An approach to 2,3-dihydropyrroles and β-iodopyrroles based on 5-*endo-dig* cyclisations

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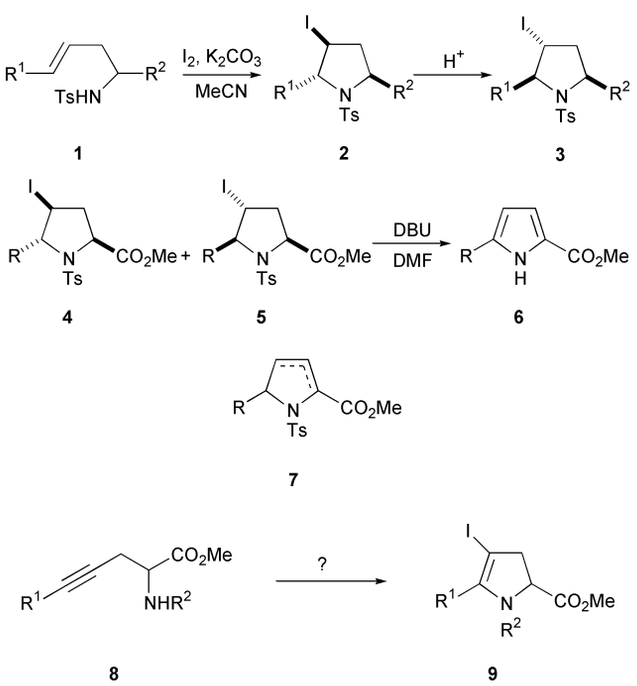
A representative series of homopropargylic sulfonamides **19** and **22b** have been found to undergo smooth 5-*endo-dig* cyclisation upon exposure to excess iodine in acetonitrile containing potassium carbonate. The resulting 4-iodo-2,3-dihydropyrroles **23** readily react with two equivalents of DBU in DMF at 20 °C to give the corresponding β-iodopyrroles **24** and **26** in excellent yields by the elimination of toluene-*p*-sulfinic acid. Use of less than two equivalents of base results in some loss of iodine. The iodo-2,3-dihydropyrroles **23** can be used in palladium-catalysed coupling reactions as shown by the efficient formation of the Sonogashira product **29** under mild conditions.

Introduction

We have recently reported that our stereoselective approaches to both *trans*-2,5- and *cis*-2,5-disubstituted-3-iodopyrrolidines (**2** and **3**) using 5-*endo-trig* cyclisations of homoallylic **1**[1] can be successfully applied to the elaboration of substituted proline derivatives **4** and **5**.[2] While investigating the chemistry of these, we found conditions for effecting the elimination of the elements of both hydrogen iodide and toluene-*p*-sulfinic acid, leading to high yields of the 5-substituted pyrrole-2-carboxylates **6**.[2] That base-induced eliminations were successful was not particularly surprising, especially as many attempts to displace the β-iodine atom in the electron-poor pyrrolidines **4** and **5** using a variety of nucleophiles by a projected S_N2 mechanism led instead to elimination products, consisting of mixtures of 2,3- and 2,5-dihydropyrroles **7**.[2] Further, while this approach overall is relatively efficient, there are many other seemingly as effective routes to 5-substituted pyrrole-2-carboxylates **6**.[3] We also reasoned that loss of the potentially useful iodide atom was somewhat wasteful. All of these considerations led us to speculate that related 5-*endo-dig* cyclisations of the corresponding homopropargylic† sulfonamides **8** could lead to synthetically more useful products **9**, given the obvious provisos that such cyclisations could be achieved and also that the dihydropyrroles **9** were stable. We were encouraged to attempt such a sequence as, in complete contrast to 5-*endo-trig* processes, 5-*endo-dig* cyclisations are favoured according to Baldwin's rules.[4] Despite this, such cyclisations have not enjoyed a prominence in the literature which this fact would suggest they deserve, as has recently been highlighted by Carreira and co-workers.[5] We have gone some way to addressing this apparent deficiency in synthetic methodology with the finding that alk-3-yne-1,2-diols **10** undergo clean electrophile-induced 5-*endo-dig* cyclisations to give highly substituted furans **12**; the presumed intermediate hydroxydihydrofurans **11** have yet to be observed, suggesting that dehydration to the heteroaromatic nuclei **12** is faster than cyclisation, at least under the conditions used.[6] However, despite the favoured nature of 5-*endo-dig* processes, recent attempts to effect iodocyclisations of homopropargylic alcohols **13** have yet to be productive in this sense, leading not to the anticipated dihydrofurans **14** but rather to the diiodides **15**.[7] It was therefore very unclear at the outset whether homopropargylic sulfonamides **8** would indeed undergo the desired cyclisations. Herein, we report in full that these are indeed viable processes which provide a rapid approach to both 4-iodo-2,3-dihydropyrroles and 4-iodopyrrole-2-carboxylates.[8]



Results and discussion

In view of our previous findings with regard to the preparation of the iodopyrrolidines **2** and **3**,[1,2] we chose to once again attenuate the reactivity of the amine group by employing the

† The IUPAC name for homopropargyl is but-3-ynyl.

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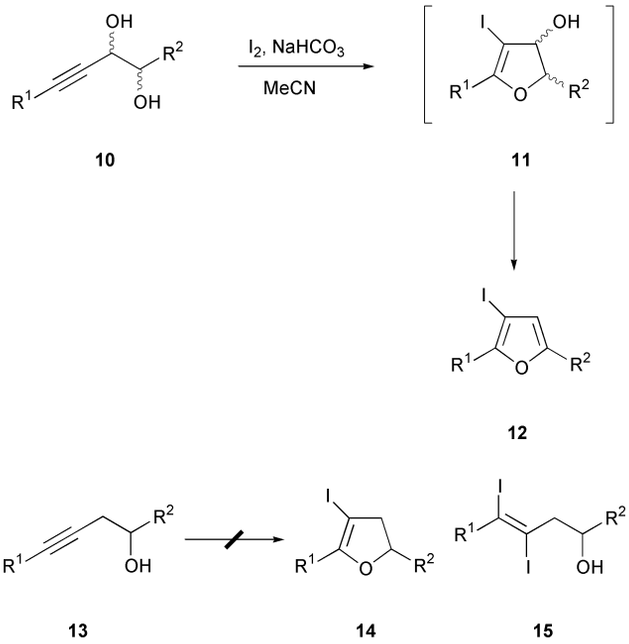
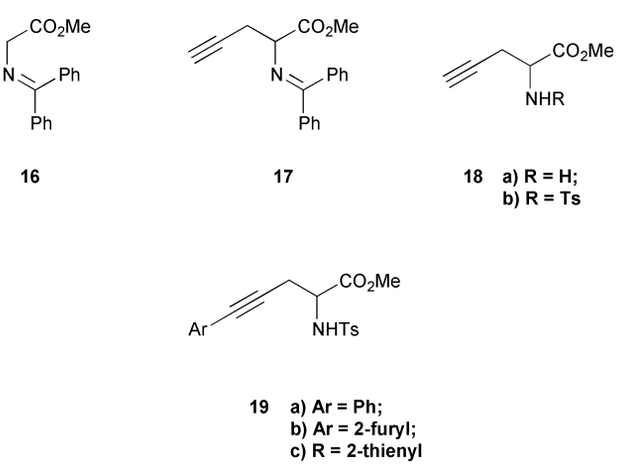
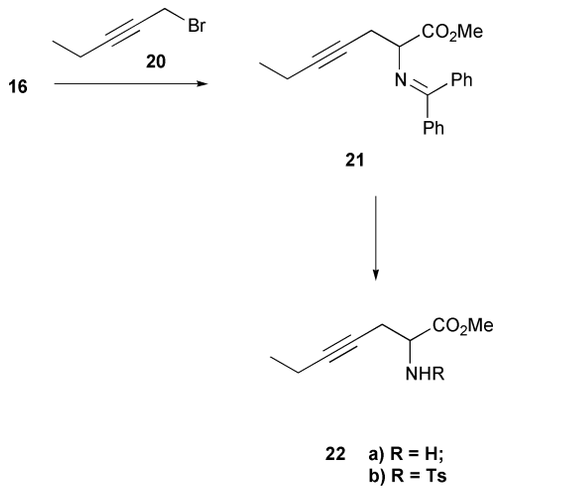


