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Design, Synthesis, and Photophysical Characterization of Water-Soluble Chlorins

K. Eszter Borbas,[†] Vanampally Chandrashaker,[†] Chinnasamy Muthiah,[†] Hooi Ling Kee,[‡] Dewey Holten,*[,‡] and Jonathan S. Lindsey*[,†]

Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27695-8204, and Department of Chemistry, Washington University, St. Louis, Missouri 63130-4889

jlindsey@ncsu.edu; holten@wustl.edu

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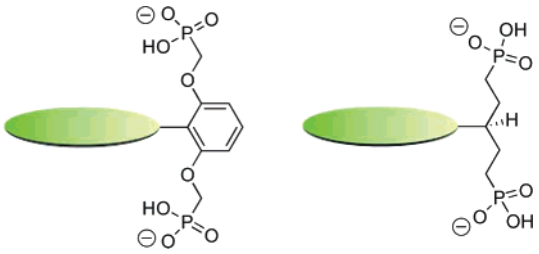

The use of chlorins as photosensitizers or fluorophores in a range of biological applications requires facile provisions for imparting high water solubility. Two free base chlorins have been prepared wherein each chlorin bears a geminal dimethyl group in the reduced ring and a water-solubilizing unit at the chlorin 10-position. In one design (**FbC1-PO$_3$H$_2$**), the water-solubilizing unit is a 1,5-diphosphonopent-3-yl ("swallowtail") unit, which has previously been used to good effect with porphyrins. In the other design (**FbC2-PO$_3$H$_2$**), the water-solubilizing unit is a 2,6-bis(phosphonomethoxy)phenyl unit. Two complementary routes were developed for preparing **FbC2-PO$_3$H$_2$** that entail introduction of the protected phosphonate moieties either in the Eastern-half precursor to the chlorin or by derivatization of an intact chlorin. Water-solubilization is achieved in the last step of each synthesis upon removal of the phosphonate protecting groups. The chlorins **FbC1-PO$_3$H$_2$** and **FbC2-PO$_3$H$_2$** are highly water-soluble (>10 mM) as shown by ^{1}H NMR spectroscopy (D_2O) and UV−vis absorption spectroscopy. The photophysical properties of the water-soluble chlorins in phosphate-buffered saline solution (pH 7.4) at room temperature were investigated using static and time-resolved absorption and fluorescence spectroscopic techniques. Each chlorin exhibits dominant absorption bands in the blue and the red region (λ = 398, 626 nm), a modest fluorescence yield ($\Phi_f \approx 0.11$), a long singlet excited-state lifetime (τ = 7.5 ns), and a high yield of intersystem crossing to give the triplet state (Φ_{isc} = 0.9). The properties of the water-soluble chlorins in aqueous media are comparable to those of hydrophobic chlorins in toluene. The high aqueous solubility combined with the attractive photophysical properties make these compounds suitable for a wide range of biomedical applications.

Introduction

A large number of areas of photomedicine and clinical diagnostics can benefit from the availability of porphyrinic molecules that are suitably tailored with regard to photochemical attributes, solubility, and tethers for coupling to other molecules. The chief applications encompass photodynamic therapy,[1] optical imaging,[2] flow cytometry,[3] and combinatorial barcoding.[4] One particular challenge has entailed rendering the large, hydrophobic tetrapyrrole macrocycles soluble in aqueous media. A handful of naturally occurring porphyrins have moderate

[†] North Carolina State University.
[‡] Washington University.

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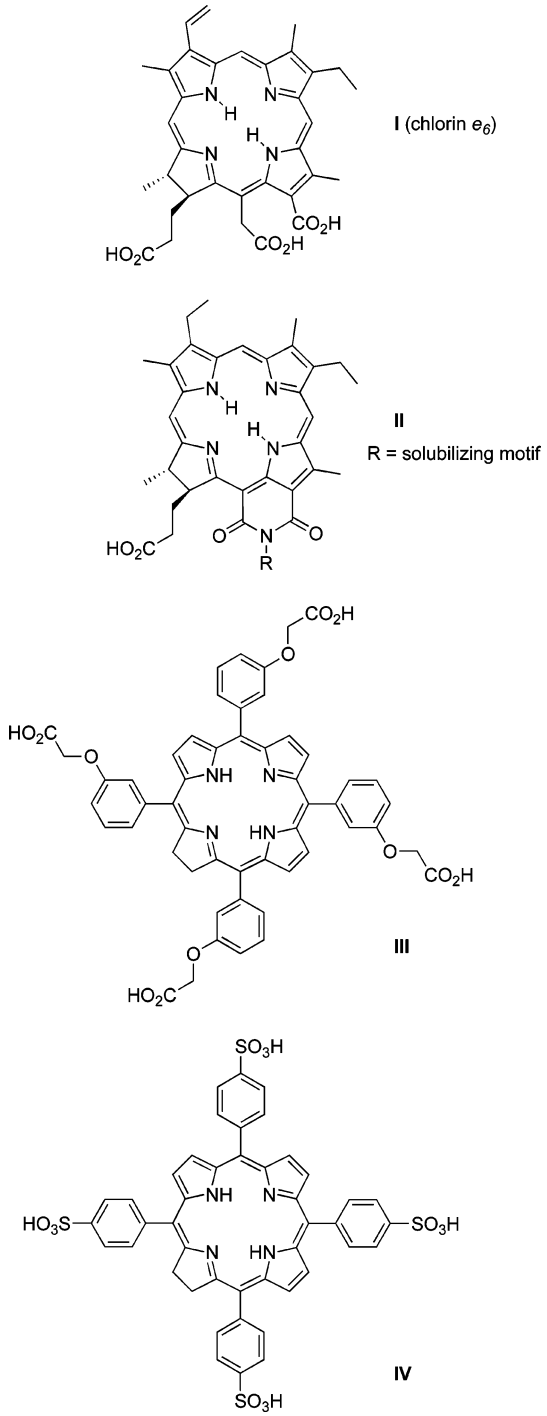
aqueous solubility, but the presence of a full complement of functional groups renders selective synthetic modification rather difficult. Synthetic porphyrins offer the possibility of gaining control over the substitution pattern. Traditional approaches for imparting water solubility to synthetic porphyrins have relied on sulfonation of meso-aryl substituents or quaternization of meso-pyridyl groups.[5] Although modestly water-soluble, many such compounds still tend to aggregate and precipitate from solution over time.

A second challenge lies in the use of porphyrinic compounds that absorb strongly in the red or near-infrared region of the spectrum. The red or infrared region is of great interest owing to the deep tissue penetration afforded by light in this spectral region,[6] and the availability of this comparatively underutilized spectral region for diverse labeling applications.[7] Chlorins and bacteriochlorins absorb strongly in the red and near-infrared regions, respectively.[8] However, water-soluble derivatives of chlorins and bacteriochlorins have generally not been available, though a number of naturally occurring compounds have polar side chains.[9] Chlorin e_6 (**I**)[10] is a readily accessible derivative of chlorophyll *a* and contains three ionizable carboxylic acid groups, one of which is thrust over the plane of one face of the molecule (Chart 1). The presence of three carboxylic acid groups along with substituents at nearly all the other peripheral positions of the macrocycle can impede synthetic manipulation, though a number of water-soluble analogues have been prepared.[11−13] Purpurinimides (**II**), which are also derived from chlorophylls, afford a single site for derivatization, but the designs employed to date have resulted in a hydrophobic macrocycle bearing an appended polar group.[14,15] Synthetic chlorins have typically relied on the presence of up to four substituted meso-aryl groups to impart polarity;[16−21] examples include chlorins **III**[17] and

CHART 1



IV[16,20] shown in Chart 1. Access to such synthetic chlorins typically entails reduction of the corresponding porphyrin.[22] To fulfill the promise of chlorins in photomedical applications, versatile and compact molecular designs are required that afford both water solubility and synthetic malleability.

Recently we reported the synthesis and characterization of a series of highly water-soluble porphyrins for applications in flow cytometry,[23,24] fluorescence imaging,[23,24] and molecular brachytherapy[25] (Figure 1). The macrocycles were equipped with a

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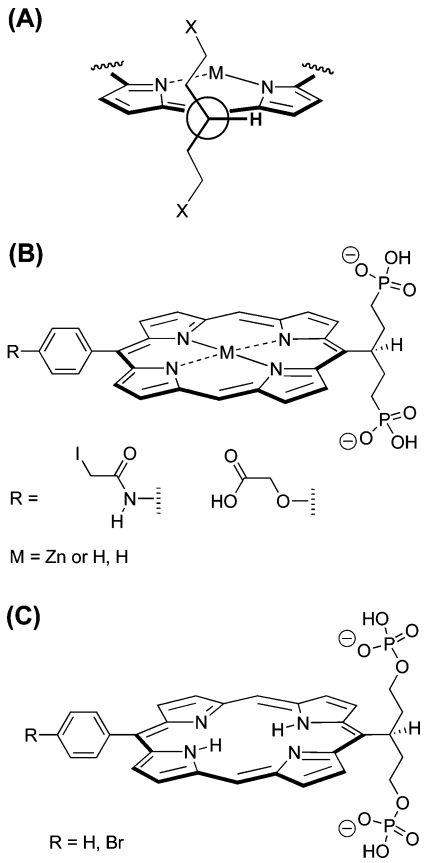

FIGURE 1. (A) Newman projection showing the alkyl chains of the swallowtail motif above and below the plane of the tetrapyrrole macrocycle. (B) Water-soluble porphyrin-alkyldiphosphonates prepared previously for bioconjugation.[23,24] (C) Water-soluble porphyrin-alkyl-diphosphates prepared for targeted molecular brachytherapy.[25]

symmetrically branched diphosphonate- or diphosphate-terminated alkyl chain ('swallowtail motif'), which resulted in solubility in pure water at concentrations of up to 20 mM. The origin of the high solubility stems from the projection of the alkyl groups above and below the plane of the macrocycle.[26] The alkyl groups block access to the π faces of the macrocycle; moreover, the polar terminal groups are ionized (phosphate or phosphonate) in aqueous media and are expected to suppress aggregation by electrostatic repulsion. The conformation of the swallowtail motifs with respect to the plane of the porphyrin macrocycle was established with EPR spectroscopy of porphyrin cation radicals (for hydrophobic swallowtail motifs),[26] and ^{1}H NMR spectroscopy and molecular modeling for the polar-terminated swallowtail derivatives.[23,24] The porphyrin-alkyl-diphosphonate solutions were found to be stable at room temperature for extended periods of time (>1 year) when shielded from light, and aggregation or precipitation was not observed.[23,24] A similar solubilizing unit bearing carboxylic acid termini was recently reported for bis- and tris-porphyrin arrays.[27] Only two chlorin-phosphonates have been reported previously, an analogue of deuteroporphyrin wherein the carboxylic acids have been replaced with phosphonic acids,[28] and a synthetic chlorin bearing a 4-phosphonophenyl unit at the chlorin 10-position.[29]

In this paper, we describe the synthesis of a chlorin bearing a phosphonate-terminated swallowtail motif. The chlorin macrocycle was synthesized by a route developed recently,[30] and makes use of a swallowtail-substituted dipyrromethane[24] that was employed in the synthesis of the analogous swallowtail porphyrins. The success of the diphosphonate-terminated swallowtail motif prompted the design of a diphosphonate-substituted aryl motif. The latter was investigated in an effort to achieve increased versatility of design and synthesis. Two routes were investigated for the synthesis of *meso*-2,6-bis(phosphonoalkoxy)-phenyl-substituted chlorins. The photophysical properties of chlorins of both types were investigated in aqueous solution to assess the potential of the chlorins for use in photomedical and diagnostic applications. Taken together, this work provides the foundation for the synthesis of water-soluble chlorins for a range of biological applications.

