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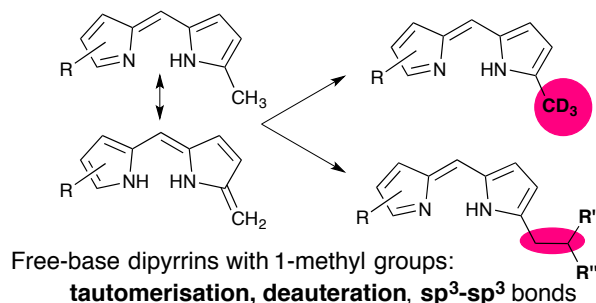
Deuteration and Tautomeric Reactivity of the 1-Methyl Functionality of Free-base Dipyrrins

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TOC graphic



Abstract

Regioselective reactivity of the 1-methyl group of free-base dipyrrins is explored, including discussion of tautomerism to provide exocyclic alkenyl reactivity. Deuterium is installed such as to generate dipyrrins substituted with deuterated methyl groups. Furthermore, the 1-methyl group reacts to become involved in C–C bonds involving only sp^3 -hybridised carbon atoms. The isolation of an elusive framework featuring a dipyrrin substituted with a pyrrole in a non-vinylous fashion is also reported. The use of asymmetric dipyrrins featuring an electron-withdrawing group on one of the pyrrolic units results in regioselective reaction of the alpha-methyl group distal to the electron-withdrawing group.

Introduction

Dipyrrins¹ were traditionally used as synthetic intermediates for the construction of porphyrins. However, recent interest in the dipyrrinato framework arises from the stunning optical properties, as well as tunable functionality, exhibited by dipyrrinato complexes.²⁻⁶ In particular, boron

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dipyrinato complexes, particularly *F*-BODIPYs, are widely used in applications such as molecular imaging and energy devices that rely upon the electronic properties of the core chelated skeleton.⁷ Likewise, reactivity promoted by Ti(IV),⁸ Mn(III),⁹ Fe(II),¹⁰⁻¹² Co(III),¹³ Rh(I),¹⁴ Rh(III),¹⁵ Ir(III),¹⁵ Sn(IV)⁸ and Pd(II)¹⁶ complexes of the dipyrinato ligand demonstrates early promise for the use of dipyrins in catalysis.

Most synthetic methodologies for manipulating the substituents about the pyrrolic and azafulvenium moieties of dipyrins involve their metal complexes, presumably because the acid/base characteristics of the nitrogen-based functionality of dipyrin free-bases and salts interfere with the success of many reactions.¹ Similarly, the chelating ability of the dipyrinato framework has been shown to be detrimental to reactions involving metal-promoted catalysis, and thus protection, and subsequent, deprotection of the dipyrin is required.^{17, 18} An alternative strategy by which to alter the nature of substituents about the dipyrinato core involves functionalizing constituent pyrroles or dipyrromethanes prior to oxidation of the central meso carbon atom to form the methylene CH= unit of the dipyrin.^{1, 19, 20} There therefore rests significant opportunity for the development of synthetic techniques to functionalise free-base dipyrins, thereby removing the requirement for protection/deprotection and instead enabling convergent syntheses that involve derivatization of a common dipyrin rather than early pyrrolic precursors.

As shown in Figure 1, a dipyrin substituted with a methyl group in the 1-position can formally be considered to exist as tautomers **A-C**,²¹ with **A** and **B** being dominant. Discussions regarding the 1-methyl group of dipyrins have suggested that reactivity follows that of the constituent 2-methyl pyrrole unit and involve an oxidative or radical mechanism.²¹ However, provided the tautomeric form **C** is conceivable, reactions such as the addition of molecular

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bromine may also involve electrophilic addition.²²⁻²⁴ The 1-methyl position of such substituted dipyrriins has been employed in carbon-carbon bond formation via base-catalyzed Knoevenagel condensations yielding conjugated, vinylagous products.^{25, 26} It is worth pondering whether such reactivity involves initial deprotonation of the 1-methyl group, which seems unlikely, or whether in fact the exo-cyclic tautomeric state **C** (Figure 1) is responsible for reaction with the aldehyde within a Knoevenagel condensation. Through exploring the use of thermal conditions to induce reactivity of 1-methyl dipyrriins in the absence of a base, we have explored the culpability of tautomeric form **C**.

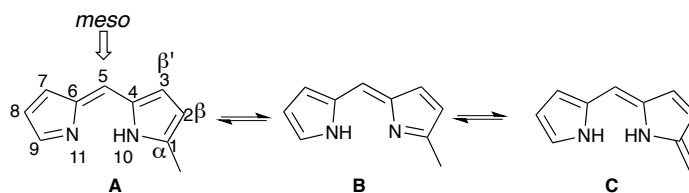


Figure 1. Tautomers of 1-methyl dipyrriin

Results and Discussion

Our interest in the reactivity of 1-methyl dipyrriins was inspired by the knowledge that free-base *meso*-H dipyrriins are much less stable than their crystalline HBr salts. Cognizant that such free-base *meso*-H dipyrriins decompose upon heating or extended exposure to air, we sought to investigate the intermediates en route to decomposition, with a goal of harnessing the reactivity for the purpose of generating useful derivatives. We began by washing a solution of **1**•HBr in CH₂Cl₂ with 1 M NaOH to produce the free-base **1** (Scheme 1). A solution of the free-base **1** in anhydrous methanol was then stirred at reflux temperature for four hours using conventional heating (oil bath, Table 1, entry 1). Although the majority of the starting material was recovered, the formation of black, amorphous material was also observed. The experiment was repeated in anhydrous toluene at 80 and 100 °C for 12 hours (Table 1, entries 2 and 3). Increased reactivity

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was evident via observation of the colour of the reaction mixture after heating: what had previously been a clear, bright yellow solution had darkened to brown. Alongside significant base-line material, analysis of the reaction mixtures using TLC analysis revealed a dark yellow apolar material. Repeating the experiments using microwave-promoted conditions (Table 1, entries 4 and 5) revealed that exposure to 100 °C for 15 minutes enabled the isolation of this material (**2**). Extended heating and higher temperatures led to complete degradation of **1**. In contrast, a solution of the corresponding salt **1•HBr** survived heating at 150 °C without decomposition (Table 1, entry 6).

Table 1. Effects of heating a solution of free-base dipyrin **1**

Entry	Heating	T (°C)	Time	Solvent	1 (% recov.)	2 (%)
1	Δ	65	4 h	MeOH	82	0
2	Δ	80	12 h	toluene	15	trace
3	Δ	100	12 h	toluene	0	trace
4	MW	80	15 min	MeOH	52	0
5	MW	100	15 min	MeOH	20	4
6 ^a	MW	150	15 min	MeOH/CHCl ₃	quant.	0

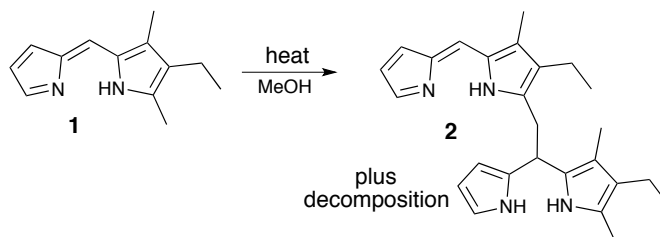
^asalt **1•HBr** used for reaction

Rapid flash chromatography over basic alumina was used to isolate **2**, which, given its dark yellow colour, was suspected to be a new free-base dipyrin. The stability of the compound was low, and attempts to purify via recrystallization were unsuccessful. Furthermore, washing a solution of **2** in CH₂Cl₂ with 1 M aq. HBr, in anticipation of generating the corresponding HBr

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salt of the dipyririn moiety, only resulted in formation of an insoluble tar-like product. Rapid manipulation, including minimal time exposed to the solid phase during chromatography, was crucial to the eventual isolation and characterization of a pure sample of **2**. Within the $^1\text{H-NMR}$ spectrum of **2**, it was evident that there were aromatic signals indicative of both dipyririn and pyrrole frameworks. The signal representing the 1-methyl CH_3 group of the starting material **1** (2.32 ppm) was no longer present, while a new signal (2.08 ppm) represented two overlapping methyl groups. Furthermore, there were two sets of ethyl signals. The appearance of a new methyl signal further up-field, relative to the methyl signals of **1**, was also observed (1.90 ppm), along with two new signals at 3.25 and 4.70 ppm representing two and one hydrogen atoms, respectively. Chemical shifts in the 3-5 ppm range are not typically observed for alkyl dipyrriins, but are to be expected for the central CH_x unit of dipyrromethanes. Analysis of **2** using ESI mass spectrometry revealed a signal at 401.3 m/z , corresponding to the mass value of two of the original dipyririn units, i.e. $[2 \times (\mathbf{1}+\text{H})]^+$. A structure for **2** was thus proposed whereby the 1-methyl functionality of the free-base had added to the *meso*-position of another equivalent of the original dipyririn (Scheme 1). This structure matched all data, including 2D NMR correlation (Supporting Information).

Scheme 1. Reactivity of asymmetrical 1-methyl dipyririn **1**.

