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Syntheses of Carbaporphyrinoid Systems Using a Carbatripyrrin Methodology

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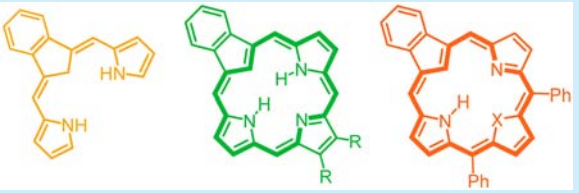
Supporting Information

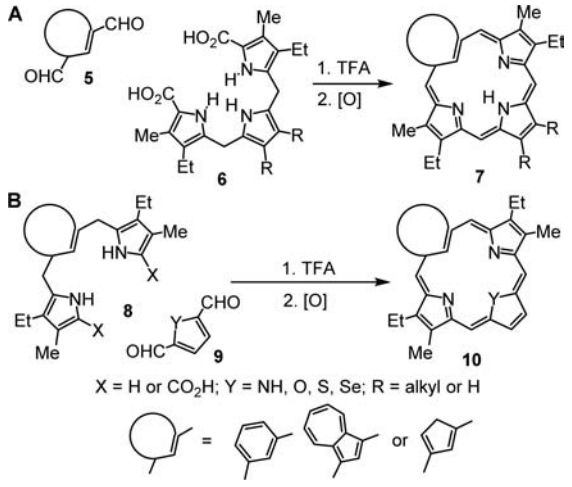
ABSTRACT: A carbatripyrrin intermediate was prepared from commercially available technical-grade indene and 2-pyrrolecarbaldehyde in three steps and 50% overall yield. This novel conjugated structure reacted with pyrroledialdehydes and 2,5-furandicarbaldehyde in the presence of TFA to give good yields of carbaporphyrins and an oxacarbaporphyrin, respectively, and unlike currently available methodologies, no oxidation step was required. The carbatripyrrin also condensed with heterocyclic dicarbinols in the presence of $BF_3 \cdot Et_2O$ to give a series of heterocarbaporphyrins.

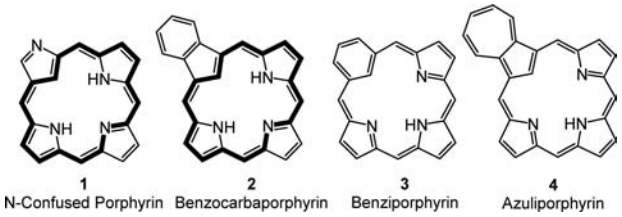


Carbaporphyrinoid systems have been widely investigated in recent years.[1,2] These macrocyclic structures consist of a porphyrin-like framework in which at least one of the interior nitrogens has been replaced by a carbon atom and include the so-called N-confused porphyrins **1**,[3,4] carbaporphyrins such as **2**,[5] benziporphyrins **3**,[6] and azuliporphyrins **4**.[7] Carbaporphyrinoids exhibit diverse characteristics and may exist as strongly aromatic, nonaromatic, or even antiaromatic species.[1,2] These systems commonly form organometallic derivatives under mild conditions[4,8] and exhibit unusual reactivity.[1,2] In addition, derivatives of benzocarbaporphyrins **2** have been shown to be effective agents in the treatment of leishmaniasis.[9] Carbaporphyrinoids can be synthesized by a "3 + 1" variant of the MacDonald reaction[10] in which an aromatic dialdehyde **5** is condensed with a tripyrrane **6** in the presence of TFA, and following an oxidation step, carbaporphyrinoids **7** are commonly isolated in good yields (Scheme 1A). Alternatively a series of carbatripyrranes **8** have been generated with central azulene,[11] benzene,[12,13] or cyclopentadiene units[14] that can be used in the preparation of porphyrin analogues by reacting them with suitable dialdehydes **9** or dicarbinols in the presence of an acid catalyst and then carrying out an oxidation to form the fully aromatic product **10** (Scheme 1B).[11−13,15] Although these strategies have been very successful, multiple steps are commonly required to prepare the tripyrrane intermediates. In addition, an oxidation step is necessary but is not always straightforward.[15−18] Therefore, not only would it be of value to have a more direct route to tripyrrane-like intermediates, but it would also be beneficial if a methodology could be developed that avoided the requirement for an oxidation step.