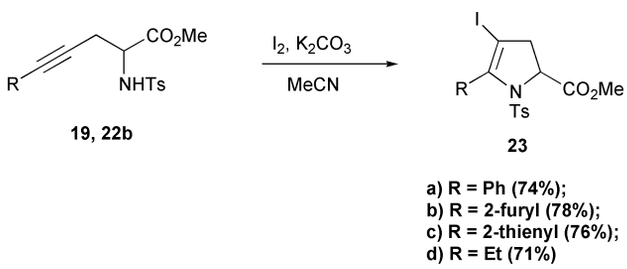
corresponding sulfonamide functions. A particularly convenient way to prepare the necessary model precursors, when having an aromatic substituent at the alkyne terminus, turned out to feature phase transfer-catalysed alkylation[9] of glycinate imine **16** with propargyl bromide[10] to give the propargylglycinate derivative **17** followed by protecting group exchange *via* the free amines **18a** and the *N*-tosylglycinate **18b**. Finally, Sonogashira coupling[11] with an iodo(hetero)arene, gave the series of precursor homopropargylic sulfonamides **19** in respectable overall yields. Attempts to carry out Sonogashira couplings with the glycinate imine **17** were not successful. An alkyl-substituted substrate **22b** was prepared by *C*-alkylation of the enolate of glycinate imine **16** generated using LDA,[10] with the propargylic bromide **20**, leading to homologue **21** followed by a similar protecting group exchange *via* amine **22a**.



We were pleased to find that exposure of these four examples of homopropargylic sulfonamides (**19** and **22b**) to three equivalents each of iodine and anhydrous potassium carbonate in dry acetonitrile resulted in relatively slow but clean 5-*endo*-*dig* cyclisation to give, after column chromatography and crystallization in the examples having (hetero)aryl substituents, the 4-iodo-2,3-dihydropyrroles **23a**–**d** in very respectable isolated yields, as shown. All such products turned out to be stable and amenable to full characterization, although the 5-ethyl derivative **23d** did begin to decompose if left at ambient temperature for extended periods. The products **23** displayed a characteristic ABX pattern for the 2-H and the 3-CH_2 spin system, with the

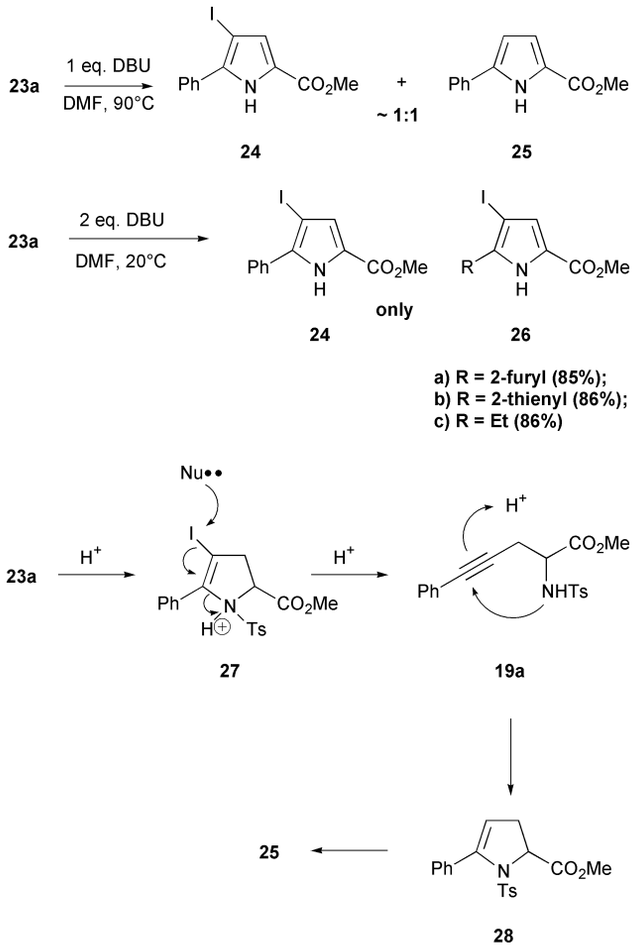


geminal β-protons resonating as double doublets between δ_H 2.5 and 3.0 while the 2-H resonances occurred around δ_H 4.6–5.0, also as double doublets. The ^{13}C data were also consistent with the structures **23**, especially the significant shielding of the quaternary carbon attached to iodine at the 4-position, which resonated around δ_C 74–79 ppm due to the heavy atom effect.[12] All other spectroscopic and analytical data were consistent with the proposed structures.

