

## Synthesis of a neo-confused porphyrin and an unusual dihydroporphyrin derivative†

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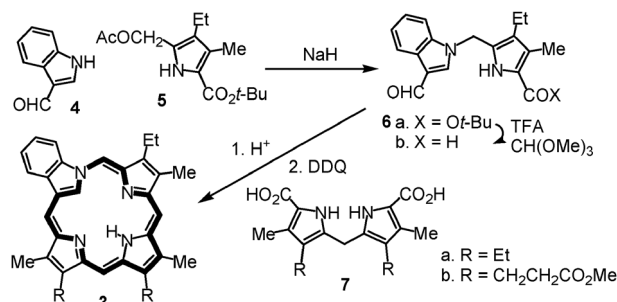
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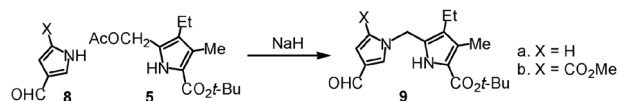
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**MacDonald “2 + 2” condensation of a 1,2'-dipyrromethane dialdehyde with a 2,2'-dipyrromethane afforded a neo-confused porphyrin in 55% yield. In addition, a novel dihydroporphyrin with two appended pyrrolic units was isolated and structurally characterized.**

Porphyrins have been widely investigated, not only due to their significance as natural pigments but also because of their non-benzenoid aromatic characteristics<sup>1</sup> and their ability to form diverse coordination complexes.<sup>2</sup> Furthermore, porphyrins possess valuable properties that make them of use in material science, catalysis and medicine.<sup>3</sup> For these reasons, many studies have been conducted on related systems such as expanded porphyrins,<sup>4</sup> porphyrin isomers<sup>5</sup> and carbaporphyrins.<sup>6,7</sup> In 1994, the first examples of N-confused porphyrins (NCPs, **1**) were reported.<sup>8</sup> These tetrapyrrolic macrocycles differ from true porphyrins by having an inverted pyrrole unit and thereby possess a CNNN coordination cavity.<sup>9</sup> NCPs can be considered to be porphyrin isomers and retain overall aromatic properties. These porphyrin analogues have been widely investigated and are easily metalated to form organometallic derivatives.<sup>9</sup> We recently proposed a new type of porphyrin isomer **2** where the nitrogen of one of the pyrrole rings is connected to a bridging methine unit and this system has been termed “neo-confused porphyrin”.<sup>10</sup> In addition, a three-step synthesis of benzo neo-confused porphyrins **3** from indole-3-carbaldehyde (**4**, Scheme 1) was reported.<sup>10</sup> Treatment of **4** with sodium hydride and subsequent reaction with acetoxymethylpyrrole **5** gave the neo-confused dipyrromethane **6a**. The *tert*-butyl ester was cleaved with TFA and immediately reacted with trimethyl orthoformate to give the corresponding dialdehyde **6b**.<sup>10</sup> This key intermediate underwent a MacDonald “2 + 2” condensation<sup>11</sup> with dipyrromethanes **7** in the presence of an acid catalyst to generate, following oxidation with DDQ, the porphyrin analogue **3**.<sup>10</sup> The system was shown to retain significant diatropic character and gave porphyrin-like UV-vis spectra.<sup>10</sup> Benzo neo-confused porphyrin **3** also readily



Scheme 1 Synthesis of benzo neo-confused porphyrins.



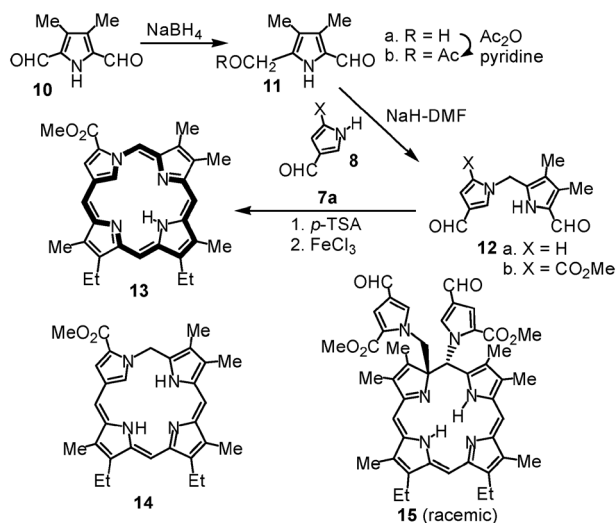
Scheme 2 Synthesis of neo-confused dipyrromethanes.

