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## Functionalization of Dipyrrromethanes via Hetero-Diels-Alder Reaction with Azo- and Nitrosoalkenes

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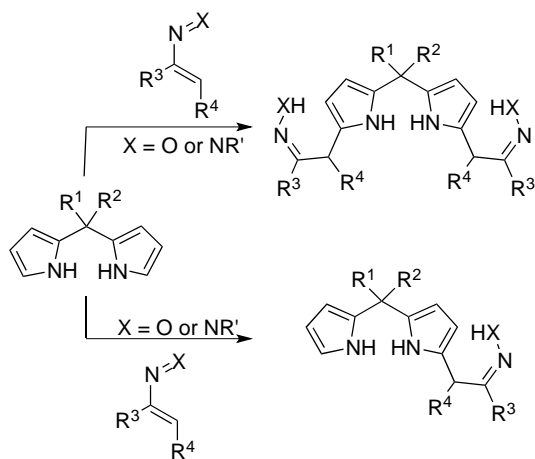
**Abstract** – 5,5'-Diethyl- and 5-phenyldipyrrromethanes participate in cycloadditions with azo- and nitrosoalkenes giving dipyrrromethanes with side chains containing open chain oximes and hydrazones. Controlling reaction stoichiometry it is possible to get mono or 1,9-disubstituted derivatives. The reported methodology gave access to a range of dipyrrromethanes with good structural features for various applications. It was demonstrated that reduction of dipyrrromethanes containing  $\alpha$ -oximino ester groups opens the way to new  $\alpha$ -amino esters.

**Keywords:** Dipyrrromethanes, Azoalkenes, Nitrosoalkenes, Hetero-Diels-Alder Reaction.

Dipyrrolic compounds<sup>1</sup> are of wide interest as building blocks in organic synthesis, namely in the synthesis of porphyrins<sup>2</sup> and porphyrin analogues such as *meso*-substituted corroles,<sup>3</sup> chlorins,<sup>4</sup> expanded porphyrins,<sup>5</sup> and calix[4]pyrroles.<sup>6</sup> On the other hand, dipyrrromethanes are the precursors of BODIPY dyes (4,4-difluoro-4-bora-3a,4a-diaza-s-indacenes) whose photophysical properties make them the ideal fluorescent scaffold for the development of high performance imaging probes.<sup>7</sup> Radioactive technetium complexes also have widespread application in molecular imaging.<sup>8</sup> Thus, we envisioned that the synthesis of dipyrrromethanes with structural requirements to act as Technetium (<sup>99m</sup>Tc) ligands for application as radiotracers in cancer detection would be of particular interest. Functionalized dipyrrromethanes are also potentially attractive structures for the development of new optical anion sensors, for application in biological systems and in the settling of environmental problems.<sup>9</sup> In fact, pyrrole based anion receptors, including dipyrrromethane derivatives,<sup>1b,9j</sup> have been shown to be selective and efficient receptors for a variety of anionic species.

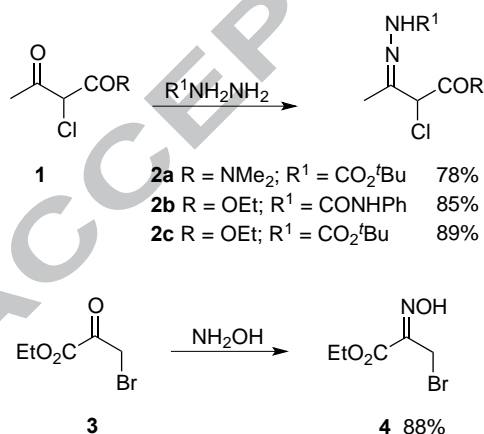
In this context, we decided to explore the hetero-Diels-Alder reaction of azoalkenes and nitrosoalkenes to achieve the functionalization of dipyrrromethane derivatives. Cycloadditions of these heterodienes has been explored as a route to tetrahydro-1,2-oxazine, tetrahydro-pyridazine, open chain oxime and hydrazone derivatives.<sup>10</sup> Our previous studies on hetero-Diels-Alder reactions of 3-tetrazolyl nitrosoalkenes and 3-tetrazolyl-1,2-diaza-1,3-butadienes demonstrated that it is an efficient approach for the synthesis of functionalized 5-(substituted)-1*H*-tetrazoles.<sup>11</sup> Using pyrrole as the 2 $\pi$  component, open chain oximes and hydrazones are obtained. We envisaged that a diversity of dipyrrromethanes might be produced through hetero-Diels-Alder reaction with azoalkenes and nitrosoalkenes, using 5,5'-di-substituted- and 5-mono-substituted