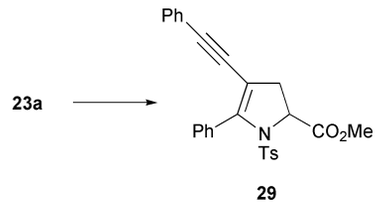


Clearly, the incorporation of the iodine atom at an sp^2 carbon centre opened up a number of additional synthetic opportunities not available to the related iodopyrrolidines (*e.g.* **4** and **5**). Firstly, we thought that elimination to the pyrrole oxidation level should be straightforward using a base to trigger the removal of the elements of toluene-*p*-sulfinic acid, one of the steps in the formation of pyrrolecarboxylates **6** from the iodopyrrolidines **4** and **5**. Now, of course, it was anticipated that the iodine would be retained. It therefore came as something of a surprise to find that treatment of the iodo-dihydropyrrole **23a** with one equivalent of 1,8-diazabicyclo[5.4.0]undecene (DBU) in hot *N*,*N*-dimethylformamide[2] led to an excellent recovery of pyrroles, but as an approximately 1 : 1 mixture of the anticipated iodopyrrole **24** and the deiodinated analogue **25**.[2] We reasoned that, somehow, the other product of elimination, toluene-*p*-sulfinic acid, was responsible for this undesired side reaction and therefore carried out the reaction using two equivalents of DBU in the anticipation of more rapidly neutralizing the acid. This, coupled with an optimization study, which showed elimination to occur smoothly at ambient temperature, led to the formation of only the desired iodopyrroles **24** and **26a**–**c** in excellent isolated yields as shown. By acting as a proton source, the toluene-*p*-sulfinic acid could cause cycloreversion by *N*-protonation to give salt **27** and iodine loss, in much the same way as we explained the isomerization of the 2,5-*trans*-pyrrolidines **2** to the corresponding 2,5-*cis*-isomers **3** when cyclisations of the precursors **1** were carried out under acidic conditions.[1,2] Subsequently, the regenerated homopropargylic sulfonamide **19a** could undergo acid-induced cyclisation to give the 2,3-dihydropyrrole **28**; elimination would then give the observed 5-phenylpyrrole-2-carboxylate **25**. In

support of this, exposure of homopropargylic sulfonamides **19** to various proton sources, including toluene-*p*-sulfinic acid, did indeed induce an overall 5-*endo*-*dig* cyclisation although, as yet, not as cleanly as in the present case.[13] In any event, use of an additional equivalent of DBU which presumably rapidly suppresses the amount of free sulfinic acid present during the elimination, resulted in excellent yields of the iodopyrroles **24** and **26a**–**c**.



The incorporation of an iodine atom at an unsaturated carbon suggests a number of strategies for further elaborations, most notably using palladium-catalysed coupling reactions or radical-based methods.[14] In the area of palladium-induced couplings, 3,4-dibromopyrroles undergo smooth Kumada-type displacements with Grignard reagents to give 3,4-dialkyl (or aryl) pyrroles.[15] The same dibromopyrroles also undergo efficient Suzuki couplings, at least with phenylboronic acid,[16] whilst a seemingly less effective alternative features conversion of a β-iodopyrrole into the corresponding boronic acid.[17] Perhaps surprisingly, it was only very recently that Wang and Scott reported that β-iodopyrroles also participate in Stille couplings, although the corresponding chloro or bromo derivatives give poor yields or fail altogether to undergo couplings with tributylstannyl species.[18] Alternatively, β-iodopyrroles can be converted into the corresponding β-stannyl derivatives which can then be coupled with aryl bromides.[17,19] In the present project, we therefore chose only to attempt to establish that the 4-iodo-2,3-dihydropyrrole functionality was compatible with a palladium-catalysed coupling reaction. The relatively electron deficient nature of the alkene bond suggested that such reactions should be relatively straightforward and this was indeed the case. When the dihydropyrrole **23a** was exposed to Sonogashira coupling conditions[11] with phenylacetylene, an excellent yield of the acetylene homologue **29** was isolated after only two hours at ambient temperature. The corresponding pyrrole which would be formed by base-induced elimination of toluenesulfinic acid was not detected. It therefore seems likely that many other Pd-catalysed processes will be applicable to homologation of both the initial dihydropyrroles **23** and the iodopyrroles **24** and **26**.



Conclusions

In conclusion, we have defined a new approach to both 4-iodo-2,3-dihydropyrroles[20] and β-iodopyrroles[21] which is relatively brief and straightforward, using a novel version of the 5-*endo*-*dig* cyclisation. While all the examples reported herein are substituted with an ester group, this was mostly due to synthetic expediency during this model study; its relative remoteness from the points of reaction during cyclisation suggests that many other homopropargylic sulfonamides should also undergo such cyclisations. Our original aim of retaining the iodine atom whilst forming a pyrrole nucleus has therefore been achieved with the bonus that the intermediate 4-iodo-2,3-dihydropyrroles can be isolated and that both types of compound seemingly have considerable potential for further elaboration, especially using palladium-catalysed methods.

Experimental

For general details, see ref. 2.

Methyl 2-[(diphenylmethylene)amino]pent-4-ynoate 17

Methyl 2-[(diphenylmethylene)amino]ethanoate **16** (10.0 g, 39.5 mmol, 1.0 equiv.), potassium carbonate (5.5 g, 39.5 mmol, 1.0 equiv.) and tetrabutylammonium iodide (1.5 g, 3.95 mmol, 0.1 equiv.) were stirred in dry acetonitrile (100 ml) at room temperature.[9] Propargyl bromide (4.70 g, 39.5 mmol, 1.0 equiv.) was then added and the resulting mixture was heated under reflux for 6.5 h. The reaction was then allowed to cool, filtered and concentrated under reduced pressure to give a crude residue which was chromatographed (6 : 1 hexane–ethyl acetate) to give the *imine* **17** (8.0 g, 70%) as a colourless solid, mp 51–52 °C; ν_{max}/cm^{-1} 3305 (m), 3059 (m), 2950 (m), 1745 (s), 1671 (s), 1451 (m), 1310 (m) and 1220 (m); δ_H 1.96 (1H, t, J = 2.6, 5-H), 2.80–2.94 (2H, m, 3-CH_2), 3.74 (3H, s, OMe), 4.33 (1H, dd, J = 8.1 and 5.2, 2-H) and 7.26–7.67 (10H, m, Ar-H); δ_C 23.5 (3-CH_2), 52.4 (OMe), 64.0 (2-CH), 70.3 (5-CH), 81.0 (4-C), 128.1, 128.2, 128.5, 128.8, 129.0, 130.6 (all Ar-CH), 136.0, 140.0 (both C), 170.0 (C=N) and 171.0 (C=O); *m*/*z* [EI] 292 (M + H$^+$, 21%), 252 (63), 232 (35), 192 (54), 165 (57), 126 (100), 82 (54) and 58 (63) [Found: M + H$^+$, 292.1338. $C_{19}H_{18}NO_2$ requires *M*, 292.1337].

