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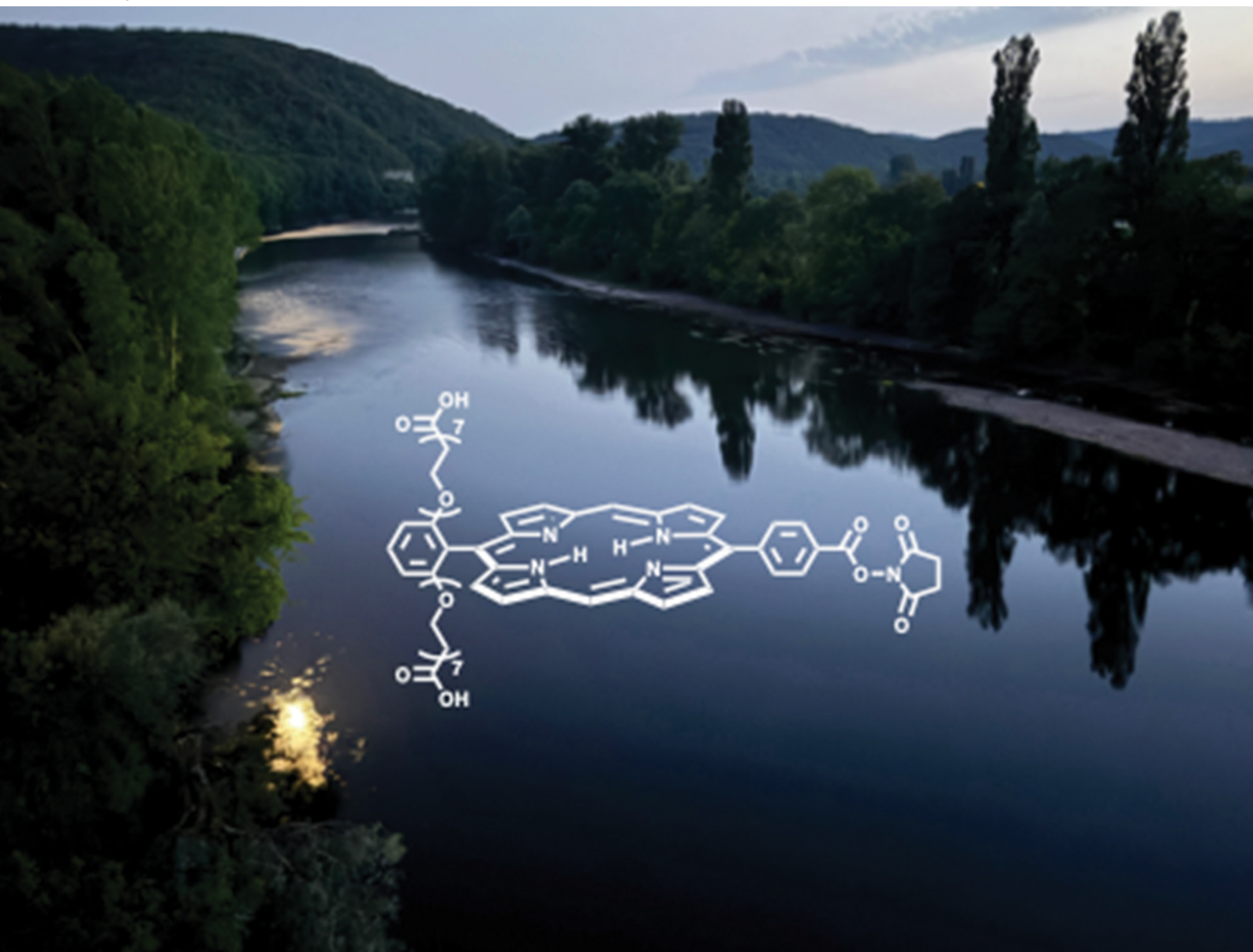
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Jonathan S. Lindsey *et al.*
Synthesis of compact water-soluble bioconjugatable
porphyrins for life sciences applications

PAPER

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Synthesis of compact water-soluble bioconjugatable porphyrins for life sciences applications†

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Porphyrins substituted in a *trans*-AB pattern bearing a single bioconjugatable group (A) and a single water-solubilizing group (B) with limited molecular weight were synthesized for potential use in aqueous solution. The synthetic approach employed the established reaction of a dipyrromethane and a 1,9-bis(*N*,*N*-dimethylaminomethyl)dipyrromethane bearing A and B substituents, respectively, which afforded in low yield the corresponding *trans*-AB-porphyrin for direct use or subsequent tailoring. Altogether, 30 porphyrins were prepared. The synthetic intermediates entailed the following (given as number of new/known): PEG alkylating agent (1/0), aldehydes (3/6), dipyrromethanes (7/4), and Eschenmoser dipyrromethanes (5/2); totaling 46 new compounds. The candidate bioconjugatable linkers included carboxaldehyde, ethylphenol, phenylisothiocyanate, ethylisothiocyanate, NHS ester of benzoic acid, and NHS ester of phenylpropanoic acid. The water-solubilization motifs included polar groups appended to the two *ortho* (2,6-) positions of a *meso*-aryl group. Water solubility was assessed by spectral-band integrity in absorption spectroscopy with a 1000-fold reciprocal change of concentration (0.1–100 μM) and cuvette pathlength (100–0.1 mm). Selected porphyrins were examined for efficacy in bioconjugation. Among all, the most suitable porphyrins were those equipped with (A) a benzoic acid or phenylpropanoic acid group and (B) a *meso*-aryl group bearing (OCH$_2$CH$_2$)$_7$-CO$_2$H groups at the 2,6-positions. The studies taken together have pruned candidate designs for bioconjugations in dilute aqueous media.

Introduction

Practitioners of porphyrin chemistry are well familiar with the diverse repertoire of functional properties presented by this extraordinarily versatile class of compounds. Yet the realization of those rich properties in applications in the life sciences may be impeded by the hydrophobic nature of the disk-like macrocycles. A large literature is available concerning the synthesis of porphyrins destined for use in biological or biotechnological systems where at least some degree of solubility in aqueous solution is desired.[1–5]

Our particular interest concerns the design and synthesis of porphyrins that bear only two substituents: a water-solubilizing motif (A) and a bioconjugatable group (B). We have prepared a number of *trans*-AB-porphyrins, where A and B are not identical and are located at opposite positions across the macrocycle (*i.e.*, 5,15-disubstitution).[6–21] The presence of only two substituents provides a compact architecture. In a recent example, a generic *trans*-AB-porphyrin chassis (**I**) was prepared for derivatization *via* click chemistry with oligo(ethyleneoxy) groups (Chart 1).[20] [The oligoethylene glycol groups that were employed were monodisperse (*i.e.*, uniform length), yet are generally referred to under the umbrella term polyethylene glycol (PEG).] Two propargyloxy groups project over the face of the porphyrin. The attachment of polar groups at these sites results in facial encumbrance and enhances solubility in aqueous media. Studies carried out to identify water-solubilizing groups revealed (1) substantial differences between carboxy-terminated and methyl-terminated PEG units, and (2) the importance of a PEG$_6$ *versus* a PEG$_2$ group.[22] The chassis was derivatized to create a porphyrin–folic acid conjugate (**II**, Chart 1) that was subsequently metalated with the

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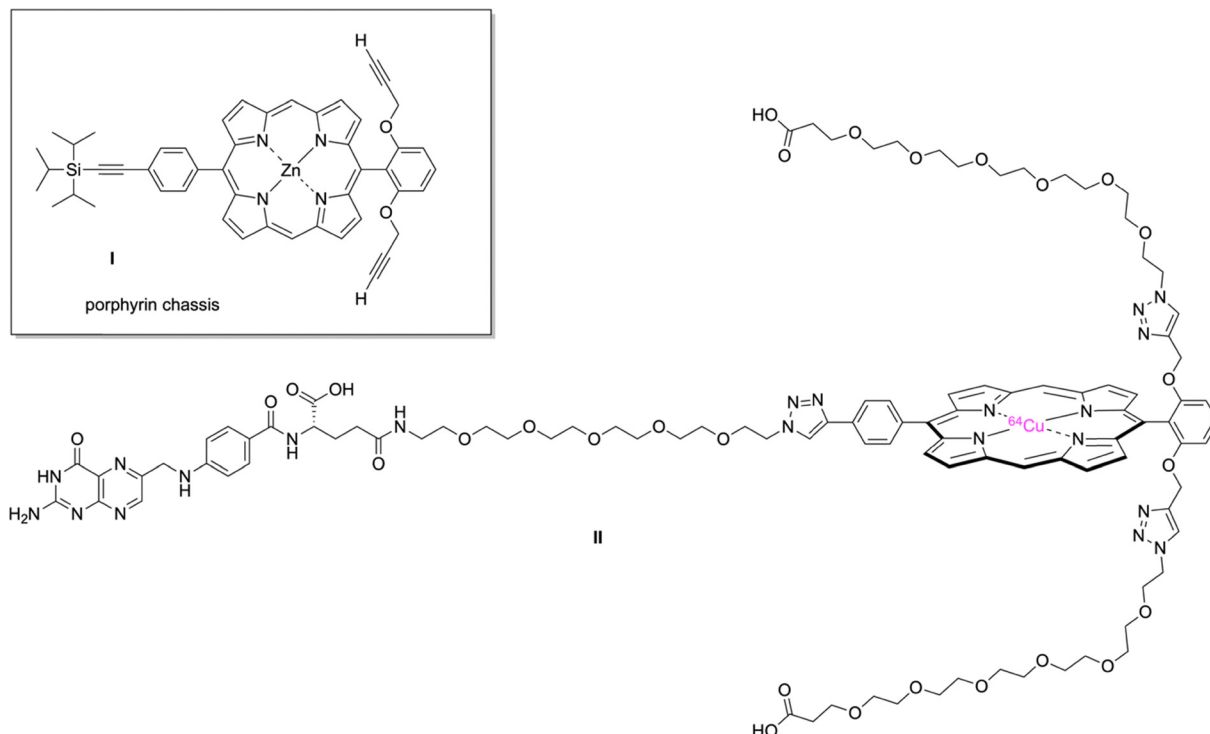
Chart 1 *trans*-AB-porphyrin chassis and a porphyrin–folate conjugate.

radionuclide ^{64}Cu for studies related to ovarian cancer, in cells and in mice.[20]

One objective of the present work has been to extend beyond the use of click chemistry for attachment of water-solubilization and bioconjugation groups. While click chemistry[23,24] enables a "snap-on" approach well-suited for use with a generic chassis, and is growing in importance in tetrapyrrole chemistry,[2,25] the method as typically practiced now to form simple triazoles requires blocking the porphyrin core (*e.g.*, with zinc metalation) to preclude copper insertion. A second objective was to explore a larger collection of bioconjugatable groups. The bioconjugatable linkers[26] include those that enable joining *via* bonds such as amide,[27,28] thiourea,[29,30] and carbamate.[31,32] A design feature that was considered essential was facial encumbrance[33–35] engendered by the 2,6-disubstitution pattern of a *meso*-aryl group to impart water solubility.

The present work reports the synthesis of *trans*-AB-porphyrins each chiefly equipped with a 2,6-bis(PEG)phenyl group for solubilization and one of a variety of bioconjugatable groups. The general synthetic approach to *trans*-AB-porphyrins relies on the reaction of a dipyrromethane and a 1,9-bis(*N*,*N*-dimethylaminomethyl)dipyrromethane wherein each bears a single substituent, the A or B group, at the *meso*-position.[6] The availability of diverse *meso*-substituted dipyrromethanes[36–38] facilitates work in this area.

The paper begins with considerations that have influenced the choice of bioconjugatable tethers and PEG groups. The synthesis of 12 target porphyrins is presented next; the candidate bioconjugatable tethers include carboxaldehyde, ethylphenol, phenylisothiocyanate, ethylisothiocyanate, *N*-hydroxysuccinimidyl

(NHS) ester of benzoic acid, and NHS ester of phenylpropanoic acid. Selected porphyrins were examined for water solubility by absorption spectroscopy over a 1000-fold range of concentration (0.1–100 μM). The preferred candidates that emerged from this broad survey were porphyrins equipped with NHS esters and a *meso*-aryl group bearing –(OCH$_2$CH$_2$)$_7$-CO$_2$H (or –(OCH$_2$CH$_2$)$_4$-OMe) groups at the 2,6-positions. The companion paper[39] focuses on quantitative evaluation of the kinetics and yields of conjugation of porphyrin-NHS esters with amines. Taken together, the studies provide insights into molecular design as well as quantitative data for bioconjugation of porphyrins with amines in aqueous solution under mild conditions.

Results and discussion

Bioconjugatable linkers – reconnaissance

The literature on bioconjugation is vast.[40] Application of new linkers in tetrapyrrole science is an ongoing area of research.[41] Only a few comments are warranted here bearing on factors that have influenced our choice of bioconjugation motifs. Treatment of an aniline with succinic anhydride affords the corresponding amido-succinimic acid, which has been used with water-soluble chlorins (*e.g.*, **III** → **III-NHS**, Scheme 1, panel 1).[42,43] Analysis of the reaction mixture upon attempted bioconjugation of the NHS ester (**III-NHS**) revealed the presence of a succinimide reaction product (**IV**) due to intramolecular cyclization,[43] a process also noted by others.[44,45] Thus, the simplicity of the installation of the amido-succinimic acid group presents a beguiling trap, which is best avoided by
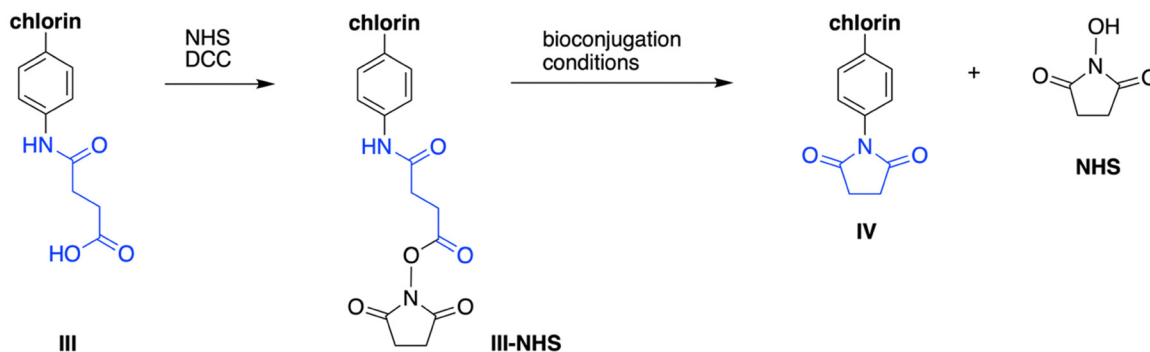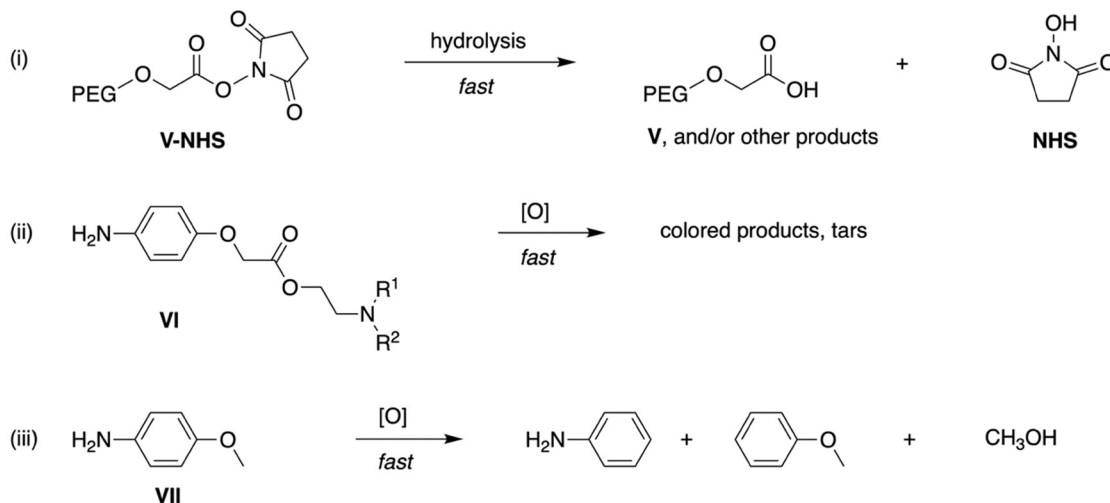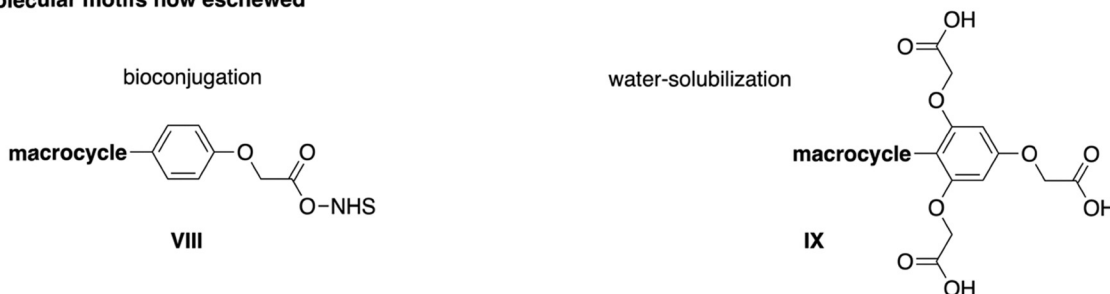
Scheme 1 Bioconjugation design considerations.

elision of the amido moiety; in other words, by use of the analogous phenylpropanoic acid[43,46] or the benzoic acid unit itself.

