# Synthesis and Characterization of All-Alkyl-Substituted Mono-, Di-, and Trioxosapphyrins

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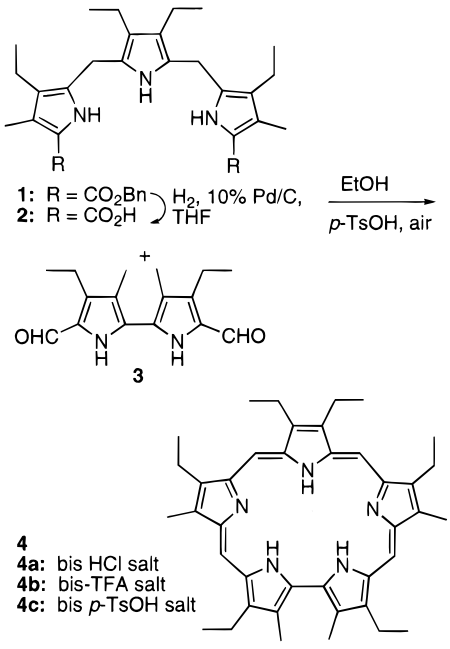
The synthesis and characterization of the following heterosapphyrins is presented: 3,7,18,22-tetraethyl-2,8,12,13,17,23-hexamethyl-27-oxasapphyrin (**5**), 3,8,12,13,17,22-hexaethyl-2,7,18,23-tetramethyl-15,29-dioxasapphyrin (**6**), and 3,7,18,22-tetraethyl-2,8,12,13,17,23-hexamethyl-15,27,29-trioxasapphyrin (**7**). These macrocycles were synthesized from the hitherto unknown precursors methyl 3,4-dimethylfuran-2-carboxylate (**11**) and methyl 4-ethyl-3-methylfuran-2-carboxylate (**12**). Single-crystal X-ray diffraction structures of the bis(hydrochloric acid) salt (**5a**) and the bis(trifluoroacetic acid) salt (**5b**) of **5** and of the bis(hydrochloric acid) salt (**6a**) of **6** were obtained. These structures are compared to those of the parent all-aza sapphyrin **4**. In this context, we report the first solid-state structural analysis of a trifluoroacetic acid salt of sapphyrin (**4b**). Crystals of **5a** are triclinic, space group $P\bar{1}$ in a cell of the dimensions $a = 11.9686(13)$ Å, $b = 12.790(2)$ Å, $c = 16.236(2)$ Å, $\alpha = 80.924(10)°$, $\beta = 88.845(9)°$, $\gamma = 80.481(10)°$, $V = 2420.5(5)$ Å$^3$, $F(000) = 1036$, $\rho = 1.38$ g cm$^3$, with $Z = 2$. Crystals of **5b** are monoclinic, space group $P2_1/c$, in a cell of the dimensions $a = 9.590(1)$ Å, $b = 33.911(3)$ Å, $c = 13.200(1)$ Å, $\beta = 94.931(6)°$, $V = 4276.8(6)$ Å$^3$, $F(000) = 1904$, $\rho = 1.42$ g cm$^3$, with $Z = 4$. Crystals of **6a** are triclinic, space group $P\bar{1}$, in a cell of the dimensions $a = 12.827(3)$ Å, $b = 13.116(3)$ Å, $c = 17.202(7)$ Å, $\alpha = 82.89(2)°$, $\beta = 82.14(2)°$, $\gamma = 80.22(1)°$, $V = 2810(2)$ Å$^3$, $F(000) = 1184$, $\rho = 1.36$ g cm$^3$, with Z = 2. Crystals of **4b** are triclinic, space group $P\bar{1}$, in a cell of the dimensions $a = 11.431(3)$ Å, $b = 11.563(2)$ Å, $c = 16.367(4)$ Å, $\alpha = 88.07(2)°$, $\beta = 75.25(2)°$, $\gamma = 86.50(2)$, $V = 2087.8(9)$ Å$^3$, $F(000) = 872$, $\rho = 1.32$, with $Z = 2$. The monooxasapphyrin salt **5a** displays a structure very similar to that of the parent all-azasapphyrin (**4a**) in that one chloride anion is bound 1.936 Å above and one chloride anion 1.814 Å below the plane of the macrocycle. These distances are 1.774 and 1.877 Å, respectively, for **4a**. Almost the same behavior is found for **5b**. Here, the carboxylate anions are bound 1.085 Å above and 1.870 Å below the plane of the macrocycle. These distances are 1.305 and 1.444 Å, respectively, for **4b**. Completely different behavior is observed in the case of **6a**. In this instance, only one chloride anion is bound directly with a distance of 1.685 Å above the plane of the macrocycle, while the other chloride anion is well removed from the dioxasapphyrin and solvated by four chloroform molecules.

## Introduction

In recent years, expanded porphyrins have become increasingly popular as synthetic targets.[1] This is due both to their intrinsic beauty and because they are perceived as being useful in a variety of applications that range from their role as models for aromatic annulenes to their use as radiation sensitizers and putative antiviral drug delivery systems. One of the better studied of all expanded porphyrins is the pentapyrrolic macrocycle sapphyrin (e.g., **4**, Scheme 1). This prototypic expanded porphyrin was first reported by Woodward and co-workers in 1966.[2,3] However, because of difficulties associated with its synthesis, sapphyrins remained but little studied prior to the late 1980s. At this time, improved syntheses of both the critical tripyrrane precursor **1**[4] and its bipyrrole coupling partner **3** were reported.[5] This, in turn, allowed sapphyrins such as **4** to be prepared in good yields and enabled the rich chemistry of these systems to be explored.[6] One of the more

**Scheme 1**




[⊗] Abstract published in *Advance ACS Abstracts,* December 1, 1997.

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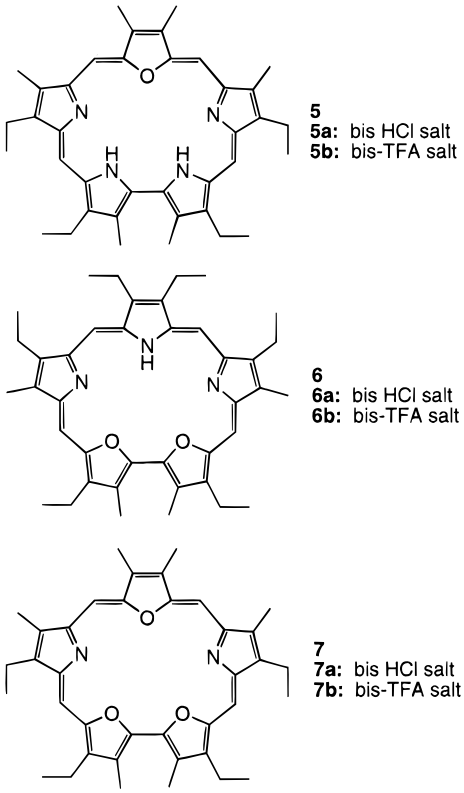
interesting findings to emerge from these studies was the discovery that various protonated sapphyrin derivatives are able to bind anionic species, such as halide[5] and phosphate anions,[7] both in solution and in the solid state.

While the binding of anions by protonated sapphyrin is now established, the exact determinants of the binding process still remain to be detailed. Inspection of the various X-ray crystal structures now available[5,7] leads to the conclusion that either electrostatic interactions or hydrogen-bonding contacts, or both, could be responsible for the sapphyrin dication-to-anion contacts observed in the solid state. In an effort to distinguish between these two limiting binding scenarios, it was considered worthwhile to prepare sapphyrin analogues where one or more of the pyrrolic subunits is replaced by a furan. Since neutral furans, unlike pyrroles, cannot serve as hydrogen-bond donors, binding and transport studies using these furan-containing sapphyrins could reveal if a forced reduction in hydrogen-bond-donor capacity is reflected in reductions in anion-binding affinity in solution or increases in anion-to-sapphyrin contact distances in the solid state. In this paper, we report the synthesis of the all-$\beta$-alkyl (i.e., 3,4)-substituted mono-, di-, and trioxasapphyrins **5**, **6**, and **7** corresponding to the all-aza-substituted sapphyrin parent **4**. We also report the X-ray structures of the bis(hydrochloride) salts of **5** and **6** (**5a** and **6a**) as well as those of the bis(trifluoroacetic acid) salts of **4** and **5** (**4b** and **5b**). Taken together, these structures serve to show that reducing the number of available hydrogen-bonding sites within the macrocyclic core leads to dramatic changes in the relevant anion-to-sapphyrin distances but does not serve to eliminate anion binding in the solid state.

