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Sapphyrins and Heterosapphyrins.

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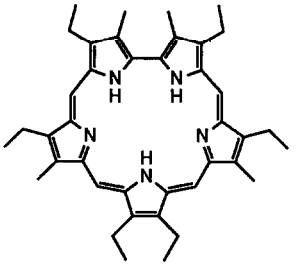
Abstract.
An improved synthesis of 3,8,12,13,17,22-hexaethyl-2,7,18,23-tetramethyl-sapphyrin (**1**), is reported. Also presented are new synthetic procedures for the formation of 8,12,13,17-tetraethyl-7,18-dimethyl-25,29-dioxasapphyrin (**2**) and 3,7,18,22-tetraethyl-2,8,17,23-tetramethyl-27-thiasapphyrin (**3**). In addition the syntheses of two completely new heteroatom substituted sapphyrins; 3,7,18,22-tetraethyl-2,8,17,23-tetramethyl-27-oxasapphyrin (**4**) and 7,18-diethyl-8,17-dimethyl-25,29-dioxa-27-thiasapphyrin (**5**), are described in detail. The procedures described provide facile routes to representative members of one of the more widely-studied classes of expanded porphyrin macrocycles.

Sapphyrins represent the first reported example of a class of macrocycles that has come to be known in general terms as "expanded porphyrins".[1] The first evidence for the existence of the sapphyrins came serendipitously from Woodward[2] and coworkers[3] as the result of their early efforts directed towards the synthesis of vitamin B_{12}. This work was extended first by Johnson[4] and more recently by our own group.[5] As a class, the expanded porphyrins are now attracting increasing attention. This interest reflects the perceived potential these compounds present in several rapidly growing fields, including photodynamic therapy (PDT),[6] photodynamic inactivation (PDI),[7,5c,f] and magnetic resonance imaging (MRI).[8]

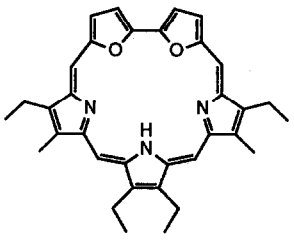
Unfortunately, while the expanded porphyrins have considerable potential they tend to be synthetically challenging to produce.[1] The sapphyrins are no exception. For instance, the synthetic procedure of Bauer *et al.*[3] for decamethylsapphyrin requires 17 steps starting from a single pyrrole precursor and that of Johnson and coworkers[4] is hardly more efficient. Thus, while these syntheses represented the state of the art in porphyrin and pyrrole chemistry, at the time of their publication, they are both limited in terms of preparing materials on a scale needed for, say biomedical use. Herein, we report a shorter full synthesis of sapphyrin **1**, improved procedures for the preparation of two previously reported heteroatom containing materials, the dioxosapphyrin **2** and the thiasaphyrin **3**, and the synthesis of two as yet unknown heteroatom analogues, the oxosapphyrin **4** and the dioxothiasaphyrin **5**. Aspects of this chemistry have been communicated previously.[5a]

Results and Discussion.

The pivotal point in this new synthesis of sapphyrins was the description by Sessler *et al.* of a simple, high yielding, three-step synthesis of symmetric tripyrranes.[9] This synthesis involves, as its key transformation (shown in Scheme 1), the condensation of two equivalents of a suitably functionalized pyrrole, such as benzyl 5-(acetoxymethyl)-3-methyl-4-ethylpyrrole-2-carboxylate (**6**), with a di-α-free pyrrole such as 3,4-diethylpyrrole



1



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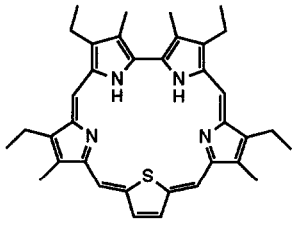

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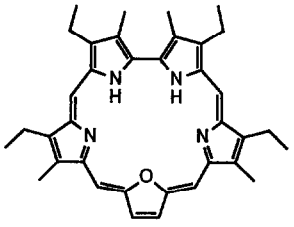

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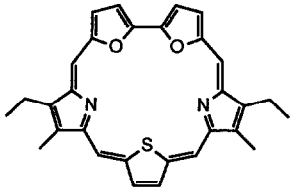


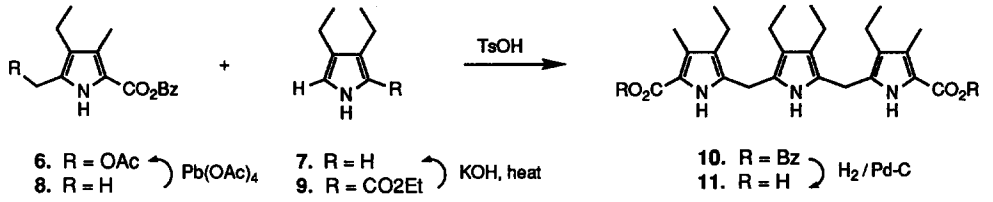
5

(**7**) under acidic conditions. Pyrrole **6** is easily prepared by oxidation of the Knorr pyrrole, benzyl 2,5-dimethyl-3-ethylpyrrole-2-carboxylate (**8**), with one equivalent of lead tetraacetate.[10] 3,4-Diethylpyrrole (**7**) on the other hand, is also readily prepared by saponification and decarboxylation of pyrrole **9**.[11] The newest method for preparing pyrrole **9**, available by the procedure of Barton and Zard,[12] represents the second advance in pyrrole chemistry relevant to our sapphyrin synthesis. Here, it is important to appreciate that pyrroles bearing no substitution in one α-position and a carboxylic acid derivative in the other, were typically prepared by a low-yielding procedure involving oxidation of the α-methyl group of a Knorr pyrrole (to the carboxylic acid level) followed by decarboxylative iodination and hydrogenation.[13,14]

This convergent tripyrrane synthesis, shortening the previous synthetic method by eight steps, has allowed us to prepare tripyrrane **10** in multi-gram lots, in yields that are typically in the 80-90% range. This compound (**10**) is easily debenzylated in near quantitative yield by hydrogenation over palladium on charcoal to give the dicarboxylic acid tripyrrane[9] **11** needed for the [3+2] condensation step leading to sapphyrin.