Results and Discussion

I. Molecular Design. The key design feature for both the swallowtail-chlorin and the aryl-chlorin is the positioning of nonhydrolyzable ionic groups (i.e., phosphonates) over both faces of the chlorin macrocycle. The objective for the aryl-chlorin was to identify a diphosphonate-substituted aryl unit that would behave comparably to the alkyl swallowtails but may be more accessible. Extensive use has been made of *o*-substituted meso-aryl groups to encumber one or both faces of porphyrins for solubilization in organic media[31,32] and to obtain receptors, catalysts and enzyme mimics.[33−35] Much less work has been devoted to meso-aryl groups bearing ionic groups appended to

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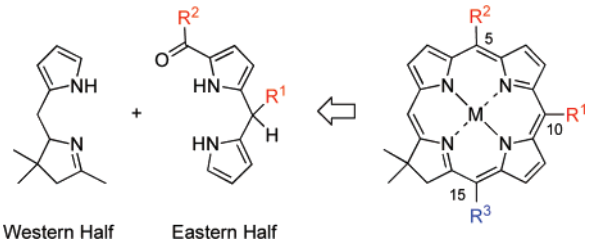
SCHEME 1

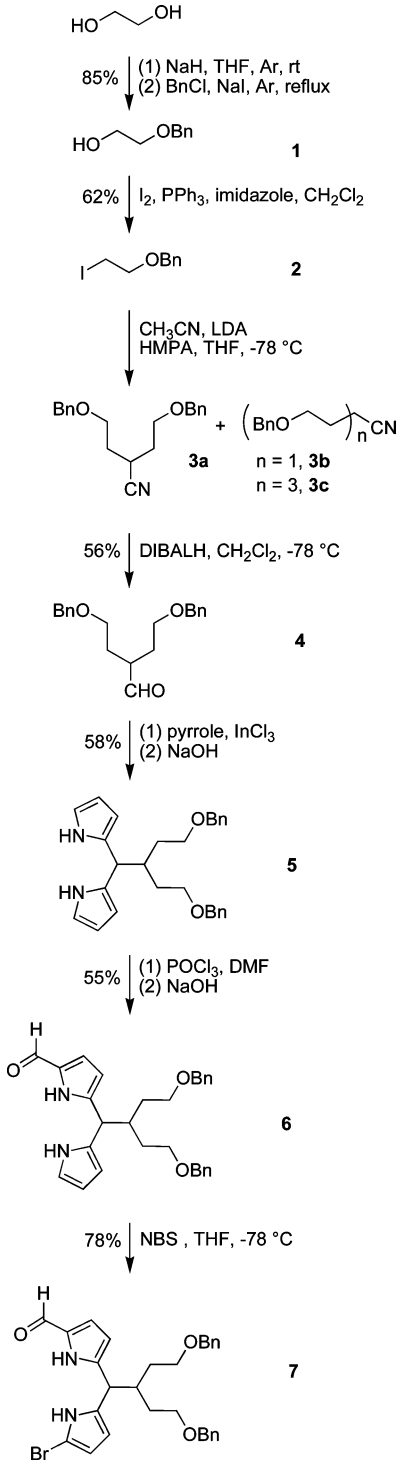


the 2- and 6-positions. Jux has employed the 2,6-bis(bromomethyl)-4-*tert*-butylphenyl unit at the four meso-positions of an A_4-porphyrin, which upon derivatization with 4-*tert*-butylpyridine gave the octa-pyridinium porphyrin.[36] Jux and co-workers extended this approach to include alkylation of the 2,6-bis(bromomethyl)-4-*tert*-butylphenyl unit in a *trans*-A_2B_2-porphyrin[37,38] or A_4-porphyrin[39] with diethyl malonate followed by saponification, thereby yielding a facially encumbered porphyrin bearing eight or sixteen carboxylate groups, respectively. Our prior success in achieving solubilization of a porphyrin upon use of a single diphosphonate-terminated swallowtail unit, and the attractive features of the Jux designs, prompted us to focus on a 2,6-bis(phosphonomethoxy)aryl unit. A key issue was whether a single such meso-aryl group also would impart the desired water solubility to the chlorin.

The swallowtail and aryl solubilizing units could be introduced most straightforwardly at the 10-position of the chlorins (Scheme 1). The 10-position is easily accessible during *de novo* chlorin synthesis given that the substituent is derived from an aldehyde via an intermediate dipyrromethane (Eastern half). In future designs, elaboration of the chlorin architecture can be achieved at the 5-position by use of a 1-acyldipyrromethane,[40] at the 15-position through electrophilic bromination followed by palladium coupling reactions,[41,42] or at other sites by preparation of substituted Eastern or Western halves.[43−45]

II. Synthesis. A. Swallowtail-Chlorins. We have previously reported the preparation of a swallowtail-aldehyde bearing TBDMS protecting groups for the terminal alcohol groups and application of the swallowtail-aldehyde in dipyrromethane synthesis.[23] It was expected that the TBDMS groups would not resist the acid catalysis conditions used in the chlorin-forming macrocyclization.[30] Therefore, a benzyl ether protecting group was investigated (Scheme 2). Selective protection of one

SCHEME 2



hydroxy function of ethylene glycol gave 2-benzyloxyethanol (**1**), which underwent OH → I exchange upon treatment with I_2/PPh_3/imidazole to give 2-benzyloxy-1-iodoethane (**2**). Both **1** and **2** are known compounds,[46] for which improved syntheses were recently reported[47] that are nearly identical to those we developed (see Supporting Information). Deprotonation of CH_3-CN with LDA followed by bis-alkylation with **2** was employed

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to obtain nitrile **3a**; however, the product obtained upon column chromatography contained di-, mono- and trialkylated nitriles **3a**, **3b** and **3c** in approximately 4:1:1 ratio, respectively, as shown by ^{1}H NMR analysis. The reduction of the mixture of nitriles in CH_2Cl_2 at −78 °C using DIBALH gave the desired aldehyde **4** in pure form after column chromatography.

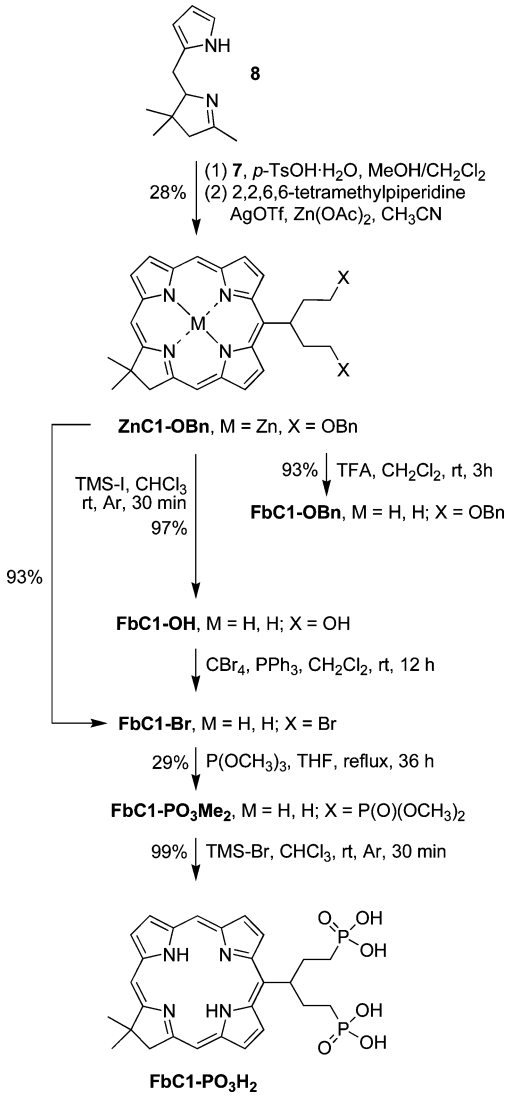
Treatment[48] of **4** with excess pyrrole in the presence of $InCl_3$ gave the 5-substituted dipyrromethane **5** in 58% yield after column chromatography. Vilsmeier formylation[49] of dipyrromethane **5** at 0 °C followed by workup with aqueous NaOH and chromatographic separation gave the 1-formyldipyrromethane **6** as a pale yellow oil in 55% yield. The facile separation enabled removal of the diformylated side-product without resort to use of dialkyl-tin complexation,[49,50] a process that is specific for the diformyl species. The simpler separation explains the superior yield of **6** compared to that of **10** (*vide infra*). Bromination of the remaining α-pyrrolic position following standard procedures [NBS, THF, −78 °C][30,43] afforded Eastern half **7** in excellent yield after column chromatography.

Eastern half **7** was condensed with unsubstituted tetrahydrodipyrrin **8**[51] in a two-step one-flask synthesis[30] to furnish bis(benzyloxy)swallowtail-chlorin **ZnC1-OBn** in 28% yield as a dark green solid after column chromatography on silica (Scheme 3). In some preparations, laser desorption mass spectrometry (LD-MS) and UV−vis analysis of the crude product showed the presence of unmetalated species, although the major product was always the zinc chlorin. The presence of small quantities of free base chlorin was not a problem given that quantitative demetalation occurs in the subsequent step of the synthesis, which entails cleavage of the benzyl protecting groups. Alternatively, uniform products could be obtained by remetalation with zinc acetate (in CH_2Cl_2/MeOH, 5:1, 18 h) or by demetalation with TFA in CH_2Cl_2 (1:2, 3 h). An example of the latter procedure yielding **FbC1-OBn** is shown in Scheme 3.

Cleavage of the benzyl protecting groups was initially attempted under hydrogenation conditions. However, direct hydrogenolysis (H_2, Pd/C) and catalytic transfer hydrogenation (NH_4HCO_2, THF, Pd/C) both proved sluggish and gave only partially deprotected products. Furthermore, partial reduction of the chlorin to give the bacteriochlorin was observed upon UV−vis absorption analysis of the reaction mixture. Quantitative and rapid debenzylation occurred upon treatment of **ZnC1-OBn** in dry $CHCl_3$ with excess TMS−I. After simple aqueous−organic workup, the product (**FbC1-OH**) was suitable for use in the subsequent step. Clean samples could be obtained upon chromatography either on neutral alumina or silica using CH_2Cl_2/MeOH as the eluent.

Hydroxy-bromine exchange following reported procedures[23,28] yielded the dibrominated chlorin **FbC1-Br** in excellent yield (93% yield over two steps from **ZnC1-OBn**). The Arbuzov reaction with $P(OCH_3)_3$ in THF (to ensure complete dissolution of **FbC1-Br**) provided chlorin-alkyldiphosphonate **FbC1-PO_3Me_2** in moderate yield. Straightforward cleavage of the methyl protecting groups was achieved by treatment of **FbC1-PO_3Me_2** with TMS−Br in dry $CHCl_3$ followed by neutralization with aqueous $NaHCO_3$. All methods for phosphonoester cleavage with trialkylsilyl halides stem from the seminal work of Rabinowitz[52] (for subsequent elaboration see ref 29 and 53). The resulting crude **FbC1-PO_3H_2** was obtained as a clear, dark green solution. Purification on C-18-modified silica followed by freeze-drying from water yielded **FbC1-PO_3H_2** as a dark green, voluminous solid.

SCHEME 3



B. Aryl-Chlorins. The target was a chlorin bearing a 2,6-diphosphonate-substituted aryl group at the 10-position. The first route relied on preparation of a dimethoxyphenyl-substituted chlorin, which is then transformed into the diphosphonate derivative. The second route entailed the preparation of the diphosphonate-substituted benzaldehyde, which carries the phosphonate groups (in protected form) through all steps leading to the chlorin. The latter route circumvents manipulations of the chlorin macrocycle, which are typically carried out at low concentrations and with small amounts of reactants. Both routes are described below.

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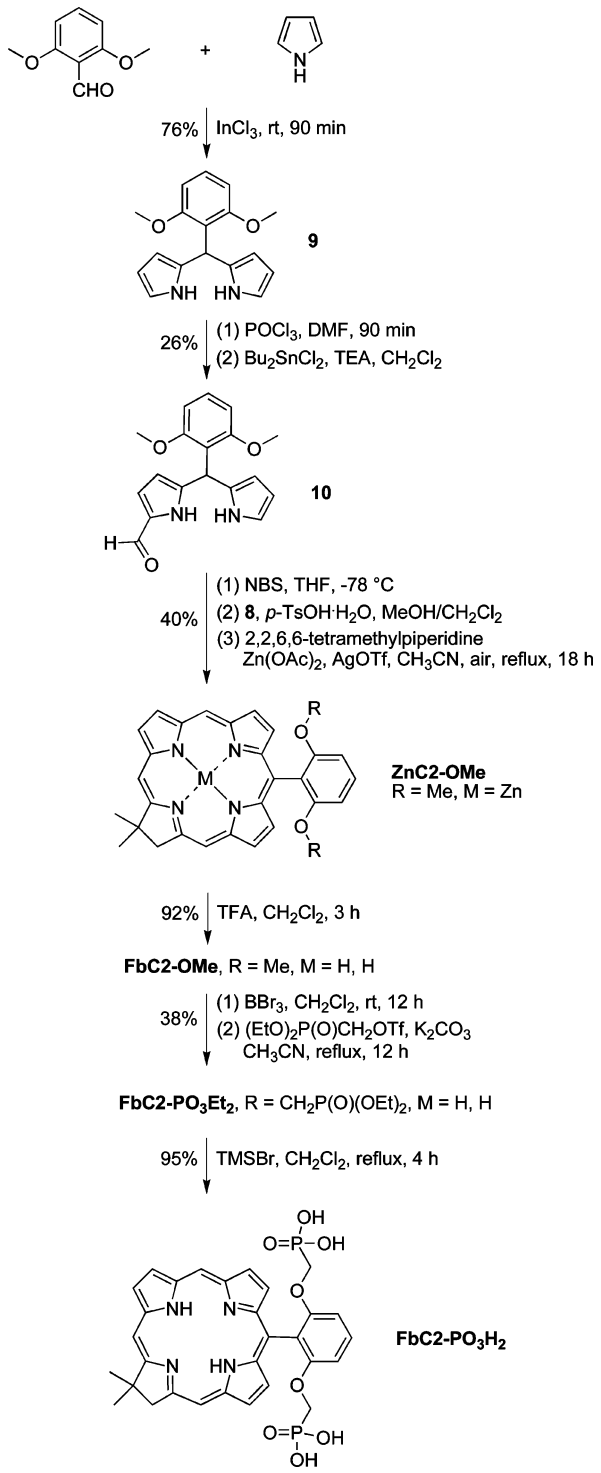
SCHEME 4



Route 1. The synthesis begins with the preparation of a dipyrromethane (**9**) bearing the 2,6-dimethoxyphenyl substituent (Scheme 4). Condensation[48] of commercially available 2,6-dimethoxybenzaldehyde with excess pyrrole in the presence of $InCl_3$ afforded dipyrromethane **9** as a yellowish brown solid in 76% yield following column chromatography. Vilsmeier formylation[49] of **9** was carried out followed by removal of the diformyl byproduct by complexation with Bu_2SnCl_2[49,50] whereupon 1-formyldipyrromethane **10** was obtained as a red solid in 26% yield. Following a streamlined procedure for chlorin synthesis,[30] **10** was brominated by treatment with 1 equiv of NBS at low temperature, followed by aqueous−organic workup. The resulting crude Eastern half was condensed with tetrahydrodipyrrin **8** (Western half) in the presence of *p*-TsOH·H_2O under argon, affording a clear reddish-brown solution over 40−50 min. The reaction mixture was neutralized (with 2,2,6,6-tetramethylpiperidine), concentrated, and exposed to metal-mediated oxidative cyclization with $Zn(OAc)_2$ and AgOTf in refluxing CH_3CN exposed to air. The resulting zinc chlorin **ZnC2-OMe** was obtained in 40% yield after silica column chromatography. Demetalation with TFA afforded the free base chlorin **FbC2-OMe** in 92% yield. Demethylation using excess BBr_3 followed by alkylation of the crude product using $(EtO)_2P(O)CH_2OTf$[54] yielded chlorin-aryldiphosphonate **FbC2-PO$_3$Et$_2$** in 38% yield after column chromatography. Hydrolysis of the phosphonoesters followed by preparative reverse-phase column chromatography afforded water-soluble chlorin-aryldiphosphonate **FbC2-PO$_3$H$_2$** in excellent yield.