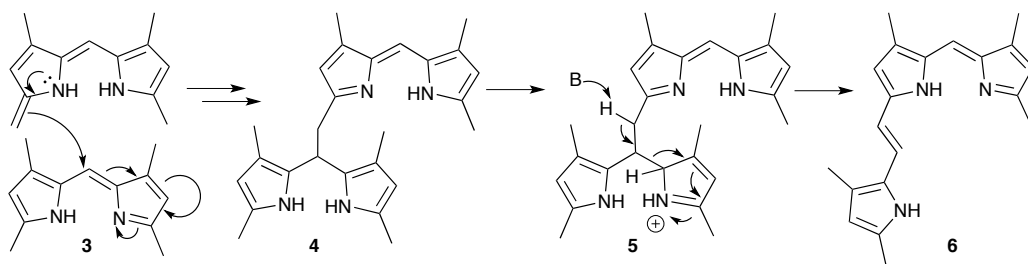


To the best of our knowledge, the framework of **2** has been proposed just once.²⁵ Treibs *et al.* observed a highly unstable dark yellow synthetic intermediate **4** after heating a solution of a free-base dipyririn **3** in methanol at reflux temperature under an ammonia atmosphere. Treibs

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acidified the unstable mixture and isolated the green/blue 1-(vinylpyrrolyl)-dipyrriin **6** in low yields alongside significant amounts of black amorphous byproducts. A compound analogous to **6** was subsequently reported by Bröring et al.,²⁶ following treatment with $\text{Mn}(\text{OAc})_2$ and oxygen.

Scheme 2. Reported reactivity of free-base dipyrriin 3



To investigate the notion that the tautomeric form **C** (Figure 1) of 1-methyl dipyrriins is accessible and reactive at elevated temperatures, we explored the possibility of deuterium exchange at this position. Using microwave-promoted conditions, a solution of dipyrriin **1** in methanol- d_4 was heated at 100 °C for 15 minutes (Table 2, entry 1) such as to effect formation of **2**, baseline products and 17% recovery of dipyrriin within which the 1-methyl position had been deuterated. Notably, as for the formation of **2**, no reactivity occurred below this temperature threshold. The ^1H -NMR spectrum of the recovered dipyrriin revealed that the methyl signal at 2.31 ppm had been significantly suppressed upon exposure to the deuteration conditions. Given the presence of D_1 , D_2 , D_3 , and D_4 dipyrriins, according to mass spectrometry, the methyl group would have undergone both partial and complete deuterium exchange but extended reaction time served merely to promote decomposition rather than to facilitate complete deuteration. Suppression of the signal due to the 1-methyl carbon atom was apparent in the ^{13}C -NMR spectrum of the recovered dipyrriin, as multiple 2J coupling with deuterium splits the signal corresponding to the carbon atom to below the detectable baseline. A solution of **1**•HBr did not undergo deuterium exchange, in keeping with the previous observation that the hydrobromide

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salt does not undergo ready reaction or decomposition under the conditions evaluated for the formation of **2**. Given these results, it is evident why storage of dipyrrens as their HBr salts is advantageous.

Table 2. Deuterium exchange of various 1-methyl dipyrins



Entry	Dipyrin	R ¹ :R ² :R ³ :R ⁴ :R ⁵ :R ⁶	Solvent	t (min)	T (°C)	Yield (%)
1	1	Et:Me:H:H:H:H	CD ₃ OD	15	100	17
2	7	Et:Me:H:Me:Et:Me	CD ₃ OD: CDCl ₃	15	150	15
3	8	Et:Et:H:H:H:H	CD ₃ OD	15	100	5
4	9	Et:Et:H:Me:H:H	CD ₃ OD	15	100	18 ^d
5	10^a	Et:Me:H:H:H:H	CD ₃ OD	15	100	0
6	11	Et:Me:Ph:Me:Et:Me	CD ₃ OD: CDCl ₃	30	150	40
7	12	CO ₂ Bn:Me:H:Me:Et:Me	CD ₃ OD: CDCl ₃	15	100	0 ^b
8	12	CO ₂ Bn:Me:H:Me:Et:Me	CD ₃ OD: CDCl ₃	15	150	81 ^{c,d}
9	13	CO ₂ Et:Me:H:Me:Et:Me	CD ₃ OD: CDCl ₃	15	150	89 ^{c,d}
10	14	COMe:Me:H:Me:Et:Me	CD ₃ OD: CDCl ₃	15	125	76 ^{c,d}

^aN-methyl protected on R⁴⁻⁶ pyrrolic unit; starting materials did not survive reaction conditions. ^bStarting materials reclaimed. ^cExchange only occurred on electron-rich pyrrolic unit. ^dFree-base product was sufficiently stable for conversion to HBr salt following isolation as free-base.

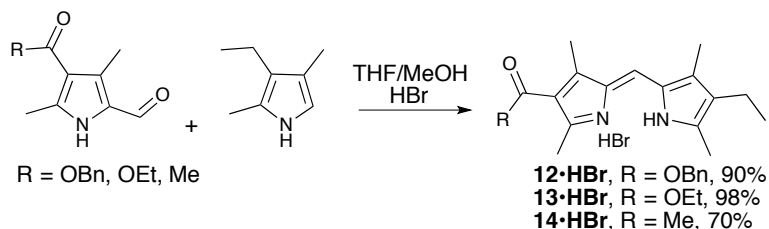
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Consistent with the fully unsubstituted dipyrin being barely stable,²⁷ we knew from attempts to transform the fully alkyl substituted dipyrin **7** (Table 2, entry 2) into tetra- and tri-pyrrolic skeletons akin to those of **4** and **6**, that this free-base was relatively stable at temperatures up to 150 °C. Clearly the more substituted analog **7** was more stable than **1**. At 150 °C, solutions of **7** in a 1:1 solution of methanol-d₄ and CDCl₃ reacted to form intractable material as well as a 1-(vinylpyrrolyl)-dipyrin with the same skeleton as **6**. However, the solvatochromic material derived from **7** was highly unstable and we were unable to isolate and characterise a pure sample. Such solvatochromic behaviour has been alluded to previously for similarly unstable polypyrrolic compounds.²⁶ Nevertheless, deuteration of free-base dipyrin **7** at 150 °C resulted in recovery of **7-D₇**. Notably, under these conditions, all six of the 1,9-dimethyl protons, plus N-H, underwent exchange, resulting in observation of the D₇ species via mass spectrometry. To unequivocally establish that reactivity was occurring at the 1-methyl (rather than 3-methyl) positions, dipyrin **7** (undeuterated) was fully characterised, as a free-base, using HSQC and HMBC experiments. Subsequent analysis of the deuterated material enabled the conclusive elucidation of the reactive methyl functionality at the α -position (see Supporting Information) matching the suggestions of Treibs *et al.* as shown in Scheme 2.²⁵

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A variety of other dipyrins were reacted to determine the scope of this deuteration technique. Free-base dipyrins **8** and **9** underwent deuteration (Table 2, entries 3 and 4), although the *N*-methylated derivative of **1**, compound **10**, did not (Table 2, entry 5). The inability of *N*-methyl 1-methyl dipyrin **10** to undergo deuteration supports the hypothesis that access to the exo-cyclic tautomeric state **C** (Figure 1) is crucial for the 1-methyl carbon atom to exhibit basic, or nucleophilic, reactivity. All examples of deuterium exchange were thus far performed on *meso*-H dipyrins. To determine whether *meso*-substitution affects this reactivity, a solution of *meso*-phenyl-1,9-dimethyl dipyrin **11** was subjected to microwave-promoted heating (Table 2, entry 6). Although considerable decomposition occurred, deuterated **11** was recovered in 40% yield. The *m/z* base-peak in the low-resolution mass spectrum correlated to the D₇ dipyrin. Interestingly, a mass spectrometric signal correlating to the D₉ species was differentiable from baseline noise, indicating minor deuterium exchange with hydrogen at positions other than the 1,9-dimethyl and *N-H* positions. This change was not detectable in either the ¹H or ¹³C spectra, supporting the notion that deuteration at the 1- and 9-positions is dominant, alongside exchange at the pyrrolic nitrogen.

Moving away from the simple alkyl substituted dipyrins, the role of electron withdrawing groups upon the deuterium exchange of 1-methyl protons was explored. The reactivity of pyrroles is significantly modified by the presence of carbonyl substitution at any of the ring positions,²¹ whereby the compound is generally less reactive and will tolerate harsher conditions.²⁸ Three new asymmetric dipyrins containing a deactivated, carbonyl-containing pyrrolic unit were synthesised²⁹⁻³¹ in good yield as shown in Scheme 3.^{32, 33} The structure of **12•HBr** was confirmed using X-ray crystallography (Supporting Information).

Scheme 3. Synthesis of asymmetric β -carbonyl dipyrins

The deuteration of these new dipyrins was then explored, after conversion to their free-bases. As observed for **7**, minimal reactivity was obtained after treatment of **12** with methanol- d_4 at 100 °C, and starting material was recovered (Table 2, entry 7). Upon heating at 150 °C for 15 minutes, analysis of the crude $^1\text{H-NMR}$ spectrum revealed that one of the four methyl signals was significantly suppressed. Several smaller shoulder signals had arisen slightly up-field of the suppressed signal and corresponding to the partially deuterated products (D_1 , D_2 , D_3 and D_4). The presence of the acyl functional group granted significant thermal stability, and a drastic increase in the yield was observed (81%, Table 2, entry 8). Although a wash with aq. HBr induced decomposition of the partially alkyl substituted dipyrins described above (whereby only decomposition was observed), the carbonyl-bearing analogs efficiently formed the hydrobromide salts. Deuteration was also performed with the ethyl ester (**13**) and acetyl analog (**14**), with isolated yields of the deuterated compounds of 89 and 71%, respectively, following conversion to the hydrobromide salts (Table 2, entries 9 and 10).