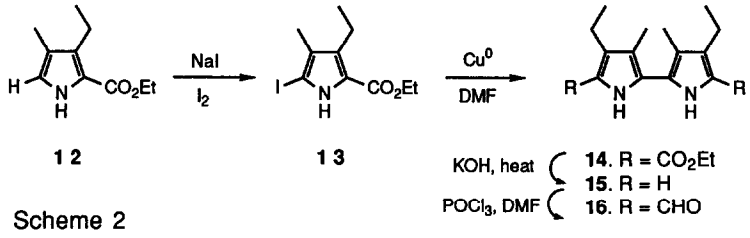
Given that the tripyrrane part could be made easily, attention was then turned to synthesis of a diformyl bipyrrole intermediate (the "2" part of the [2+3] condensation). In the paper describing their sapphyrin synthesis, Bauer *et al.*[3] discuss two methods of diformyl bipyrrole preparation. Both methods rely on an Ullmann coupling reaction to form the carbon-carbon bond joining the two pyrrole subunits. The two methods differed basically only at which point the formyl substituents were introduced.

One method introduced the aldehydes *after* the Ullmann coupling reaction, while the other method introduced an aldehyde *before* coupling. This latter method, required protection of the formyl moiety as a Knoevenagel derivative, prepared from malononitrile or esters of cyanoacetic acid,[14] before coupling and, then, deprotection after bipyrrole formation.



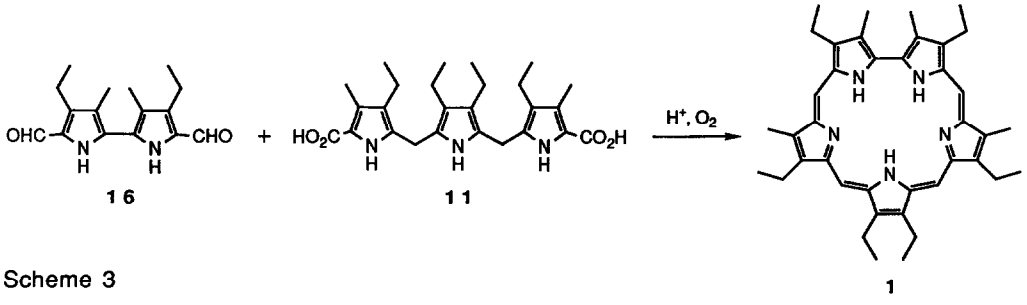
Scheme 1

We recognized, however, that a Barton-Zard pyrrole,[12] in which an α-free position is obtained directly as a consequence of the method of synthesis, offers several advantages over the strategies described above. For example, the low yielding oxidation of an α-methyl group on a Knorr pyrrole (which is required for the first method described above) could be avoided. In addition, the protection-deprotection steps required in the second method would no longer be required. Hence, direct iodination of pyrrole **12** with NaI and I_2 gave the iodopyrrole **13** in excellent yield (Scheme 2). This pyrrole was then coupled to form the bipyrrole **14** using copper bronze and DMF in ca 50% yield. Subsequent saponification and decarboxylation using KOH in ethylene glycol and heat gave the di-α-free bipyrrole **15** which was isolated in only a crude form before subjecting it to formylation under Vilsmeier conditions. This, then gave the diformyl bipyrrole **16** in 59% yield from 3 steps.[14] Thus, by using the Barton-Zard pyrrole-forming procedure and subsequent elaboration, another step of the synthesis outlined by Bauer *et al.*[3] was avoided. As a result the net number of steps required to form the requisite intermediates is reduced by half.



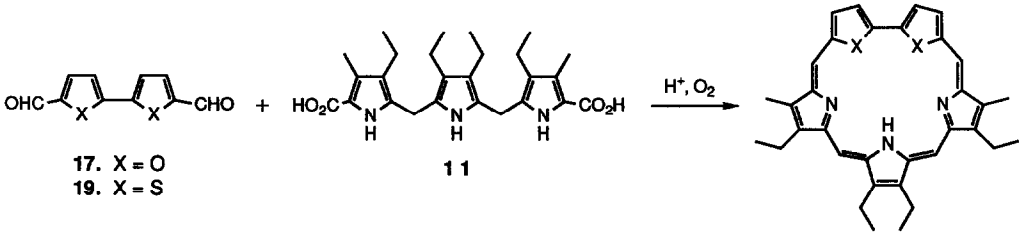
Scheme 2

Once the requisite intermediates were in hand, the coupling steps was effected using the reported procedures of Bauer[3] or Johnson,[4] In terms of specifics, condensation of the diformyl bipyrrole **16** and diacid tripyrrane **11** under acidic conditions in the presence of O_2 gave the decaalkylsapphyrin **1** in 45% yield after chromatographic purification (Scheme 3).



Scheme 3

In the case of dioxasapphyrin **2**, one of the analogues known from early work,[4a] it was found that the needed intermediates could be obtained easily by virtue of advances in heterocyclic chemistry made subsequent to the original report of this macrocycle.[4a] For example, diformyl bifuran **17** could be prepared in one step by treatment of furfural (**18**) with palladium (II) acetate.[15,16] Subsequent [3+2] coupling of **17** with tripyrrane **11** gave dioxasapphyrin **2** in 40% yield after chromatographic purification (Scheme 4).