Earlier we had employed the phenoxyacetic acid unit as a water-solubilization motif[14,15] and as a linker (*via* an NHS ester).[8,15,16,42,47] While attractive from the viewpoint of convenient synthetic installation and versatile conjugation with amides, it has come to our attention that the linkage is not stable. Data concerning the hydrolysis half-lives of diverse NHS esters are published on the website of a bioconjugation company,[48] and while not peer-reviewed, the results, if credible, point to the instability of the oxyacetic acid motif: at pH 8 and 25 °C, the half-life of PEG–OCH_2CO_2–NHS (**V-NHS**, Scheme 1, panel 2) is 0.75 min, to be compared with PEG–$OCH_2CH_2CO_2$–NHS (16.5 min) and PEG–$OCH_2CH_2CH_2CO_2$–NHS (23.3 min).[48] Studies carried out in the mid-20th century – and seemingly little noticed since then – by the estimable Campaigne and Boucher flagged the instability of the *p*-aminophenoxyacetate systems denoted by **VI**.[49] The electron-rich amino and oxygen atoms in a 1,4-arrangement are susceptible to oxidation leading

to a quinonoid moiety, from which subsequent bond cleavage occurs as demonstrated by studies of *p*-anisidine (**VII**). Indeed, in the presence of a mild oxidizing agent,[49] "Aniline, methanol and anisole were isolated from the reaction mixtures even after the reactions [of *p*-anisidine (**VII**)] had been run only a few minutes" as shown in Scheme 1, panel 2, reaction iii. The tetrapyrrole macrocycle typically is electron-rich and likely could serve an analogous function as the amino group in **VI**. All told, the *p*-substituted phenoxyacetate systems that we employed previously (**VIII**, **IX**)[8,14–16,42,47] are undesired and henceforth shunned either as a bioconjugatable linker (**VIII**) or as a solubilization motif (**IX**) (Scheme 1, panel 3). Again, a

stable analogue is the phenylpropanoic acid group, where the ether oxygen atom of the phenoxyacetate is replaced with a methylene group, or simply the benzoic acid itself.

The above considerations led to the design of *trans*-AB-porphyrins (labeled **P1**–**P9** with various modifiers to designate functional group changes) that are equipped with a variety of candidate bioconjugatable linkers (Chart 2). The ethyl groups in selected designs were proposed with the notion to shift the reaction site some distance from the porphyrin ring. By contrast with the choice of bioconjugatable linkers, the designer faced with choice of PEG groups encounters an almost unlimited range of candidates. PEG groups are widely used for
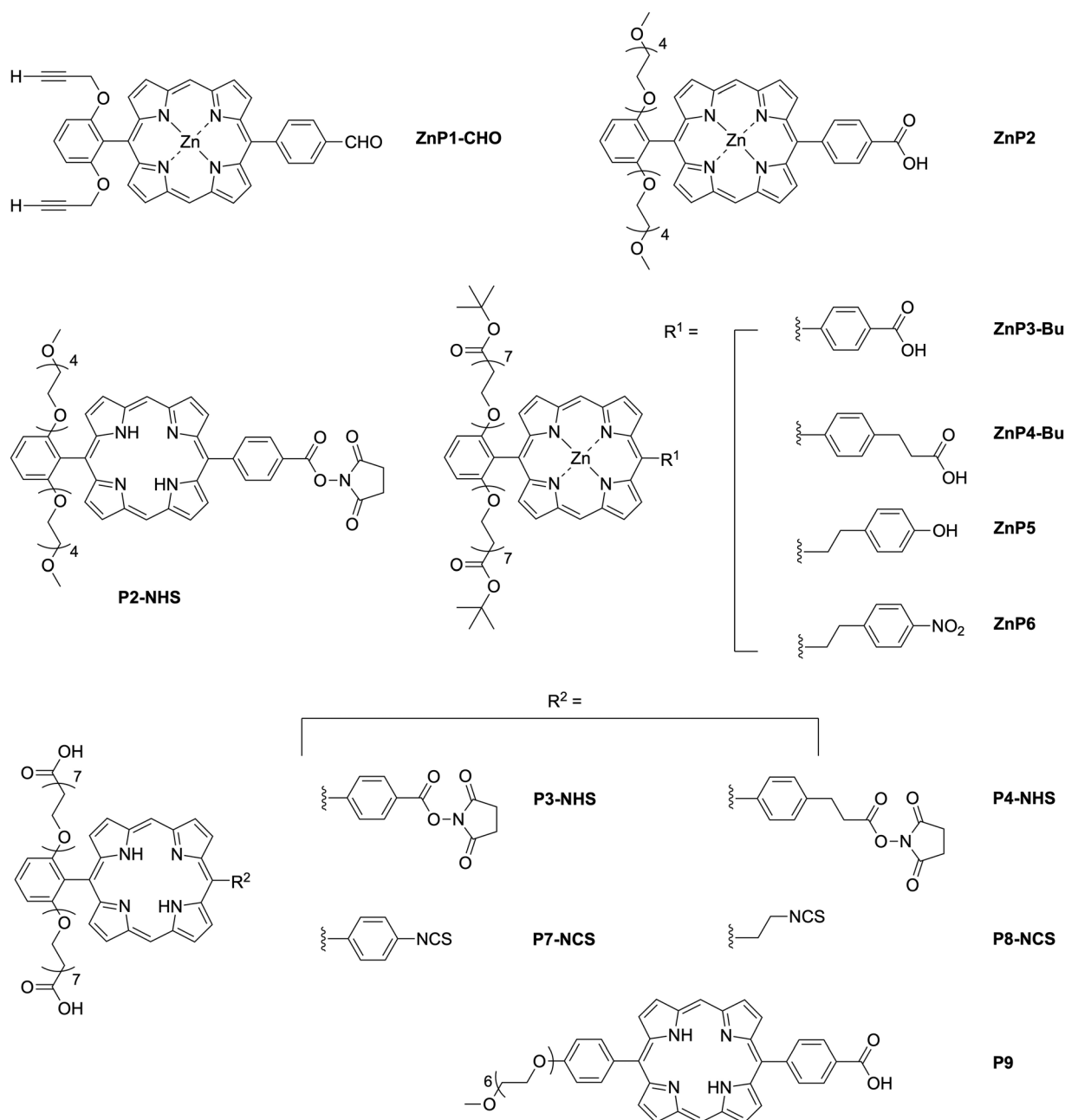

Chart 2 Target porphyrins.

aqueous solubilization across the molecular sciences,[50,51] in the pharmaceutical industry to increase systemic circulation,[52–54] and in tetrapyrrole chemistry.[2,5,25,55] The special properties of PEG groups have been the topic of extensive studies.[56–59] The PEG groups here differ in length (although in all cases short: 4–7 oligoethylene units), position of substitution on the aryl ring, and the presence of carboxylic acid or methyl terminal groups. The synthesis is reported next.
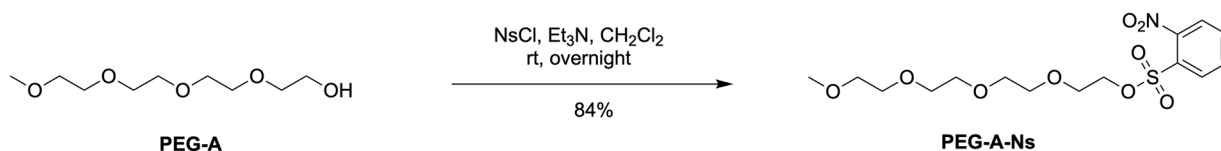
Syntheses of building blocks

Heterotelechelic monodisperse PEG reagents are widely available,[53,60–62] but often additional tailoring is required for specific applications. Here, m-PEG$_4$-OH (**PEG-A**) was reacted with 4-nitrobenzenesulfonyl chloride (NsCl) under basic condition[63] to give 2,5,8,11-tetraoxatridecan-13-yl 4-nitrobenzenesulfonate (**PEG-A-Ns**) in 84% yield (Scheme 2).

Two aldehydes used for the ultimate preparation of NHS esters include 4-formylbenzoic acid (**A1**) and 3-(4-formylphenyl)-propanoic acid (**A2**). The coupling reaction[64] of aldehyde **A2** and 2-(trimethylsilyl)ethanol with N,N'-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) gave aldehyde **A3** in 78% yield (Scheme 3).

For facial encumbrance of the porphyrin, 2,6-dihydroxy-benzaldehyde (**A4**) was used as a scaffold onto which two types of PEG groups were grafted. The reaction[65] of **PEG-A-Ns** with **A4** in N,N-dimethylformamide (DMF) containing K$_2$CO$_3$ gave the diPEGylated benzaldehyde **A5** as an oil in 60% yield (Scheme 3). Similarly, the reaction of **A4** with **PEG-B** gave the diPEGylated benzaldehyde **A6** in 65% yield.

The aldehydes used here for preparing dipyrromethanes (Scheme 4) include those that are new (**A3**, **A5**, **A6**), known (**A7**,[20] **A8**,[6] **A9**,[64] **A10**,[66] **A11**,[67] **A14**[68]), or commercially available (**A1**, **A2**, **A4**, **A12**, **A13**). Known aldehyde **A14**[68] was prepared herein from p-hydroxybenzaldehyde and bromo **PEG-C** (see Scheme S1, ESI†), which proceeded in higher yield and larger scale (94%, 1.51 g) than with the corresponding iodo-PEG reagent[68] (67%, 0.12 g). Each aldehyde was subjected to a standard dipyrromethane-formation strategy,[69,70] taking neat pyrrole as the solvent and reactant under acidic condition following by treatment of base (typically triethylamine or NaOH) to give the desired product. In this manner, aldehydes **A3** and **A5–A14** were converted to the corresponding dipyrromethanes **D3** and **D5–D14**. The dipyrromethanes include those that are new (**D3**, **D5**, **D6**, **D10**, **D11**, **D13**, **D14**) and those that are known (**D7**,[20] **D8**,[71] **D9**,[72] **D12**[9]). The reactions were carried out using trifluoroacetic acid (TFA), a catalyst employed in an early method of synthesis,[69] with triethylamine for neutralization upon workup. In so doing, the yields varied from 47% to 89%. Examination in one case (aldehyde **A5**) of InCl$_3$[70] as catalyst instead of TFA, and workup with NaOH instead of triethylamine, gave the dipyrromethane **D5** in 33% yield. The reaction of aldehyde **A13** was worked up with NaOH.

Seven of the dipyrromethanes were treated with Eschenmoser's reagent (N,N-dimethylmethyleneiminium iodide)[6] to afford the desired counterparts **D3-Esch** and **D8-Esch–D13-Esch** in 33% to quantitative yield (Scheme 4). The dipyrromethane derivatives include two that are known (**D8-Esch**,[19] **D12-Esch**[9]) whereas all others are new. The reaction was carried out at 0 °C to room temperature and worked up by aqueous–organic

Scheme 2 Activation of a PEG moiety.
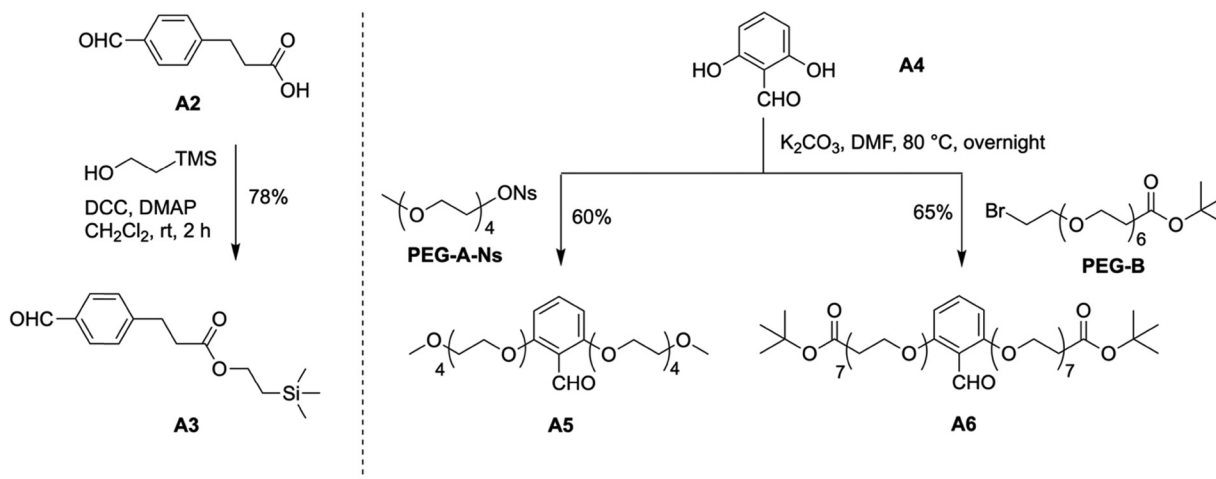
Scheme 3 New aldehyde building blocks.
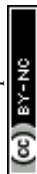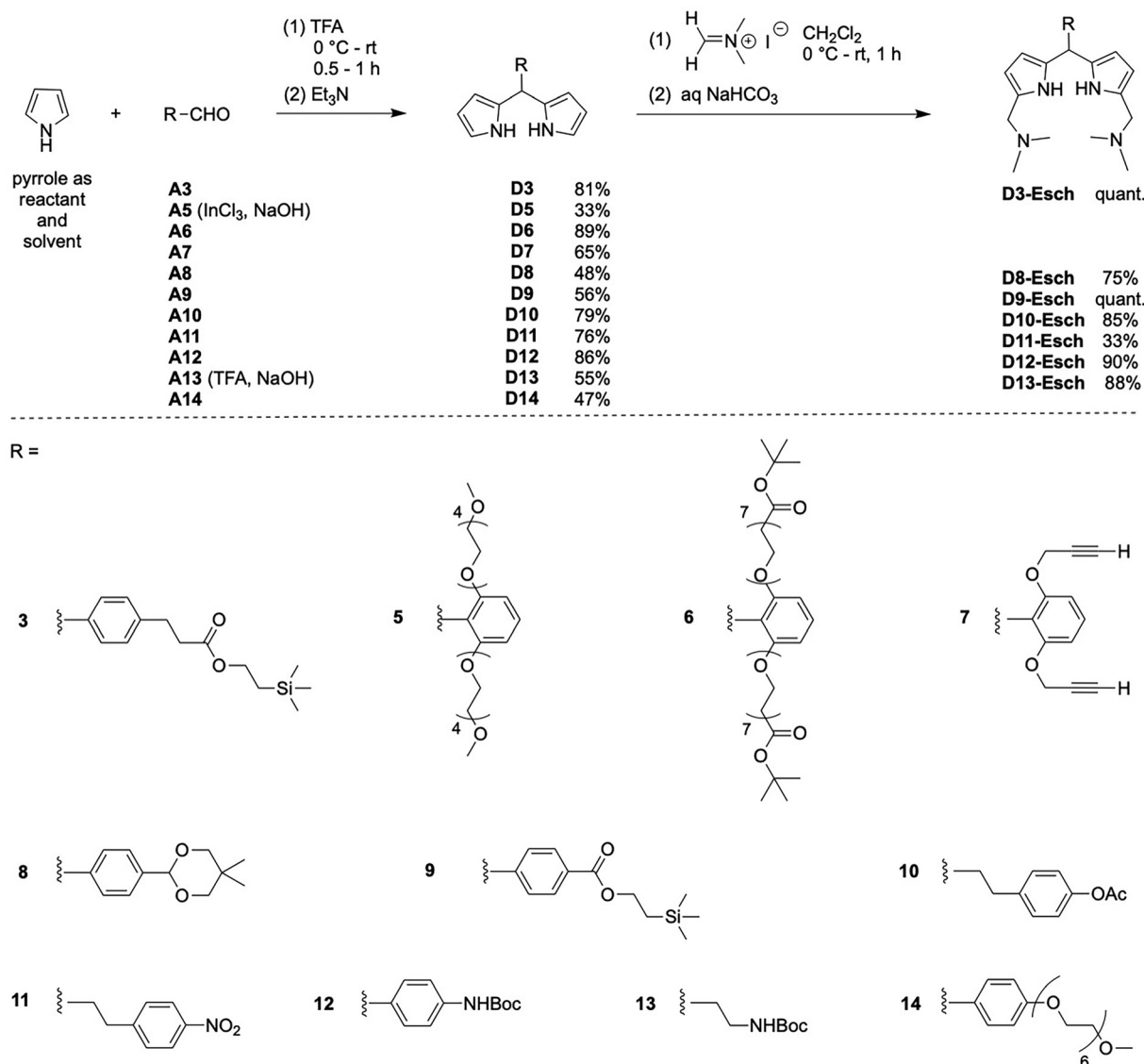
Scheme 4 Synthesis of dipyrromethanes.

