Synthetic studies related to the akuammiline alkaloids

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Dedicated to Professor Rod Rickards on his 70th birthday
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Abstract
6-Ethyl-2,3-dihydro-1-phenyl-1*H*-pyrrolizine **19** and 1-(2-aminophenyl)-6-ethyl-2,3-dihydro-1*H*-pyrrolizine **30** were synthesized starting from the pyrroles 4-acetylpyrrol-2-yl phenyl ketone **13** and 4-acetylpyrrol-2-yl 2-(dimethylaminomethylenamino)phenyl ketone **26**, respectively, using vinyltriphenylphosphonium bromide in an intramolecular Wittig reaction for the formation of the second five-membered ring.

Keywords: Pyrroles, pyrrolizidines, akuamma alkaloids, vinyltriphenylphosphonium bromide, Wittig reaction

Introduction

The variety of indole alkaloid skeleta,[1] of greater or lesser complexity, has been a frequently employed proving ground for novel synthetic methodologies and strategies. Some indole alkaloid types have been the subject of frequent attention – the alkaloid ellipticine[2] probably holds the record for the most frequently synthesised alkaloid ever – the Aspidosperma skeleton[3] has seen Stork's synthesis, an early illustration of enamine β-alkylation, Overman's approach, illustrating his aza-Cope/Mannich sequence, and Magnus' route utilising an indole-2,3-quinodimethane intermediate, amongst others. One of the few groups of monoterpenoid indole alkaloids which has not yet been the subject of a successful total synthesis, is the group characterised by the presence of a C-7–C-16 bond[4] – akuammiline **1** represents this structural type in its simplest form. Approximately 100 indole bases are now known (more than 20 in the last decade) which fall into the akuammiline structural category, and the chemistry and pharmacology of these have been recently reviewed.[5]

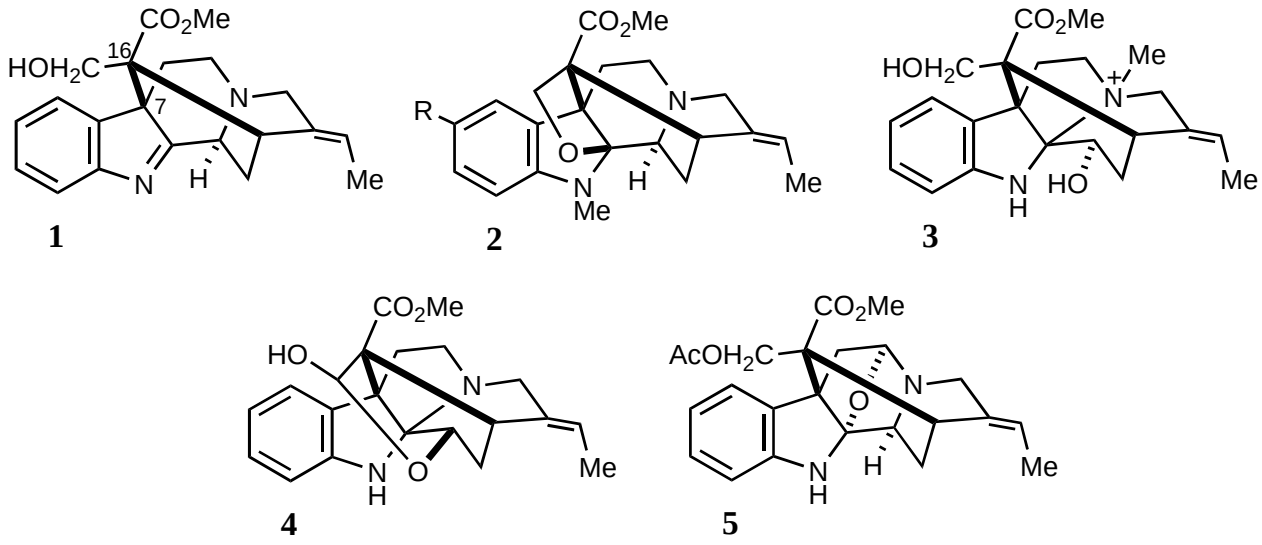
Our personal interest in this group of alkaloids traces back to that period when the Manchester Chemistry Department was priviliged to number amongst its academic staff Arthur Birch and Rod Rickards, and one of the present authors studied Akuamma alkaloids for PhD.[6] It is a pleasure to contribute this paper for the issue of *Arkivoc* which commemorates Professor

Rickards' 70th Birthday, in recognition of his contributions to natural product chemistry in Manchester, and subsequently in Canberra, and of his friendship and encouragement as a colleague in Manchester.

Background

The use of plants and plant extracts containing akuammiline alkaloids is widespread in traditional medicine. For example, the aqueous extracts of *Picralima nitida* (the "akuamma" tree) are used in West Africa as painkillers;[7] in Ghana, pulverised and encapsulated seeds can be found for sale for medicinal purposes in the market. In the rural areas of Saudi Arabia, decoctions of *Rhazya stricta* are employed as a cure for helminthiasis[8] while in the Philippines the bark of *Rauwolfia sumatrana* is believed to alleviate the symptoms of malaria.[9]

Prompted by the traditional medicinal use of the seeds of the *Picralima nitida* tree in the Gold Coast, Henry and Sharp were the first to examine the alkaloidal content.[10] These authors adopted the word "akuamma", used by natives in the region to designate the tree, as the prefix for the name given to the major alkaloidal constituent, akuammine **2** (R=HO). Subsequently, Henry isolated, and characterised Ψ-akuammigine **2** (R=H) and akuammiline.[11] In 1961, the determination of the X-ray crystal structure of the quaternary salt echitamine **3**[12] then allowed the final establishment of the structures and absolute configurations[13] of Ψ-akuammigine, akuammine and akuammiline based on their chemical correlation with echitamine.



Studies of extracts of seeds, fruit and bark of *Picralima nitida* revealed anti-protozoal, anti-microbial and *in vitro* anti-malarial activity.[14] Extracts from *Hunteria zeylanica* (rich in corymine **4**) showed anti-inflammatory activity and stimulation of the CNS,[15] while extracts from *Alstonia scholaris* (which contain picraline **5** and Ψ-akuammigine amongst other akuammiline alkaloids) showed hepato-protective activity.[16] Echitamine chloride has been reported to have antitumour activity coupled with a low toxicity profile.[17] It is probably appropriate to apply the term *privileged structures*, as employed by Evans *et al*.[18] to designate

those substrates that bind to diverse categories of protein receptors with high affinities, to the unique rigid skeleton of the Akuamma alkaloids, exposing as it does, a variety of functional groups in a defined alignment.

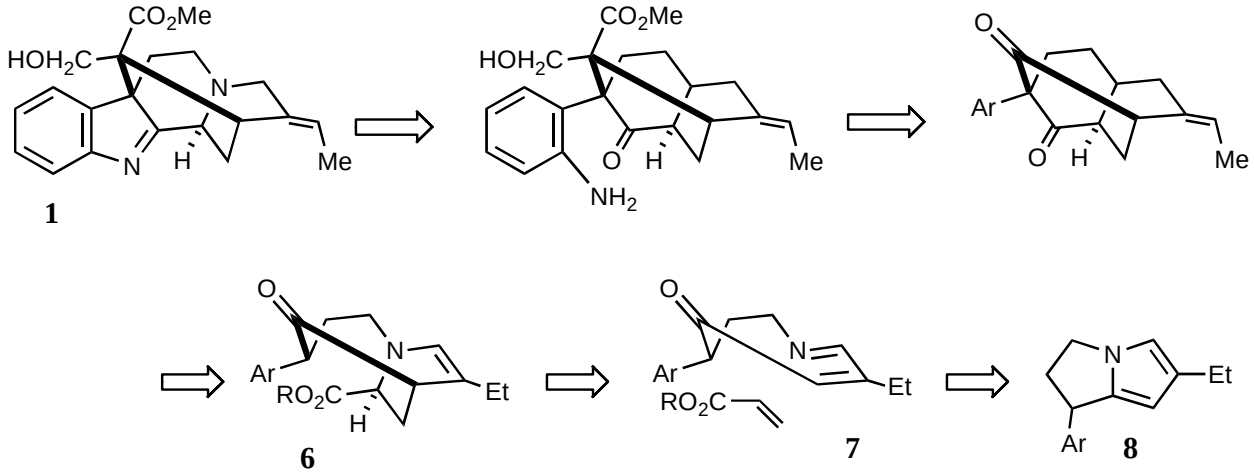
Previous synthetic approaches

Early work[19,20] was followed by attempts to achieve formation of a C-7–C-16 bond by a means parallel to that proposed[21] for its biosynthetic formation, but these were unsuccessful.[22] Lévy[23] described a significantly novel approach, which awaits further development, but the most extensive and interesting, though also, in the end, unsuccessful work has come from the Catalan group of Bosch and Bennasar.[24]

It remains the situation that no successful synthesis of the Akuamma skeleton has been achieved; this paper describes work that is designed to provide the platform for an alternative strategy for the synthesis of this type of indole alkaloid.