17. X = O
19. X = S

11

2. X = O
21. X = S

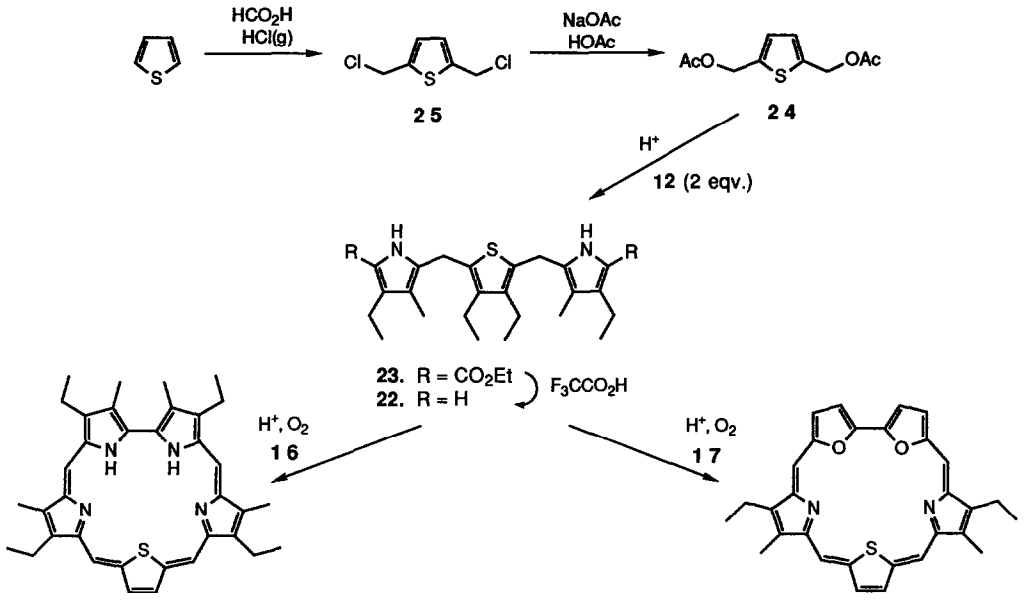
Scheme 4

The second type of heteroatom substituted sapphyrin that was know from the earlier work,[4a] is the class of thiasapphyrins of which **3** is a new example. The synthesis of thiasapphyrin **3** requires dipyrrolylthiophene **22** and diformyl bipyrrole **16** for the final [3+2] condensation. While dipyrrolylthiophene **22** is not sufficiently stable to enable its complete characterization, it may be obtained (and used without further purification) from the hydrolysis and subsequent decarboxylation of the dipyrrolylthiophene diethylester **23** in trifluoroacetic acid at 60° C (reaction monitored by TLC).[17] The dipyrrolylthiophene diester **23** was obtained, in 56% yield, from the condensation of 2 equivalents of the Barton-Zard pyrrole **12** with 2,5-(diacetoxymethyl)thiophene (**24**) as shown in Scheme 5. In turn, thiophene **24** was prepared by the method of Griffing and Salisbury[18] in which thiophene is reacted with formic acid in the presence of HCl gas to give (2,5-dichloromethyl)thiophene (**25**). This substituted thiophene (**25**) was transformed into the diacetoxymethyl thiophene **24** by exchanging the chlorides for acetates using sodium acetate in acetic acid.

The final condensation of the intermediate **22** and diformyl bipyrrole **11** was then carried out using the standard conditions. This gave thiasapphyrin **3** in 35% yield after chromatographic purification. This represents an increase in yield over the previous reported synthesis of a thiasapphyrin in which a *diacid* dipyrrolylthiophene was condensed with a bipyrrole to give the product in 19% yield.[19]

Since thiophene and furan had been shown to be easily incorporated into the sapphyrin skeleton,[4] it was surprising to find that macrocyclic analogs such as oxasapphyrin **4**, dioxathiasapphyrin **5**, and trioxasapphyrin **26** (Scheme 6) had not been prepared. What was not clear, however, was whether this reflected an inherent instability of these systems, an insurmountable difficulty in synthesis, or problems in preparing the required intermediates. Therefore, it was considered worthwhile to devote effort to the synthesis of these macrocycles. The result of this effort is now described.

The key intermediates needed for the synthesis macrocycles **4** and **26**, is the dipyrrolylfuran **27**. This in turn was prepared from precursor **28** as shown in Scheme 6. Following the method of Finan,[20] the furan intermediate **28** was formed from methyl 2-furancarboxylate (**29**) as shown in Scheme 6. Here, the furan **29** was first chloromethylated in the 5 position using paraformaldehyde and HCl gas to give furan **30** in 73%