Although furan-containing sapphyrins are known,[3,8] systems wherein the furan subunits are substituted with alkyl groups in the $\beta$-positions are, to our knowledge, currently unknown. Such materials are considered necessary if reliable comparisons "back to" the alkyl-substituted sapphyrins are to be made. This desideratum, in turn, has prompted us to develop suitable syntheses of appropriately functionalized precursors. Therefore, in this paper, we also present the synthesis of the hitherto unknown 3,4-dialkyl-substituted furans **11** and **12** and show how these can be elaborated into a range of sapphyrin-type macrocycles. The synthetic method used to generate **11** and **12** appears to be general. It thus opens the way to preparing a range of nonsapphyrin, heteroatom-containing expanded porphyrins. This is potentially important since $\beta$-substituents both improve product solubility and facilitate macrocyclization via what has been termed a "helical effect".[9]

## Results and Discussion

**Synthesis of the Furan Precursors.** Three general approaches toward the synthesis of 3,4-dialkyl-substituted furans have been reported in the literature.[10−12] All three were thus considered in the context of trying to prepare targets **5** and **7**. However, the first one[10] was quickly ruled out due to (i) the large number of transformations involved and (ii) perceived difficulties associated with scale-up. The second approach, the inverse Diels−Alder procedure of Vogel et al. used to prepare 3,4-diethylfuran,[12] was also ruled out due to the rather harsh conditions required and because sophisticated syntheses of the starting materials are necessary. The third conceivable literature approach, based on a generalized furan synthesis of Backer et al.,[11] was tried. However, it failed to prove viable in our hands. Therefore, a new procedure involving the thermal rearrangement of glycidic ester intermediates was tested. This procedure, which involves a generalization of an approach introduced previously to prepare mono-$\beta$-alkyl furans,[13] was found to give 3,4-dialkylfurans with sufficient efficiency that follow-up syntheses of sapphyrins could be conceived (see Scheme 2).




The specific precursors we wanted for the synthesis of **5**−**7** were methyl 3,4-dimethylfuran-2-carboxylate, **11**, and methyl 3-ethyl-4-methylfuran-2-carboxylate, **12**. These precursors were chosen because, in terms of their $\beta$-substitution pattern, they are directly analogous to the precursors used to prepare the decaalkyl-substituted sapphyrins currently in hand (e.g., **4**). In the event, the $\beta$-keto acetal precursors required to prepare **11** and **12**,

(6) Brückner, C.; Sternberg, E. D.; Boyle, R. W.; Dolphin, D. *Chem. Commun.* **1997**, 1689. Other syntheses of sapphyrin that are not predicated on the use of tripyrranes have been reported recently: (a) Sessler, J. L.; Lisowski, J.; Boudreaux, K. A.; Lynch, V.; Barry, J.; Kodadek, T. J. *J. Org. Chem.* **1995**, *60*, 5975. (b) Latos-Grazynski, L.; Rachlewics, K. *Chem. Eur. J.* **1995**, *1*, 68. (c) Paolesse, R.; Licoccia, S.; Spagnoli, M.; Boschi, T.; Khoury, R. G.; Smith, K. *J. Org. Chem.* **1997**, *62*, 5133.

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(9) Sessler, J. L.; Weghorn, S. J.; Hiseada, Y.; Lynch, V. *Chem. Eur. J.* **1995**, *1*, 56.

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(11) Backer, H. J.; Stevens, W. *Rec. Trav. Chim.* **1940**, *59*, 423.

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(13) (a) Burness, D. M. *Organic Synthesis*; Wiley: New York, 1963; Collect. Vol. IV, p 649. (b) Klein, L. L. *Synth. Commun.* **1986**, *16*, 431.

(14) (a) Royals, E. E.; Brannock, K. C. *J. Am. Chem. Soc.* **1953**, *75*, 2050. (b) Royals, E. E.; Brannock, K. C. *J. Am. Chem. Soc.* **1954**, *76*, 1180. (c) Fletcher, G. L.; Hull, J. S. U.S. Patent 2,760,986, 1956.

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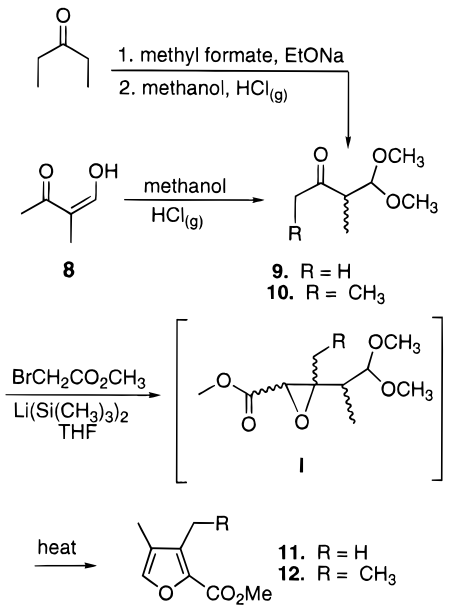
**Scheme 2**

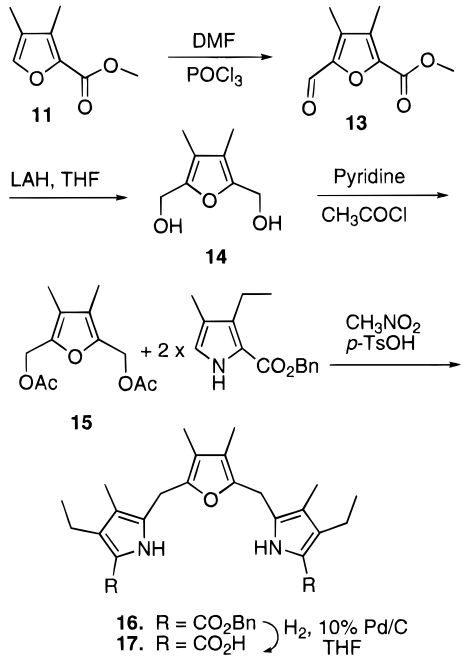



namely **9** and **10**, were synthesized using literature procedures.[14,15] These materials were then transformed into the corresponding glycidic ester intermediates. These latter were not isolated. Rather, the reaction mixtures in which they were contained were subjected to warming and distillation prior to conversion to the corresponding furans. In this way, any unreacted $\beta$-keto acetal and enol ether could be removed first via distillation, leaving the crude glycidic esters to be converted to the respective furan.

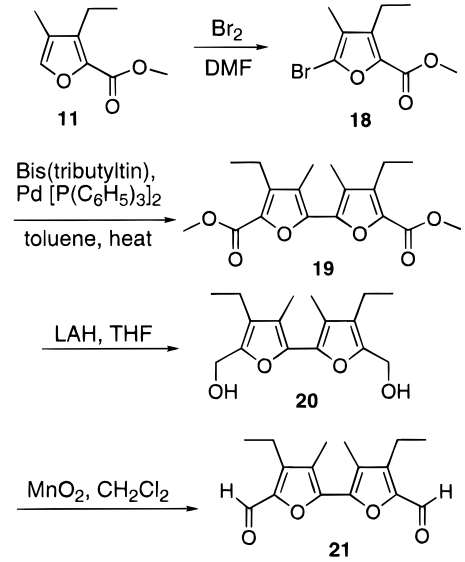
Once the desired 3,4-dialkyl-substituted furans were in hand, the 2 and 5 positions had to be modified so as to allow incorporation of these subunits into the sapphyrin skeleton. On the basis of previous experience,[8] it was considered likely that this could most easily be effected, at least in the case of **11**, if reactive acetoxymethyl groups could be introduced at the 2 and 5 positions. To accomplish this, the 5 position was first subject to formylation under Vilsmeier-type conditions (to give **13**; Scheme 3). Next, both the aldehyde and ester groups were reduced to the symmetrical bis(hydroxymethyl)furan, **14**. This material was then acetylated using acetyl chloride in the presence of pyridine. The resulting diacetoxy furan, **15**, was then reacted with 2 equiv of benzyl 3-ethyl-4-methylpyrrole-2-carboxylate to give the furan-containing tripyrrane analogue **16**.

The key precursor considered necessary for the synthesis of dioxasapphyrin **6** (and the trioxa target **7**) was the dialdehyde **21**. This material was synthesized by first brominating the 5 position of **12** using $Br_2$ in DMF (Scheme 4).[16] Then, using bis(tributyltin) in the presence of $Pd^0$, the resulting bromofuran, **18**, was coupled to give the bifuran diester, **19**. Reduction of both esters with lithium aluminum hydride and oxidation of the resulting dialcohol, **20**, with $MnO_2$ then gave the desired intermediate target **21**. This synthetic strategy was chosen after more-standard strategies, such as those based on coupling procedures such as Ullmann couplings[17] and oxidative dimerization,[18] failed to produce any of the desired product (i.e., **21** or its direct bifuranic precursors).

**Scheme 3**




**Scheme 4**




**Synthesis of the Oxasapphyrins.** With the furan-containing precursors **16** and **21** in hand, cyclization reactions leading to oxasapphyrins **5**−**7** were carried out. In all cases, a standard[2,8] 3 + 2 MacDonald-type condensation procedure akin to that shown in Scheme 1 was employed. However, as detailed in the Experimental Section, slight modifications in the solvents and conditions were made as appropriate.

Use of this general procedure required conversion of the requisite dibenzyl ester tripyrrane (i.e., **1**) or oxatripyrrane analogue (i.e., **16**) into the corresponding dicarboxylic acid (**2** or **17**, respectively). This was done via hydrogenolysis using 10% Pd/C as the catalyst. The resulting dicarboxcylic acids were treated as being un-

(16) Itahara, T.; Hashimoto, M.; Yumisashi, H. *Synthesis* **1984**, 255.
(17) Diels, O.; Ilberg, K. *Ber*. **1916**, 158.
(18) Grigg, R.; Knight, J. A.; Sargent, M. V. *J. Chem. Soc.* **1966**, 976.

