 77%; iii) phenyl boronic acid, $Pd(OAc)_2$, $K_2CO_{3(aq)}$, acetone, reflux 94%; iv) 10% Pd/C, CH_3OH, H_2 (40 psi), 87%.

This method now allows the preparation of any of the monoarylated C2-carboxylic ester derivatives, therefore we extended the investigation to bisarylated pyrroles. As C4 and C5-diaryl pyrroles can be readily prepared from the corresponding diiodide or dibromide we targeted the more challenging C3,C4 diaryl derivatives. Compounds of this type are related to a number of naturally occurring pyrroles such as lamellarin Q (**20**) and lukinol A (**21**).[13] To highlight the synthetic method we targeted the bis 4-methoxyphenyl derivative **25** which has previously been converted to lukinol A in three steps.[14]



To achieve this synthesis, the 4-iodo derivative **10** from above was reacted with sulfuryl chloride to introduce a chloride at C5 followed by further iodination at C3 to give the Suzuki–Miyaura coupling precursor (Scheme 5). The bisarylation proceeded in lower yield than previous mono arylations to give the desired product in 45% yield. As with the fully substituted pyrrole **18**, characterisation of the product was difficult due to the lack of diagnostic resonances in the ^{1}H NMR spectrum. However, **24** was a crystalline product and an X-ray crystal structure was obtained to confirm the introduction of the two aryl groups and also the confirmation of the chlorine atom at C5 (Fig. 1). The reduction of the remaining halogen proceeded smoothly to give the pyrrole **25** which is the dimethyl ether of lamellarin Q. The spectral data



Scheme 5 *Reaction conditions:* i) SO_2Cl_2, $CHCl_3$, 84%; ii) I_2, AgTFA, $CHCl_3$ 89%; iii) 4-methoxyphenyl boronic acid pinacol ester, $Pd(OAc)_2$, $K_2CO_{3(aq)}$, acetone, reflux 45%; iv) 10% Pd/C, CH_3OH, H_2 (40 psi), 52%; v) Ref. 14.

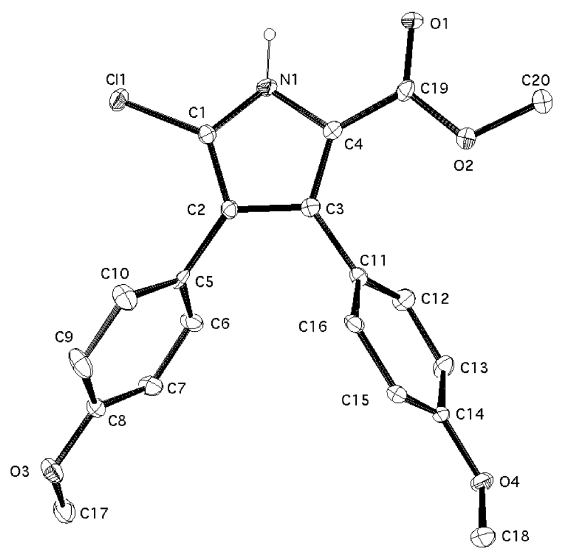


Fig. 1 An ORTEP diagram of compound **24** (with 20% probability ellipsoids) derived from X-ray crystallographic data. The asymmetric unit contains three molecules, which differ slightly with respect to the conformations of the aryl substituents. Only one molecule is shown for clarity.

was consistent with that reported in the literature and as **25** has previously been transformed to lukinol A in three steps[14] this completes a formal synthesis of this natural product.

Conclusions

In conclusion, we have shown that ligandless catalysis is effective for the Suzuki–Miyaura reaction of electron rich pyrrole derivatives without activation by acylation on nitrogen and that chlorine can act as a removable blocking group to allow regioselective iodination and subsequent arylation to yield the C3, C4 or C5 aryl pyrrole derivatives. This methodology was then exploited to complete a formal synthesis of the natural product lukinol A in a few short steps. We are currently investigating the generality of this method for the regioselective synthesis of pyrroles of greater structural diversity.

