An efficient method for the synthesis of unsymmetrical 2,2′-bis(pyrrolyl)alkanes†

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A new strategy for the preparation of unsymmetrical 2,2′-bis(pyrrolyl)alkanes has been developed. It involved the condensation of pyrrole derivatives onto *N*-benzylhydroxylamines in the presence of HCl. This two-step procedure provided access to a wide variety of 2,2′-dipyrromethanes (**3a–m**). It has also been extended to the synthesis of tripyrromethanes **4a–d** and of *N*-confused dipyrromethanes **6a–d**.

Introduction

2,2′-Bis(pyrrolyl)alkanes (or dipyrromethanes) are important precursors for the preparation of porphyrins and related molecules.[1] They also occupy a central place in the synthesis of BODIPY (4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacenes or boron dipyrromethenes dyes).[2] The first one-flask synthesis of these compounds was described in 1994 by Lindsey and Lee.[3] Since this report, a large number of methods have been developed for the obtention of dipyrromethanes. Most of them are based on the condensation of a pyrrole and an aldehyde in the presence of acids, such as trifluoroacetic acid,[4] hydrogen chloride,[5] BF_3–etherate,[6] or *para*-toluenesulfonic acid.[7] More recently, new methods have been proposed. For example, addition of pyrrole to acetylenic sulfones in the presence of $Cu(OTf)_2$ has been performed.[8] Other methods involved a macroporous cation exchange resin as the catalyst,[9] water as the solvent,[10] or the condensation of pyrroles on *N*-tosyl imines in the presence of a metal triflate.[11]

The major limitation of existing methods concerns the ability to obtain unsymmetrically substituted 2,2′-bis(pyrrolyl)alkanes. Indeed, when an aldehyde reacts with a pyrrole derivative, an unstable carbinol is formed,[12] which is often trapped by a second equivalent of pyrrole to yield the corresponding symmetrical dipyrromethane.

Although a large number of publications is recorded on the synthesis of symmetrical 2,2′-bis(pyrrolyl)alkanes,[4–11,13] very few reports are found dealing with the synthesis of unsymmetrical dipyrromethanes.[14]

Previous studies in our group have dealt with the reaction of nitrones with various pyrroles.[15] We have shown that, depending on the conditions, the reaction of nitrones with pyrroles in the presence of hydrogen chloride yields either *N*-benzylhydroxylamines or symmetrical dipyrromethanes (Scheme 1).[15a] We report here, a novel and efficient method for the preparation of unsymmetrical 2,2′-bis(pyrrolyl)alkanes in two steps, involving *N*-benzylhydroxylamines as intermediates.

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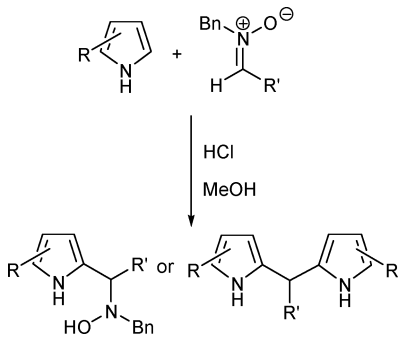


Scheme 1 Addition of pyrroles to nitrones.

Results and discussion

N-Benzylhydroxylamines can be isolated after the condensation of a first equivalent of a pyrrole derivative onto nitrones in the presence of hydrogen chloride as the promoter. In a second step, treatment of the *N*-hydroxylamines with various pyrrole derivatives has been carried out (Scheme 1).

First, a series of known *N*-benzylhydroxylamines were obtained using conditions described in a previous report (Scheme 1).[15a] New *N*-benzylhydroxylamines, **1c** and **1f–h** (Fig. 1) were also synthesized under different sets of experimental conditions. The

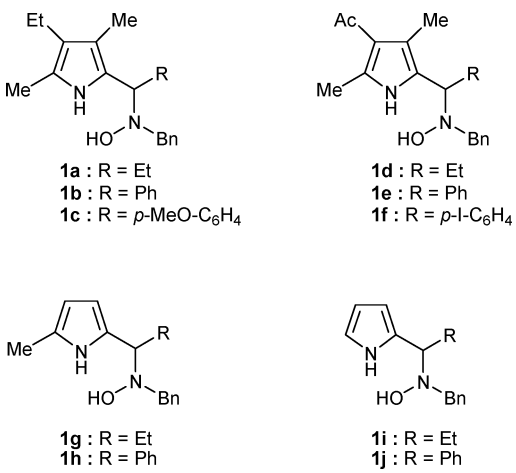
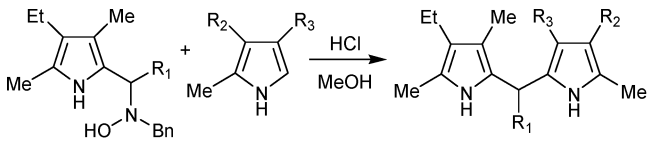


Fig. 1 Structures of *N*-hydroxylamines.

Table 1 Preparation of unsymmetrically substituted 2,2′-bis(pyrrolyl)alkanes **3a–f**



1a : R_1 = Et
1b : R_1 = Ph
1c : R_1 = *p*-MeO-C_6H_4

2a : $R_2 = R_3$ = H
2b : R_2 = Ac, R_3 = Me

3a : R_1 = Et, $R_2 = R_3$ = H
3b : R_1 = Et, R_2 = Ac, R_3 = Me
3c : R_1 = Ph, $R_2 = R_3$ = H
3d : R_1 = Ph, R_2 = Ac, R_3 = Me
3e : R_1 = *p*-MeO-C_6H_4, $R_2 = R_3$ = H
3f : R_1 = *p*-MeO-C_6H_4, R_2 = Ac, R_3 = Me

Entry	**1**	**2** (equiv.)	Conditions[a]	**3**	Yield (%)[b,c]
1	**1a**	**2a** (1)	–40 °C, 1.5 h	**3a**	55
2	**1a**	**2a** (2)	–40 °C, 1.5 h	**3a**	56
3	**1a**	**2a** (2)	–40 °C, 3 h	**3a**	**67**
4	**1a**	**2a** (2)	–40 °C, 13 h	**3a**	36
5	**1a**	**2a** (2)	–20 °C, 1.5 h	**3a**	52
6	**1a**	**2b** (1)	–40 °C, 2 h	**3b**	56
7	**1a**	**2b** (1)	0 °C, 2 h	**3b**	**77**
8	**1b**	**2a** (1)	–78 °C, 1.5 h	**3c**	44
9	**1b**	**2a** (2)	–78 °C, 3 h	**3c**	66
10	**1b**	**2a** (2)	–40 °C, 1.5 h	**3c**	38
11	**1b**	**2a** (2)	–40 °C, 3 h	**3c**	**73**
12	**1b**	**2b** (1)	–40 °C, 1.5 h	**3d**	**82**
13	**1b**	**2b** (1)	0 °C, 1 h	**3d**	54
14	**1c**	**2a** (1)	–78 °C, 2 h	**3e**	**68**
15	**1c**	**2a** (1)	–40 °C, 2 h	**3e**	52
16	**1c**	**2a** (1)	–20 °C, 2 h	**3e**	30
17	**1c**	**2b** (1)	–40 °C, 8 h	**3f**	40
18	**1c**	**2b** (1)	–20 °C, 5 h	**3f**	**60**
19	**1c**	**2b** (1)	0 °C, 4 h	**3f**	47

[a] In the presence of 1 equiv. of HCl. [b] Isolated yields. [c] For each substrate, the best result is shown in bold.

optimized reaction conditions gave compounds **1c** and **1f–h** in 63, 52, 77 and 32% yields respectively.[16]

In a second step, the isolated *N*-hydroxylamines were treated with HCl in the presence of substituted pyrroles **2a–c** (Fig. 2).[17]

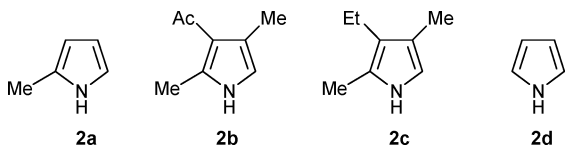


Fig. 2 Structures of pyrroles.

The reaction with 2-methylpyrrole (**2a**) and 3-acetyl-2,4-dimethylpyrrole (**2b**) as nucleophilic partners was studied under various conditions. The most representative results are summarized in Table 1.

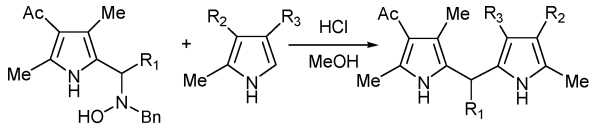
We started the synthesis of unsymmetrical 2,2′-bis(pyrrolyl)-alkanes with *N*-hydroxylamines bearing an ethyl and two methyl substituents on the pyrrole ring (**1a–c**).