extraction. In general, the crude product so obtained was examined by ^{1}H NMR spectroscopy to confirm the integrity and then used without further purification in the following reaction. A more expansive description of conditions for use of the Eschenmoser salt with dipyrromethanes is provided in the Experimental section.
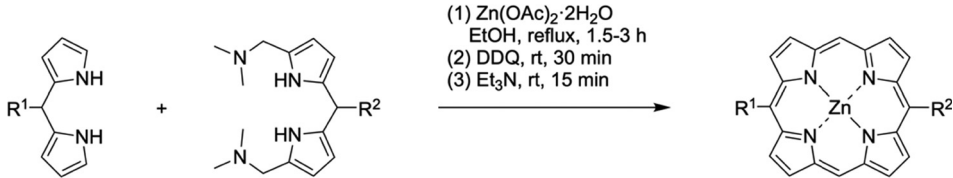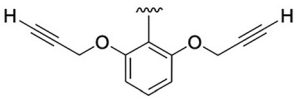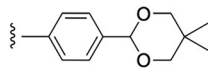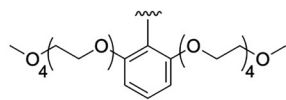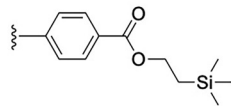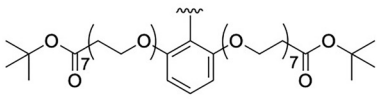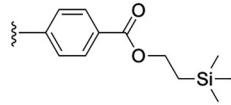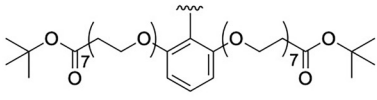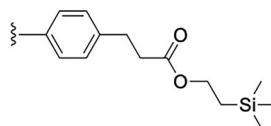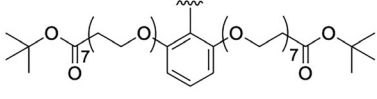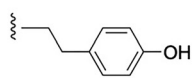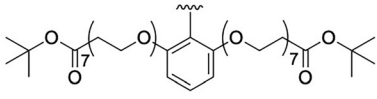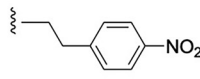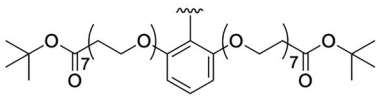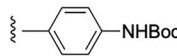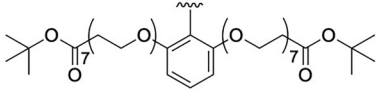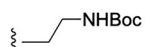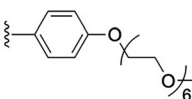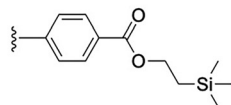
Rational syntheses of porphyrins

One rational synthetic approach to access *trans*-AB-porphyrins entails the condensation of a dipyrromethane and a 1,9-bis(*N*,*N*-dimethylaminomethyl)dipyrromethane in the presence of zinc acetate followed by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[6] The product is the zinc(II) *trans*-AB-porphyrin (Table 1). Thus, dipyrromethanes (**D5–D7**, and **D14**) characterized by distinct R^1 substituents and 1,9-bis(*N*,*N*-dimethylaminomethyl)dipyrromethanes (**D3-Esch**, **D8-Esch**, **D9-Esch**, **D10-Esch**, **D11-Esch**, **D12-Esch**, and **D13-Esch**) with varying R^2 groups were used to form the corresponding

trans-AB-porphyrins. This route yielded nine *trans*-AB-porphyrins in yields ranging from 5–12% (Table 1). The porphyrin abbreviations denote key protecting groups *tert*-butyl (Bu), *tert*-butoxycarbonyl (Boc), 2-(trimethylsilyl)ethyl (ETMS), and 4,4-dimethylisopropylidene acetal (acetal). The dipyrromethanes were used to carry the moieties for aqueous solubilization (R^1) whereas the 1,9-bis(*N*,*N*-dimethylaminomethyl)dipyrromethanes carried the bioconjugatable linker (R^2). The R^1 substituents in these porphyrins were PEG groups except for the alkyne-functionalized R^1 in **ZnP1-acetal**, which provides a versatile handle for click chemistry. Conversely, under appropriate deprotection conditions, the R^2 substituents in all porphyrins (except **ZnP5** and **ZnP6**) function as reactive sites for bioconjugation. In the case of porphyrin **ZnP5**, the reactive site is directly available without deprotection. The *O*-acetyl group of **D10-Esch** was cleaved during the formation of **ZnP5**. Porphyrin **ZnP5**, which contains a *p*-hydroxyphenethyl group, was unstable at room temperature.

Table 1 Synthesis of *trans*-AB zinc(II) porphyrins

Reagents: (1) Zn(OAc)$_2$·2H$_2$O, EtOH, reflux, 1.5–3 h; (2) DDQ, rt, 30 min; (3) Et$_3$N, rt, 15 min

D + DEsch/porphyrin	R^1	R^2	Yield
D7 + D8-Esch **ZnP1-acetal**	dipropargyloxy aryl	aryl dimethyl-dioxane acetal	8%
D5 + D9-Esch **ZnP2-ETMS**	bis(tetraethyleneglycol methyl ether) aryl	aryl ester–CH$_2$CH$_2$–TMS	5%
D6 + D9-Esch **ZnP3-Bu/ETMS**	bis(Boc-PEG) aryl	aryl ester–CH$_2$CH$_2$–TMS	7%
D6 + D3-Esch **ZnP4-Bu/ETMS**	bis(Boc-PEG) aryl	aryl propanoate–TMS	6%
D6 + D10-Esch **ZnP5**	bis(Boc-PEG) aryl	phenethyl–OH	6%
D6 + D11-Esch **ZnP6**	bis(Boc-PEG) aryl	phenethyl–NO$_2$	7%
D6 + D12-Esch **ZnP7-Bu/Boc**	bis(Boc-PEG) aryl	aryl–NHBoc	5%
D6 + D13-Esch **ZnP8-Bu/Boc**	bis(Boc-PEG) aryl	alkyl–NHBoc	7%
D14 + D9-Esch **ZnP9-ETMS**	aryl–O–PEG$_6$	aryl ester–CH$_2$CH$_2$–TMS	12%

The attempted reduction of the nitro group of **ZnP6** by treatment with SnCl$_2$ failed to give the *p*-aminophenethyl free base porphyrin. Both phenethyl designs (**ZnP5, ZnP6**) were discontinued.

The removal of protecting groups or modification of functional groups is required in some cases to unveil moieties for bioconjugation.[73,74] Here, treatment of **ZnP1-acetal** to acidic conditions[19] unveiled the formyl group and caused dezincation to give free base porphyrin-aldehyde **P1-CHO** (Scheme 5). The aldehyde group allows further bioconjugation through the formation of oxime or hydrazone linkages.[75] For click chemistry,[23–25] to prevent the insertion of copper ion into the porphyrin core,[22,46] zinc was subsequently reintroduced using
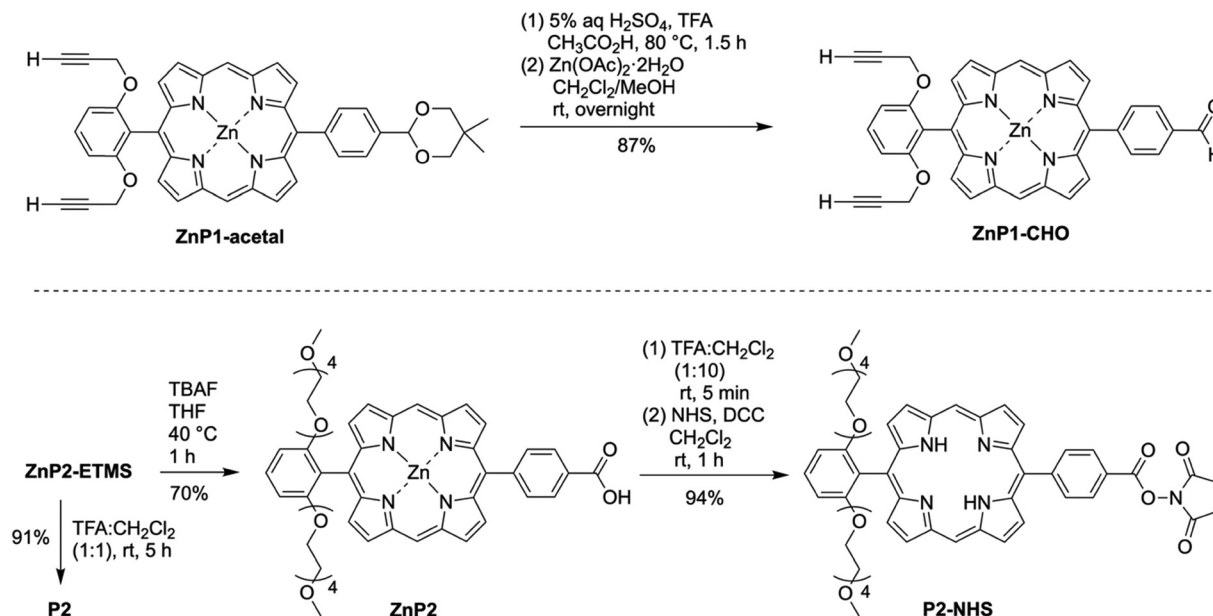
Scheme 5 Elaboration of porphyrins.

zinc acetate in a solution of dichloromethane and methanol to give **ZnP1-CHO** in 87% yield. The protected trimethylsilylethyl ester of **ZnP2-ETMS** was cleaved with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF)[21] to give zinc porphyrin–carboxylic acid **ZnP2** in 70% yield. Treatment of the latter with TFA caused dezincation, and reaction with N-hydroxysuccinimide (NHS) mediated by DCC[42] afforded the porphyrin-NHS ester **P2-NHS** following preparative thin layer chromatography (TLC) in 94% yield (3.5 mg) suitable for bioconjugation (Scheme 5). Additionally, **ZnP2-ETMS** was treated[22] with TFA in CH$_2$Cl$_2$ to give deprotected free base porphyrin **P2** in 91% yield.

Porphyrins **ZnP3-Bu/ETMS** and **ZnP4-Bu/ETMS** resemble **ZnP2-ETMS** but contain a *tert*-butyl ester at the terminus of each PEG chain. Treatment with TBAF in THF selectively cleaved the ETMS protecting group in the presence of the *tert*-butyl esters to give porphyrin–carboxylic acid **ZnP3-Bu** or **ZnP4-Bu** in 85% or 88% yield, respectively (Scheme 6). Subsequent esterification with NHS and DCC[42] gave the respective porphyrin-NHS ester **ZnP3-Bu/NHS** or **ZnP4-Bu/NHS** in high yield. Finally, treatment of **ZnP3-Bu/NHS** with TFA in CH$_2$Cl$_2$ gave the bis(carboxy-terminated PEG)porphyrin-NHS ester **P3-NHS** in 90% yield (8.7 mg, by preparative TLC), whereas **ZnP4-Bu/NHS** gave the analogous free base porphyrin-NHS ester **P4-NHS** in 85% yield (2.4 mg, by reversed-phase HPLC).

Hydrolyzed products of porphyrin-NHS esters **P3-NHS** and **P4-NHS** were sought for use in studies of amidation. Thus, treatment of porphyrin **ZnP3-Bu/ETMS** or **ZnP4-Bu/ETMS** with TFA in CH$_2$Cl$_2$ (1 : 1) gave global deprotection and dezincation to afford the free base porphyrin–tricarboxylic acid **P3** or **P4** in 63% yield or 89% yield, respectively (Scheme 7).

Porphyrins **ZnP7-Bu/Boc** and **ZnP8-Bu/Boc** differ from **ZnP3-Bu/ETMS** and **ZnP4-Bu/ETMS** in the nature of the bioconjugatable group – the presence of a protected amino group rather than a protected carboxylic acid group. Treatment of porphyrin

ZnP7-Bu/Boc or **ZnP8-Bu/Boc** with TFA in CH$_2$Cl$_2$ gave free base porphyrin-amine **P7** or **P8**, respectively (Scheme 8). Subsequent reaction with 1,1′-thiocarbonyldi-2(1H)-pyridone[76] in CH$_2$Cl$_2$ gave the corresponding bioconjugatable porphyrin-isothiocyanate **P7-NCS** or **P8-NCS** upon preparative TLC in 80% (5.6 mg) or 64% (2.6 mg) yield, respectively.

Finally, treatment of zinc porphyrin **ZnP9-ETMS** with TFA in CH$_2$Cl$_2$ caused cleavage of the ETMS group and dezincation to afford free base porphyrin–carboxylic acid **P9** in 78% yield (Scheme 9).

Statistical syntheses of porphyrins

Studies of bioconjugation showed the value of porphyrins **P3-NHS** and **P4-NHS**, as reported in the companion paper.[39] The syntheses shown in Scheme 6 afforded each porphyrin-NHS ester in small quantities (8.7 mg and 2.4 mg, respectively). A chief focus became to increase the quantities of the target porphyrins. While doing so, we also sought to avoid reliance on time-consuming and scale-limiting specialized chromatography: **P3-NHS** was prepared with use of two preparative TLC procedures, while **P4-NHS** was prepared with use of one preparative TLC procedure and with reversed-phase HPLC.

trans-AB-porphyrins can be prepared in a rational manner as described above, or in a statistical process.[69] The latter, with two aldehydes and one dipyrromethane, affords a mixture of three *trans*-substituted porphyrins bearing A$_2$-, B$_2$-, or AB-substituents. The statistical process is more expedient but relies on the ability to separate the resulting mixture of porphyrins. Thus, the condensation of aldehyde **A1**, dipyrromethane, and aldehyde **A6** with TFA catalysis followed by oxidation with DDQ gave porphyrin **P3-Bu** in 10% yield (Scheme 10). Similarly, statistical condensation of aldehyde **A2**, dipyrromethane, and aldehyde **A6** gave porphyrin **P4-Bu**
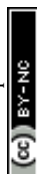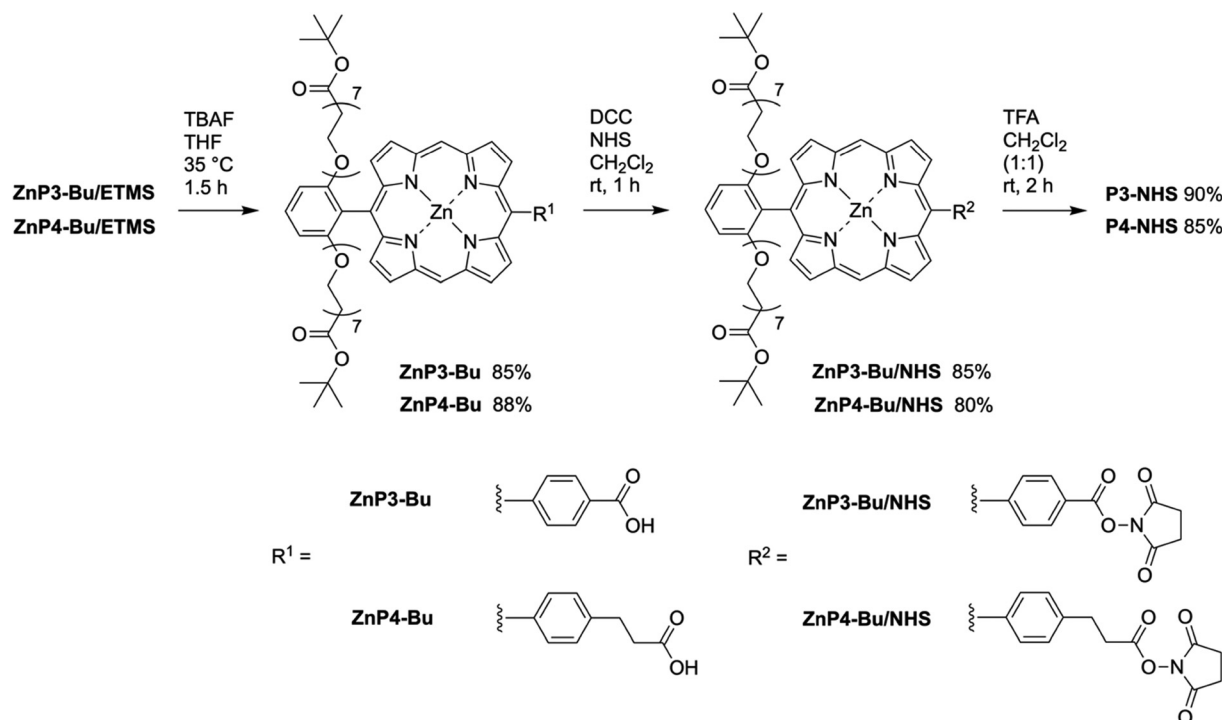
Scheme 6 Synthesis of bioconjugatable porphyrins.
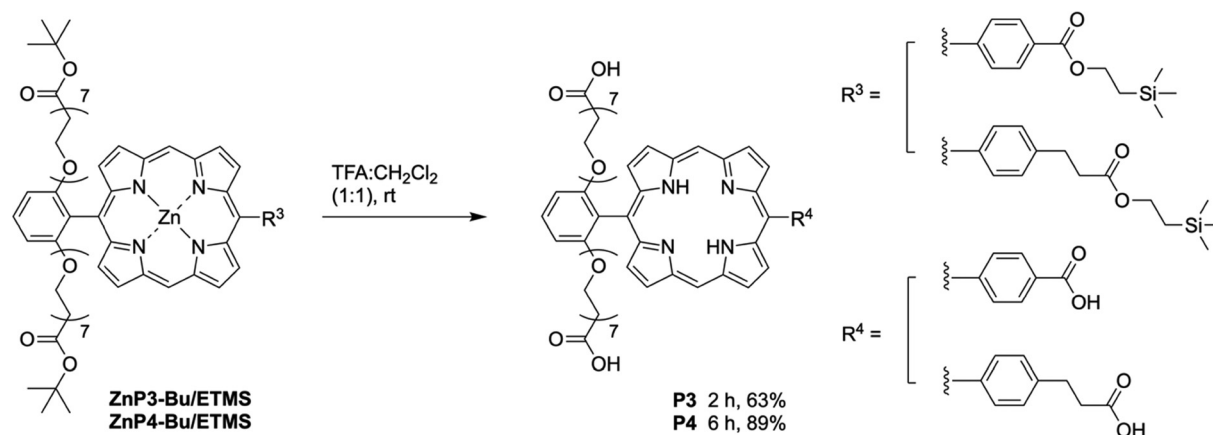
Scheme 7 Synthesis of hydrolyzed porphyrin standards.