Route 2. As a more straightforward means to access **FbC2-PO$_3$H$_2$**, we considered the introduction of the phosphonate groups into the aryl aldehyde precursor of the chlorin. In addition, a modified route[30,45] to the chlorin was employed that relies on a 9-formyltetrahydrodipyrrin (Western half)[55] and a 1-bromodipyrromethane (Eastern half). The synthesis of the target chlorin began with the preparation of known[31] 2,6-dihydroxybenzaldehyde (Scheme 5). Treatment[56] of 2,6-dihydroxybenzaldehyde (obtained from 2,6-dimethoxybenzaldehyde in 54% yield)[31] with $(EtO)_2P(O)CH_2OTf$ in CH_3CN in the presence of K_2CO_3 gave aryl-diphosphonate **11** in 81% yield. The condensation[48] of **11** with pyrrole in the presence of $InCl_3$ afforded dipyrromethane **12** in 88% yield. Following a streamlined procedure for chlorin formation,[30,45] treatment of **12** with 1 equiv of NBS at −78 °C gave a mixture of the α-bromodipyrromethane **12-α-Br**, the α,α′-dibromodipyrromethane, and the unreacted dipyrromethane (5:2:1 on the basis of ^{1}H NMR spectroscopy). Given the expected inert nature of the 1,9-dibromodipyrromethane in the condensation step, the crude sample of **12-α-Br** was condensed with formyltetrahydrodipyrrin **13**[55] under the standard conditions of *p*-TsOH·H_2O catalysis. The putative tetrahydrobiladiene-*ab* formed was subjected to metal-mediated oxidative cyclization (2,2,6,6-tetramethylpiperidine, $Zn(OAc)_2$ and AgOTf in refluxing CH_3CN in the presence of air) for 16 h, affording the zinc chelate of the 10-arylchlorin **ZnC2-PO$_3$Et$_2$** in 42% yield. Demetalation of **ZnC2-PO$_3$Et$_2$** with *p*-TsOH·H_2O afforded the free base chlorin **FbC2-PO$_3$Et$_2$** in 72% yield. The free base chlorin **FbC2-PO$_3$Et$_2$** prepared in this manner agreed in all respects with the sample of **FbC2-PO$_3$Et$_2$** prepared as shown in Scheme 4.

The route shown in Scheme 5 to obtain the 10-arylchlorin **FbC2-PO$_3$Et$_2$** has the following noteworthy features compared to that of Scheme 4: (i) the synthesis of **FbC2-PO$_3$Et$_2$** was achieved in 4 steps rather than 5; (ii) the reactions were performed under milder conditions; and (iii) the overall isolated yield of **FbC2-PO$_3$Et$_2$** was greater (12% versus 2.6% starting from 2,6-dimethoxybenzaldehyde).

C. Chemical Characterization. The hydrophobic chlorins were characterized by ^{1}H NMR spectroscopy, laser-desorption mass spectrometry in the absence of a matrix (LD-MS),[57] high-

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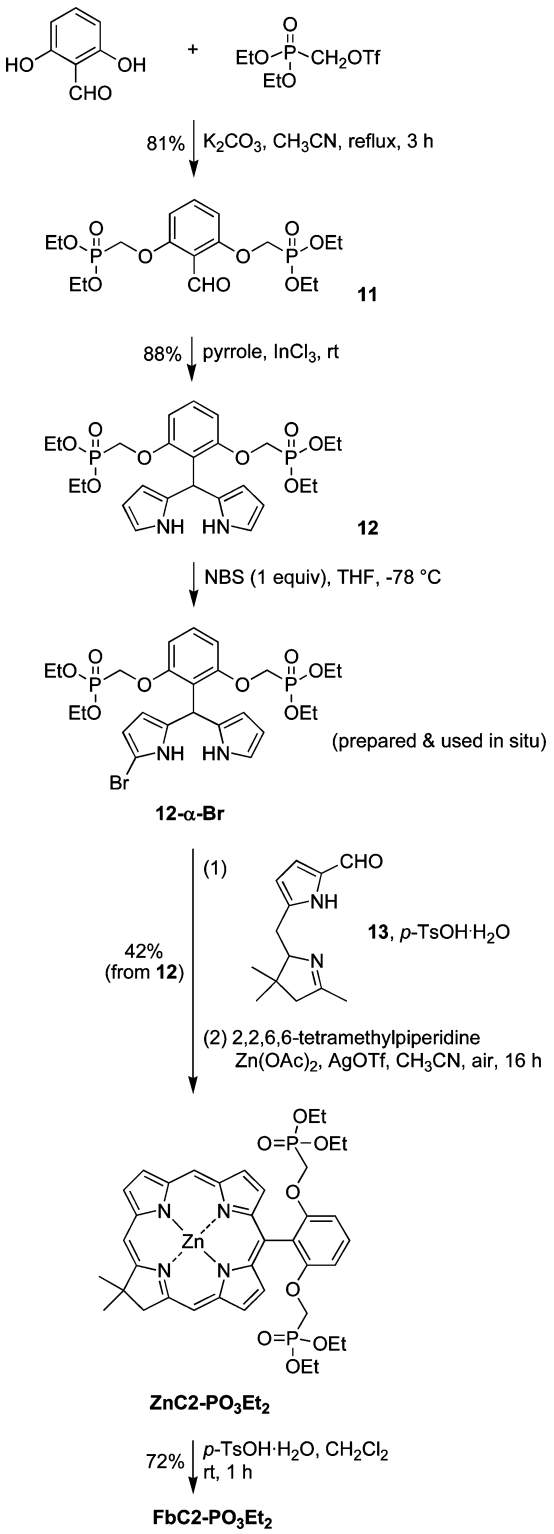
SCHEME 5



resolution FAB-MS or ESI-MS spectrometry, UV−vis absorption spectroscopy, and where permitted by solubility and sample size, ^{13}C NMR spectroscopy. Chlorin **FbC1-Br** gave a poor quality ^{1}H NMR spectrum in a range of solvents (THF-d_8, $CDCl_3$, CD_3OD, and mixtures thereof), presumably due to aggregation. The deprotected chlorin-diphosphonates (**FbC1-PO$_3$H$_2$**, **FbC2-PO$_3$H$_2$**) displayed excellent solubility in aqueous solution (at least 10 mM), enabling ^{1}H NMR analysis in D_2O, although the ^{1}H NMR spectrum of **FbC1-PO$_3$H$_2$** displayed broad peaks. We attribute the signal broadening to the presence of two rotamers (*vide infra*), and partial deprotonation of the phosphonate groups, giving rise to multiple species. The addition of small amounts of pyridine-d_5 to the D_2O solution of **FbC1-PO$_3$H$_2$** did not improve the spectral quality. The spectrum of **FbC2-PO$_3$H$_2$** in D_2O was sharp with all peaks readily assigned (except for NH and OH owing to exchange). ^{31}P NMR analysis of the D_2O solution of **FbC1-PO$_3$H$_2$** gave a cluster of four peaks centered at 23.0 ppm and a cluster of four peaks centered at 30.2 ppm, to be compared with two peaks for **FbC1-PO$_3$Me$_2$** (centered at ∼34.1 ppm in $CDCl_3$), a single peak for **FbC2-PO$_3$H$_2$** (10.35 ppm, in D_2O), a single peak for **FbC2-PO$_3$Et$_2$** (16.7 ppm, in $CDCl_3$) and a single peak for **ZnC2-PO$_3$Et$_2$** (14.0 ppm, in THF-d_8). The data can be compared with that of the following compounds: $CH_3PO_3H_2$ (29.8 ppm),[58] $HOCH_2PO_3H_2$ (22.6 ppm),[58] and $CH_3P(O)(OEt)_2$ (29.4 ppm),[58] and related alkylphosphonic acids.[59] The chemical shift of phosphorus is reported to be sensitive to ionization state.[60] Further ^{31}P NMR studies, including variable-temperature measurements, were performed of the swallowtail-chlorins (see Supporting Information).

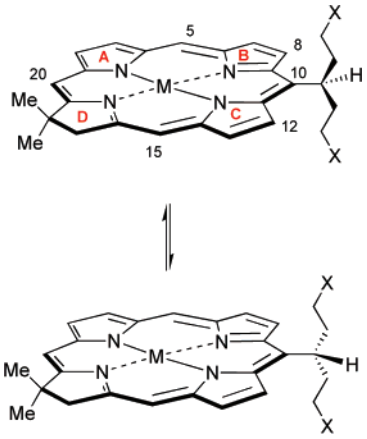


FIGURE 2. Interconversion of two rotamers of **FbC1-PO$_3$H$_2$**. Other conformations are possible upon rotation of the swallowtail group such that the tertiary proton (at the swallowtail branch point) is positioned slightly above or below the face of the macrocycle (not shown).

Each swallowtail-chlorin described herein exists as a diastereomeric mixture of rotamers. The origin of the rotamers is a consequence of the orientation of the two alkyl groups and tertiary proton at the branch point of the swallowtail substituent (Figure 2). The tertiary proton projects toward one or the other of the flanking β-pyrrole protons, either H^8 (ring B) or H^{12} (ring

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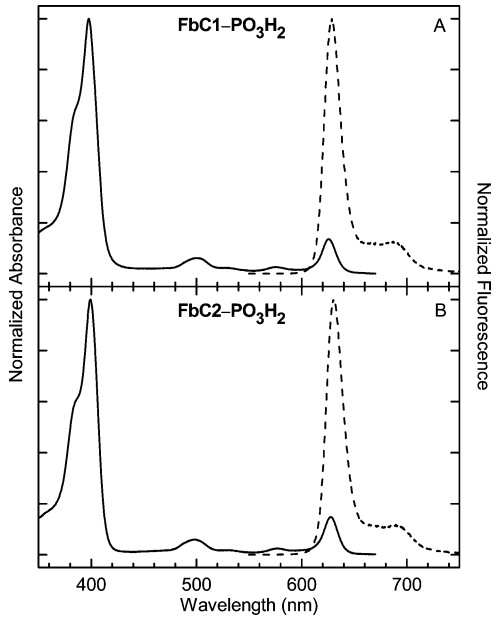

FIGURE 3. Normalized absorption (solid) and fluorescence (dashed) spectra of **FBC1-PO$_3$H$_2$** (A) and **FBC2-PO$_3$H$_2$** (B) in PBS at room temperature.

C). Rings B and C are not equivalent to each other owing to their location with respect to the reduced ring (ring D) of the chlorin macrocycle. The rotamers were typically observed in ratios of 40:60 to 25:75 (depending on the end-groups of the swallowtail motif) by ^{1}H NMR spectroscopy. The diagnostic features were the inner NH protons, the CH_2 moiety of the reduced ring, and the meso-protons (particularly H^5), whereas other regions of the spectrum were quite complex. In particular, the aromatic region consisted of a large number of signals, only some of which could be unambiguously assigned after extensive gCOSY and NOESY experiments. NOESY experiments conducted on **ZnC1-OBn** were inconclusive concerning the AB versus CD direction of orientation of the tertiary proton of the swallowtail motif. ^{31}P NMR spectra also were consistent with the presence of two rotamers. HPLC analysis of a pure sample of **FbC1-PO$_3$H$_2$** showed two peaks (74:26 ratio), which were attributed to the two rotamers. By contrast, aryl-chlorin **FbC2-PO$_3$H$_2$**, for which rotamers are not expected, gave a single peak.