(19) The use of a solvent system different from that employed in the case of the all-aza sapphyrin **4** resulted from an inability to effect oxidation of the furan containing dihydrosapphyrins in ethanol. Various oxidants, air, DDQ, and chloranil were tried, but in no case did oxidation to the fully conjugated oxosapphyrin occur. Use of a halogenated solvent system on the other hand, allowed these critical oxidations to be effected readily in what is literally a one-pot procedure.

**Table 1. Optical Properties of Sapphyrin and Oxasapphyrin Salts in $CHCl_3$**

| salt | Soret/ nm (log $\epsilon$) | Q-bands/nm (log $\epsilon$) |
|---|---|---|
| **4b** | 454 (5.49) | 576 (3.76), 623 (3.88), 676 (4.00) |
| **5b** | 450 (5.54) | 609 (3.94), 625 (4.11), 667 (3.79), 689 (3.91) |
| **6b** | 452 (5.65) | 610 (3.94), 637 (4.09), 671 (4.25), 703 (3.00) |
| **7b** | 451 (5.26) | 593 (3.81), 646 (3.75), 717 (3.68) |

stable and were thus used without purification or isolation. Specifically, using a chloroform/methanol solvent system,[19] they were combined with the appropriate diformylbifuran **21** or diformylbipyrrole **3**. Aqueous hydrochloric acid was then added in small amounts and the solution left stirring at room temperature exposed to air but protected from light. At the point where starting materials could no longer be detected, 1 equiv of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was added as the oxidant.[20] The resulting sapphyrins were then purified by column chromatography in the form of their trifluoroacetic acid (TFA) salts.

## Characterization and Properties

**Solution-State Structure.** The synthesis of **4**−**7** provides a matched set of sapphyrin congeners with which detailed spectroscopic comparisons can be made. The first set of such putative comparisons involved looking at UV/vis spectra of **4**−**7**. Because sapphyrins are easily protonated and because the UV/vis spectra of sapphyrins and heterosapphyrins (when protonated) are influenced by the identity of the counteranion,[5,7,8] sapphyrins **4**−**7** were all studied in the form of their bis(trifluoroacetic acid) salts (**4b**−**7b**). Under these conditions, it was found that all three $\beta$-alkyl-substituted oxasapphyrins display visible spectra in dichloromethane that are not only similar to each other but also to that of the parent all azasapphyrin (**4b**). The only observable difference is a hypsochromic shift of the Soret bands and a bathochromic shift of the Q-type bands in the case of the oxasapphyrins (see Table 1). Interestingly, in the case of the $\beta$-free systems similar but much more intense shifts in the Soret bands are observed.[8] This observation underscores the need to use systems of like substitution when making detailed UV/vis spectroscopic comparisons.

Proton NMR spectroscopy was also used to characterize the new sapphyrin analogues **5**−**7**. As is true for the azasapphyrins (e.g., **4**)[5] and the $\beta$-unsubstituted oxasapphyrins,[8] the $^1$H NMR spectra of the oxasapphyrins **5**−**7** reveal the upfield and downfield shifts for the internal NH protons and external (*meso*) ring protons characteristic of aromatic macrocycles (see Table 2). One general trend that is observed is that the internal NH protons are shifted to lower field as the number of pyrroles replaced by furans is increased. This finding most likely reflects the known deshielding effect of the oxygen atoms.[21] Another observable change is the way in which the relative chemical shifts of the *meso* proton signals are seen to vary once oxygen is introduced into the system. These changes most likely reflect the different locations of the furan subunits in **5**−**7**. However, even by including **4** in the basis set, no clear pattern can be deduced (except that the effect, whatever its origin, is strongest for **7**). Further insight into this matter could come with the synthesis of other $\beta$-substituted heterosapphyrin derivatives.

**Table 2. $^1$H NMR Spectroscopic Properties of Sapphyrin and Oxasapphyrin Bis(TFA) Salts in $CDCl_3$**

| salt | $\delta$ (ppm), NH | $\delta$ (ppm), meso-H | $\Delta\delta$ (ppm) meso-H |
|---|---|---|---|
| **4b** | −5.11 (2H), −4.73 (1H), −4.45 (2H) | 11.53 (2H), 11.58 (2H) | 0.05 |
| **5b** | −4.12 (2H), −2.99 (2H) | 11.40 (2H), 11.65 (2H) | 0.2 |
| **6b** | −4.08 (2H), −3.11 (1H) | 11.65 (2H), 11.78 (2H) | 0.13 |
| **7b** | −2.9 (2H) | 11.29 (2H), 11.57 (2H) | 0.28 |

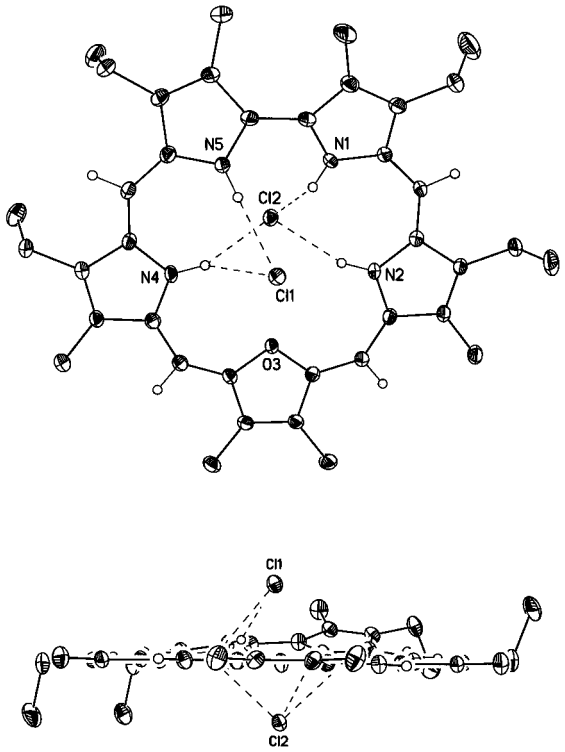



**Figure 1.** Top and side view of **5a** showing parts of the atom-labeling scheme. Thermal ellipsoids are scaled to the 30% probability level. Hydrogen atoms shown are drawn to an arbitrary scale, although most have been omitted for clarity.

**Solid-State Structure.** In addition to being characterized in organic solution, two of the new oxasapphyrins reported here were characterized via single-crystal X-ray diffraction. In the case of the oxasapphyrin derivative **5**, X-ray structures were obtained for the bis(hydrochloride) (**5a**, Figure 1) and bis(TFA) (**5b**, Figure 2) salts, whereas in the case of **6** a structure could be obtained only for the bis(hydrochloride) salt (**6a**, Figure 3).

Having structural data available for **5a** and **6a** allows comparison to be made to the X-ray structure of the already known bis(hydrochloride) complex of **4** (**4a**, Figure 4).[5b] Further, because of a desire to compare salt **5b** "back to" the corresponding all-aza system **4b**, efforts were made to obtain solid-state structural information for this latter bis(TFA) salt (**4b**). These efforts proved successful (Figure 5), thus allowing a detailed comparison of both the effect of heteroatom substitution on the binding of anions by sapphyrin in the solid state and the effect of the counteranion on the structure of sapphyrins and heterosapphyrins as manifested in single crystals.

The three comparisons that we chose to make within this series of complexes concerned (1) the pyrrolic nitrogen-

(20) Although the dihydrosapphyrin intermediates will oxidize if left in solution exposed to air (roughly 10, 24, and 48 h in the case of the mono-, di-, and trioxasapphyrins, respectively), extensive decomposition is detected.

(21) Streitwieser, A.; Heathcock, C. H. *Introduction to Organic Chemistry*, 3rd ed.; Macmillan Publishing Company: New York, 1985; pp 332−334.

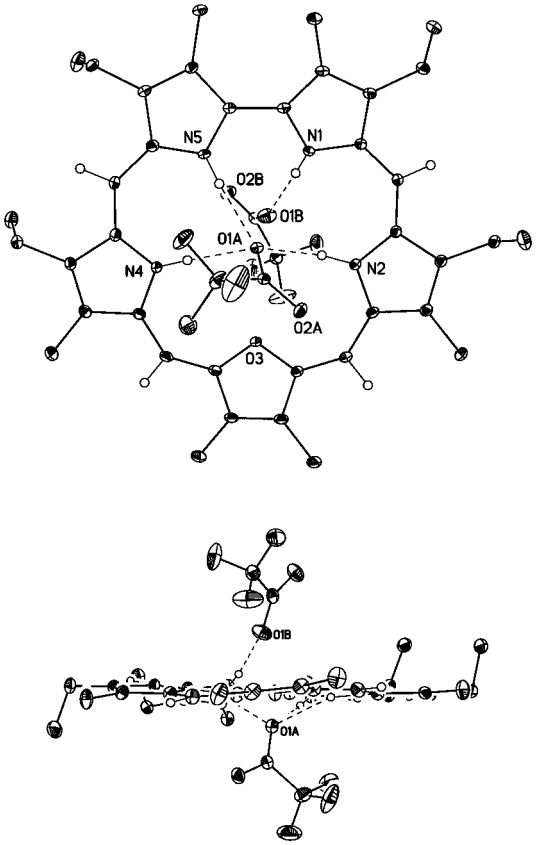



**Figure 2.** Top and side view of **5b** showing parts of the atom-labeling scheme. Thermal ellipsoids are scaled to the 30% probability level. Hydrogen atoms shown are drawn to an arbitrary scale, although most have been omitted for clarity.

to-counteranion distance, (2) the distance of the counteranion from the plane of the macrocycle, and (3) the deviation from planarity of the bipyrrolic or bifuran subunit (bipyrrole or bifuran dihedral angle). As seen in Figure 4 and discussed in detail previously,[5b] the bis(hydrochloride salt) of **4** is almost planar. The tripyrrane portion of the macrocycle is extremely flat, while the bipyrrolic portion is slightly twisted (the relevant dihedral angle is 25.2°). The first bound chloride anion, Cl 1, is bound by a three-hydrogen-bond interaction to the three nitrogen atoms of the macrocycle and lies 1.77 Å above the plane of the macrocycle (defined by the five heteroatoms). The second chloride counteranion, Cl 2, on the other hand, is involved in hydrogen-bond interactions with but two of the five nitrogen atoms and is located 1.88 Å below this plane (cf. Table 3).