in 11% yield. In each case, three red bands were observed upon chromatography, with the desired porphyrin as the middle band, which was easily isolated by column chromatography. Treatment of porphyrin **P3-Bu** or **P4-Bu** with NHS and DCC[42] afforded **P3-Bu/NHS** or **P4-Bu/NHS** in high yield. Finally, **P3-Bu/NHS** or **P4-Bu/NHS** was treated with TFA in CH_2Cl_2 to obtain the porphyrin-NHS ester **P3-NHS** or **P4-NHS** in 97% or 94% yield, respectively. The two target porphyrins were obtained in quantity of 19.7 or 26.6 mg, respectively, without use of preparative TLC or HPLC procedures for purification.

Characterization

The porphyrins were typically characterized by absorption spectroscopy, ^{1}H NMR and ^{13}C{^{1}H} NMR spectroscopy, matrix-assisted

laser desorption ionization mass spectrometry (MALDI-MS), and electrospray ionization mass spectrometry (ESI-MS). Selected results are described in the following.

The ^{1}H NMR spectra of the zinc *trans*-AB-porphyrins **ZnP9-ETMS** and **ZnP2-ETMS** are displayed in Fig. 1. The resonances from the PEG unit in the 4-phenyl-substituted **ZnP9-ETMS** appear in the range δ 4.4–2.8 ppm, while those of 2,6-disubstituted **ZnP2-ETMS** were observed in the range δ 4.0–1.4 ppm. The lone terminal methyl group of the 4-phenyl-substituted **ZnP9-ETMS** resonates as a singlet at δ 2.85 ppm, whereas both terminal methyl groups of the 2,6-disubstituted **ZnP2-ETMS** resonate as a singlet at δ 2.33 ppm. The distinct chemical shift pattern is attributed to the location of the PEG groups with respect to the aromatic ring current of the
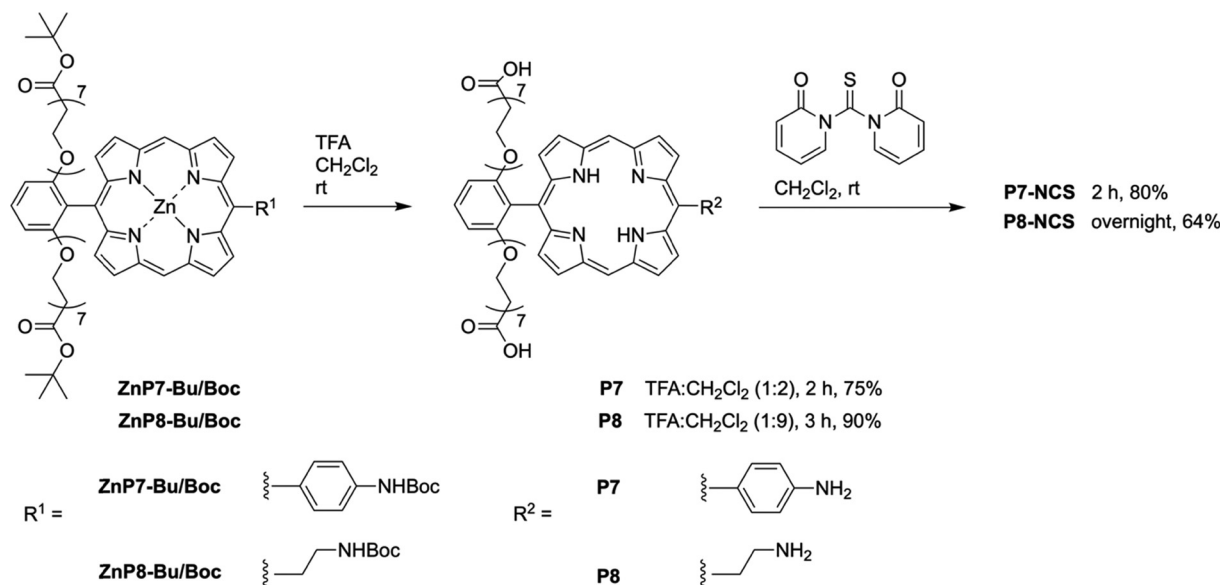
Scheme 8 Synthesis of porphyrins for bioconjugation.
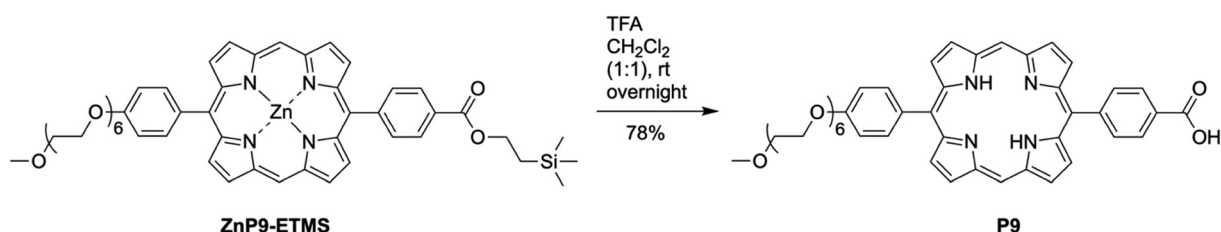
Scheme 9 Synthesis of porphyrin–benzoic acid **P9**.

porphyrin macrocycle: thrust outward in the equatorial plane of **ZnP9-ETMS** *versus* projected over the faces of the porphyrin π-system in **ZnP2-ETMS**.

The absorption spectra of the free base or zinc porphyrins showed the characteristic strong (Soret) band in the near-ultraviolet region and the expected manifold of weaker peaks in the visible region. Representative spectra are shown in methanol for free base porphyrin **P3-Bu/NHS** (405 nm Soret; 500, 534, 573, 629 nm) and zinc porphyrin **ZnP3-Bu/NHS** (412 nm Soret; 544, 580 nm) in Fig. S1 (ESI†).

The structure of dipyrromethane **D7** (Fig. S2, ESI†) and zinc porphyrin **ZnP1-acetal** were determined by single-crystal X-ray diffraction (Fig. S3, ESI†). In the porphyrin, the propargyloxy groups project above and below the plane of the porphyrin macrocycle, as observed for analogous porphyrins bearing 2,6-disubstituted aryl groups.[22,77]

The ESI-MS spectrum of free base porphyrin–tricarboxylic acid **P3** displayed the expected m/z isotopic manifolds for species with $z = 1$ and $z = 2$, where the charged species stemmed from protonation. The most intense peak in each respective manifold was as follows: 1211.5260 ($z = 1$) and 606.2669 ($z = 2$). The observed and calculated masses were in good agreement for double protonation, $\Delta[M + 2H]^{2+} = 0.0007\ m/z$, which corresponds to 1.15 ppm (Fig. S4, ESI†). Multiply charged ions

have been observed of analogous PEGylated porphyrin[19] or PEGylated chlorins.[46]

Solubility assessments in aqueous solution

Porphyrins **P2**, **P3**, **P4**, and **P9** were selected for self-aggregation studies and $\log P$ measurements, where P is the partition coefficient between 1-octanol and an aqueous medium. The rationale for selecting such porphyrins was as follows. Porphyrins **P3** and **P4** were of highest importance given structural similarity to the porphyrin chassis used to prepare porphyrin–folate **II** (Chart 1). Porphyrin **P2** was chosen as an analogue of **P3** but without carboxylate-terminated PEG groups. Porphyrin **P9** was chosen as an additional analogue but with a single PEG group disposed at the *p*-position rather than the *o*-positions of the *meso*-aryl group.

Self-aggregation in aqueous solution. Following the general method for aggregation studies,[22,78] the samples were dissolved in phosphate-buffered saline (PBS). Here, PBS has pH 7.4 and contains 137 mM NaCl, 10 mM phosphate, and 2.7 mM KCl. Self-aggregation was assessed by the integrity of the spectral bands in absorption spectroscopy upon examination of the porphyrin in solution over a large concentration range. With a fixed cuvette pathlength, the range of available concentrations is limited, and observed changes may reflect limitations
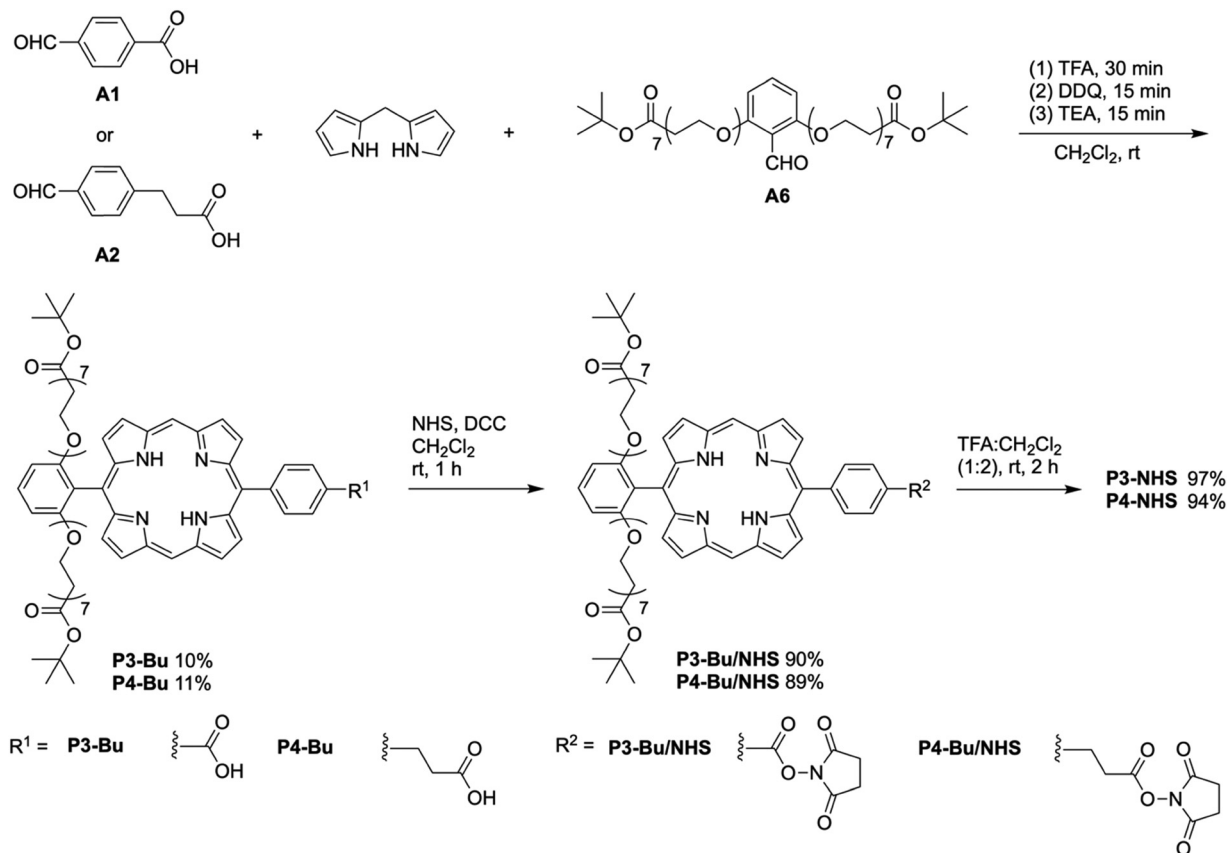
Scheme 10 Synthesis of porphyrins.

in dynamic range of the absorption spectrophotometer rather than changes in solution of the solubilized/aggregated chromophores. But upon reciprocal change of analyte concentration (0.1–100 μM) and cuvette pathlength (100–0.1 mm), a concentration range of 1000-fold or larger can be examined.[22,78] For homogeneous dispersions of chromophores in solution, the absorbance (A) is expected to remain constant as the product of the concentration (c) and pathlength (l) remains constant, as specified in Beer's law: $A = \varepsilon l c$. On the other hand, the occurrence of self-aggregation is expected to give rise to band broadening.

The results over a 1000-fold range of concentration and of cuvette pathlength are shown in Fig. 2. Porphyrin **P2** displayed peak broadening at 100 μM, indicative of aggregation. No peak broadening was detected at concentrations less than 10 μM. The absorption spectra of porphyrin **P3** were essentially identical with each other over the 1000-fold range of concentration, consistent with a homogeneous solution at each concentration. The absorption spectra of porphyrin **P4** showed a very slight change in intensity; on the other hand, spectral broadening, a telltale sign of aggregation, was hardly detected. Porphyrin **P9**, which bears a neutral PEG group at the *p*-position, displayed an expected broad Soret band even at 1 μM (not shown). Examination of **P9** at higher concentrations was not carried out due to insolubility in aqueous solution. As observed previously,[22] PEG groups at the *o*-aryl positions (**P2**, **P3** and **P4**) project above and

below the plane of the macrocycle, and may suppress π–π stacking, with additional repulsion imparted by the negative charges of the carboxylate termini in porphyrins **P3** and **P4**.

Log P measurements. The partitioning of an organic compound between octanol and aqueous solution was assessed for porphyrins **P2**, **P3**, **P4**, and **P9** (∼10^{-4} M total porphyrin concentration). A sample was removed from each layer and analyzed by absorption spectroscopy in dimethylsulfoxide (DMSO).[22,78] Porphyrin **P2**, which bears neutral PEG groups at the 2,6-positions of the aryl group, was found entirely in the octanol layer (log $P > 2$), while porphyrin **P4**, which bears PEG groups with carboxylic acid termini, was found entirely in the aqueous solution (log $P < -2$). Porphyrins **P3** and **P4**, which bear identical PEG chains but different functional groups on the distal side (benzoic acid and phenylpropanoic acid, respectively), exhibited slightly different log P values: −1.5 for **P3**, < −2 for **P4**. A log P value of **P9** could not be determined due to insolubility in aqueous solution, which was as expected given the position of the PEG group relative to the porphyrin macrocycle (Table 2).