Experimental

^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz respectively on a Varian Mercury 2000 spectrometer. Spectra were run in $CDCl_3$ unless otherwise stated. Chemical shifts are measured in ppm and referenced internally to residual $CHCl_3$ for ^{1}H NMR (δ 7.26) and the central peak of $CDCl_3$ for ^{13}C NMR (δ 77.04). Infrared spectra were recorded on a Perkin Elmer FT-IR Paragon 1000 spectrometer as thin films on NaCl plates unless otherwise stated. High resolution and low resolution mass spectrometry were performed on a Kratos Concept ISQ mass instrument. Analytical analyses were performed by The Central Sciences Laboratory at the University of Tasmania. Melting points were carried out on a Yanagomoto Seisakusho micro melting point apparatus and are uncorrected. Flash chromatography was performed according to the method of Still and co-workers using silica gel 60 (32–63 μm).[15] Palladium acetate was obtained from precious metals online and used as received. Acetone was from AJAX fine chemicals, AR grade and used as received. Boronic acids and boronic esters were sourced from Boron Molecular and used as received. Solutions for Suzuki reactions were subjected to three freeze-thaw cycles to remove dissolved oxygen. All other solvents and reagents were available from Aldrich, AJAX or BDH chemicals and used as supplied or purified by standard laboratory methods as required.[16] Organic extracts were dried with anhydrous magnesium sulfate unless otherwise stated.

Methyl 4-phenyl-1*H*-pyrrole-2-carboxylate (11)

Palladium acetate (0.020 g, 0.09 mmol) was added to a mixture of iodopyrrole methyl ester **10** (1.27 g, 5.07 mmol) in acetone (10 mL) and phenyl boronic acid (0.68 g, 5.6 mmol) in 2 M potassium carbonate (5 mL) under a nitrogen atmosphere and was refluxed for 3 h. A further portion of boronic acid (0.15 g, 1.27 mmol) and palladium acetate (0.020 g, 0.09 mmol) was added to the mixture and refluxed for a further 3 h. The reaction was cooled to room temperature, water added (10 mL) and the solution extracted with ethyl acetate (2 × 10 mL). The organic layer was dried and evaporated to give the crude product, which was purified by flash chromatography (elution with 25% ethyl acetate–hexanes). The *title product* was recrystallised from dichloromethane–hexanes

(1 : 4) to give colourless crystals in 83% yield: mp 176–180 °C; (Found: $M^{+\bullet}$, 201.0789. $C_{12}H_{11}NO_2$ requires $M^{+\bullet}$, 201.0789); ν_{max} (cm^{-1}) 3416, 1677; δ_H 3.89 (3H, s), 7.22 (3H, m), 7.36 (2H, m), 7.52 (2H, m), 9.20 (1H, br s); δ_C 51.6,106.7, 119.5, 120.7, 122.6, 127.5, 129.3, 135.6, 136.4, 159.9, *m/z* 201 (50%, M^+), 169 (100), 141 (50), 140 (40), 115 (30), 114 (30).

Methyl 4-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (12)

The *title compound* was obtained in 52% yield as a semi-solid by the above procedure except phenyl boronic acid was substituted with 4-methoxyphenylboronic acid pinacol ester. (Found: $M^{+\bullet}$, 231.0898. $C_{12}H_{11}NO_2$ requires $M^{+\bullet}$, 231.0895); ν_{max} (cm^{-1}) 3836, 1680; δ_H 3.82 (3H, s), 3.88 (3H, s), 6.90 (2H, m), 6.35 (1H, dd, *J* 3.0, 1.9 Hz), 7.15 (1H, dd, *J* 3.0, 1.5 Hz), 7.43, (2H, m), 9.15 (1H, br s); δ_C 51.5, 55.3, 112.3, 114.2, 118.8, 126.4, 128.5, 129.4, 135.6, 159.2, 160.9; *m/z* 231 (50%, M^+), 199 (100), 184 (50), 156 (25), 128 (20), 101 (15).