Synthetic plan

The route proposed for the assembly of molecules with the akuammiline skeleton is summarised in retrosynthetic Scheme 1. A key step would be an aza-Diels-Alder cycloaddition to form ring D (**7** to **6**). Scheme 1 shows this as an intermolecular process, though an alternative would be to bring this about in an intramolecular sense, with the acrylate linked to N-1, *i.e.* with the dienophile as an acrylamide. We envisage producing the required 1-aza-1,3-diene **7** by an oxidative ring opening of a precursor bicyclic pyrrole **8**. The conversion of the bicyclic pyrrole into the azadiene would be based on one of two precedents: (1) the first is the addition[25] of singlet oxygen to a pyrrole, eventually producing a 5-hydroxy-5*H*-pyrrol-2-one,[26] which, we speculate, would react with TMSOTf to produce a ring-cleaved azadiene-ketone ready for cycloaddition; (2) alternatively, based on Martin's work in a furan series,[27] the use of *tert*-BuOOH/$VO(acac)_2$, on a pyrrol-2-ylcarbinol might have a comparable effect. In this paper we describe our synthesis of an appropriate bicyclic pyrrole, **8**.

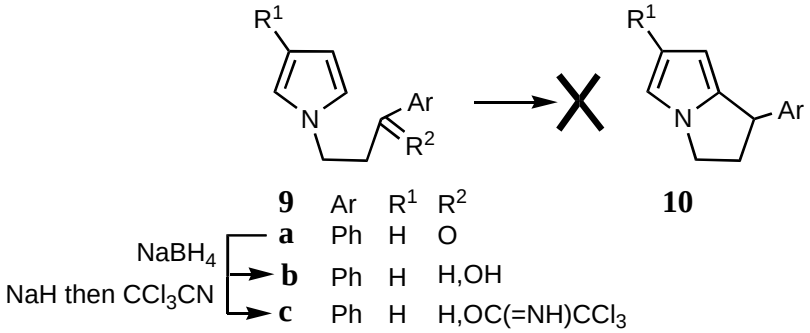


Scheme 1

Synthesis of bicycles 8

Our first plan (Scheme 2) was to close an intermediate of the form **9**, via an intramolecular electrophilic attack at the pyrrole α-position (ignoring questions of regioselectivity), to give **10**. 2-Aminoethyl phenyl ketone hydrochloride[28] was prepared via addition of phthalimide to phenyl vinyl ketone,[29] then hydrolysis with 1:1 AcOH-*conc* HCl.[30] Reaction of the amine with 2,5-dimethoxytetrahydrofuran gave the pyrrole ketone **9a**, borohydride reduction of which gave the alcohol **9b**. Alcohol **9b** was also prepared from 3-hydroxy-3-phenylpropanamine[31] by reaction[32] with 2,5-dimethoxytetrahydrofuran.

Attempts to effect ring closure by conversion of the benzylic alcohol in **9b** into a triflate were disappointing. Despite seemingly excellent precedents in which an analogous 5,6-ring system was constructed,[33] the best that could be claimed in our experiments were signals in ^{1}H NMR spectra, of complex product mixtures, which could have represented some of the desired product. We explored the possibility of achieving the desired benzylic electrophilic reactivity by decomposition of a trichloroacetimidate;[34,35] the required derivative **9c** was easily prepared following a literature precedent,[36] but various attempts to effect the desired acid-catalysed closure were unsuccessful (Scheme 2).

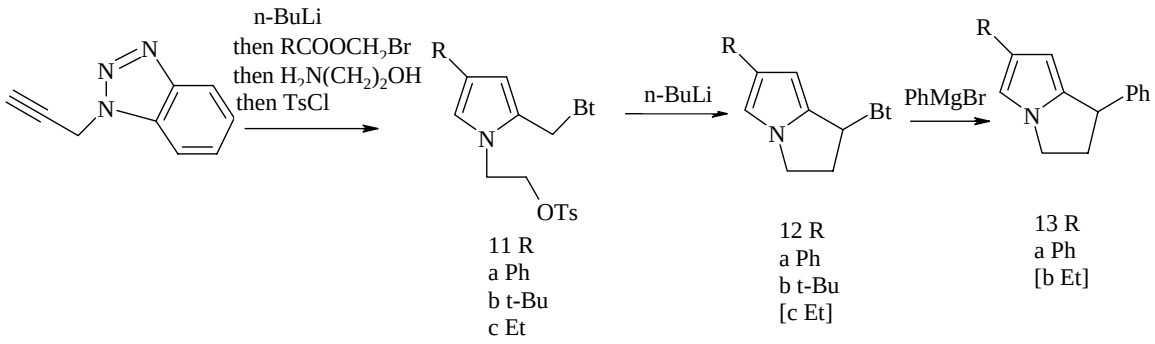


Scheme 2

Katritzky had described[37] the synthesis of bicycles **12a** and **12b**, the key step, in which the saturated five-membered ring is fused to the pyrrole nucleus, involving intramolecular displacement of tosylate in 2-(benzotriazol-1-ylmethyl)-1-(2-tosyloxyethyl)pyrrole precursors **11a** and **11b**, subsequent nucleophilic displacement of the benzotriazolyl unit in **12a** with phenylmagnesium bromide completing a synthesis of **13a**. Although we were able to reproduce the literature report and prepare **13a**, in attempting to adapt this sequence for the synthesis of the desired **13b**, we were only able to reach **11c**, as shown in Scheme 3, failing completely in attempts to bring about ring closure to **12c** from this intermediate.

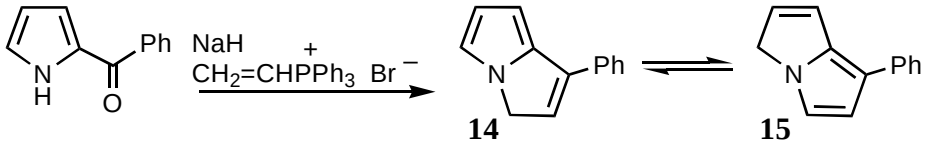
We turned to construction of the five-membered ring via an intramolecular Wittig reaction. Linderman and Meyers had shown[38] that addition of pyrrolyl anions to vinyltriphenylphosphonium bromide, directly generates ylides which react with aldehydes to produce substituted 1-allylpyrroles. The process had been earlier carried out in an intramolecular sense starting from 2-formylpyrrole, to generate a five-five bicycle of the type required in the

present work, though an attempt to use 2-benzoylpyrrole produced only tars.[39] A comparable five-membered ring formation was reported with 2-formylindole.[39]



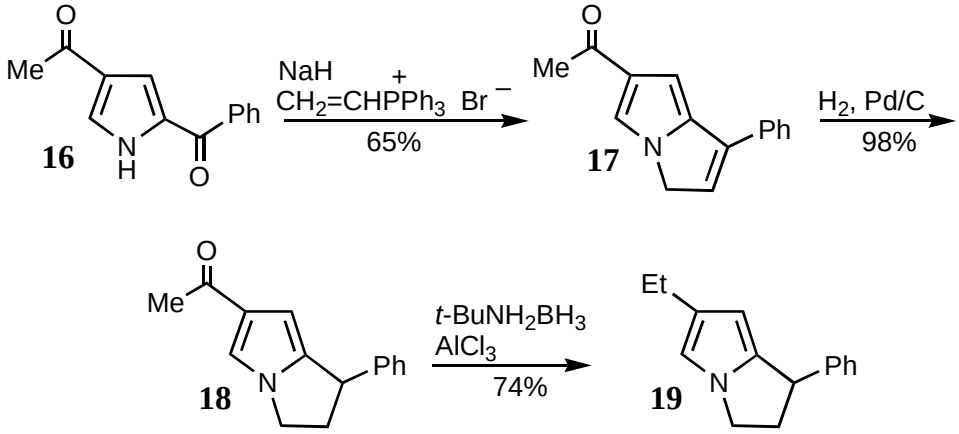
Scheme 3

In our hands, a preliminary investigation using 2-benzoylpyrrole in reaction with vinyltriphenylphosphonium bromide was encouraging but sounded a warning: there was clear evidence that an initial product **14** was in equilibrium (*ca.* 1:1) with an isomer **15** (Scheme 4). In an attempt to prevent this complication, we turned to the use of a 3-acetylpyrrole, arguing that conjugation with this ketone carbonyl would maintain the first-formed system of double bonds. The acetyl substituent also corresponds to the two-carbon side-chain eventually required in the alkaloid.



Scheme 4

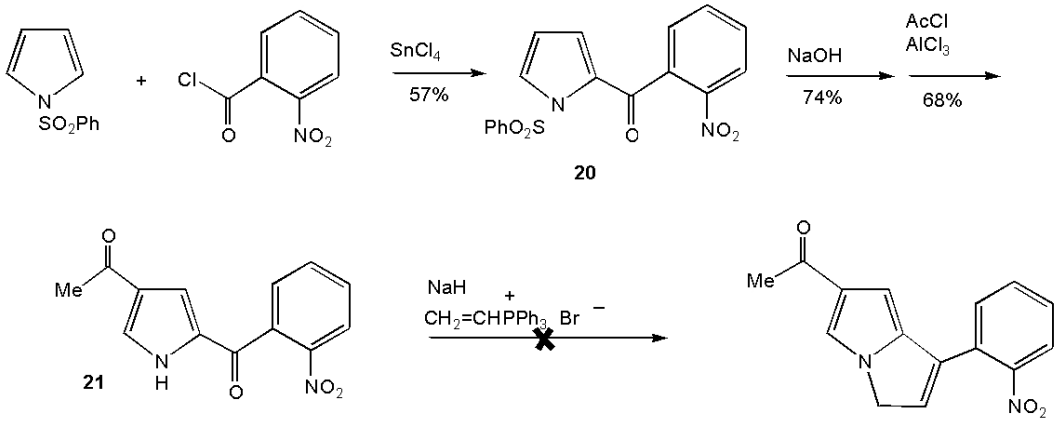
Of various routes to 4-acetyl-2-benzoylpyrrole **16** we found the best was to start with 3-acetylpyrrole, itself available via Friedel-Crafts acetylation of 1-phenylsulfonylpyrrole, then de-*N*-protection;[40,41] benzoylation of 3-acetylpyrrole gave **16** in 20% overall yield for the four steps from pyrrole.