Analogous effects of the swallowtail group on the ^{1}H NMR features also were observed previously with the swallowtail-porphyrins (e.g., those displayed in Figure 1).[23] However, unlike the chlorins, the two halves of the porphyrin macrocycle disposed about the 5,15-axis are identical with each other (ignoring NH tautomers in the free base porphyrins); thus, no isomers were present. The energy of activation for rotation about the C−C bond that joins the swallowtail branch carbon and the meso carbon of the free base swallowtail-porphyrin was estimated by variable temperature ^{1}H NMR spectroscopy to be 68−70 kJ·mol^{-1}.[23]

III. Photophysical Characterization. A. Absorption Spectra. The electronic ground-state absorption spectra of water-soluble chlorins **FbC1-PO$_3$H$_2$** and **FbC2-PO$_3$H$_2$** in phosphate-buffered saline (PBS) solution at room temperature are shown in Figure 3 (solid lines). The spectra for the two compounds are very similar to one another and exhibit the standard features observed for typical metal-free chlorins in organic solvents. The main features are x or y polarized due to the directional inequivalence that results primarily from saturation of one pyrrole ring (ring D in Figure 2). The standard convention[8] places the saturated pyrrole ring along the *x*-axis; this choice places the central protons of the free base chlorin along the *y*-axis. Within Gouterman's four-orbital model, the near-UV (B_x and B_y) and visible (Q_x and Q_y) transitions of the chlorin are derived primarily from linear combinations of the electronic configurations resulting from one-electron promotions among the frontier molecular orbitals.

The near-UV Soret (B) absorption contains overlapping $B_x(0,0)$ and $B_y(0,0)$ components. The peak wavelength of the most intense Soret feature for each chlorin (398 nm, **FbC1-PO$_3$H$_2$**; 399 nm, **FbC2-PO$_3$H$_2$**) is listed in Table 1 along with the maxima of the other features in the absorption spectra. The longest-wavelength feature in each spectrum is the $Q_y(0,0)$ band (626 nm, **FbC1-PO$_3$H$_2$**; 628 nm, **FbC2-PO$_3$H$_2$**); this is the origin transition from the ground to lowest-energy singlet excited state. Table 1 also shows the ratio of the peak intensities of the B(0,0) and $Q_y(0,0)$ bands. This ratio has been used extensively as a first-order gauge of the variation in Q_y intensity among chlorins, and typically is more reliable than trends based on molar absorption coefficients (determined with tiny quantities of material).[43,61] For both chlorins, the peak intensity of the $Q_y(0,0)$ band is roughly 7-fold lower than that of the Soret maximum (Table 1). A weaker $Q_y(1,0)$ vibronic component lies in the vicinity of 580 nm, which is ∼1400 cm^{-1} above the Q_y origin band. The most prominent of the features between the B and Q_y manifolds is the $Q_x(1,0)$ band (501 nm, **FbC1-PO$_3$H$_2$**; 498 nm, **FbC2-PO$_3$H$_2$**). This vibronic satellite is more intense than the $Q_x(0,0)$ origin transition at ∼530 nm.

Although the absorption spectra of water-soluble chlorins **FbC1-PO$_3$H$_2$** and **FbC2-PO$_3$H$_2$** contain all the main characteristics of the spectra for typical hydrophobic chlorins, there are several modest differences. To facilitate such comparisons, Table 1 also lists the properties of two synthetic chlorins (**FbC3** and **FbC4**) that we have studied recently in the nonpolar organic solvent toluene (Chart 2).[61,62] Chlorin **FbC3** contains no substituents other than the chemically stabilizing geminal dimethyl groups in the reduced pyrrole ring (also present in **FbC1-PO$_3$H$_2$** and **FbC2-PO$_3$H$_2$**). Chlorin **FbC4** differs from **FbC3** by the addition of a 10-mesityl group. Thus, the closest comparison is between **FbC4** and **FbC2-PO$_3$H$_2$**; the 10-aryl group of the latter chlorin bears the terminal phosphonate groups that impart water solubility.

Inspection of Table 1 indicates that the Soret maximum of **FbC2-PO$_3$H$_2$** is red-shifted by 3 nm from that of **FbC4** (an ∼190 cm^{-1} downshift in energy), while the $Q_y(0,0)$ band is blue-shifted by 9 nm (an ∼225 cm^{-1} upshift in energy). These small spectral differences are accompanied by a change in the relative intensities of the two bands. In particular, the $B(0,0)/Q_y(0,0)$ peak-intensity ratio is 6.7 for **FbC2-PO$_3$H$_2$** and 2.7 for **FbC4** (Table 1). Thus, the presence of the phosphonate groups in **FbC2-PO$_3$H$_2$** results in an ∼60% reduction of the relative $Q_y(0,0)$ intensity. This difference does not require the presence of a 10-aryl core in the water-solubilizing entity. This point follows because **FbC1-PO$_3$H$_2$**, which utilizes instead a diphosphonate-terminated aliphatic swallowtail motif, has a B(0,0)/

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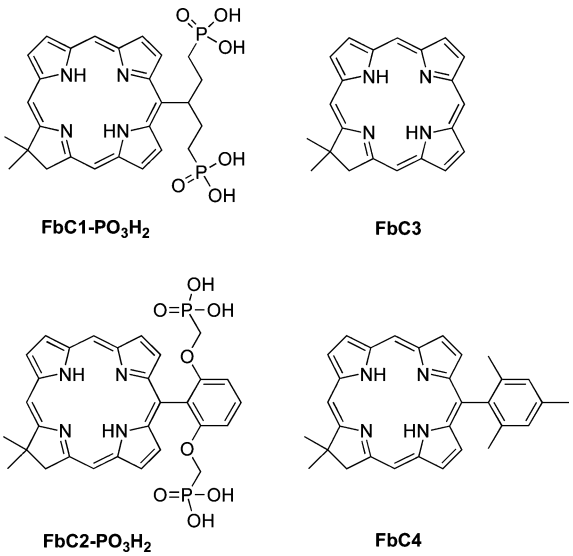
TABLE 1. Summary of Photophysical Properties[a]

		absorbance				emission					
compound	solvent	B(0,0) (nm)	Q_x(1,0) (nm)	Q_y(0,0) (nm)	B(0,0)[b]/ Q_y(0,0)	Q_y(0,0) (nm)	Φ_f[c]	τ[d] (ns)	Φ_{isc}[e]	$[(k_f)^{-1}]$[f] (ns)	$[(k_{nr})^{-1}]$[g] (ns)
FbC1-PO$_3$H$_2$	PBS	398	501	626	7.3	629	0.12	7.7	0.9	64	8.8
FbC2-PO$_3$H$_2$	PBS	399	498	628	6.7	631	0.11	7.5	0.9	68	8.4
FbC3	toluene	398	492	633	2.4	633	0.20	9.0	0.9	46	11
FbC4	toluene	396	499	637	2.7	637	0.22	10	0.9	45	11

[a] Measurements at room temperature. Data for **FbC3** and **FbC4** are from refs 61 and 62. [b] Peak-intensity ratio of the B(0,0) and Q_y(0,0) bands. [c] Fluorescence quantum yield of compound ±5%. [d] Singlet excited-state lifetime ±5%. [e] Intersystem crossing (triplet) yield ±10%. [f] Radiative rate constant for decay of the Q_y excited-state determined from eq 3. [g] Net nonradiative rate constant for decay of the Q_y excited-state determined from eq 4.

CHART 2



Q_y(0,0) intensity ratio of 7.3, which is only slightly larger than that for **FbC2-PO$_3$H$_2$**.

In summary, these comparisons along with the other absorption spectral data in Table 1 indicate the following: (i) Starting with the parent chlorin **FbC3**, the incorporation of a 10-mesityl group to give **FbC4** results in a small (4 nm) red shift and small (10%) decrease in the relative intensity of the Q_y(0,0) band; this trend continues upon the incorporation of additional *meso*-aryl rings.[61,62] (ii) Starting with the parent chlorin **FbC3**, the incorporation of a diphosphonate-bearing water-solubilizing group at the 10-position, based on either an aromatic or aliphatic core, leads to a small (5−7 nm) blue shift and a modest (60%) decrease in the relative Q_y intensity. This modest absorption-intensity decrease is paralleled by differences in the Q_y excited-state fluorescence yield and decay characteristics described below, with the common link being the radiative transition probability.

B. Fluorescence Spectra, Quantum Yields, and Lifetimes. The Q_y excited-state fluorescence spectra of chlorins **FbC1-PO$_3$H$_2$** and **FbC2-PO$_3$H$_2$** are shown in Figure 3 (dashed lines). For each compound, the main feature is the Q_y(0,0) band and the weaker feature at longer wavelength is the Q_y(0,1) vibronic satellite. The Q_y(0,0) peak for each chlorin is shifted 3 nm from the corresponding absorption maximum (Table 1), which corresponds to a Stokes shift of ∼75 cm^{-1}.

The fluorescence quantum yields (Φ_f) for deoxygenated **FbC1-PO$_3$H$_2$** and **FbC2-PO$_3$H$_2$** in PBS are 0.12 and 0.11, respectively. The corresponding lifetimes of the lowest-energy excited singlet state (Q_y), measured by fluorescence methods, are τ = 7.7 and 7.5 ns. The fluorescence yields for the two water-soluble chlorins are roughly 40% lower than the values for parent chlorin **FbC3** (0.20) and its 10-mesityl analogue **FbC4** (0.22) in toluene, and the lifetimes are reduced roughly 20% (Table 1).

The yields of intersystem crossing to give the triplet excited state (Φ_{isc}) for both water-soluble chlorins **FbC1-PO$_3$H$_2$** and **FbC2-PO$_3$H$_2$** are the same as for the two benchmark hydrophobic chlorins **FBC3** and **FBC4** within experimental uncertainty (0.9 ± 0.1). This value is comparable to those reported for the unsubstituted chlorin (0.78)[63] and tetrakis(*m*-*h*ydroxyphenyl)chlorin (0.89)[64] in organic solvents, but is somewhat larger than that for tetrakis(4-sulfonatophenyl)chlorin (0.48)[20] in aqueous media.

C. Excited-State Decay Pathways and Rates. The modest differences in photophysical properties of the water-soluble and hydrophobic chlorins can be analyzed with the aid of eqs 1−4.

$$\tau = (k_f + k_{nr})^{-1} \quad (1)$$

$$\Phi_f = k_f \div (k_f + k_{nr}) \quad (2)$$

$$k_f = \Phi_f \div \tau \quad (3)$$

$$k_{nr} = (1 - \Phi_f) \div \tau \quad (4)$$

In these equations, the Q_y excited-state lifetime (τ) and fluorescence yield (Φ_f) are expressed in terms of the rate constants for radiative (spontaneous fluorescence) decay (k_f) and nonradiative decay (k_{nr}). Here, $k_{nr} = (k_{ic} + k_{isc})$ is the sum of the rate constants for internal conversion to the ground state and intersystem crossing to the triplet excited state. On the basis of eqs 3 and 4 and the measured fluorescence yields and excited-state lifetimes, the last two columns of Table 1 list the values of $(k_f)^{-1}$ and $(k_{nr})^{-1}$ expressed in nanoseconds.

The calculated radiative rates k_f for water-soluble chlorins **FbC1-PO$_3$H$_2$** and **FbC2-PO$_3$H$_2$** in aqueous media are reduced by ∼25% from those for the hydrophobic chlorins **FbC** and **FbC-M^{10}** in toluene. This factor is somewhat smaller than the ∼60% reduction factor obtained above for the relative Q_y absorption intensities of the water-soluble versus hydrophobic reference chlorins. However, the effects are in the same direction and the agreement is good considering experimental uncertainties. The connection between these two observables is the direct proportionality of the Einstein coefficients for spontaneous fluorescence and induced absorption. Thus, the modest diminution of the Q_y absorption intensity and fluorescence yield upon incorporation of the water-solubilizing motifs used in **FbC1-PO$_3$H$_2$** and **FbC2-PO$_3$H$_2$** go hand in hand.

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Several factors could contribute to the modest reductions in radiative absorption and fluorescence decay rates, and small shifts in spectral positions, for the chlorins upon incorporation of a water-solubilization motif. One is a purely electronic effect owing to the attachment at the meso position of the alkyl or aryl substituent for water solubilization. Such substituent effects can modulate the relative energies of the frontier molecular orbitals of the chlorin and thereby the energies and oscillator strengths of the optical transitions.[61,62] However, the fact that the water-solubilizing motifs based on 10-aryl and 10-alkyl cores give such similar effects suggests that purely inductive or conjugative effects are likely not the sole source of the effects on the radiative probabilities. A second factor involves slight distortion of the chlorin macrocycle by the solubilizing groups, with resulting electronic consequences. However, our studies of the effects of the swallowtail motif on the electronic properties of porphyrin analogues indicates that such structural-based perturbations are not likely to be substantial.[26] A third factor derives from the partial ionization of the phosphonate groups at the pH (7.4) of the PBS buffer. Calculations have shown that the presence of a charge 3−4 Å above a bacteriochlorin can shift the energies of the frontier molecular orbitals and thereby alter the optical spectra.[65] Such charge-induced perturbations likely play a role, along with the other factors described above, in the small spectral shifts and modest changes in radiative transition probabilities caused by the water-solubilizing groups utilized in **FbC1-PO$_3$H$_2$** and **FbC2-PO$_3$H$_2$**.