Methyl 4-chloro-5-iodo-1*H*-pyrrole-2-carboxylate (13)

Iodine (0.88 g, 6.9 mmol) was added into a mixture of methyl 4-chloropyrrole-2-carboxylate[5] (1.0 g, 6.3 mmol) and silver trifluoroacetate (1.4 g, 6.3 mmol) in chloroform (10 mL) at 0 °C (ice-bath) under a nitrogen atmosphere. The reaction mixture was removed from the ice-bath and stirred at room temperature for 7 h with the exclusion of light. The reaction was quenched with aqueous sodium sulfite and brine solution before extraction with ethyl acetate (3 × 20 mL). The combined organic extracts were dried, filtered through a thin layer of silica gel and evaporated to give the *title compound* (1.6 g, 86%) as a white solid that was used in the next step without further purification. (Found: $M^{+\bullet}$, 284.9053. $C_6H_5{}^{35}ClINO_2$ requires $M^{+\bullet}$, 284.9583); ν_{max} (cm^{-1}) 3250, 1692; δ_H 3.91 (3H, s), 6.80 (1H, d, *J* 2.7 Hz), 10.19 (1H, br s); δ_C 52.1, 109.4, 114.4, 121.8, 122.4, 159.3; *m/z* 287 (30%, M^+, $C_6H_5NO_2{}^{37}ClI$) 285 (80%, M^+, $C_6H_5{}^{35}ClINO_2$) 255 (40), 253 (90), 181 (35), 169 (30), 131 (40), 119 (35), 69 (100).

Methyl 4-chloro-5-phenyl-1*H*-pyrrole-2-carboxylate (14)

Palladium acetate (0.020 g, 0.09 mmol) was added to a mixture of chloro iodo pyrrole **13** (0.081 g, 0.28 mmol) in acetone (10 mL) and phenyl boronic acid (0.038 g, 0.31 mmol) in 2 M aqueous potassium carbonate (5 mL) under a nitrogen atmosphere and was refluxed for 3 h. A further portion of boronic acid (0.090 g, 0.073 mmol) and palladium acetate (0.020 g, 0.09 mmol) was added to the mixture and refluxed for a further 3 h. The reaction was cooled to room temperature, water added (10 mL) and the solution extracted with ethyl acetate (2 × 10 mL). The organic layer was dried and evaporated to give the crude product which was purified by flash chromatography (20% ethyl acetate–hexanes) to give the *title compound* as an oil in 75% yield: δ_H 3.84 (3H, s), 6.91 (1H, d, *J* 3 Hz), 7.40 (3H, m), 7.72 (2H, m), 9.82 (1H, br s); δ_C 51.5, 110.7, 114.5, 121.9, 123.7, 127.7, 128.3, 128.4, 133.6, 159.4.

Methyl 5-phenyl-1*H*-pyrrole-2-carboxylate (15)

A solution of methyl 4-chloro-5-phenyl-1*H*-pyrrole-2-carboxylate **14** (0.040 g, 0.17 mmol) in methanol (5 mL) containing 10% w/w palladium on carbon (30 mg) was hydrogenated under an atmosphere of hydrogen at 40 psi in a Parr shaker for 6 h. The reaction mixture was filtered through a plug of Celite, the solvent removed and the product purified by flash chromatography (20% ethyl acetate–hexanes). The *title compound* was obtained as a semi-solid in 82% yield: (Found: $M^{+\bullet}$, 201.0789. $C_{12}H_{11}NO_2$ requires $M^{+\bullet}$, 201.0789); ν_{max} (cm^{-1}) 3319, 1686; δ_H 3.88 (3H, s), 6.54 (1H, dd, *J* 3.9, 2.7 Hz), 6.96 (1H, dd, *J* 3.9, 2.4 Hz), 7.31 (1H, m), 7.41 (2H, m), 7.60 (2H, m), 9.52 (1H, br s); δ_C 51.8, 108.3, 115.3, 117.1, 128.0, 129.2, 131.5, 134.5, 161.9; *m/z* 201 (90%, M^+), 169 (100), 141 (70), 140 (45), 115 (45), 114 (30).