Looking at the same parameters for the oxasapphyrin **5a** complex (Figure 1), one sees that the dihedral angle of the bipyrrole subunit is 22.5°. This is a value that is slightly smaller than that present in **4a**. The relevant chloride to nitrogen distances are shown in Table 3. Here Cl 1 has only two hydrogen-bond interactions with the macrocycle and is located 1.934 Å above the plane of the macrocycle (defined as before), while Cl 2 shows three hydrogen-bond interactions and resides 1.81 Å below this plane.

Although the characteristics for the bis(chloride) anion complex **5a** are fairly similar to those of **4a**, those of the bis(oxasapphyrin) complex **6a** are very different. In fact, even though the diprotonated sapphyrin ligand in this instance bears an overall 2+ charge (just as it does in salts **4a** and **5a**), only one chloride anion is found to be

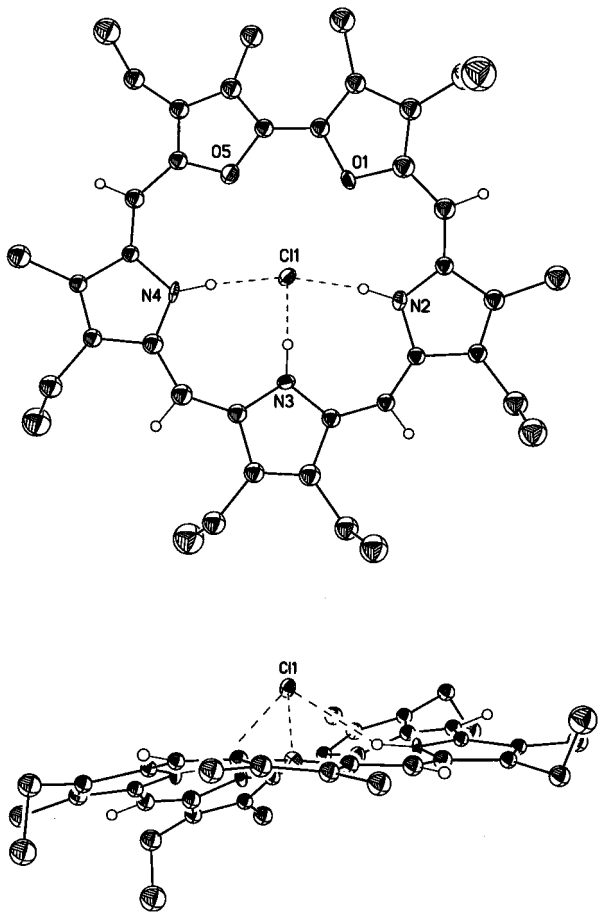



**Figure 3.** Top and side view of **6a** showing parts of the atom-labeling scheme. Thermal ellipsoids are scaled to the 30% probability level. Hydrogen atoms shown are drawn to an arbitrary scale although most have been omitted for clarity.

coordinated directly to the macrocycle (Figure 3). This bound chloride anion, Cl 1, is found to lie 1.69 Å above the plane of the macrocycle (Table 3). By contrast, the second chloride anion is solvated by four chloroform molecules and is well removed from the sapphyrin.

Another interesting characteristic evident in the structure of salt **6a** is the rather large dihedral angle of 30.8° present within the bifuran subunit. This bigger angle may reflect the fact that neither of the bifuran heteroatoms is coordinated to the bound chloride anion. This absence of binding "permits" the bifuran moiety to twist and, in so doing, reduce the steric interactions that would otherwise result from contacts between the $\beta$-substituents.

The congruent pair of bis(trifluoroacetic acid) salts **4b** and **5b** (Figures 5 and 2, respectively) also permits interesting comparisons to be made. On first inspection both complexes look very similar in that two sapphyrin frameworks are both nearly planar with two TFA molecules being hydrogen-bonded above and below the planes defined by these two macrocycles. However, closer inspection reveals that the binding interactions between the TFA anions and the macrocycle are different in **4b** and **5b**. In the case of **4b** one TFA anion is bound to two nitrogen atoms while the other TFA anion is bound to three nitrogen atoms (for relevant distances see Table 4). The distance from the plane of the macrocycle of the TFA anion with three hydrogen-bond interactions is 1.31 Å, while the corresponding distance is 1.44 Å for the other TFA molecule (i.e., the one with only two hydrogen-bond

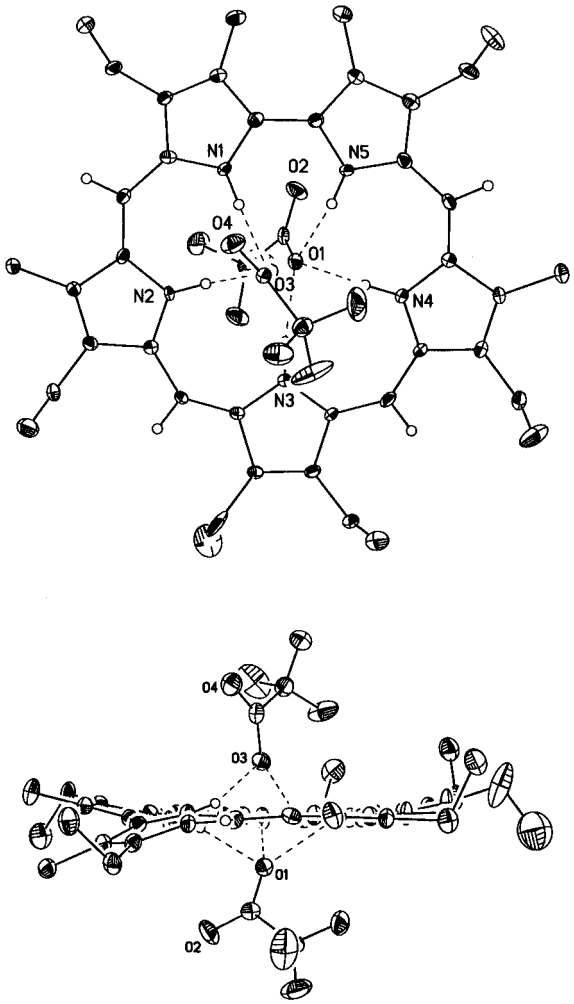



**Figure 4.** Top and side view of the molecular structure of complex **4a**. Thermal ellipsoids are scaled to 30% probability level; H-atoms are drawn to an arbitrary size, although most have been omitted for clarity. See ref 5b for further details of this structure.

interactions). For **5b**, a dihedral angle of 21.1° between the bipyrrole subunits was found, a value smaller than those observed for **4b**. In this salt, one TFA anion is found bound to one nitrogen while the other TFA anion is bound to three nitrogens. The relevant distances are listed in Table 4. The distances of the triple-bound and the single-bound TFA anion from the plane of the macrocycle are 1.09 Å above and 1.87 Å below, respectively (Table 4).

While it is not surprising that the TFA anions are bound differently in **5b** than in **4b** (after all, there is one hydrogen-bond donor less in **5b**), the actual mode of binding is unexpected. A priori, one might have been inclined to expect that the two TFA anions would share the remaining four hydrogen-bonding sites in **5b**, thus giving rise to a binding motif wherein two hydrogen bonds are used to stabilize the binding of each TFA anion. While such a binding scenario pertains to a first approximation in the case of the bis(hydrochloric acid) salt **5a**, it clearly does not in the case of **5b**. This last set of comparative results thus serves to highlight in a very dramatic way how the anion-binding properties of protonated sapphyrins can depend in the solid state not just on the choice of macrocycle but on the nature of the anions as well. It also underscores how, at least in this

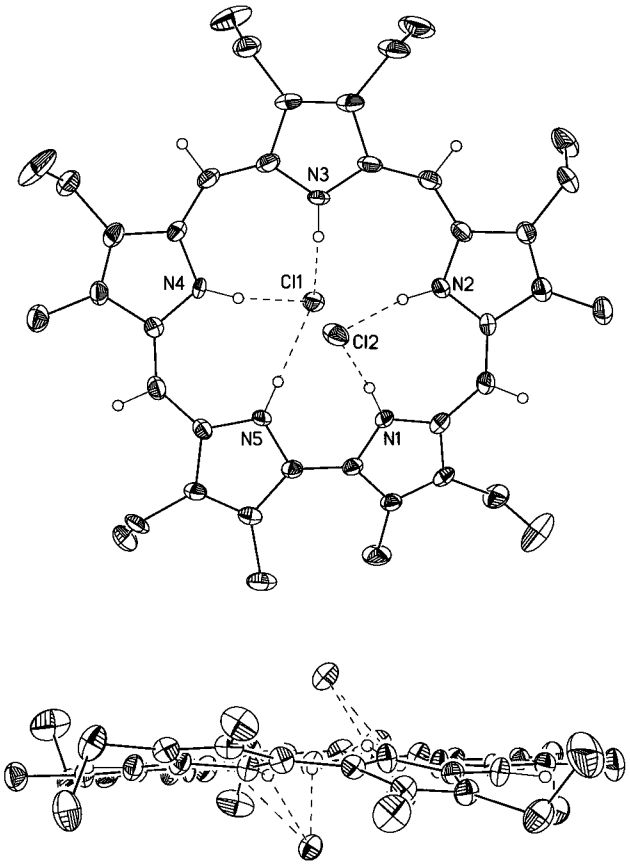



**Figure 5.** Top and side view of **4b** showing parts of the atom-labeling scheme. Thermal ellipsoids are scaled to the 30% probability level. Hydrogen atoms shown are drawn to an arbitrary scale, although most have been omitted for clarity.