dipyrromethanes as  $2\pi$  components. On the other hand, the possibility of controlling mono- or di-functionalization would lead to a wider range of dipyrromethane derivatives allowing the diversification of potential applications. In this communication, details of this new synthetic strategy for the introduction of side-chains in positions 1 and 9 of dipyrromethanes *via* hetero-Diels-Alder reaction are presented (Scheme 1).



**Scheme 1.** Synthetic strategy for the functionalization of dipyrromethanes.

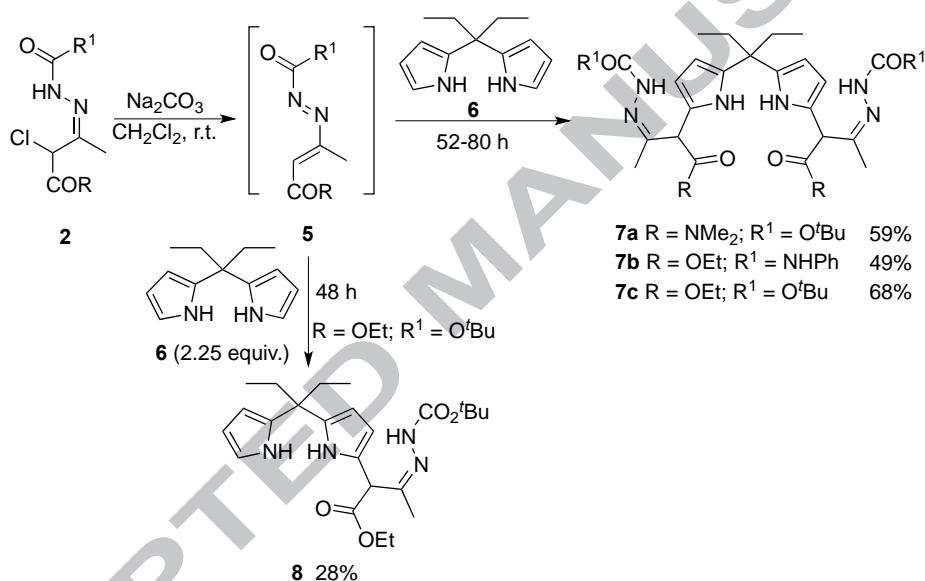
The heterodienes selected to carry out this study were generated *in situ* through base mediated dehydrohalogenation of  $\alpha$ -halohydrazones **2** or  $\alpha$ -halooxime **4**. These azo- and nitrosoalkene precursors were obtained from the reaction of the corresponding hydrazine with  $\alpha$ -halo carbonyl compounds **1** and from the condensation of hydroxylamine with ethyl bromopyruvate (**3**), respectively (Scheme 2).<sup>12</sup>