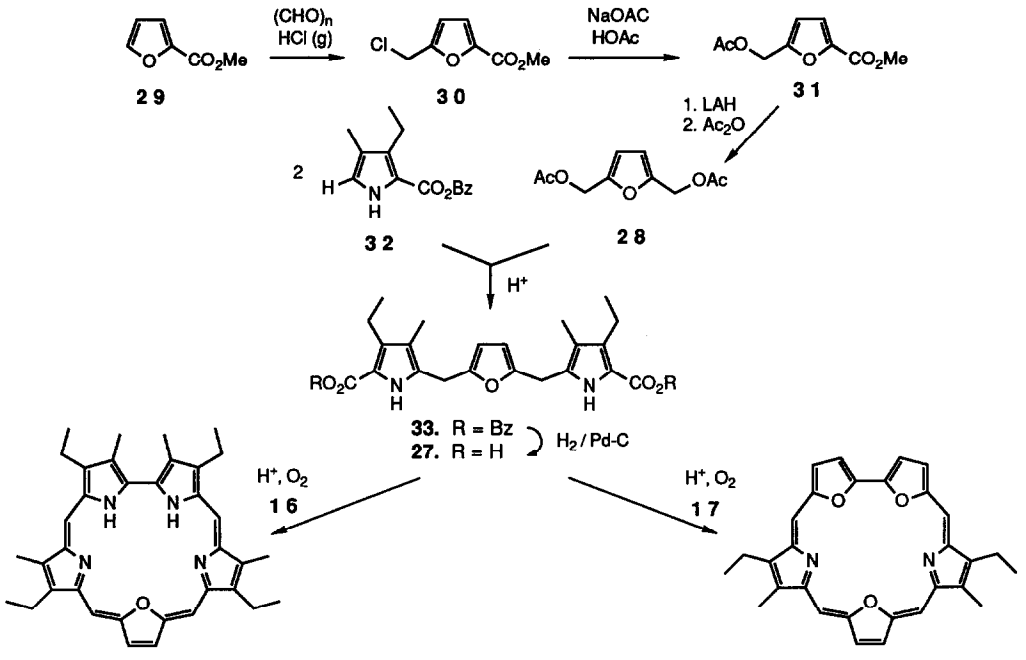


Scheme 5

yield.[21] Then, the chloride substituent was replaced with acetate using sodium acetate in acetic acid to give **31**. This gave **31** which was then reduced with LAH and quenched with acetic anhydride to give the needed 2,5-diacetoxymethyl furan (**28**). Condensation of this furan intermediate with two equivalents of pyrrole **32** then gave the tricyclic dipyrrolylfuran **33** in 56% yield provided methylene chloride, rather than the "usual" ethanol (which gave only 20% yield), was employed as the solvent. Hydrogenation over palladium on charcoal then served to removed the benzyl esters and give the diacid dipyrrolylfuran **27**.

With the above-described intermediates in hand, a "mix and match" approach was pursued in attempting to make the new sapphyrin analogs **4**, **5**, and **26**. It was found, for instance, that condensation of **22** with bifuran **17** gave dioxathiasapphyrin **5** in 35% yield (Scheme 5). Likewise, condensation of **27** with bipyrrole **16** gave oxasapphyrin **4** in 35% yield (Scheme 6). Finally, condensation of bifuran **17** with **27** gave, presumably, trioxasapphyrin **26** (Scheme 6). Unfortunately, this latter material proved unstable and could not be isolated. Its formation, however, was supported by the presence of a Soret-like band at 450 nm in the optical spectrum of the reaction mixture. Compounds **4** and **5**, on the other hand, proved fully stable and were characterized by the full range of normal spectroscopic and analytical techniques (c.f. Experimental Section).

The decaalkylsapphyrin (**1**), and the heterosapphyrins, described herein (compounds **2**, **3**, **4**, and **5**) show colors that range from deep blues to dark greens in the solid state, depending on the exact nature of the macrocycle. In solution, however, all are intense green. In terms of spectroscopic specifics, all of the sapphyrin macrocycles have a very intense Soret-like absorption in the region 435-470 nm spectral region (Table 1) with the most red-shifted bands being observed for **1** and **3**, respectively. The ε values for these absorption bands vary slightly from sapphyrin to sapphyrin, with one major caveat (see below). In general the protonated forms of the sapphyrins have ε values much larger than those of their free-base (Table 1).



Scheme 6

Not revealed by the data in Table 1, but of critical importance (and this is the caveat alluded to above), is that the exact position of the Soret-like absorption band of the protonated sapphyrins is significantly influenced by the identity of the counter anion (see Table 2). This phenomenon, which has been most thoroughly studied in the case of the parent system **1**, is supported by several crystal structures of protonated sapphyrins[5a,g,h,22] where, at least in the solid state, the anion is bound by hydrogen bonds to some or all of the pyrrole protons. This supports the recent[22] proposal that the protonated forms of sapphyrins could act as anion receptors.

The present report details efficient preparations for several heteroatom sapphyrin analogues and this, could allow a wealth of new chemistry. In the parent sapphyrin series, for instance, the availability of material has allowed the coordination chemistry to be further advanced[5e,j] and has led to the finding that these materials are effective PDI photosentitizers[5c] and fluoride selective halide anion receptors.[22] It is likely that the heteroatom analogues **2**, **3**, **4** and **5**, will also prove effective as anion chelating agents. In addition, because of the differing nature of the donor atoms, these materials may display a coordination chemistry that differs from that of the parent all-aza systems. Preliminary studies confirm this expectation: The X-ray structure of **3·[Rh(CO)2]2** has recently been solved[23] and reveals that the complex is analogous in structure to **1·[Rh(CO)2]2**.[5e,g] On the other hand, the heterosapphyrins **2**, **3**, **4** and **5**, all appear to differ from their "parent" **1**, in showing no propensity to coordinate uranyl (UO_2^{2+}).[5j] Given these similarities and differences in reactivity, it appears likely that this class of macrocycles will continue to be of interest for some time to come.

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Table 1 Visible Spectra of Sapphyrins and Heteroatom Substituted Sapphyrins.

Sapphyrin	Soret /nm (log ε)	Q-Bands /nm (log ε)
1	456 (5.45)	616 (4.25), 668 (4.32), 711(4.17)
2	442	555, 590, 673, 684, 752
3	463 (5.55)	644 (4.03), 691 (4.17)
4	455	582, 636, 682, 722, 749
5	438	587, 670, 744

Table 2. Optical Properties of Sapphyrin and Heterosapphyrin Salts in CH_2Cl_2.[a]

Salt	Soret /nm (log ε)	Q-Bands /nm (log ε)
$H_21 \cdot 2Cl$[b]	456 (5.73)	576 (3.76), 624 (4.19), 675 (4.29), 686 (4.26)
$H_21 \cdot 2Br$[b]	458 (5.72)	578 (3.43), 624 (4.18), 678 (4.30), 689 (4.24; sh)
$H_21 \cdot 2OAc$	450	622, 676
$H_21 \cdot 2NO_3$	449	620, 674
$H_21 \cdot 2ClO_4$	447	619, 472
$H_21 \cdot 2F$[b]	446 (5.81)	572 (3.33), 619 (4.17), 670 (4.19), 676 (4.12; sh)
$H_22 \cdot 2Cl$	439 (5.54)	594 (3.94), 625 (3.94), 650 (3.71), 691 (3.70)
$H_22 \cdot 2Br$	442	597, 625, 652, 690
$H_22 \cdot 2OAc$	439	588, 624, 670, 687, 721
$H_22 \cdot 2NO_3$	440	595, 625, 650, 690
$H_22 \cdot 2ClO_4$	440	595, 625, 652, 690
$H_22 \cdot 2F$	439	595, 624, 651, 690
$H_23 \cdot 2Cl$	466	640, 690
$H_23 \cdot 2Br$	470	644, 696
$H_23 \cdot 2OAc$	465	589, 635, 684, 747
$H_23 \cdot 2NO_3$	466	642, 692
$H_23 \cdot 2ClO_4$	466	645, 695
$H_23 \cdot 2F$	436(sh), 460	639, 679, 687, 696, 749
$H_24 \cdot 2Cl$[b]	445 (5.46), 453 (5.50)	606 (3.98), 627 (4.11), 634 (4.07), 665 (4.06), 692 (4.02)
$H_24 \cdot 2Br$	455, 460 (sh)	613, 628, 636, 670, 693
$H_24 \cdot 2OAc$	452	607, 638, 689
$H_24 \cdot 2NO_3$	450(sh), 457	610, 628, 667, 694
$H_24 \cdot 2ClO_4$	453	609, 628, 667, 693
$H_24 \cdot 2F$	440 and 450 (split)	605, 627, 658, 688
$H_25 \cdot 2Cl$[b]	447 (5.55)	600 (3.95), 651 (3.91), 721 (3.11)
$H_25 \cdot 2Br$	440	596, 646
$H_25 \cdot 2NO_3$	440	596, 646
$H_25 \cdot 2ClO_4$	440	596, 646