For these asymmetrically substituted dipyrins, the regiochemistry of deuteration was conclusively elucidated using 2D-NMR techniques. Deuterium exchange occurred exclusively at the 9-methyl functionality, distal from the conjugated carbonyl group (see Supporting Information). To rationalise the regioselectivity observed for **12**, **13** and **14**, consideration of the relevant conjugate bases may be useful. Although many uncharged and zwitterionic tautomers

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may be visualized, Figure 2 (top) depicts equilibria about the dipyrinato core and the 1-methyl group, i.e. adjacent to the carbonyl functionality. Tautomer **E** features an isolated exo-cyclic π -system. In contrast, tautomerization involving the dipyrinato core and the 9-methyl group (**G** in Figure 2, bottom) places the exo-cyclic π -system in extended conjugation with the skeleton. As such, tautomer **G** would be most accessible, and reactivity (deuteration) would favour the electron-rich ring as observed.

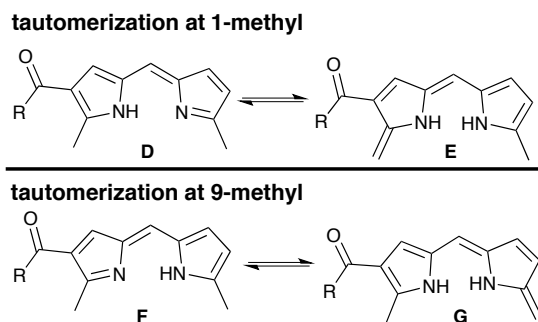


Figure 2. Resonance forms of a 1,9-dimethyl-2-acyl dipyrin

The method identified in Table 2 gives access to dipyrrens deuterated at the 1-methyl position. To the best of our knowledge, there are no reported routes by which to access such labelled dipyrrens even though it is evident that such compounds would have significant utility in the synthesis of meso-substituted tetrapyrroles such as biliverdin and porphyrins. The meso position within biliverdin has been deuterated via treatment with boiling methanol- d_4 ³⁴ or stronger acids such as CF_3CO_2D or D_2SO_4/D_2O .³⁵⁻³⁸ The *meso*-position of porphyrins has been deuterated through a reduction/oxidation strategy using $NaBD_4$ ³⁹ as the reductant, as well as via treatment with strong deuterated acids.³⁵⁻³⁸ However, conversion and recovery were variable, due to the generation of intractable tars, as was the extent of deuteration. Our method provides a

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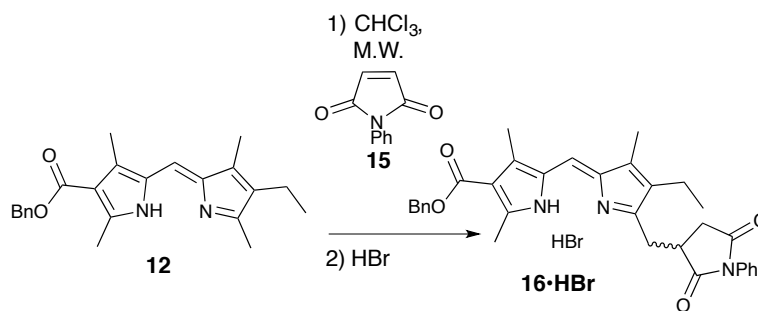
route by which labelling can be introduced earlier in a synthesis, thus providing significantly enhanced access to labelled dipyrrolic materials.

Beyond the scope of the Knoevenagel type reactions, as well as a class of reactions utilizing similar reactivity in dipyrinones for the synthesis of bilirubin derivatives,⁴⁰ carbon-carbon bond formation from the 1-methyl substituent of dipyrrins is otherwise unreported. Furthermore, with the exception of the report of Treibs *et al.*²⁵ that details the formation of an intermediate analogous to **2**, no reactions are known whereby the 1-methyl moiety of dipyrrins maintains its sp^3 hybridised nature. Due to the success of our deuterium exchange at elevated temperature, we hypothesised that electrophilic attack could occur at 1-methyl positions of dipyrrins to generate a sp^3 centre bearing $-CH_2R$ functionality.

As **12** proved to be a durable substrate for deuteration, this compound was chosen as a model with which to work. α,β -Unsaturated carbonyl compounds serve as excellent acceptors of nucleophiles, and thus the conjugate addition of **12** to *N*-phenylmaleimide (**15**) was explored (

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Table 3).

Table 3. Conjugate addition of dipyrin **12** to *N*-phenyl maleimide (**15**)

Entry	Eq. 15	t (min)	T (°C)	12	Yield
				(% recov.)	(%)
1	1	15	100	100	0
2	1	15	125	95	0 ^a
3	1	15	150	54	42
4	1.5	45	150	22	73
5	2	90	150	10	85

^aTrace product detectable via TLC analysis.

The first reaction was performed in the microwave reactor at 100 °C (

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Table 3, entry 1). No reactivity was observed after 15 minutes, and the experiment was thus repeated at 125 °C (entry 2). An observable darkening of the solution from yellow to brown occurred. Although a significant amount of starting material was present in the reaction mixture, a second compound was evident via TLC analysis on alumina. A trace amount of the expected conjugate addition product was obtained, within a mixture of impurities, using column chromatography. Although ¹H-NMR spectroscopy was not useful in confirming the identity of the material, analysis via mass spectrometry confirmed the presence of the desired adduct, **16**. It should be noted that in addition to these products, the formation of blue-coloured products, presumably analogous to the 1-(vinylpyrrolyl)-dipyrins discussed earlier, were observed via TLC analysis. Although attempts were made to isolate these compounds via chromatographic methods, the trace amounts and compound instability hindered success.

The temperature of the experiment was thus increased to 150 °C. After 15 minutes, formation of the (2,5-dioxo-1-phenylpyrrolidin-3-yl)methyl)-dipyrin **16** was evident. Separation of the product from unreacted dipyrin starting material via chromatography was performed. Unfortunately, unreacted *N*-phenylmaleimide co-eluted with the product under these solvent conditions. The mixture was dissolved in CHCl₃, washed with 1 M aq. HBr, concentrated, and poured into diethyl ether to precipitate the salt **16•HBr** as a brown solid (42%,

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Table 3, entry 3). As both starting materials were present in the final reaction mixture, another trial was performed for 45 minutes at 150 °C. As polymerization of maleimide occurs at high temperatures,⁴¹ 1.5 equivalents were utilised to account for lost electrophile. After 45 minutes at 150 °C, a small amount of pyrrolic starting material still remained, as did unreacted maleimide. However, the isolated yield of **16•HBr** was much-improved (73%,

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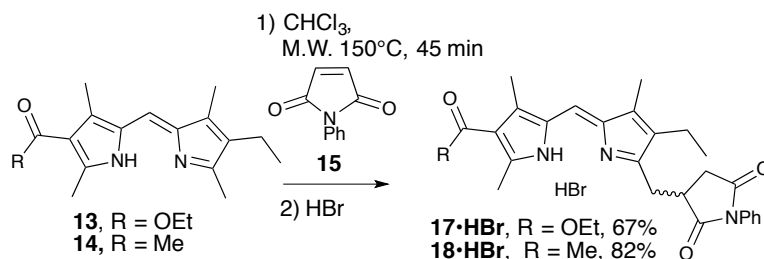
Table 3, entry 4). The conditions were further optimised through the addition of 2 equiv. *N*-phenylmaleimide, with microwave heating at 150 °C for 1.5 hours. The product, **16•HBr**, was thus obtained in a yield of 85% (

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Table 3, entry 5). Excess unreacted maleimide was identified in the product mixture, and the colour of the solution had darkened considerably, indicating some decomposition of starting materials.

The reaction was repeated using ethyl ester dipyrin **13** and acyl dipyrin **14**. Adapting the procedures used for **12** (1.5 equiv. dipyrin; 45 minute reaction time) the maleimide addition products **17•HBr** and **18•HBr** were isolated in yields of 67 and 82%, respectively (Scheme 4). The work-up and general appearance of the reactions involving **13** and **14** were comparable to those described for **12**.