**Table 3. Chloride to Nitrogen Distances of the Sapphyrin Complexes 4a, 5a, and 6a Given in Å[3b]**

| sapphyrin/ chloride | nitrogen 1 | nitrogen 2 | nitrogen 3 | nitrogen 4 | nitrogen 5 |
|---|---|---|---|---|---|
| **4a**/Cl 1 | | | 3.212 | 3.198 | 3.189 |
| **4a**/Cl 2 | 3.128 | 3.186 | | | |
| **5a**/Cl 1 | | | | 3.316(3) | 3.136(4) |
| **5a**/Cl 2 | 3.105(3) | 3.224(3) | 3.334(3) | | |
| **6a**/Cl 1 | | 3.176(13) | 3.039(12) | 3.200(12) | |

**Table 4. TFA Oxygen to Nitrogen Distances of the Sapphyrin Complexes 4b and 6b Given in Å**

| sapphyrin/ TFA oxygen | nitrogen 1 | nitrogen 2 | nitrogen 3 | nitrogen 4 | nitrogen 5 |
|---|---|---|---|---|---|
| **4b**/O3 | 2.781(7) | 2.899(7) | | | |
| **4b**/O1 | | | 2.921(7) | 2.913(7) | 2.927(7) |
| **5b**/O1b | 2.847(4) | | | | |
| **5b**/O1a | | 2.967(3) | | 2.910(4) | 2.830(3) |

congeneric series, the anion-to-protonated macrocycle distances relate directly to the number of hydrogen bonds formed.

## Conclusion

In this paper, we have described the synthesis of various $\beta$-alkyl-substituted furans and their incorporation into sapphyrin-type expanded porphyrins. This synthesis uses relatively cheap starting materials, can be scaled up, and gives moderate to good yields. The resulting $\beta$-substituted oxasapphyrins provide a "matched set" of materials with which comparisons can be made. Solid-state structural studies of the diprotonated forms

of **4**−**6**, for instance, have served to reveal that the details of anion binding in the solid state depend not only on the choice of sapphyrin (i.e., number and nature of heteroatom) but also on the specific anion being probed. Current work is focused on exploring the solution-phase substrate binding properties of these systems. While, in contradistinction to what is true for **4**,[5b] we have been unable to find a spectroscopic "handle" that will allow us to measure the anion affinities of the protonated forms of oxasapphyrins **5**−**7** in solution, we have found that monooxasapphyrin **5** will stabilize a $UO_2^{2+}$ complex under conditions where the pentaaza system **4** will not.[22] Taken together, these findings lead us to suggest that further study of these and other heteroatom-containing expanded porphyrins could prove informative.

## Experimental Section

**General Methods.** Melting points, $^1$H and $^{13}$C NMR spectra, UV/vis spectra, elemental analyses, and low- and high-resolution FAB and CI mass spectra were obtained using instrumentation described previously.[6a,8,9] Dichloromethane was dried by distillation under nitrogen from calcium hydride. Tetrahydrofuran (THF) was dried by distillation under nitrogen from sodium. Methanol was dried by distillation under nitrogen from calcium hydride. All other solvents, acids, bases, and reagents were obtained from commercial sources and used as received unless indicated otherwise.

**Synthetic Experimental Procedures. 2-Methyl-3-oxobutanal (8).** Methyl ethyl ketone (268 mL, 3 mol), methyl formate (182 mL, 3 mol), and dry diethyl ether (3 L) were placed under a nitrogen atmosphere in a 5 L, three-neck round-bottomed flask (RBF), equipped with a mechanical stirrer. The resulting solution was then stirred while being cooled in an ice−water bath, and sodium metal (69 g, 3 mol) was added portionwise over 2 h. After all of the sodium had been added, the orange solution was allowed to warm to room temperature by stirring under a nitrogen atmosphere overnight. The resulting yellow/orange sodium salt was filtered off, rinsed with diethyl ether, and dried in vacuo. After drying 246.1 g (67.3%) of the yellow sodium salt was obtained. This salt (96.4 g, 0.79 mol) was placed in an Erlenmeyer flask, and anhydrous diethyl ether (900 mL) was added. The mixture was stirred and cooled in an ice−water bath as dry HCl gas was bubbled through the mixture until the solution became neutral to acidic. The resulting white solids were filtered off and rinsed with ether. The combined red filtrates were taken to dryness on a rotary evaporator. This afforded a red solid that was then dried in vacuo without heating. Once dry, the red/orange solid was sublimed directly into a 100 mL RBF cooled with liquid nitrogen at 0.05 mmHg and 45 °C. This gave 44.4 g (56%) of **8** as a hard white solid: mp 65−68 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.80 (s, 3H), 2.14 (s, 3H), 7.74 (d, 1H), 14.65 (d, 1H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 13.2, 25.2, 107.8, 173.3, 197.3; HRMS *m*/*z* calcd for $C_5H_9O_2$ 101.0603, found 101.0608. Anal. Calcd for $C_5H_8O_2$: C, 59.97; H, 8.06. Found: C, 60.08; H, 8.01.

**4,4-Dimethoxy-3-methyl-2-butanone (9).** Dry HCl gas (6 g, 0.16 mol) was dissolved in dry methanol (250 mL) in a dry 1000 mL RBF. The keto aldehyde **8** (38 g, 0.38 mol) was dissolved in dry methanol (250 mL) and added dropwise over 30 min to this HCl/methanol solution at room temperature. The solution was stirred for 48 h under an argon atmosphere and then neutralized with solid sodium methoxide as the solution was cooled in an ice−water bath. The precipitated salts were filtered off and rinsed with dichloromethane. The original red filtrate and the dichloromethane washings were combined and taken to dryness on a rotary evaporator. This afforded a dark oil that was fractionally distilled under high vacuum (28−32 °C, 0.05−0.5 mmHg) using a 26 cm Vigreux column to afford four fractions (34.3 g total) of the desired $\beta$-keto acetal mixed with the enol ether byproduct. Fraction (Fr.) weights and percent $\beta$-keto acetal (as determined from $^1$H NMR analysis): Fr. 1 (11.7 g, 91%); Fr. 2 (13.1 g, 83%); Fr. 3 (6.4 g, 67%); Fr. 4 (3.2 g, 26%). Fractions 1−3 were combined (31.1 g total; 25.7 g or 82% of the $\beta$-keto acetal **9**) and used in the next reaction without further purification. Analytical samples were obtained by carrying out repeated fractionated distillations: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.08 (d, 3H), 2.18 (s, 3H), 2.86−2.91 (m, 1H), 3.34 (s, 3H), 3.35 (s, 3H), 4.41 (d, 1H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 12.3, 30.1, 49.6, 52.9, 55.4, 106.0; HRMS *m*/*z* calcd for $C_7H_{14}O_3$ 146.0943, found 146.0935. Anal. Calcd for $C_7H_{14}O_3$: C, 57.50; H, 9.66. Found: C, 57.25; H, 9.62.