In a study aimed at the preparation of *ansa*-cyclopentadienyl pyrrolyl titanium complexes,[14] a synthesis of tripyrrane analogue **11** was carried out (Scheme 2). Fulvene **12** was reduced with lithium aluminum hydride to give dihydro derivative **13** (mixture of isomers), which was then condensed with 2-pyrrolecarbaldehyde (**14**) to afford a mixture of *E* and *Z* isomers of **15**. Further reduction of this mixture with $LiAlH_4$ gave carbatripyrrane **11** (mixture of isomers),[14] and it is notable that others used this compound in the preparation of a thiacarbachlorin, albeit in only 5.2% yield.[15] We speculated that this type of approach might be improved if a tripyrrene-like intermediate similar to **15** could be isolated in the *Z*

Scheme 1. MacDonald-Type "3 + 1" Syntheses of Carbaporphyrinoid Systems





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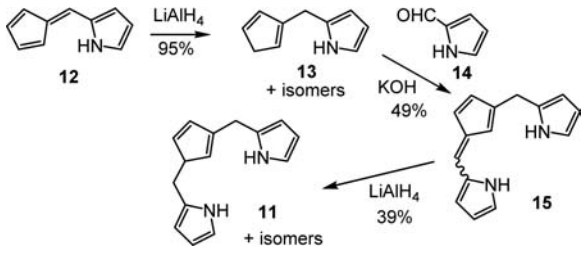
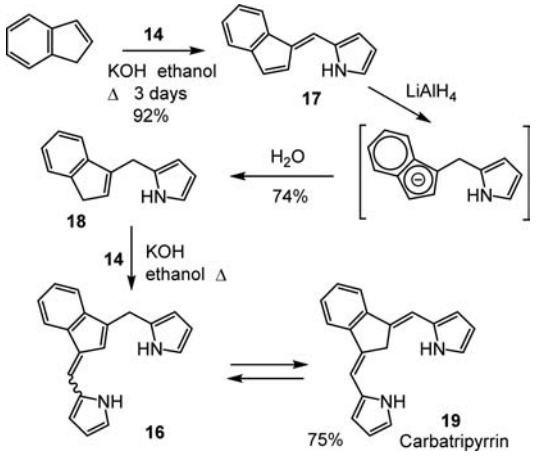
Scheme 2. Synthesis of a Carbatripyrrane



configuration, as this system would be geometrically preorganized to facilitate macrocycle formation and, importantly, the oxidation step would no longer be needed. In order to assess this strategy, an indene-derived carbatripyrrene **16** was targeted (Scheme 3). In previous work, we have found that it is far easier

Scheme 3. Synthesis of a Benzocarbatripyrrin



to work with indene than with cyclopentadiene derivatives in this type of chemistry,[19] and it was anticipated that the presence of the fused benzene ring might help in directing the stereoselectivity of the proposed chemistry. Reaction of **14** with indene in refluxing KOH/ethanol has been reported to give benzofulvene **17** in 12% yield.[20] Some improvements were noted when *N*-BOC-protected pyrrole-2-carbaldehyde was reacted with the indenyl anion, but **17** was still isolated in only 16% yield.[21] However, we found that indene and **14** reacted in refluxing 1% KOH/ethanol to give the desired fulvene product in 92% yield. Clearly the solvent plays a crucial role, possibly by raising the temperature of the reaction mixture. Furthermore, the reaction can be carried out using inexpensive technical-grade indene without any decrease in the yield, and multigram quantities of **17** are easily prepared. Reduction of **17** with $LiAlH_4$ in refluxing THF gave a dihydro derivative that primarily consisted of structure **18** in 74% yield. Although the reduction is fairly slow, requiring an overnight reflux in THF, it is facilitated by the formation of an intermediate indenyl anion (Scheme 3). The crude product was reacted with **14** in refluxing 1% KOH/methanol in an attempt to prepare carbatripyrrene **16**. The reactions were carried out for 2 days, and following workup, complex mixtures were obtained. Column chromatography gave deep-yellow-orange-colored fractions that appeared to correspond to **16**, but the NMR spectra showed that both stereoisomers were present. This result was disappointing because the *E* isomer is not structurally compatible with macrocycle formation. During the course of these experiments, a small amount of a rather insoluble byproduct was observed. This compound gave a surprisingly simple proton NMR spectrum (Figure 1) that