**Scheme 2.** Synthesis of azo- and nitrosoalkene precursors.

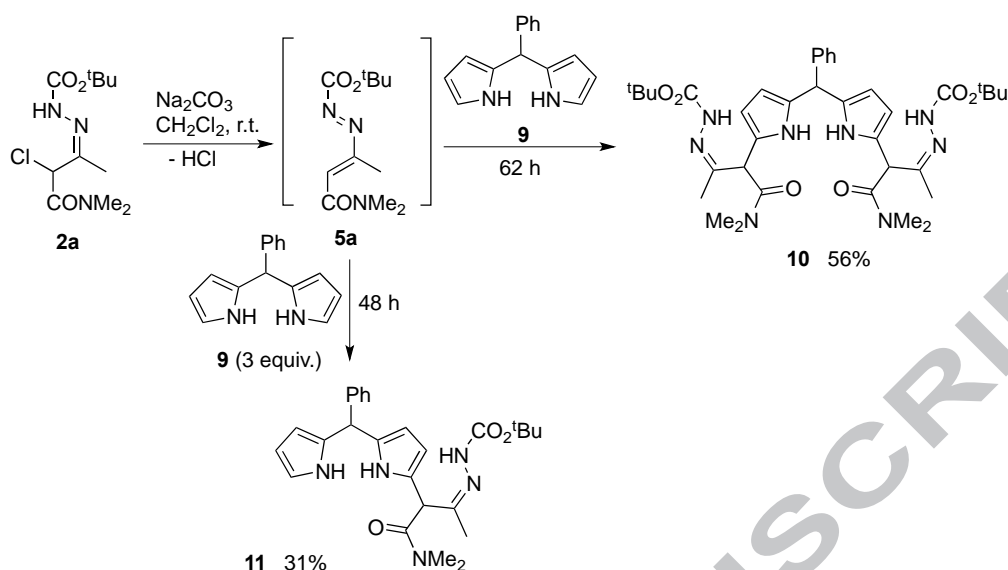
Initially, the behaviour of 5,5'-diethyldipyrromethane (**6**) towards 1,2-diaza-1,3-butadienes was explored (Scheme 3). Dipyrromethane **6** was prepared by a known synthetic methodology involving the acid-catalyzed condensation of 3-pentanone with pyrrole in aqueous medium.<sup>1c</sup> By treatment with sodium carbonate in dichloromethane at room temperature, hydrazones **2** were converted into the transient 1,2-diaza-1,3-

butadienes **5** which were trapped *in situ* by dipyrromethane **6** affording the corresponding open chain hydrazones **7**<sup>13</sup> and **8**<sup>14</sup>. Carrying out the reaction using an excess of pyrromethane **6** (2.25 equiv.) the mono-functionalized derivative **8** could be isolated in moderate yield as single product whereas the reaction using a slight excess of hydrazones **2** afforded the di-functionalized pyrromethanes **7** in good yield. These reactions can be regarded as “formal” alkylation reactions, which are the result of hetero-Diels-Alder reactions followed by 1,4,5,6-tetrahydropyridazine ring opening via a 1,5-sigmatropic rearrangement and finally a enolization-type step, as previously observed in the reaction of 1,2-diaza-1,3-butadienes with heterocycles possessing high aromatic character such as pyrrole and indole.<sup>10,11</sup>



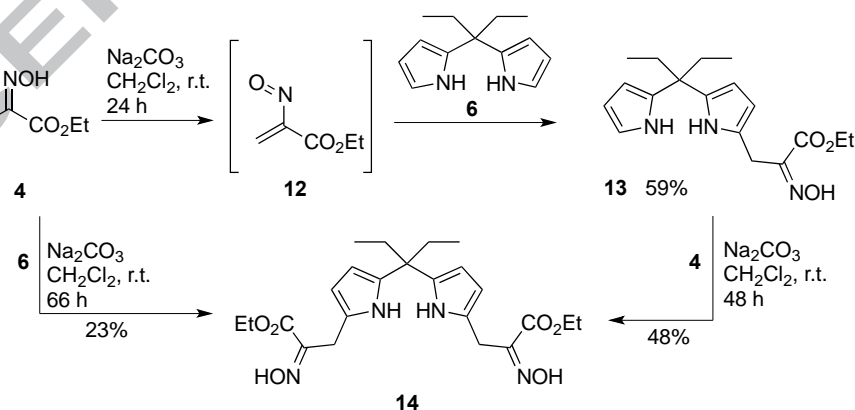
**Scheme 3.** Hetero-Diels-Alder reaction of 5,5'-diethyldipyrromethane (**6**) with 1,2-diaza-1,3-butadienes.