Scheme 5

Reaction of **16** with vinyltriphenylphosphonium bromide produced a single, though rather unstable bicyclic alkene **17**, which was hydrogenated giving **18**, the acetyl group then reduced, producing **19**, using[42] *t*-$BuNH_2BH_3$ with $AlCl_3$ (Scheme 5). That the orientation of double bonds was, as desired, and as shown in **17**, **18** and **19**, was verified by the ^{1}H NMR spectra of these substances. For example, in **17** the methylene signal at δ 4.68 was split (*J* 2.3 Hz) by the adjacent alkene proton and in the spectrum of **18** there was a triplet (*J* 7.7) at δ 4.40 for the doubly benzylic proton, in addition to multiplet signals for the other four aliphatic protons.

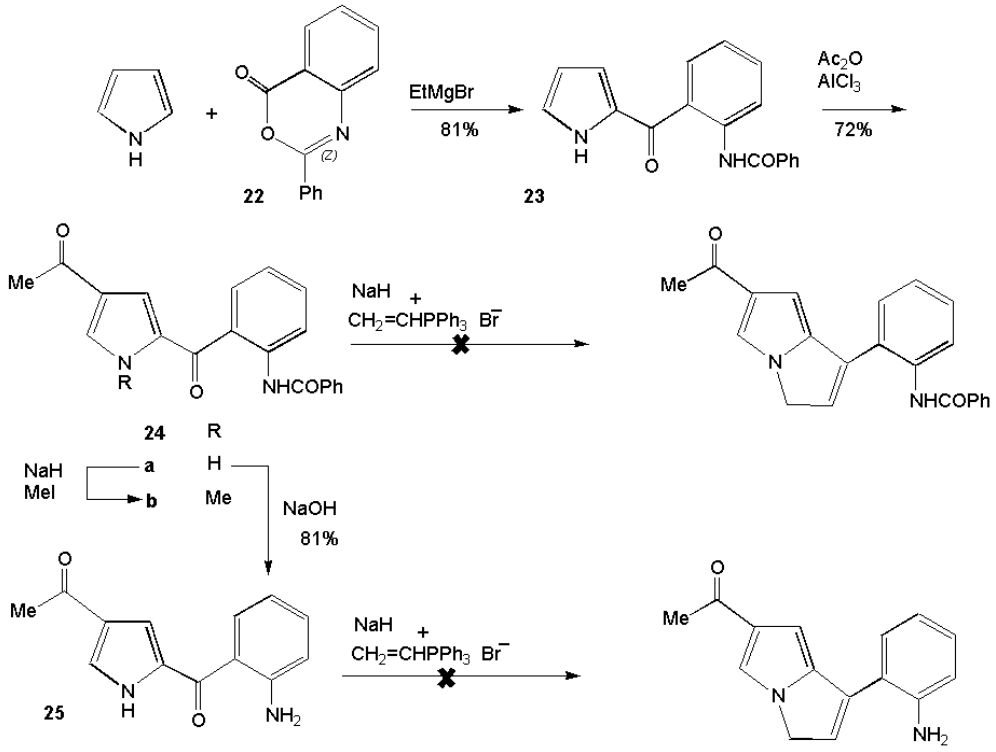
The further development of this successful route, to provide an appropriate bicycle for the alkaloid synthesis, required that the benzenoid ring carry an *ortho* nitrogen substitutent. We reacted the 2-lithio-1-phenylsulfonylpyrrole with *ortho*-nitrobenzaldehyde, then immediately oxidised the resulting mixture, but were only able to obtain a 10% yield of ketone **20**. However, following work using 1-*para*-toluenesulfonylpyrrole,[43] Friedel-Crafts *ortho*-nitrobenzoylation of 1-phenylsulfonylpyrrole proceeded satisfactorily, giving **20**, the orientation of substitution being confirmed by the ^{1}H-NMR spectrum of the product which showed signals for the three *ortho*-related pyrrole protons at δ 6.34 (1H, m), 6.50 (1H, dd, *J* 1.8,3.8 Hz) and 7.97 (1H, dd, *J* 1.8,3.8 Hz). After *N*-deprotection, $AlCl_3$-catalysed acetylation gave the desired diketone **21**, by substitution *meta* to the nitrobenzoyl group, as confirmed by the small coupling constants for the remaining two pyrrole protons, at δ 6.90 (bs) and 7.92 (bs). Disappointingly, the Wittig cyclisation with nitro-substituted substrate **21** failed completely – only polar material that could not be characterised was obtained (Scheme 6).



Scheme 6

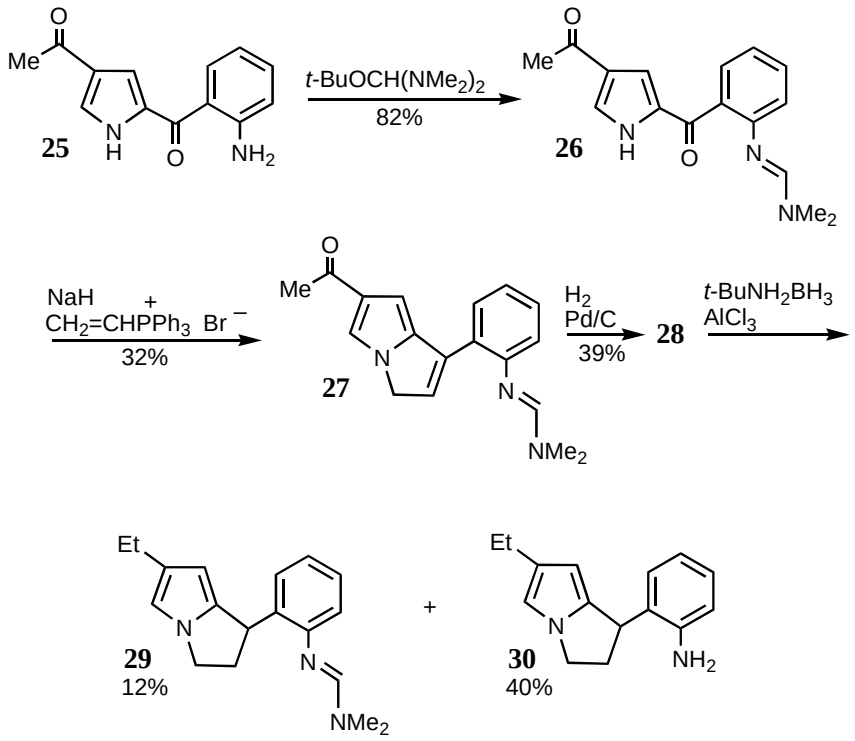
It was clear that an alternative nitrogen substitutent would have to be used – a protected amine was the obvious choice. There appeared to be a rather direct route through to a benzamide following a strong earlier precedent.[44] Anthranilic acid was converted into 2-phenyl-4*H*-benzoxazin-4-one **22** by reaction with benzoyl chloride and this reacted with the Grignard derivative of pyrrole giving **23**. *C*-Acetylation proceeded normally and the resulting diketone **24a** was subjected to the Wittig cyclisation conditions, but once again we were to be disappointed, and no bicyclic product was obtained (Scheme 7). There are two *N*-hydrogens in

24a and the cyclisation requires that base remove the pyrrole *N*-hydrogen. By reaction of **24a** with one equivalent of NaH and then iodomethane we confirmed that the pyrrole *N*-proton is the most acidic proton, by the formation of **24b**, in which the typical signal for a pyrrole *N*-hydrogen (δ 10.6 in **24a**) was no longer present, but the amide proton signal remained, and at exactly the same shift, δ 11.4, as in **24a**. It is not clear why **24a** would not take part in the Wittig cyclisation. Hydrolysis of the benzamide revealed the amine **25**, but, as expected, no Wittig cyclisation could be achieved with this, either.



Scheme 7

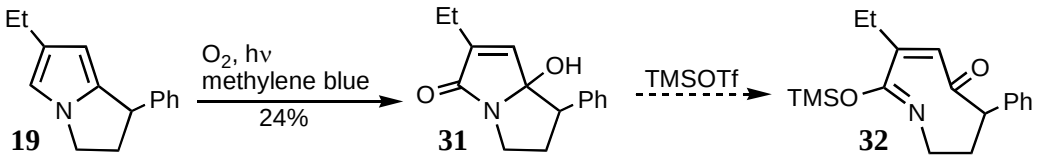
It seemed that it would be necessary to mask both of the side-chain *N*-hydrogens. Attempts to convert the amino group in **25** into a 1,3,5-triazine,[45,46] a phthalimide, or to effect a condensation (Schiff's base) with benzaldehyde, all failed. However, reaction with Bredereck's reagent [*t*-BuOCH(NMe_2)$_2$] converted **25** efficiently into **26**. An interesting practical point concerning the relative mobilities on silica gel chromatography of starting primary amine **25** and product amidine **26** is that the latter was by far the slower, despite the absence of *N*-hydrogens, presumably because of its greater basicity. To our delight, the Wittig cyclisation strategy was now successful, producing **27** from **26**, the relatively low yield undoubtedly reflecting the practical difficulty in separating the product from the triphenylphosphine oxide byproduct. Now, catalytic reduction gave **28** then conversion of acetyl into ethyl, as before, produced a mixture of **29** and deprotected **30**, in unoptimised yields of 12% and 40% respectively (Scheme 8).