Scheme 4. Conjugate addition of dipyrins **13** and **14** to *N*-phenylmaleimide (**15**)

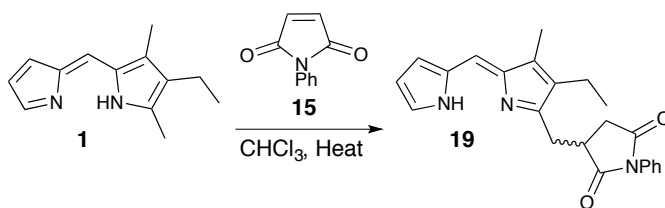


Addition of *N*-phenyl maleimide to the less stable, alkyl-substituted dipyrins was less fruitful than reactions involving dipyrins **12-14** bearing electron-withdrawing substituents (Table 4). Free-base dipyrin **1** was dissolved in anhydrous chloroform, and the solution was bubbled with nitrogen before the addition of **15**. After heating the solution at 100°C for 15 minutes in the microwave reactor, a noticeable darkening of the solution had occurred. A considerable amount of starting material was observed via TLC analysis. As with dipyrins **12-14**, a second dark-yellow, dipyrin-like compound was observable using TLC analysis, with a higher polarity relative to the starting material. Unfortunately, co-elution with **15** occurred. Analysis of an ESI^+ mass spectrum of the mixture revealed that a compound with a mass

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matching the target conjugate addition product, **19**, had indeed been synthesised. Unfortunately, purification via conversion to the hydrobromide salt was unsuccessful, instead resulting in decomposition of the products. Neither a wash with 1 M aq. HBr nor the controlled reaction of a single equivalent of concentrated HBr at 0 °C provided **19•HBr**. This result is reminiscent of the previously mentioned attempts to form the HBr salt of the alkyl substituted, deuterated dipyrin **1** directly from the free-base. As such, the product **19** was not successfully purified, but was isolated as a mixture.

Table 4. Conjugate addition of dipyrin **1 to *N*-phenylmaleimide (**15**)**



Entry	Eq. 3-17	t	T (°C)	Heating	Yield ^a (%)
1	1.5	15 min	100	MW	18
2	1.5	15 min	150	MW	15
3	1.5	24 h	61	Δ	15

^a Product isolated as a mixture of **15** and **19**. Yield calculated from % molar ratio of products, as observed via ¹H-NMR spectra.

A brief attempt was made to optimise the conditions of this reaction; a second trial was performed at 150 °C. However, a decrease in the crude yield of product was observed.

Conversely, mild heating under thermal conditions for a longer amount of time was explored (Table 4, entry 3). Heating of a solution of the starting materials in chloroform at reflux temperature for a period of 24 hours did, gratifyingly, result in the formation of some of the

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expected adduct (15%). However, the starting material had decomposed in this time. This result indicates that temperatures lower than those used for deuterium conversion (100 °C, microwave heating for 15 minutes) are capable of activating the 1-methyl position of compound **1**. In a similar vein, reactions with pyrrolinones, conventional 1,2- and 1,4- Michael acceptors, alkyl and benzyl bromides and electron-poor alkynes all met with reactivity that resulted in complex mixtures of unstable materials containing dipyrins that had undergone addition. It is clear that elucidation of the temperature and manner of activation is critical to achieving desired reactivity with specific electrophiles. The sensitivity of microwave-promoted heating is exceedingly useful for this purpose.

To verify that the deuterated dipyrin could be manipulated and reacted in a manner akin to the starting material, **7-D₇** was converted into the corresponding *F*-BODIPY featuring six deuterium atoms (two α -CD₃ groups). Similarly, deuteration of **12** followed by reaction with *N*-phenyl maleimide, in a one-pot process, gave the expected deuterated addition product (see Supporting Information).

Conclusions

The activation of the 1-methyl moiety of free-base dipyrins has been utilised to several ends. This has been achieved through use of microwave-promoted heating whereby precise and responsive temperature control can be attained. We are able to intercept what have traditionally been decomposition routes of dipyrins and instead harness them to effect useful functionalization. Firstly, the thermal decomposition products, 1-(pyrrolyl)-dipyrin dimers, have been isolated and characterised following their proposal in 1978.²⁵ The stability of these compounds is certainly low. Deuteration of 1-methyl dipyrin free-bases has been shown to be accessible following a simple procedure. As the 1-methyl substituent often serves as a synthetic

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handle for the synthesis of porphyrins,⁴² this methodology allows for facile incorporation of a deuterium label at the *meso*-position of a porphyrin. Similarly, this deuteration phenomenon could have potential for the labelling dipyrinato-based catalysts to enable mechanistic studies, as well as provide access to labelled prodigiosenes and *F*-BODIPYs. Furthermore, selective deuteration has been shown to occur where appropriate carbonyl-containing functionalities are present. This allows for additional synthetic control of the labeling process. Finally, a methodology for the conjugate addition of *N*-phenylmaleimide to the 1-methyl position of free-base dipyrins has been developed. This is the first report of sp³-sp³ C-C bond formation between the α -methyl group of a free-base dipyrin and any other carbon source. Optimum yields are attainable with dipyrins containing an electron-withdrawing carbonyl functionality.

Experimental procedures

All chemicals were purchased and used as received unless otherwise indicated. Hexanes and CH₂Cl₂ used for chromatography were obtained crude and purified via distillation under atmospheric conditions before use. Anhydrous solvents were used as received. Flash chromatography was performed using ultra pure silica (230-400 mesh) or Brockmann III (150 mesh) activated basic or neutral alumina oxide, as indicated. TLC was performed using glass-backed silica gel plates or on plastic-backed neutral alumina plates. Visualization of TLC plates was performed using UV light (254 nm) and/or vanillin stain. Moisture-sensitive reactions were performed using flame-dried glassware under a positive pressure of nitrogen. Air and moisture-sensitive compounds were introduced via syringe. NMR spectra were recorded at the NMR-3 facility (Dalhousie University) using either 500 MHz or 300 MHz spectrometers. ¹H and ¹³C chemical shifts are expressed in parts per million (ppm) using the solvent signal as reference.⁴³ ¹¹B and ¹⁹F chemical shifts were referenced using the absolute referencing procedure standard

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for digital spectrometers, with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (15% in CDCl_3) and CCl_3F defining the 0 ppm position, respectively. All coupling constants (J) are reported in Hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Splitting patterns preceded by an “a” are defined as apparent signals. Methyl assignments are numbered according to Figure 1. All mass spectra were recorded using TOF and LCQ Duo ion trap instruments operating in ESI+ mode. The reported masses of deuterated compounds correspond to the base-peak of the low-resolution spectrum. All microwave-promoted reactions were performed using a Biotage Initiator 8 laboratory microwave apparatus, 0-400 W power, 2.45 GHz. Compounds **7•HBr**,⁴⁴ **8•HBr**, **9•HBr**²¹ and **11**⁴⁵ were prepared according to literature procedures, as were the pyrroles required for synthesis of dipyrren salts **1•HBr** and **12-14•HBr**.²⁹⁻³¹

General Procedure 1 (GP1) for the Synthesis of Asymmetric Dipyrren•HBr

The appropriate 1-formyl pyrrole and 1-H pyrrole were dissolved in tetrahydrofuran/methanol (10 mL, 1/1), at room temperature with stirring under a nitrogen atmosphere. Concentrated HBr (1.5 equivalents) was added drop-wise to the solution. The mixture was stirred until the starting materials were consumed, as monitored using TLC analysis. The solution and the precipitate were poured into chilled Et_2O (50 mL) with stirring, and the precipitate was collected through suction filtration (colours ranged from bright orange and red, with varying levels of crystallinity). The product was washed with Et_2O and dried under vacuum to render the dipyrren HBr salt.

General Procedure 2 (GP2) for the Preparation and use of Free-Base Dipyrins in Deuterium Exchange Experiments

A sample of dipyrin•HBr salt (50 or 100 mg) was dissolved in CH₂Cl₂ (30 mL) and the solution then washed with NaOH (1 M, aq., 30 mL). The organic layer was dried over Na₂SO₄, and the solvent removed under vacuum to give a solid that was then dried using a vacuum oven. The resulting free-base was sealed in a microwave vessel under a nitrogen atmosphere, by way of a septum cap. Anhydrous, deuterated methanol (4 mL), or a 1:1 mixture of deuterated methanol and chloroform (to improve solubility), was added to dissolve the free-base. The reaction mixture was heated for 15 minutes (between 100 and 150 °C, as stated and necessary for the specific experiment). Purification of the reaction products was achieved through chromatography over Brockman III basic alumina eluting with ethyl acetate:hexanes (1:19 → 1:4, as necessary), followed by removal of the solvent *in vacuo* to give the deuterated dipyrins as bright yellow films. The dipyrins were dissolved in CH₂Cl₂ (30 mL) and the solutions washed with aq. HBr (1 M, 30 mL). *In vacuo* removal of the solvent from the organic layer gave the dipyrin•HBr salts as brightly coloured solids.

(Z)-2-((2H-Pyrrol-2-ylidene)methyl)-4-ethyl-3,5-dimethyl-1H-pyrrole hydrobromide (1•HBr)

This compound was synthesised according to GP1 from 3,5-dimethyl-4-ethyl-2-formylpyrrole (400 mg, 4.21 mmol)³⁰ and freshly distilled pyrrole (567 μL, 4.21 mmol), as a bright orange solid (953 mg, 80%). δ_H (500 MHz, CDCl₃) 1.09 (t, 3H, *J* = 7.6 Hz, CH₂CH₃), 2.29 (s, 3H, 3-CH₃), 2.44 (q, 2H, *J* = 7.6 Hz, CH₂CH₃), 2.74 (s, 3H, 1-CH₃), 6.48 (s, 1H, Pyr-H), 7.09 (s, 1H, Pyr-H), 7.20 (s, 1H, *meso*-H), 7.67 (s, 1H, Pyr-H), 13.34 (bs, 1H, NH), 13.54 (bs, 1H, NH); δ_C

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(125 MHz, CDCl₃) 10.2, 13.5, 14.2, 17.3, 114.7, 124.7, 127.3, 129.3, 132.0, 133.6, 137.7, 145.3, 162.0; ESI: [M+H]⁺ (C₁₃H₁₇N₂): 201.1392 (calculated); 201.1385 (experimental).