Methyl 2-aminopent-4-ynoate 18a

The imine **17** (8.0 g, 27.5 mmol) was vigorously stirred in 2 M hydrochloric acid (95 ml) and diethyl ether (135 ml) until the hydrolysis was complete by TLC (approx. 1 h). The organic layer was then separated and discarded and the aqueous layer washed with ether (50 ml), then taken to pH 9 with solid sodium carbonate and extracted with ether (4 × 50 ml). The combined organic extracts were dried, filtered and concentrated under reduced pressure to yield the crude *amine* **18a** (1.9 g, 54%) which was used without further purification in the subsequent tosylation reaction and which showed ν_{max}/cm^{-1} [film] 3289 (s), 2955 (m), 2180 (w), 1748 (s), 1438 (m), 1208 (s), 1150 (m) and 1021 (m); δ_H 1.60–1.70 (2H, br s, NH_2), 2.06 (1H, t,

J = 2.6, 5-H), 2.57–2.68 (2H, m, 3-CH_2), 3.64 (1H, dd, J = 5.7 and 5.7, 2-H) and 3.75 (3H, s, OCH_3); δ_C 24.7 (3-CH_2), 52.3 (OMe), 53.0 (2-CH), 71.2 (5-CH), 79.4 (4-C) and 174.1 (C=O); *m/z* [EI] 163 (M^+, 0.01%), 151 (7), 128 (11), 104 (16), 88 (16) and 67 (100).

Methyl 2-(4-tolylsulfonylamino)pent-4-ynoate 18b

The propargylic amine **18a** (1.83 g, 14.4 mmol, 1.0 equiv.) was stirred in dry dichloromethane (37 ml) at room temperature. Tosyl chloride (3.02 g, 15.8 mmol, 1.1 equiv.) and a crystal of DMAP were then added, followed by the dropwise addition of triethylamine (2.42 ml, 17.3 mmol, 1.2 equiv.). The mixture was stirred overnight at room temperature and then 2 M hydrochloric acid (20 ml) was added and the organic phase separated. The aqueous phase was extracted with dichloromethane (2 × 20 ml) and the combined organic solutions were washed with brine (20 ml), dried, filtered and concentrated under reduced pressure to give the crude product as a brown oil. The oil was chromatographed (6 : 1 hexane–ethyl acetate) to give the *tosylamide* **18b** (2.80 g, 69%) as a colourless solid, mp 83 °C; ν_{max}/cm^{-1} 3304 (w), 3053 (m), 2184 (w), 1747 (m), 1599 (w), 1441 (w), 1422 (m), 1351 (m), 1286 (m), 1258 (s), 1221 (w), 1165 (s) and 1093 (w); δ_H, 2.02 (1H, t, J = 2.5, 5-H), 2.36 (3H, s, Ar-CH_3), 2.56–2.67 (2H, m, 3-CH_2), 3.55 (3H, s, OCH_3), 4.05 (1H, ddd, J = 9.0 and 4.7 and 4.7, 2-H), 5.35 (1H, d, J = 9.0, NH), 7.23 (2H, d, J = 8.2, 2 × Ar-H) and 7.68 (2H, d, J = 8.2, 2 × Ar-H); δ_C 21.5 (CH_3), 24.1 (3-CH_2), 52.9 (OCH_3), 53.9 (2-CH), 77.0 (5-CH), 72.3 (4-C), 127.2 (2 × CH), 129.7 (2 × CH), 136.4 (C), 143.0 (C) and 169.7 (C=O); *m/z* [EI] 282 (M + H^+, 20%), 264 (19), 242 (52), 222 (51), 155 (69), 91 (100) and 65 (74) [Found: M + H^+, 282.0800. $C_{13}H_{16}NO_4S$ requires *M*, 282.0808]; [Found: C, 55.70; H, 5.25; N, 5.03. $C_{13}H_{15}NO_4S$ requires C, 55.50; H, 5.38; N, 4.98%].

Sonogashira reactions: general procedure

The tosylamide **18b** (1 mmol, 1.0 equiv.) was stirred in degassed diethylamine (7 ml) with copper(I) iodide (0.2 mmol, 0.2 equiv.) and tetrakis(triphenylphosphine)palladium(0) (0.1 mmol, 0.1 equiv.). The aryl iodide (1 mmol, 1.0 equiv.) was then added and the reaction was stirred under nitrogen for approximately 3 h, until complete according to TLC. The reaction mixture was then concentrated, diluted with ether (10 ml), filtered through Celite and the filtrate concentrated to give a brown oil which was purified by column chromatography.

Methyl 5-phenyl-2-(4-tolylsulfonylamino)pent-4-ynoate 19a. The tosylamide **18b** (0.50 g, 1.78 mmol, 1.0 equiv.) was stirred in diethylamine (12.5 ml) with CuI (0.07 g, 0.36 mmol, 0.2 equiv.) and $Pd(PPh_3)_4$ (0.21 g, 0.18 mmol, 0.1 equiv.) and iodobenzene (0.2 ml, 1.78 mmol, 1.0 equiv.) was added. The crude product was chromatographed (3 : 1 hexane–ethyl acetate) to give the *acetylene* **19a** (0.37 g, 58%), mp 91 °C; ν_{max}/cm^{-1} 3045 (s), 1747 (s), 1599 (w), 1491 (w), 1443 (w), 1418 (w), 1350 (m) 1219 (w) and 1165 (s); δ_H 2.41 (3H, s, Ar-CH_3), 2.88 (1H, dd, J = 16.9 and 5.1, 3-H_a), 2.91 (1H, dd, J = 16.9 and 5.1, 3-H_b), 3.64 (3H, s, OCH_3), 4.20 (1H, ddd, J = 9.1, 5.1 and 5.1, 2-CH), 5.46 (1H, d, J = 9.1, NH), 7.28–7.38 (7H, m, Ar-H) and 7.62 (2H, d, J = 8.3, 2 × Ar-H); δ_C 21.6 (Ar-CH_3), 25.1 (3-CH_2), 52.9 (OCH_3), 54.4 (2-CH), 127.2 (3 × CH), 128.4 (2 × CH), 129.7 (2 × CH), 131.7 (2 × CH), 144.0, 152.5, 157.0 (all C) and 171.0 (C=O); *m/z* [EI] 357 (M^+, 21%), 242 (49), 186 (67), 155 (71), 115 (83) and 91 (100) [Found: M^+, 357.1035. $C_{19}H_{19}NO_4S$ requires *M*, 357.1035] [Found: C, 63.62; H, 5.17; N, 3.85. $C_{19}H_{19}NO_4S$ requires C, 63.85; H, 5.36 N, 3.92%].

