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Synthesis of sapphyrins via a '3+1+1' procedure

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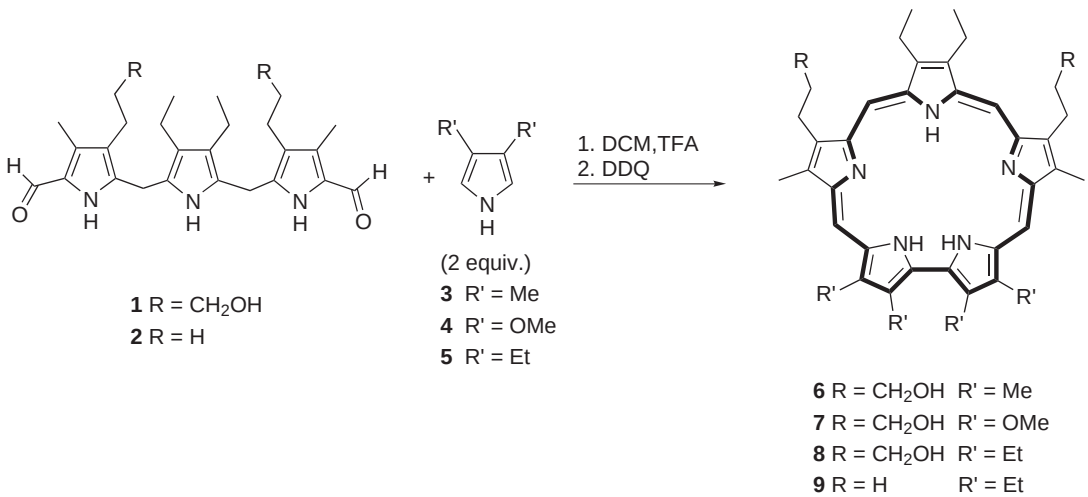
Abstract—Sapphyrins may be obtained in ca. 30% yield via the condensation of 1 equivalent of a tripyrrane dialdehyde with 2 equivalents of a β-substituted pyrrole, followed by oxidation with DDQ.

Porphyrins, the so-called pigments of life,[1] are arguably among the most widely studied of all macrocyclic compounds. Less well studied are the so-called expanded porphyrins. The chemistry of these systems, macrocycles that, like porphyrin, are comprised of pyrrolic rings and *meso*-carbon bridges had its genesis in the early 1960s when researchers in the Woodward group, while working on the synthesis of corroles, isolated a brilliant blue–green solid by-product.[2] This system, called sapphyrin in light of its startling color, was found to contain a 22 π-electron aromatic periphery (highlighted in bold in Scheme 1).[3–5] It was also found to be 'expanded' relative to porphyrin in that it was seen to contain one additional pyrrole, 'inserted' into its macrocyclic core. As a consequence, sapphyrins contain a direct α–α pyrrole link, something not seen in porphyrins. They also contain a larger central cavity than porphyrins and reduced molecular symmetry. Sapphyrins thus display properties, such as pyrrole ring inversion[6] and anion binding,[7] that differ dramatically from those of the porphyrins. Needless to say, therefore, the synthetic chemistry of sapphyrins has received considerable attention of late.[6–17] Still, improved syntheses are needed. In this letter, a novel '3+1+1' approach to sapphyrin is detailed. The strengths and weakness of this new method are highlighted by comparison to two other routes, one a well-known approach,[5,7–9] and the second a seemingly obvious variation of a classic synthetic strategy that has apparently so far escaped mention in the literature.



1 R = CH_2OH
2 R = H

3 R' = Me
4 R' = OMe
5 R' = Et

6 R = CH_2OH R' = Me
7 R = CH_2OH R' = OMe
8 R = CH_2OH R' = Et
9 R = H R' = Et

Scheme 1.

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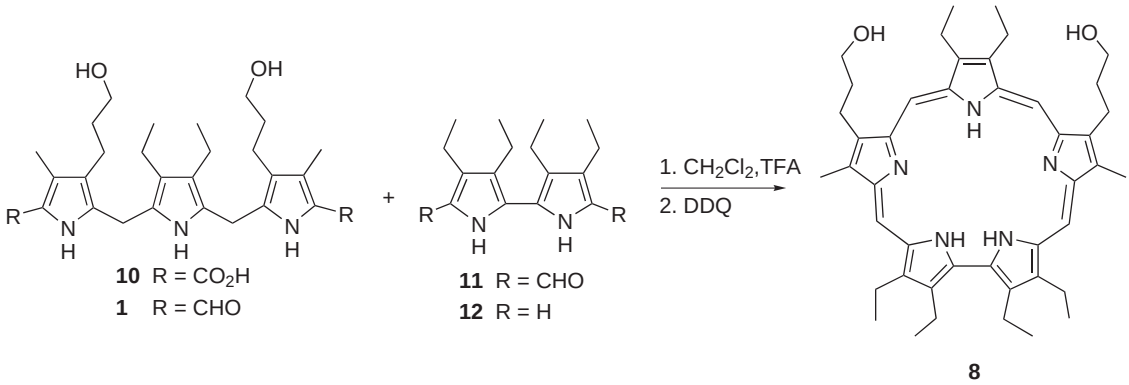


Scheme 2.