Except for the formation of compound **3b** (entry 7), the best yields were obtained at low temperature. Formation of symmetrical 2,2′-bis(pyrrolyl)alkanes was detected during the synthesis of compounds **3a**, **3c**, **3d** and **3e** (entries 3, 11, 12 and 14). This result could be explained by the well-known "scrambling" phenomenon, which is frequently met in porphyrin synthesis.[18]

Next, we carried on a study involving *N*-hydroxylamines **1e** and **1f**. Low conversions were observed when the reactions were performed at –40 °C. The temperature was then increased and excellent yields were obtained at 0 °C in the presence of one equivalent of nucleophilic partner (Table 2). Insofar as we had *N*-hydroxylamine **1e** at our disposal, we had the possibility to synthesize compound **3d** once again. This one was obtained with a very good yield (92%) *via* a reaction between **1e** and pyrrole **2c** (Table 2, entry 3). This way was then more efficient than the one described in Table 1 (entry 12). It could be explained by the high stability of *N*-hydroxylamine **1e** and the higher nucleophilicity of compound **2c**. All attempts to obtain 2,2′-bis(pyrrolyl)alkanes starting from **1g–j** were unsuccessful. Whatever the conditions used, the degradation of the starting materials occurred. One can assume that such observations are due to an acid-catalyzed polymerization process starting from the free β-positions of the pyrrole nucleus.

Encouraged by these results, we decided to turn our attention onto unsubstituted pyrrole **2d** in order to prepare new 2,2′-bis(pyrrolyl)alkanes. A first series of condensations was run using one equivalent of pyrrole **2d** and *N*-hydroxylamines **1a**, **1b**, **1e** and **1f** in the presence of one equivalent of hydrogen chloride. Representative results are summarized in Table 3. In all cases, a mixture of unsymmetrical dipyrromethanes **3** and tripyrromethanes **4** was obtained (Table 3, entries 1, 4 and 6). The formation of by-products **4** could be easily explained

Table 2 Preparation of unsymmetrically substituted 2,2′-bis(pyrrolyl)-alkanes **3d**, **3g–i**



1e : R_1 = Ph
1f : R_1 = *p*-I-C_6H_4

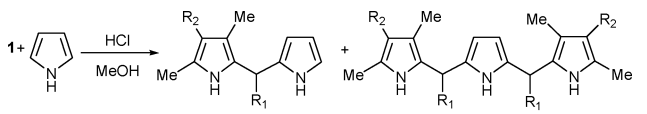
2a : R_2 = R_3 = H
2c : R_2 = Et, R_3 = Me

3g : R_1 = Ph, R_2 = R_3 = H
3h : R_1 = *p*-I-C_6H_4, R_2 = R_3 = H
3i : R_1 = *p*-I-C_6H_4, R_2 = Et, R_3 = Me

Entry	1	2	Conditions[a]	3	Yield (%)[b,c]
1	**1e**	**2a**	0 °C, 1 h	**3g**	**95**
2	**1e**	**2a**	0 °C, 4 h	**3g**	91
3	**1e**	**2c**	0 °C, 1.5 h	**3d**	**92**
4	**1f**	**2a**	0 °C, 1.5 h	**3h**	**98**
5	**1f**	**2c**	0 °C, 1.5 h	**3i**	**95**

[a] In the presence of 1 equiv. of substrates **1**, **2** and HCl. [b] Isolated yields. [c] For each substrate, the best result is shown in bold.

Table 3 Preparation of unsymmetrically substituted 2,2′-bis(pyrrolyl)-alkanes **3j–m**



2d

3j : R_1 = Et, R_2 = Et
3k : R_1 = Ph, R_2 = Et
3l : R_1 = Ph, R_2 = Ac
3m : R_1 = *p*-I-C_6H_4, R_2 = Ac

4a : R_1 = Et, R_2 = Et
4b : R_1 = Ph, R_2 = Et
4c : R_1 = Ph, R_2 = Ac
4d : R_1 = *p*-I-C_6H_4, R_2 = Ac

Entry	1	2d (equiv.)	Conditions[a]	Ratio 3 : 4	3 (%)[b,c]
1	**1a**	1	–40 °C, 2 h	59 : 41 **3j** : **4a**	**3j** (37)
2	**1a**	2	–40 °C, 2 h	65 : 35 **3j** : **4a**	**3j** (**40**)
3	**1a**	2	–40 °C, 13 h	15 : 85 **3j** : **4a**	**3j** (10)
4	**1b**	1	–40 °C, 1.5 h	61 : 39 **3k** : **4b**	**3k** (23)
5	**1b**	2	–40 °C, 1.5 h	58 : 42 **3k** : **4b**	**3k** (**28**)
6	**1e**	1	0 °C, 1 h	50 : 50 **3l** : **4c**	**3l** (37)
7	**1e**	2	0 °C, 1 h	56 : 44 **3l** : **4c**	**3l** (**41**)
8	**1f**	2	0 °C, 1 h	70 : 30 **3m** : **4d**	**3m** (**59**)

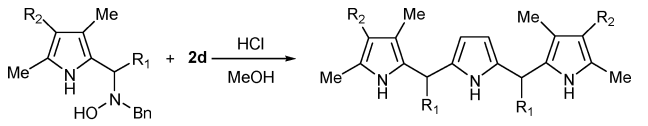
[a] In the presence of 1 equiv. of substrate **1** and HCl. [b] Isolated yields. [c] For each substrate, the best result is shown in bold.

by the addition of dipyrromethanes **3** onto the starting *N*-hydroxylamines **1**. When the same reactions were performed with 2 equivalents of pyrrole **2d**, the 2,2′-bis(pyrrolyl)alkanes were formed with higher yields, but they were still accompanied by tripyrromethanes (Table 3, entries 2, 5, 7 and 8). Finally, we found that the control of reaction time was essential to minimize the formation of the by-product. Indeed, when the reaction time was longer than 2 h, the yield of dipyrromethane dramatically fell (Table 3, entry 3).

We took advantage of the formation of tripyrromethanes in order to prepare such interesting compounds[19] *via* simple modifications of the experimental procedure. Highly selective transformations were observed by decreasing the relative amount of pyrrole **2d**. Indeed, the target molecules were prepared using *N*-hydroxylamines **1** with 0.5 equivalent of pyrrole **2d** in the presence of one equivalent of hydrogen chloride. Results are summarized in Table 4.

Finally, we tried to apply the present reaction to the synthesis of unsymmetrically *N*-confused dipyrromethanes.[20] With this

Table 4 Preparation of tripyrromethanes **4a–d**



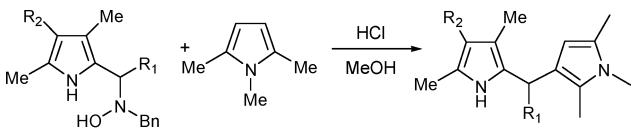
1a : R_1 = Et, R_2 = Et
1b : R_1 = Ph, R_2 = Et
1e : R_1 = Ph, R_2 = Ac
1f : R_1 = *p*-I-C_6H_4, R_2 = Ac

4a : R_1 = Et, R_2 = Et
4b : R_1 = Ph, R_2 = Et
4c : R_1 = Ph, R_2 = Ac
4d : R_1 = *p*-I-C_6H_4, R_2 = Ac

Entry	1	Conditions[a]	4	Yield (%)[b]
1	**1a**	–40 °C, 2 h	**4a**	55
2	**1b**	–40 °C, 2 h	**4b**	66
3	**1e**	0 °C, 0.5 h	**4c**	74
4	**1f**	0 °C, 0.5 h	**4d**	74

[a] In the presence of 2 equiv. of substrate **1** and HCl, and 1 equiv. of **2d**. [b] Isolated yields.

Table 5 Preparation of unsymmetrically *N*-confused dipyrromethanes **6a-c**



1a : R_1 = Et, R_2 = Et
1b : R_1 = Ph, R_2 = Et
1d : R_1 = Et, R_2 = Ac
1e : R_1 = Ph, R_2 = Ac

5

6a : R_1 = Et, R_2 = Et
6b : R_1 = Ph, R_2 = Et
6c : R_1 = Et, R_2 = Ac
6d : R_1 = Ph, R_2 = Ac

Entry	1	5 (equiv.)	Conditions[a]	6	Yield (%)[b]
1	**1a**	1.5	–20 °C, 1 h	**6a**	66
2	**1b**	1.5	–40 °C, 2 h	**6b**	63
3	**1d**	1.5	rt, 2 h	**6c**	73
4	**1e**	1.5	0 °C, 0.5 h	**6d**	66

[a] In the presence of 1 equiv. of HCl. [b] Isolated yields.

purpose in mind, we first chose *N*-triisopropylsilylpyrrole as the starting material. The large steric bulk of the triisopropylsilyl group has a C-3 directing effect, and the C-3 regioisomer is usually formed as the main product when electrophilic substitutions are run on the pyrrolic ring.[21] All of our preliminary attempts left the starting material unreacted. The lack of reactivity of *N*-triisopropylsilylpyrrole could be attributed to its low nucleophilicity. Then, we turned our attention on 1,2,5-trimethylpyrrole **5** as the starting material.