In principle, a reduction in k_f may also transform into a change in the Q_y excited-state lifetime. However, the effect is expected to be much smaller than that on the quantum yield. This difference arises because of the following: (i) The values of τ and Φ_f depend markedly differently on k_f (eq 1 versus 2). (ii) The net nonradiative decay rate k_{nr} dominates over k_f in determining the excited-state lifetime for the chlorins (via eq 1). This latter point is indicated by the fact that the fluorescence accounts for a small fraction of the Q_y excited-state decay for **FbC1-PO$_3$H$_2$** and **FbC2-PO$_3$H$_2$**, as well as for **FbC3** and **FbC4**, as is reflected in the fluorescence yields (Table 1). (iii) There may be a small increase in the net nonradiative rate k_{nr} for the water-soluble versus hydrophobic chlorins (Table 1) that partially offsets the effect of a diminution in k_f (eq 1). The net result is that the Q_y excited-state lifetimes (∼7.5 ns) for water-soluble chlorins **FbC1-PO$_3$H$_2$** and **FbC2-PO$_3$H$_2$** are only ∼20% shorter than those for the hydrophobic chlorins **FbC3** and **FbC4** (Table 1).

It should be noted that more detailed analysis of spectroscopic results beyond the scope of the present paper would take into account the structures of the chlorin-diphosphonates that are present in aqueous solution. A distribution of structures is expected owing to the conformations of the solubilizing units and the ionization of each of the two phosphonate moieties in each solubilizing unit:

(1) Considerable conformational motion is available to the phosphonate moieties for each type of chlorin-diphosphonate, **FbC1-PO$_3$H$_2$** and **FbC2-PO$_3$H$_2$**. In the swallowtail-chlorin **FbC1-PO$_3$H$_2$**, two rotamers are present (*vide supra*). In addition, rotation about the two methylene groups between the branch point and the phosphonate moiety of the swallowtail unit can result in the projection of the phosphonate directly over or away from the chlorin macrocycle. In the aryl-chlorin **FbC2-PO$_3$H$_2$**, rotation about the single methylene group between the aryl oxygen and the phosphonate moiety also enables conformational freedom, as does limited torsional motion about the carbon−carbon bond between the chlorin meso-carbon and the aryl unit.

(2) The pK_a values expected for the phosphonic acid moieties can be gauged by comparison with similar reference compounds: *n*-propylphosphonic acid exhibits pK_1 = 2.49 and pK_2 = 8.18; hydroxymethylphosphonic acid exhibits pK_1 = 1.91 and pK_2 = 7.15.[66] Thus, at pH 7.4 each phosphonic acid group is expected to bear 1−2 negative charges owing to ionization.

The presence of two phosphonate moieties in each solubilizing unit creates further structural diversity in aqueous solution, given that the two phosphonates on opposite sides of the chlorin macrocycle can have predominant charge combinations of −1/−1, −1/−2, and −2/−2. The multiplicity of charge states and the conformational motion of each solubilizing unit is expected to give rise to a distribution of molecular species in solution. The collection of such chlorin-diphosphonates may give rise to a small spread of properties in a given solution.

In summary, the modest differences in photophysical properties of the water-soluble porphyrins compared to hydrophobic analogues in organic solvents may arise from (1) small changes in electronic structure due to a different pattern of substituents, (2) a difference in electronic/physical structure due to electronic/steric effects of the water-solubilizing entity, particularly if the terminal (e.g., phosphonate) group extends over the face of the macrocycle and is ionized, (3) the charged character of the water-solubilizing group upon ionization, and (4) differences in the media used to solubilize and study the molecules. On this latter point, the photophysical properties of hydrophobic porphyrins normally vary minimally with solvent characteristics, particularly free base species for which axial ligation of the solvent to the central metal is not relevant. The same is likely true of the water-soluble versus hydrophobic porphyrins, except for the potentially significant role that the medium plays in the ionization state of the water-solubilizing entity. However, solvent effects alone would not appear to underlie the systematic differences in photophysical properties (Q_y absorption strength, Φ_f, τ) connected by the radiative rate. The distributions of rotamers and ionization states associated with the water-solubilizing entities most likely give rise to a spread of properties for a given chlorin in a given medium. Regardless, the photophysical properties of the water-soluble chlorins studied here are quite similar to those of the hydrophobic analogues.

Conclusions and Outlook

Two designs have been developed to achieve high aqueous solubility of relatively compact, sparsely substituted chlorins. Both designs rely on the projection of charged, phosphonate substituents above and below the plane of the chlorin macrocycle, thereby suppressing $\pi-\pi$ interaction between chlorin macrocycles. The core unit in each design is either a pentyl group in a swallowtail architecture or a 2,6-dimethoxyphenyl unit. The diphosphonate-terminated swallowtail unit provides the most compact design, yet requires a more lengthy synthesis. The diphosphonate-substituted aryl unit can be introduced either by derivatization of a 2,6-dihydroxyphenyl-substituted chlorin or by use of a diphosphonate-substituted benzaldehyde as a precursor to the chlorin.

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The chlorins bearing deprotected phosphonates (**FbC1-PO_3H_2**, **FbC2-PO_3H_2**) are soluble at >10 mM in water. The swallowtail unit used herein (pent-3-yl) provides a two-atom linker between the carbon attached to the chlorin meso-carbon whereas the aryl unit used herein provides a 3-atom linker; both designs afford water solubility. The water-soluble chlorins in aqueous media exhibit photophysical features that are comparable to those of hydrophobic chlorins in toluene. The water-soluble chlorins exhibit only small perturbations to the optical spectral positions, a modest diminution in the intensity of the long-wavelength absorption band and the fluorescence yield ($\Phi_f \approx 0.1$), and little change in the lifetime of the lowest singlet excited singlet state, which remains quite long ($\tau \approx 7.5$ ns). The long lifetime may prove very attractive for applications in optical imaging. The fluorescence features are similar to those of the tetrakis(4-sulfonatophenyl)chlorin (**IV**, Chart 1) at pH 7.4, which exhibits $\Phi_f = 0.086$ and $\tau = 8.5$ ns.[16,20] The collective photophysical properties are quite attractive in conjunction with aqueous solubility in the millimolar range. Furthermore, recent insights into the effects of auxochromes on the photophysical properties of synthetic chlorins[61,62] should allow tuning of the characteristics of the water-soluble chlorins for a variety of applications.

Experimental Section

Photophysical Measurements. The photophysical properties of **FbC1-PO_3H_2** and **FbC2-PO_3H_2** were investigated at room temperature using 1× PBS (phosphate-buffered saline; 137 mM NaCl, 2.7 mM KCl, 10 mM Na_3PO_4, pH 7.4) as the solvent. Static absorption and fluorescence measurements were performed using dilute (μM) solutions, as described previously.[67,68] Fluorescence lifetimes were obtained using a phase modulation technique.[67] Argon-purged solutions with an absorbance of ≤0.10 at the Soret-band excitation wavelength were used for the fluorescence spectral and lifetime measurements. For fluorescence spectra, the excitation and detection monochromators had a band-pass of 1.5 and 3.3 nm, respectively, and spectra were obtained using 0.2 nm data intervals. The fluorescence spectra were corrected for detection-system spectral response. Fluorescence quantum yields were determined using argon-purged solutions and several excitation wavelengths for **FbC1-PO_3H_2** (387, 398, 405, 501 nm) and **FbC2-PO_3H_2** (387, 399, 405, 498 nm) relative to chlorophyll *a* in benzene [$\Phi_f = 0.325$],[69] **H_2TPP** in toluene [$\Phi_f = 0.09$],[63] and **FbC3** in toluene [$\Phi_f = 0.20$],[61] and the results were averaged. Yields of the lowest excited triplet state (Φ_T) were obtained using a transient-absorption technique similar to that described previously.[70,71] The extent of bleaching of the ground-state $Q_x(1,0)$ band at ~500 nm (relative to the featureless transient absorption) due to the lowest singlet excited-state was measured immediately following a 130 fs flash in either the Soret (418 nm) or Q_y (583) bands. The amplitude of this signal was compared to that due to the lowest triplet excited state, which was derived from two methods. In the first method, the triplet bleaching signal was taken as the long-time asymptote of the fitted exponential singlet-excited-state bleaching decay (4 ns time course) with the time constant fixed at the fluorescence lifetime. In the second method, the triplet bleaching was measured directly at a long (~20 ns) time delay. The triplet yields obtained using the different methods were averaged.

1,5-Dibenzyloxy-3-cyanopentane (3). A solution of HMPA (11.0 mL) and LDA (15.2 mL of a 2.0 M solution in THF/hexanes/ethylbenzene) in dry THF (23 mL) at −78 °C under argon was treated with CH_3CN (1.62 mL, 31.6 mmol). The solution was stirred for 30 min, whereupon **2** (6.86 g, 26.2 mmol) in THF (23 mL) was added dropwise. Stirring was continued for 2 h, after which a second portion of LDA (15.2 mL) was added. The solution was stirred for 30 min, whereupon a second portion of **2** (6.86 g, 26.2 mmol) in THF (23 mL) was added dropwise. The reaction was allowed to proceed for 2 h. Saturated aqueous NH_4Cl was added, and the mixture was allowed to reach room temperature. Diethyl ether was added, the phases were separated, and the aqueous layer was extracted with diethyl ether. The organic extract was washed with water and brine, dried over Na_2SO_4, and concentrated. Column chromatography [silica, hexanes/diethyl ether (3:1)] afforded a colorless liquid (8.94 g, 4:1:1 mixture of **3a**:**3b**:**3c**). The following data from analysis of the mixture are for **3a**: ^{1}H NMR (300 MHz) δ 1.84−1.94 (m, 4H), 3.08−3.13 (m, 1H), 3.63−3.70 (m, 4H), 4.53 (s, 4H), 7.32−7.34 (m, 10H); ESI-MS obsd 310.17995, calcd 310.18016 [$(M + H)^+$, $M = C_{20}H_{23}NO_2$]. The sample was used without further purification.

1,5-Dibenzyloxy-3-formylpentane (4). A solution of **3** (8.94 g, 4:1:1 mixture of **3a**:**3b**:**3c**) in dry CH_2Cl_2 (134 mL) at −78 °C under argon was treated with DIBALH (50.8 mL of a 1.0 M solution in CH_2Cl_2), and the reaction was allowed to proceed for 1 h. Water (6.3 mL) was added, and the mixture was allowed to reach room temperature. Aqueous NaOH (6.3 mL, 2.5 M solution) was added, and stirring was continued for 15 min. Water (12.6 mL) was added, and the suspension was stirred for 15 min. A large amount of Na_2SO_4 was added. The resulting mixture was filtered. The filtrate was concentrated under reduced pressure, and chromatographed [silica, hexanes/diethyl ether (85:15)] to afford a colorless liquid (3.94 g, 56%): ^{1}H NMR (300 MHz) δ 1.75−1.84 (m, 2H), 1.98−2.05 (m, 2H), 2.60−2.64 (m, 1H), 3.51 (t, $J = 6.2$ Hz, 4H), 4.47 (s, 4H), 7.26−7.36 (m, 10H), 9.66 (d, $J = 1.8$ Hz, 1H); ^{13}C NMR (75 MHz) δ 29.5, 47.0, 67.9, 73.3, 127.87, 127.89, 128.6, 138.4, 204.5; ESI-MS obsd 335.1620, calcd 335.1617 [$(M + Na)^+$, $M = C_{20}H_{24}O_3$].

5-(1,5-Dibenzyloxypent-3-yl)dipyrromethane (5). Following a standard procedure,[48] aldehyde **4** (762 mg, 2.44 mmol) was dissolved in pyrrole (17.4 mL, 0.250 mol), and the solution was flushed with argon for 10 min. $InCl_3$ (56.0 mg, 0.0670 mmol) was added, and the reaction was allowed to proceed for 3 h. The reaction was quenched by addition of powdered NaOH (301 mg, 7.53 mmol). The mixture was stirred for 45 min. The mixture was filtered. The filtrate was concentrated under reduced pressure. Chromatography [silica, hexanes/CH_2Cl_2/ethyl acetate (7:2:1)] afforded a pale yellow oil (604 mg, 58%): ^{1}H NMR (300 MHz) δ 1.46−1.53 (m, 2H), 1.74−1.83 (m, 2H), 2.40−2.48 (m, 1H), 3.49−3.59 (m, 4H), 4.37 (d, $J = 4.5$ Hz, 1H), 4.49 (s, 4H), 6.00 (app s, 2H), 6.13−6.14 (m, 2H), 6.56 (app s, 2H), 7.30−7.35 (m, 10H), 8.51 (br, 2H); ^{13}C NMR (75 MHz) δ 32.4, 37.1, 40.8, 45.3, 69.5, 73.4, 106.8, 108.3, 116.4, 127.9, 128.0, 128.7, 131.9, 138.5, 149.9; FAB-MS obsd 428.2476, calcd 428.2464 ($C_{28}H_{32}N_2O_2$).