**Methyl 3,4-Dimethyl-2-carboxyfuran (11).** Anhydrous diethyl ether (70 mL) and 1,1,1,3,3,3-hexamethyldisilazane (98% pure) (37.7 mL, 0.175 mol) were combined in an oven-dried, 500 mL, three-neck RBF equipped with a magnetic stir bar, reflux condenser, and argon inlet. A solution of 1.6 M *n*-butyllithium (*n*-BuLi) in hexanes (110 mL, 0.175 mol) was added via syringe at a rate sufficient to maintain a gentle reflux. After the addition was complete, the solution was heated at reflux for 0.5 h. Then, after the solution was cooled to room temperature, the solvents were removed under aspirator vacuum. The remaining white solid was dissolved in dry THF (125 mL) and stirred in a dry ice/acetone bath. Methyl bromoacetate (97% pure) (17.1 mL, 0.175 mol), dissolved in dry THF (35 mL), was then added dropwise to this chilled, amide-containing THF solution over 20 min. The resulting solution was stirred for an additional 10 min in the cooling bath. After this time, a solution of **9** (25.6 g, 0.175 mol) in THF (35 mL) was added over 20 min with continued cooling. The orange solution obtained as a result of this addition was stirred in the dry ice/acetone bath with the bath and the solution allowed to warm to approximately −10 °C over 3 h. The solution was then stirred at room temperature for an additional 1 h. The resulting dark brown solution was then poured into an ice−water/diethyl ether mixture (600 mL; 1:1). The two phases were separated from each other, and the aqueous layer was extracted three times with 200 mL portions of diethyl ether. The organic layers were combined and washed once with aqueous 10% HCl and twice with a brine solution, and the remaining solvent was then removed using a rotary evaporator. This gave a yellow oil that was distilled under high vacuum (0.5 mmHg), keeping the bath temperature below 70 °C. Once all the unreacted starting materials were removed, the still pot and the crude glycidic ester that remained in it were heated to 180 °C. This resulted in the production and distillation of methanol. Once the distillation head temperature dropped below 50 °C, the RBF was removed from the oil bath and allowed to cool. The dark oil that remained was then distilled under high vacuum with the fraction boiling at 49 °C/0.15 mmHg being collected. This gave 9.7 g of **11** (36% yield) in >93% purity. An analytical sample was obtained by column chromatography using silica gel as the solid support and 17% ethyl acetate in hexanes as the eluent. For **11**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.96 (s, 3H), 2.26 (s, 3H), 3.88 (s, 3H), 7.26 (s, 1H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 7.8, 9.3, 51.3, 123.0, 131.4, 140.0, 141.9, 160.0; HRMS *m*/*z* calcd for $C_8H_{11}O_3$ 155.0708, found 155.0697. Anal. Calcd for $C_8H_{11}O_3$: C, 62.33; H, 6.54. Found: C, 62.21; H, 6.50.

**Methyl 5-Formyl-3,4-dimethylfuran-2-carboxylate (13).** Dry DMF (32 mL) was placed in an oven-dried RBF equipped with an argon inlet and a magnetic stirrer. The DMF was cooled in an ice−water bath while phosphorus oxychloride ($POCl_3$) (12.8 mL, 0.137 mol) was added portionwise. After the addition was complete, the pink solution was removed from the bath, and dichloroethane (55 mL) was added. The resulting solution was placed back into the ice−water bath as furan **11** (10.6 g, 0.0686 mol) dissolved in a second portion of dichloroethane (55 mL) was added dropwise over 15 min. After the addition, the resulting bright red solution was allowed to come to room temperature and then set to reflux for 5 h. After the reflux period, the solution was brought to room temperature and then cooled in an ice water bath as a concentrated aqueous sodium acetate solution (100 mL) was added dropwise. This two-phase mixture was heated at reflux for 30 min and then allowed to cool. The organic layer was

(22) Sessler, J. L.; Gebauer, A.; Hoehner, M. C.; Lynch, V. Submitted to *J. Am. Chem. Soc.*

separated off, and the aqueous layer was extracted four times (600 mL total) with dichloromethane. All the organic layers were combined and washed with aqueous 10% HCl (four times; 700 mL total) and then with brine (1 × 175 mL). The resulting brown organic solution was then dried over sodium sulfate and placed on a rotary evaporator to remove the solvents. Hexanes (25 mL) were added to the resulting brown oil, and the mixture was cooled in an ice water bath while crystallization was induced with a glass rod. The resulting dark solid was dissolved in hot hexanes (175 mL), giving a small amount of an immiscible oil. The hexane solution was decanted from the oil and allowed to cool, resulting in a powdery, yellow precipitate that was filtered and rinsed with cold hexanes. A second crop was obtained by removing the solvents from the filtrate and cooling the oil that remained. The solid that formed was dissolved in dichloromethane and passed through a glass frit containing 17.5 g of silica gel using so-called flash conditions. The resulting filtrate was taken to dryness using a rotary evaporator, giving an orange oil that solidified upon cooling. To remove the small amount of starting furan from both the first and second crops, both crops were combined with 70 mL of pentane and heated at reflux for 10 min. The resulting solution was allowed to cool, first to room temperature, and then in an ice−water bath. The solids obtained by this procedure were collected by filtration and rinsed with cold pentane to give product **13** (7.38 g, 59%) as a tan solid: mp 65−68 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.29 (s, 3H), 2.31 (s, 3H), 3.93 (s, 3H), 9.86 (s, 1H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 8.6, 9.0, 52.1, 132.2, 132.4, 142.3, 148.2, 159.5, 180.2; HRMS *m/z* calcd for $C_9H_{11}O_4$ 183.0657, found 183.0660. Anal. Calcd for $C_9H_{11}O_4$: C, 59.34; H, 5.53. Found: C, 59.05; H, 5.59.

**2,5-Bis(hydroxymethyl)-3,4-dimethylfuran (14).** A 1 M solution of $LiAlH_4$ in THF (100 mL) was placed in a dry 500 mL RBF under an argon atmosphere. This solution was then stirred at room temperature in a water bath as **13** (6 g, 0.033 mol) dissolved in THF (70 mL) was added dropwise over 30 min. The resulting solution was allowed to stir at room temperature for 3 h. The reaction was then cooled in an ice−water bath and quenched via careful addition of water (100 mL). After the water addition, a dilute sodium hydroxide solution (100 mL) was added, resulting in a white precipitate that was filtered off and washed first with water and then with copious amounts of dichloromethane. The aqueous layer of the filtrate was separated off and extracted with copious amounts of dichloromethane. All of the organic phases were then combined and washed once with aqueous 10% HCl and once with brine prior to being dried over sodium sulfate. After drying, the solvents were removed using a rotary evaporator to give an orange oil, **14** (3.9 g, 76%), that solidified upon cooling: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.92 (s, 6H), 2.60 (bs, 2H), 4.50 (s, 4H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 8.1, 55.3, 118.8, 148.2; HRMS *m/z* calcd for $C_8H_{12}O_3$ 156.0786, found 156.0781. Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.26; H, 7.69.

**2,5-Bis(acetoxymethyl)-3,4-dimethylfuran (15).** The furan dialcohol **14** (3.0 g, 0.0192 mol) was placed in a 250 mL RBF equipped with a magnetic stirrer. First THF (125 mL) and then pyridine (4.3 mL, 0.0532 mol) were added. The solution was cooled in an ice−water bath and acetyl chloride (3.7 mL, 0.052 mol) subsequently added. The reaction flask was removed from the ice−water bath and stirred at room temperature for 4 h. Then a solution of aqueous concentrated sodium bicarbonate (100 mL) was added portionwise. The resulting two-phase solution was separated and the aqueous layer extracted twice with dichloromethane. The combined organic layers were washed twice with aqueous 5% HCl, once with saturated, aqueous sodium bicarbonate and once with brine. The organic solution was dried over sodium sulfate and the solvent removed using a rotary evaporator to give a brown oil, **15** (4.6 g, 99%), which solidified upon cooling. The $^1$H NMR spectrum of this material showed it to be >98% pure, and it was, therefore, used in the next reaction step without further purification. For analysis, a purified sample was obtained via column chromatography using silica gel as the solid support and dichloromethane as the eluent. For **15**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.96 (s, 6H), 2.06 (s, 6H), 5.00 (s, 4H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 8.2, 20.8, 56.5, 121.7, 144.8, 170.7; HRMS *m/z* calcd for $C_{12}H_{17}O_5$ 241.1076, found 241.1074. Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 60.07; H, 6.73.

**3,4-Dimethyl-2,5-bis[[5-(benzyloxycarbonyl)-4-ethyl-3-methylpyrrol-2-yl]methyl]furan (16).** Diacetoxy furan **15** (3.0 g, 0.125 mol) and benzyl 3-ethyl-4-methylpyrrole-2-carboxylate[8] (6.1 g, 0.025 mol) were combined in a 500 mL RBF and dissolved in nitromethane (145 mL). The clear yellow solution was heated to 50 °C and *p*-toluenesulfonic acid monohydrate (1.5 g, 0.0079 mol) added. The solution was stirred at 50 °C for 4 h, at which time saturated aqueous sodium bicarbonate (100 mL) was added. The resulting two-phase mixture was separated and the aqueous layer extracted (1 × 100 mL) with dichloromethane. The organic layers were combined and washed (1 × 100 mL) with brine and dried over sodium sulfate. Solvents were removed using a rotary evaporator to afford a black/brown oil. The oil was placed under high vacuum under which conditions the oil solidified after approximately 5 min. Purification of the sticky solid was accomplished by column chromatography using silica gel that was pretreated with anhydrous ammonia as the solid support and dichloromethane as the eluent. After one column (6 cm × 17 cm), 3.3 g (43%) of **16** was obtained in >98% purity. This was used in the ensuing cyclizations without further purification. An analytical sample, however, was obtained as the result of a second chromatographic purification made using the above conditions: TLC reference (silica gel, 100% dichloromethane eluent) $R_f$ pyrrole = 0.62, $R_f$ **15** = 0.38, $R_f$ **16** = 0.49; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.10 (t, 6H), 1.83 (s, 6H), 1.96 (s, 6H), 2.75 (q, 4H), 3.77 (s, 4H), 5.28 (s, 4H), 7.30−7.41 (m, 10H), 8.57 (bs, 2H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 8.3, 8.5, 15.1, 18.5, 23.4, 65.4, 116.3, 116.9, 127.9, 128.4, 130.0, 134.4, 136.7, 144.6, 161.1; HRMS *m/z* calcd for $C_{38}H_{42}N_2O_5$ 606.3094, found 606.3093. Anal. Calcd for $C_{38}H_{42}N_2O_5 \cdot H_2O$: C, 73.05; H, 7.10; N, 4.48. Found: C, 73.07; H, 6.83; N, 4.46.