Methyl 4,5-dichloro-1*H*-pyrrole-2-carboxylate

Sulfuryl chloride (1.08 g, 7.9 mmol) was added into a solution of methyl pyrrole-2-carboxylate **16** (0.50 g. 4.0 mmol) in chloroform (10 mL) and the reaction mixture stirred for 4 h with the exclusion of light. The reaction was quenched by the addition of 2 M sodium bicarbonate and the solution extracted with dichloromethane (2 × 10 mL). The organic extracts were combined, dried, and concentrated under reduced pressure to give the crude product which was passed through a plug of silica gel eluting with dichloromethane. The product was obtained as an off-white solid in 91% yield which was used in the next step without further purification: δ_H 3.87 (3H, s), 6.81 (1H, d, *J* 3.0 Hz), 9.51 (1H, br s); δ_C 95.4, 109.4, 116.4, 124.4, 131.6, 171.8.

Methyl 4,5-dichloro-3-iodo-1*H*-pyrrole-2-carboxylate (17)

Iodine (1.1 g, 4.3 mmol) was added to a mixture of methyl 4,5-dichloropyrrole-2-carboxylate (0.76 g, 3.9 mmol) and silver trifluoroacetate (0.86 g, 4.3 mmol) in chloroform (10 mL) at 0 °C (ice-bath) under a nitrogen atmosphere. The reaction was stirred at room temperature for 7 h with the exclusion of light before the addition of aqueous sodium sulfite and brine. The reaction mixture was extracted with ethyl acetate (3 × 20 mL), and the combined organic extracts dried and filtered through a thin layer of silica gel. The solution was concentrated under reduced pressure to give the *title product* as a yellow solid (0.97 g, 77% yield): mp = 188–195 °C; (Found: $M^{+\bullet}$, 318.8661. $C_6H_4{}^{35}Cl_2INO_2$ requires $M^{+\bullet}$, 318.8663); ν_{max} (cm^{-1}) 3199, 1689; δ_H 3.92 (3H, s), 9.72 (1H, br s); δ_C 52.3, 72.9, 76.6, 122.0, 123.4, 159.3; *m/z* 321 (45%, M^+, $C_6H_4{}^{35}Cl^{37}ClINO_2$) 319 (60%, M^+, $C_6H_4{}^{35}Cl_2INO_2$), 289 (60), 287 (100), 277 (20), 275 (20), 235 (15), 233 (20).

Methyl 4,5-dichloro-3-phenyl-1*H*-pyrrole-2-carboxylate (18)

Palladium acetate (0.020 mg, 0.09 mmol) was added to a mixture of chloro iodo pyrrole **17** (0.062 mg, 0.82 mmol) in acetone (10 mL) and phenyl boronic acid (110 mg, 0.90 mmol) in 2 M aqueous potassium carbonate (5 mL) under a nitrogen atmosphere and refluxed for 3 h. A further portion of boronic acid (0.100 mg, 0.82 mmol) and palladium acetate (0.020 g, 0.09 mmol) was added to the mixture and reflux continued for a further 3 h. The reaction was cooled to room temperature, water added (10 mL) and the mixture extracted with ethyl acetate (2 × 10 mL). The organic layer was dried and evaporated to give the crude product which was purified by flash chromatography (10% ethyl acetate–hexanes). The *title compound* was obtained as colourless crystals

by recrystallisation from chloroform–hexane (94% yield): mp 129–131 °C; ν_{max}(cm^{-1}) 3235, 1677; δ_H 3.73 (3H, s), 7.41 (5H, m), 10.20 (1H, br s); δ_c 50.9, 106.2, 116.8, 124.4, 126.9, 128.7, 129.4, 131.5, 136.4, 159.7; *m/z* 272 (5%, M$^+$, $C_{12}H_9{}^{37}Cl_2NO_2$), 271 (50%, M$^+$, $C_{12}H_9{}^{35}Cl^{37}ClNO_2$), 269 (75%, M$^+$, $C_{12}H_9{}^{35}Cl_2NO_2$), 239 (75), 237 (100), 176 (30), 174 (75).