(Z)-2-((2H-Pyrrol-2-ylidene)methyl)-4-ethyl-3,5(²H₃)-dimethyl-1²H-pyrrole (1-D₄)

Deuteration was performed according to GP2, using dipyrin **1**•HBr (100 mg, 0.36 mmol) and heating at 100 °C for 15 min. Conversion of the product to the hydrobromide salt via wash with aq. HBr (1 M, 30 mL) induced decomposition; instead, the compound was characterised as the free-base dipyrin, and isolated as a yellow film (12 mg, 17%). δ_H (300 MHz, CDCl₃) 1.07 (t, 3H, *J* = 7.6 Hz, CH₂CH₃), 2.08 (s, 3H, 3-CH₃), 2.31 (s, 3H, 1-CH₃, signal depressed), 2.36 (q, 2H, *J* = 7.6 Hz, CH₂CH₃), 6.23 (s, 1H, Pyr-H), 6.55 (s, 1H, Pyr-H), 6.66 (s, 1H, *meso*-H), 7.07 (s, 1H, Pyr-H); δ_C (125 MHz, CDCl₃) 9.6, 14.4, 16.6 (m, splitting observed due to deuterium coupling in D₁₋₃ compounds) 18.2, 110.5, 117.6, 117.7, 125.4, 131.4, 137.8, 139.7, 149.4, 171.4; ESI: [M+H]⁺ (C₁₃H₁₄D₃N₂): 204.1580 (calculated); 204.1575 (experimental). *ND signal not observed in ¹H-NMR spectrum.

(Z)-2-((2H-Pyrrol-2-ylidene)methyl)-4-ethyl-5-(2-(4-ethyl-3,5-dimethyl-1H-pyrrol-2-yl)-2-(1H-pyrrol-2-yl)ethyl)-3-methyl-1H-pyrrole (2)

A sample of **1**•HBr (100 mg, 0.36 mmol) was dissolved in CH₂Cl₂ (30 mL), and the solution washed with NaOH (1 M, 30 mL). The organic layer was dried over Na₂SO₄, and the solvent removed *in vacuo*. The resulting solid was dissolved in dry methanol (4 mL) and the solution sealed in a microwave vessel, via a septum, under a nitrogen atmosphere. The solution was heated for 15 minutes, in the microwave, at 100 °C. Following removal of the solvent *in vacuo*, purification over Brockman III basic alumina, eluting with a gradient of EtOAc:hexanes (1:19 to 1:9), and removal of the solvent *in vacuo* gave **2** as a brown film (6 mg, 4 %). δ_H (300 MHz,

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CDCl₃) 0.98 (t, 3H, $J = 7.3$ Hz, CH₂CH₃), 1.04 (t, 3H, $J = 7.4$ Hz, CH₂CH₃), 1.90 (s, 3H, Pyr-CH₃), 2.08 (s, 6H, overlapping Pyr-CH₃ and Dipyr-CH₃), 2.25 (adt, 2H, $J = 14.5, 7.2$ Hz, Dipyr-CH₂CH₃), 2.36 (adt, 2H, $J = 15.1, 7.6$ Hz, Pyr-CH₂CH₃), 3.26 (dd, 2H, $J = 16.1, 6.6$ Hz, Dipyr-CH₂CH), 4.70 (t, 1H, $J = 6.6$ Hz, CH₂CH(Pyr)₂), 6.03 (d, 1H, $J = 2.5$ Hz, Pyr-H), 6.16 (t, 1H, $J = 3.0$ Hz, Pyr-H), 6.24 (t, 1H, $J = 3.1$ Hz, Dipyr-H), 6.58 (dd, 1H, $J = 3.7, 1.0$ Hz, Dipyr-H), 6.66 (bs, 1H, Pyr-H), 6.70 (s, 1H, *meso*-H), 7.01 (bs, 1H, Dipyr-H), 7.67 (bs, 1H, Pyr-NH), 8.55 (bs, 1H, Pyr-NH); δ_C (125 MHz, CDCl₃) 9.2, 9.6, 11.2, 14.4, 15.8, 17.7, 17.9, 34.2, 36.1, 105.4, 108.2, 110.7, 113.7, 116.6, 117.7, 118.2, 118.6, 120.6, 121.2, 125.9, 126.1, 131.2, 134.5, 138.1, 140.0, 173.1; ESI: [M+H]⁺ (C₂₆H₃₃N₄): 401.2705 (calculated); 401.2709 (experimental). Partial reversion to starting material (**1**) occurred over the time-frame of NMR analysis for ¹³C-UDEFT, COSY, HSQC and HMBC experiments; one ¹³C signal is missing for **2**.

(Z)-3-Ethyl-5-((4-ethyl-3,5(²H₃)-dimethyl-2H-pyrrol-2-ylidene)methyl)-2,4(²H₃)-dimethyl-1²H-pyrrole (7-D₇)

Deuteration was performed according to GP2, using 100 mg (0.30 mmol) of **7•HBr**⁴⁴ and heating at 150 °C for 15 min. Following purification over alumina, the product was sufficiently stable as the free-base dipyrin without concern of deterioration, and was isolated as a yellow film (12 mg, 15%). δ_H (500 MHz, CDCl₃) 1.06 (t, 6H, $J = 7.6$ Hz, CH₂CH₃) 2.13 (s, 6H, 3-CH₃), 2.31 (s, 6H, 1-CH₃, signal depressed), 2.38 (q, 4H, $J = 7.6$ Hz, CH₂CH₃), 6.64 (s, 1H, *meso*-H), 9.46 (s, 1H, NH, signal depressed); δ_C (125 MHz, CDCl₃) 9.6, 14.3 (m, splitting observed due to deuterium coupling in D₁₋₆ compounds), 15.0, 17.9, 115.4, 130.0, 133.3, 136.8, 151.1; ESI: [M+H]⁺ (C₁₇H₁₈D₆N₂): 262.2316 (calculated); 262.2311 (experimental).

(Z)-2-((2H-Pyrrol-2-ylidene)methyl)-3,4-diethyl-5-methyl-1H-pyrrole (8)

Compound **8•HBr**²¹ was dissolved in CH₂Cl₂ (30 mL) and washed with NaOH (1M, 30 mL) to yield the free-base material as a brown solid after removal of solvent from the organic layer. δ_{H} (500 MHz, CDCl₃) 1.11 (t, 3H, $J = 7.6$ Hz, CH₂CH₃), 1.17 (t, 3H, $J = 7.6$ Hz, CH₂CH₃), 2.34 (s, 3H, Pyr-CH₃), 2.38 (q, 2H, $J = 7.6$ Hz, CH₂CH₃), 2.52 (q, 2H, $J = 7.6$ Hz, CH₂CH₃), 6.25 (at, 1H, $J = 2.9$ Hz, Pyr-H), 6.58 (d, 1H, $J = 3.2$ Hz, Pyr-H), 6.68 (s, 1H, *meso*-H), 7.08 (bs, 1H, Pyr-H), 10.30, 1H, N-H); δ_{C} (125 MHz, CDCl₃) 14.9, 16.9, 17.1, 18.0, 18.1, 110.5, 117.6, 117.8, 125.5, 131.4, 137.1, 146.2, 148.2, 171.2. Free-base dipyrin NMR values reported rather than HBr salt for comparison to deuterated sample (**8-D₄**), as **8-D₄** was not stable to reconversion to salt either via wash with 1 M HBr or via treatment with 1 equiv. HBr in MeOH.

(Z)-2-((2H-Pyrrol-2-ylidene)methyl)-3,4-diethyl-5(²H₃)-methyl-1²H-pyrrole (8-D₄)

Deuteration was performed according to GP2, using 100 mg (0.32 mmol) of **8•HBr**²¹ and heating at 150 °C for 15 min. Only minimal deuteration of the compound was observed.

Conversion to the hydrobromide salt induced decomposition, and thus the free-base dipyrin was isolated as a yellow film following purification over alumina (3 mg, 5%). δ_{H} (300 MHz, CDCl₃) 1.08 (t, 3H, $J = 7.6$ Hz, CH₂CH₃), 1.15 (t, 3H, $J = 7.6$ Hz, CH₂CH₃), 2.32 (s, 3H, Pyr-H, signal depressed), 2.37 (q, 2H, $J = 7.6$ Hz, CH₂CH₃), 2.50 (q, 2H, $J = 7.6$ Hz, CH₂CH₃), 6.23 (dd, 1H, $J = 3.5, 2.7$ Hz, Pyr-H), 6.55 (dd, 1H, $J = 3.5, 0.9$ Hz, Pyr-H), 6.65 (s, 1H, *meso*-H), 7.07 (bs, 1H, Pyr-H); ESI: [M+H]⁺ (C₁₄H₁₇D₂N₂): 217.1674 (calculated); 217.1671 (experimental).