Initial assessments of bioconjugation in aqueous solution

Porphyrins **P3-NHS**, **P4-NHS**, **P7-NCS**, and **P8-NCS** were subjected to reaction with a short amino-PEG to assess conjugation efficacy. The porphyrin NHS-esters (**P3-NHS**, **P4-NHS**) gave excellent results, which are described in the companion paper.[39]
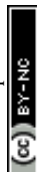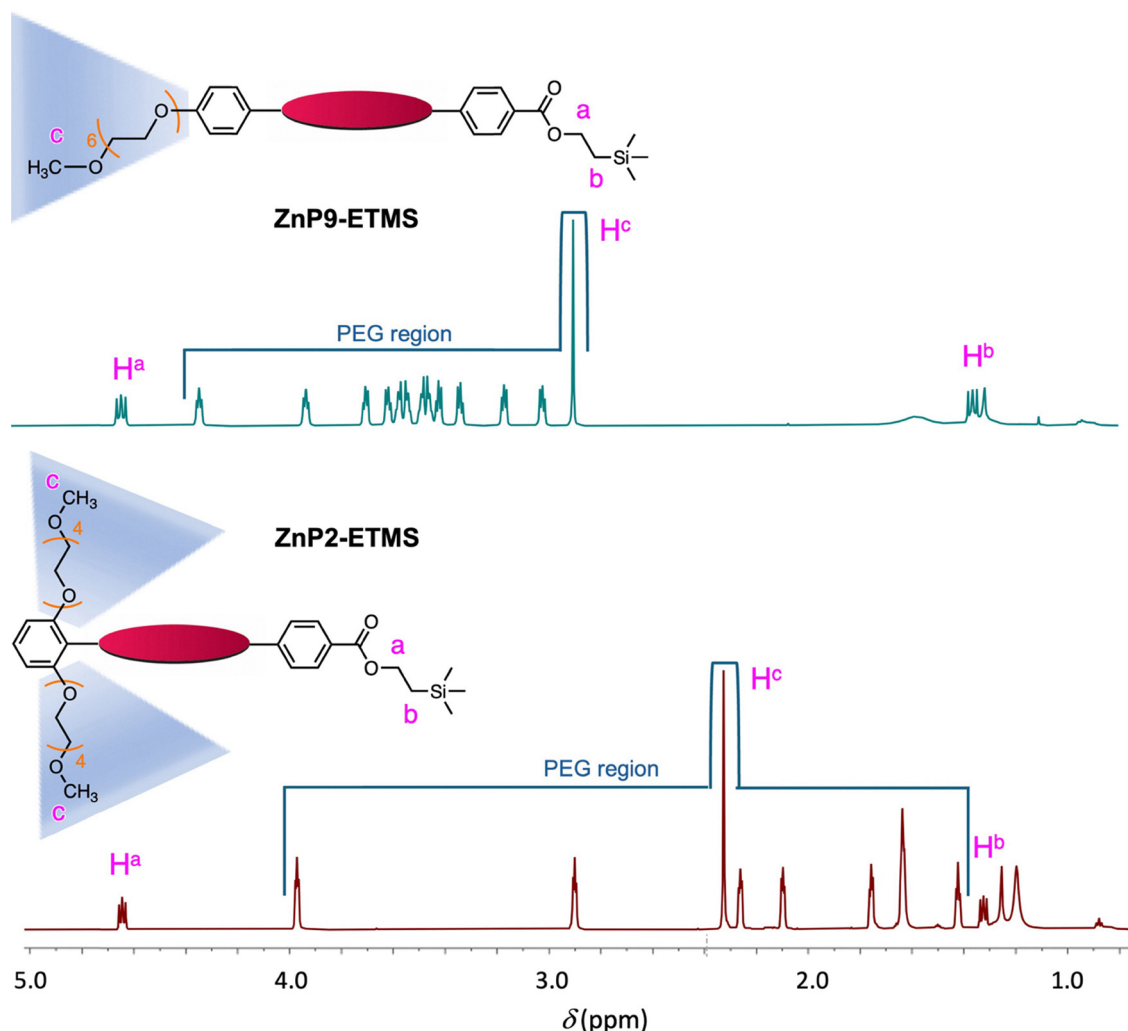
Fig. 1 Partial upfield region of the ¹H NMR spectra in CDCl₃ at room temperature of two zinc porphyrins. Peaks assigned to the PEG chains and the ethyl moiety of the ETMS linker are indicated.

With **P7-NCS**, the crude mixture after 1 h showed numerous components upon HPLC analysis (Fig. S5, ESI†). With **P8-NCS**, almost no reaction occurred after 24 h, but a major unknown product derived from the porphyrin was observed (Fig. S6, ESI†). The isothiocyanate derivatives proved quite inferior to the NHS esters in the conjugation reactions, and were not studied further. More extensive bioconjugation studies are described in the companion paper.[39]

Outlook

The challenges and solutions for creating water-soluble tetra-pyrrole macrocycles have been reviewed by several research groups.[1–5] The evolution of tetrapyrrole-compatible water-soluble designs investigated by our group has been outlined in various treatments.[22,43,46,55] The target porphyrins prepared herein were designed to bear one water-solubilization group and one bioconjugatable linker in the sparsely substituted architecture of a *trans*-AB-porphyrin. The syntheses of the 12 target porphyrins (Chart 2) have pointed up limitations, particularly in yields, of existing approaches for porphyrin

synthesis. The low yield in turn generally gave small quantities of porphyrins, which while workable for studies of solubility properties and bioconjugation, often led to challenges in purification. Porphyrins **P2-NHS**, **P3-NHS**, **P4-NHS**, **P7-NCS**, and **P8-NCS** were prepared in a rational fashion in quantities of 2.4–8.7 mg. On the other hand, porphyrins **P3-NHS** and **P4-NHS** were prepared in a statistical fashion at larger scale (19.7 or 27.6 mg, respectively).

A comparison of the rational *versus* statistical methods can be seen upon examination of the syntheses of **P3-NHS** and **P4-NHS**. Both afford good yields following macrocycle formation but differ in accessible scale.

● The rational method requires two designer dipyrro-methanes (each of which requires a synthetic aldehyde), affords a single zinc porphyrin, and requires use of an ester (here, ETMS) in the constituent that is used to make the Eschenmoser dipyrromethane (Table 1 and Scheme 6). The rational method required one or two chromatography columns to obtain the macrocycle, preparative TLC following TBAF cleavage of the ETMS group, one chromatography column upon NHS installation, and
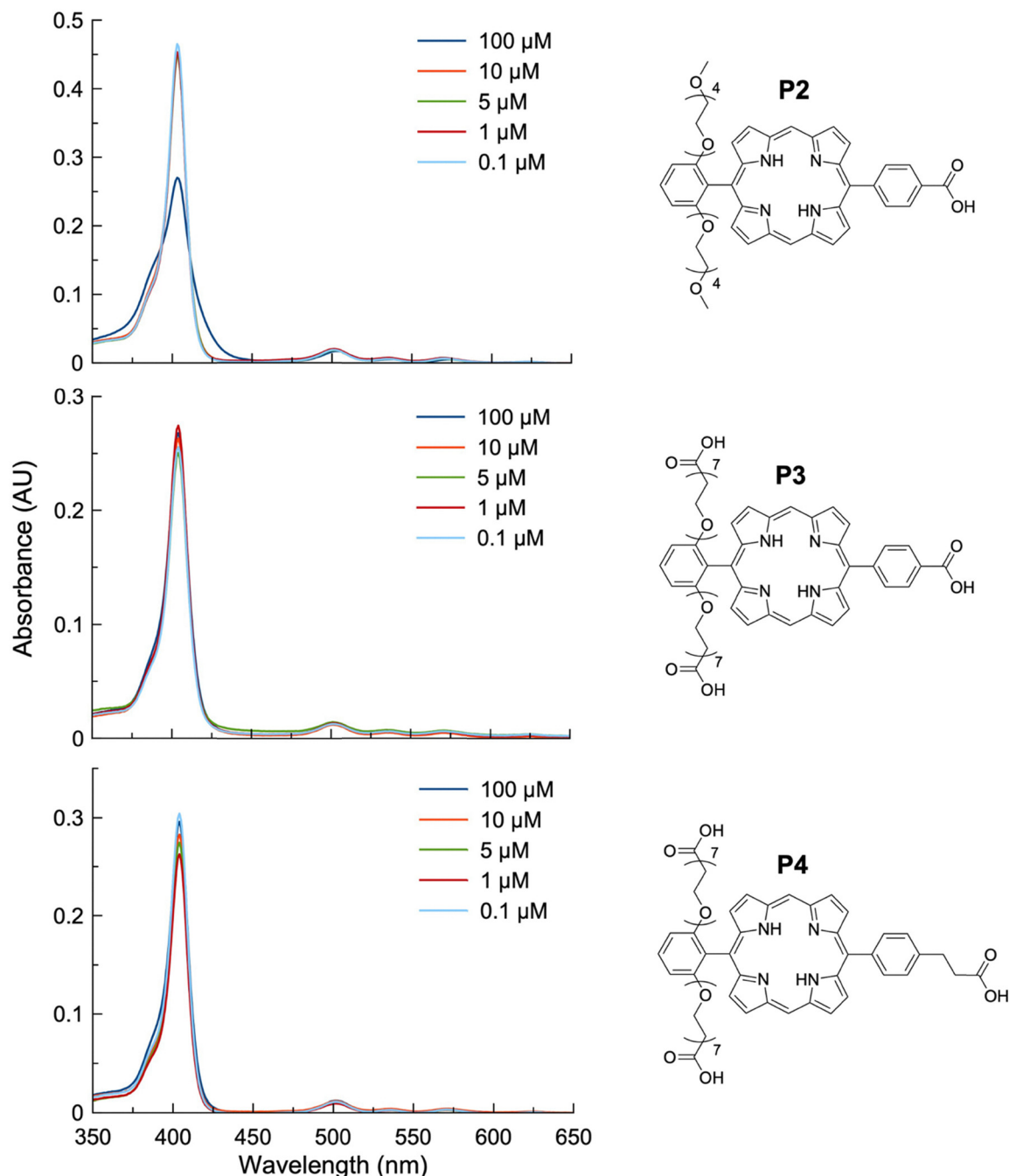
Fig. 2 Absorption spectra of porphyrins in aqueous PBS at room temperature. Spectra were collected as described previously[22,78] with reciprocal change of cuvette pathlength (0.1, 1.0, 2.0, 10, and 100 mm) and sample concentration (100, 10, 5, 1 and 0.1 μM).

Table 2 Aqueous–organic partitioning of porphyrins

Compounds	Projection	PEG number	Terminus	Log P
P2	2,6-	4	–OMe	> 2
P3	2,6-	6	–CO$_2$H	-1.5
P4	2,6-	6	–CO$_2$H	< -2
P9	4-	6	–OMe	ND[a]

[a] Not determined because of insolubility in aqueous solution.

preparative TLC or reversed-phase HPLC upon TFA cleavage of the *tert*-butyl groups to give the porphyrin-NHS ester.

● The ostensibly more complex statistical method requires one generic dipyrromethane and two aldehydes (one of which is commercially available and is used as the free carboxylic acid rather than the ester) to afford three free base porphyrins (Scheme 10). The statistical method required two chromatography columns to obtain the free base *trans*-AB-porphyrin, one chromatography column upon NHS installation, and a

C18-silica pad upon TFA cleavage of the *tert*-butyl groups. Given the availability of the two aldehydes and the dipyrromethane, the overall synthesis entails three steps (macrocycle formation, NHS ester formation, and *tert*-butyl ester cleavage.

• Quantitative comparison is provided here for the syntheses of **P3-NHS**. The statistical route used 461 mg of **A6** (and stoichiometric amounts of 4-formylbenzoic acid (**A1**) and dipyrromethane) to obtain 65.9 mg (10% yield) of free base porphyrin **P3-Bu**. One-third thereof was carried forward to obtain **P3-Bu/NHS** (23.5 mg) and the latter then on to **P3-NHS** (19.7 mg). The rational route used 208 mg of **D6** and 96 mg of **DEsch-9** to obtain 20 mg (7% yield) of zinc porphyrin **ZnP3-Bu/ETMS**, which upon TBAF treatment gave porphyrin **ZnP3-Bu** (16.2 mg). Subsequent transformations mirrored the statistical route to give **ZnP3-Bu/NHS** (13.2 mg) and **P3-NHS** (11.0 mg), with about 85% of each intermediate carried through to the following step. The total quantity of **P3-NHS** obtained *via* the two routes was not substantially different, but the rational route entailed a greater number of steps and more extensive chromatography.

The implementation of the C18-silica pad for final purification (following TFA cleavage of the *tert*-butyl groups) was adopted at a later stage during the course of the research program, and likely could be used in both routes; however, the impediments to scale in the rational route appear to accrete in several stages: (1) the several-step synthesis of bespoke *meso*-substituted dipyrromethanes, (2) the acutely low yield in the Eschenmoser route to the porphyrin macrocycles, and (3) the difficulties in purification upon cleavage of ETMS esters with these intrinsically polar PEG-containing porphyrins. While both routes install the PEG-containing water-solubilization motifs at early stages of the synthesis (prior to macrocycle formation), the statistical route employs the free carboxylic acid and does not require a deprotection step with TBAF. Higher yields in macrocycle formation would obviously be greatly beneficial, but short of that refined ideal, further studies are required to better understand the issues of synthetic steps, purification challenges, and yields to gain better access to the PEG-containing porphyrin-NHS esters.

Water-soluble synthetic porphyrins have been known for more than one-half century, yet most contain four *meso*-substituents and are not equipped for bioconjugation.[22] Key to the use of a single bioconjugatable motif is a companion design strategy for aqueous solubilization. Here, solubilization in aqueous media was gauged by investigation of the absorption spectrum upon reciprocal change in concentration and cuvette pathlength. Upon doing so with a porphyrin bearing a single benzoic acid, the presence of a 2,6-bis[CH$_3$O(CH$_2$CH$_2$O)$_4$-]phenyl group (**P2**) or 2,6-bis[HO$_2$C(CH$_2$CH$_2$O)$_7$-]phenyl group (**P3** or **P4**) was found to afford solubility up to 10 or 100 μM, respectively. In this design, the ionizable carboxylic acid unit at the terminus of each short PEG unit imparts a significant difference for aqueous solubility at slightly basic pH values. The PEG groups, while relatively short, provide adequate facial encumbrance of the hydrophobic porphyrin π-system. While an effort has been made in recent years to investigate other

chromophores, there remains much interest in porphyrins. Indeed, PEGylated porphyrins have been widely used; representative examples include to treat solid tumors with photo-dynamic therapy (PDT),[79–82] to facilitate imaging-guided disease treatment,[83–86] to detect toxic inorganic species in water *via* turn-off[87,88] or turn-on[89–91] of generic fluorescent probes, and to achieve oxidative catalysis in aqueous media.[92–96]

Porphyrins **P3**, **P4**, and **III–VIII** displayed no band broadening over the accessible concentration regime, which reaches to ∼0.1 mM, and are regarded as highly soluble in aqueous solution. It warrants emphasis that in the presence of success – where no spectral band broadening is observed at the highest concentrations accessible (∼0.1 mM) – little insight can be gleaned; in other words, the reciprocal concentration–cuvette pathlength method is not effective for discrimination among the various architectures to identify superior molecular designs for aqueous solubilization. Regardless, the emergence of **P3** and **P4** as compact porphyrins that are water-soluble and accessible without use of copper-mediated click chemistry represents a successful outcome. Quantitative studies of bioconjugation with the porphyrin-NHS esters **P3-NHS** and **P4-NHS** are reported in the companion paper.[39] Taken together, the work reported herein should facilitate the design, synthesis, and bioconjugation of water-soluble porphyrins in diverse applications.

Experimental section

General methods

THF was freshly distilled from sodium/benzophenone ketyl and used immediately. Commercially available compounds were used as received. Silica (SiliaFlash® P60, 40–63 μm, Silicycle, R12030B) and C$_{18}$-silica (C18 60A, 40–63 μm, Silicycle, R33230B) were used for column chromatography. Preparative reversed-phase HPLC was performed on a Buchi® PrepPure C850 with a Buchi® column (C18 100 Å, 10 μm, LC column 250 × 10 mm).

^{1}H and ^{13}C{^{1}H} NMR spectra were recorded in CD$_3$OD, CD$_2$Cl$_2$ or CDCl$_3$ at room temperature. Chemical shifts for ^{1}H NMR spectra are reported in parts per million (δ) relative to tetramethylsilane or a solvent signal [CD$_3$OD, δ = 3.31 ppm; CD$_2$Cl$_2$, δ = 5.32 ppm; CDCl$_3$, δ = 7.26 ppm]. Chemical shifts for ^{13}C{^{1}H} NMR spectra are reported in parts per million (δ), and spectra were calibrated by using tetramethylsilane or solvent signals [CD$_3$OD, δ = 49.00 ppm; CD$_2$Cl$_2$, δ = 53.84 ppm; CDCl$_3$, δ = 77.16 ppm].

MALDI-MS was performed using the matrix α-cyano-4-hydroxycinnamic acid (α-CHCA). Absorption spectra were collected in toluene, MeOH, DMSO, MeCN/H$_2$O (80 : 20), and MeCN/H$_2$O (95 : 5) at room temperature. ESI-MS data are reported for the molecular ion, anionized or cationized molecular ion.