**2-Methyl-3-oxo-1,1-dimethoxypentane (10).** Sodium methoxide (54 g, 1 mol) was weighed into an oven-dried 1 L, three-neck RBF equipped with a mechanical stirrer, reflux condenser, and an addition funnel. The RBF was cooled in an ice−water bath, and methyl formate (557 g, 9.28 mol) was added via an addition funnel over 10 min. The resulting thick slurry was stirred at room temperature for 10 min, after which time 3-pentanone (86 g, 1 mol) was added over 10 min. The nonhomogeneous solution was set to reflux for 2 h. During the reflux period, dry HCl gas (38.9 g, 1.08 mol) was dissolved in dry methanol (226 mL, 5.59 mol) and the solution placed in a 2 L, three-neck RBF equipped with a mechanical stirrer and an argon inlet. After the reflux period, the methyl formate slurry was cooled to room temperature and then added portionwise over 20 min to the HCl/methanol solution, which was being cooled in an ice−water bath. After the addition was complete, the mixture was stirred at room temperature under argon for 18 h. To neutralize the solution, sodium methoxide (14 g, 0.26 mol) was dissolved in methanol (200 mL) and added portionwise to the reaction until the pH of the reaction mixture was between 6 and 7. The resulting salts were filtered and washed with dichloromethane, and the filtrate was placed on a rotary evaporator to remove all solvents. The remaining oil was vacuum distilled using a 30 cm fractional distillation column. Six fractions were taken that distilled between 30 and 36 °C/0.4−0.6 mmHg. Proton NMR spectral analysis indicated that the first five fractions (98.4 g total) contained between 98% and 80% pure **10**. Fraction 6 (10.1 g; <20% of the total yield) was discarded, and fractions 1−5 were combined to afford 98.4 g of **10** that was >95% pure as judged by $^1$H NMR spectral analysis. This material was carried on in the synthesis of **12**, while analytical samples were obtained by performing a second fractional distillation: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.00−1.07 (m, 6H), 2.49 (m, 2H), 2.89 (m, 1H), 3.34 (s, 6H), 4.39 (d, 1H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 7.4, 12.6, 36.3, 48.7, 52.7, 55.6, 106.3; HRMS *m/z* calcd for $C_8H_{16}O_3$ 160.1100, found 160.1099. Anal. Calcd for $C_8H_{16}O_3$: H, 10.07; C, 59.96. Found: H, 10.02; C, 60.03.

**Methyl 3-Ethyl-4-methylfuran-2-carboxylate (12).** Anhydrous diethyl ether (110 mL) and 1,1,1,3,3,3-hexamethyldisilazane (66 mL, 0.313 mol) were combined in an oven-dried,

1 L, three-neck RBF equipped with a magnetic stir bar, reflux condenser, and an argon inlet. A solution of 1.6 M *n*-butyllithium in hexanes (195 mL, 0.313 mol) was added via syringe at a rate sufficient to maintain a gentle reflux. After the addition was complete, the solution was set to reflux for 0.5 h. After this time, the solvents were removed under aspirator vacuum to give a white solid. This solid was dissolved in dry THF (200 mL) and stirred in a dry ice/acetone bath. Once cool, methyl bromoacetate (29.6 mL, 0.313 mol), dissolved in dry THF (60 mL), was added over the course of 20 min. The resulting thick, yellow mixture was stirred an additional 10 min in the cooling bath before **10** (50 g, 0.313 mol), dissolved in dry THF (60 mL), was added over a period of 15 min with continued cooling. After the addition was complete, the reaction was stirred in the cooling bath while being allowed to warm to approximately −10 °C over a period of 3 h. The reaction was then stirred at room temperature for an additional 1 h. The resulting orange-colored solution was poured into an ice−water/diethyl ether mixture (1000 mL; 1:1). The two-phase solution that resulted was separated and the aqueous layer extracted three times with diethyl ether (600 mL total). The combined organic layers were washed once with aqueous 10% HCl and twice with an aqueous brine solution. This solution was dried over sodium sulfate, and the solvent was removed using a rotary evaporator to give an orange oil that was subjected to distillation under high vacuum with the heating bath not exceeding 70 °C. This served to remove unreacted **10** and enol ether. After this operation, the dark oil that remained in the still pot was heated to 180 °C, resulting in the distillation of methanol. The RBF was removed from the heating bath after the distillation head temperature dropped below 50 °C. The oil remaining in the still pot was allowed to cool and subjected anew to vacuum distillation with the fraction boiling between 45 and 50 °C/0.025−0.05 mmHg being collected. Proton NMR spectral analysis confirmed that this fraction (13.9 g, 28%) was product **12** that was at least 95% pure. This material was carried on in the subsequent reactions. Analytical samples were obtained by column chromatography using silica gel and 17% ethyl acetate in hexanes: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.14 (t, 3H), 1.99 (s, 3H), 2.75 (q, 2H), 3.88 (s, 3H), 7.26 (s, 1H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 7.7, 14.0, 17.3, 51.4, 122.4, 137.4, 139.5, 142.1, 159.8; HRMS *m*/*z* calcd for $C_9H_{13}O_3$ 169.0865, found 169.0868. Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.18; H, 7.22.

**Methyl 2-Bromo-4-ethyl-3-methylfuran-2-carboxylate (18).** Furan **12** (4.0 g, 0.024 mol) was placed in a dry 100 mL RBF and dissolved in dry dimethylformamide (DMF, 10 mL). A second portion of dry DMF (10 mL) was placed in a 25 mL RBF and cooled in a dry ice/acetone bath under argon. Bromine (2.5 mL, 0.048 mol) was added dropwise to the latter portion of cooled DMF via an addition funnel and with stirring. As the addition progressed, the solution solidified. The reaction flask was then allowed to warm until this solid dissolved and a homogeneous solution was produced. This solution was placed in an addition funnel in portions and added dropwise with stirring to the original furan/DMF solution still at room temperature. After all of the $Br_2$/DMF had been added (ca. 1 h), the reaction was allowed to stir at room temperature for an additional 2 h. The resulting dark red solution was extracted eight times with a total of about 400 mL of 8.5% ethyl acetate in hexanes. The ethyl acetate/hexane solution was reduced to an orange oil by use of a rotary evaporator. This oil was distilled under high vacuum (ca. 0.5 mmHg). The fractions collected consisted sequentially of (1) DMF; (2) furan, **12**; and finally (3) bromofuran, **18** (4.3 g, 74%, boiling point: 85 °C/0.1 mmHg). Analytical samples were obtained by column chromatography using silica gel as the solid support and 17% ethyl acetate in hexanes as the eluent: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.13 (t, 3H), 1.95 (s, 3H), 2.77 (q, 2H), 3.87 (s, 3H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 8.7, 13.9, 18.0, 51.6, 122.3, 125.3, 139.0, 140.7, 158.9; HRMS *m*/*z* calcd for $C_9H_{12}O_3Br$: 246.9970, found 246.9960. Anal. Calcd for $C_9H_{11}O_3Br$: C, 43.75; H, 4.49. Found: C, 43.65; H, 4.52.

**Dimethyl 4,4′-Diethyl-3,3′-dimethyl-2,2′-bifuran-5,5′-dicarboxylate (19).** Bromofuran **18** (14.6 g, 0.0591 mol) and bis(tributyltin) (34.3 g, 0.0591 mol) were combined in an oven-dried 250 mL RBF equipped with an argon inlet, magnetic stir bar, and reflux condenser. Distilled toluene (450 mL) was added and the clear, yellowish solution stirred at room temperature while argon was bubbled through the solution for approximately 10 min. Tetrakis(triphenylphosphine)-palladium (1.2 g, 1 mmol) was added, and the solution was set to reflux while keeping it under argon atmosphere. The solution was heated at reflux for 48 h and then allowed to cool to room temperature. Once cool, the dark solution was filtered through Celite. The solvent was then removed using a rotary evaporator to give a dark solid. Hexanes were added to this solid and then filtered to give **19** (5.35 g, 54%). A second crop was obtained by removing the solvent from the hexanes filtrate and placing the oil in the freezer for 48 h. The solid that formed was filtered and rinsed with cold hexanes to give an additional 0.78 g of **19**: mp 157−160 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.13 (t, 6H), 2.26 (s, 6H), 2.75 (q, 4H), 3.87 (s, 6H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 8.5, 14.1, 17.4, 51.5, 121.4, 138.4, 138.8, 144.2, 159.8; HRMS *m*/*z* calcd for $C_{18}H_{22}O_6$ 334.1416, found 334.1418. Anal. Calcd for $C_{18}H_{22}O_6$: H, 6.64; C, 64.64. Found: H, 6.69; C, 64.36.