(Z)-3,4-Diethyl-2-methyl-5-((3-methyl-2H-pyrrol-2-ylidene)methyl)-1H-pyrrole hydrobromide (9•HBr)

Compound **9•HBr**²¹ was recrystallised from cold methanol and obtained as a dark-red solid. δ_{H} (500 MHz, CDCl₃) 1.11 (t, 3H, $J = 7.6$ Hz, CH₂CH₃), 1.22 (t, 3H, $J = 7.6$ Hz, CH₂CH₃), 2.38 (s, 3H, 7-CH₃), 2.44 (q, 2H, $J = 7.6$ Hz, CH₂CH₃), 2.69 (q, 2H, $J = 7.6$ Hz, CH₂CH₃), 2.72 (s, 3H, 1-CH₃), 6.32 (s, 1H, Pyr-H), 7.17 (s, 1H, *meso*-H), 7.61 (s, 1H, Pyr-H), 13.13 (bs, 1H, NH), 13.31 (bs, 1H, NH). δ_{C} (125 MHz, CDCl₃) 12.3, 13.4, 14.8, 17.19, 17.24, 18.3, 115.5, 120.9, 126.2, 127.1, 132.0, 137.9, 143.1, 150.5, 159.8;

(Z)-3,4-Diethyl-2(²H₃)-methyl-5-((3-methyl-2H-pyrrol-2-ylidene)methyl)-1H-pyrrole hydrobromide (9-D₃•HBr)

Deuteration was performed according to GP2 using 100 mg (0.34 mmol) of **10•HBr**²¹ and heating at 150 °C for 15 min. The product was sufficiently stable for conversion to the hydrobromide salt, via washing with 1 M HBr (30 mL) while dissolved in CH₂Cl₂, and was isolated as an orange, crystalline solid (18 mg, 18%). δ_{H} (300 MHz, CDCl₃) 1.10 (t, 3H, $J = 7.6$ Hz, CH₂CH₃), 1.22 (t, 3H, $J = 7.6$ Hz, CH₂CH₃), 2.38 (s, 3H, 7-CH₃), 2.44 (q, 2H, $J = 7.6$ Hz, CH₂CH₃), 2.70 (q, 2H, $J = 7.6$ Hz, CH₂CH₃), 2.72 (s, 3H, 1-CH₃, signal depressed), 6.31 (d, 1H, $J = 1.4$ Hz, Pyr-H), 7.16 (s, 1H, *meso*-H), 7.60 (bs, 1H, Pyr-H), 13.12 (bs, 1H, NH), 13.29 (bs, 1H, NH). ESI: [M+H]⁺ (C₁₅H₁₈D₂N₂): 230.1752 (calculated); 230.1747 (experimental).

(Z)-3-Ethyl-5-((4-ethyl-3,5-dimethyl-2H-pyrrol-2-ylidene)(phenyl)methyl)-2,4-dimethyl-1H-pyrrole (11)

Compound **11** was synthesised according to a literature procedure,⁴⁵ from 3,5-dimethyl-4-ethyl-2-formylpyrrole (163 μ L, 1.21 mmol)³⁰ and freshly distilled benzaldehyde. The free-base

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product was isolated as a red, crystalline solid (782 mg, 82%). δ_{H} (300 MHz, CDCl_3) 0.98 (t, 6H, $J = 7.5$ Hz, CH_2CH_3), 1.21 (s, 6H, 3- CH_3), 2.29 (q, 4H, $J = 7.5$ Hz, CH_2CH_3), 2.33 (s, 6H, 1- CH_3), 7.27-7.35 (m, 2H, Ar-H), 7.36-7.45 (m, 3H, Ar-H). These data match reported literature values.⁴⁵

(Z)-3-Ethyl-5-((4-ethyl-3,5(²H₃)-dimethyl-2H-pyrrol-2-ylidene)(phenyl)methyl)-2(²H₃),4-dimethyl-1²H-pyrrole (11-D₇)

Deuteration was performed according to GP2, using 50 mg (0.30 mmol) of free-base **11**⁴⁵ and heating at 150 °C for 30 min. Significant decomposition was observed. The free-base product was sufficiently stable to enable purification over basic alumina and was isolated as a brown solid (20 mg, 40%). δ_{H} (300 MHz, CDCl_3) 0.98 (t, 6H, $J = 7.5$ Hz, CH_2CH_3), 1.20 (s, 6H, 3- CH_3), 2.28 (q, 4H, $J = 7.5$ Hz, CH_2CH_3), 2.32 (s, 6H, 1- CH_3 , signal depressed), 7.28-7.35 (m, 2H, Ar-H), 7.38-7.45 (m, 3H, Ar-H); ESI: $[\text{M}+\text{H}]^+$ ($\text{C}_{23}\text{H}_{22}\text{D}_7\text{N}_2$): 340.2770 (calculated); 340.2765 (experimental).

(Z)-Benzyl 5-((4-ethyl-3,5-dimethyl-2H-pyrrol-2-ylidene)methyl)-2,4-dimethyl-1H-pyrrole-3-carboxylate hydrobromide (12•HBr)

This compound was synthesised according to GP1 from benzyl 5-formyl-2,4-dimethyl-1H-pyrrole-3-carboxylate (400 mg, 1.55 mmol)³¹ and 3,5-dimethyl-4-ethyl-2-formylpyrrole (210 μL , 1.55 mmol)³⁰ to yield **12•HBr** as an orange, crystalline solid (617 mg, 90%). δ_{H} (500 MHz, CDCl_3) 1.02 (t, 3H, $J = 7.6$ Hz, CH_2CH_3), 2.31 (s, 3H, 7- CH_3), 2.35 (q, 2H, $J = 7.6$ Hz, CH_2CH_3), 2.56 (s, 3H, 3- CH_3), 2.62 (s, 3H, 9- CH_3), 2.82 (s, 3H, 1- CH_3), 5.28 (s, 2H, OCH_2Ph), 7.20 (s, 1H, *meso-H*), 7.28-7.42 (m, 5H, Ar-H), 13.01 (bs, 1H, NH), 13.42 (bs, 1H, NH); δ_{C} (125 MHz, CDCl_3); 10.3, 12.3, 13.2, 14.1, 15.0, 17.2, 66.2, 117.1, 120.4, 124.6, 128.4, 128.4, 128.7, 132.9,

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135.9, 144.7, 145.7, 154.8, 160.5, 163.5. ESI: $[M+H]^+$ ($C_{23}H_{27}N_2O_2$): 363.2073 (calculated); 363.2069 (experimental).

(Z)-Benzyl 5-((4-ethyl-3,5(2H_3)-dimethyl-2H-pyrrol-2-ylidene)methyl)-2(2H_3),4-dimethyl-1H-pyrrole-3-carboxylate hydrobromide (12- D_3 •HBr)

Deuteration was performed according to GP2, using 100 mg (0.22 mmol) of **12•HBr** and heating at 150 °C for 15 min. The free-base product was sufficiently stable for conversion to the hydrobromide salt, through washing with 1.0 HBr (30 mL) while dissolved in CH_2Cl_2 , and was isolated as an orange, crystalline solid (81 mg, 81%). δ_H (300 MHz, $CDCl_3$) 1.06 (t, 3H, $J = 7.6$ Hz, CH_2CH_3), 2.30 (s, 3H, 7- CH_3), 2.39 (q, 2H, $J = 7.6$ Hz, CH_2CH_3), 2.57 (s, 3H, 3- CH_3), 2.62 (s, 3H, 9- CH_3 , signal depressed), 2.87 (s, 3H, 1- CH_3), 5.30 (s, 2H, OCH_2Ph), 7.19 (s, 1H, *meso-H*), 7.32-7.42 (m, 5H, Ar-H), 13.10 (bs, 1H, NH), 13.53 (bs, 1H, NH); $[M+H]^+$ ($C_{23}H_{24}D_3N_2O_2$): 366.2261 (calculated); 366.2218 (experimental).

(Z)-Ethyl 5-((4-ethyl-3,5-dimethyl-2H-pyrrol-2-ylidene)methyl)-2,4-dimethyl-1H-pyrrole-3-carboxylate hydrobromide (13•HBr)

This compound was synthesised according to GP1 from ethyl 5-formyl-2,4-dimethyl-1H-pyrrole-3-carboxylate (500mg, 2.56 mmol)³¹ and 3,5-dimethyl-4-ethyl-2-formylpyrrole (346 μ L, 2.56 mmol)³⁰ to yield **13•HBr** as an orange, crystalline solid (956 mg, 98%). δ_H (500 MHz, $CDCl_3$) 1.07 (t, 3H, $J = 7.6$ Hz, Pyr- CH_2CH_3), 1.37 (t, 3H, $J = 7.1$ Hz, OCH_2CH_3), 2.32 (s, 3H, 7- CH_3), 2.43 (q, 2H, $J = 7.6$ Hz, Pyr- CH_2CH_3), 2.57 (s, 3H, 3- CH_3), 2.71 (s, 3H, 9- CH_3), 2.88 (s, 3H, 1- CH_3), 4.31 (q, 2H, $J = 7.1$ Hz, OCH_2CH_3), 7.21 (s, 1H, *meso-H*), 13.09 (bs, 1H, NH), 13.52 (s, 1H, NH); δ_C (125 MHz, $CDCl_3$) 10.3, 12.2, 13.3, 14.3, 14.5, 15.1, 17.3, 60.4, 117.7, 120.3,

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124.8, 128.4, 133.0, 144.5, 145.9, 155.1, 160.4, 163.9; ESI: $[M+H]^+$ ($C_{18}H_{25}N_2O_2$): 301.1916 (calculated); 301.1911 (experimental).