Known compounds

Known aldehydes (**A7**,[20] **A8**,[6] **A9**,[64] **A10**,[66] **A11**,[67] **A14**[68]), dipyrromethanes (**D7**,[20] **D8**,[71] **D9**,[72] **D12**[9]), and Eschenmoser dipyrromethanes (**D8-Esch**,[19] **D12-Esch**[9]) were prepared as described in

the literature. Known aldehyde **A14**[68] was prepared as described in the ESI.†

SCXRD analysis

The diffraction data of known dipyrromethane **D7** and the porphyrin **ZnP1-acetal** reported here were collected using a Bruker D8 Venture diffractometer at 100 K with MoKα (0.71073 Å). The diffraction data were obtained and integrated by APEX4 software with SAINT and SADABS. The crystal structure was calculated, refined, and visualized using ShelXLe,[97] OLEX2 with ShelXL,[98] and Mercury 4.0[99] software. Hydrogen atoms were placed at calculated positions and refined using a riding model.

Examination of concentration-dependent self-aggregation

A porphyrin sample was dissolved in PBS 1× to prepare a 1 mM stock solution of porphyrin. PBS 1× (pH 7.4) contains 137 mM NaCl, 10 mM phosphate, and 2.7 mM KCl. The porphyrin stock solution was filtered through a 0.2 μm PTFE filter, and the concentration of the filtrate was determined based on the absorbance. The filtrate was diluted with PBS 1× to prepare solutions of porphyrin at 100 μM, 10 μM, 5 μM, 1 μM and 0.1 μM solutions. The absorption spectra of those solutions were recorded at room temperature.

Determination of log P values

Values were determined at room temperature following a reported method.[78] The quantity of porphyrin employed was ~0.2–0.4 mg in an octanol–aqueous solution of 2 mL. An aliquot (100 μL) of each phase was removed by microsyringe and was placed in 3.0 mL of DMSO, and the absorption spectrum of each phase was measured. In each case, octanol refers to 1-octanol. The ratio between the intensity of maximum absorption for the two phases (octanol/water) was calculated.

Initial bioconjugation assessments

The initial bioconjugation assessment was carried out with a porphyrin and the amino-PEG reactant **NH$_2$-PEG$_6$-OH** in aqueous solution (pH 9.0) at room temperature. Reaction mixtures were analyzed after 1 h by HPLC with absorption spectral and mass spectral detection. The experimental methods are described in the companion paper.[39]

Formation of 1,9-bis(N,N-dimethylaminomethyl)dipyrromethanes by use of Eschenmoser's reagent

Key points are as follows:

(1) Eschenmoser's reagent (N,N-dimethylmethyleneiminium iodide) was employed as obtained commercially as a fine powder.

(2) For workup, the reaction mixture typically was diluted with additional CH$_2$Cl$_2$ and washed several times with aqueous NaHCO$_3$ solution to completely remove unreacted remaining reagent and any iodide. The organic layer was collected, washed with brine, dried with Na$_2$SO$_4$, and concentrated under reduced

pressure to afford a dark (brown or black) amorphous solid that often consisted of a dry powder.

(3) Thorough washing of the crude reaction product is essential to avoid carryover of iodide into the porphyrin-forming reaction, whereupon DDQ oxidation, a mono-iodo-substituted porphyrin can result. Here, the high polarity of the PEG-containing porphyrins rendered difficult the separation of any iodo-porphyrin byproduct from the target porphyrin.

(4) The crude, Eschenmoser dipyrromethane was generally characterized by ^{1}H NMR and ^{13}C{^{1}H} NMR spectroscopy and then used in the next step without further purification.

(5) The Eschenmoser dipyrromethanes (as dry solids under an inert atmosphere) can be stored at room temperature for a long period.

(6) Use of the chloride salt of Eschenmoser's reagent was not fruitful. The synthesis of **D13-Esch** was attempted in this manner, but a complex reaction mixture formed, containing tri- or tetra-alkylated products, which were difficult to remove from the desired dialkylated, 1,9-bis(N,N-dimethylaminomethyl)-dipyrromethane (the Eschenmoser dipyrromethane).

PEG reagent

2,5,8,11-Tetraoxatridecan-13-yl 4-nitrobenzenesulfonate (PEG-A-Ns). Following a reported method[63] with some modifications, a solution of **PEG-A** (2.1 g, 10 mmol) and 4-nitrobenzenesulfonyl chloride (2.7 g, 12 mmol) in CH$_2$Cl$_2$ (20 mL) at 0 °C was treated dropwise with triethylamine (2 mL) for 10 min. The reaction mixture was allowed to warm to room temperature and stirred overnight. After the reaction was completed on the basis of TLC analysis [silica, CH$_2$Cl$_2$/ethyl acetate (1:1)], the resulting solution was washed with water and brine, dried (Na$_2$SO$_4$), and then concentrated to dryness under reduced pressure. The crude product was chromatographed [CH$_2$Cl$_2$/ethyl acetate (1:1)] to afford a colorless liquid (3.3 g, 84%): ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.16 (d, J = 7.8 Hz, 1H), 7.83–7.73 (m, 3H), 4.43–4.41 (m, 2H), 3.79–3.77 (m, 2H), 3.64–3.53 (m, 12H), 3.37 (s, 3H); ^{13}C{^{1}H} NMR (175 MHz, CDCl$_3$) δ 148.5, 134.8, 132.5, 131.4, 130.0, 124.9, 72.1, 71.4, 70.9, 70.71, 70.70, 70.66, 70.6, 68.7, 59.1; ESI-MS obsd 394.1157, calcd 394.1161 [(M + H)$^+$], M = C$_{15}$H$_{23}$NO$_9$S.

Aldehydes

4-(3-(2-(Trimethylsilyl)ethoxy)-3-oxopropyl)benzaldehyde (A3). Following a reported method[64] with some modifications, a solution of **A2** (356 mg, 2.00 mmol) and 2-(trimethylsilyl)ethanol (1.18 g, 10.0 mmol) in CH$_2$Cl$_2$ (10.0 mL) was stirred at room temperature. After 10 min, DMAP (36.7 mg, 0.300 mmol) and DCC (454 mg, 2.20 mmol) were added. The reaction mixture was stirred at room temperature for 2.5 h, then filtered to remove the precipitate. The filtrate was concentrated under reduced pressure. The crude residue was chromatographed [silica, hexanes/CH$_2$Cl$_2$ (1:2)] to afford a colorless oil (436 mg, 78%): ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.98 (s, 1H), 7.81 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 4.18–4.14 (m, 2H), 3.03 (t, J = 7.7 Hz, 2H), 2.64 (t, J = 7.7 Hz, 2H), 0.97–0.94 (m, 2H), 0.03 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 192.0, 172.7, 148.1, 135.0, 130.2, 129.2, 63.0, 35.5, 31.2,

17.5, −1.4; ESI-MS obsd 301.1221, calcd 301.1230 [(M + Na)$^+$], M = $C_{15}H_{22}O_3Si$.

2,6-Bis((2,5,8,11-tetraoxatridecan-13-yl)oxy)benzaldehyde (A5). Following a reported method[65] with some modifications, a solution of **A4** (31 mg, 0.22 mmol) in DMF (1.0 mL) was treated with K_2CO_3 (125 mg, 0.904 mmol) at 60 °C (oil bath). After 30 min, a sample of **PEG-A-Ns** (224 mg, 0.570 mmol) was slowly added, and the resulting suspension was heated to 80 °C (oil bath) and stirred overnight at 80 °C (oil bath). The reaction mixture was washed with water (×2) and brine, dried (Na_2SO_4), and then concentrated to dryness under reduced pressure. The crude residue was chromatographed [CH_2Cl_2/MeOH (12 : 1)] to afford a brown liquid (69 mg, 60%): ^1H NMR (700 MHz, $CDCl_3$) δ 10.51 (s, 1H), 7.39 (t, J = 8.4 Hz, 1H), 6.58 (d, J = 8.5 Hz, 2H), 4.19 (t, J = 5.0 Hz, 4H), 3.90–3.89 (m, 4H), 3.76–3.75 (m, 4H), 3.67–3.63 (m, 16H), 3.55–3.54 (m, 4H), 3.37 (s, 6H); $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$) δ 189.1, 161.3, 135.5, 115.1, 105.4, 71.9, 71.0, 70.7, 70.59, 70.58, 70.5, 69.4, 68.8, 59.0; ESI-MS obsd 519.2800, calcd 519.2787 [(M + H)$^+$], M = $C_{25}H_{42}O_{11}$.

2,6-Bis((1-tert-butyloxy-1-oxo-4,7,10,13,16,19-hexaoxahenicosan-21-yl)oxy)benzaldehyde (A6). Following a reported method[65] with some modifications, a solution of **A4** (414 mg, 3.00 mmol) in DMF (7.5 mL) was treated with K_2CO_3 (1.66 g, 0.0120 mol) for 30 min at 65 °C (oil bath) followed by the addition of **PEG-B** (2.98 g, 6.30 mmol). The mixture was stirred overnight at 80 °C (oil bath). After the reaction was completed as determined by TLC (CH_2Cl_2/MeOH, 15 : 1) analysis, the reaction mixture was concentrated under reduced pressure to remove DMF. The crude product was dissolved in CH_2Cl_2 (50 mL), extracted with water (2 × 50 mL), extracted with brine (2 × 50 mL), and dried (Na_2SO_4). The combined organic extract was dried under reduced pressure. The residue was purified by chromatography [silica, CH_2Cl_2/MeOH (40 : 1)] to give a yellow liquid (1.79 g, 65%): ^1H NMR (700 MHz, $CDCl_3$) δ 10.25 (s, 1H), 7.15 (t, J = 8.4 Hz, 1H), 6.34 (d, J = 8.4 Hz, 2H), 3.94 (q, J = 4.9, 4.2 Hz, 4H), 3.50–3.32 (m, 48H), 2.24–2.21 (m, 4H), 1.21–1.19 (m, 18H); $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$) δ 188.5, 170.5, 161.0, 135.4, 114.8, 105.2, 80.0, 70.7, 70.4, 70.3, 70.2, 70.1, 69.1, 68.6, 66.6, 36.0, 27.9; ESI-MS obsd 923.5191, calcd 923.5210 [(M + H)$^+$], M = $C_{45}H_{78}O_{19}$.

Dipyrromethanes

5-(4-(3-(2-(Trimethylsilyl)ethoxy)-3-oxopropyl)phenyl)dipyrromethane (D3). Following a reported method[69] with some modifications, a sample of **A3** (399 mg, 1.43 mmol) in distilled pyrrole (20.0 mL, 286 mmol) was stirred at 0 °C (ice bath) under argon. After 10 min, TFA (16 μL, 0.210 mmol) was slowly added, and the reaction mixture was stirred at 0 °C (ice bath) for 30 min. Then, triethylamine (200 μL, 1.43 mmol) was added to quench the reaction. The solvent was removed under reduced pressure. The crude residue was chromatographed [silica, CH_2Cl_2] to afford a pale-yellow solid (459 mg, 81%): ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (s, 2H), 7.16–7.12 (m, 4H), 6.69 (td, J = 2.7, 1.5 Hz, 2H), 6.15 (q, J = 2.9 Hz, 2H), 5.92–5.90 (m, 2H), 5.45 (s, 1H), 4.19–4.15 (m, 2H), 2.93 (t, J = 7.9 Hz, 2H), 2.61–2.58 (m, 2H), 1.00–0.96 (m, 2H), 0.04 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 173.2, 140.1, 139.5, 132.7, 128.7, 128.6, 117.3, 108.6,

107.3, 62.8, 43.8, 36.1, 30.7, 17.5, −1.3; ESI-MS obsd 417.1954, calcd 417.1969 [(M + Na)$^+$], M = $C_{23}H_{30}N_2O_2Si$.

5-[2,6-Bis((2,5,8,11-tetraoxatridecan-13-yl)oxy)phenyl]dipyrromethane (D5). Following a reported method[70] with some modifications, a solution of **A5** (295 mg, 0.569 mmol) in pyrrole (4.0 mL) was stirred at room temperature under argon. After 15 min, $InCl_3$ (38 mg, 0.17 mmol) was added to the mixture. The reaction mixture was stirred for 1.5 h at room temperature, then NaOH (68 mg, 1.7 mmol) was added, and the mixture was stirred for 45 min. The mixture was filtered (Fisher brand qualitative paper), and the filtrate was concentrated under reduced pressure to remove residual pyrrole. The crude mixture was chromatographed [silica, CH_2Cl_2/MeOH (15 : 1)] to give a brown liquid (118 mg, 33%): ^1H NMR (500 MHz, $CDCl_3$) δ 9.30 (s, 2H), 7.07 (t, J = 8.4 Hz, 1H), 6.62 (q, J = 2.1 Hz, 2H), 6.50 (s, 2H), 6.22 (s, 1H), 6.03 (q, J = 2.8 Hz, 2H), 5.90–5.88 (m, 2H), 4.04 (s, 4H), 3.72–3.49 (m, 28H), 3.35 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 156.9, 132.9, 127.7, 120.6, 116.1, 107.2, 105.8, 71.9, 70.8, 70.58, 70.55, 70.45, 70.43, 69.7, 59.0, 32.9; ESI-MS obsd 635.3521, calcd 635.3538 [(M + H)$^+$], M = $C_{33}H_{50}N_2O_{10}$.

5-[2,6-Bis((1-tert-butyloxy-1-oxo-4,7,10,13,16,19-hexaoxahenicosan-21-yl)oxy)phenyl]dipyrromethane (D6). Following a reported method[69] with some modifications, a sample of **A6** (1.38 g, 1.50 mmol) in distilled pyrrole (20.8 mL, 300 mmol) was stirred at 0 °C (ice bath) under argon. After 10 min, TFA (18 μL, 0.235 mmol) was slowly added, and the reaction mixture was stirred at 0 °C (ice bath) for 30 min. Then, triethylamine (209 μL, 1.50 mmol) was added. The solvent was removed under reduced pressure. The crude residue was chromatographed [silica, CH_2Cl_2/MeOH (40 : 1)] to afford a yellow liquid (1.40 g, 89%): ^1H NMR (500 MHz, $CDCl_3$) δ 9.25 (s, 2H), 7.06 (t, J = 8.2 Hz, 1H), 6.61–6.60 (m, 2H), 6.49 (s, 2H), 6.21 (s, 1H), 6.03–6.01 (m, 2H), 5.90–5.85 (m, 2H), 4.05 (s, 4H), 3.72–3.53 (m, 48H), 2.49 (t, J = 6.6 Hz, 4H), 1.44 (s, 18H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 170.9, 132.9, 127.7, 120.6, 116.1, 107.3, 105.8, 80.5, 77.3, 70.8, 70.59, 70.57, 70.54, 70.52, 70.51, 70.48, 70.43, 70.35, 69.7, 66.9, 36.3, 32.9, 28.1; ESI-MS obsd 1039.5939, calcd 1039.5948 [(M + H)$^+$], M = $C_{53}H_{86}N_2O_{18}$.

5-(2-(4-Acetoxyphenyl)ethyl)dipyrromethane (D10). Following a reported method[69] with some modifications, a sample of **A10** (288 mg, 1.50 mmol) in distilled pyrrole (20.8 mL, 300 mmol) was stirred at 0 °C (ice bath) under argon. After 10 min, TFA (18 μL, 0.235 mmol) was slowly added, and the reaction mixture was stirred at 0 °C (ice bath) for 45 min. Then, triethylamine (209 μL, 1.50 mmol) was added. The solvent was removed under reduced pressure. The crude residue was chromatographed [silica, CH_2Cl_2/ethyl acetate (40 : 1)] to afford a pale-yellow solid (366 mg, 79%): ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (s, 2H), 7.16 (d, J = 8.5 Hz, 2H), 6.99 (d, J = 8.5 Hz, 2H), 6.63 (td, J = 2.7, 1.5 Hz, 2H), 6.16 (q, J = 2.9 Hz, 2H), 6.09 (td, J = 2.9, 1.7 Hz, 2H), 3.97 (t, J = 7.6 Hz, 1H), 2.63–2.60 (m, 2H), 2.30–2.24 (m, 5H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 169.8, 148.9, 139.5, 133.2, 129.5, 121.5, 121.4, 117.3, 108.3, 105.7, 37.0, 36.1, 33.0, 21.3; ESI-MS obsd 309.1590, calcd 309.1598 [(M + H)$^+$], M = $C_{19}H_{20}N_2O_2$.

5-(2-(4-Nitrophenyl)ethyl)dipyrromethane (D11). Following a reported method[70] with some modifications, a solution of **A11**

(964 mg, 5.38 mmol) and pyrrole (70 mL) was stirred at 0 °C (ice bath) under argon for 5 min, then TFA (62 μL) was added slowly. The reaction was stirred at 0 °C (ice bath) for 30 min, then triethylamine (750 μL) was added. The mixture was concentrated under reduced pressure. The crude product was chromatographed [silica, hexanes/CH_2Cl_2 (1:4) to CH_2Cl_2] to afford a yellow liquid (1.2 g, 76%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 (d, J = 6.0 Hz, 2H), 7.78 (s, 2H), 7.31 (d, J = 6.0 Hz, 2H), 6.66–6.65 (m, 2H), 6.18–6.15 (m, 2H), 6.11–6.09 (m, 2H), 3.99 (t, J = 7.6 Hz, 1H), 2.74 (t, J = 6Hz, 2H), 2.32–2.28 (m, 2H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 149.8, 146.4, 132.5, 129.3, 123.7, 117.5, 108.3, 105.7, 37.0, 35.6, 33.5; ESI-MS obsd 296.1388, calcd 296.1394 [$(M + H)^+$], M = $C_{17}H_{17}N_3O_2$.