**5,5′-Bis(hydroxymethyl)-4,4′diethyl-3,3′-dimethyl-2,2′-bifuran (20).** Lithium aluminum hydride (LAH, 3.5 g, 0.0922 mol) was weighed out in an oven-dried 1000 mL RBF. Dry THF (325 mL) was placed in an addition funnel and added dropwise to the LAH while the reaction flask was being cooled in an ice−water bath. Bifuran **19** (3.0 g, 9 mmol) was then dissolved in dry THF (170 mL), placed in an addition funnel, and added dropwise to the above LAH/THF mixture. After the addition was complete, the reaction was allowed to stir at room temperature for 0.5 h and then heated at reflux for 1 h. The solution was allowed to cool to room temperature in the air and then cooled further in an ice−water bath. The reaction was carefully quenched with water (75 mL), and then a 1 M aqueous NaOH solution (75 mL) was added. The white solid that formed as the result of the sodium hydroxide addition was filtered off and washed first with water and then copious amounts of dichloromethane. The two-phase filtrate was separated and the aqueous layer extracted five times with dichloromethane. The combined organic layers were washed one time with an aqueous brine solution and dried over sodium sulfate. The solvent was removed using a rotary evaporator to give a cream-colored solid that was taken up in hexanes and filtered to give methylethylbifuran dialcohol **20** (2.3 g, 94%): mp > 270 °C dec; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.14 (t, 6H), 2.12 (s, 6H), 2.43 (q, 4H), 4.59 (s, 4H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 9.0, 15.3, 16.7, 55.8, 118.4, 126.1, 141.6, 148.0; HRMS *m*/*z* calcd for $C_{16}H_{22}O_4$ 278.1518, found 278.1525. Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.92; H, 7.93.

**4,4′-Diethyl-5,5′-diformyl-3,3′-dimethyl-2,2′-bifuran (21).** The bifuran dialcohol **20** (2.3 g, 0.0084 mol) was placed in a 500 mL RBF under a nitrogen atmosphere. Dry dichloromethane (250 mL) was added and the solution stirred at room temperature for 6 h during which time $MnO_2$ (24 g, 0.2760 mol) was added portionwise. After the addition was complete, the solution was set to reflux for 18 h. The resulting dark mixture was filtered through Celite to give a clear, orange-tinted solution. The solvent was removed using a rotary evaporator. This produced a brown solid that was dissolved in a minimum of hot dichloromethane. Hexanes were added, and the resulting dark solution was placed on a rotary evaporator. The solvents were removed until a yellow solid started to precipitate, at which time more hexanes (ca. 50 mL) were added and the mixture placed in the freezer overnight. The solid that formed was filtered and rinsed with cold hexanes to give **21** (1.38 g, 60.4%): mp 128−130 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.22 (t, 6H), 2.35 (s, 6H), 2.79 (q, 4H), 9.76 (s, 2H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 8.5, 14.6, 16.6, 123.0, 141.1, 146.1, 147.4, 177.3; HRMS *m*/*z* calcd for $C_{16}H_{19}O_4$ 275.1283, found 275.1286. Anal. Calcd for $C_{16}H_{18}O_4$: H, 6.62; C, 70.04. Found: H, 6.67; C, 69.77.

**3,7,18,22-Tetraethyl-2,8,12,13,17,23-hexamethyl-27-oxasapphyrin (5).** The oxatripyrrane **16** (0.323 g, 5.3 mmol) was placed in a 250 mL RBF along with 10% palladium on

carbon (0.2 g), triethylamine (4 drops), and THF (150 mL). A hydrogen atmosphere was introduced at atomospheric pressure and the solution stirred at room temperature for 24 h protected from light. The resulting solution was filtered through Celite with the Celite being rinsed with THF. The solvent was removed with the aid of a rotory evaporator to give the oxatripyrrane dicarboxylic acid **17** as a brown film in the RBF. Diformylbipyrrole **3** (0.145 g, 5.3 mmol) was placed in a 2 L RBF and dissolved in methanol (100 mL). Once **3** had dissolved, chloroform (900 mL) was added to the 2 L RBF while a second portion of chloroform (100 mL) was used to dissolve **17**. This latter solution was combined with the chloroform/methanol/**3** solution with concentrated aqueous HCl (10 drops) then being added. The solution was stirred open to air, protected from light for 6 h after which the 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (1 equiv) was added. After this solution was stirred for 10 min, the solvents were removed from the reaction mixture giving a dark green film in the RBF. The crude sapphyrin was purified by column chromatography using silica gel as the solid phase and a dichloromethane/trifluoroacetic acid (TFA)/methanol gradient as the mobile phase. Fractions that contained the sharp absorption band at 450 nm were combined and crystallized using chloroform layered with hexanes to afford the oxasapphyrin **5** (0.153 g, 27%) as metallic blue needles. By washing a chloroform solution of **5b** (the bis(TFA) salt) with aqueous 1 M NaOH (3 × 50 mL) and then with aqueous 10% HCl (3 × 50 mL) the dihydrochloride salt was obtained. This salt was also crystallized as blue metallic needles by dissolving **5a** in a small amount of chloroform that was then layered with hexanes. **5b**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −4.12 (bs, 2H), −2.99 (bs, 2H), 2.10 (t, 6H), 2.21 (t, 6H), 4.04 (s, 6H), 4.19 (s, 6H), 4.29 (s, 6H), 4.45 (q, 4H), 4.66 (q, 4H), 11.40 (s, 2H), 11.65 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 12.7, 13.4, 15.3, 17.6, 17.9, 20.7, 21.2, 89.3, 101.2, 127.4, 130.9, 131.2, 132.3, 134.6, 136.3, 138.8, 142.6, 145.2, 150.6; HRMS *m/z* calcd for $C_{38}H_{45}N_4O$ 573.3593, found 573.3585.

**3,8,12,13,17,22-Hexaethyl-2,7,18,23-tetramethyl-25,29-dioxasapphyrin (6).** The oxasapphyrin **6** was synthesized using the same procedure used to prepare **5**. The following reagents amounts were used: Tripyrrane **2** (0.501 g, 0.8 mmol), 10% palladium on carbon (0.3 g), triethylamine (3 drops), THF (150 mL), and hydrogen (1 atm). Cyclization: Diformylbifuran **21** (0.207 g, 0.8 mmol), methanol (100 mL), chloroform (1300 mL), and concentrated aqueous concentrated HCl (10 drops). Purification was achieved by column chromatography using silica gel as the solid phase and a dichloromethane/TFA/methanol gradient as the mobile phase. Fractions that contained the sharp absorption band at 450 nm were combined, and solvents were removed. The metallic blue film that remained in the RBF was dissolved in a minimum amount of chloroform and then layered with hexanes. The dioxasapphyrin **6** (53 mg, 17.1%) crystallized as metallic blue needles. By washing a chloroform solution of of **6b** (bis(TFA) salt) with aqueous 1 M NaOH (3 × 50 mL) and then with aqueous 10% HCl (3 × 50 mL), the dihydrochloride salt was obtained. This analogue was also crystalized as metallic blue needles by dissolving **6a** in a small amount of chloroform and layering with hexanes. For **6b**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −4.08 (bs, 2H), −3.11 (bs, 1H), 2.15 (t, 6H), 2.20−2.29 (m, 12H), 4.16 (s, 6H), 4.27 (s, 6H), 4.62−4.74 (m, 12H), 11.65 (s, 2H), 11.78 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$/$CD_3OD$) $\delta$ 12.8, 15.4, 16.8, 17.6, 18.3, 20.8, 21.0, 21.1, 94.3, 97.8, 133.1, 134.8, 137.5, 137.9, 140.0, 144.6, 145.4, 145.9, 146.2, 147.9; HRMS *m/z* calcd for $C_{40}H_{48}N_3O_2$ 602.3747, found 602.3737.

**3,7,18,22-Tetraethyl-2,8,12,13,17,23-hexamethyl-25,27,29-trioxasapphyrin (7).** The trioxasapphyrin **7** was synthesized using the same procedure used to prepare **6**. The following reagents and amounts were used: oxatripyrrane **16** (0.349 g, 0.6 mmol), 10% palladium on carbon (0.2 g), triethylamine (3 drops), THF (150 mL), and hydrogen (1 atm). Cyclization: Diformylbifuran **21** (0.158 g, 0.6 mmol), methanol (50 mL), chloroform (1000 mL), and concentrated aqueous concentrated HCl (10 drops). Purification was achieved by column chromatography using silica gel as the solid phase and a dichloromethane/TFA/methanol gradient as the mobile phase. Fractions that contained the sharp absorption band at 450 nm were combined and solvents removed giving a metallic blue film in the RBF. This material was purified twice more using the same conditions as above to afford the trioxasapphyrin **7** (0.167 g, 29%) as a metallic blue solid. For **7b**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −2.9 (bs, 2H), 2.06 (t, 12H), 4.08 (s, 6H), 4.10 (s, 6H), 4.18 (s, 6H), 4.50−4.63 (m, 8H), 11.29 (s, 2H), 11.57 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 12.7, 13.1, 14.9, 16.6, 17.5, 20.8, 21.0, 91.2, 99.3, 133.5, 134.1, 138.6, 139.3, 142.4, 146.2, 146.8, 147.7, 148.0, 152.2; HRMS *m/z* calcd for $C_{38}H_{44}N_2O_3$ 576.3352, found 576.3345.

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**Supporting Information Available:** Tables of crystallographic data collection procedures and parameters, complete atomic coordinates and thermal parameters, bond distances and angles, torsion angles, and least-squares planes (99 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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