Methyl 5-(2-furyl)-2-(4-tolylsulfonylamino)pent-4-ynoate 19b. The tosylamide **18b** (0.30 g, 1.07 mmol, 1.0 equiv.) was stirred in diethylamine (7.5 ml) with CuI (0.04 g, 0.21 mmol, 0.2 equiv.) and $Pd(PPh_3)_4$ (0.12 g, 0.11 mmol, 0.1 equiv.) and 2-iodofuran (0.21 g, 1.07 mmol, 1.0 equiv.) was added. The crude product was chromatographed (4 : 1 hexane–ethyl acetate) to give the *acetylene* **19b** (0.28 g, 76%), as a pale brown solid, mp 92–93 °C; ν_{max}/cm^{-1} 3062 (s), 1747 (m), 1430 (w), 1351 (m), 1306 (w), 1268 (m), 1214 (m), 1165 (s), 1119 (w) and 1093 (m); δ_H 2.42 (3H, s, Ar-CH_3), 2.89 (1H, dd, J = 17.0 and 5.1, 3-H_a), 2.94 (1H, dd, J = 17.0 and 5.1, 3-H_b), 3.64 (3H, s, OCH_3), 4.18 (1H, ddd, J = 8.8, 5.1 and 5.1, 2-H), 5.48 (1H, d, J = 8.8, NH), 6.36 (1H, dd, J = 3.3 and 1.9, 4′-H), 6.50 (1H, d, J = 3.3, 3′-H), 7.29 (2H, d, J = 8.2, 2 × Ar-H), 7.35 (1H, app br s, 5′-H) and 7.69 (2H, d, J = 8.2, 2 × Ar-H); δ_C 21.7 (Ar-CH_3), 25.1 (3-CH_2), 53.0 (OCH_3), 54.1 (2-CH), 75.4 (5(4)-C), 87.4 (4(5)-C), 110.8 (4′-CH), 115.2 (3′-CH), 127.2 (2 × CH), 129.7 (2 × CH), 137.1 (C), 140.0 (C), 143.4 (5′-CH), 144.0 (C) and 171.0 (C=O); *m/z* [EI] 347 (M^+, 4%), 288 (5), 242 (41), 176 (100), 155 (100), 105 (79), 91 (100), 77 (95) and 65 (76) [Found: M^+, 347.0828. $C_{17}H_{17}NO_5S$ requires *M*, 347.0828].

Methyl 5-(2-thienyl)-2-(4-tolylsulfonylamino)pent-4-ynoate 19c. The tosylamide **18b** (0.50 g, 1.78 mmol, 1.0 equiv.) was stirred in diethylamine (12.5 ml) with CuI (0.07 g, 0.36 mmol 0.2 equiv.) and $Pd(PPh_3)_4$ (0.21 g, 0.18 mmol, 0.1 equiv.), then 2-iodothiophene (0.37 g, 1.78 mmol, 1.0 equiv.) was added. The crude product was chromatographed (4 : 1 hexane–ethyl acetate) to give the *acetylene* **19c** (0.46 g, 71%) as a pale brown solid, mp 100–102 °C; ν_{max}/cm^{-1} 3056 (s), 2955 (w), 1747 (s), 1599 (w), 1437 (m), 1415 (w), 1350 (s), 1270 (m), 1262 (s), 1220 (m), 1118 (w) and 1093 (m); δ_H 2.42 (3H, s, Ar-CH_3), 2.89 (1H, dd, J = 17.0 and 4.8, 3-H_a), 2.93 (1H, dd, J = 17.0 and 5.4, 3-H_b), 3.64 (3H, s, OCH_3), 4.18 (1H, app br s, 2-H), 5.46 (1H, br s, NH), 6.95 (1H, dd, J = 5.1 and 3.6, 4′-H), 7.12 (1H, d, J = 3.6, 3′-H), 7.22 (1H, d, J = 5.1, 5′-H), 7.29 (2H, d, J = 8.2, 2 × Ar-H) and 7.76 (2H, d, J = 8.2, 2 × Ar-H); *m/z* [EI] 363 (M^+, 1%), 304 (2), 242 (21), 192 (76), 177 (21), 155 (100), 20.9 (88), 91 (100), 76.9 (41) and 64.8 (29) [Found: M^+, 363.0599. $C_{17}H_{17}NO_4S_2$ requires *M*, 363.0599] [Found: C, 56.39; H, 4.99; N, 4.01. $C_{17}H_{17}NO_4S_2$ requires C, 56.19; H, 4.72; N, 3.86%].

Methyl 2-[(diphenylmethylene)amino]hept-4-ynoate 21

Phosphorus tribromide (2.79 ml, 29.7 mmol, 1.0 equiv.) was added dropwise to a stirred, ice-cooled solution of pent-2-yn-1-ol (5.00 g, 59.4 mmol, 2.0 equiv.) and pyridine (0.53 ml) in ether (110 ml). After stirring overnight at room temperature, the reaction mixture was poured into ice–water (100 ml). The organic layer was separated and the aqueous layer was extracted with ether (3 × 50 ml). The combined organic solutions were dried, filtered and evaporated under reduced pressure to yield *1-bromopent-2-yne* **20** as a brown oil (5.50 g, 63%). The product was reacted immediately without further purification.

Methyl 2-[(diphenylmethylene)amino]ethanoate **16** (4.73 g, 18.7 mmol, 1.0 equiv.), potassium carbonate (2.58 g, 18.7 mmol, 1.0 equiv.) and tetrabutylammonium iodide (0.69 g, 1.87 mmol, 0.1 equiv.) were stirred in acetonitrile (50 ml) at room temperature. 1-Bromopent-2-yne **20** (18.7 mmol, 1.0 equiv.) was then added dropwise and the resulting mixture heated under reflux for 7 h. The mixture was allowed to cool, filtered and concentrated under reduced pressure to give a crude residue, which was then chromatographed (6 : 1 hexane–ethyl acetate) to give the *imine* **21** (2.60 g, 44%) as a pale yellow oil, ν_{max}/cm^{-1} [film] 3058 (w), 2950 (w), 1741 (s), 1660 (s), 1447 (m), 1318 (m) and 1277 (s); δ_H 0.97 (3H, t, J = 7.5, 7-CH_3), 2.03 (2H, q, J = 7.5, 6-CH_2), 2.61–2.78 (2H, m, 3-CH_2), 3.65 (3H, s, OCH_3), 4.20 (1H, dd, J = 8.4 and 5.1, 2-H) and 7.17–7.74 (10H, m, Ar-H); δ_C 12.4 (CH_2), 14.0 (CH_3), 23.7 (CH_2), 52.2 (OCH_3), 64.7 (2-H), 75.6 (4(5)-C), 83.6 (5(4)-C), 128.0, 128.2, 128.3, 128.7, 128.9, 130.3 (all Ar-H), 136.0 (C), 139.5 (C). 171.3 (C=N) and 171.4 (C=O); *m/z* [EI] 318 (M − H^+, 49%), 260 (61), 252 (83), 191 (50), 164 (100), 120 (82) and 90 (33) [Found: M − H^+, 318.1489. $C_{21}H_{20}NO_2$ requires *M*, 318.1493].