The present route is predicated on the direct formation of an α–α pyrrole linkage during ring closure (Scheme 1). While it has been known for some time that direct α–α pyrrole links can be formed during the condensation/oxidation reaction used to obtain sapphyrins,[5] the power of this approach as a general synthetic strategy has only recently begun to be appreciated. It has been used to prepare sapphyrin by '4+1'[10] and '1+1+1+1+1'[6] procedures, as well as corrole[18,19] and new expanded porphyrins.[20] It has not, however, been applied to prepare sapphyrins via a '3+1+1' approach involving the condensation between bisformyl tripyrrane and two molar equivalents of a bis-α-free pyrrole. We report here the successful development of such a route.

The specific chemistry in question is summarized in Scheme 1. Briefly, acid-catalyzed condensation between a diformyl tripyrrane (e.g. **1** or **2**) and two molar equivalents of a bis-α-free, β-substituted pyrrole (e.g. **3**, **4**, or **5**), followed by oxidation with DDQ, is found to produce the corresponding sapphyrins (**6**–**9**) in 28–34% yield† (Scheme 1). As one might expect, porphyrin was also isolated from the reaction mixture ($\leq$10% yield), presumably as the result of **1** or **2** reacting with only one equivalent of pyrrole prior to ring closure.‡

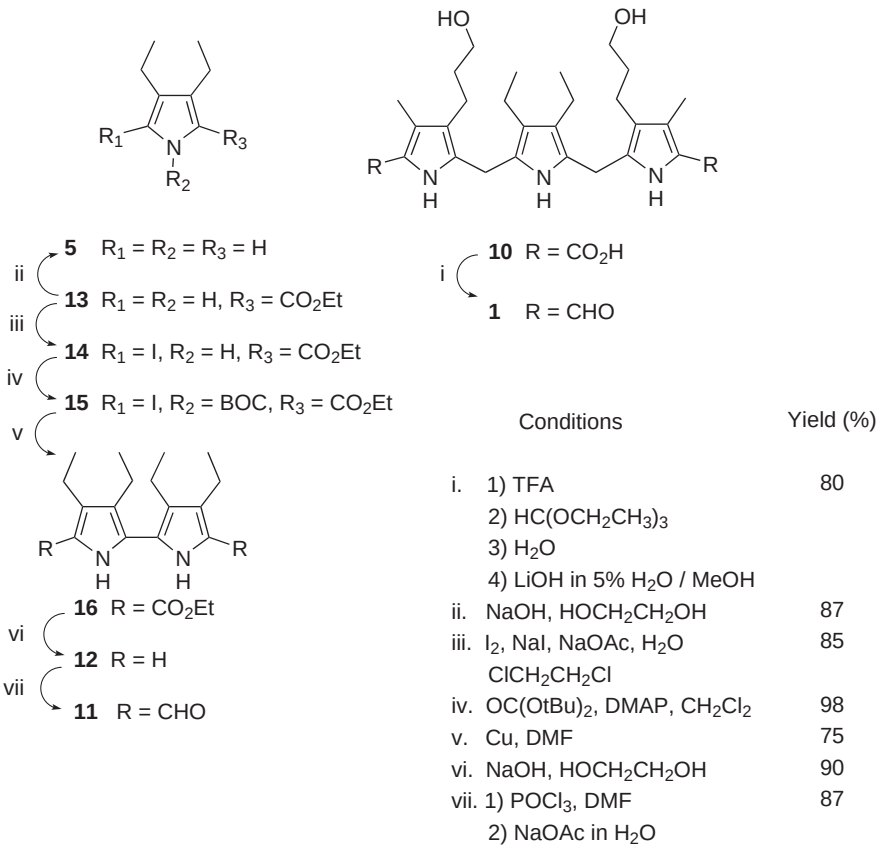
In order to assess the synthetic value of this new '3+1+1' approach, sapphyrin **8** was also prepared via two '3+2' methods (Scheme 2). The first, referred to as Method II, involved reacting bisformyl tripyrrane **1** and bis-α-free bipyrrole **12**. By contrast, the second involved the condensation of tripyrrane diacid **10** with bisformyl bipyrrole **11**. This latter alternative strategy, referred to as Method III, is the classic one first developed by the groups of Woodward[4] and Johnson[3] and then later optimized by us.[6]