(Z)-Ethyl 5-((4-ethyl-3,5(2H_3)-dimethyl-2H-pyrrol-2-ylidene)methyl)-2(2H_3),4-dimethyl-1H-pyrrole-3-carboxylate hydrobromide (13- D_3 •HBr)

Deuteration was performed according to GP2, using 100 mg (0.26 mmol) of **13•HBr** and heating at 150 °C for 15 min. The free-base product was sufficiently stable for conversion to the hydrobromide salt, through washing with 1.0 HBr (30 mL) while dissolved in CH_2Cl_2 , and was isolated as an orange, crystalline solid (89 mg, 89%). δ_H (500 MHz, $CDCl_3$) 1.07 (t, 3H, $J = 7.6$ Hz, Pyr- CH_2CH_3), 1.37 (t, 3H, $J = 7.1$ Hz, OCH_2CH_3), 2.31 (s, 3H, 7- CH_3), 2.43 (q, 2H, $J = 7.6$ Hz, Pyr- CH_2CH_3), 2.57 (s, 3H, 3- CH_3), 2.69 (s, 3H, 9- CH_3 , signal depressed), 2.89 (s, 3H, 1- CH_3), 4.32 (q, 2H, $J = 7.1$ Hz, OCH_2CH_3), 7.21 (s, 1H, *meso*-H), 13.11 (bs, 1H, NH), 13.54 (s, 1H, NH); δ_C (125 MHz, $CDCl_3$) 10.3, 12.2, 13.3 (m, splitting observed due to deuterium coupling in D_{1-3} compounds) 14.3, 14.5, 15.1, 17.3, 60.4, 117.7, 120.3, 124.8, 128.5, 133.0, 144.5, 145.9, 155.1, 160.4, 163.9; ESI: $[M+H]^+$ ($C_{18}H_{22}D_3N_2O_2$): 304.2104 (calculated); 304.2099 (experimental).

(Z)-1-(5-((4-Ethyl-3,5-dimethyl-2H-pyrrol-2-ylidene)methyl)-2,4-dimethyl-1H-pyrrol-3-yl)ethanone hydrobromide (14•HBr)

This compound was synthesised according to GP1 from 4-acetyl-2-formyl-3,5-dimethyl-1H-pyrrole (200 mg, 1.21 mmol)²⁹ and 3,5-dimethyl-4-ethyl-2-formylpyrrole (163 μ L, 1.21 mmol)³⁰ to yield **14•HBr** as an orange, crystalline solid (296 mg, 70%). δ_H (500 MHz, $CDCl_3$) 1.10 (t, 3H, $J = 7.6$ Hz, CH_2CH_3), 2.33 (s, 3H, 7- CH_3), 2.46 (q, 2H, $J = 7.6$ Hz, CH_2CH_3), 2.50 (s, 3H, $COCH_3$), 2.57 (s, 3H, 3- CH_3), 2.76 (s, 3H, 9- CH_3), 2.96 (s, 3H, 1- CH_3), 7.22 (s, 1H, *meso*-H),

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13.15 (bs, 1H, NH), 13.66 (bs, 1H, NH); δ_C (125 MHz, CDCl₃) 10.3, 12.8, 13.5, 14.3, 15.8, 17.4, 31.7, 120.3, 124.7, 126.7, 129.0, 133.4, 144.2, 144.7, 153.5, 161.4, 194.3; ESI: [M+H]⁺ (C₁₇H₂₃N₂O): 278.1810 (calculated); 278.1805 (experimental).

(Z)-1-(5-((4-Ethyl-3,5(²H₃)-dimethyl-2*H*-pyrrol-2-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrol-3-yl)ethanone hydrobromide (14-D₃•HBr)

Deuteration was performed according to GP2, 50 mg (0.14 mmol) of **14•HBr** and heating at 125 °C for 15 min. The product was sufficiently stable for conversion to the hydrobromide salt, and was isolated as an orange, crystalline solid (38 mg, 76%). δ_H (500 MHz, CDCl₃) 1.10 (t, 3H, $J = 7.6$ Hz, CH₂CH₃), 2.32 (s, 3H, 7-CH₃), 2.45 (q, 2H, $J = 7.6$ Hz, CH₂CH₃), 2.49 (s, 3H, COCH₃), 2.57 (s, 3H, 3-CH₃), 2.76 (s, 3H, 9-CH₃, signal depressed), 2.96 (s, 3H, 1-CH₃), 7.22 (s, 1H, *meso*-H), 13.15 (bs, 1H, NH), 13.65 (bs, 1H, NH); δ_C (125 MHz, CDCl₃) 10.3, 12.9, 13.5 (m, splitting observed due to deuterium coupling in D_{1,3} compounds), 14.3, 15.8, 17.4, 31.7, 120.3, 124.7, 126.7, 129.0, 133.4, 144.2, 144.7, 153.5, 161.4, 194.3; ESI: [M+H]⁺ (C₁₇H₂₁D₂N₂O): 273.1936 (calculated); 273.1928 (experimental).

(Z)-Benzyl 5-((5-((2,5-dioxo-1-phenylpyrrolidin-3-yl)methyl)-4-ethyl-3-methyl-2*H*-pyrrol-2-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate hydrobromide (16•HBr)

A sample of **12•HBr** (50 mg, 0.11 mmol) was dissolved in CH₂Cl₂ (30 mL) and the solution washed with aq. NaOH (1 M, 30 mL). The organic layer was dried over Na₂SO₄, and the solvent then removed *in vacuo*. Free-base **12** and *N*-phenyl maleimide (39 mg, 0.23 mmol) were dissolved in anhydrous chloroform (4 mL) in a microwave vessel under a nitrogen atmosphere, and the vessel then sealed by way of a septum cap. The reaction mixture was heated for 1.5 hours at 150 °C in the microwave reactor. Removal of the solvent *in vacuo*, followed by purification of

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the resulting crude material over Brockman III basic alumina eluting with a solvent gradient of EtOAc:hexanes (1:9 → 2:8) gave a mixture of **16** and residual *N*-phenylmaleimide. The material was dissolved in CH₂Cl₂ (30 mL) and the solution was then washed with aq. HBr (1M, 30 mL) to form the dipyrin hydrobromide salt. The organic layer was concentrated, and the product precipitated upon the addition of diethyl ether. After isolation using suction filtration, and washing of the solid with diethyl ether, **16•HBr** was obtained as a brown solid (70 mg, 85%). δ_{H} (500 MHz, CDCl₃) 1.11 (t, 3H, $J = 7.5$ Hz, CH₂CH₃), 2.34 (s, 3H, 7-CH₃), 2.49 (dd, 1H, $J = 14.1$, 6.8 Hz, 8-CHHCH₃), 2.53 (dd, 1H, $J = 14.2$, 7.0 Hz, 8-CHHCH₃), 2.60 (s, 3H, 3-CH₃), 2.93 (s, 3H, 1-CH₃), 3.02 (dd, 1H, $J = 18.3$, 5.9 Hz, COCHHCH), 3.20 (dd, 1H, $J = 18.3$, 9.3 Hz, COCHHCH), 3.43 (dd, 1H, $J = 14.4$, 8.0 Hz, 9-CHH), 3.60 (dd, 1H, $J = 14.1$, 7.2 Hz, 9-CHH), 3.96 (adt, 1H, $J = 14.9$, 7.6 Hz, CH₂CHCH₂), 5.33 (s, 2H, OCH₂Ph), 7.46-7.27 (m, 11H, ArH and *meso*-H), 13.25 (bs, 1H, NH), 13.63 (bs, 1H, NH); δ_{C} (125 MHz, CDCl₃) 10.5, 12.4, 14.7, 15.5, 17.4, 27.8, 34.9, 40.7, 66.5, 118.3, 121.4, 125.7, 126.6, 128.4, 128.6, 128.6, 128.7, 128.8, 129.3, 131.9, 133.0, 135.9, 145.0, 148.0, 157.1, 158.2, 163.4, 174.4, 177.1; ESI: [M+H]⁺ (C₃₃H₃₄N₃O₄): 536.2549 (calculated); 536.2544 (experimental).