Scheme 8

Reaction of bicycle 19 with singlet oxygen

We have so far examined only the ring opening of bicyclic pyrrole **19** as a model, under the singlet oxygen conditions. In an unoptimised 24% yield, we obtained the hydroxy-pyrrolidinone **31**, as desired. It would now be the plan to convert this into an azadiene **32**, perhaps with a suitable silylating agent (Scheme 9).



Scheme 9

Experimental Section

1-(3-Oxo-3-phenylpropyl)pyrrole (**9a).** To a stirred solution of 2-aminoethyl phenyl ketone hydrochloride[28] (2.5 g, 13. 5 mmol) in water (22 ml) heated at 90 °C, was added sodium ethoxide (1.85 g, 27 mmol, 2.4 equiv), acetic acid (12 ml, 0.22 mol, 20 equiv), and 2,5-dimethoxytetrahydrofuran (1.43 ml, 11.05 mmol, 1 equiv). The reaction mixture was heated at

100 °C for 15 min, allowed to cool to rt then extracted with AcOEt (50 ml) and the extract washed with sat. aq. $NaHCO_3$ (3 x 50 ml). The organic layer was dried with $MgSO_4$ and evaporated to dryness. Purification by column SiO_2 chromatography (30% of petroleum ether in CH_2Cl_2) gave *1-(3-oxo-3-phenylpropyl)pyrrole* **9a** (0.937 g, 42%) as a brown crystalline solid, mp 74.5-76 °C; (found MH^+, 200.1073. $C_{13}H_{13}NO$ requires *MH*, 200.1075); ν_{max} (film): 1448, 1681 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.49 (2H, t, *J* 7.0, CH_2), 4.42 (2H, t, *J* 7.0, CH_2), 6.18 (2H, m, pyrrole β-Hs), 6.75 (2H, m, pyrrole α-Hs), 7.50 (2H, t, *J* 8.3, ArH), 7.61 (1H, m, ArH), 7.96 (2H, d, *J* 8.3, ArH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 40.5, 44.2, 108.3, 120.6, 127.9, 128.6, 133.4, 136.4, 197.4; *m/z* (CI): 200 (MH^+, 100%).

1-(3-Hydroxy-3-phenylpropyl)pyrrole (9b). (a) To a stirred solution of 1-(3-oxo-3-phenylpropyl)pyrrole **9a** (0.295 g, 1.48 mmol) in *i*-PrOH:THF:H_2O (2:2:1, 25 ml) was slowly added $NaBH_4$ (0.225 g, 5.9 mmol, 4 equiv). After 45 min when TLC analysis indicated the complete consumption of the starting material, sat. aq. NH_4Cl (20 ml) was added and the compound extracted with CH_2Cl_2 (3 x 20 ml). The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column SiO_2 chromatography (CH_2Cl_2) provided *1-(3-hydroxy-3-phenylpropyl)pyrrole* **9b** (207 mg, 70%) as a colourless oil; (found M^+, 201.1155. $C_{13}H_{15}NO$ requires *M*, 201.1154); ν_{max} (film): 701, 727, 1056, 1089, 1455, 1449, 3313-3567 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.22 (2H, m, CH_2), 4.08 (2H, m, CH_2), 4.63 (1H, t, *J* 4.2, C*H*OH), 6.20 (2H, d, *J* 1.3, pyrrole β-Hs), 6.73 (2H, d, *J* 1.3, pyrrole α-Hs), 7.28-7.40 (5H, m, _-ArHs); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 40.3, 46.1, 71.5, 108.0, 120.5, 125.7, 127.8, 128.6, 143.9; *m/z* (CI): 202 (MH^+, 100%), 184 (60), 81 (79). (b) To a stirred solution of 3-hydroxy-3-phenylpropanamine[31] (3.13 g, 20.7 mmol) in AcOH (300 ml), was added NaOAc.3H2O (56.63 g, 414 mmol, 20 equiv), and 2,5-dimethoxytetrahydrofuran (2.95 ml, 22.8 mmol, 1.1 equiv). The reaction mixture was slowly heated up to 70 °C, kept at that temperature for 2 h then was concentrated under reduced pressure. 2M NaOH was added until a basic pH was reached and the mixture was extracted with Et2O. The organic layer was dried over $MgSO_4$ and evaporated to dryness. Purification by column SiO_2 chromatography (5% of Et_2O in petroleum ether) gave 1-(3-hydroxy-3-phenylpropyl)pyrrole **9b** (1.238 g, 30%) as a colourless oil, with spectroscopic properties identical to those reported above.

1-Phenyl-3-(pyrrol-1-yl)trichloroacetimidate (9c). A solution of 1-(3-hydroxy-3-phenylpropyl)pyrrole **9b** (0.2 g, 1 mmol) in anhydrous THF (0.8 ml), was added dropwise to a suspension of NaH (3.5 mg of a 60% dispersion in mineral oil, 0.087 mmol) in THF (4 ml). After 15 min, this mixture was added dropwise to a solution of trichloroacetonitrile (0.1 ml, 1 mmol, 1 equiv) in THF (1 ml) kept between –5 °C and 0 °C. The cooling bath was removed after the addition and the solution allowed to warm up to rt. After vigorous stirring, the residue was filtered and evaporated under reduced pressure providing *1-phenyl-3-(pyrrol-1-yl)trichloroacetimidate* **9c** (209 mg, 63%) as a yellow low mp solid, sufficiently pure for subsequent use; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.23 (1H, m, CH_2), 2.41 (1H, m, CH_2), 4. 00 (2H, m, CH_2), 5.65 (1H, dd, *J* 9.4, 4.1 Hz, CH), 6.10 (2H, t, *J* 2.1, pyrrole H), 6.60 (2H, t, *J* 2.1, pyrrole H), 7.21-7.31 (5H, m, ArH), 8.27 (1H, bs, NH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 29.6,

38.9, 45.6, 108.3, 119.3, 120.4, 125.9, 128.1, 128.5, 139.3, 161.0 *m/z* (CI): 184 (MH^+-146 (trichloroacetimidate fragment), 100%).

2-(Benzotriazol-1-ylmethyl)-4-ethyl-1-(2-(4-methylphenylsulfonyloxy)ethyl)pyrrole (11c). To a stirred solution of 1-propargylbenzotriazole[47] (0.706 g, 4.5 mmol) in THF (22.5 ml) was added a solution of *n*-BuLi (2.81 ml, 1.6 M, 1 equiv) at -78 °C; the solution was stirred at this temperature for 30 min. A solution of 1-bromo-2-butanone (0.459 ml, 4.5 mmol, 1 equiv) in THF (0.4 ml) was added, and the reaction mixture was stirred at -78 °C for 20 h. Sat. aq. NH_4Cl (25 ml) was added, and the solution was extracted with Et_2O (50 ml). The organic phase was separated, washed with sat. aq. NH_4Cl (3 x 25 ml) dried over $MgSO_4$, and concentrated under reduced pressure. The resulting *2-[3-(benzotriazol-1-yl)propyn-1-yl]-2-ethyloxirane* was used immediately without characterisation or further purification.

2-[3-(Benzotriazol-1-yl)propyn-1-yl]-2-ethyloxirane (4.5 mmol) was dissolved in *i*-PrOH (30 ml), 2-hydroxyethanamine (0.539 ml, 9 mmol, 2 equiv) was added, and the solution was refluxed for 24 h. *i*-PrOH was removed and the residue subjected to column SiO_2 chromatography (25-70% of AcOEt in petroleum ether) to give *2-(benzotriazol-1-ylmethyl)-4-ethyl-1-(2-hydroxyethyl)pyrrole* (0.385 g, 32% from 1-propargylbenzotriazole) as a white foam (found M^+, 270.1471. $C_{15}H_{18}N_4O$ requires *M*, 270.1481); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.10 (3H, t, *J* 7.5, CH_3), 2.52 (2H, q, *J* 7.5, CH_2), 3.51 (2H, t, *J* 5.3, CH_2), 3.94 (2H, t, *J* 5.3, CH_2), 5.76 (2H, s, CH_2), 6.18 (1H, d, *J* 1.9, pyrrole H), 6.42 (1H, d, *J* 1.9, pyrrole H), 7.23-7.42 (3H, m, ArH), 8.01 (1H, d, *J* 8.2, ArH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 15.0, 19.8, 44.8, 48.8, 62.5, 110.2, 110.9, 119.7, 120.3, 123.9, 124.2, 125.7, 127.4, 132.6, 146.0; *m/z* (CI): 271 (MH^+, 5%), 152 (95), 120 (54).