a) Unless otherwise indicated the salts in question were prepared by washing a CH_2Cl_2 solution of the free-base form of the macrocycle with the appropriate aqueous acids.

b) Analytical sample crystalized and dried after formation of the salt in accord with method described in footnote a.

Experimental.

Melting points were measured on a Mel-Temp apparatus and are uncorrected. Electronic spectra were recorded on a Beckman DU-7 spectrophotometer. Proton and ^{13}C NMR spectra were recorded on either a General Electric QE-300 or a Bruker EM-250 spectrometer. Low resolution mass spectra were measured with either a Finnigan-MAT 4023 or Bell and Howell 21-491 instrument. High resolution mass spectra (HRMS) were obtained using a VG Analytical ZAB E/SE instrument. Fast atom bombardment mass spectra (FAB MS) were determined using a Finnigan-MAT TSQ-70 instrument and 3-nitrobenzyl alcohol matrix. All solvents and reagents, including compounds **18, 20** and **29**, were of reagent grade quality, purchased commercially, and used without further purification except where noted. Phosphorus oxychloride was heated at reflux with, and distilled from, PCl_5 prior to use. Tetrahydrofuran was dried by heating at reflux with, and distilling from, elemental potassium. Merck type 60 (230-400 mesh) silica gel was used for column chromatography. Thin layer chromatography (TLC) was performed on silica gel plates purchased from Analtech, Inc.

3,8,12,13,17,22-Hexaethyl-2,7,18,23-tetramethylsapphyrin (1). 4,4'-Diethyl-5,5'-diformyl-3,3'-dimethyl-2,2'-bipyrrole (**16**, 468 mg, 1.72 mmol) and 2,5-bis(5-carboxy-3-ethyl-4-methylpyrrol-2-ylmethyl)-3,4-diethylpyrrole (**11**,[24] 780 mg, 1.72 mmol) were dissolved in absolute EtOH (1.72 L) to make a 1 mM solution (based on biheterocycle) with the aid of a heat gun. The mixture was allowed to cool to room temperature before *p*-toluenesulfonic acid monohydrate (1.31 g, 6.88 mmol, 4 equiv.) was added all at once. Ethanol saturated O_2 was then bubbled through the mixture for 18 h with good stirring. The ethanol was then removed on the rotary evaporator, the residue taken up in $CHCl_3$ and purified by column chromatography, using increasingly polar $CHCl_3$/MeOH mixtures as the eluent and collecting the dark green fraction. The solvent was removed on the rotary evaporator to leave a dark blue solid. The free-base form of the macrocycle was then prepared by the following procedure. The solid was dissolved in CH_2Cl_2 and diluted to an optical density of less than 2 absorbance units. This solution was then washed with an equal volume of 1N NaOH and dried with Na_2SO_4 before removing the solvent on the rotary evaporator. ^1H NMR ($CDCl_3$) δ -1.59 (7 H, br s, N*H*), 1.95 (6 H, t, CH_2CH_3), 2.10 (6 H, t, CH_2CH_3), 2.14 (6 H, t, CH_2CH_3), 3.88 (6 H, s, CH_3), 3.98 (6 H, s, CH_3), 4.30 (4 H, q, CH_2CH_3), 4.48 (4 H, q, CH_2CH_3), 4.53 (4 H, q, CH_2CH_3), 10.83 (2 H, s, *meso-H*), 10.88 (2 H, s, *meso-H*); ^{13}C NMR (250 MHz, $CDCl_3$) δ 12.4, 15.8, 17.8, 17.9, 18.3, 20.6, 20.8, 20.9, 90.4, 99.2, 126.5, 134.8, 135.3, 135.8, 136.2, 137.3, 138.7, 141.1, 141.4 (one quaternary carbon unobserved); HRMS 601.4136 (calcd. for $C_{40}H_{51}N_5$: 601.4144); ^1H NMR ($CDCl_3$) δ -4.97 (2 H, s, N*H*), -4.64 (1 H, s, N*H*), -4.31 (2 H, s, N*H*), 2.18 - 2.34 (9 H, m, CH_2CH_3), 4.13 (6 H, s, CH_3), 4.24 (6 H, s, CH_3), 4.56 (4 H, q, CH_2CH_3), 4.69 - 4.75 (8 H, m, CH_2CH_3), 11.67 (2 H, s, *meso-H*), 11.71 (2 H, s, *meso-H*). If the fully protonated macrocycle, with known counterion composition was required, the CH_2Cl_2 solution of the free-base macrocycle was washed with an equal volume of a 1N solution of the desired acid before briefly drying with Na_2SO_4 and removing the solvent on the rotary evaporator. In this way, 460 mg (44%) of H_2**1**·2Cl was isolated following treatment with 1N HCl . The macrocyclic product and its diprotonated salts can be further purified by recrystallization from $CHCl_3$/hexanes.