5-(1,5-Dibenzyloxypent-3-yl)-1-formyldipyrromethane (6). A sample of $POCl_3$ (212 μL, 2.32 mmol) was added to DMF (1.41 mL) cooled in an ice−water bath under argon. The solution was stirred for 10 min to form the Vilsmeier reagent. A solution of **5** (604 mg, 1.41 mmol) in DMF (4.65 mL) at 0 °C under argon was treated with 1.06 mL of the Vilsmeier reagent. Stirring was continued for 1.5 h. The solution was quenched at 0 °C by addition of aqueous sodium hydroxide (50 mL of 2.5 M solution). The resulting mixture was poured into ethyl acetate. The phases were separated. The organic extract was washed with water and brine, dried (Na_2SO_4), and concentrated. Chromatography [silica, hexanes/ethyl acetate (2:1)] gave a pale brown oil (354 mg, 55%): ^{1}H NMR

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(300 MHz) δ 1.40−1.48 (m, 2H), 1.69−1.78 (m, 2H), 2.47−2.49 (m, 1H), 3.42−3.60 (m, 4H), 4.41 (d, J = 5.4 Hz, 1H), 4.44−4.55 (m, 4H), 5.96 (app s, 1H), 6.11−6.16 (m, 2H), 6.55 (d, J = 1.2 Hz, 1H), 6.87−6.89 (m, 1H), 7.26−7.36 (m, 10H), 8.90 (br, 1H), 9.34 (s, 1H), 10.06 (br, 1H); ^{13}C NMR (75 MHz) δ 32.18, 32.23, 37.1, 41.4, 68.8, 69.2, 73.4, 73.6, 107.6, 108.5, 110.7, 117.1, 128.0, 128.1, 128.2, 128.7, 128.8, 130.0, 132.1, 138.25, 138.34, 143.1, 178.5, 203.9; FAB-MS obsd 456.2424, calcd 456.2413 ($C_{29}H_{32}N_2O_3$); Anal. Calcd C, 76.29; H, 7.06; N, 6.14. Found C, 76.34; H, 7.16; N, 6.00.

5-(1,5-Dibenzyloxypent-3-yl)-1-bromo-9-formyldipyrromethane (7). Following a standard procedure,[30,43] a solution of **6** (338 mg, 0.741 mmol) in anhydrous THF (7.6 mL) at −78 °C under argon was treated with NBS (127 mg, 0.713 mmol), and the reaction was allowed to proceed for 1 h. Water and ethyl acetate were added, and the mixture was allowed to warm to 0 °C. The phases were separated. The organic extract was washed with water, dried (Na_2SO_4), and concentrated. Chromatography [silica, hexanes/ethyl acetate (3:1)] gave a pale brown oil (307 mg, 78%): ^{1}H NMR (300 MHz) δ 1.42−1.49 (m, 2H), 1.64−1.77 (m, 2H), 2.45−2.50 (m, 1H), 3.42−3.56 (m, 4H), 4.32 (d, J = 6.0 Hz, 1H), 4.45−4.55 (m, 4H), 5.86 (app s, 1H), 6.00 (app s, 1H), 6.15 (app s, 1H), 6.88 (s, 1H), 7.26−7.34 (m, 10H), 9.27 (s, 1H), 9.52 (br, 1H), 10.40 (s, 1H); ^{13}C NMR (75 MHz) δ 32.0, 32.1, 36.9, 41.9, 68.5, 69.0, 73.4, 73.6, 96.8, 109.5, 110.3, 111.1, 128.0, 128.1, 128.2, 128.7, 128.8, 131.7, 132.2, 138.1, 138.3, 143.2, 178.7, 217.3; FAB-MS obsd 534.1507, calcd 534.1518 ($C_{29}H_{31}N_2O_3Br$); Anal. Calcd C, 65.05; H, 5.84; N, 5.23. Found C, 64.94; H, 5.91; N, 5.03.

Zinc(II)-10-(1,5-Dibenzyloxypent-3-yl)-17,18-dihydro-18,18-dimethylporphyrin (ZnC1-OBn). Following a standard procedure,[30,43] a solution of **7** (1.02 g, 1.90 mmol) and **8** (362 mg, 1.90 mmol) in anhydrous CH_2Cl_2 (52 mL) under argon was treated dropwise with a solution of p-TsOH·H_2O (1.80 g, 9.46 mmol) in anhydrous methanol (12.9 mL). The mixture was stirred at room temperature for 50 min. 2,2,6,6-Tetramethylpiperidine (3.23 mL, 19.1 mmol) was added, and the mixture was stirred for 5 min. The mixture was concentrated in vacuo without heating. The residue was suspended in CH_3CN (194 mL), and the sample was treated with 2,2,6,6-tetramethylpiperidine (8.08 mL, 47.8 mmol), $Zn(OAc)_2$ (5.24 g, 28.8 mmol) and AgOTf (1.46 g, 5.68 mmol). The reaction mixture was heated at reflux for 22 h open to the air. The reaction mixture was concentrated. Column chromatography [silica, hexanes/CH_2Cl_2 (1:1), then CH_2Cl_2] yielded a dark green solid (366 mg, 28%). Carrying out the reaction on smaller scale (0.15 mmol of **8**) resulted in yields of up to 40%. ^{1}H NMR analysis revealed the presence of two interconverting rotamers. Data for the major rotamer: ^{1}H NMR (300 MHz) δ 2.02 (s, 6H), 2.75−2.82 (m, 2H), 3.08−3.26 (m, 6H), 3.93−4.03 (m, 4H), 4.74 (s, 2H), 5.31−5.42 (m, 1H), 6.88−7.01 (m, 4H), 7.01−7.09 (m, 6H), 8.53 (s, 1H), 8.61−8.66 (m, 2H), 8.70 (d, J = 4.2 Hz, 1H), 8.86 (d, J = 4.5 Hz, 1H), 9.02 (d, J = 4.2 Hz, 1H), 9.18 (d, J = 4.5 Hz, 1H), 9.46 (d, J = 4.2 Hz, 1H), 9.51 (s, 1H). Data for the minor rotamer: ^{1}H NMR (300 MHz) δ 2.02 (s, 6H), 2.75−2.82 (m, 2H), 3.08−3.26 (m, 4H), 3.93−4.03 (m, 4H), 4.74 (s, 2H), 5.31−5.42 (m, 1H), 6.88−7.01 (m, 4H), 7.01−7.09 (m, 6H), 8.56 (s, 1H), 8.61−8.66 (m, 2H), 8.75 (d, J = 4.5 Hz, 1H), 8.92 (d, J = 4.2 Hz, 1H), 9.06 (d, J = 4.2 Hz, 1H), 9.31 (d, J = 4.5 Hz, 1H), 9.39 (d, J = 5.1 Hz, 1H), 9.59 (s, 1H). The rotamers were not distinguished by the following methods: ^{13}C NMR (75 MHz) δ 31.1, 31.2, 39.2, 39.3, 40.5, 41.3, 45.4, 45.6, 50.3, 50.4, 69.1, 69.3, 72.4, 72.5, 94.1, 96.7, 96.8, 109.1, 109.4, 125.6, 126.3, 126.8, 127.1, 127.2, 127.4, 127.7, 128.2, 128.3, 128.6, 131.1, 131.5, 133.0, 138.3, 144.5, 144.8, 145.7, 146.0, 147.1, 147.9, 149.2, 151.0, 153.9, 154.2, 154.3, 158.5, 159.2, 171.1; LD-MS obsd 684.4 (major), 621.7 (trace), 549.9 (trace); ESI-MS obsd 684.24345, calcd 684.24372 ($C_{41}H_{40}N_4O_2Zn$); λ_{abs} (CH_2Cl_2) 384 (shoulder), 402, 501, 560, 604 nm; λ_{em} (λ_{exc} 402 nm) 610, 660 (shoulder) nm.

10-(1,5-Dibenzyloxypent-3-yl)-17,18-dihydro-18,18-dimethylporphyrin (FbC1-OBn). A sample of **ZnC1-OBn** (6.5 mg, 0.0095 mmol) in CH_2Cl_2 (1 mL) was treated with TFA (0.5 mL) for 3 h at room temperature. The sample was diluted with CH_2Cl_2, and neutralized with small portions of dilute aqueous $NaHCO_3$. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The organic extract was washed with water, dried (Na_2SO_4), and concentrated. Chromatography [silica, hexanes/CH_2Cl_2 (1:4)] yielded a dark green solid (5.5 mg, 93%): ^{1}H NMR (300 MHz) δ −2.27 (s, 0.45H), −2.17 (s, 0.55H), −1.58, −1.52 (2s, 1H), 2.05 (s, 6H), 2.95−3.04 (m, 2H), 3.22−3.30 (m, 3H), 3.38−3.42 (m, 3H), 4.09−4.21 (m, 4H), 4.63 (s, 2H), 5.51−5.67 (m, 1H), 7.17−7.26 (m, 10H), 8.83−9.02 (m, 5H), 9.22 (app s, 1H), 9.35 (d, J = 3.6 Hz, 0.55H), 9.46 (d, J = 3.9 Hz, 0.45H), 9.54 (s, 1H), 9.82, 9.85 (2s, 1H); ^{13}C NMR (75 MHz) δ 29.9, 31.4, 38.8, 39.2, 41.5, 46.4, 52.1, 52.3, 69.5, 69.6, 73.1, 94.0, 96.6, 96.9, 99.2, 106.9, 107.45, 122.7, 123.3, 124.0, 124.3, 126.0, 126.9, 127.6, 127.9, 128.4, 128.7, 129.9, 130.1, 133.1, 133.4, 133.9, 134.4, 137.5, 137.7, 138.7, 140.1, 141.5, 148.2, 162.7; LD-MS obsd 622.5; ESI-MS obsd 623.33876, calcd 623.33805 [(M + H^+), M = $C_{41}H_{42}N_4O_2$]; λ_{abs} (CH_2Cl_2) 356, 401, 501, 582, 635 nm; λ_{em} (λ_{exc} 401 nm) 639, 680 (shoulder) nm.

17,18-Dihydro-10-(1,5-dihydroxypent-3-yl)-18,18-dimethylporphyrin (FbC1-OH). A solution of **ZnC1-OBn** (46 mg, 0.067 mmol) in anhydrous $CHCl_3$ (3 mL) under argon was treated with TMS−I (60 μL). Stirring was continued for 1 h. The reaction mixture was diluted with CH_2Cl_2. The solid residue was dissolved in a small volume of MeOH. Water was added to the solution, and the phases were separated. The aqueous layer was extracted three times with CH_2Cl_2 containing 5% MeOH. The organic extract was washed with water. The organic phase was dried (Na_2SO_4) and concentrated. ^{1}H NMR analysis of the crude product showed the disappearance of the benzylic (CH_2 and CH) signals. The sample could be used without further purification. Samples of analytical purity could be obtained upon chromatography [neutral alumina, CH_2Cl_2/MeOH (0→10%)]. Evaporation of the solvents afforded a dark green solid (29 mg, 97%). ^{1}H NMR analysis revealed the presence of two interconverting rotamers (∼2:3 ratio). Data for the major rotamer: ^{1}H NMR (300 MHz) δ −2.19 (s, 1H), −1.58 (br, 1H), 1.99 (s, 6H), 2.67−2.71 (m, 2H), 2.85−3.04 (m, 2H), 3.36−3.46 (m, 4H), 4.46 (s, 2 H), 5.33 (m, 1H), 8.72−8.96 (m, 5H), 9.15 (app s, 2H), 9.46−9.47 (m, 1H), 9.76 (s, 1H). Data for the minor rotamer: ^{1}H NMR (300 MHz) δ −2.29 (s, 0.4H), −1.58 (br, 1H), 2.01 (s, 6H), 2.67−2.71 (m, 2H), 2.85−3.04 (m, 2H), 3.36−3.46 (m, 4H), 4.54 (s, 2H), 5.45 (m, 1H), 8.72−8.96 (m, 5H), 9.30−9.31 (m, 1H), 9.40−9.41 (m, 1H), 9.46−9.47 (m, 1H), 9.76 (s, 1H). The rotamers were not distinguished by the following methods: ^{13}C NMR δ (75 MHz) 30.0, 31.3, 38.1, 38.5, 43.7, 43.9, 46.4, 46.6, 52.1, 52.2, 61.7, 94.2, 96.8, 97.0, 107.0, 107.4, 122.9, 123.5, 123.6, 124.1, 124.3, 124.7, 125.9, 126.1, 128.8, 129.0, 129.1, 130.0, 130.4, 133.1, 133.5, 133.6, 134.0, 134.4, 137.1, 137.6, 140.0, 141.6, 141.7, 147.8, 148.3, 151.0, 152.0, 162.2, 162.9, 175.8, 176.0; LD-MS obsd 441.5; ESI-MS obsd 443.24418, calcd 443.24415 [(M + $H)^+$, M = $C_{27}H_{30}N_4O_2$]; λ_{abs} (CH_2Cl_2) 356, 393, 403, 501, 635 nm; λ_{em} (λ_{exc} 403 nm) 637, 680 (shoulder), 700 nm (shoulder).