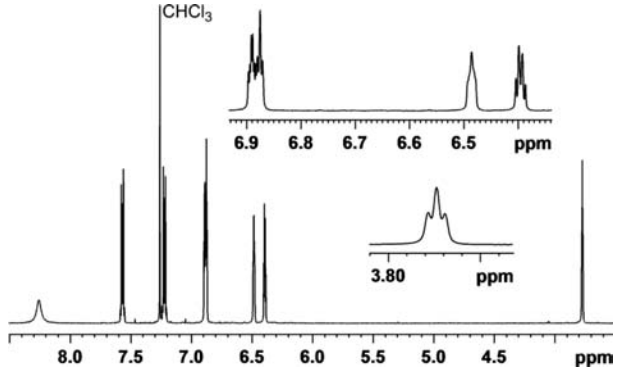


Figure 1. Proton NMR spectrum (500 MHz) of carbatripyrrin **19** in $CDCl_3$.

indicated that the structure has a plane of symmetry. A broad peak at 8.26 ppm was consistent with a pyrrolic NH, while two multiplets at 7.22 and 7.57 ppm corresponded to the benzo unit and three other signals at 6.39, 6.48, and 6.89 ppm could be assigned to the pyrrole units. In addition, two triplets (J = 2.3 Hz) were evident at 3.77 and 6.87 ppm. All of the resonances integrated for two protons. These data demonstrated that carbatripyrrin **19** had been isolated, and the triplets at 3.77 and 6.87 ppm correspond to a long-range-coupled methylene unit interacting with the methine bridging protons. This assignment was confirmed by high-resolution mass spectrometry. We have observed similar indene intermediates in our earlier studies,[22,23] and these are somewhat favored because this arrangement facilitates continuous conjugation. The built-in geometry of this structure is even better suited for macrocycle formation than the originally targeted (*Z*)-carbatripyrrene **16**. Carbatripyrrin **19** was originally isolated in very poor yields, but we reasoned that if **19** were in equilibrium with (*E*)- and (*Z*)-**16** under the reaction conditions, it might be possible to shift the equilibrium in favor of this product. Given the low solubility of **19**, this was easily achievable by reducing the volume of ethanol solvent used to carry out the reaction. Under the optimized conditions, **19** was consistently isolated in 75% yield from crude dihydrofulvene (55% in two steps from fulvene **17**).

In order to assess the utility of this novel intermediate for synthesizing carbaporphyrinoid systems, **19** was reacted with pyrroledialdehyde **20a**[24] in dichloromethane with catalytic TFA (Scheme 4). The reaction occurred very rapidly, and following workup, purification by column chromatography, and recrystallization from chloroform/methanol, carbaporphyrin **21a** was isolated in 51% yield. Unlike structurally similar benzocarbaporphyrins,[5] which give brown solutions, **21a** gave green-colored solutions, but the UV−vis spectrum remained very porphyrin-like, showing a strong Soret band at 419 nm and a series of Q bands at 500, 603, and 663 nm (Figure 2). The proton NMR spectrum of **21a** (Figure 3) also attested to the formation of a strongly aromatic compound, as the internal CH was observed near −7 ppm while the *meso* protons gave rise to two 2H singlets at 9.92 and 10.21 ppm. The pyrrolic protons also gave two 2H downfield doublets at 9.27 and 9.37 ppm. As has been reported for related benzocarbaporphyrins, addition of TFA initially forms a monocation, and further protonation at