8,12,13,17-Tetraethyl-7,18-dimethyl-25,29-dioxasapphyrin (2). This material was obtained from a procedure identical to that used to prepare **1**. 5,5'-Diformyl-2,2'-bifuran[15] (**17**, 282 mg, 1.0 mmol) and 2,5-bis(5-carboxy-3-ethyl-4-methylpyrrol-2-ylmethyl)-3,4-diethylpyrrole[24] (**11**, 673 mg, 1.0 mmol) were condensed. After column chromatography ($CHCl_3$:MeOH, 9:1, v:v, eluent) and conversion to the bis-hydrochloride salt *via* the method described above (for H_2**1**·2Cl), 357 mg (41%) of H_2**2**·2Cl was prepared: ^1H NMR ($CDCl_3$ + TFA) δ -6.63 (2H, br s, N*H*), -5.21 (1H, br s, N*H*), 2.34 (12H, t, CH_2CH_3), 4.44 (6H, s,

CH_3), 4.96 (8H, q, CH_2CH_3), 11.40, 11.97, 12.32, 12.35 (4 x 2H, s, *meso*- and β-*H*); ^{13}C NMR ($CDCl_3$ + TFA) δ 12.8, 17.8, 18.5, 21.1, 21.4, 95.8, 99.1, 127.4, 131.4, 135.7, 137.0, 140.2, 142.3, 146.3, 146.8, 150.0 (one quaternary carbon unobserved); HRMS 518.2797 $(MH)^+$, (calcd for $C_{34}H_{35}N_3O_2 \cdot H^+$: 518.2808).

3,7,18,22-Tetraethyl-2,8,17,23-tetramethyl-27-thiasapphyrin (3). 4,4'-Diethyl-5,5'-diformyl-3,3'-dimethyl-2,2'-bipyrrole (**16**, 272 mg, 1.0 mmol) and 2,5-bis(4-ethyl-3-methylpyrrol-2-ylmethyl)thiophene (**22**, 327 mg, 1.0 mmol) were condensed in the usual way. After chromatography ($CHCl_3$:MeOH, 9:1, v:v, eluent), 200 mg (36%) of free-base **3** was obtained: ^1H NMR ($CDCl_3$) δ -3.34 (2H, br s, N*H*), 2.12 (6H, t, CH_2CH_3), 2.26 (6H, t, CH_2CH_3), 3.82 (6H, s, CH_3), 3.94 (6H, s, CH_3), 4.34-4.46 (8H, m, CH_2CH_3), 10.03 (2H, s, thiophene-β*H*), 10.77 (2H, s, *meso-H*), 10.99 (2H, s, *meso-H*); ^{13}C NMR ($CDCl_3$) δ 11.7, 15.4, 17.4, 18.0, 20.1, 20.2, 103.3, 106.7, 126.9, 134.4, 134.6, 136.5, 136.7, 139.1, 140.4, 142.0, 143.5, 144.9; HRMS 560.2986 (calcd for $C_{36}H_{40}N_4S$: 560.2974).

3,7,18,22-Tetraethyl-2,8,17,23-tetramethyl-27-oxasapphyrin (4). Bis(5-benzyloxycarbonyl-4-ethyl-3-methylpyrrol-2-ylmethyl)furan (**33**, 145 mg, 0.25 mmol) was dissolved in 100 mL of dry THF and hydrogenated over 10% palladium-charcoal (40 mg, ca. 5 wt%) at 1 atm H_2 until the reaction was deemed complete as judged by TLC. The catalyst was removed by filtration before the solvent was reduced in volume on a rotary evaporator. The resulting concentrated mixture was then triturated with n-heptane and placed in the freezer for several hours. A white precipitate formed which was collected by filtration, washed with cold hexanes, and dryed *in vacuo* to give diacid dipyrrolylfuran **27**. This product was then used without purification: It (**27**, 100 mg, 0.25 mmol), and 4,4'-Diethyl-5,5'-diformyl-3,3'-dimethyl-2,2'-bipyrrole (**16**, 82 mg, 0.3 mmol) were condensed as per the procedure for **1**. After chromatography ($CHCl_3$:MeOH, 9:1, v:v as the eluent), 35 mg (26%) of $H_24 \cdot 2Cl$ was prepared using 1N HCl: ^1H NMR ($CDCl_3$) δ -5.55 (2H, s, N*H*), -5.24 (2H, s, N*H*), 2.16 (6H, t, CH_2CH_3), 2.22 (6H, t, CH_2CH_3), 4.14 (6H, s, CH_3), 4.24 (6H, s, CH_3), 4.54 (4H, q, CH_2CH_3), 4.76 (4H, q, CH_2CH_3), 10.94 (2H, s, furan β-*H*), 11.72 (2H, s, *meso-H*), 11.81 (2H, s, *meso-H*); ^{13}C NMR (CD_3OD) δ 12.8, 12.9, 16.0, 18.1, 21.6, 21.8, 92.9, 98.6, 127.5, 128.7, 129.3, 130.6, 133.8, 133.9, 136.6, 143.7, 145.8, 151.0; HRMS 544.3245 (calcd for $C_{36}H_{40}N_4O$: 544.3202).

7,18-Diethyl-8,17-dimethyl-25,29-dioxa-27-thiasapphyrin (5). 5,5'-Diformyl-2,2'-bifuran (**17**, 190 mg, 1.0 mmol) and 2,5-bis(4-ethyl-3-methylpyrrol-2-ylmethyl)thiophene (**22**, 326 mg, 1.0 mmol) were condensed as usual. After chromatography ($CHCl_3$:MeOH, 9:1, v:v, eluent) and HCl washing, 126 mg (26%) of $H_25 \cdot 2Cl$ was obtained: ^1H NMR ($CDCl_3$) δ 1.98 (6H, t, CH_2CH_3), 3.70 (6H, s, CH_3), 4.15 (4H, q, CH_2CH_3), [10.06 (2H, d), 10.47 (2H, d), 10.59 (2H, s), 10.74 (2H, s), 11.41 (2H, s) all meso- or β-*H*]; ^{13}C NMR ($CDCl_3$+CD_3OD) δ 11.4, 17.1, 19.8, 131.8, 137.7, 137.8, 137.9, 141.6, 144.4, 144.5, 144.6, 149.7, 157.3 (*meso*-carbons not seen); HRMS 479.1812 $(MH)^+$, (calcd for $C_{30}H_{26}N_2O_2S \cdot H^+$: 479.1793).