To a stirred solution of 2-(benzotriazol-1-ylmethyl)-4-ethyl-1-(2-hydroxyethyl)pyrrole (0.5 g, 1.85 mmol) in CH_2Cl_2 (10 ml) was added triethylamine (2.77 ml, 19.6 mmol, 10 equiv) then *p*-toluenesulfonyl chloride (1.05 g, 5.55 mmol, 3 equiv) in portions over a period of 1 h, and the reaction mixture was stirred at room temperature overnight. It was then washed with 2 M HCl (2 x 10 ml), followed by 10% $NaHCO_3$ (2 x 10 ml) and water (3 x 10 ml). The organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. Column SiO_2 chromatography gave *2-(benzotriazol-1-ylmethyl)-4-ethyl-1-(2-(4-methylphenylsulfonyloxy)ethyl)pyrrole* **11c** as a colourless oil (0.7 g, 89%); (found M^+ 424.1563. $C_{22}H_{24}N_4O_3S$ requires *M*, 424.1569); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.10 (3H, t, *J* 7.5, CH_3), 2.44 (5H, m, NCH_2 + CH_3), 3.96 (2H, t, *J* 5.2, CH_2), 4.20 (2H, t, *J* 5.2, CH_2), 5.76 (2H, s, CH_2), 6.23 (1H, d, *J* 1.9, pyrrole H), 6.42 (1H, d, *J* 1.9, pyrrole H), 7.26 (2H, d, *J* 8.2, ArH), 7.36 (1H, m, ArH), 7.46 (2H, m, ArH), 7.60 (2H, d, *J* 8.2, ArH), 8.05 (1H, d, *J* 8.2, ArH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.9, 19.7, 21.5, 44.4, 45.2, 69.1, 109.9, 111.3, 119.8, 120.1, 123.9, 124.1, 126.0, 127.4, 127.7, 129.7, 132.2, 132.5, 144.8, 146.1; *m/z* (CI): 425 (MH^+, 4%), 306 (20), 255 (15), 120 (100).

4-Acetyl-2-benzoylpyrrole (16). A solution of benzoyl chloride (0.65 ml, 5.6 mmol, 1.12 equiv) in CH_2Cl_2 (2.5 ml) was slowly added to a stirred suspension of $AlCl_3$ (1.60 g, 12 mmol, 2.4 equiv) in CH_2Cl_2 (10 ml) at rt. After 30 min, a solution of 3-acetylpyrrole (0.54 g, 5 mmol) was added dropwise during 10 min and the resulting solution was left stirring for 75 min. The

mixture was poured into cold water, extracted with CH_2Cl_2, the extract washed with aq. $NaHCO_3$, followed by brine, dried over $MgSO_4$, and concentrated under reduced pressure. Column SiO_2 chromatography (60% Et_2O in petroleum ether) yielded 4-acetyl-2-benzoylpyrrole **16** as a white solid (0.65 g, 60%), mp 102-103 °C, lit[41] 103-104 °C; ν_{max} (film): 728, 892, 932, 1181, 1214, 1285, 1376, 1433, 1547, 1626, 1655, 3259 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.40 (3H, s, CH_3), 7.23 (1H, d, *J* 1.5, pyrrole H), 7.43 (2H, t, *J* 7.5, ArH), 7.53 (1H, m, ArH), 7.67 (1H, d, *J* 1.5, pyrrole H), 7.8 (2H, dd, *J* 7.5, 1.5), 10.6 (1H, bs, NH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 27.3, 118.2, 127.7, 128.4, 128.5, 128.9, 131.7, 132.5, 137.2, 185.4, 193.2; *m/z* (CI): 231 (MNH_4^+, 20%), 213 (MH^+, 100).

6-Acetyl-1-phenyl-3*H*-pyrrolizine (17). To a stirred suspension of 4-acetyl-2-benzoylpyrrole **16** (2.13 g, 10 mmol), and vinyltriphenylphosphonium bromide (3.69 g, 10 mmol, 1 equiv) in anhydrous THF (200 ml) at -10 °C, NaH (0.56 g of a 60% dispersion in mineral oil, 14 mmol, 1.4 equiv) was added. After 15 min, the reaction mixture was poured into cold water, extracted with Et_2O, the extract washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Column SiO_2 chromatography (25% of AcOEt in hexane) yielded *6-acetyl-1-phenyl-3H-pyrrolizine* **17** as a clear yellow oil (1.4 g, 65%); (found M^+, 223.0996. $C_{15}H_{13}NO$ requires *M*, 223.0997); ν_{max} (film): 741, 1072, 1185, 1198, 1258, 1375, 1445, 1491, 1506, 1640 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.48 (3H, s, CH_3), 4.68 (2H, d, *J* 2.3, CH_2), 6.50 (1H, t, *J* 2.3, CH), 6.70 (1H, s, pyrrole H), 7.46 (3H, m, ArH), 7.64 (1H, s, pyrrole H), 7.75 (2H, d, *J* 7.5, ArH); ^{1}H-NMR (300 MHz, $(CD_3)_2CO$): δ 2.34 (3H, s, CH_3), 4.74 (2H, bs, CH_2), 6.63 (1H, s, pyrrole H), 6.73 (1H, t, *J* 2.3, CH), 7.39 (1H, m, ArH), 7.47 (2H, t, *J* 7.3, ArH), 7.78 (1H, s, pyrrole H), 7.80 (2H, d, *J* 7.3, ArH); ^{13}C-NMR (75 MHz, $(CD_3)_2CO$): δ 26.4, 52.1, 98.3, 123.2, 124.6, 126.5, 128.7, 129.0, 130.2, 133.0,138.0, 140.9, 192.0; *m/z* (CI): 241 (MNH_4^+, 1%), 224 (MH^+, 100), 214 (4), 182 (1).

6-Acetyl-2,3-dihydro-1-phenyl-1*H*-pyrrolizine (18). To a stirred solution of 1-phenyl-6-acetyl-pyrrolizine **17** (2.67 g, 11.9 mmol) in MeOH (30 ml) was added Pd/C (0.27 g, 10%). The resulting mixture was purged three times with H_2, and left under a H_2 atmosphere overnight. The mixture was then purged with N_2, passed through a pad of celite, and evaporated to dryness. Column SiO_2 chromatography (30% of EtOAc in hexane) yielded *6-acetyl-2,3-dihydro-1-phenyl-1H-pyrrolizine* **18** as a clear oil (2.67 g, 98%); (found M^+, 225.1157. $C_{15}H_{15}NO$ requires *M*, 225.1154); ν_{max} (film): 751, 936, 1064, 1207, 1286, 1371, 1426, 1447, 1469, 1509, 1547, 1650 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.49 (3H, s, CH_3), 2.51 (1H, m, C*H*H), 2.99 (1H, m, CH*H*), 4.05 (1H, m, C*H*H), 4.16 (1H, m, CH*H*), 4.40 (1H, t, *J* 7.7, CH), 6.29 (1H, s, H pyrrole), 7.25-7.31 (3H, m, ArH), 7.29 (1H, s, H pyrrole), 7.33-36 (2H, d, *J* 7.5, ArH); ^{1}H-NMR (300 MHz, $(CD_3)_2CO$): δ 2.35 (3H, s, CH_3), 2.40 (1H, m, C*H*H), 2.92 (1H, m, CH*H*), 4.02 (1H, m, C*H*H), 4.15 (1H, m, CH*H*), 4.32 (1H, t, *J* 7.7, CH), 6.12 (1H, s, H pyrrole), 7.20 (3H, t, ArH), 7.27 (2H, m, ArH), 7.52 (1H, s, H pyrrole); ^{13}C-NMR (75 MHz, $(CD_3)_2CO$): δ 26.8, 38.5, 43.0, 45.8, 101.2, 119.4, 126.8, 127.2, 128.6, 130.3, 140.8, 142.2, 193.7; *m/z* (CI): 226 ($M+H^+$, 100%), 214 (5).

6-Ethyl-2,3-dihydro-1-phenyl-1*H*-pyrrolizine (19). To a stirred suspension of $AlCl_3$ (0.23 g, 1.73, 3 equiv) in CH_2Cl_2 (7 ml) at rt was added *t*-$BuNH_2BH_3$ (0.23 g, 1.73 mmol, 3 equiv). The

mixture was stirred for 30 min and a solution of 6-acetyl-2,3-dihydro-6-phenyl-1*H*-pyrrolizine **18** (0.13 g, 0.57 mmol) in CH_2Cl_2 (3 ml) was added. After 2 h the reaction mixture was poured onto ice and extracted with CH_2Cl_2. The combined organic extracts were rapidly washed with dil. citric acid, sat. aq. $NaHCO_3$, then brine, dried over $MgSO_4$ and concentrated under reduced pressure. Column SiO_2 chromatography (10% of EtOAc in hexane) yielded *6-ethyl-2,3-dihydro-1-phenyl-1H-pyrrolizine* **19** as a clear oil (0.9 g, 74%); (found M^+, 211.1357 $C_{15}H_{17}N$ requires *M*, 211.1361); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.12 (3H, t, *J* 7.5, CH_3), 2.28 (1H, m, C*H*H), 2.44 (2H, q, *J* 7.5, CH_2), 2.81 (1H, m, CH*H*), 3.84 (1H, m, C*H*H), 3.95 (1H, m, CH*H*), 4.25 (1H, t, *J* 7.7, CH), 5.20 (1H, s, pyrrole H), 6.40 (1H, s, pyrrole H), 7.14-7.25 (5H, m, ArH); ^{1}H-NMR (300 MHz, $(CD_3)_2CO$): δ 1.05 (3H, t, *J* 7.5, CH_3), 2.20 (1H, m, C*H*H), 2.35 (2H, q, *J* 7.5, CH_2), 2.80 (1H, m, CH*H*), 3.80 (1H, m, C*H*H), 3.95 (1H, m, CH*H*), 4.20 (1H, t, *J* 7.7, CH), 5.43 (1H, s, H pyrrole), 6.35 (1H, s, H pyrrole), 7.15 (5H, m, ArH); *m/z* (CI): 212 (MH^+, 100%), 186 (62), 96 (20).