The work was extended to the cycloaddition of a 5-mono-substituted dipyrromethane with 1,2-diaza-1,3-butadiene **5a** (Scheme 4). The TFA catalyzed condensation of benzaldehyde with neat excess of pyrrole afforded 5-phenyldipyrromethane (**9**), as reported by Lindsey *et al.*<sup>1b</sup> We were pleased to observe that the conversion of dipyrromethane **9** into 1,9-disubstituted dipyrromethane **10** showed similar efficiency to the one observed in the cycloaddition of 5,5'-diethyldipyrromethane (**6**) with the same diene. In fact, dipyrromethane **10** was obtained in 56% yield.<sup>13</sup> Using an excess of 5-phenyldipyrromethane (**9**) the mono-functionalized derivative **11**<sup>14</sup> could be obtained in 31% yield.



**Scheme 4.** Hetero-Diels-Alder reaction of 5-phenyldipyrromethane (**9**) with 1,2-diaza-1,3-butadiene **5a**.

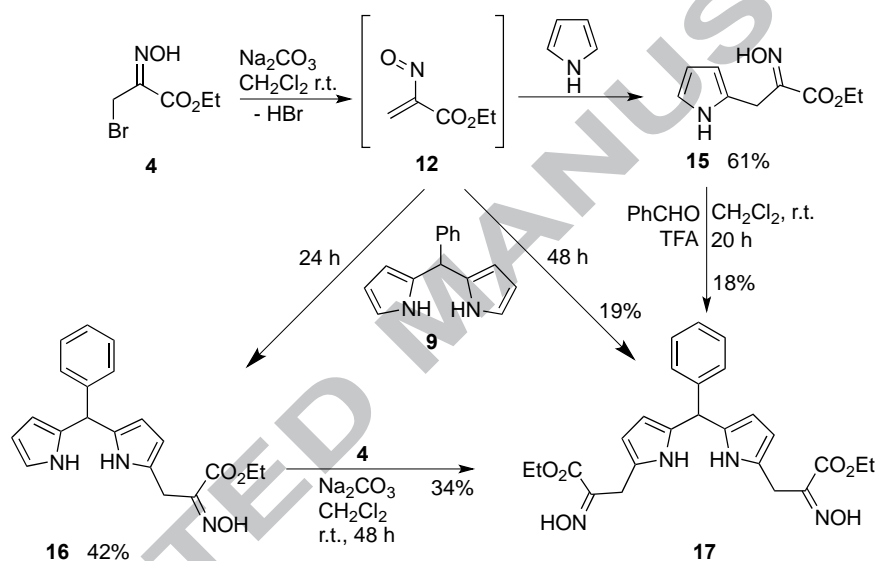
We have also explored the hetero-Diels–Alder reaction of nitrosoalkene **12**, generated *in situ* from the corresponding bromooxime **4**, with dipyrromethane **6** (Scheme 5). In this case, it was observed that carrying out the mono-functionalization to give **13**, followed by the subsequent cycloaddition leading to the target compound **14**, was more efficient than a one-pot procedure. In fact, the latter led to a more difficult isolation since the formation of derivative **13** was also observed. Under the optimized reaction conditions dipyrromethane **13** was isolated in 59% yield and di-functionalized derivative **14** was obtained from **13** in 48% yield. It is noteworthy that compounds **13** and **14** have the structural requirements to act as Technetium ( $^{99\text{m}}\text{Tc}$ ) ligands for application in cancer radioimaging.