Methyl 2-aminohept-4-ynoate 22a

The imine **21** (2.60 g, 8.15 mmol) was vigorously stirred in 2 M hydrochloric acid (25 ml) and diethyl ether (40 ml) until the hydrolysis was complete by TLC (approx. 1 h). The organic layer was then separated and discarded and the aqueous layer washed with ether (10 ml), then taken to pH 9 with solid sodium carbonate and extracted with ether (4 × 10 ml). The combined organic extracts were then dried, filtered and concentrated under reduced pressure to yield the crude *amine* **22a** (0.64 g, 51%) which was used without further purification in the subsequent tosylation reaction and which showed ν_{max}/cm^{-1} [film] 3060 (m), 2975 (m), 1743 (s), 1660 (s), 1599 (m), 1447 (m), 1318 (s), 1278 (s) and 1216 (m); δ_H 1.04 (3H, t, J = 7.5, 7-CH_3), 1.62–1.69 (2H, br s, NH_2), 2.13–2.19 (2H, m, 6-CH_2), 2.50–2.54 (2H, m, 3-CH_2), 3.50–3.53 (1H, m, 2-H) and 3.69 (3H, s, OCH_3); δ_C 12.2 (CH_2), 14.0 (CH_3), 25.1 (CH_2), 52.0 (OCH_3), 53.4 (2-CH), 74.0 (4(5)-C), 84.8 (5(4)-C) and 174.0 (C=O).

Methyl 2-(4-tolylsulfonylamino)hept-4-ynoate 22b

The amine **22a** (0.50 g, 3.23 mmol, 1.0 equiv.) was stirred in dichloromethane (10 ml) at room temperature. Tosyl chloride (0.68 g, 3.55 mmol, 1.1 equiv.) and a crystal of DMAP were then added, followed by the dropwise addition of triethylamine (0.54 ml, 3.88 mmol, 1.2 equiv.). The resulting mixture was stirred overnight at room temperature, then 2 M hydrochloric acid (10 ml) was added and the organic phase separated. The aqueous phase was extracted with dichloromethane (2 × 10 ml) and the combined organic solutions washed with brine (10 ml), dried, filtered and concentrated under reduced pressure to give a brown oil. This was chromatographed (4 : 1 hexane–ethyl acetate) to give the *tosylamide* **22b** (0.72 g, 72%) as a pale oil, ν_{max}/cm^{-1} 3283 (m), 3061 (w), 1745 (s), 1436 (m), 1338 (s), 1219 (m), 1163 (s) and 1092 (s); δ_H 0.99 (3H, t, J = 7.5, 7-CH_3), 1.97–2.05 (2H, m, 6-CH_2), 2.61–2.66 (2H, m, 3-CH_2), 2.42 (3H, s, Ar-CH_3), 3.58 (3H, s, OCH_3), 4.07 (1H, ddd, J = 9.3, 5.0 and 5.0, 2-H), 5.48 (1H, d, J = 9.3, NH), 7.30 (2H, d, J = 8.2, 2 × Ar-H) and 7.75 (2H, d, J = 8.2, 2 × Ar-H); δ_C 12.2 (6-CH_2), 13.9 (7-CH_3), 21.5 (Ar-CH_3), 24.2 (3-CH_2), 52.6 (OCH_3), 54.4 (2-CH), 72.2 (5(4)-C), 85.9 (4(5)-C), 127.1 (2 × CH), 129.6 (2 × CH), 136.8 (C), 143.6 (C) and 170.3 (C=O); *m*/*z* [EI] 309 (M^+, 7%), 250 (32), 242 (67), 155 (99), 139 (36), 91 (100) and 65 (74) [Found: C, 58.06; H, 6.37; N, 4.37. $C_{15}H_{19}NO_4S$ requires C, 58.23; H, 6.19; N, 4.53%].

Iodocyclisation of homopropargylic sulfonamides: general procedure

The homopropargylic sulfonamide **19a**–**c** or **22b** (1 mmol, 1.0 equiv.) was stirred in dry acetonitrile (2 ml) with anhydrous potassium carbonate (3 mmol, 3 equiv.) at 0 °C. Iodine (3 mmol, 3 equiv.) in acetonitrile (0.6 ml) was added dropwise and the resulting mixture allowed to warm to room temperature overnight. The reaction was quenched with saturated aqueous sodium thiosulfate until the mixture was decolourised and the organic layer was separated. The aqueous layer was then extracted with dichloromethane (2 × 5 ml) and the organic solutions were combined, dried and concentrated under reduced pressure. The crude product was then purified by column chromatography.

Methyl 4-iodo-5-phenyl-1-(4-tolylsulfonyl)-2,3-dihydropyrrole-2-carboxylate 23a. The tosylamide **19a** (0.25 g, 0.70 mmol, 1.0 equiv.) was cyclised according to the general procedure with potassium carbonate (0.29 g, 2.1 mmol, 3.0 equiv.) and iodine (0.54 g, 2.1 mmol, 3.0 equiv.). The crude residue was chromatographed (6 : 1 hexane–ethyl acetate) to give the *dihydropyrrole* **23a** (0.25 g, 74%) as a pale yellow solid, mp 130–133 °C; ν_{max}/cm^{-1} [$CHCl_3$] 3058 (m), 2999 (m), 1740 (s), 1650 (s), 1598 (w), 1443 (m), 1363 (s), 1282 (s), 1245 (m), 1212 (m), 1171 (s), 1091 (m) and 1028 (m); δ_H 2.44 (3H, s, Ar-CH_3), 2.87 (1H, dd, J = 16.7 and 3.6, 3-H_a), 2.94 (1H, dd, J = 16.7 and 9.7, 3-H_b), 3.87 (3H, s, OMe), 4.99 (1H, dd, J = 9.7 and 3.6, 2-H) and 7.23–7.50 (9H, m, Ar-H); δ_C 21.7 (Ar-CH_3), 43.3 (3-CH_2), 53.1 (OCH_3), 62.0 (2-CH), 73.0 (4-C), 127.7, 127.2, 129.2, 129.5, 129.9 (all Ar-CH), 132.0, 134.6, 144.3, 144.4 (all C), and 171.7 (C=O); *m*/*z* [EI] 483 (M^+, 92%), 424 (17), 197 (16), 201 (100), 169 (52), 142 (61), 115 (80), 91 (82) and 65 (60) [Found: M^+, 483.0001. $C_{19}H_{18}INO_4S$ requires *M*, 483.0003].