When *N*-hydroxylamines **1a** and **1b** were used, the reaction took place in the presence of one equivalent of hydrogen chloride at –20 and –40 °C, respectively. A scrambling process was observed and the formation of symmetrical dipyrromethanes was detected (Table 5, entries 1 and 2). As expected, addition of compound **5** onto *N*-hydroxylamines bearing an acetyl group on the pyrrole ring was efficient at higher temperatures. Indeed, at 0 °C, dipyrromethane **6d** was obtained in 66% yield, whereas room temperature was required for the formation of **6c**.

In conclusion, we have developed an efficient and practical method for the preparation of unsymmetrically substituted 2,2′-bis(pyrrolyl)alkanes using a two-step strategy that allows the formation of a large number of diverse substituted compounds.

Work is now in progress to use these very interesting compounds as precursors for the synthesis of new BODIPY dyes that are powerful tools for biologists.

Experimental

General experimental

All reactions were carried out using oven-dried glassware under an argon atmosphere. Solvents were purified prior to use by conventional methods. Pyrroles were dried by refluxing over calcium hydride and then distilled. Acetyl chloride was distilled over calcium chloride and used fresh. Triethylamine was refluxed over potassium hydroxide and then distilled. All other reagent-grade chemicals were used as supplied (analytical or HPLC grade) without prior purification. Thin layer chromatography was performed on aluminium plates coated with 60 PF254 silica. Plates were visualised using UV light (254 nm), followed by heating after treatment with an appropriate revelatory agent ($KMnO_4$, TTC, phosphomolybdic acid, ninhydrin). Flash column chromatography was performed on Kieselgel 60 silica (40-60 mesh) over silica gel pretreated with 3% triethylamine (v/v).

Elemental analyses were recorded by the microanalysis service of the Département de Chimie Moléculaire, Grenoble, France. Melting points were recorded on Büchi B35 apparatus and are uncorrected. IR spectra were recorded on a Nicolet Impact-400 Fourier transform infrared spectrometer (FTIR) as either thin films on NaCl plates (thin film) or as a KBr disc (KBr disc), as stated. Selected characteristic bands are reported in cm^{-1}. NMR spectra were recorded either on a Bruker Advance300 or on an Advance400 spectrometer in the deuterated solvent as stated. The field was locked by external referencing to the relevant deuteron resonance. Low Resolution Mass Spectra (LRMS) were recorded on a Bruker Esquire 3000 plus (ESI) or a Thermo Finnigan Polaris Q ion-trap spectrometer, using DCI (ammonia–isobutane 63 : 37). Accurate mass measurements were run in the "Structure et Fonction de Molécules Bioactives" laboratory, Paris, France.

General procedure for the preparation of unsymmetrical bis(pyrrolyl)alkanes

Freshly distilled acetyl chloride (1 equiv.) was added dropwise at 0 °C to anhydrous methanol and the mixture was stirred for 15 min. The appropriate pyrrolic *N*-benzylhydroxylamine (1 equiv.) was added and the mixture was cooled at –78 °C before the addition of the appropriate pyrrole derivative. The mixture was warmed to the appropriate temperature and stirred until complete disappearance of the starting material (followed by TLC). The mixture was then treated with saturated aqueous $NaHCO_3$ solution. The pH value was 8–9. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. The obtained unsymmetrical bis(pyrrolyl)alkane was purified by flash chromatography on silica gel.

3-Ethyl-2,4-dimethyl-5-(1-(5-methyl-1*H*-pyrrol-2-yl)propyl)-1*H*-pyrrole 3a. Prepared according to the above general procedure from *N*-benzylhydroxylamine **1a** (50 mg, 0.18 mmol) in 2.0 mL of MeOH, 2-methylpyrrole **2a** (28 mg, 0.35 mmol) and acetyl chloride (14 mg, 0.18 mmol). The mixture was stirred at –40 °C for 3 h. Purification (eluent: pentane–EtOAc, 90 : 10) afforded unsymmetrical 2,2′-bis(pyrrolyl)alkane **3a** (29 mg, 0.12 mmol, 67%) as a yellow oil; ν_{max}/cm^{-1} 3375 (br, NH), 2972, 2920, 2876, 1679, 1458, 1384, 1115 and 1059; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.91 (3H, t, $J = 7.6$ Hz, CH_3), 1.08 (3H, t, $J = 7.6$ Hz, CH_3), 1.73-1.80 (2H, m, CH_2), 1.99 (3H, s, CH_3), 2.09 (3H, s, CH_3), 2.19 (3H, s, CH_3), 2.38 (2H, q, $J = 7.6$ Hz, CH_2), 3.84 (1H, t, $J = 7.6$ Hz, CH), 5.80 (1H, br s, H_{Pyr}), 5.94 (1H, br s, H_{Pyr}), 7.10 (1H, br s, NH), 7.58 (1H, br s, NH); δ_C (100 MHz; $CDCl_3$) 9.2 (CH_3), 11.0 (CH_3), 12.3 (CH_3), 12.9 (CH_3), 15.7 (CH_3), 17.7 (CH_2), 27.7 (CH_2), 37.2 (CH), 104.3 (CH_{Pyr}), 105.4 (CH_{Pyr}), 113.6 (C_{Pyr}), 120.2 (C_{Pyr}), 120.9 (C_{Pyr}), 126.1 (C_{Pyr}), 126.5 (C_{Pyr}), 132.7 (C_{Pyr}); MS (ESI^-) m/z 243 ($[M - H]^-$, 100); HRMS (ESI^-) $C_{16}H_{23}N_2$ ($[M - H]$) requires 243.1939 found 243.1938.

1-(5-(1-(4-Ethyl-3,5-dimethyl-1*H*-pyrrol-2-yl)propyl)-2,4-dimethyl-1*H*-pyrrol-3-yl)ethanone 3b. Prepared according to the above general procedure from *N*-benzylhydroxylamine **1a** (50 mg, 0.18 mmol) in 2.0 mL of MeOH, 3-acetyl-2,4-dimethylpyrrole **2b** (23 mg, 0.17 mmol) and acetyl chloride (14 mg, 0. 18 mmol). The mixture was stirred at 0 °C for 2 h. Purification (eluent: CH_2Cl_2–EtOAc, 95 : 5) afforded unsymmetrical 2,2′-bis(pyrrolyl)alkane **3b** (39 mg, 0.13 mmol, 77%) as a pink foam; mp 66-67 °C; ν_{max}/cm^{-1} 3300 (br, NH), 2980, 2945, 2900, 1690 (CO), 1450, 1405 and 1385; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.88 (3H, t, $J = 7.6$ Hz, CH_3), 1.04 (3H, t, $J = 7.6$ Hz, CH_3), 1.89 (3H, s, CH_3), 1.92-2.00 (2H, m, CH_2), 2.12 (3H, s, CH_3), 2.25 (3H, s, CH_3), 2.34 (2H, q, $J = 7.6$ Hz, CH_2), 2.41 (3H, s, CH_3), 2.42 (3H, s, CH_3), 3.96 (1H, t, $J = 7.6$ Hz, CH), 7.65 (1H, br s, NH), 8.22 (1H, br s, NH); δ_C (100 MHz; $CDCl_3$) 9.2 (CH_3), 11.0 (CH_3), 12.0 (CH_3), 12.3 (CH_3), 15.3 (CH_3), 15.6 (CH_3), 17.6 (CH_2), 27.3 (CH_2), 30.9 (CH_3), 35.2 (CH), 113.4 (C_{Pyr}), 115.2 (C_{Pyr}), 120.9 (C_{Pyr}), 121.3 (C_{Pyr}), 125.4 (C_{Pyr}), 128.1 (C_{Pyr}), 128.6 (C_{Pyr}), 133.8 (C_{Pyr}), 196.1 (CO); MS (ESI^+) m/z 323 ($[M + Na]^+$, 20), 301 ($[M + H]^+$, 80); HRMS (ESI^+) $C_{19}H_{28}N_2ONa$ ($[M + Na]^+$) requires 323.2093 found 323.2093.