Ethyl 3-ethyl-5-iodo-4-methylpyrrole-2-carboxylate (13). This procedure is an adaptation of an earlier iodopyrrole formation procedure[13] where pyrrole[12,26] (**12**) has been substituted for ethyl 5-carboxy-3-ethyl-4-methylpyrrole-2-carboxylate. A solution of $NaHCO_3$ (15.7 g, 0.19 mol) in 60 mL of H_2O was heated to 50 °C in a 1 L round bottom flask. To this was added 700 mL of 1,2-dichloroethane followed by ethyl 3-ethyl-4-methylpyrrole-2-carboxylate[12,13] (**12**, 10 g, 55 mmol). A solution of I_2 (15.7 g, 62 mmol) and NaI (19.8 g, 0.13 mol) in 60 mL of H_2O was then added to the mixture over a 5 minute period. Undissolved I_2 was washed into the mixture with H_2O and the resulting mixture was heated at reflux for one hour. The mixture was then cooled to room temperature and crystalline $Na_2S_2O_3$ (4 g) added to discharge excess iodine. The mixture was then transferred to a separatory funnel, the organic layer separated, and the aqueous phase washed with $CHCl_3$ (3 x 50 mL). The combined organic layers were washed with a 5% solution of $Na_2S_2O_3$ (3 x 50 mL), a

5% solution of $NaHCO_3$ (3 x 50 mL), a saturated brine solution (3 x 50 mL), and then dried over Na_2SO_4 before the solvent was removed on the rotary evaporator to leave an off-white solid which was recrystallized from CH_2Cl_2/hexanes to give 11.8 g (70%) of **13** with m.p. 122-124 °C (lit.[13] m.p. 120-121 °C).

Diethyl 4,4'-diethyl-3,3'-dimethyl-2,2'-bipyrrole-5,5'-dicarboxylate (14). Ethyl 3-ethyl-5-iodo-4-methylpyrrole-2-carboxylate (**13**, 18.42 g, 0.06 mol) was dissolved in 120 mL of DMF. Copper bronze (18.5 g, Aldrich Chemical Co.) was added and the mixture heated to 140 °C for one hour. If the mixture coagulated during the coarse of the reaction, small crystals of I_2 were added until the mass redissolved. After the required time, the mixture was filtered through celite to remove the copper, which was washed with hot $CHCl_3$ until the washings were colorless. The filtrate was then washed with 1N HCl (3 x 100 mL), 10% aqueous sodium thiosulfate (3 x 100 mL), and saturated brine (3 x 100 mL). The solution was dried over Na_2SO_4 before the solvent was removed on the rotary evaporator to leave an oil. Pentane (ca. 100 mL) was added, and the mixture placed in the refrigerator for a few hours. The product precipitated out as white plates which were collected by filtration and washed with hexanes. The mother liquor can be chromatographed over silica gel to recover a small amount of additional bipyrrole as well as a modest quantity of starting ethyl 3-ethyl-4-methylpyrrole-2-carboxylate (**12**, 5.6 g, 0.03 mol). Thus, based on the amount of recovered **12** the yield of **14** is 50% (6.48 g). Further purification can be accomplished by recrystallization from CH_2Cl_2/hexanes: m.p. 178-181 °C ; ^{1}H NMR ($CDCl_3$) δ 1.15 (6 H, t, CH_2CH_3), 1.36 (6 H, t, $CO_2CH_2CH_3$), 2.06 (6 H, s, CH_3), 2.79 (4 H, q, CH_2CH_3), 4.32 (4 H, q, $CO_2CH_2CH_3$), 8.71 (2 H, s, NH); ^{13}C NMR ($CDCl_3$) δ 9.7, 14.5, 15.0, 18.4, 60.0, 118.7, 118.9, 124.8, 134.0, 161.5; MS (EI), m/z (relative intensity) 360 (100), 314 (48.6), 267 (11.6), 240 (28.2); HRMS 360.2059 (calcd for $C_{20}H_{28}N_2O_4$: 360.2049).

4,4'-Diethyl-3,3'-dimethyl-2,2'-bipyrrole (15) and 4,4'-diethyl-5,5'-diformyl-3,3'-dimethyl-2,2'-bipyrrole (16). Diethyl 4,4'-diethyl-3,3'-dimethyl-2,2'-bipyrrole-5,5'-dicarboxylate (**14**, 0.54 g, 1.5 mmol) was saponified and decarboxylated in ethylene glycol (10 mL) by heating at 180 °C (oil bath) in the presence of NaOH (99 mg, 2.3 mmol) under N_2 until no starting material or sodium salts of bipyrrole carboxylates were present (as indicated by TLC). After cooling, the contents of the flask were diluted with water (10 mL) and extracted with $CHCl_3$ (3 x 15 mL). The combined $CHCl_3$ extracts were then dried over Na_2SO_4 and the solvent removed on the rotary evaporator to give compound **15** (0.201 g, 62%) as a solid which was quickly carried on to the formylation step since this product darkens upon standing: ^{1}H NMR ($CDCl_3$) δ 1.22 (6 H, t, CH_2CH_3), 2.02 (6 H, s, CH_3), 2.48 (4 H, q, CH_2CH_3), 6.55 (2 H, s, pyrrole α-H), 7.73 (2 H, s, NH); MS (EI), m/z (relative intensity) 216 (100), 201 (53.3), 187 (15.7), 171 (10.4). 4,4'-Diethyl-3,3'-dimethyl-2,2'-bipyrrole (**15**, 1.28 g, 6 mmol) was dissolved in dry DMF (40 mL, 0.52 mol) under N_2. Freshly distilled $POCl_3$ (4 mL, 43 mmol) was added dropwise with stirring. After all the $POCl_3$ had been added, the mixture that resulted was heated to 100 °C for 2 h, and then cooled to room temperature. The resulting solution was poured into cold water (100 mL) and a 10% solution of NaOH added (ca. 60 mL) until a smell of amine was apparent. The resulting precipitate was collected, washed with water, and dried *in vacuo* to yield 0.95 g (59%) of **16**: m.p. 241-242 °C; ^{1}H NMR ($CDCl_3$) δ 1.25 (6 H, t, CH_2CH_3), 2.12 (6 H, s, CH_3), 2.78 (4 H, q, CH_2CH_3), 9.67 (2 H, s, NH), 9.96 (2 H, s, CHO); ^{13}C NMR (DMSO-d_6) δ 9.3, 16.0, 16.9, 119.1, 128.1, 128.8, 135.8, 177.7; MS (EI), m/z (relative intensity) 272 (100), 244 (39.2), 165 (26.0); HRMS 272.1530 (Calcd for $C_{16}H_{20}N_2O_2$: 272.1525).