**Scheme 5.** Hetero-Diels-Alder reaction of 5,5'-diethyldipyrromethane (**6**) with nitrosoalkene **12**.

The reaction of nitrosoalkene **12** with 5-phenyldipyrromethane (**9**) was not as straightforward as with the 5,5'-diethyldipyrromethane (**6**), which prompted us to prepare dipyrromethane **17** using different strategies (Scheme 6). The hetero-Diels–

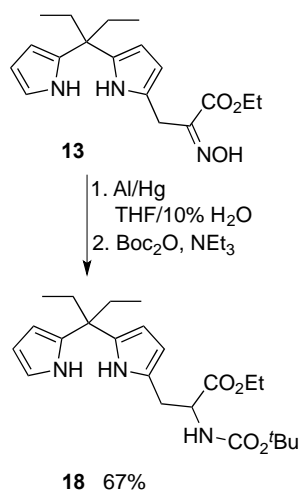
Alder reaction requires long reaction times leading to oxidation of the dipyrromethanes making the isolation of the target compounds harder. The one-pot approach afforded the di-functionalized dipyrromethane **17** in 19% yield. Reacting oxime **4** with an excess of 5-phenyldipyrromethane (**9**) in the presence of sodium carbonate led to the formation of dipyrromethane **16** in 42% yield. This heterocyclic compound, when subjected to another cycloaddition with nitrosoalkene **12**, gave compound **17** in moderate yield (34%). Finally, an alternative strategy was devised. Dipyrromethane **17** was obtained in 18% yield from the condensation of benzaldehyde with two equivalents of pyrrole **15**<sup>12f</sup> in dichloromethane, in the presence of a catalytic amount of TFA, a general procedure described by Lindsey *et al.*<sup>15</sup>



**Scheme 6.** Synthesis of dipyrromethane **17**.

The functionalities introduced on the dipyrromethane nucleus can be used for other useful transformations, as in the case of the reduction of  $\alpha$ -oximino ester to  $\alpha$ -amino esters.<sup>12f,11a</sup>

Therefore, the reduction of  $\alpha$ -oximino ester **13** was carried out using aluminum amalgam in aqueous THF giving the corresponding  $\alpha$ -amino ester which underwent *N*-protection with di-*t*-butyldicarbonate to afford compound **18** in 67% overall yield<sup>16</sup> (Scheme 7).



**Scheme 7.** Reduction of  $\alpha$ -oximino ester **13**.

A new synthetic strategy for the introduction of side-chains in positions 1 and 9 of dipyrromethanes *via* hetero-Diels-Alder reaction with azo- and nitrosoalkenes is reported. This allowed the synthesis of new 5,5'-diethyl- and 5-phenyldipyrromethanes functionalized with side chains containing open chain oximes and hydrazones. Furthermore, it was demonstrated that reduction of dipyrromethanes containing  $\alpha$ -oximino ester groups opens the way to new  $\alpha$ -amino esters.

The new dipyrromethanes have good structural features for various applications, namely for the synthesis of BODIPY dyes and Technetium (<sup>99m</sup>Tc) ligands to be used as radiotracers, the synthesis of porphyrin analogues and the development of new optical anion sensors.

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### Supplementary Material

Experimental procedures and characterization data all new compounds. <sup>1</sup>H and <sup>13</sup>C NMR spectra for all new compounds. Supplementary data associated with this article can be found, in the online version, at [XXX](#).