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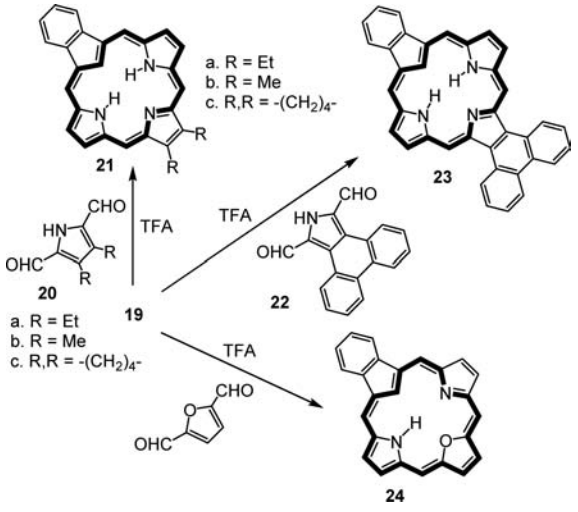
Scheme 4. Synthesis of Carbaporphyrins and an Oxacarbaporphyrin



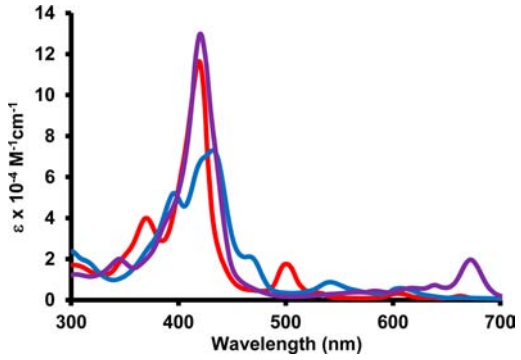


Figure 2. UV−vis spectra of carbaporphyrin **21a** in 1% Et_3N/CH_2Cl_2 (free base, red line), with 10 equiv of TFA/CH_2Cl_2 (monocation **21a**-H^+, blue line), and with 50% TFA/CH_2Cl_2 (dication **21a**-H_2^{2+}, purple line).

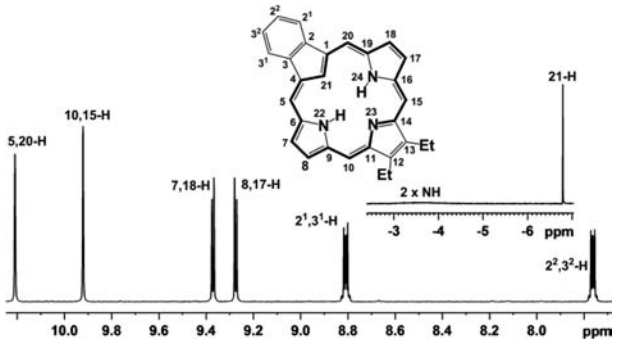
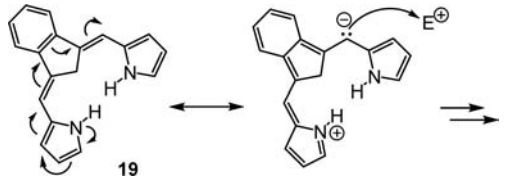


Figure 3. Partial 500 MHz proton NMR spectrum of carbaporphyrin **21a** in $CDCl_3$. It should be noted that the observed chemical shifts are somewhat sensitive to concentration.