2-(2-Nitrobenzoyl)-1-phenylsulfonylpyrrole (20). To a stirred solution of $SnCl_4$ (9.4 ml, 36.22 mmol, 1.5 equiv) in anhydrous 1,2-dichloroethane (150 ml) at -10 °C, was added slowly *o*-nitrobenzoyl chloride (6.27 g, 33.81 mmol, 1.4 equiv). The resulting mixture was stirred for 10 min. A solution of 1-phenylsulfonylpyrrole[48] (5 g, 24.2 mmol) in 1,2-dichloroethane (100 ml) was added dropwise, and the mixture stirred at -10 °C for 30 min and at rt for 90 min. The reaction was then poured into ice water and extracted with CH_2Cl_2. The combined organic extracts were washed with sat. aq. $NaHCO_3$, then brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column SiO_2 chromatography (10-20-30% of AcOEt in hexane) afforded *2-(2-nitrobenzoyl)-1-phenylsulfonylpyrrole* **20** as a white solid (4.87 g, 57%), mp 133-134 °C; (found MH^+, 357.0549. $C_{17}H_{12}N_2SO_5$ requires *MH*, 357.0554); ν_{max} (film): 726, 1061, 1154, 1346, 1448, 1429, 1527, 1663, 3649 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.34 (1H, m, pyrrole H), 6.50 (1H, dd, *J* 3.8, 1.8 pyrrole H), 7.51 (2H, dd, *J* 7.7, 1.6 ArH), 7.67 (4H, m, ArH), 7.97 (1H, dd, *J* 3.2, 1.8, pyrrole H), 8.12 (3H, m, ArH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 110.7, 122.0, 124.3, 126.8, 128.4, 128.8, 129.2, 130.6, 131.4, 133.6, 134.0, 135.3, 146.7, 179.8; *m/z* (CI): 374 (MNH_4^+, 42%), 357 (MH^+, 100), 93 (50).

2-(2-Nitrobenzoyl)pyrrole. To a stirred solution of 1-(phenylsulfonyl)-2-(2-nitrobenzoyl)pyrrole **20** (2.7 g, 7.5 mmol) in MeOH (150 ml) was added 2 M NaOH (6 ml, 12 mmol, 1.6) equiv and the resulting mixture was refluxed for 4 h. After cooling to rt, the solvent was evaporated under reduced pressure, water was added (15 ml) and the pH adjusted to 4-5 by dropwise addition of 2 M HCl. The suspension was extracted with $CHCl_3$ and the combined organic extracts washed with brine, dried over $MgSO_4$ and concentrated to give 2-(2-nitrobenzoyl)pyrrole as a yellowish solid (1.23 g, 74%). An analytical sample was purified by column SiO_2 chromatography (20% of AcOEt in hexane), mp 137-139 °C, lit[43] 138-140 °C; ν_{max} (film): 895, 1347, 1401, 1526, 1625, 3292 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.31 (1H, m, pyrrole H), 6.51 (1H, m, pyrrole H), 7.21 (1H, m, pyrrole H), 7.63 (1H, td, *J* 7.4, 1.6 ArH), 7.70 (1H, dd, *J* 8.0, 1.6, ArH), 7.76 (1H, td, *J* 7.4, 1.4, ArH), 8.18 (1H, dd, *J* 8.0, 1.4, ArH), 9.75 (1H,

bs, NH); ^{13}C-NMR (75 MHz, CD_3CO): δ 110.8, 119.2, 124.7, 127.0, 129.7, 131.1, 131.2, 133.8, 135.6, 148.1, 181.2; *m/z* (CI): 234 (MNH_4^+, 100%), 217 (MH^+, 10), 187 (24).

4-Acetyl-2-(2-nitrobenzoyl)pyrrole (21). To a stirred suspension of $AlCl_3$ (2.46 g, 18.5 mmol, 4 equiv) in 1,2-dichloroethane (50 ml), acetic anhydride (1.3 ml, 13.8 mmol, 3 equiv) was added slowly. After 30 min stirring at rt, a solution of 2-(2-nitrobenzoyl)pyrrole (1 g, 4.6 mmol) in 1,2-dichloroethane (10 ml) was added and the reaction mixture was left at reflux overnight. The reaction mixture was poured onto ice water, extracted with CH_2Cl_2, the extract washed with brine, dried over $MgSO_4$ and concentrated. Column SiO_2 chromatography (25-50% of AcOEt in hexane) afforded *4-acetyl-2-(2-nitrobenzoyl)pyrrole* **21** as an orange solid (0.81 g, 68%), mp 151 °C; (found M^+, 258.0637. $C_{13}H_{10}N_2O_4$ requires *M*, 258.0641); ν_{max} (film): 708, 1347, 1377, 1526, 1551, 1637 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.44 (3H, s, CH_3), 6.87 (1H, s, pyrrole H), 7.60 (1H, d, *J* 7.3, ArH), 7.74 (1H, s, pyrrole H), 7.76 (2H, m, ArH), 8.18 (1H, d, *J* 8.0, ArH), 9.84 (1H, bs, NH); ^{1}H-NMR (300 MHz, $(CD_3)_2CO$): δ 2.20 (3H, s, CH_3), 6.90 (1H, s, pyrrole H), 7.75 (1H, d, *J* 7.3, ArH), 7.92 (3H, m, pyrrole H + ArH), 8.25 (1H, d, *J* 8.0, ArH); ^{13}C-NMR (75 MHz, CD_3CO): δ 26.7, 117.5, 124.9, 128.1, 129.6, 130.0, 131.9, 133.1, 134.2, 135.6, 139.4, 182.5, 192.2; *m/z* (CI): 276 (MNH_4^+, 46%), 259 (MH^+, 5), 229 (100).

2-Phenyl-4*H*-benzoxazin-4-one (22). To a stirred mixture of anthranilic acid (8.88 g, 64.8 mmol) in THF (130 ml) at 0-5 °C, Na_2CO_3 (powder, 13.73 g, 129.6 mmol, 2 equiv) was added followed by benzoyl chloride (18.8 ml, 162 mmol, 2.5 equiv). After 10 min, the cold bath was removed and the mixture was stired at rt overnight. Water (130 ml), was added and the mixture was stirred for 10 min prior to filtration. The solid was washed with water and then 50% aq. MeOH. The additional material precipitated from the filtrate was collected by filtration and washed. The combined crops were dried at 50 °C under high vacuum to give 2-phenyl-4*H*-benzoxazin-4-one **22** (14.2 g, 98%) as a white solid, mp 119 °C, lit[49] 124 °C; Λ_{max} (film): 765, 1257, 1688, 1762 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): ∝ 7.55 (4H, m, ArH), 7.72 (1H, dd, *J* 8.2, 0.69, ArH), 7.86 (1H, dt, *J* 7.6, 1.6, ArH), 8.27 (1H, dd, *J* 7.6, 1.5, ArH), 8.34 (2H, dd, *J* 8.2, 1.5, ArH); ^{13}C-NMR (75 MHz, $CDCl_3$): ∝ 127.1, 128.1, 128.2, 128.7, 130.1, 132.5, 133.7, 136.5, 146.9, 157.4, 159.8, 171.2; *m/z* (CI): 224 (MH^+, 100%), 105 (20).

***N*-[2-(1*H*-Pyrrol-2-ylcarbonyl)phenyl]benzamide (23).** After a solution of EtMgCl (52.5 ml, 2 M solution in THF, 105 mmol, 2.1 equiv) in anhydrous THF (20 ml) was cooled to 0 °C, a solution of freshly distilled pyrrole (7.98 ml, 115 mmol, 2.3 equiv) in dry toluene (7.98 ml) was added dropwise over 20 min, keeping the mixture in an ice bath. After the mixture was stirred to rt for 20 min, a suspension of 2-phenyl-4*H*-benzoxazin-4-one **22** (11.15 g, 50 mmol) in THF (35 ml) was added. After 45 min stirring, the mixture was refluxed for 3 h. Sat. aq. NH_4Cl (11.5 ml) was then added to the hot mixture over 5 min. After 20 min of stirring, Na_2SO_4 (11.5 g) was added. The suspension was stirred for 20 min prior to filtration. The collected solid was washed with THF, and the combined organic filtrate and washes were concentrated to dryness. The residue was suspended in toluene (50 ml), and the suspension cooled in an ice bath for 20 min. The solid was collected by filtration and washed with hexane. Drying at rt overnight under high vacuum gave *N*-[2-(1*H*-pyrrol-2-ylcarbonyl)phenyl]benzamide **23** as light green crystals (11.7 g, 81%). An analytical sample was recrystallised from acetone, mp 185 °C, lit[50]

(mp not given); ν_{max} (film): 760, 888, 1127, 1500, 1335, 1393, 1421, 1513, 1590, 1658, 3277 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.28 (1H, m, pyrrole H), 6.81 (1H, m, pyrrole H), 7.17 (1H, m, pyrrole H), 7.23 (1H, dt, 7.8, 0.8, ArH), 7.42 (3H, m, ArH), 7.53 (1H, t, *J* 7.8, ArH), 7.91 (3H, dt, *J* 7.8, 1.5, ArH), 8.69 (1H, d, *J* 8.3, 0.8, ArH), 9.63 (1H, bs, NH), 11.04 (1H, bs, NH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 111.5, 120.9, 121.5, 122.5, 124.5, 126.1, 127.2, 128.7, 131.3, 131.4, 131.8, 133.2, 134.7, 139.5, 165.5, 186.1; *m/z* (CI): 308 (MNH_4^+, 13%), 291 (MH^+, 100), 124 (46), 105 (92), 68 (79).