3-Ethyl-2,4-dimethyl-5-((5-methyl-1*H*-pyrrol-2-yl)(phenyl)-methyl)-1*H*-pyrrole 3c. Prepared according to the above general procedure from *N*-benzylhydroxylamine **1b** (50 mg, 0.15 mmol) in 2.0 mL of MeOH, 2-methylpyrrole **2a** (24 mg, 0.30 mmol) and acetyl chloride (12 mg, 0.15 mmol). The mixture was stirred at –40 °C for 3 h. Purification (eluent: pentane–EtOAc, 95 : 5) afforded unsymmetrical 2,2′-bis(pyrrolyl)alkane **3c** (31 mg, 0.11 mmol, 73%) as a yellow oil; ν_{max}/cm^{-1} 3431 (br, NH), 2963, 2920, 2854, 1675, 1584 and 1440; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.04 (3H, t, $J = 7.5$ Hz, CH_3), 1.82 (3H, s, CH_3), 2.08 (3H, s, CH_3), 2.18 (3H, s, CH_3), 2.35 (2H, q, $J = 7.5$ Hz, CH_2), 5.37 (1H, s, CH), 5.61-5.64 (1H, m, H_{Pyr}), 5.75-5.77 (1H, m, H_{Pyr}), 7.16-7.30 (6H, m, $5H_{Ar}$ and NH), 7.54 (1H, br s, NH); δ_C (75 MHz; $CDCl_3$; Me_4Si) 9.2 (CH_3), 11.2 (CH_3), 13.2 (CH_3), 15.8 (CH_3), 17.8 (CH_2), 42.4 (CH), 106.0 (CH_{Pyr}), 107.5 (CH_{Pyr}), 114.0 (C_{Pyr}), 121.2 ($2C_{Pyr}$), 125.0 (C_{Pyr}), 126.6 (CH_{Ar}), 127.1 (C_{Pyr}), 128.5 ($2CH_{Ar}$), 128.6 ($2CH_{Ar}$), 131.5 (C_{Ar}), 142.7 (C_{Pyr}); MS (ESI^-) m/z 291 ($[M - H]^-$, 100); HRMS (ESI^-) $C_{20}H_{23}N_2$ ($[M - H]^-$) requires 291.1855 found 291.1856.

1-(5-((4-Ethyl-3,5-dimethyl-1*H*-pyrrol-2-yl)(phenyl)methyl)-2,4-dimethyl-1*H*-pyrrol-3-yl)ethanone 3d. Prepared according to the above general procedure from *N*-benzylhydroxylamine **1e**

(40 mg, 0.12 mmol) in 2.0 mL of MeOH, 2,4-dimethy-3-ethylpyrrole **2c** (15 mg, 0.12 mmol) and acetyl chloride (9 mg, 0.12 mmol). The mixture was stirred at 0 °C for 1.5 h. Purification (eluent: CH_2Cl_2–EtOAc, 90 : 10) afforded unsymmetrical 2,2′-bis(pyrrolyl)alkane **3d** (38 mg, 0.11 mmol, 92%) as an orange foam; mp 84-85 °C; ν_{max}/cm^{-1} 3300 (br, NH), 2960, 2920, 2860, 1630 (CO), 1440 and 1410; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.05 (3H, t, $J = 7.6$ Hz, CH_3), 1.78 (3H, s, CH_3), 2.07 (3H, s, CH_3), 2.08 (3H, s, CH_3), 2.33-2.42 (8H, m, CH_2, $2CH_3$), 5.46 (1H, s, CH), 6.96 (1H, br s, NH), 7.10-7.13 (2H, m, $2H_{Ar.}$), 7.22-7.33 (3H, m, $3H_{Ar.}$), 7.65 (1H, br s, NH); δ_C (100 MHz; $CDCl_3$) 9.1 (CH_3), 11.1 (CH_3), 11.8 (CH_3), 15.2 (CH_3), 15.6 (CH_3), 17.6 (CH_2), 30.9 (CH_3), 40.0 (CH), 114.3 (C_{Pyr}), 115.8 ($2C_{Pyr}$), 121.5 ($2C_{Pyr}$), 122.0 (C_{Pyr}), 123.6 (C_{Pyr}), 126.8 (CH_{Ar}), 126.9 (C_{Pyr}), 128.2 ($2CH_{Ar}$), 128.8 ($2CH_{Ar}$), 133.9 (C_{Ar}), 141.4 (C_{Pyr}), 195.8 (CO); MS (ESI^+) *m/z* 371 ([M + Na]$^+$, 23), 349 ([M + H]$^+$, 77); HRMS (ESI^+) $C_{23}H_{28}N_2ONa$ ([M + Na]$^+$) requires 371.2093 found 371.2091.

3-Ethyl-5-((4-methoxyphenyl)(5-methyl-1*H*-pyrrol-2-yl)methyl)-2,4-dimethyl-1*H*-pyrrole 3e. Prepared according to the above general procedure from *N*-benzylhydroxylamine **1c** (40 mg, 0.11 mmol) in 2.0 mL of MeOH, 2-methylpyrrole **2a** (9 mg, 0.11 mmol) and acetyl chloride (9 mg, 0.11 mmol). The mixture was stirred at −78 °C for 2 h. Purification (eluent: pentane–EtOAc, 90 : 10) afforded unsymmetrical 2,2′-bis(pyrrolyl)alkane **3e** (24 mg, 75 μmol, 68%) as a yellow oil; ν_{max}/cm^{-1} 3427 (br, NH), 2954, 2924, 2846, 1683, 1506, 1245, 1185 and 1033; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.07 (3H, t, $J = 7.5$ Hz, CH_3), 1.85 (3H, s, CH_3), 2.10 (3H, s, CH_3), 2.20 (3H, s, CH_3), 2.37 (2H, q, $J = 7.5$ Hz, CH_2), 3.80 (3H, s, OCH_3), 5.35 (1H, s, CH), 5.65 (1H, br s, H_{Pyr}), 5.78 (1H, br s, H_{Pyr}), 6.84 (2H, d, $J = 8.7$ Hz, H_{Ar}), 7.11 (2H, d, $J = 8.7$ Hz, H_{Ar}), 7.14 (1H, br s, NH), 7.56 (1H, br s, NH); δ_C (75 MHz; $CDCl_3$) 9.2 (CH_3), 11.2 (CH_3), 13.2 (CH_3), 15.8 (CH_3), 17.8 (CH_2), 41.6 (CH), 55.4 (OCH_3), 106.0 (CH_{Pyr}), 107.4 (CH_{Pyr}), 113.8 (C_{Pyr}), 114.0 ($2CH_{Ar}$), 121.0 (C_{Pyr}), 121.2 (C_{Pyr}), 125.4 (C_{Pyr}), 127.0 (C_{Pyr}), 129.5 ($2CH_{Ar}$), 131.9 (C_{Pyr}), 134.8 (C_{Ar}), 158.3 (C-OCH_3); MS (ESI^+) *m/z* 361 ([M + K]$^+$, 19), 345 ([M + Na]$^+$, 19).

1-(5-((4-Ethyl-3,5-dimethyl-1*H*-pyrrol-2-yl)(4-methoxyphenyl)methyl)-2,4-dimethyl-1*H*-pyrrol-3-yl)ethanone 3f. Prepared according to the above general procedure from *N*-benzylhydroxylamine **1c** (40 mg, 0.11 mmol) in 2.0 mL of MeOH, 3-acetyl-2,4-dimethylpyrrole **2b** (15 mg, 0.11 mmol) and acetyl chloride (9 mg, 0.11 mmol). The mixture was stirred at −20 °C for 5 h. Purification (eluent: pentane–EtOAc, 60 : 40) afforded unsymmetrical 2,2′-bis(pyrrolyl)alkane **3f** (25 mg, 66 μmol, 60%) as a yellow solid; mp 67-68 °C; ν_{max}/cm^{-1} 3334 (br, NH), 2962, 2924, 2860, 1630 (CO), 1440 and 1410; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.05 (3H, t, $J = 7.5$ Hz, CH_3), 1.77 (3H, s, CH_3), 2.07 (3H, s, CH_3), 2.08 (3H, s, CH_3), 2.34-2.41 (8H, m, CH_2, $2CH_3$), 3.79 (3H, s, CH_3), 5.40 (1H, s, CH), 6.84 (2H, d, $J = 8.8$ Hz, $2H_{Ar}$), 6.93 (1H, br s, NH), 7.02 (2H, d, $J = 8.8$ Hz, $2H_{Ar.}$), 7.59 (1H, br s, NH); δ_C (75 MHz; $CDCl_3$) 9.2 (CH_3), 11.2 (CH_3), 11.9 (CH_3), 15.3 (CH_3), 15.8 (CH_3), 17.8 (CH_2), 31.1 (CH_3), 39.4 (CH_3), 55.4 (CH), 114.3 ($2CH_{Ar}$), 115.8 (C_{Pyr}), 121.5 (C_{Pyr}), 121.7 (C_{Pyr}), 122.2 (C_{Pyr}), 124.2 ($2C_{Pyr}$), 127.3 (C_{Pyr}), 129.4 ($2CH_{Ar}$), 133.1 (C_{Pyr}), 133.5 (C_{Ar}), 158.5 (C-OCH_3), 195.9 (CO); MS (ESI^+) *m/z* 401 ([M + Na]$^+$, 50], 379 ([M + H]$^+$, 50]; HRMS (ESI^+) $C_{24}H_{30}O_2N_2Na$ ([M + Na]$^+$) requires 401.2199 found 401.2198.