2,5-Bis(4-ethyl-3-methylpyrrol-2-ylmethyl)thiophene (22). 2,5-Bis(5-ethoxycarbonyl-4-ethyl-3-methylpyrrol-2-ylmethyl)thiophene (**23**, 470 mg, 1 mmol) was dissolved in 30 mL of TFA and heated at 50 °C under N_2 until deemed complete by TLC. The solution was then poured into 100 mL of water and

extracted with $CHCl_3$ (2 x 50 mL). The organic phase was washed with water (2 x 50 mL), saturated aqueous $NaHCO_3$ (2 x 50 mL), dried with Na_2SO_4, and concentrated on the rotary evaporator to a viscous red oil which due to its sensitivity was generally not isolated but, rather, used immediately in the ensuing reaction. ^1H NMR ($CDCl_3$) δ 1.19 (6H, t, CH_2CH_3), 2.00 (6H, s, CH_3), 2.44 (4H, q, CH_2CH_3), 4.00 (4H, s, pyrrole-CH_2-thiophene), 6.42 (2H, d, pyrrole-α*H*), 6.61 (2H, s, thiophene-β*H*), 7.57 (2H, br s, N*H*).

2,5-Bis(5-ethoxycarbonyl-4-ethyl-3-methylpyrrol-2-ylmethyl)thiophene (23). 2,5-Bis(acetoxymethyl)thiophene[25] (**24**, 5.19 g, 23 mmol), ethyl 3-ethyl-4-methylpyrrole-2-carboxylate[12] (**12**, 8.25 g, 46 mmol), and 80 mg of *p*-TsOH·H_2O were dissolved in 280 mL of absolute ethanol. The mixture was heated and held at reflux for 12 h under N_2. The solvent was reduced to about 100 mL on the rotary evaporator before placing the mixture in the freezer for several hours. The solid was collected by filtration and washed with cold absolute ethanol to give product **23** as a white solid (6 g, 56%) : m.p. 179-181 °C; ^1H NMR ($CDCl_3$) δ 1.11 (6H, t, CH_2CH_3), 1.32 (6H, t, $CO_2CH_2CH_3$), 1.96 (6H, s, CH_3), 2.73 (4H, q, CH_2CH_3), 4.00 (4H, s, (pyrrole-CH_2)$_2$-thiophene), 4.27 (4H, q, $CO_2CH_2CH_3$), 6.59 (2H, s, thiophene-β*H*), 8.63 (2H, br s, N*H*); ^{13}C NMR ($CDCl_3$) δ 8.6, 14.5, 15.1, 18.5, 26.9, 59.7, 116.5, 116.9, 125.1, 130.8, 133.9, 140.0, 161.5; MS (EI), m/z (relative intensity) 470 (4.4), 373 (71.3), 344 (8.6), 335 (100), 300 (34.1), 290 (34.9), 262 (48.7), 244 (21.0), 97 (27.0); HRMS 470.2244 (calcd for $C_{26}H_{34}N_2SO_4$: 470.2246).

2,5-Bis(5-benzyloxycarbonyl-4-ethyl-3-methylpyrrol-2-ylmethyl)furan (33). In a flame-dried 250 mL round bottom flask, 2,5-bis(acetoxymethyl)furan[20] (**28**, 1.06 g, 5 mmol), benzyl 3-ethyl-4-methylpyrrole-2-carboxylate[13] (**32**, 2.43 g, 10 mmol), and 150 mg of *p*-toluenesulfonic acid monohydrate were dissolved in 150 mL of dry CH_2Cl_2 and 75 mL of dry THF. The mixture was heated and then held at reflux for 12 h under N_2. The solvent was reduced to about 75 mL on a rotary evaporator and then put in the freezer for several hours. The solid was collected by filtration and washed with cold absolute ethanol. Recrystallization from hot EtOH (95%) gave **33** as a white solid (1.67 g, 56%): m.p. 184-185 °C; ^1H NMR ($CDCl_3$) δ 0.91 (6H, t, CH_2CH_3), 1.76 (6H, s, CH_3), 2.56 (4H, q, CH_2CH_3), 3.68 (4H, s, (pyrrole)$_2$-CH_2-furan), 5.11 (4H, s, $CO_2CH_2C_6H_5$), 7.14 - 7.25 (10H, m, $CO_2CH_2C_6H_5$), 9.45 (2H, br s, N*H*); ^{13}C NMR δ 8.2, 14.9, 18.2, 25.0, 65.0, 106.8 (2 carbons,(2C)), 115.9, 116.4, 127.7 (2C), 128.1 (2C), 129.4, 134.0, 136.3, 150.8, 160.9; MS (EI), m/z (relative intensity) 578 (25.1), 470 (23.2), 443 (14.1), 379 (15.3), 335 (47.5), 91 (100); HRMS 578.2768 (calcd for $C_{36}H_{38}N_2O_5$: 578.2781).

References and Notes.

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