***N*-[2-(4-Acetyl-1*H*-pyrrol-2-ylcarbonyl)phenyl]benzamide (24a).** Acetic anhydride (6.1 ml, 64.68 g, 2.68 equiv) was added at 0 °C to a suspension of aluminium chloride (19.31 g, 144.8 mmol, 6 equiv) in CH_2Cl_2 (50 ml). After 30 min of stirring at rt, the reaction mixture was cooled at 0 °C and then a solution of *N*-[2-(1*H*-pyrrol-2-ylcarbonyl)phenyl]benzamide **23** (7 g, 24.13 mmol) in CH_2Cl_2 (50 ml) was added and the reaction was allowed to warm to rt overnight. The reaction mixture was poured into cold water, extracted with CH_2Cl_2, the extract washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Column SiO_2 chromatography (50-100% of EtOAc in hexane) gave *N-[2-(4-acetyl-1H-pyrrol-2-ylcarbonyl)phenyl]benzamide* **24a** (5.75 g, 72%) as a white crystalline solid, mp 179 °C; (found M^+, 332.1161. $C_{20}H_{16}N_2O_3$ requires *M*, 332.1161); ν_{max} (film): 755, 1076, 1247, 1298, 1407, 1445, 1524, 1590, 1678, 3649, 3854 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.38 (3H, s, CH_3), 7.15 (1H, t, *J* 7.8, ArH), 7.18 (1H, m, pyrrole H), 7.43 (3H, m, ArH), 7.56 (1H, t, *J* 7.8, ArH), 7.61 (1H, m, pyrrole H), 7.92 (3H, d, *J* 7.8, ArH), 8.69 (1H, d, *J* 8.3, ArH), 10.06 (1H, bs, NH), 11.37 (1H, bs, NH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 27.3, 119.0, 121.6, 122.8, 123.4, 127.2, 127.9, 128.3, 128.5, 128.7, 131.4, 131.9, 134.1, 134.5, 139.8, 165.5, 186.6, 193.1; *m/z* (EI): 332 (M^+, 17%), 196 (33), 105 (21), 49 (100).

***N*-[2-(4-Acetyl-1-methylpyrrol-2-ylcarbonyl)phenyl]benzamide (24b).** To a stirred solution of *N*-[2-(4-acetyl-1*H*-pyrrol-2-ylcarbonyl)phenyl]benzamide **24a** (0.15 g, 0.45 mmol) in anhydrous THF (10 ml) at 0 °C, NaH (0.019 g, 60% dispersion in mineral oil, 0.495 mmol, 1.1 equiv) was added and the reaction was left stirring for 30 min before the addition of methyl iodide (0.028 ml, 0.45 mmol, 1 equiv). The reaction mixture was allowed to warm up to rt overnight. It was then poured into cold water, product extracted into CH_2Cl_2, the extract washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Column SiO_2 chromatography (25-50% of EtOAc in hexane) afforded *N-[2-(4-acetyl-1-methylpyrrol-2-ylcarbonyl)phenyl]benzamide* **24b** (0.075 g, 50%) as a white solid, mp 140 °C; (found M^+, 346.1312. $C_{21}H_{18}N_2O_3$ requires *M*, 346.1317); ν_{max} (film): 759, 919, 1196, 1268, 1384, 1447, 1525, 1580, 1597, 1670 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.45 (3H, s, CH_3), 4.09 (3H, s, NCH_3), 7.09 (1H, d, *J* 1.9, pyrrole H), 7.22 (1H, dt, *J* 7.5, 1.1, ArH), 7.56 (4H, m, 3ArH and pyrrole H), 7.67 (1H, t, *J* 7.8, ArH), 7.87 (3H, dd, *J* 7.8, 1.5, ArH), 8.04 (2H, dd, *J* 8.0, 1.5), 8. 80 (1H, d, *J* 8.0, 1.5 ArH), 11.40 (1H, bs, NH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 27.1, 37.9, 121.6, 122.4, 122.5, 124.6, 124.9, 127.2, 128.7, 131.3, 131.9, 132.2, 133.7, 134.1, 134.6, 139.8, 165.5, 184.6, 192.7; *m/z* (CI): 347 (MH^+, 100%), 223 (40), 124 (79), 104 (78), 94 (64), 74 (72), 58 (99).

2-Aminophenyl 4-acetylpyrrol-2-yl ketone (25). A mixture of *N*-[2-(4-acetyl-1*H*-pyrrol-2-ylcarbonyl)phenyl]benzamide **24a** (2.18 g, 6.3 mmol, 1 equiv), 10 M NaOH (2 ml) and MeOH (7 ml) was heated at reflux overnight. Water (10 ml) was added and the mixture was slowly cooled down to rt and left stirring for 3 h (pH was adjusted to neutral). The reaction mixture was extracted with CH_2Cl_2, the extract washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Column SiO_2 chromatography (25% of EtOAc in hexane) gave *2-aminophenyl 4-acetylpyrrol-2-yl ketone* **25** (1.21 g, 81%) as a yellow solid, mp 129-130 °C; (found M^+, 228.0898. $C_{13}H_{12}N_2O_2$ requires *M*, 228.0899); ν_{max} (film): 1212, 1259, 1293, 1379, 1430, 1546, 1582, 1614, 1655, 3261, 3347 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.39 (3H, s, CH_3), 5.63 (2H, bs, NH_2), 6.67 (2H, m, pyrrole H), 7.16 (1H, m, ArH), 7.25 (1H, dt, *J* 8.2, 1.5, ArH), 7.58 (1H, m, ArH), 7.82 (1H, dd, *J* 8.2, 1.5, ArH), 9.84 (1H, bs, NH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 26.7, 115.4, 116.4, 117.1, 118.3, 127.4, 128.3, 131.9, 132.8, 133.8, 151.1, 186.1, 192.4; *m/z* (CI): 246 (MNH_4^+, 5%), 229 (MH^+, 100).

4-Acetylpyrrol-2-yl 2-(dimethylaminomethylenamino)phenyl ketone (26). To a stirred solution of 2-aminophenyl 4-acetylpyrrol-2-yl ketone **25** (0.8 g, 3.5 mmol) in anhydrous DMF (5 ml), *t*-butoxybis(dimethylamino)methane (Bredereck's reagent) (0.86 ml, 4.2 mmol, 1.2 equiv) was added and the reaction mixture was left to stir at rt for 48 h. The reaction mixture was then extracted with CH_2Cl_2, the extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column SiO_2 chromatography (50-100% of EtOAc in hexane + 1% of Et_3N) and subsequent recrystallisation from EtOH afforded *4-acetylpyrrol-2-yl 2-(dimethylaminomethylenamino)phenyl ketone* **26** as a white-yellow solid (0.8 g, 82%), mp 178-179 °C; (found C, 67.92; H, 5.86; N, 14.46%; $C_{16}H_{17}N_3O_2$ requires C, 67.83, H, 6.05, N, 14.83%); ν_{max} (film): 1098, 1375, 1414, 1432, 1632 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.43 (3H, s, CH_3), 2.86 (3H, bs, NCH_3), 2.98 (3H, bs, NCH_3), 6.95 (1H, d, *J* 8.1, ArH), 7.10 (1H, t, *J* apparent t, *J* 7.9, ArH), 7.16 (1H, s, pyrrole H), 7.42 (1H, apparent t, *J* 7.9, ArH), 7.47 (1H, s, CH), 7.50 (1H, m, ArH), 7.59 (1H, s, pyrrole H), 11.05 (1H, bs, NH); ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): δ 27.6, 118.3, 121.2, 122.6, 127.1, 127.6, 129.7, 131.9, 132.0, 133.4, 134.1, 153.7, 186.9, 194.0; *m/z* (CI): 284 (MH^+, 70%), 110 (37), 74 (100).