1-(2,4-Dimethyl-5-((5-methyl-1*H*-pyrrol-2-yl)(phenyl)methyl)-1*H*-pyrrol-3-yl)ethanone 3g. Prepared according to the above general procedure from *N*-benzylhydroxylamine **1e** (34 mg, 0.10 mmol) in 2.0 mL of MeOH, 2-methylpyrrole **2a** (8 mg, 0.10 mmol) and acetyl chloride (8 mg, 0.10 mmol). The mixture was stirred at 0 °C for 1 h. Purification (eluent: pentane–EtOAc, 60 : 40) afforded unsymmetrical 2,2′-bis(pyrrolyl)alkane **3g** (29 mg, 95 μmol, 95%) as a white solid; mp 72-73 °C; ν_{max}/cm^{-1} 3314 (br, NH), 2950, 2920, 2850, 1631 (CO), 1480, 1436 and 1414; δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.15 (3H, s, CH_3), 2.21 (3H, s, CH_3), 2.39 (3H, s, CH_3), 2.42 (3H, s, CH_3), 5.44 (1H, s, CH), 5.66 (1H, br s, H_{Pyr}), 5.80 (1H, br s, H_{Pyr}), 7.17 (2H, d, $J = 7.2$ Hz, $2H_{Ar}$), 7.27-7.34 (3H, m, $3H_{Ar}$), 7.61 (1H, br s, NH), 7.72 (1H, br s, NH); δ_C (100 MHz; $CDCl_3$) 11.9 (CH_3), 13.2 (CH_3), 15.3 (CH_3), 31.1 (CH_3), 41.5 (CH), 106.2 (CH_{Pyr}), 108.0 (CH_{Pyr}), 116.3 (C_{Pyr}), 122.0 (C_{Pyr}), 126.8 (C_{Pyr}), 127.1 (CH_{Ar}), 127.7 (C_{Pyr}), 128.3 ($2CH_{Ar}$), 128.9 ($2CH_{Ar}$), 130.3 (C_{Pyr}), 133.6 (C_{Ar}), 141.6 (C_{Pyr}), 195.7 (CO); MS (ESI^+) *m/z* 329 [(M + Na)$^+$, 50), 307 ([M + H]$^+$, 50); HRMS (ESI^+) $C_{20}H_{22}N_2ONa$ ([M + Na]$^+$) requires 329.1624 found 309.1621.

1-(5-((4-Iodophenyl)(5-methyl-1*H*-pyrrol-2-yl)methyl)-2,4-dimethyl-1*H*-pyrrol-3-yl)ethanone 3h. Prepared according to the above general procedure from *N*-benzylhydroxylamine **1f** (40 mg, 84 μmol) in 2.0 mL of MeOH, 2-methylpyrrole **2a** (7 mg, 86 μmol) and acetyl chloride (7 mg, 89 μmol). The mixture was stirred at 0 °C for 1.5 h. Purification (eluent: pentane–EtOAc, 50 : 50) afforded unsymmetrical 2,2′-bis(pyrrolyl)alkane **3h** (36 mg, 83 μmol, 98%) as a yellow solid; mp 108-109 °C; ν_{max}/cm^{-1} 3409 (br, NH), 2967, 2922, 2850, 1623 (CO), 1435 and 1001; δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.12 (3H, s, CH_3), 2.21 (3H, s, CH_3), 2.40 (3H, s, CH_3), 2.42 (3H, s, CH_3), 5.37 (1H, s, CH), 5.63-5.65 (1H, m, H_{Pyr}), 5.79-5.81 (1H, m, H_{Pyr}), 6.91 (2H, d, $J = 8.4$ Hz, $2H_{Ar}$), 7.57 (1H, br s, NH), 7.63 (3H, m, $2H_{Ar}$ and NH); δ_C (100 MHz; $CDCl_3$) 11.8 (CH_3), 13.2 (CH_3), 15.3 (CH_3), 31.1 (CH_3), 41.1 (CH), 92.4 (C–I), 106.4 (CH_{Pyr}), 108.2 (CH_{Pyr}), 116.5 (C_{Pyr}), 122.1 (C_{Pyr}), 126.1 (C_{Pyr}), 128.1 (C_{Pyr}), 129.6 (C_{Pyr}), 130.3 ($2CH_{Ar}$), 133.7 (C_{Ar}), 137.9 ($2CH_{Ar}$), 141.4 (C_{Pyr}), 195.6 (CO); MS (ESI^+) *m/z* 433 ([M + H]$^+$, 100); HRMS (ESI^+) $C_{20}H_{21}ON_2INa$ ([M + Na]$^+$) requires 455.0590 found 455.0596.

1-(5-((4-Ethyl-3,5-dimethyl-1*H*-pyrrol-2-yl)(4-iodophenyl)methyl)-2,4-dimethyl-1*H*-pyrrol-3-yl)ethanone 3i. Prepared according to the above general procedure from *N*-benzylhydroxylamine **1f** (40 mg, 84 μmol) in 2.0 mL of MeOH, 2,4-dimethyl-3-ethylpyrrole **2b** (11 mg, 89 μmol) and acetyl chloride (7 mg, 89 μmol). The mixture was stirred at 0 °C for 1.5 h. Purification (eluent: CH_2Cl_2–EtOAc, 95 : 5) afforded unsymmetrical 2,2′-bis(pyrrolyl)alkane **3i** (38 mg, 80 μmol, 95%) as an orange solid; mp 84-85 °C; ν_{max}/cm^{-1} 3418 (br, NH), 2960, 2920, 2850, 1614 (CO), 1475, 1440 and 1007; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.05 (3H, t, $J = 7.5$ Hz, CH_3), 1.77 (3H, s, CH_3), 2.05 (3H, s, CH_3), 2.09 (3H, s, CH_3), 2.35-2.42 (8H, m, CH_2, $2CH_3$), 5.40 (1H, s, CH), 6.86 (2H, d, $J = 7.5$ Hz, $2H_{Ar}$), 6.93 (1H, br s, NH), 7.58 (1H, br s, NH), 7.62 (2H, d, $J = 7.5$ Hz, $2H_{Ar}$); δ_C (100 MHz; $CDCl_3$) 9.3 (CH_3), 11.2 (CH_3), 12.0 (CH_3), 15.3 (CH_3), 15.7 (CH_3), 17.8 (CH_2), 31.1 (CH_3), 39.7 (CH), 92.3 (C–I), 114.7 (C_{Pyr}), 116.2 (C_{Pyr}), 121.8 (C_{Pyr}), 122.0 (C_{Pyr}), 122.2 (C_{Pyr}), 123.1 (C_{Pyr}), 126.3 (C_{Pyr}), 130.5 ($2CH_{Ar}$), 133.5 (C_{Ar}), 138.0 ($2CH_{Ar}$), 141.4 (C_{Pyr}), 195.8 (CO); MS (ESI^+) *m/z* 497 ([M + Na]$^+$, 7), 475 ([M + H]$^+$, 93]; HRMS (ESI^+) $C_{23}H_{27}ON_2INa$ ([M + Na]$^+$) requires 497.1060 found 497.1051.

2-(1-(1*H*-Pyrrol-2-yl)propyl)-4-ethyl-3,5-dimethyl-1*H*-pyrrole 3j. Prepared according to the above general procedure from *N*-benzylhydroxylamine **1a** (50 mg, 0.18 mmol) in 2.0 mL of MeOH, pyrrole **2d** (24 mg, 0.36 mmol) and acetyl chloride (14 mg, 0.18 mmol). The mixture was stirred at –40 °C for 2 h. Purification (eluent: pentane–EtOAc, 95 : 5) afforded unsymmetrical 2,2′-bis(pyrrolyl)alkane **3j** (16 mg, 70 μmol, 40%) as a yellow oil and tripyrromethane **4a** (8 mg, 20 μmol, 23%) as a yellow oil; compound **3j**: ν_{max}/cm^{-1} 3375 (br, NH), 2959, 2920, 2850, 1597, 1562, 1453 and 1107; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.93 (3H, t, $J = 7.2$ Hz, CH_3), 1.08 (3H, t, $J = 7.6$ Hz, CH_3), 1.77-1.85 (2H, m, CH_2), 1.99 (3H, s, CH_3), 2.09 (3H, s, CH_3), 2.35-2.41 (2H, q, $J =$ 7.6 Hz, CH_2), 3.89 (1H, t, $J = 8.4$ Hz, CH), 6.09 (1H, br s, H_{Pyr}), 6.17 (1H, br s, H_{Pyr}), 6.64 (1H, br s, H_{Pyr}), 7.08 (1H, br s, NH), 7.82 (1H, br s, NH); δ_C (100 MHz; $CDCl_3$) 9.1 (CH_3), 11.0 (CH_3), 12.3 (CH_3), 15.7 (CH_3), 17.7 (CH_2), 27.6 (CH_2), 37.3 (CH), 104.3 (CH_{Pyr}), 108.0 (CH_{Pyr}), 113.9 (C_{Pyr}), 116.4 (CH_{Pyr}), 120.3 (C_{Pyr}), 121.0 (C_{Pyr}), 125.7 (C_{Pyr}), 134.3 (C_{Pyr}); MS (ESI$^-$) *m*/*z* 228.9 ([M – H]$^-$, 100); HRMS (ESI$^-$) $C_{15}H_{21}N_2$ ([M – H]$^-$) requires 229.1699 found 229.1697.