5-(4-(*tert*-Butyloxycarbonylamino)phenyl)dipyrromethane (D12). Following a reported method[69] with some modifications, a sample of A12 (443 mg, 2.00 mmol) in distilled pyrrole (28.0 mL, 400 mmol) was stirred at 0 °C (ice bath) under argon. After 10 min, TFA (23 μL, 0.30 mmol) was slowly added, and the reaction mixture was stirred at 0 °C (ice bath) for 30 min. Then, triethylamine (280 μL, 2.0 mmol) was added. The mixture was concentrated under reduced pressure. The crude residue was chromatographed [silica, CH_2Cl_2] to afford a yellow solid (580 mg, 86%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (s, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.13 (d, J = 8.5 Hz, 2H), 6.68 (td, J = 2.6, 1.5 Hz, 2H), 6.46 (s, 1H), 6.15 (q, J = 2.9 Hz, 2H), 5.92–5.90 (m, 2H), 5.43 (s, 1H), 1.52 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 152.9, 137.3, 136.8, 132.7, 129.1, 119.0, 117.3, 108.6, 107.2, 43.5, 28.5; ESI-MS obsd 360.1674, calcd 360.1683 [$(M + Na)^+$], M = $C_{20}H_{23}N_3O_2$.

5-(2-(*tert*-Butyloxycarbonylamino)ethyl)dipyrromethane (D13). Following a reported method[70] with some modifications, a solution of A13 (2.3 g, 13 mmol) in pyrrole (50 mL, 720 mmol) was treated dropwise with TFA (99 μL, 1.3 mmol) over 5 min. The mixture at room temperature was stirred under argon for 1 h followed by the addition of NaOH (1.0 g, 25 mmol). The crude mixture was stirred for 1 h, then filtered through a Celite pad (5 cm × 2 cm). The filtrate was concentrated and then chromatographed [silica, CH_2Cl_2/ethyl acetate (20:1 to 10:1)] to give a brown oil (2.07 g, 55%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (s, 2H), 6.75–6.57 (m, 2H), 6.14 (q, J = 2.9 Hz, 2H), 5.98 (s, 2H), 4.61 (t, J = 6.6 Hz, 1H), 4.03 (t, J = 7.4 Hz, 1H), 3.18 (q, J = 6.4 Hz, 2H), 2.09 (q, J = 6.7 Hz, 2H), 1.45 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 156.9, 133.3, 117.2, 108.2, 105.4, 79.7, 38.6, 36.2, 34.8, 28.5; ESI-MS obsd 290.1860, calcd 290.1863 [$(M + H)^+$], M = $C_{16}H_{23}N_3O_2$.

5-(4-((2,5,8,11,14,17-Hexaoxanonadecan-19-yl)oxy)phenyl)dipyrromethane (D14). Following a procedure[69] with modification, a sample of TFA (28 μL, 0.36 mmol) was added to a solution of A14 (1.47 g, 3.67 mmol) in freshly distilled pyrrole (26.0 mL, 382 mmol) at 0 °C (ice bath). The reaction mixture was stirred for 1 h at 0 °C (ice bath). Subsequently, triethylamine (0.55 mL) was added, and the resulting mixture was stirred for 15 min at 0 °C (ice bath). The mixture was concentrated under reduced pressure and then chromatographed [silica, CH_2Cl_2/ethyl acetate (2:1) followed by CH_2Cl_2/methanol (15:1)] to afford a brownish oil (0.89 g, 47%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01 (s, 2H), 7.12–7.10

(m, 2H), 6.68–6.84 (m, 2H), 6.69–6.68 (m, 2H), 6.14 (q, J = 3.0 Hz, 2H), 5.90–5.89 (m, 2H), 5.42 (s, 1H), 4.11–4.10 (m, 2H), 3.85–3.83 (m, 2H), 3.72–3.70 (m, 2H), 3.67–3.61 (m, 16H), 3.54–3.52 (m, 2H), 3.36 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 157.8, 134.4, 132.9, 129.4, 117.1, 114.7, 108.3, 107.0, 71.9, 70.8, 70.64, 70.59, 70.57, 70.55, 70.5, 69.7, 67.5, 59.0, 43.1; ESI-MS obsd 534.3177, calcd 534.3174 [$(M + NH_4)^+$], M = $C_{28}H_{40}N_2O_7$.

Eschenmoser dipyrromethanes

1,9-Bis(*N,N*-dimethylaminomethyl)-5-(4-(3-(2-(trimethylsilyl)ethoxy-3-oxopropyl)phenyl)dipyrromethane (D3-Esch). Following a reported method[6] with some modifications, a sample of D3 (450 mg, 1.14 mmol) in CH_2Cl_2 (11.4 mL) was stirred at 0 °C (ice bath) under argon. After 15 min, *N,N*-dimethylmethyleneiminium iodide (442 mg, 2.39 mmol) was added, and the reaction mixture was stirred at 0 °C (ice bath) for 35 min. Then, saturated aqueous NaHCO$_3$ (7.0 mL) was added. The reaction mixture was diluted with CH_2Cl_2 (40 mL) and washed with saturated aqueous NaHCO$_3$ (7 × 40 mL). The organic extract was dried (Na$_2$SO$_4$) and concentrated under reduced pressure to afford a yellow solid (561 mg, 97%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 2H), 7.12 (s, 4H), 5.90 (t, J = 2.9 Hz, 2H), 5.75–5.73 (m, 2H), 5.34 (s, 1H), 4.18–4.15 (m, 2H), 3.38–3.29 (m, 4H), 2.91 (dd, J = 8.7, 7.2 Hz, 2H), 2.59–2.58 (m, 2H), 2.17 (s, 12H), 0.99–0.96 (m, 2H), 0.04 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 173.2, 140.5, 139.1, 132.8, 128.9, 128.6, 128.5, 107.5, 106.8, 62.8, 56.8, 45.1, 44.0, 36.2, 30.7, 17.4, −1.3; ESI-MS obsd 509.3295, calcd 509.3306 [$(M + H)^+$], M = $C_{29}H_{44}N_4O_2Si$.

1,9-Bis(*N,N*-dimethylaminomethyl)-5-(4-(2-(trimethylsilyl)ethoxycarbonyl)phenyl)dipyrromethane (D9-Esch). Following a reported method[6] with some modifications, a solution of D9 (366 mg, 1.00 mmol) in CH_2Cl_2 (10 mL) was treated with *N,N*-dimethylmethyleneiminium iodide (726 mg, 3.92 mmol) under argon. The mixture was stirred for 1 h at room temperature, then CH_2Cl_2 (40 mL) was added to afford a homogeneous solution. The organic layer was washed (saturated aqueous NaHCO$_3$ (50 mL) and brine (50 mL)), dried (Na$_2$SO$_4$), and concentrated under reduced pressure to give a brown solid (479 mg, 100%): mp 67–69 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 2H), 7.98–7.93 (m, 2H), 7.30–7.26 (m, 2H), 5.93 (t, J = 2.9 Hz, 2H), 5.77–5.73 (t, J = 2.9 Hz, 2H), 5.43 (s, 1H), 4.43–4.37 (m, 2H), 3.50–3.34 (m, 4H), 2.23 (s, 12H), 1.15–1.08 (m, 2H), 0.08 (s, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 168.1, 149.0, 133.5, 131.1, 130.5, 129.75, 129.67, 109.4, 108.5, 64.6, 57.9, 46.1, 45.7, 18.8, 0.00; ESI-MS obsd 479.2848, calcd 479.2848 [$(M − H)^-$], M = $C_{27}H_{40}N_4O_2Si$.

1,9-Bis(*N,N*-dimethylaminomethyl)-5-(2-(4-acetoxyphenyl)ethyl)dipyrromethane (D10-Esch). Following a reported method[6] with some modifications, a sample of D10 (158 mg, 0.513 mmol) in CH_2Cl_2 (5.1 mL) was stirred at 0 °C (ice bath) under argon. After 10 min, *N,N*-dimethylmethyleneiminium iodide (199 mg, 1.08 mmol) was added, and the reaction mixture was stirred at 0 °C (ice bath) for 35 min. Then, saturated aqueous NaHCO$_3$ (5 mL) was added. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with saturated aqueous NaHCO$_3$

(6 × 25 mL). The organic extract was dried (Na_2SO_4), and concentrated under reduced pressure to afford a yellow solid (183 mg, 85%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 2H), 7.15 (d, J = 8.5 Hz, 2H), 6.97 (d, J = 8.5 Hz, 2H), 5.90 (d, J = 2.7 Hz, 4H), 3.91 (t, J = 7.6 Hz, 1H), 3.36–3.29 (m, 4H), 2.61–2.58 (m, 2H), 2.28 (s, 3H), 2.26–2.21 (m, 2H), 2.15 (s, 12H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 169.8, 148.9, 139.7, 133.5, 129.6, 128.6, 121.4, 107.4, 105.0, 56.8, 45.1, 37.4, 36.1, 33.2, 21.3; ESI-MS obsd 423.2744, calcd 423.2755 [(M + H)$^+$], M = $C_{25}H_{34}N_4O_2$.

1,9-Bis(*N,N*-dimethylaminomethyl)-5-(2-(4-nitrophenyl)ethyl)-dipyrromethane (D11-Esch). Following a reported method[6] with some modifications, *N,N*-dimethylmethyleneiminium iodide (740 mg, 4.00 mmol) was added to a solution of **D11** (614 mg, 2.08 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 1 h, then saturated aqueous $NaHCO_3$ was added. The organic phase was washed saturated aqueous $NaHCO_3$ (20 mL × 5) and brine), dried (Na_2SO_4), and then concentrated under reduced pressure to afford a yellow solid (268 mg, 33%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 2H), 8.13 (d, J = 8.7 Hz, 2H), 7.29 (d, J = 8.7 Hz, 2H), 5.90 (s, 4H), 3.90 (t, J = 7.7 Hz, 1H), 3.32 (q, J = 13.4 Hz, 4H), 2.73–2.70 (m, 2H), 2.29–2.24 (m, 2H), 2.15 (s, 12H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 150.0, 146.4, 133.0, 129.3, 128.5, 123.6, 107.5, 104.9, 56.6, 44.9, 37.4, 35.6, 33.7.

1,9-Bis(*N,N*-dimethylaminomethyl)-5-(4-(*tert*-butyloxy-carbonylamino)phenyl)dipyrromethane (D12-Esch). Following a reported method[6] with some modifications, a sample of **D12** (236 mg, 0.700 mmol) in CH_2Cl_2 (7.0 mL) was stirred at 0 °C (ice bath) under argon. After 15 min, *N,N*-dimethylmethyleneiminium iodide (272 mg, 1.47 mmol) was added, and the reaction mixture was stirred at 0 °C (ice bath) for 35 min. Then, saturated aqueous $NaHCO_3$ (7 mL) was added. The reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed with saturated aqueous $NaHCO_3$ (6 × 30 mL). The organic extract was dried (Na_2SO_4) and then concentrated under reduced pressure to afford a yellow solid (285 mg, 90%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (s, 2H), 7.25 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.6 Hz, 2H), 6.56 (s, 1H), 5.90 (t, J = 2.9 Hz, 2H), 5.74 (t, J = 3.0 Hz, 2H), 5.32 (s, 1H), 3.38–3.29 (m, 4H), 2.16 (s, 12H), 1.51 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 153.0, 137.2, 137.1, 132.9, 129.0, 128.8, 118.8, 107.6, 106.7, 56.8, 45.1, 43.7, 28.5; ESI-MS obsd 452.3009, calcd 452.3020 [(M + H)$^+$], M = $C_{26}H_{37}N_5O_2$.

1,9-Bis(*N,N*-dimethylaminomethyl)-5-(2-(*tert*-butyloxycarbonyl-amino)ethyl)dipyrromethane (D13-Esch). Following a reported method[6] with some modifications, a solution of **D13** (1.87 g, 6.50 mmol) in CH_2Cl_2 (65 mL) was treated with *N,N*-di-methylmethyleneiminium iodide (2.6 g, 14 mmol) at room temperature under argon. After 1 h, the crude reaction mixture was washed three times with saturated aqueous $NaHCO_3$. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to afford a black, non-crystalline solid (2.3 g, 88%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.10 (s, 2H), 5.95 (t, J = 2.9 Hz, 2H), 5.88–5.87 (m, 2H), 4.68 (s, 1H), 3.99 (t, J = 7.5 Hz, 1H), 3.56–3.50 (m, 4H), 3.12 (q, J = 6.2 Hz, 2H), 2.29 (s, 12H), 1.42 (s, 9H); ESI-MS obsd 404.3017, calcd 404.3020 [(M + H)$^+$], M = $C_{22}H_{37}N_5O_2$.

Porphyrin formation

Zn(II)-5-(2,6-bis(propargyloxy)phenyl)-15-(4-(5,5-dimethyl-1,3-dioxan-2-yl)phenyl)porphyrin (ZnP1-acetal). Following a method[6] with some modifications, a solution of **D8-Esch** (544 mg, 1.21 mmol) and **D7** (396 mg, 1.20 mmol) in EtOH (120 mL) was treated with Zn(OAc)$_2$·$2H_2O$ (2.63 g, 0.0120 mol). The mixture was heated to reflux. After 2 h, the reaction mixture was allowed to cool to room temperature. The reaction mixture was treated with DDQ (821 mg, 3.62 mmol) and stirred at room temperature for 15 min followed by the addition of triethylamine (850 µL, 6.10 mmol). After 10 min, the crude mixture was concentrated under reduced pressure followed by column chromatography [CH_2Cl_2] and recrystallization (hexane/$CHCl_3$) to afford a red solid (73 mg, 8%): ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.23 (s, 2H), 9.39 (d, J = 4.4 Hz, 2H), 9.35 (d, J = 4.4 Hz, 2H), 9.09 (d, J = 4.4 Hz, 2H), 9.06 (d, J = 4.4 Hz, 2H), 8.25 (d, J = 7.5 Hz, 2H), 7.94 (d, J = 7.5 Hz, 2H), 7.81 (t, J = 8.7 Hz, 1H), 7.28 (d, J = 8.7 Hz, 2H), 5.79 (s, 1H), 4.36 (s, 4H), 4.00 (d, J = 10.3 Hz, 2H), 3.89 (d, J = 10.3 Hz, 2H), 2.31 (s, 2H), 1.51 (s, 3H), 0.94 (s, 3H); ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$) δ 158.6, 150.8, 149.71, 149.67, 149.4, 143.6, 137.7, 134.7, 132.4, 132.3, 132.0, 131.5, 129.9, 124.6, 122.0, 119.8, 110.7, 107.2, 106.0, 102.3, 78.8, 78.1, 75.4, 56.4, 53.6, 30.6, 23.4, 22.2; λ_{abs} (toluene) 414, 539, 573 nm; MALDI-MS obsd 746.43, calcd 746.19 [M$^+$]; ESI-MS obsd 747.1930, calcd 747.1944 [(M + H)$^+$], M = $C_{44}H_{34}N_4O_4Zn$. Slow evaporation from THF at 20 °C afforded a crystalline sample that was then examined by SCXRD analysis.