formed a nickel(II) organometallic derivative.<sup>10</sup> In independent work, Furuta and coworkers have reported the synthesis of related neo-confused corroles that also exhibit aromatic characteristics.<sup>12</sup>

In order to follow up on these important observations, the synthesis of neo-confused porphyrins without fused benzene units were targeted for investigation. However, the crucial dialdehyde intermediates could not be obtained by the strategy used for the synthesis of the benzo-fused structures **3**. Acetoxymethylpyrrole **5** was reacted with NaH and pyrrole aldehydes **8** in THF to give good yields of the 1,2'-dipyrromethanes **9** (Scheme 2), but attempts to cleave the ester moiety with TFA and formylate the structure with trimethyl orthoformate resulted in decomposition and the corresponding dialdehyde could not be isolated. Following numerous attempts to carry out this conversion, an alternative approach was adopted (Scheme 3). Pyrrole dialdehyde **10** was selectively reduced with 0.25 equiv. of sodium borohydride to give the carbinol **11a** and further reaction with acetic anhydride in pyridine afforded the corresponding acetate **11b**. This was further reacted with NaH and pyrrole aldehydes **8a** or **8b** to give the neo-confused dipyrromethane dialdehydes **12**. Very poor yields of **12a** were obtained

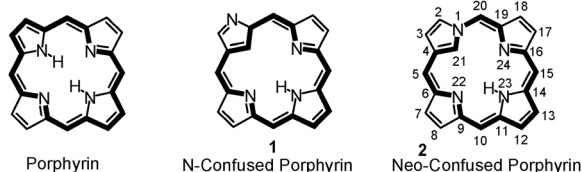
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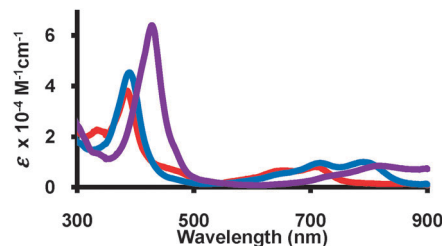


**Scheme 3** Synthesis of a neo-confused porphyrin and a dihydroporphyrin by-product.

but under optimized conditions (30 °C in DMF), **12b** could be isolated in 75% yield.



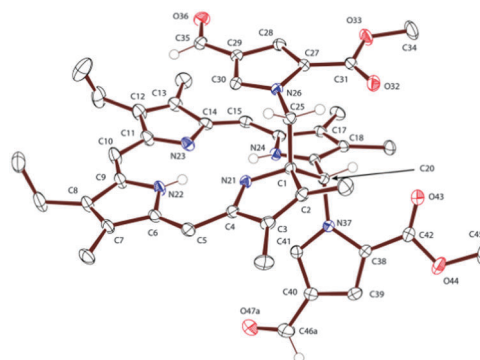
Dialdehyde **12b** was reacted with dipyrromethane **7a** in the presence of *p*-toluenesulfonic acid in methanol-dichloromethane (Scheme 3). These conditions would be expected to give a dihydroporphyrinoid and an oxidation step is required to form the final product **13**. When the reaction mixture was neutralized by washing with aqueous sodium bicarbonate solution, and the crude product was run through a grade 3 alumina column, a bright blue colored phlorin fraction could be isolated in up to 69% yield. Phlorin **14** (Scheme 3) was somewhat unstable but could be characterized by NMR spectroscopy and mass spectrometry. Attempts to oxidize the crude reaction mixture with DDQ led to decomposition, but when the reaction mixture was shaken with a 0.2% aqueous ferric chloride solution for 20 min, neo-confused porphyrin **13** was generated in 55% yield. The product was again purified by chromatography on a grade 3 alumina column and eluted as a pink-purple fraction. However, a second green colored band subsequently eluted corresponding to an unexpected by-product. The second fraction was recrystallized from chloroform-hexane and was isolated as a green powder in 28% yield. The UV-vis spectrum for this compound (**15**) gave a moderately strong band at 385 nm and two broad bands at 644 and 709 nm (Fig. 1). Addition of trace amounts of TFA gave rise to a new species with an absorption at 390 nm and bathochromically shifted broad bands at 717 and 791 nm, and at higher concentrations of TFA a third species evolved showing a strong absorption at 428 nm and broad peaks at higher wavelengths (Fig. 1). These results are not consistent with a porphyrin-like species and suggest that two separate protonation steps are occurring. The proton NMR spectrum for **15** showed the absence of a macrocyclic ring current and a lack of overall symmetry. Six unique methyl substituents, two ethyl groups, two methyl esters and two aldehyde moieties were