3-Ethyl-2,4-dimethyl-5-(phenyl(1*H*-pyrrol-2-yl)methyl)-1*H*-pyrrole 3k. Prepared according to the above general procedure from *N*-benzylhydroxylamine **1b** (50 mg, 0.15 mmol) in 2.5 mL of MeOH, pyrrole **2d** (20 mg, 0.30 mmol) and acetyl chloride (12 mg, 0.15 mmol). The mixture was stirred at –40 °C for 1.5 h. Purification (eluent: pentane–EtOAc, 90 : 10) afforded unsymmetrical 2,2′-bis(pyrrolyl)alkane **3k** (12 mg, 43 μmol, 28%) as a yellow oil and tripyrromethane **4b** (11 mg, 22 μmol, 30%) as a red oil; compound **3k**: ν_{max}/cm^{-1} 3332 (br, NH), 2963, 2928, 2841, 1675, 1601, 1453, 1401 and 1106; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.05 (3H, t, $J = 7.6$ Hz, CH_3), 1.84 (3H, s, CH_3), 2.08 (3H, s, CH_3), 2.36 (2H, q, $J = 7.6$ Hz, CH_2), 5.45 (1H, s, CH), 5.82 (1H, br s, H_{Pyr}), 6.15 (1H, br s, H_{Pyr}), 6.67 (1H, br s, H_{Pyr}), 7.10 (1H, br s, NH), 7.18-7.32 (5H, m, $5H_{Ar}$), 7.87 (1H, br s, NH); δ_C (100 MHz; $CDCl_3$) 9.2 (CH_3), 11.2 (CH_3), 15.8 (CH_3), 17.8 (CH_2), 42.3 (CH), 107.3 (CH_{Pyr}), 108.5 (CH_{Pyr}), 113.9 (C_{Pyr}), 116.9 (CH_{Pyr}), 121.2 (C_{Pyr}), 121.3 (C_{Pyr}), 124.8 (C_{Pyr}), 126.7 (CH_{Ar}), 128.5 ($2CH_{Ar}$), 128.7 ($2CH_{Ar}$), 133.0 (C_{Ar}), 142.5 (C_{Pyr}); MS (ESI$^-$) *m*/*z* 277 ([M – H]$^-$, 100); HRMS (ESI$^-$) $C_{19}H_{21}N_2$ requires ([M – H]$^-$) 277.1699 found 277.1699.

1-(2,4-Dimethyl-5-(phenyl(1*H*-pyrrol-2-yl)methyl)-1*H*-pyrrol-3-yl)ethanone 3l. Prepared according to the above general procedure from *N*-benzylhydroxylamine **1e** (40 mg, 0.12 mmol) in 2.0 mL of MeOH, pyrrole **2d** (16 mg, 0.24 mmol) and acetyl chloride (9 mg, 0.12 mmol). The mixture was stirred at 0 °C for 1 h. Purification (eluent: pentane–EtOAc, 50 : 50) afforded unsymmetrical 2,2′-bis(pyrrolyl)alkane **3l** (14 mg, 48 μmol, 41%) as a white solid and a mixture of tripyrromethane and BnNHOH. The latter mixture was washed twice with aqueous HCl 0.1 N to afford tripyrromethane **4c** (12 mg, 23 μmol, 38%); compound **3l**: mp 71-72 °C; ν_{max}/cm^{-1} 3423 (br, NH), 2928, 1623 (CO), 1436 and 1414; δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.15 (3H, s, CH_3), 2.40 (3H, s, CH_3), 2.41 (3H, s, CH_3), 5.50 (1H, s, CH), 5.84 (1H, br s, H_{Pyr}), 6.17 (1H, br s, H_{Pyr}), 6.99 (1H, br s, H_{Pyr}), 7.16-7.18 (2H, m, $2H_{Ar}$), 7.27-7.35 (3H, m, $3H_{Ar}$), 7.58 (1H, br s, NH), 7.83 (1H, br s, NH); δ_C (100 MHz; $CDCl_3$) 11.9 (CH_3), 15.3 (CH_3), 31.1 (CH_3), 41.5 (CH), 107.8 (CH_{Pyr}), 108.8 (CH_{Pyr}), 116.5 (C_{Pyr}), 117.6 (CH_{Pyr}), 122.0 (C_{Pyr}), 126.6 (C_{Pyr}), 127.2 (CH_{Ar}), 128.3 ($2CH_{Ar}$), 128.9 ($2CH_{Ar}$), 131.7 (C_{Pyr}), 133.7 (C_{Ar}), 141.4 (C_{Pyr}), 195.8 (CO); MS (ESI$^+$) *m*/*z* 607 ([2M + Na]$^+$, 10), 315 ([M + Na]$^+$, 20), 293 ([M + H]$^+$, 70); HRMS (ESI$^+$) $C_{19}H_{20}N_2ONa$ ([M + Na]$^+$) requires 315.1467 found 315.1465.

1-(5-((4-Iodophenyl)(1*H*-pyrrol-2-yl)methyl)-2,4-dimethyl-1*H*-pyrrol-3-yl)ethanone 3m. Prepared according to the above general procedure from *N*-benzylhydroxylamine **1f** (40 mg, 84 μmol) in 2.0 mL of MeOH, pyrrole **2d** (11 mg, 0.16 mmol) and acetyl chloride (7 mg, 89 μmol). The mixture was stirred at 0 °C for 1 h. Purification (eluent: pentane–EtOAc, 50 : 50) afforded unsymmetrical 2,2′-bis(pyrrolyl)alkane **3m** (21 mg, 50 μmol, 59%) as a bright pink solid and a mixture of tripyrromethane and BnNHOH. The latter mixture was washed twice with aqueous HCl 0.1 N to afford tripyrromethane **4d** (10 mg, 13 μmol, 31%); compound **3m**: mp 82 °C; ν_{max}/cm^{-1} 3362 (br, NH), 2915, 2959, 1631 (CO), 1466, 1440, 1419, 1267 and 1002; δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.12 (3H, s, CH_3), 2.37 (3H, s, CH_3), 2.40 (3H, s, CH_3), 5.44 (1H, s, CH), 5.81 (1H, s, H_{Pyr}), 6.16 (1H, s, H_{Pyr}), 6.73 (1H, s, H_{Pyr}), 6.90 (2H, d, $J = 7.6$ Hz, $2H_{Ar}$), 7.62 (2H, d, $J = 7.6$ Hz, $2H_{Ar}$), 7.78 (1H, br s, NH), 8.12 (1H, br s, NH); δ_C (100 MHz; $CDCl_3$) 11.9 (CH_3), 15.3 (CH_3), 31.1 (CH_3), 41.0 (CH), 92.5 (C–I), 108.0 (CH_{Pyr}), 108.8 (CH_{Pyr}), 116.7 (C_{Pyr}), 117.9 (CH_{Pyr}), 122.0 (C_{Pyr}), 126.1 (C_{Pyr}), 130.3 ($2CH_{Ar}$), 131.0 (C_{Pyr}), 134.0 (C_{Ar}), 137.9 ($2CH_{Ar}$), 141.2 (C_{Pyr}), 195.8 (CO); MS (ESI$^+$) *m*/*z* 441 ([M + Na]$^+$, 6), 419 ([M + H]$^+$, 94); HRMS (ESI$^+$) $C_{19}H_{19}ON_2INa$ ([M + Na]$^+$) requires 441.0434 found 441.0438.

3-(1-(4-Ethyl-3,5-dimethyl-1*H*-pyrrol-2-yl)propyl)-1,2,5-trimethyl-1*H*-pyrrole 6a. Prepared according to the above general procedure from *N*-benzylhydroxylamine **1a** (40 mg, 0.14 mmol) in 2.0 mL of MeOH, 1,2,5-trimethylpyrrole **5** (23 mg, 0.21 mmol) and acetyl chloride (11 mg, 0.14 mmol). The mixture was stirred at –20 °C for 1 h. Purification (eluent: pentane–EtOAc, 95 : 5) afforded unsymmetrical 2,3′-bis(pyrrolyl)alkane **6a** (25 mg, 92 μmol, 66%) as a yellow oil; ν_{max}/cm^{-1} 3431 (br, NH), 2963, 2924, 2859, 1679, 1657, 1436 and 1371; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.84 (3H, t, $J = 7.5$ Hz, CH_3), 1.04 (3H, t, $J = 7.5$ Hz, CH_3), 1.74-1.83 (2H, m, CH_2), 2.01 (3H, s, CH_3), 2.04 (3H, s, CH_3), 2.07 (3H, s, CH_3), 2.20 (3H, s, CH_3), 2.34 (2H, q, $J = 7.5$ Hz, CH_2), 3.33 (3H, s, CH_3), 3.69 (1H, t, $J = 7.5$ Hz, CH), 5.81 (1H, s, H_{Pyr}), 7.20 (1H, br s, NH); δ_C (100 MHz; $CDCl_3$) δ 9.5 (CH_3), 10.2 (CH_3), 11.2 (CH_3), 12.7 (CH_3), 13.0 (CH_3), 15.8 (CH_3), 17.9 (CH_2), 29.9 (CH_2), 30.2 (CH_3), 35.7 (CH), 103.5 (CH_{Pyr}), 111.4 (C_{Pyr}), 119.6 (C_{Pyr}), 119.8 (C_{Pyr}), 120.1 (C_{Pyr}), 124.0 (C_{Pyr}), 126.9 (C_{Pyr}), 129.5 (C_{Pyr}); MS (ESI$^+$) *m*/*z* 273 ([M + H]$^+$, 100); HRMS (ESI$^+$) $C_{18}H_{28}N_2Na$ ([M + Na]$^+$) requires 295.2144 found 295.2147.