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13. *1-(2'-t-Butoxycarbonylhydrazono-1'-ethoxycarbonylpropyl)-5,5'-diethyldipyrromethane (8)*. Obtained in 28% yield (0.018 g) from dipyrromethane **6** (0.060 g, 0.30 mmol) and hydrazone **2c** (0.041 g, 0.15 mmol) as a yellow solid. Mp 43-45 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 8.33 (s, 1H, NH), 8.06 (s, 1H, NH), 7.53 (s, 1H, NH), 6.63 (bs, 1H, α-H pyrrolic), 6.11-6.10 (m, 1H, β-H pyrrolic), 6.05 (bs, 1H, β-H pyrrolic), 5.97 (bs, 1H, β-H pyrrolic), 4.65 (s, 1H, CH), 4.16 (q, J = 7.0 Hz, 2H, CH<sub>2</sub>), 1.95-1.92 (m, 4H, CH<sub>2</sub>), 1.77 (s, 3H, Me), 1.50 and 1.46 (2s, 9H, Me), 1.23 (t, J = 7.0 Hz, 3H, Me), 0.73 - 0.68 (m, 6H, Me) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 170.0, 152.4, 148.0, 137.3, 136.2, 129.4, 128.2, 123.1, 116.7, 107.2, 105.8, 105.5, 81.2, 61.4, 53.2, 43.5, 29.6, 28.1, 13.3, 13.2, 8.3 ppm. HRMS (ESI): calcd. 467.2629 for C<sub>24</sub>H<sub>36</sub>N<sub>4</sub>NaO<sub>4</sub> [M + Na]<sup>+</sup>, found 467.2618. *1-(2'-t-Butoxycarbonylhydrazono-1'-dimethylaminocarbonylpropyl)-5-phenyldipyrromethane (11)*. Obtained in 31% yield (0.038 g) yield from dipyrromethane **9** (0.140 g, 0.63 mmol) and hydrazone **2a** (0.07 g, 0.28 mmol) as a purple solid. Mp 97-99 °C [from diethyl ether

/ hexane] (obtained as mixture of two conformers)  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.97 (s, 1H, NH), 8.17 and 8.12 (2s, 1H, NH), 7.46 (s, 1H, NH), 7.28 - 7.15 (m, 5H, Ph), 6.68 (bs, 1H,  $\alpha$ -H pyrrolic), 6.12 (bs, 1H,  $\beta$ -H pyrrolic), 5.97-5.96 (m, 1H,  $\beta$ -H pyrrolic), 5.86-5.74 (m, 2H,  $\beta$ -H pyrrolic), 5.40 (s, 1H, CH *meso*), 5.00 (s, 2H, CH), 3.05 and 3.04 (2s, 3H, Me), 2.92 and 2.91 (2s, 3H, Me), 1.77 and 1.76 (2s, 3H, Me), 1.49 (s, 9H, Me) ppm.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 170.0, 152.7, 150.6, 142.3, 133.3, 132.5, 132.4, 128.6, 128.5, 128.4, 128.3, 126.8, 124.7, 124.6, 117.3, 117.2, 108.2, 107.9, 107.6, 107.5, 107.2, 107.1, 81.3, 50.2, 50.2, 44.2, 37.9, 35.9, 28.3, 13.1, 13.0 ppm. HRMS (ESI): calcd. for  $\text{C}_{26}\text{H}_{34}\text{N}_5\text{O}_3$   $[\text{M} + \text{H}]^+$  464.2656, found 464.2652.