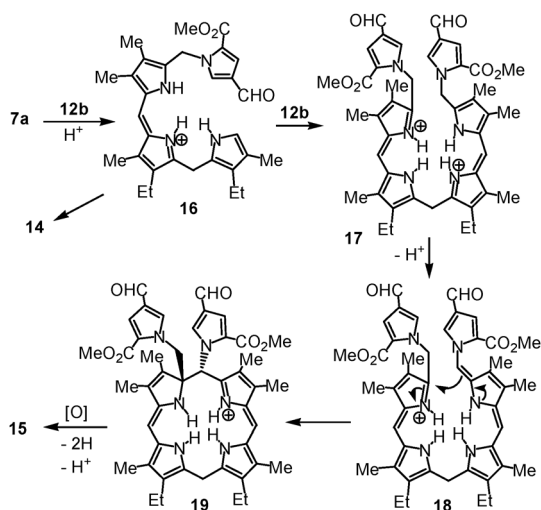
**Fig. 1** UV-vis spectra of dihydroporphyrin **15** in 1% Et<sub>3</sub>N-CH<sub>2</sub>Cl<sub>2</sub> (free base, red line), 5 equiv. TFA-CH<sub>2</sub>Cl<sub>2</sub> (monocation, blue line) and 1% TFA-CH<sub>2</sub>Cl<sub>2</sub> (dication, purple line).

noted, and two 1H doublets ( $J = 14.0$  Hz) were observed at 4.30 and 5.79 ppm corresponding to a highly diastereotopic methylene unit. Four 1H singlets were observed at 4.90, 5.58, 6.19 and 6.96 ppm, and two pairs of doublets ( $J = 1.8$  Hz) were seen at 7.04, 7.26, 7.99 and 8.46 ppm. These data showed that the product was constructed from two units of **12b** and one dipyrromethane **7a**. HR MS data was obtained for the  $[M + H]^+$  peak by ESI MS and this showed that the product had the molecular formula C<sub>45</sub>H<sub>48</sub>N<sub>6</sub>O<sub>6</sub>. The structure of this interesting by-product was finally demonstrated by X-ray crystallography (Fig. 2), which clearly established its identity as a dihydroporphyrin with two appended pyrrole units that are *trans* to one another (the 169.37(9)° C(25)-C(1)-C(20)-N(37) torsion angle places these substituents on opposing faces of the main macrocycle). The hydrogen atoms attached to N24 and N22 were clearly present in the difference Fourier and the assignments correlate with the framework bond metrics which classify C(2)-C(3), C(5)-C(6), C(7)-C(8), C(9)-C(10), C(12)-C(13), and C(14)-C(15) as double bonds and C(1)-C(2), C(3)-C(4), C(6)-C(7), C(8)-C(9), C(10)-C(11), C(11)-C(12), C(13)-C(14), C(15)-C(16), and C(19)-C(20) as more single bond like.

Although the formation of hexapyrrole product **15** under MacDonald reaction conditions is unprecedented, the generation of this system can easily be explained (Scheme 4). Initial reaction between **12b** and **7a** can give rise to a bilene intermediate **16** and subsequent cyclization will then afford phlorin **14**. However, if **16** condenses with a second molecule of **12b**, the open-chain hexapyrrole **17** will be generated. Deprotonation can form an enamine-type structure **18** and subsequent cyclization will then lead to a tetrahydroporphyrin **19**. The observed product **15** would then be produced by oxidation and deprotonation. Although this type of chemistry has never previously been observed in MacDonald-type reactions, 5,6-dihydroporphyrins



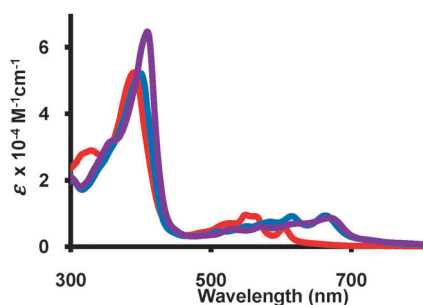
**Fig. 2** ORTEP III drawing (50% probability level, hydrogen atoms drawn arbitrarily small) of **15**. The external hydrogens, apart from the 20-CH, 25-CH<sub>2</sub> and aldehyde units, are omitted for clarity.