10-(1,5-Dibromopent-3-yl)-17,18-dihydro-18,18-dimethylporphyrin (FbC1-Br). A suspension of crude **FbC1-OH** (from 0.173 mmol of **ZnC1-OBn**) in CH_2Cl_2 (36 mL) in an ice−water bath was treated with CBr_4 (162 mg, 0.488 mmol). The mixture was stirred for 10 min, after which PPh_3 (254 mg, 0.977 mmol) was added. Stirring was continued for 30 min with cooling, and for 10 h thereafter at room temperature. Water was added to the reaction mixture, and the phases were separated. The aqueous layer was extracted with CH_2Cl_2. The organic extract was washed with water, dried (Na_2SO_4), and concentrated. Chromatography (silica, CH_2Cl_2) yielded a dark green solid that was poorly soluble in common organic solvents (CH_2Cl_2, $CHCl_3$, MeOH, THF) (90.9 mg, 93% over two steps). ^{1}H NMR analysis revealed the presence of two interconverting rotamers (∼1:3 ratio): ^{1}H NMR (300 MHz) δ −2.38 (s, 0.25H), −2.24 (s, 0.75H), −1.85 (s, 0.25H), −1.56 (s, 0.75H), 2.05 (s, 6H), 3.16−3.40 (m, 6H), 3.60−3.73 (m, 2H), 4.63

(s, 2H), 5.45−5.72 (m, 1H), 8.87−9.87 (m, 9H). The rotamers were not distinguished by the following methods: LD-MS obsd 565.4; ESI-MS obsd 567.07571, calcd 567.07535 [$(M + H)^+$, $M = C_{27}H_{28}Br_2N_4$]; λ_{abs} (CH_2Cl_2) 404, 502, 584, 635 nm; λ_{em} (λ_{exc} 404 nm) 638 nm.

17,18-Dihydro-18,18-dimethyl-10-[1,5-bis(dimethylphosphono)pent-3-yl]porphyrin (FbC1-PO$_3$Me$_2$). A solution of **FbC1-Br** (90.4 mg, 0.160 mmol) in THF (3 mL) and $P(OCH_3)_3$ (27 mL) was heated at reflux for 24 h. The sample was concentrated. The residue was dissolved in a small volume of CH_2Cl_2, and washed with water and dilute $NaHCO_3$. The organic layer was concentrated and chromatographed [silica, CH_2Cl_2/MeOH (0 → 5%)] to afford a dark green solid (29 mg, 29%): ^{1}H NMR (300 MHz) δ −2.36, −2.27 (2s, 1H), −1.63, −1.55 (2s, 1H), 1.27−1.50 (m, 2H), 1.84−1.97 (m, 2H), 2.05 (s, 6H), 2.93−3.02 (m, 2H), 3.21−3.28 (m, 2H), 3.42−3.54 (m, 12H), 4.63 (s, 2H), 5.17−5.24 (m, 1H), 8.86−9.09 (m, 5H), 9.23 (s, 1H), 9.34 (d, J = 4.5 Hz, 1H), 9.48−9.54 (two d, 1H), 9.84, 9.86 (2s, 1H); ^{31}P NMR (162 MHz) δ 34.1 (two peaks); LD-MS obsd 625.8; ESI-MS obsd 627.25005, calcd 627.24958 [$(M + H)^+$, $M = C_{31}H_{40}N_4O_6P_2$]; λ_{abs} (CH_2Cl_2) 357 (shoulder), 404, 501, 635 nm; λ_{em} (λ_{exc} 404 nm) 638, 701 (shoulder) nm.

17,18-Dihydro-18,18-dimethyl-10-[1,5-diphosphonopent-3-yl]porphyrin (FbC1-PO$_3$H$_2$). A solution of **FbC1-PO$_3$Me$_2$** (11.0 mg, 0.0176 mmol) in anhydrous $CHCl_3$ (1 mL) under argon was treated with TMS−Br (100 μL). Stirring was continued for 1 h. MeOH (1 mL) was added to the reaction mixture, and stirring was continued for 30 min. The sample was concentrated, and the residue was dissolved in dilute aqueous $NaHCO_3$ (3 mL). The solution was chromatographed [C-18 silica, H_2O/MeOH (0 → 50%)] to afford a dark green solution. The sample was concentrated to dryness, and the residue was dissolved in water. The solution was filtered through a plug of cotton wool. The filtrate was freeze-dried, yielding a dark green, fluffy solid (9.9 mg, 99%): ^{1}H NMR (D_2O, 60 °C, 300 MHz) δ 0.98−1.06 (br, 4H), 1.62−1.85 (br, 2H), 2.20−2.50 (br, 2H), 3.13−3.31 (br, 2H); 3.59−3.62 (br, 4H), 5.57 (br, 1H), 7.89−8.32 (m, 4H), 8.90−9.22 (m, 3H), 9.85 (br 1H), 10.16 (br 1H); ^{31}P NMR (D_2O, 162 MHz) δ 23.0 (cluster of four peaks), 30.2 (cluster of four peaks); ESI-MS obsd 571.18665, calcd 571.18698 [$(M + H)^+$, $M = C_{27}H_{32}N_4O_6P_2$]; λ_{abs} (H_2O, pH 7) 398, 501, 627 nm, λ_{em} (λ_{exc} 398 nm) 632, 692 nm; t_R = 22.75 min (major), 23.76 min (minor).

5-(2,6-Dimethoxyphenyl)dipyrromethane (9). Following a reported procedure,[48] a mixture of pyrrole (139 mL, 2.00 mol) and 2,6-dimethoxybenzaldehyde (1.66 g, 10.0 mmol) under argon was treated with $InCl_3$ (221 mg, 1.00 mmol) at room temperature for 1.5 h. The reaction mixture was treated with powdered NaOH (2.0 g, 50 mmol). The mixture was stirred for 45 min and filtered. The filtrate was concentrated, and unreacted pyrrole was recovered. The residue was purified by column chromatography [silica, hexanes/CH_2Cl_2/ethyl acetate (7:2:1)] to afford a yellowish brown solid (2.14 g, 76%, 92% purity by GC): mp 93−94 °C: ^{1}H NMR (400 MHz) δ 3.75 (s, 6H), 5.93 (s, 2H), 6.08−6.16 (m, 2H), 6.19 (s, 1H), 6.61−6.68 (m, 4H), 7.20 (t, J = 8.4 Hz, 1H), 8.52 (brs, 2H); ^{13}C NMR (100 MHz) δ 32.7, 56.6, 106.0, 107.8, 116.3, 119.7, 128.3, 133.1, 158.3; FAB-MS obsd 282.1380, calcd 282.1368 ($C_{17}H_{18}N_2O_2$).

1-Formyl-5-(2,6-dimethoxyphenyl)dipyrromethane (10). Following a reported procedure,[49] anhydrous DMF (10 mL) was treated with $POCl_3$ (1.50 mL, 16.4 mmol) at 0 °C under argon, and the resulting solution was stirred for 10 min to give the Vilsmeier reagent. A solution of **9** (2.14 g, 7.57 mmol) in DMF (25 mL) at 0 °C under argon was treated with the freshly prepared Vilsmeier reagent (5.6 mL, 8.0 mmol), and the resulting solution was allowed to stir for 1.5 h at 0 °C. Saturated aqueous sodium acetate (80 mL) was added, and the reaction mixture was stirred for 4 h at room temperature. The mixture was extracted with ethyl acetate. The organic layer was washed (brine), dried (Na_2SO_4), and filtered. The filtrate was concentrated to obtain a dark red oil. Following a procedure for the dialkyltin complexation of 1,9-diacyldipyrromethanes,[50] the crude oil was dissolved in CH_2Cl_2 (35 mL) and treated with TEA (3.19 mL, 2.30 mmol) and Bu_2SnCl_2 (2.30 g, 7.60 mmol) for 30 min at room temperature. The solvent was removed. The resulting oil was chromatographed [silica, hexanes/ethyl acetate (19:1) → hexanes/ethyl acetate (3:2) containing 1% TEA] to afford a dark red solid (612 mg, 26%): mp 138 °C; ^{1}H NMR (400 MHz) δ 3.74 (s, 6H), 5.90−5.94 (m, 1H), 6.08−6.14 (m, 2H), 6.15 (s, 1H), 6.62 (d, J = 8.4 Hz, 2H), 6.67−6.71 (m, 1H), 6.83−6.87 (m, 1H), 7.22 (t, J = 8.4 Hz, 1H), 8.82 (brs, 1H) 9.07 (brs, 1H), 9.33 (s, 1H); ^{13}C NMR (100 MHz) δ 33.0, 56.4, 105.7, 107.6, 108.0, 109.4, 117.5, 117.8, 122.3, 129.0, 130.2, 131.5, 144.6, 158.0. 178.1; FAB-MS obsd 310.1323, calcd 310.1317 ($C_{18}H_{18}N_2O_3$).

Zinc(II)-17,18-Dihydro-10-(2,6-dimethoxyphenyl)-18,18-dimethylporphyrin (ZnC2-OMe). Following a streamlined procedure,[30] a solution of **10** (399.5 mg, 1.287 mmol) in dry THF (13 mL) at −78 °C under argon was treated portionwise with NBS (229.0 mg, 1.287 mmol). The reaction mixture was stirred for 1 h at −78 °C. The cooling bath was removed, and the reaction mixture was allowed to warm to 0 °C. Ethyl acetate was added. The organic layer was washed with water, dried (Na_2SO_4), and concentrated. The resulting crude bromo-formyldipyrromethane was dissolved in anhydrous CH_2Cl_2 (38 mL), and **8** (244.8 mg, 1.287 mmol) was added. The solution was treated dropwise with a solution of *p*-TsOH·H_2O (1.22 g, 6.43 mmol) in anhydrous methanol (9 mL) under argon. The resulting red reaction mixture was stirred at room temperature for 50 min. A sample of 2,2,6,6-tetramethylpiperidine (2.18 mL, 12.9 mmol) was added. The reaction mixture was concentrated. The resulting solid was suspended in CH_3CN (128 mL) and subsequently treated with 2,2,6,6-tetramethylpiperidine (5.46 mL, 32.1 mmol), $Zn(OAc)_2$ (3.54 g, 19.3 mmol), and AgOTf (992 mg, 3.86 mmol). The resulting suspension was refluxed for 18 h exposed to air. The crude mixture was filtered through a pad of silica (CH_2Cl_2). The filtrate was concentrated and chromatographed [silica, hexanes/CH_2Cl_2 (1:2) → CH_2Cl_2] to afford a purple solid (283.3 mg, 40%): ^{1}H NMR (400 MHz) δ 2.02 (s, 6H), 3.55 (s, 6H), 4.52 (s, 2H), 6.98 (d, J = 8.4 Hz, 2H), 7.68 (t, J = 8.4 Hz, 1H), 8.48 (d, J = 4.4 Hz, 1H), 8.59 (s, 1H), 8.62 (d, J = 4.4 Hz, 1H), 8.65−8.71 (m, 2H), 8.74 (d, J = 4.4 Hz, 1H), 8.85 (d, J = 4.4 Hz, 1H), 9.06 (d, J = 4.4 Hz, 1H), 9.60 (s, 1H); LD-MS obsd 539.4; FAB-MS obsd 538.1332, calcd 538.1347 ($C_{30}H_{26}N_4O_2Zn$); λ_{abs} (toluene) 406, 607 nm.

17,18-Dihydro-10-(2,6-dimethoxyphenyl)-18,18-dimethylporphyrin (FbC2-OMe). A solution of **ZnC2-OMe** (119 mg, 0.219 mmol) in CH_2Cl_2 (5 mL) was treated dropwise with TFA (507 μL, 6.58 mmol) over a 3 min period. The solution was stirred at room temperature for 3 h. CH_2Cl_2 was added, and the organic layer was washed (saturated aqueous $NaHCO_3$ and water) and then dried (Na_2SO_4). The organic layer was concentrated and chromatographed [silica, hexanes then hexanes/CH_2Cl_2 (1:1)] to afford a purple solid (96.5 mg, 92%): ^{1}H NMR (400 MHz) δ −2.25 (brs, 1H), −1.95 (brs, 1H), 2.05 (s, 6H), 3.52 (s, 6H), 4.63 (s, 2H), 6.99 (d, J = 8.4 Hz, 2H), 7.70 (t, J = 8.4 Hz, 1H), 8.56 (d, J = 4.4 Hz, 2H), 8.74 (d, J = 4.4 Hz, 1H), 8.78 (d, J = 4.4 Hz, 1H), 8.80 (s, 1H), 8.92 (d, J = 4.4 Hz, 1H), 8.98 (s, 1H), 9.20 (d, J = 4.4 Hz, 1H), 9.81 (s, 1H); ^{13}C NMR (100 MHz) δ 31.3, 46.4, 52.2, 56.2, 94.2, 96.6, 104.4, 107.2, 113.5, 119.4, 122.7, 123.7, 127.8, 130.2, 131.3, 132.7, 133.9, 135.8, 139.6, 140.4, 150.9, 153.7, 160.6, 162.7, 174.5; LD-MS obsd 476.9; ESI-MS obsd 477.2295, calcd 477.2285 [$(M + H)^+$, $M = C_{30}H_{28}N_4O_2$]; λ_{abs} (toluene) 402, 639 nm.