3-((4-Ethyl-3,5-dimethyl-1*H*-pyrrol-2-yl)(phenyl)methyl)-1,2,5-trimethyl-1*H*-pyrrole 6b. Prepared according to the above general procedure from *N*-benzylhydroxylamine **1b** (40 mg, 0.12 mmol) in 2.0 mL of MeOH, 1,2,5-trimethylpyrrole **5** (19 mg, 0.18 mmol) and acetyl chloride (9 mg, 0.12 mmol). The mixture was stirred at –40 °C for 2 h. Purification (eluent: pentane–EtOAc, 95 : 5) afforded unsymmetrical 2,3′-bis(pyrrolyl)alkane **6b** (24 mg, 75 μmol, 63%) as a yellow solid; mp 122-123 °C; ν_{max}/cm^{-1} 3430 (br NH), 2951, 2905, 2848 and 1443; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.05 (3H, t, $J = 7.5$ Hz, CH_3), 1.79 (3H, s, CH_3), 2.09 (3H, s, CH_3), 2.11 (3H, s, CH_3), 2.15 (3H, s, CH_3), 2.37 (2H, q, $J = 7.5$ Hz, CH_2), 3.36 (3H, s, CH_3), 5.26 (1H, s, CH), 5.50 (1H, s, H_{Pyr}),

7.13-7.15 (3H, m, $3H_{Ar}$), 7.21-7.23 (2H, m, $2H_{Ar}$), 7.28 (1H, br s, NH); δ_C (100 MHz; $CDCl_3$) 9.4 (CH_3), 10.4 (CH_3), 11.3 (CH_3), 12.7 (CH_3), 15.9 (CH_3), 17.9 (CH_2), 30.3 (CH_3), 40.5 (CH), 105.7 (CH_{Pyr}), 112.7 (C_{Pyr}), 119.6 (C_{Pyr}), 119.8 (C_{Pyr}), 120.8 (C_{Pyr}), 123.9 (C_{Pyr}), 125.6 (CH_{Ar}), 127.0 (C_{Pyr}), 127.1 (C_{Pyr}), 128.2 ($2CH_{Ar}$), 128.3 ($2CH_{Ar}$), 145.6 (C_{Ar}); MS (ESI^+) m/z 321 ($[M + H]^+$, 100); HRMS (ESI^+) $C_{22}H_{28}N_2Na$ ($[M + Na]^+$) requires 343.2144 found 343.2144.

1-(2,4-Dimethyl-5-(1-(1,2,5-trimethyl-1*H*-pyrrol-3-yl)propyl)-1*H*-pyrrol-3-yl)ethanone 6c. Prepared according to the above general procedure from *N*-benzylhydroxylamine **1d** (40 mg, 0.13 mmol) in 2.0 mL of MeOH, 1,2,5-trimethylpyrrole **5** (22 mg, 0.20 mmol) and acetyl chloride (11 mg, 0.14 mmol). The mixture was stirred at room temperature for 2 h. Purification (eluent: pentane–EtOAc, 50 : 50) afforded unsymmetrical 2,3′-bis(pyrrolyl)alkane **6c** (28 mg, 98 µmol, 73%) as a beige solid; mp 84-85 °C; ν_{max}/cm^{-1} 3427 (br, NH), 3280, 2950, 2920, 2867, 1618 (CO), 1440 and 1419; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.86 (3H, t, J = 7.2 Hz, CH_3), 1.76-1.82 (2H, m, CH_2), 2.01 (3H, s, CH_3), 2.21 (3H, s, CH_3), 2.27 (3H, s, CH_3), 2.38 (3H, s, CH_3), 2.39 (3H, s, CH_3), 3.34 (3H, s, CH_3), 3.74 (1H, t, J = 7.6 Hz, CH), 5.82 (1H, s, H_{Pyr}), 7.69 (1H, br s, NH); δ_C (100 MHz; $CDCl_3$) 10.1 (CH_3), 12.1 (CH_3), 12.7 ($2CH_3$), 15.5 (CH_3), 29.3 (CH_2), 30.3 (CH_3), 31.1 (CH_3), 34.7 (CH), 103.2 (CH_{Pyr}), 113.9 (C_{Pyr}), 118.8 (C_{Pyr}), 121.4 (C_{Pyr}), 124.3 (C_{Pyr}), 127.3 (C_{Pyr}), 130.9 (C_{Pyr}), 132.8 (C_{Pyr}), 195.7 (CO); MS (ESI^+) m/z 309 ($[M + Na]^+$, 13), 287 ($[M + H]^+$, 87); HRMS (ESI^+) $C_{18}H_{26}N_2ONa$ ($[M + Na]^+$) requires 309.1937 found 309.1937.

1-(2,4-Dimethyl-5-(phenyl(1,2,5-trimethyl-1*H*-pyrrol-3-yl)methyl)-1*H*-pyrrol-3-yl)ethanone 6d. Prepared according to the above general procedure from *N*-benzylhydroxylamine **1e** (33 mg, 95 µmol) in 2.0 mL of MeOH, 1,2,5-trimethylpyrrole **5** (15 mg, 0.14 mmol) and of acetyl chloride (8 mg, 0.10 mmol). The mixture was stirred at 0 °C for 30 min. Purification (eluent: pentane–EtOAc, 50 : 50) afforded unsymmetrical 2,3′-bis(pyrrolyl)alkane **6d** (21 mg, 63 µmol, 66%) as a beige solid; mp 68-69 °C; ν_{max}/cm^{-1} 3414 (br, NH), 2950, 2924, 2859, 1627 (CO), 1440 and 1410; δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.06 (3H, s, CH_3), 2.10 (3H, s, CH_3), 2.14 (3H, s, CH_3), 2.39 (3H, s, CH_3), 2.43 (3H, s, CH_3), 3.37 (3H, s, CH_3), 5.29 (1H, s, CH), 5.41 (1H, s, H_{Pyr}), 7.08-7.26 (5H, m, $5H_{Ar}$), 7.77 (1H, br s, NH); δ_C (100 MHz; $CDCl_3$) 10.3 (CH_3), 12.0 (CH_3), 12.6 (CH_3), 15.4 (CH_3), 30.4 (CH_3), 31.1 (CH_3), 39.5 (CH), 105.5 (CH_{Pyr}), 115.0 (C_{Pyr}), 118.5 (C_{Pyr}), 121.8 (C_{Pyr}), 124.2 (C_{Pyr}), 126.0 (CH_{Ar}), 127.5 (C_{Pyr}), 128.1 ($2CH_{Ar}$), 128.4 ($2CH_{Ar}$), 128.8 (C_{Pyr}), 132.8 (C_{Ar}), 144.3 (C_{Pyr}), 195.9 (CO); MS (ESI^+) m/z 357 ($[M + Na]^+$, 13), 335 ($[M + H]^+$, 87); HRMS (ESI^+) $C_{22}H_{26}N_2ONa$ ($[M + Na]^+$) requires 357.1937 found 357.1935.

General procedure for the preparation of tripyrromethanes

Freshly distilled acetyl chloride (1 equiv.) was added dropwise at 0 °C to anhydrous methanol, and the mixture was stirred for 15 min. The appropriate pyrrolic *N*-benzylhydroxylamine (1 equiv.) was added and the mixture was cooled at −78 °C before the addition of freshly distilled pyrrole (0.5 equiv.). The mixture was warmed to the appropriate temperature and stirred until complete disappearance of the starting material (followed by TLC). The mixture was treated with saturated aqueous $NaHCO_3$ solution. The pH value was 8–9. The aqueous layer was then extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. The obtained tripyrromethane was purified by flash chromatography on silica gel.