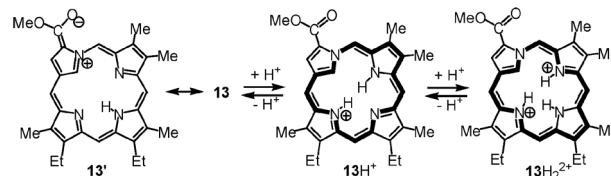
**Scheme 4** Proposed mechanism for the formation of **15**.

have been obtained by the cyclization of *a,c*-biladienes<sup>13</sup> and have been proposed as intermediates in the formation of metalloporphyrins from these types of acyclic tetrapyrroles.<sup>14</sup>

Porphyrinoid **13** gave a porphyrin-like UV-vis spectrum (Fig. 3) with a Soret band at 390 nm and a series of Q bands between 486 and 604 nm. Addition of TFA led initially to a species with a Soret band at 396 nm and red shifted Q absorptions, and this was tentatively attributed to the formation of a monocation **13H<sup>+</sup>** (Scheme 5). At higher concentrations of TFA, a third species was observed with a Soret band at 409 nm corresponding to the dication **13H<sub>2</sub><sup>2+</sup>** (Scheme 5 and Fig. 3). These observations differ from those obtained for benzo-neo-confused porphyrin **3**, which showed the direct formation of a dicationic species from the free base structure. These differences were attributed to the presence of an electron-withdrawing ester moiety in **13**. Neo-confused porphyrin **13** also showed reduced diatropic character compared to the benzo-fused system **3**. The proton NMR spectrum of **13** in CDCl<sub>3</sub> gave a 1H resonance for the internal CH (21-CH) at 1.23 ppm, while the NH was observed at 1.69 ppm, and this compares to values of −0.74 and −0.33 ppm, respectively for **3**. Nevertheless, these results demonstrate that **13** still retains a significant diatropic ring current. The external *meso*-protons gave rise to four 1H singlets at 8.20, 8.30, 8.74 and 10.57 ppm (the latter resonance is due to the CH connected to the neo-confused nitrogen) compared to values of 8.91, 8.96, 9.68 and 9.99 ppm for **3**. A doublet (*J* = 1.6 Hz) was also observed at 8.60 ppm for the external pyrrolic proton due to



**Fig. 3** UV-vis spectra of neo-confused porphyrin **13** in 1% Et<sub>3</sub>N–CH<sub>2</sub>Cl<sub>2</sub> (free base, red line), 50 equiv. TFA–CH<sub>2</sub>Cl<sub>2</sub> (monocation, blue line) and 1% TFA–CH<sub>2</sub>Cl<sub>2</sub> (dication, purple line).



**Scheme 5** Resonance interactions and protonation of **13**.

transannular coupling with the interior CH (demonstrated by <sup>1</sup>H–<sup>1</sup>H COSY). However, the peak for CH-21 only showed this interaction as a slight broadening of the resonance. In TFA–CDCl<sub>3</sub>, the corresponding dication **13H<sub>2</sub><sup>2+</sup>** showed a substantially enhanced diatropic ring current and the internal CH shifted upfield to −0.66 ppm, while the *meso*-proton resonances moved downfield to give four 1H singlets at 8.69, 8.75, 9.44 and 10.99 ppm. However, these shifts were much reduced compared to those observed for the dication derived from porphyrinoid **3**. The reduced diatropicity of **13** was again attributed to presence of the ester moiety that can introduce cross-conjugated dipolar resonance contributors such as **13'** which interrupt the  $\pi$  conjugation pathway (Scheme 5).

In conclusion, an efficient synthetic route to a neo-confused porphyrin has been developed and this will allow the properties of this porphyrin isomer to be explored in detail. Furthermore, a remarkable pyrrole-appended dihydroporphyrin system has been isolated and this system also shows promise for further investigation.

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