Methyl 3-phenyl-1*H*-pyrrole-2-carboxylate (19)

A solution of dichloro pyrrole **18** (0.083 g, 0.307 mmol) in methanol (5 mL) containing 10% w/w palladium on carbon (0.030 g) was hydrogenated under an atmosphere of hydrogen at 40 psi in a Parr shaker for 6 h. The reaction mixture was then filtered through a plug of Celite, the solvent removed and the product purified by flash chromatography (30% ethyl acetate–hexanes). The *title compound* was obtained in 87% yield as a yellow oil: (Found: M$^{+\bullet}$, 201.0792. $C_{12}H_{11}NO_2$ requires M$^{+\bullet}$, 201.0789); ν_{max}(cm^{-1}) 3321, 1685; δ_H 3.78 (3H, s), 6.36 (1H, at, *J* 3.0), 6.96 (1H, at, *J* 3.0), 7.35 (3H, m), 7.56 (2H, m), 9.25 (1H, br s); δ_C 51.6, 112.8, 118.0, 122.2, 127.2, 127.9, 129.6, 132.5, 135.3, 161.9.; *m/z* 201 (80%, M$^+$), 169 (100), 141 (35), 140 (50), 115 (40), 114 (25).

Methyl 5-chloro-4-iodo-1*H*-pyrrole-2-carboxylate (22)

Sulfuryl chloride (0.59 g, 4.4 mmol) was added to a solution of methyl 4-iodo-1*H*-pyrrole-2-carboxylate (1.00 g. 4.3 mmol) in chloroform (15 mL) and the mixture stirred for 5 h with the exclusion of light. The reaction was quenched by the addition of 2 M sodium bicarbonate solution and extracted with dichloromethane (2 × 10 mL). The combined organic extracts were dried, and concentrated under reduced pressure to give the product as a white solid in 84% yield which was used in the next step without further purification: mp = 154–156 °C; (Found: M$^{+\bullet}$, 284.9055. $C_6H_5{}^{35}ClINO_2$ requires M$^{+\bullet}$, 284.9583); ν_{max} (cm^{-1}) 3222, 1700; δ_H 3.86 (3H, s), 6.94 (1H, d, *J* 2.7 Hz), 9.50 (1H, s); *m/z* 287 (45%, M$^+$, $C_6H_5{}^{37}ClINO_2$) 285 (70%, M$^+$, $C_6H_5{}^{35}ClINO_2$) 255 (30), 253 (100), 266 (10), 161 (15), 127 (20), 98 (30).

Methyl 5-chloro-3,4-diiodo-1*H*-pyrrole-2-carboxylate (23)

Iodine (322 mg, 1.27 mmol) was added to a mixture of pyrrole **22** (302 mg, 1.06 mmol) and silver trifluoroacetate (257 mg, 1.16 mmol) in chloroform (15 mL) at 0 °C (ice-bath) under a nitrogen atmosphere. The reaction mixture was then stirred at room temperature for 16 h with the exclusion of light before the addition of aqueous sodium sulfite and brine solution. The reaction mixture was extracted with ethyl acetate (3 × 20 mL), and the combined organic extracts dried and filtered through a thin layer of silica gel. The solution was concentrated under reduced pressure to give the *title product* as a yellow solid in 89% yield: mp = 200–204 °C; (Found: M$^{+\bullet}$, 410.8022. $C_6H_4{}^{35}ClI_2NO_2$ requires M$^{+\bullet}$, 410.8020); ν_{max} (cm^{-1}) 3204, 1678; δ_H 3.91 (3H, s), 9.63 (1H, s), *m/z* 413 (30%, M$^+$, $C_6H_4NO_2{}^{37}ClI_2$) 411 (85%, M$^+$, $C_6H_4{}^{35}ClI_2NO_2$) 381 (35), 379 (100), 345 (15), 319 (15), 287 (30), 253 (20), 224 (25), 163 (10), 127 (10).