Predicative transformations, required to obtain precursors **11** and **12** (as well as **1** from **10**), are shown in Scheme 3. The relative yields of sapphyrin **8** produced by Methods I, II, and III (as well as **6** and **7** produced by Method I) are summarized in Table 1. Taken in concert, Table 1 and Scheme 3 reveal that the macrocyclization step of Method I is not as efficient as that of the '3+2' condensations. On the other hand, since the need to prepare a bipyrrole precursor is obviated, the '3+1+1' method is three steps shorter and hence more efficient than the '3+2' approaches in terms of the overall yield from common precursors, namely **10** and **13**. Reversing the nucleophile/electrophile roles in the traditional '3+2' approach offers a small boost in yield in the macrocyclization step, although this gain is offset by the fact that the formylation of tripyrrane **10** is less efficient than that of bipyrrole **12**.

A further advantage of the present '3+1+1' approach is that it allows ready access to sapphyrins such as **7** for which the requisite bi- or polypyrrole precursors are not available. On the other hand, the '3+1+1' approach does require that the two β-substituents of the pyrrole (e.g. **3**–**5**) must be identical to avoid the statistical formation of three different regioisomers. Still, the specific hydroxypropyl sapphyrins (i.e. **6**–**9**) of this study can be further derivitized via their hydroxyl groups. Thus, subject to the symmetry constraints noted, the

† Typical procedure: A 200 ml mixture of 5% TFA in CH_2Cl_2 was added to a round bottom flask containing 96 mg (0.2 mmol) of tripyrrane dialdehyde **1** and 49 mg (0.4 mmol) of diethyl pyrrole **5**. The reaction mixture was stirred overnight at ambient temperature. The solution was neutralized with TEA, and 45 mg of DDQ (0.2 mmol) was added. The mixture was concentrated to a volume of 100 ml on the rotary evaporator and washed with a saturated aqueous solution of $NaHCO_3$ (2×100 ml) and H_2O (2×100 ml). The organic layer was dried over $MgSO_4$, filtered, and stripped of solvents using a rotary evaporator. Purification by column chromatography on silica gel, using CH_2Cl_2:MeOH (96:4) as the eluent, gave 47 mg (34%) of **8** as dark blue–green crystals. Mp >300°C; UV–vis (CH_2Cl_2): λ_{max}, nm (log ε) 447 (5.45), 612 (4.17), 664 (4.03), 714; CI–MS: 689 (M^+); ^{1}H NMR (500 MHz, $CDCl_3$): δ, ppm −5.02 (1H, NH, s), −4.63 (1H, NH, s), −4.53 (1H, NH, s), 1.80 (6H, CH_2CH_3, t), 2.00 (6H, CH_2CH_3, t), 2.17 (6H, CH_2CH_3, t), 2.74 (4H, $CH_2CH_2CH_2OH$, m), 3.95 (4H, $CH_2CH_2CH_2OH$, t), 4.14 (6H, CH_3, s), 4.47 (4H, CH_2CH_3, q), 4.53 (4H, CH_2CH_3, q), 4.62 (4H, CH_2CH_3, q), 4.71 (4H, $CH_2CH_2CH_2OH$, t), 11.53 (4H, *meso*-H, s); ^{13}C NMR (125 MHz, $CDCl_3$): 12.8, 16.9, 18.3, 18.4, 20.8, 21.7, 23.5, 35.2, 61.7, 91.6, 98.7, 128.9, 130.4, 132.7, 132.9, 135.7, 136.3, 137.6, 138.8, 140.5, 143.1; anal. calcd for $C_{44}H_{57}N_5O_2{\cdot}2CF_3CO_2H$: C, 62.94; H, 6.49; N, 7.65; found: C, 62.95; H, 6.47; N, 7.66%.

‡ Unfortunately, the reaction of **1** and β-unsubstituted pyrrole did not produce useful quantities of the corresponding sapphyrin (yield <2%).



Scheme 3.

Table 1. Comparison of the three synthetic pathways discussed in this letter

Method	Ring formation yield (%)	Overall yield from **10** and **13** (%)	Number of steps from **10** and **13**
I (**1**+**3**→**6**)	28	–	–
I (**1**+**4**→**7**)	30	–	–
I (**1**+**5**→**8**)	34	24	3 (i, ii)[a]
I (**2**+**5**→**9**)	33	–	–
II (**1**+**12**→**8**)	55	20	6 (i, iii–vi)[a]
III (**10**+**11**→**8**)	50	20	6 (iii–vii)[a]

[a] Refers to steps shown in Scheme 3.

present approach appears to be attractive as one that offers the possibility of preparing β-substituted sapphyrins with controlled regiochemistry and controlled solubility without requiring the intermediate synthesis of bipyrrolic precursors.

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