Methyl 5-(2-furyl)-4-iodo-1-(4-tolylsulfonyl)-2,3-dihydropyrrole-2-carboxylate 23b. The tosylamide **19b** (70 mg, 0.20 mmol) was cyclised according to the general procedure with potassium carbonate (84 mg, 0.61 mmol, 3.0 equiv.) and iodine (153 mg, 0.61 mmol, 3.0 equiv.). The crude residue was chromatographed (6 : 1 hexane–ethyl acetate) to give the *dihydropyrrole* **23b** (74 mg, 78%) as a pale yellow solid, mp 88–92 °C; ν_{max}/cm^{-1} 2953 (w), 1742 (s), 1597 (w), 1437 (w), 1361 (s), 1210 (m), 1170 (s), 1089 (m) and 1017 (m); δ_H 2.45 (3H, s, Ar-CH_3), 2.59 (1H, dd, J = 17.1 and 9.7, 3-H_a), 2.85 (1H, dd, J = 17.1 and 2.3, 3-H_b), 3.82 (3H, s, OMe), 4.83 (1H, dd, J = 9.7 and 2.3, 2-H), 6.50 (1H, dd, J = 3.4 and 1.8, 4′-H), 6.89 (1H, d, J = 3.4, 3′-H), 7.31 (2H, d, J = 8.2, 2 × Ar-H), 7.47 (1H, app br s, 5′-H) and 7.60 (2H, d, J = 8.2, 2 × Ar-H); δ_C 21.6 (Ar-CH_3), 43.5 (3-CH_2), 53.1 (OMe), 62.2 (2-CH), 77.6 (4-C), 111.0 (4′-CH), 113.9 (3′-CH), 127.8 (2 × CH), 129.6 (2 × CH), 133.5 (C), 135.8 (C), 143.1 (5′-CH), 144.6 (C), 144.8 (C) and 170.6 (C=O); *m*/*z* [EI] 473 (M^+, 27%), 318 (17), 191 (88), 159 (51), 132 (56), 104 (55) and 91 (100) [Found: M^+, 472.9796. $C_{17}H_{16}INO_5S$ requires *M*, 472.9796] [Found: C, 42.83; H, 3.41; N, 3.10. $C_{17}H_{16}INO_5S$ requires C, 43.13; H, 3.41; N, 2.96%].

Methyl 4-iodo-5-(2-thienyl)-1-(4-tolylsulfonyl)-2,3-dihydropyrrole-2-carboxylate 23c. The tosylamide **19c** (0.20 g, 0.55 mmol, 1.0 equiv.) was cyclised according to the general procedure with potassium carbonate (0.23 g, 1.65 mmol, 3.0 equiv.) and iodine (0.42 g, 1.65 mmol, 3.0 equiv.). The crude residue was chromatographed (6 : 1 hexane–ethyl acetate) to give the *dihydropyrrole* **23c** (0.21 g, 76%) as a pale yellow solid, mp 103–105 °C; ν_{max}/cm^{-1} 2953 (m), 1744 (s), 1597 (m), 1436 (m), 1362 (s), 1296 (m), 1212 (m), 1169 (s), 1090 (m), 1026 (m) and 911 (m); δ_H 2.45 (3H, s, Ar-CH_3), 2.67 (1H, dd, J = 17.0 and 9.6, 3-H_a), 2.83 (1H, dd, J = 17.0 and 2.6, 3-H_b), 3.84 (3H, s, OCH_3), 4.91 (1H, dd, J = 9.6 and 2.6, 2-H), 7.05 (1H, dd, J = 5.0 and 3.7, 4′-H), 7.28 (2H, d, J = 8.2, 2 × Ar-H), 7.40–7.45 (2H, m, 3′- and 5′-H) and 7.58 (2H, d, J = 8.2, 2 × Ar-H); δ_C 21.6 (Ar-CH_3), 43.7 (3-CH_2), 53.1 (OCH_3), 62.2 (2-CH), 78.7 (4-C), 126.4 (4′-CH), 127.7 (3′(5′)-CH), 127.8 (2 × CH), 129.6 (2 × CH), 130.8 (5′(3′)-CH), 132.6, 133.8, 138.9, 144.6 (all C) and 170.8 (C=O); *m*/*z* [EI] 489 (M^+, 7%), 275 (2), 207 (16), 148 (20), 121 (16), 91 (100) and 65 (73) [Found: M^+, 488.9566. $C_{17}H_{16}INO_4S_2$ requires *M*, 488.9567].

Methyl 5-ethyl-4-iodo-1-(4-tolylsulfonyl)-2,3-dihydropyrrole-2-carboxylate 23d. The tosylamide **22b** (0.20 g, 0.65 mmol, 1.0 equiv.) was cyclised according to the general procedure with potassium carbonate (0.27 g, 1.94 mmol, 3.0 equiv.) and iodine (0.50 g, 1.94 mmol, 3.0 equiv.). The crude residue was chromatographed (6 : 1 hexane–ethyl acetate) to give the *dihydropyrrole* **23d** (0.20 g, 71%) as a brown oil, ν_{max}/cm^{-1} [film] 3500 (w), 2925 (s), 1745 (s), 1598 (w), 1454 (m), 1356 (s), 1215 (m) 1187 (s) and 1090 (m); δ_H 1.04–1.09 (3H, m, 5b-CH_3), 2.38 (3H, s, Ar-CH_3), 2.43–2.63 (4H, m, 1′-CH_2 and 3-CH_2), 3.73 (3H, s, OCH_3), 4.62 (1H, app s, 2-H), 7.30 (2H, d, J = 8.4, 2 × Ar-H) and 7.66 (2H, d, J = 8.4, 2 × Ar-H); δ_C 11.7 (2′-CH_3), 21.7 (Ar-CH_3), 23.5 (1′-CH_2), 41.9 (3-CH_2), 52.9 (OCH_3), 62.1 (2-CH), 73.9 (4-C), 127.5 (2 × CH), 129.9 (2 × CH), 134.5, 144.5, 146.9 (all C) and 171.2 (C=O); *m*/*z* [EI] 435 (M^+, 2%), 155 (24), 127 (16), 91 (100), 89 (18), 77 (9) and 65 (61) [Found: M + H^+, 436.0080. $C_{16}H_{19}INO_4S$ requires *M*, 436.0081].

Preparation of β-iodopyrroles 24 or 26a–c: general procedure

To a stirred solution of the dihydropyrrole **23** (1 mmol, 1 equiv.) in DMF (5 ml) at room temperature was added DBU (2.1 mmol, 2.1 equiv.) dropwise. The reaction was then stirred at room temperature until complete by TLC analysis (approx. 2 h). 2 M Hydrochloric acid (5 ml) was added and the mixture was then extracted with hexane (4 × 20 ml). The combined organic extracts were dried, filtered and concentrated under reduced pressure. The crude product was purified by dissolving it in ethyl acetate and filtering the resulting solution through a small pad of silica to yield the iodopyrrole **24** or **26a**–**c**.

Methyl 4-iodo-5-phenylpyrrole-2-carboxylate 24. The dihydropyrrole **23a** (50 mg, 0.104 mmol, 1.0 equiv.) was treated with DBU (31 μl, 0.208 mmol, 2.0 equiv.) according to the general procedure to give the *iodopyrrole* **24** (45 mg, 90%) as a colourless solid, mp 62–65 °C; ν_{max}/cm^{-1} 3280 (s), 1689 (s), 1463 (m), 1438 (m), 1319 (m), 1257 (m) and 1207 (m); δ_H 3.83 (3H, s, OCH_3), 7.10 (1H, d, J = 2.6, 3-H), 7.38–7.48 (3H, m, Ar-H), 7.67 (2H, dd, J = 7.2 and 7.2, Ar-H) and 9.57 (1H, br s, NH); δ_C 51.9 (OCH_3), 62.2 (4-C), 124.4 (3-CH), 127.9 (Ar-CH), 128.7 (Ar-CH), 131.2 (C), 137.1 (C) and 162.0 (C=O); *m*/*z* [EI] 327 (M^+, 80%), 295 (51), 267 (14), 140 (100) and 113 (43) [Found: M^+ 326.9759. $C_{12}H_{10}INO_2$ requires *M*, 326.9758].