10-[2,6-Bis(diethylphosphonomethoxy)phenyl]-17,18-dihydro-18,18-dimethylporphyrin (FbC2-PO$_3$Et$_2$). A solution of **FbC2-OMe** (56.2 mg, 0.117 mmol) in anhydrous CH_2Cl_2 (6 mL) under argon was treated with BBr_3 (2.3 mL, 2.3 mmol, 1 M solution in CH_2Cl_2). The mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with CH_2Cl_2 (40 mL)and saturated aqueous $NaHCO_3$. The organic layer was separated, dried (Na_2SO_4), and concentrated. The resulting solid was dissolved in CH_3CN (8 mL). The solution was treated with K_2CO_3 (355 mg, 2.57

mmol) and $(EtO)_2P(O)CH_2OTf$ (702 mg, 2.34 mmol). The reaction mixture was refluxed for 12 h. The mixture was concentrated. The residue was dissolved in CH_2Cl_2 and chromatographed [silica, $CH_2Cl_2 \rightarrow CH_2Cl_2$/MeOH (49:1)] to afford a greenish purple solid (34.2 mg, 38%): ^{1}H NMR (400 MHz) δ −2.36 (brs, 1H), −2.06 (brs, 1H), −0.34 (t, J = 7 Hz, 6H), −0.15 (t, J = 7 Hz, 6H), 2.08 (s, 6H), 2.23−2.55 (m, 6H), 2.58−2.81 (m, 2H), 4.16 (d, J = 10.4 Hz, 4H), 4.66 (s, 2H), 7.07 (d, J = 8.4 Hz, 2H), 7.74 (t, J = 8.4 Hz, 1H), 8.50 (d, J = 4.4 Hz, 1H), 8.72 (d, J = 4.4 Hz, 1H), 8.79 (d, J = 4.4 Hz, 1H), 8.87 (d, J = 4.4 Hz, 1H), 8.93 (s, 1H); 8.96 (d, J = 4.4 Hz, 1H), 9.00 (s, 1H), 9.22 (d, J = 4.4 Hz, 1H), 9.78 (s, 1H); ^{31}P NMR (162 MHz) δ 16.71; LD-MS obsd 748.7; ESI-MS obsd 749.2865, calcd 749.2863 [$(M + H)^+$, M = $C_{38}H_{46}N_4O_8P_2$]; λ_{abs} (toluene) 403, 638 nm.

17,18-Dihydro-18,18-dimethyl-10-[2,6-bis(phosphonomethoxy)phenyl]porphyrin (FbC2-PO$_3$H$_2$). A solution of **FbC2-PO$_3$Et$_2$**(21.3 mg, 0.0284 mmol) in anhydrous $CHCl_3$ (1 mL) under argon was treated with TMS−Br (250 μL, 1.89 mmol). The solution was stirred for 1 h at room temperature. The solution was concentrated, and the residue was dissolved in MeOH (2 mL). The solution was stirred at room temperature for 1 h. Evaporation of the solvent yielded a dark green solid, which was dissolved in dilute aqueous NaOH (2 M). The solution was chromatographed (C-18 silica, water/MeOH gradient) to obtain a blue solid (17.2 mg, 95%): ^{1}H NMR (400 MHz, D_2O) δ 2.05 (s, 6H), 3.84−3.95 (m, 4H), 4.71 (s, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.90 (t, J = 8.0 Hz, 1H), 8.79 (d, J = 4.4 Hz, 1H), 9.00 (d, J = 4.4 Hz, 1H), 9.08 (d, J = 4.4 Hz, 1H), 9.11 (d, J = 4.4 Hz, 1H), 9.18−9.25 (m, 2H), 9.29 (s, 1H), 9.41 (d, J = 4.4 Hz, 1H), 10.09 (s, 1H); ^{13}P NMR (D_2O, 162 MHz) δ 10.35; ESI-MS obsd 637.1620, calcd 637.1611 [$(M + H)^+$, M = $C_{30}H_{30}N_4O_8P_2$]; λ_{abs} (pH 7, H_2O) 399, 628 nm; t_R = 27.20 min.

2,6-Bis(diethylphosphonomethoxy)benzaldehyde (11). Following a reported procedure,[56] a suspension of 2,6-dihydroxybenzaldehyde (401 mg, 2.90 mmol) and K_2CO_3 (1.60 g, 11.5 mmol) in CH_3CN (20 mL) was refluxed for 30 min. The reaction mixture was allowed to cool to room temperature. A solution of $(EtO)_2P(O)CH_2OTf$ (2.09 g, 6.96 mmol) in CH_3CN (12 mL) was added, and the mixture was refluxed for 2.5 h. The reaction mixture was concentrated, and CH_2Cl_2 was added. The organic layer was washed with water, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (silica, $CH_2Cl_2 \rightarrow CH_2Cl_2$/methanol (7:3)] to give a colorless gummy oil. The product was dissolved in ethyl acetate, filtered to remove any residual silica gel, and the filtrate was concentrated (1.03 g, 81%): ^{1}H NMR (THF-d_8, 400 MHz) δ 1.30 (t, J = 7.2 Hz, 12H), 4.15−4.23 (m, 8H), 4.36 (d, J = 10 Hz, 4H), 6.84 (d, J = 8.0 Hz, 2H), 7.13 (t, J = 8.8 Hz, 1H), 10.5 (s, 1H); ^{13}C NMR (THF-d_8, 100 MHz) δ 17.0, 63.3, 65.0, 107.3, 136.0, 162.0, 162.2, 187.6; ESI-MS obsd 439.1284, calcd 439.1281 [$(M + H)^+$, M = $C_{17}H_{28}O_9P_2$].

5-[2,6-Bis(diethylphosphonomethoxy)phenyl]dipyrromethane (12). Following a reported procedure,[48] a mixture of pyrrole (32.0 mL, 460 mmol) and **11** (1.01 g, 2.30 mmol) was treated under argon with $InCl_3$ (51.0 mg, 0.230 mmol) at room temperature for 1.5 h. The reaction mixture was diluted with CH_2Cl_2, and saturated aqueous $NaHCO_3$ was added. The organic layer was separated, dried (Na_2SO_4), and concentrated with recovery of unreacted pyrrole. The residue was purified by column chromatography [silica, hexanes $\rightarrow CH_2Cl_2$/methanol (19:1)] to obtain a yellow gummy oil. Storage at −20 °C afforded a yellowish brown solid (1.12 g, 88%): mp 104−106 °C: ^{1}H NMR (THF-d_8, 400 MHz) δ 1.26 (t, J = 7.2 Hz, 12H), 3.88−4.34 (br m, 12H), 5.84−5.86 (m, 4H), 6.22 (s, 1H), 6.52−6.54 (m, 2H), 6.74 (brs, 2H), 7.13 (t, J = 8.8 Hz, 1H), 10.0 (brs, 2H); ^{13}C NMR (THF-d_8, 100 MHz) δ 17.0, 34.2, 63.3, 65.0 (br), 107.3, 107.4, 117.3, 122.5, 128.5, 132.8, 158.7 (br); ESI-MS obsd 555.20041, calcd 555.20197 [$(M + H)^+$, M = $C_{25}H_{36}N_2O_8P_2$].

Zn(II)-10-[2,6-Bis(diethylphosphonomethoxy)phenyl]-17,18-dihydro-18,18-dimethylporphyrin (ZnC2-PO$_3$Et$_2$). Following a streamlined procedure,[30,45] a solution of **12** (204 mg, 0.367 mmol) in dry THF (6.5 mL) at −78 °C under argon was treated with NBS (65.5 mg, 0.367 mmol). The reaction mixture was stirred for 1 h at −78 °C. The cooling bath was removed, and the reaction mixture was allowed to warm to ~ −30 °C. Ethyl acetate was added. The organic layer was washed with water, dried (Na_2SO_4), and concentrated. The resulting crude bromo-dipyrromethane was dissolved in anhydrous CH_2Cl_2 (8 mL), and **13** (80.1 mg, 0.367 mmol) was added. The solution was treated dropwise with a solution of p-TsOH·H_2O (349 mg, 1.83 mmol) in anhydrous methanol (2 mL) under argon. The resulting red reaction mixture was stirred at room temperature for 35 min. A sample of 2,2,6,6-tetramethylpiperidine (685 μL, 4.02 mmol) was added. The reaction mixture was concentrated. The resulting solid was suspended in CH_3CN (37 mL) and was subsequently treated with 2,2,6,6-tetramethylpiperidine (1.55 mL, 9.17 mmol), $Zn(OAc)_2$ (1.01 g, 5.50 mmol), and AgOTf (283 mg, 1.10 mmol). The resulting suspension was refluxed for 16 h exposed to air. The crude mixture was filtered through a pad of silica [CH_2Cl_2/ethyl acetate (1:2)]. The filtrate was chromatographed [silica, $CH_2Cl_2 \rightarrow CH_2Cl_2$/ethyl acetate (1:2)] to afford a green solid (128 mg, 42%): ^{1}H NMR (THF-d_8, 400 MHz) δ 0.12 (t, J = 7.0 Hz, 6H), 0.17 (t, J = 7.0 Hz, 6H), 2.04 (s, 6H), 2.65−2.90 (m, 8H), 4.11 (d, J = 10 Hz, 4H), 4.54 (s, 2H), 7.20 (d, J = 8.0 Hz, 2H), 7.70 (t, J = 8.8 Hz, 1H), 8.35 (d, J = 4.4 Hz, 1H), 8.53 (s, 2H), 8.61 (d, J = 4.4 Hz, 2H), 8.72 (d, J = 4.4 Hz, 1H), 8.74 (d, J = 4.4 Hz, 1H), 9.02 (d, J = 4.4 Hz, 1H), 9.54 (s, 1H); ^{13}C NMR (THF-d_8, 100 MHz) δ 15.97, 15.99, 16.02, 16.05, 31.4, 46.2, 51.4, 62.30, 62.32, 62.36, 63.38, 63.0, 64.6, 94.4, 96.7, 106.6, 109.4, 115.1, 122.4, 127.5, 127.6, 128.5, 128.6, 130.5, 132.8, 133.0, 146.8, 147.1, 147.5, 148.6, 154.0, 154.6, 159.3, 160.6, 160.8, 170.7; ^{31}P NMR (THF-d_8, 162 MHz) δ 14.0; LD-MS obsd 810.4; ESI-MS obsd 810.19150, calcd 810.19204 ($C_{38}H_{44}N_4O_8P_2Zn$); λ_{abs} (toluene) 408, 608 nm.

10-[2,6-Bis(diethylphosphonomethoxy)phenyl]-17,18-dihydro-18,18-dimethylporphyrin (FbC2-PO$_3$Et$_2$). Following a reported procedure,[25] a solution of **ZnC2-PO$_3$Et$_2$** (40.0 mg, 0.219 mmol) in CH_2Cl_2 (15 mL) was treated with p-TsOH·H_2O (543 mg, 6.58 mmol) at room temperature for 1 h. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution. The organic layer was separated, dried (Na_2SO_4), and concentrated. The resulting residue was chromatographed [silica, $CH_2Cl_2 \rightarrow CH_2Cl_2$/MeOH (98:2)] to afford a greenish purple solid (26.2 mg, 72%): ^{1}H NMR (400 MHz) δ −2.36 (brs, 1H), −2.06 (brs, 1H), −0.34 (t, J = 7.0 Hz, 6H), −0.15 (t, J = 7.0 Hz, 6H), 2.08 (s, 6H), 2.23−2.55 (m, 6H), 2.58−2.81 (m, 2H), 4.16 (d, J = 10 Hz, 4H), 4.66 (s, 2H), 7.07 (d, J = 8.0 Hz, 2H), 7.74 (t, J = 8.8 Hz, 1H), 8.50 (d, J = 4.4 Hz, 1H), 8.72 (d, J = 4.4 Hz, 1H), 8.79 (d, J = 4.4 Hz, 1H), 8.87 (d, J = 4.4 Hz, 1H), 8.93 (s, 1H); 8.96 (d, J = 4.4 Hz, 1H), 9.00 (s, 1H), 9.22 (d, J = 4.4 Hz, 1H), 9.78 (s, 1H); ^{13}C NMR (THF-d_8, 100 MHz) δ 15.42, 15.48, 15.5, 15.6, 31.5, 47.2, 52.8, 62.09, 62.16, 62.23, 63.0, 64.7, 95.2, 97.3, 106.5, 107.7, 113.8, 120.8, 123.7, 124.5, 128.5, 128.6, 131.2, 132.2, 133.4, 135.1, 136.7, 140.6, 141.6, 152.1, 154.6, 160.6, 160.7, 163.7, 175.5; LD-MS obsd 748.7; ESI-MS obsd 749.28592, calcd 749.28636 [$(M + H)^+$, M = $C_{38}H_{46}N_4O_8P_2$]; λ_{abs} (toluene) 403, 638 nm.

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Supporting Information Available: Variable-temperature ^{31}P NMR spectroscopic results for the swallowtail-chlorins; procedures for preparing compounds **1** and **2**; spectral data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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