higher acid concentrations affords a dicationic species (Figure 2). Reaction of **19** with pyrroledialdehydes **20b** and **20c** similarly gave the related carbaporphyrins **21b** and **21c** in 29% and 20% yield, respectively. Carbatripyrrin **19** was also condensed with phenanthropyrroledialdehyde **22**[25] to give phenanthrocarbaporphyrin **23** in 22% yield (Scheme 4). As expected, the presence of a fused phenanthrene ring leads to significant bathochromic shifts in the UV−vis spectrum, giving the Soret band at 438 nm and Q bands at 513, 550, 617, and 678 nm. The effect was more pronounced for the corresponding dication **23**-H_2^{2+}, which gave the Soret band at 463 nm, compared with a value of 420 nm for **21a**-H_2^{2+}. Reaction of **19** with 2,5-furandicarbaldehyde gave oxacarbaporphyrin **24** in 43% yield (Scheme 4). Porphyrinoid **24** proved to be sensitive to the presence of trace amounts of acid that tend to be present in chlorinated solvents, and good results were obtained only when these solvents were either avoided or were carefully deacidified prior to use. Oxacarbaporphyrin is also highly diatropic, and the proton NMR spectrum shows the internal CH resonance at −4.86 ppm, while the external *meso* protons appear downfield at 9.89 and 10.20 ppm. The UV−vis spectrum is again porphyrin-like with a Soret band at 422 nm and Q bands at 517, 551, 618, and 678 nm. Unfortunately, 2,5-thiophenedicarbaldehyde failed to react with **19** to give the corresponding thiacarbaporphyrin.

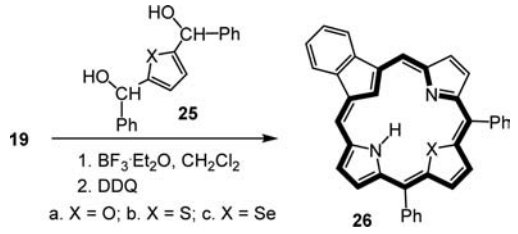
The carbatripyrrin strategy has a number of benefits, including the high-yielding three-step synthesis of the key intermediate from commercially available materials. In addition, good yields of structurally diverse porphyrinoids have been obtained. However, it is worth noting that the presence of conjugated methine bridges may be responsible for side reactions, as these will also be prone to protonation or electrophilic substitution (Scheme 5). Nevertheless, macrocycle formation appears to occur sufficiently rapidly to successfully compete with unwanted condensations at the bridging sites.

Scheme 5. Potential Reactivity at the Bridge Carbons of 19



We also investigated the condensation of **19** with a series of heterocyclic dicarbinols in the presence of $BF_3{\cdot}Et_2O$ (Scheme 6). In these reactions, two *meso*-phenyl substituents can be

Scheme 6. Synthesis of Diphenylheterocarbaporphyrins



introduced, although it is necessary in these cases to include an oxidation step. Reaction of furandialcohol **25a** with **19** for 30 min and subsequent oxidation with DDQ afforded diphenyloxacarbaporphyrin **26a** in 25% yield, and thiophene- and selenophenedicarbinols gave similar results, producing thiacarbaporphyrin **26b** and selenacarbaporphyrin **26c** in 25% and 24% yield, respectively. This is the first ring synthesis of a selenacarbaporphyrin, although this system has been obtained previously by oxidative ring contraction of selenaazuliporphyrins.[7b,26] All three diphenylheterocarbaporphyrins exhibited strongly aromatic properties, although the proton NMR spectra

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suggested that the diatropic character increased in the sequence **26a** < **26c** < **26b**. The electronegativity of the oxygen atom may be responsible for the slight reduction in diatropicity, while the larger selenium atom is likely to have mildly reduced the aromatic character by decreasing the planarity of the porphyrinoid system.

In conclusion, a novel carbatripyrrin structure **19** has been synthesized in good overall yield in three steps from commercially available technical-grade indene and 2-pyrrolecarbaldehyde. Furthermore, four different pyrroledialdehydes and 2,5-furandicarbaldehyde condensed with **19** in the presence of TFA to give good yields of carbaporphyrins and an oxacarbaporphyrin without the need to carry out an oxidation step. In addition, reactions with dicarbinols gave a series of diphenyloxa-, -thia-, and -selenacarbaporphyrins. Hence, this synthetic strategy provides a valuable alternative to existing routes for the preparation of carbaporphyrins.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02219.

Full experimental details, UV−vis spectra, and NMR spectra (PDF)

Additional NMR spectra and MALDI and ESI mass spectra (PDF)

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Notes

The authors declare no competing financial interest.

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