Methyl 5-(2-furyl)-4-iodopyrrole-2-carboxylate 26a. The dihydropyrrole **23b** (49 mg, 0.104 mmol, 1.0 equiv.) was treated with DBU (31 μl, 0.208 mmol, 2.1 equiv.) according to the general method to give the *iodopyrrole* **26a** (28 mg, 85%) as a colourless solid, mp 72–75 °C; ν_{max}/cm^{-1} 3282 (m), 2951 (m), 1697 (s), 1508 (m), 1437 (m), 1395 (m), 1317 (m), 1262 (m) and 1203 (m); δ_H 3.88 (3H, s, OCH_3), 6.53 (1H, dd, J = 3.5 and 1.6, 4′-H), 7.07 (1H, d, J = 2.7, 3-H), 7.21 (1H, d, J = 3.5, 3′-H), 7.47 (1H, d, J = 1.6, 5′-H) and 9.45 (1H, br s, NH); δ_C 51.9 (OCH_3), 65.2 (4-C), 107.8, 111.8, 124.5, 142.0 (all Ar-H), 129.0, 136.0, 140.5 (all Ar-C) and 162.5 (C=O); *m*/*z* [EI] 317 (M^+, 79%), 285 (59), 130 (70), 76 (79) and 56 (100) [Found: M^+, 316.9551. $C_{10}H_8INO_3$ requires *M*, 316.9551].

Methyl 4-iodo-5-(2-thienyl)pyrrole-2-carboxylate 26b. The dihydropyrrole **23c** (51 mg, 0.104 mmol, 1.0 equiv.) was treated with DBU (31 μl, 0.208 mmol, 2.0 equiv.) according to the general procedure to give the *iodopyrrole* **26b** (30 mg, 86%) as a colourless solid, mp 120–124 °C; ν_{max}/cm^{-1} 3295 (m), 2952 (w), 1688 (s), 1472 (m), 1438 (m), 1317 (m), 1263 (s) and 1204 (s); δ_H 3.88 (3H, s, OCH_3), 7.08 (1H, d, J = 2.6, 3-H), 7.14 (1H, dd, J = 5.0 and 3.7, 4′-H), 7.38 (1H, d, J = 5.0, 3′-H), 7.48 (1H, d, J = 3.7, 5′-H) and 9.66 (1H, br s, NH); δ_C 51.9 (OCH_3), 72.5 (4-C), 124.5, 127.0, 128.0, 128.5 (all Ar-H), 133.4, 135.0, 147.0 (all C) and 169.5 (C=O); *m*/*z* [EI] 333 (M^+, 81%), 301 (87), 174 (13), 146 (100), 120 (85) and 69 (50) [Found: M^+, 332.9322. $C_{10}H_8INO_2S$ requires *M*, 332.9322].

Methyl 5-ethyl-4-iodopyrrole-2-carboxylate 26c. The dihydropyrrole **23d** (100 mg, 0.23 mmol, 1.0 equiv.) was treated with DBU (0.07 ml, 0.46 mmol, 2.0 equiv.) according to the general procedure to give the *iodopyrrole* **26c** (50 mg, 86%) as a pale brown oil, ν_{max}/cm^{-1} 3279 (s), 2975 (w), 1682 (s), 1489 (s), 1319 (m), 1280 (m) and 1206 (s); δ_H 1.24 (3H, t, J = 7.6, 2′-CH_3), 2.66 (2H, q, J = 7.6, 1′-CH_2), 3.84 (3H, s, OCH_3), 6.94 (1H, d, J = 2.6, 3-H) and 9.28 (1H, br s, NH); δ_C 13.2 (2′-CH_3), 21.6 (1′-CH_2), 51.6 (OCH_3), 63.0 (4-C), 122.6 (3-CH), 141.0 (C), 142.0 (C) and 162.0 (C=O); *m*/*z* [ES] 280 (M + H^+, 10%), 204 (49), 239 (14), 154 (10), 102 (37) and 61 (100) [Found: M + H^+, 279.9835. $C_8H_{11}INO_2$ requires *M*, 279.9836].

Methyl 5-phenyl-4-(phenylethynyl)-1-(4-tolylsulfonyl)-2,3-dihydropyrrole-2-carboxylate 29. The dihydropyrrole **23a** (50 mg, 0.104 mmol, 1.0 equiv.) was stirred in degassed diethylamine (1 ml) with CuI (4 mg, 0.0208 mmol, 0.2 equiv.) and $Pd(PPh_3)_4$ (12 mg, 0.0104 mmol, 0.1 equiv.). Phenylacetylene (11 mg, 0.104 mmol, 1.0 equiv.) was then added and the mixture stirred at room temperature under nitrogen for 2 h. The reaction was then concentrated, diluted with ether (5 ml), filtered through Celite and the filtrate concentrated to give a brown oil. This was purified by column chromatography (4 : 1 hexane–ethyl acetate) to give the *dihydropyrrole* **29** (39 mg, 82%) as a pale yellow solid, mp 139–141 °C; ν_{max}/cm^{-1} 2953 (w), 2245 (w), 1756 (s), 1595 (m), 1488 (m), 1365 (s), 1210 (s), 1170 (s), 1089 (m) and 1030 (m); δ_H 2.43 (3H, s, Ar-CH_3), 2.62 (1H, dd, J = 16.3 and 9.6, 3-H_a), 2.72 (1H, dd, J = 16.3 and 2.6, 3-H_b), 3.84 (3H, s, OCH_3), 4.90 (1H, dd, J = 9.6 and 2.6, 2-H) and 7.25–7.81 (14H, m, Ar-H); δ_C 21.7 (Ar-CH_3), 36.5 (3-CH_2), 53.1 (OCH_3), 62.0 (2-CH), 84.4, 95.5, 108.3, 122.8 (all C), 127.6, 127.7, 128.4, 128.5, 129.2, 129.4, 129.8, 131.3 (all Ar-CH), 131.4 (C), 134.4 (CH), 144.5 (C), 146.3 (C) and 171.3 (C=O); *m*/*z* [EI] 457 (M^+, 22%), 302 (75), 270 (82), 243 (75) and 91 (100) [Found: M^+, 457.1348. $C_{27}H_{23}NO_4S$ requires *M*, 457.1348].

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