Methyl 5-chloro-3,4-bis(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (24)

Palladium acetate (20 mg, 0.09 mmol) was added to a mixture of chloro iodo pyrrole **23** (254 mg, 0.62 mmol) in acetone (10 mL) and 4-methoxyphenylboronic acid pinacol ester (318 mg, 1.36 mmol) in 2 M aqueous potassium carbonate (5 mL) under a nitrogen atmosphere and refluxed for 3 h. A further portion of boronic ester (135 mg, 0.62 mmol) and palladium acetate (20 mg, 0.09 mmol) was added to the mixture and refluxed for further 3 h. The reaction was cooled to room temperature, water added (10 mL) and the mixture extracted with ethyl acetate (2 × 10 mL). The organic layer was dried and evaporated to give the crude product which was purified by flash chromatography (20% ethyl acetate–hexanes). The *title compound* was obtained as yellow crystals from dichloromethane–hexane (1 : 4) in 45% yield. (Found: M$^{+\bullet}$, 371.0924. $C_{20}H_{18}ClNO_4$ requires M$^{+\bullet}$, 371.814); mp 168–171 °C; δ_H 3.74 (3H, s), 3.77 (3H, s), 3.79 (3H, s), 6.78 (4H, m), 7.04 (2H, m), 7.11 (2H, m), 9.71 (1H, s); *m/z* 373 (10%, M$^+$, $C_{20}H_{18}{}^{37}ClNO_4$) 371 (30%, M$^+$, $C_{20}H_{18}{}^{35}ClNO_4$), 341 (30), 339 (100), 324 (10), 276 (50), 261 (15), 233 (10), 190 (15).

Methyl 3,4-bis(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (25)

A solution of methyl 5-chloro-3,4-bis(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate **24** (0.010 g, 0.027 mmol) in methanol (5 mL) containing 10% w/w palladium on carbon (0.030 g) was hydrogenated under an atmosphere of hydrogen at 40 psi in a Parr shaker for 5 h. The reaction mixture was then filtered through a plug of Celite, the solvent removed and the product purified by passing through a plug of silica gel with methanol to give the product as a yellow oil in 52% yield: δ_H 3.73 (3H, s), 3.76 (3H, s), 3.82 (3H, s), 6.75 (2H, m), 6.84 (2H, m), 7.03 (3H, m), 7.19 (2H, m), 9.23 (1H, s); δ_C 51.6, 55.4, 55.5, 113.4, 113.9, 120.3, 129.7, 132.1, 141.2, 216.9.

X-Ray crystallography

Crystal data for **24**: $C_{20}H_{18}ClNO_4$ M = 371.80, triclinic, a = 10.7431(8) Å, b = 13.5397(10) Å, c = 19.3750(15) Å, α = 101.138(2)°, β = 99.04(1)°, γ = 96.572(2)°, V = 2713.5(4) Å^3, T = 130(2) K, space group P–1, Z = 6, D_{calc} = 1.365 mg m^{-3}, μ(Cu-Kα) = 0.236 mm^{-1}, 14434 reflections measured ($2\theta_{max}$ = 50°), 9442 unique (R_{int} = 0.0623), 3608 having $I > 2\sigma(I)$. Full matrix least squares on F^2, R_1 = 0.0510, wR_2 = 0.0793 (all data), max. and min. difference peak and hole 0.215 and −0.266 resp. CCDC reference number 604156. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b604692d

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