(Z)-Ethyl 5-((5-((2,5-dioxo-1-phenylpyrrolidin-3-yl)methyl)-4-ethyl-3-methyl-2H-pyrrol-2-ylidene)methyl)-2,4-dimethyl-1H-pyrrole-3-carboxylate hydrobromide (17•HBr)

A sample of **13•HBr** (50 mg, 0.13 mmol) was dissolved in CH₂Cl₂ (30 mL) and the solution washed with NaOH (1M, aq. 30 mL). The organic layer was dried over Na₂SO₄, and the solvent then removed *in vacuo*. The free-base **13** and *N*-phenyl maleimide (34 mg, 0.20 mmol) were dissolved in anhydrous chloroform (4 mL) in a microwave vessel under a nitrogen atmosphere, and the vessel then sealed by way of a septum cap. The reaction mixture was heated for 45 minutes at 150 °C in the microwave reactor. Removal of the solvent *in vacuo*, purification of the

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resulting crude material over Brockman III basic alumina eluting with a solvent gradient of EtOAc:hexanes (1:9 → 3:7) gave **17** as a brown film. The material was dissolved in CH₂Cl₂ (30 mL) and the solution was then washed with aq. HBr (1M, 30 mL) to form the dipyrren hydrobromide salt. The organic layer was concentrated, and the product precipitated using diethyl ether. After isolation using suction filtration, the solid was washed with diethyl ether to give **17•HBr** as a fluffy, brown-green solid (49 mg, 67%). δ_{H} (500 MHz, CDCl₃) 1.12 (t, 3H, $J = 7.6$ Hz, CH₂CH₃), 1.40 (t, 3H, $J = 7.1$ Hz, OCH₂CH₃) 2.36 (s, 3H, 7-CH₃), 2.49 (adt, 1H, $J = 14.1, 6.8$ Hz, 8-CH₂CH₃), 2.62 (s, 3H, 3-CH₃), 2.95 (s, 3H, 1-CH₃), 3.03 (dd, 1H, $J = 18.4, 6.0$ Hz, COCHHCH), 3.21 (dd, 1H, $J = 18.3, 9.3$ Hz, COCHHCH), 3.44 (dd, 1H, $J = 14.1, 8.3$ Hz, 9-CHH), 3.60 (dd, 1H, $J = 14.1, 7.3$ Hz, 9-CHH), 3.96 (adt, 1H, $J = 14.9, 7.6$ Hz, CH₂CHCH₂), 4.35 (q, 2H, $J = 7.1$ Hz, OCH₂CH₃), 7.28-7.29 (m, 3H, *o*-Ar-H and *meso*-H), 7.37 (t, 1H, $J = 7.4$ Hz, *p*-Ar-H), 7.45 (t, 2H, $J = 7.7$ Hz, *m*-Ar-H), 13.26 (bs, 1H, NH), 13.63 (bs, 1H, NH); δ_{C} (125 MHz, CDCl₃) 10.5, 12.3, 14.5, 14.8, 15.4, 17.5, 27.7, 35.0, 40.8, 60.7, 118.7, 121.4, 125.7, 126.6, 128.5, 128.8, 129.3, 131.9, 132.9, 144.8, 148.0, 157.2, 157.8, 163.7, 174.5, 177.1; ESI: [M+H]⁺ (C₂₈H₃₂N₃O₄): 474.2393 (calculated); 474.2387 (experimental).

(Z)-3-((2-((4-Acetyl-3,5-dimethyl-1H-pyrrol-2-yl)methylene)-4-ethyl-3-methyl-2H-pyrrol-5-yl)methyl)-1-phenylpyrrolidine-2,5-dione hydrobromide (18•HBr)

A sample of **14•HBr** (50 mg, 0.14 mmol) was dissolved in CH₂Cl₂ (30 mL) and the solution washed with aqueous sodium hydroxide (1 M, 30 mL). The organic layer was dried over Na₂SO₄, and the solvent then removed *in vacuo*. The free-base **14** and *N*-phenyl maleimide (37 mg, 0.21 mmol) were dissolved in anhydrous chloroform (4 mL) in a microwave vessel under a nitrogen atmosphere, and the vessel then sealed by way of a septum cap. The reaction mixture was heated for 45 minutes at 150 °C in the microwave reactor. Removal of the solvent *in vacuo*,

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and purification of the resulting crude material over Brockman III basic alumina eluting with a solvent gradient of EtOAc:hexanes (1:9 → 3:7) gave **18** as a brown film. The material was dissolved in CH₂Cl₂ (30 mL) and the solution was then washed with aq. HBr (1M, 30 mL) to form the dipyrin hydrobromide salt. The organic layer was concentrated, and the product precipitated with diethyl ether. After isolation using suction filtration, the solid was washed with diethyl ether to give **18•HBr** as a fluffy, brown-green solid (60 mg, 82%). δ_{H} (500 MHz, CDCl₃) 1.12 (t, 3H, $J = 7.6$ Hz, CH₂CH₃), 2.36 (s, 3H, 7-CH₃), 2.54-2.47 (m, 5H, COCH₃ and 8-CH₂CH₃), 2.59 (s, 3H, 3-CH₃), 2.96 (s, 3H, 1-CH₃), 3.02 (dd, 1H, $J = 18.4, 5.9$ Hz, COCHHCH), 3.20 (dd, 1H, $J = 18.5, 9.3$ Hz, COCHHCH), 3.44 (dd, 1H, $J = 14.1, 8.3$ Hz, 9-CHH), 3.59 (dd, 1H, $J = 14.1, 7.3$ Hz, 9-CHH), 3.95 (aquintet, 1H, $J = 7.8$, CH₂CHCH₂), 7.28 (d, 2H, $J = 7.7$ Hz, *o*-Ar-H), 7.32 (s, 1H, *meso*-H), 7.36 (t, 1H, $J = 7.4$ Hz, *p*-Ar-H), 7.44 (t, 2H, $J = 7.7$ Hz, *m*-Ar-H), 13.22 (bs, 1H, NH), 13.65 (bs, 1H, NH); δ_{C} (125 MHz, CDCl₃) 10.5, 12.9, 14.7, 16.0, 17.4, 27.8, 31.7, 34.9, 40.9, 121.5, 125.5, 126.6, 127.4, 128.8, 128.9, 129.3, 131.9, 133.2, 145.2, 145.9, 155.5, 158.6, 174.5, 177.1, 194.1; ESI: [M+H]⁺ (C₂₇H₃₀N₃O₄): 444.2287 (calculated); 444.2282 (experimental).

(Z)-3-((2-((1*H*-Pyrrol-2-yl)methylene)-4-ethyl-3-methyl-2*H*-pyrrol-5-yl)methyl)-1-phenylpyrrolidine-2,5-dione (19)

A sample of **1•HBr** (100 mg, 0.36 mmol) was dissolved in CH₂Cl₂ (30 mL) and the solution washed with aq. NaOH (1 M, 30 mL). The organic layer was dried over Na₂SO₄, and the solvent then removed *in vacuo*. The free-base **1** and *N*-phenyl maleimide (**15**, 39 mg, 0.54 mmol) were dissolved in anhydrous chloroform (4 mL) in a microwave vessel under a nitrogen atmosphere, and the vessel then sealed by way of a septum cap. The mixture was heated for 15 minutes at 100 °C in the microwave reactor. Removal of the solvent *in vacuo*, followed by purification of the

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resulting crude mixture over Brockman III basic alumina, eluting with a solvent gradient of EtOAc:hexanes (1:9 $t \rightarrow$ 2:8), gave a mixture of **19** and residual *N*-phenylmaleimide. The product was unstable to salt conversion, thereby hindering removal of *N*-phenylmaleimide, and thus a mixture of **15** and **19** was isolated as a brown solid (21 mg total, 19 mg product, 18%. Yield determined via comparing the integral ratio of the $^1\text{H-NMR}$ peaks at 6.64 ppm, corresponding to a pyrrolic aromatic proton of the desired product, to the peak at 6.85 ppm, corresponding to the 2H of the alkenyl functionality of *N*-phenylmaleimide). δ_{H} (500 MHz, CDCl_3) 1.10 (t, 3H, $J = 7.6$ Hz, CH_2CH_3), 2.10 (s, 3H, 3- CH_3), 2.38 (q, 2H, $J = 7.6$ Hz, CH_2CH_3), 3.05 (dd, 1H, $J = 18.4$, 5.4 Hz, COCHH), 3.15 (dd, 1H, $J = 18.4$, 9.4 Hz, COCHH), 3.21 (dd, 1H, $J = 17.8$, 4.2 Hz, 1- CHH), 3.27 (dd, 1H, $J = 17.7$, 6.6 Hz, 1- CHH), 3.51 (td, 1H, $J = 10.1$, 5.9 Hz, CH_2CHCH_2), 6.13 (t, 1H, $J = 3.1$ Hz, Pyr-H), 6.56 (d, 1H, $J = 2.8$ Hz, Pyr-H), 6.64 (bs, 1H, Pyr-H), 6.71 (s, 1H, *meso*-H), 6.85 (s, **15** alkene signal), 7.25-7.29 (m, 2H, Ar-H, with some **15** aromatic signal), 7.34-7.49 (m, 3H, Ar-H, with some **15** aromatic signal); δ_{C} (125 MHz, CDCl_3) 9.6, 14.6, 17.9, 30.3, 34.7, 38.1, 110.7, 118.6, 119.3, 126.2, 126.6, 128.6, 129.2, 130.5, 132.2, 137.2, 140.8, 148.8, 170.0, 176.5, 179.0; ESI: $[\text{M}+\text{H}]^+$ ($\text{C}_{23}\text{H}_{24}\text{N}_3\text{O}_2$): 374.1863 (calculated); 374.1853 (experimental).

Supplementary Information

NMR spectra of all new compounds. X-Ray crystal structure of **12•HBr**.

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