2,5-Bis(1-(4-ethyl-3,5-dimethyl-1*H*-pyrrol-2-yl)propyl)-1*H*-pyrrole 4a. Prepared according to the above general procedure from *N*-benzylhydroxylamine **1a** (50 mg, 0.18 mmol) in 2.5 mL of MeOH, pyrrole **2d** (6 mg, 89 µmol) and acetyl chloride (14 mg, 0.18 mmol). The mixture was stirred at –40 °C for 2 h. Purification (eluent: pentane–EtOAc, 90 : 10) afforded tripyrromethane **4a** (19 mg, 48 µmol, 55%) as a yellow oil; ν_{max}/cm^{-1} 3365 (br, NH), 2960, 2924, 2856, 1597, 1562, 1460, 1147 and 1101; δ_H (300 MHz; $CDCl_3$; Me_4Si) 0.89 (6H, m, $2CH_3$), 1.03 (6H, m, $2CH_3$), 1.78 (2H, m, CH_2), 1.90 (3H, s, CH_3), 1.92 (3H, s, CH_3), 1.95 (2H, m, CH_2), 2.05 (3H, s, CH_3), 2.07 (3H, s, CH_3), 2.34 (4H, m, $2CH_2$), 3.78 (2H, dd, J = 5.7 and 11.1 Hz, 2CH), 5.97 (2H, dd, J = 2.1 and 5.7 Hz, $2H_{Pyr}$), 7.06 (2H, br s, 2NH), 7.51 (1H, br s, NH); δ_C (75 MHz; $CDCl_3$) 9.3 ($2CH_3$), 11.1 ($2CH_3$), 12.5 ($2CH_3$), 15.8 ($2CH_3$), 17.8 ($2CH_2$), 28.0 ($2CH_2$), 37.5 (CH), 37.7 (CH), 104.1 (CH_{Pyr}), 104.4 (CH_{Pyr}), 113.5 ($2C_{Pyr}$), 120.5 ($2C_{Pyr}$), 120.8 ($2C_{Pyr}$), 126.3 ($2C_{Pyr}$), 133.2 ($2C_{Pyr}$); MS (ESI^+) m/z 394 ($[M + H]^+$, 100); HRMS (ESI^+) $C_{26}H_{40}N_3$ ($[M + H]^+$) requires 394.3222 found 394.3222.

2,5-Bis((4-ethyl-3,5-dimethyl-1*H*-pyrrol-2-yl)(phenyl)methyl)-1*H*-pyrrole 4b. Prepared according to the above general procedure from *N*-benzylhydroxylamine **1b** (50 mg, 0.15 mmol) in 2.5 mL of MeOH, pyrrole **2d** (5 mg, 74 µmol) and acetyl chloride (12 mg, 0.15 mmol). The mixture was stirred at –40 °C for 2 h. Purification (eluent: pentane–EtOAc, 90 : 10) afforded tripyrromethane **4b** (24 mg, 49 µmol, 66%) as a red oil; ν_{max}/cm^{-1} 3418 (br, NH), 2959, 2924, 2850, 1597 and 1449; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.02 (6H, t, J = 7.6 Hz, $2CH_3$), 1.78 (6H, s, $2CH_3$), 2.06 (6H, s, $2CH_3$), 2.33 (4H, q, J = 7.6 Hz, $2CH_2$), 5.35 (2H, s, 2CH), 5.67 (2H, br s, $2H_{Pyr}$), 7.08 (2H, br s, 2NH), 7.14-7.29 (10H, m, $10H_{Ar}$), 7.63 (1H, br s, NH); δ_C (75 MHz; $CDCl_3$) 7.5 ($2CH_3$), 9.6 ($2CH_3$), 14.3 ($2CH_3$), 16.3 ($2CH_2$), 41.6 (2CH), 108.0 ($2CH_{Pyr}$), 114.6 ($2C_{Pyr}$), 121.9 ($2C_{Pyr}$), 122.0 ($2C_{Pyr}$), 125.7 ($2C_{Pyr}$), 127.6 ($2CH_{Ar}$), 129.4 ($4CH_{Ar}$), 129.6 ($4CH_{Ar}$), 133.5 ($2C_{Ar}$), 143.9 ($2C_{Pyr}$); MS (ESI^+) m/z 490 ($[M + H]^+$, 100); HRMS (ESI^+) $C_{34}H_{40}N_3$ ($[M + H]^+$) requires 490.3222 found 490.3222.

1,1′-(5,5′-(1*H*-Pyrrole-2,5-diyl)bis(phenylmethylene)bis(2,4-dimethyl-1*H*-pyrrole-5,3-diyl))diethanone 4c. Prepared according to the above general procedure from *N*-benzylhydroxylamine **1e** (40 mg, 0.12 mmol) in 2.0 mL of MeOH, pyrrole **2d** (4 mg, 59 µmol) and acetyl chloride (9 mg, 0.11 mmol). The mixture was stirred at 0 °C for 30 min. The media was then washed with aqueous HCl 0.1 N and flash purification (eluent: pentane–EtOAc, 50 : 50) afforded tripyrromethane **4c** (22 mg, 42 µmol, 74%) as a beige solid; mp 148-149 °C; ν_{max}/cm^{-1} 3418 (br, NH), 3314, 2963, 2915, 1631 (CO), 1605, 1445, 1419, 1362 and 1237; δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.10 (6H, s, $2CH_3$), 2.35 (6H, s, $2CH_3$), 2.38 (6H, s, $2CH_3$), 5.40 (2H, s, 2CH), 5.70 (2H, s, $2H_{Pyr}$), 7.11-7.13 (4H, m, $4H_{Ar}$), 7.24-7.32 (6H, m, $6H_{Ar}$), 7.75 (2H, br s, 2NH), 7.82 (1H, br s, NH); δ_C (100 MHz; $CDCl_3$) 11.7 ($2CH_3$), 15.2 ($2CH_3$), 30.9 ($2CH_3$), 41.3 (2CH), 108.0 ($2CH_{Pyr}$), 116.3 ($2C_{Pyr}$), 121.8 ($2C_{Pyr}$), 126.3 ($2C_{Pyr}$), 127.1 ($2CH_{Ar}$), 128.1 ($4CH_{Ar}$), 128.7 ($4CH_{Ar}$), 131.8 ($2C_{Pyr}$), 133.6 ($2C_{Ar}$), 141.2 ($2C_{Pyr}$), 195.6 (2CO); MS (ESI^+) m/z 540 ($[M + Na]^+$, 23), 518 ($[M + H]^+$, 77); HRMS (ESI^+) $C_{34}H_{35}N_3O_2Na$ ($[M + Na]^+$) requires 540.2621 found 540.2613.

1,1′-(5,5′-(1*H*-Pyrrole-2,5-diyl)bis((4-iodophenyl)methylene)-bis(2,4-dimethyl-1*H*-pyrrole-5,3-diyl))diethanone 4d. Prepared according to the above general procedure from *N*-benzylhydroxylamine **1f** (40 mg, 84 μmol) in 2.0 mL of MeOH, pyrrole **2d** (3 mg, 44 μmol) and acetyl chloride (7 mg, 89 μmol). The mixture was stirred at 0 °C for 30 min. The media was then washed with aqueous HCl 0.1 N and flash purification (eluent: pentane–EtOAc, 50 : 50) afforded tripyrromethane **4d** (24 mg, 31 μmol, 74%) as a beige solid; mp 177-178 °C; ν_{max}/cm^{-1} 3275 (br NH), 2959, 2915, 2854, 1627, 1601, 1480, 1445, 1423 and 1002; δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.06 (3H, s, CH_3), 2.07 (3H, s, CH_3), 2.35 (3H, s, CH_3), 2.36 (3H, s, CH_3), 2.37 (3H, s, CH_3), 2.40 (3H, s, CH_3), 5.34 (2H, s, 2CH), 5.67-5.69 (2H, m, $2H_{Pyr}$), 6.85-6.88 (4H, m, $4H_{Ar}$), 7.61-7.63 (4H, d, J = 8.4 Hz, $4H_{Ar}$), 7.79 (1H, br s, NH), 7.84 (1H, br s, NH), 8.01 (1H, br s, NH); δ_C (100 MHz; $CDCl_3$) 11.8 ($2CH_3$), 15.3 ($2CH_3$), 31.0 ($2CH_3$), 41.0 (CH), 41.1 (CH), 92.7 (2C-I), 108.4 ($2CH_{Pyr}$), 116.8 (C_{Pyr}), 116.9 (C_{Pyr}), 122.1 ($2C_{Pyr}$), 125.8 ($2C_{Pyr}$), 130.2 ($4CH_{Ar}$), 131.6 (C_{Pyr}), 131.7 (C_{Pyr}), 134.0 ($2C_{Ar}$), 137.9 ($4CH_{Ar}$), 141.1 ($2C_{Pyr}$), 195.7 (2CO); MS (ESI$^+$) m/z 792 ([M + Na]$^+$, 33), 770 ([M + H]$^+$, 67); HRMS (ESI$^+$) $C_{34}H_{33}N_3O_2I_2Na$ ([M + Na]$^+$) requires 792.0554 found 792.0565.

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