6-Acetyl-1-(2-(dimethylaminomethylenamino)phenyl)-3*H*-pyrrolizine (27). To a stirred suspension of 4-acetylpyrrol-2-yl 2-(dimethylaminomethylenamino)phenyl ketone **26** (0.65 g, 2.29 mmol) and vinyltriphenylphosphonium bromide (0.82 g, 2.29 mmol, 1 equiv) in anhydrous THF (50 ml) at –10 °C, NaH (0.124 g of a 60% dispersion in mineral oil, 3.1 mmol, 1.35 equiv) was added. After 20 min, the reaction mixture was poured into cold water, extracted with Et_2O, the extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Column SiO_2 chromatography (25-50% of AcOEt in hexane + 1% of Et_3N) yielded *6-acetyl-1-(2-(dimethylaminomethylenamino)phenyl)-3H-pyrrolizine* **27** as a clear yellow oil (0.217 g, 32%); (found M^+, 293.1577. $C_{18}H_{19}N_3O$ requires *M*, 293.1578); ν_{max} (film): 759, 1097, 1182, 1207, 1448, 1287, 1372, 1436, 1478, 1504, 1589, 1632 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.45 (3H, s, CH_3), 3.05 (6H, s, $N(CH_3)_2$), 4.66 (2H, bs, CH_2), 6.56 (1H, bs, CH), 6.87 (1H, s, H pyrrole), 6.90 (1H, m, ArH), 7.14 (1H, apt, *J* 7.5, ArH), 7.28 (1H, m, ArH), 7.48 (1H, s, NCHN), 7.59 (1H, s, H pyrrole), 7.74 (2H, apd, *J* 7.5, ArH); ^{1}H-NMR (300 MHz, $(CD_3)_2CO$):

δ 2.32 (3H, s, CH_3), 2.99 (3H, bs, NCH_3), 3.04 (3H, bs, NCH_3), 4.74 (2H, bs, CH_2), 6.48 (1H, bs, CH), 6.89 (1H, t, *J* 7.3, ArH), 7.05 (1H, m, pyrrole H), 7.07 (1H, s, NCHN), 7.22 (1H, t, *J* 7.3, ArH), 7.33 (1H, t, *J* 7.3, ArH), 7.58 (1H, s, pyrrole H), 7.73 (2H, d, *J* 7.3, ArH); ^{13}C-NMR (75 MHz, $(CD_3)_2CO$): δ 26.4, 27.2, 52.6, 99.1, 117.8, 120.7, 121.0, 122.2, 122.7, 123.0, 126.7, 129.1, 129.4, 130.5, 134.7, 153.6, 192.6; *m/z* (CI): 294 (MH^+, 100%).

6-Acetyl-1-(2-(dimethylaminomethylenamino)phenyl)-2,3-dihydro-1*H*-pyrrolizine (28). To a stirred solution of 6-acetyl-2-dimethylaminomethylenamino)phenylpyrrolizine **27** (0.18 g, 0.61 mmol, 1 equiv) in MeOH (3 ml) was added Pd/C (0.018 g, 10% by wt). The resulting mixture was purged three times with H_2, and left under a H_2 atmosphere overnight. The mixture was then purged with N_2, passed through a pad of celite, and evaporated to dryness. Column SiO_2 chromatography (50-100% of EtOAc in hexane, 1% Et_3N) yielded *6-acetyl-1-(2-(dimethylaminomethylenamino)phenyl)-2,3-dihydro-1H-pyrrolizine* **28** as a clear yellow oil (0.071 g, 39%); (found M^+, 295.1685. $C_{18}H_{21}N_3O$ requires *M*, 295.1685); ν_{max} (film): 1100, 1207, 1370, 1435, 1589, 1693, 3258 cm^{-1}; ^{1}H-NMR (300 MHz, $(CD_3)_2CO$): δ 2.28 (3H, s, CH_3), 2.36 (1H, m, C*H*H), 2.93 (1H, m, CH*H*), 3.04 (6H, s, $N(CH_3)_2$), 4.03 (1H, m, C*H*H), 4.13 (1H, m, CH*H*), 4.87 (1H, t, *J* 7.7, CH), 6.07 (1H, s, H pyrrole), 6.86 (2H, m, ArH), 7.02 (1H, d, *J* 7.6, ArH), 7.10 (1H, dt, *J* 7.6, 1.3, ArH), 7.41 (1H, s, pyrrole H), 7.62 (1H, s, NCHN); ^{13}C-NMR (75 MHz, $(CD_3)_2CO$): δ 25.8, 28.2, 36.8, 38.2, 45.4, 99.7, 118.3, 119.3, 121.9, 126.2, 127.1, 127.2, 135.8, 141.5, 150.0, 152.4, 191.2 ; *m/z* (CI): 296 (MH^+, 100%), 280 (5), 149 (2).

1-(2-Aminophenyl)-6-ethyl-2,3-dihydro-1*H*-pyrrolizine 30 and 1-(2-(dimethylaminomethyl enamino)phenyl)-6-ethyl-2,3-dihydro-1*H*-pyrrolizine (29). To a stirred suspension of $AlCl_3$ (0.067 g, 0.51 mmol, 3 equiv) in CH_2Cl_2 (5 ml) at rt was added *t*-$BuNH_2BH_3$ (0.088 g, 1.02 mmol, 6 equiv). The mixture was stirred for 30 min and then a solution of 6-acetyl-2-dimethylaminomethylenamino)phenyl-2,3-dihydro-1*H*-pyrrolizine **25** (0.05 g, 0.17 mmol, 1 equiv) in CH_2Cl_2 (2 ml) was added. After 2 h the reaction was poured into ice and extracted with CH_2Cl_2. The combined organic extracts were washed with sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Column SiO_2 chromatography (10% of EtOAc in hexane) provided firstly *1-(2-aminophenyl)-6-ethyl-2,3-dihydro-1H-pyrrolizine* **30** (0.015 g, 40%) and secondly *1-(2-(dimethylaminomethylenamino)phenyl)-6-ethyl-2,3-dihydro-1H-pyrrolizine* **29** (0.006 g, 12%), both as clear oils; *spectroscopic data* for **30**: (found M^+, 226.1470. $C_{15}H_{18}N_2$ requires *M*, 226.1470); ^{1}H-NMR (300 MHz, $(CD_3)_2CO$): δ 1.14 (3H, t, *J* 7.5, CH_3), 2.28 (1H, m, C*H*H), 2.44 (2H, q, *J* 7.5, CH_2), 2.88 (1H, m, CH*H*), 3.86 (1H, m, C*H*H), 3.95 (1H, m, CH*H*), 4.34 (1H, t, *J* 7.3, CH), 4.36 (2H, bs, NH_2), 5.80 (1H, s, pyrrole H), 6.45 (1H, s, pyrrole H), 6.53 (1H, dt, *J* 7.4, 1.1, ArH), 6.70 (1H, dd, *J* 7.9, 1.1, ArH), 6.90 (2H, m, ArH); ^{13}C-NMR (75 MHz, $(CD_3)_2CO$): δ 15.5, 20.5, 36.0, 39.6, 46.3, 100.4, 111.4, 116.3, 117.9, 123.6, 125.3, 126.5, 127.2, 127.9, 139.1; *m/z* (CI): 227 (MH^+, 100%), 197 (1), 170 (1);
spectroscopic data for **29**: (found M^+, 281.1896 $C_{18}H_{23}N_3$ requires *M*, 281.1892); ^{1}H-NMR (300 MHz, $(CD_3)_2CO$): δ 1.13 (3H, t, *J* 7.6, CH_3), 2.15 (1H, m, C*H*H), 2.42 (2H, q, *J* 7.6, CH_2), 2.85 (1H, m, CH*H*), 3.01 (6H, bs, $N(CH_3)_2$), 3.83 (1H, m, C*H*H), 3.94 (1H, m, CH*H*), 4.78 (1H, t, *J* 7.3, CH), 5.48 (1H, s, pyrrole H), 6.41 (1H, s, pyrrole H), 6.77 (1H, dd, *J* 7.6, 1.2, ArH), 6.83 (1H, dt, *J* 7.6, 1.2, ArH), 7.03 (2H, m, ArH), 7.58 (1H, s, NCHN); *m/z* (CI): 282 (MH^+, 100%).

6-Ethyl-2,3,4,7a-tetrahydro-7a-hydroxy-1*H-1*-phenylpyrrolizin-5-one (31). To a stirred solution of 6-ethyl-2,3-dihydro-1-phenyl-1*H*-pyrrolizine **19** (0.07 g, 0.33 mmol) in CH_2Cl_2 (20 ml) at -78 °C was added methylene blue (3.3 ml of a 0.001 M solution in CH_2Cl_2, 0.0033 mmol, 0.01 equiv). The mixture was maintained at -78 °C and irradiated for 90 min with a Hg medium pressure lamp. The solvent was evaporated at less than 45 °C, and the residue purified by column SiO_2 chromatography (5-25-50% of EtOAc in hexane) to give **31** as a yellow oil (0.019 g, 24%); (found M^+, 243.1262. $C_{15}H_{17}NO_2$ requires M, 243.1259); ν_{max} (film): 1069, 1409, 1446, 1706, 2928, 3191-3400 cm^{-1}; ^{1}H-NMR (300 MHz, CD_3CO): δ 1.22 (3H, t, *J* 7.5, CH_3), 2.01 (2H, m, C*H*H), 2.41 (2H, q, *J* 7.5, CH_2), 2.87 (1H, m, CH*H*), 3.50 (1H, m, C*H*H), 3.82 (1H, t, *J* 7.7, CH), 7.30 (1H, s, pyrrole H), 7.35 (2H, m, ArH), 7.47 (2H, apd, *J* 7.5, ArH), 7.52 (1H, apt, *J* 7.5, ArH); ^{13}C-NMR (75 MHz, CD_3CO): δ 12.5, 20.4, 36.7, 39.7, 68.0, 120.7, 127.8, 128.7, 129.6, 135.1, 140.0, 158.8, 188.6; *m/z* (CI): 243 (MH^+, 14%), 226 (100).

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