14. *5,5'-Diethyl-1,9-bis(1'-dimethylaminocarbonyl-2'-phenylaminocarbonylhydrazonopropyl)-dipyrrromethane (7b)*. Obtained in 49% yield (0.087 g) from dipyrrromethane **6** (0.05 g, 0.25 mmol) and hydrazone **2b** (0.240 g, 0.86 mmol) as a white solid. Mp 92-94 °C [from diethyl ether / hexane]  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.29 (s, 2H, NH), 8.12 (s, 1H, NH), 8.04 (s, 3H, NH), 7.46 (d,  $J$  = 7.6 Hz, 4H, Ph), 7.30 (t,  $J$  = 7.6 Hz, 4H, Ph), 7.08 - 7.04 (m, 2H, Me), 6.01-5.99 (m, 4H,  $\beta$ -H pyrrolic), 4.56 (s, 1H, CH), 4.53 (s, 1H, CH), 4.22 - 4.19 (m, 4H,  $\text{CH}_2$ ), 1.93-1.92 (m, 4H,  $\text{CH}_2$ ), 1.81 (s, 3H, Me), 1.79 (s, 3H, Me), 1.28-1.25 (m, 6H, Me), 0.72 - 0.70 (m, 6H, Me) ppm.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 170.1, 153.3, 153.2, 146.4, 146.3, 137.9, 137.4, 129.0, 123.4, 122.9, 122.9, 119.4, 119.3, 108.2, 108.0, 106.3, 61.6, 53.2, 43.8, 43.7, 29.8, 14.2, 13.8, 8.5, 8.4 ppm. HRMS (ESI): calcd. for  $\text{C}_{39}\text{H}_{49}\text{N}_8\text{O}_6$   $[\text{M} + \text{H}]^+$  725.3769, found 725.3746. *1,9-Bis(2'-t-butoxycarbonylhydrazono-1'-dimethylaminocarbonylpropyl)-5-phenyldipyrrromethane (10)*. Obtained in 56% yield (0.090 g) from dipyrrromethane **9** (0.055 g, 0.16 mmol) and hydrazone **2a** (0.150 g, 0.54 mmol) as a pink solid. Mp 130-132 °C [from diethyl ether / hexane].  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.91 (s, 1H, NH), 8.87 (s, 1H, NH), 7.48 (s, 2H, NH), 7.28 - 7.15 (m, 5H, Ph), 5.96 (bs, 2H,  $\beta$ -H pyrrolic), 5.73-5.69 (m, 2H,  $\beta$ -H pyrrolic), 5.34 (s, 1H, CH *meso*), 5.01 (s, 2H, CH), 3.05 (s, 6H, Me), 2.92 (s, 6H, Me), 1.79 (s, 3H, Me), 1.77 (s, 3H, Me), 1.50 (s, 18H, Me) ppm.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 170.0, 152.7, 151.0, 150.9, 142.0, 133.1, 133.0, 128.6, 128.5, 128.4, 128.3, 126.9, 124.8, 108.0, 107.9, 107.8, 107.7, 107.6, 81.3, 81.2, 50.1, 44.3, 37.9, 35.8, 28.3, 13.0, 12.9 ppm. HRMS (ESI): calcd. for  $\text{C}_{37}\text{H}_{53}\text{N}_8\text{O}_6$   $[\text{M} + \text{H}]^+$  705.4082, found 705.4077.
15. Wagner, R. W.; Lindsey, J. S. *Pure & Appl. Chem.* **1996**, *68*, 1373-1380.
16. *1-(2-t-Butoxycarbonylamino-2-ethoxycarbonyl ethyl)-5,5'-diethyldipyrrromethane (18)* was obtained as a yellow oil in 67% yield.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.12 (s, 1H, NH), 7.64 (s, 1H, NH), 6.65 (s, 1H,  $\alpha$ -H pyrrolic), 6.12-6.11 (m, 1H,  $\beta$ -H pyrrolic), 6.07 (s, 1H,  $\beta$ -H pyrrolic), 5.95 (bs, 1H,  $\beta$ -H pyrrolic), 5.84 (bs, 1H,  $\beta$ -H pyrrolic), 5.06-5.05 (m, 1H, NH), 4.38-4.37 (m, 1H, CH), 4.12-4.05 (m, 2H,  $\text{CH}_2$ ), 3.02-2.87 (m, 2H,  $\text{CH}_2$ ), 1.92-1.87 (m, 4H,  $\text{CH}_2$ ), 1.40 (s, 9H, Me), 1.24-1.21 (m, 3H, Me), 0.72-0.68 (m, 6H, Me) ppm.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 171.9, 155.1, 136.7, 136.4, 132.8, 129.5, 128.3, 125.1, 116.8, 107.4, 107.3, 106.3, 105.6, 79.9, 61.5, 53.7, 43.6, 31.3, 29.9, 29.7, 28.3, 14.1, 8.4 ppm. HRMS (ESI): calcd. for  $\text{C}_{23}\text{H}_{35}\text{N}_3\text{NaO}_4$   $[\text{M} + \text{Na}]^+$  440.2520, found 440.2514.