Zn(II)-5-(2,6-bis((2,5,8,11-tetraoxatridecan-13-yl)oxy)phenyl)-15-(4-(2-(trimethylsilyl)ethoxycarbonyl)phenyl)porphyrin (ZnP2-ETMS). Following a reported method[6] with some modifications, a solution of **D5** (64 mg, 0.10 mmol) and **D9-Esch** (48 mg, 0.10 mmol) in EtOH (10 mL) was treated with Zn(OAc)$_2$·$2H_2O$ (222 mg, 1.01 mmol) at room temperature. The mixture was heated to reflux for 2 h, then allowed to cool to room temperature. The reaction mixture was treated with DDQ (70 mg, 0.31 mmol). The reaction mixture was stirred for 30 min, and then triethylamine (100 µL) was added. After 15 min, the solution was concentrated and the crude product was chromatographed using a gradient [silica, CH_2Cl_2/ethyl acetate (4:1) to (3:2) to (1:1)] to give a red solid (5.5 mg, 5%): ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.19 (s, 2H), 9.37 (d, J = 4.2 Hz, 2H), 9.32 (d, J = 4.2 Hz, 2H), 9.04 (d, J = 4.2 Hz, 2H), 9.02 (d, J = 4.2 Hz, 2H), 8.46 (d, J = 7.7 Hz, 2H), 8.32 (d, J = 7.7 Hz, 2H), 7.73 (t, J = 8.7 Hz, 1H), 7.05 (d, J = 8.7 Hz 2H), 4.65 (t, J = 8.4 Hz, 2H), 3.97 (t, J = 4.5 Hz, 4H), 2.90 (t, J = 4.5 Hz, 4H), 2.33 (s, 6H), 2.29–2.24 (m, 4H), 2.14–2.08 (m, 4H), 1.79–1.72 (m, 4H), 1.70–1.61 (m, 8H), 1.43 (t, J = 4.9 Hz, 4H), 1.35–1.30 (m, 2H), 0.21 (s, 9H); ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$) δ 167.4, 160.0, 151.1, 149.6, 149.2, 149.1, 148.3, 134.8, 132.1, 131.9, 131.7, 131.6, 130.1, 129.6, 127.8, 121.9, 118.2, 106.1, 105.6, 70.7, 69.6, 68.99, 68.94, 68.8, 68.6, 68.51, 68.49, 63.7, 58.1; 29.9, 17.8, −1.1; λ_{abs} (toluene) 417, 548, 582 nm; MALDI-MS obsd 1080.26, calcd 1080.39 [M$^+$]; ESI-MS obsd 1081.3955, calcd 1081.3967 [(M + H)$^+$], M = $C_{56}H_{68}N_4O_{12}SiZn$.

Zn(II)-15-(2,6-bis((1-*tert*-butyloxy-1-oxo-4,7,10,13,16,19-hexa-oxahenicosan-21-yl)oxy)phenyl)-15-(4-(2-(trimethylsilyl)ethoxy-carbonyl)phenyl)porphyrin (ZnP3-Bu/ETMS). Following a
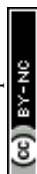
reported method[6] with some modifications, a solution of **D6** (208 mg, 0.200 mmol) and **D9-Esch** (96 mg, 0.20 mmol) in EtOH (20 mL) was treated with $Zn(OAc)_2 \cdot 2H_2O$ (439 mg, 2.00 mmol) at room temperature. The mixture was heated to reflux for 2 h, then allowed to cool to room temperature followed by treatment with DDQ (136 mg, 0.600 mmol). The reaction mixture was stirred for 30 min, then triethylamine (140 μL) was added. After 15 min, the solution was concentrated under reduced pressure. Chromatography using aluminum oxide (basic, Brockman grade I) with a gradient [CH_2Cl_2/ethyl acetate (4:1) to ethyl acetate] gave a red solid (20 mg, 7%): ^{1}H NMR (700 MHz, CD_3OD) δ 10.26 (s, 2H), 9.44 (d, J = 4.2 Hz, 2H), 9.37 (d, J = 4.2 Hz, 2H), 9.00–8.97 (m, 4H), 8.50 (d, J = 8.4 Hz, 2H), 8.39 (d, J = 8.4 Hz, 2H), 7.79 (t, J = 8.4 Hz, 1H), 7.16 (d, J = 8.4 Hz, 2H), 4.70–4.67 (m, 2H), 4.02 (t, J = 4.2 Hz, 4H), 3.55 (t, J = 6.3 Hz, 4H), 3.33–3.31 (m, 8H), 3.24–3.22 (m, 4H), 3.13–3.10 (m, 4H), 2.92–2.90 (m, 8H), 2.59–2.57 (m, 4H), 2.38 (t, J = 6.3 Hz, 4H), 2.12–2.11 (m, 4H), 1.85–1.82 (m, 8H), 1.58–1.56 (m, 4H), 1.43 (s, 18H), 1.38–1.35 (m, 2H), 0.24 (s, 9H); $^{13}C\{^1H\}$ NMR (175 MHz, CD_3OD) δ 171.3, 167.2, 166.8, 159.9, 151.0, 149.6, 149.3, 148.9, 148.5, 134.6, 131.5, 131.4, 131.3, 130.9, 130.0, 129.3, 127.3, 121.2, 117.6, 112.1, 105.3, 105.1, 80.3, 76.8, 70.14, 70.13, 70.0, 69.82, 69.78, 69.6, 69.4, 69.1, 68.9, 68.8, 68.5, 68.38, 68.35, 66.5, 66.4, 63.2, 54.8, 53.4, 35.8, 29.3, 27.0, 17.1, −2.7; λ_{abs} (toluene) 417, 548, 582 nm; MALDI-MS obsd 1484.57, calcd 1484.63 [M$^+$]; ESI-MS obsd 1507.6133, calcd 1507.6197 [(M + Na)$^+$], M = $C_{76}H_{104}N_4O_{20}SiZn$.

Zn(II)-5-(2,6-bis((1-*tert*-butyloxy-1-oxo-4,7,10,13,16,19-hexaoxa-henicosan-21-yl)oxy)phenyl)-15-(4-(3-(2-(trimethylsilyl)ethoxy)-3-oxopropyl)phenyl)porphyrin (ZnP4-Bu/ETMS). Following a reported method[6] with some modifications, a solution of **D3-Esch** (332 mg, 0.653 mmol) and **D6** (678 mg, 0.653 mmol) in EtOH (65.3 mL) was treated with $Zn(OAc)_2 \cdot 2H_2O$ (1.43 g, 6.53 mmol) at room temperature. The reaction mixture was heated to reflux for 2 h, then allowed to cool to room temperature. The reaction mixture was treated with DDQ (445 mg, 1.96 mmol). The resulting mixture was stirred for 30 min, and then triethylamine (910 μL, 6.53 mmol) was added. After 15 min, the solvent was removed under reduced pressure, and the crude product was chromatographed first [silica, CH_2Cl_2/ethyl acetate (1:1)] and second [silica, CH_2Cl_2/MeOH (25:1)] to afford a red solid (58.6 mg, 6%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.16 (s, 2H), 9.34 (d, J = 4.4 Hz, 2H), 9.31 (d, J = 4.4 Hz, 2H), 9.06 (d, J = 4.4 Hz, 2H), 9.02 (d, J = 4.3 Hz, 2H), 8.17–8.15 (m, 2H), 7.72 (t, J = 8.5 Hz, 1H), 7.62 (d, J = 7.8 Hz, 2H), 7.05 (d, J = 8.5 Hz, 2H), 4.37–4.33 (m, 2H), 3.96–3.95 (m, 4H), 3.52 (t, J = 6.6 Hz, 4H), 3.35 (t, J = 7.9 Hz, 2H), 3.24 (dd, J = 6.0, 3.9 Hz, 4H), 3.16 (dd, J = 5.9, 3.9 Hz, 4H), 2.98–2.93 (m, 6H), 2.89–2.87 (m, 4H), 2.83–2.81 (m, 4H), 2.63–2.61 (m, 4H), 2.38 (t, J = 6.6 Hz, 4H), 2.29–2.28 (m, 4H), 1.76–1.74 (m, 4H), 1.58–1.54 (m, 8H), 1.41 (s, 18H), 1.36–1.36 (m, 4H), 1.16–1.12 (m, 2H), 0.14 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 173.4, 171.0, 160.0, 151.0, 149.6, 149.4, 149.2, 141.3, 139.7, 134.9, 132.1, 132.0, 131.7, 131.2, 130.0, 126.6, 122.1, 119.5, 111.7, 106.2, 105.3, 80.6, 70.7, 70.10, 70.07, 70.0, 69.8, 69.6, 69.5, 69.2, 68.9, 68.8, 68.6, 68.44, 68.39, 66.8, 63.0, 36.5, 36.3, 31.2, 28.2, 17.6, −1.2; λ_{abs} (toluene) 415, 544, 579 nm;

MALDI-MS obsd 1513.44, calcd 1513.67 [(M + H)$^+$]; ESI-MS obsd 1535.6470, calcd 1535.6510 [(M + Na)$^+$], M = $C_{78}H_{108}N_4O_{20}SiZn$.

Zinc(II)-5-(2,6-bis((1-*tert*-butyloxy-1-oxo-4,7,10,13,16,19-hexa-oxahenicosan-21-yl)oxy)phenyl)-15-(2-(4-acetoxyphenyl)ethyl)-porphyrin (ZnP5). Following a reported method[6] with some modifications, a solution of **D10-Esch** (183 mg, 0.433 mmol) and **D6** (450 mg, 0.433 mmol) in EtOH (43.0 mL) was treated with $Zn(OAc)_2 \cdot 2H_2O$ (950 mg, 4.33 mmol) at room temperature. The reaction mixture was heated to reflux for 3 h, then allowed to cool to room temperature, and treated with DDQ (295 mg, 1.30 mmol). The resulting mixture was stirred for 30 min, and then triethylamine (600 μL, 4.33 mmol) was added. After 15 min, the solution was concentrated, and the crude product was chromatographed [silica, CH_2Cl_2/ethyl acetate (1:1) to (1:6)] to give a dark red solid (34.2 mg, 6%): ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.07 (s, 2H), 9.59 (d, J = 4.3 Hz, 2H), 9.36 (d, J = 4.3 Hz, 2H), 9.27 (d, J = 4.3 Hz, 2H), 8.98 (d, J = 4.2 Hz, 2H), 7.71 (t, J = 8.7 Hz, 1H), 7.09 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 8.7 Hz, 2H), 6.66–6.65 (m, 2H), 6.14 (s, 1H), 5.35 (t, J = 8.1 Hz, 2H), 3.96 (t, J = 4.4 Hz, 4H), 3.85 (t, J = 8.0 Hz, 2H), 3.54 (t, J = 6.6 Hz, 4H), 3.28 (dd, J = 5.9, 4.0 Hz, 4H), 3.21 (dd, J = 5.8, 4.0 Hz, 4H), 3.01 (t, J = 4.9 Hz, 4H), 2.90–2.87 (m, 8H), 2.62–2.60 (m, 4H), 2.39 (t, J = 6.6 Hz, 4H), 2.25 (dd, J = 5.7, 4.0 Hz, 4H), 1.61 (dd, J = 5.7, 3.9 Hz, 4H), 1.51 (t, J = 5.4 Hz, 4H), 1.42 (s, 18H), 1.34–1.33 (m, 4H), 1.17 (t, J = 5.3 Hz, 4H); $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$) δ 171.2, 160.0, 154.7, 151.0, 149.8, 149.2, 148.7, 133.7, 131.8, 131.7, 131.6, 130.0, 129.8, 129.1, 122.2, 118.4, 115.5, 111.2, 106.3, 105.0, 80.7, 70.14, 70.13, 70.0, 69.8, 69.7, 69.5, 69.1, 68.85, 68.78, 68.5, 68.3, 68.2, 66.8, 44.1, 38.0, 36.3, 28.2; λ_{abs} (toluene) 415, 545, 579 nm; MALDI-MS obsd 1407.87, calcd 1407.58 [(M + Na)$^+$]; ESI-MS obsd 1407.5818, calcd 1407.5852 [(M + Na)$^+$], M = $C_{72}H_{96}N_4O_{19}Zn$.

Zinc(II)-5-(2,6-bis((1-*tert*-butyloxy-1-oxo-4,7,10,13,16,19-hexa-oxahenicosan-21-yl)oxy)phenyl)-15-(2-(4-nitrophenyl)ethyl)por-phyrin (ZnP6). Following a reported method[6] with some modifications, a solution of **D11-Esch** (206 mg, 0.504 mmol) and **D6** (523 mg, 0.503 mmol) in EtOH (50 mL) was reacted with $Zn(OAc)_2 \cdot 2H_2O$ (1.11 g, 5.04 mmol) and then refluxed for 2 h. The reaction mixture was allowed to cool to room temperature. The reaction mixture was treated with DDQ (341 mg, 1.50 mmol), stirred for 15 min, and then treated with triethylamine (700 μL). The crude mixture was dried under high vacuum and then passed through a silica pad (3 cm × 3 cm, CH_2Cl_2) to give elution of black byproducts followed by a fraction containing the desired porphyrin (∼80% pure). The porphyrin fraction was concentrated and chromatographed [silica, CH_2Cl_2/ethyl acetate/methanol (6:6:1)] to give the desired product as a non-crystalline, red solid (44 mg, 7%): ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.07 (s, 2H), 9.61–9.56 (m, 2H), 9.42–9.36 (m, 2H), 9.27 (d, J = 4.3 Hz, 2H), 8.97 (d, J = 4.3 Hz, 2H), 8.27–8.19 (m, 2H), 7.71 (t, J = 8.7 Hz, 1H), 7.65–7.59 (m, 2H), 7.04 (d, J = 8.7 Hz, 2H), 5.46–5.33 (m, 2H), 4.08–3.99 (m, 2H), 3.98–3.88 (m, 4H), 3.50 (t, J = 6.6 Hz, 4H), 3.27–3.21 (m, 4H), 3.20–3.13 (m, 4H), 2.98–2.94 (m, 4H), 2.92–2.87 (m, 4H), 2.87–2.80 (m, 4H), 2.65–2.59 (m, 4H), 2.36 (t, J = 6.6 Hz, 4H), 2.34–2.30 (m, 4H), 1.89–1.82 (m, 4H), 1.71 (t, J = 5.2 Hz, 4H),
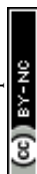
1.68–1.63 (m, 4H), 1.52–1.47 (m, 4H), 1.40 (s, 18H); $^{13}C\{^1H\}$ NMR (175 MHz, CDCl$_3$) δ 171.0, 159.8, 151.2, 150.1, 149.3, 149.2, 148.7, 146.7, 132.0, 131.9, 130.1, 129.6, 128.4, 127.7, 124.1, 121.9, 116.7, 113.0, 111.4, 106.2, 105.1, 100.3, 80.6, 70.01, 69.99, 69.9, 69.7, 69.4, 69.3, 69.1, 68.9, 68.8, 68.6, 68.4, 66.7, 44.7, 37.2, 36.2, 28.2; λ_{abs} [MeCN/H$_2$O (80 : 20)] 412, 546, 579 nm; satisfactory MALDI-MS and ESI-MS data could not be obtained; LC-MS gave obsd m/z 1436.55, calcd 1436.58, [(M + Na)$^+$], M = C$_{72}$H$_{95}$N$_5$O$_{20}$Zn.

Zn(II)-5-(2,6-bis((1-*tert*-butyloxy-1-oxo-4,7,10,13,16,19-hexa-oxahenicosan-21-yl)oxy)phenyl)-15-(4-(*tert*-butyloxycarbonyl-amino)phenyl)porphyrin (ZnP7-Bu/Boc). Following a reported method[6] with some modifications, a solution of **D12-Esch** (271 mg, 0.600 mmol) and **D6** (624 mg, 0.600 mmol) in EtOH (60.0 mL) was treated with Zn(OAc)$_2$·2H$_2$O (1.32 g, 6.00 mmol) at room temperature. The reaction mixture was heated to reflux for 1.5 h, then allowed to cool to room temperature. The reaction mixture was treated with DDQ (409 mg, 1.80 mmol). The resulting mixture was stirred for 30 min, and then triethylamine (836 μL, 6.00 mmol) was added. After 15 min, the solvent was removed under reduced pressure, and the crude product was chromatographed first [silica, CH$_2$Cl$_2$/MeOH (25 : 1)] and second [silica, CH$_2$Cl$_2$/ethyl acetate (1 : 9)] to afford a red solid (42.8 mg, 5%): ^1H NMR (500 MHz, CDCl$_3$) δ 10.14 (s, 2H), 9.34 (d, J = 4.4 Hz, 2H), 9.30 (d, J = 4.4 Hz, 2H), 9.09 (d, J = 4.4 Hz, 2H), 9.01 (d, J = 4.4 Hz, 2H), 8.17–8.14 (m, 2H), 7.81 (d, J = 7.8 Hz, 2H), 7.72 (t, J = 8.5 Hz, 1H), 7.07–7.03 (m, 3H), 3.96–3.95 (m, 4H), 3.54 (t, J = 6.6 Hz, 4H), 3.24 (dd, J = 5.9, 3.9 Hz, 4H), 3.16 (dd, J = 5.9, 3.9 Hz, 4H), 2.94–2.92 (m, 4H), 2.89–2.87 (m, 4H), 2.82–2.80 (m, 4H), 2.63–2.61 (m, 4H), 2.39 (t, J = 6.6 Hz, 4H), 2.27–2.25 (m, 4H), 1.73–1.71 (m, 4H), 1.67 (s, 9H), 1.55–1.52 (m, 8H), 1.42 (s, 18H), 1.34–1.32 (m, 4H); $^{13}C\{^1H\}$ NMR (125 MHz, CDCl$_3$) δ 171.0, 160.0, 153.3, 151.0, 149.7, 149.4, 149.2, 138.1, 137.9, 135.3, 132.1, 131.9, 131.7, 131.2, 130.0, 122.1, 119.2, 116.8, 111.6, 106.1, 105.3, 80.6, 70.1, 70.0, 69.74, 69.68, 69.5, 69.1, 68.9, 68.8, 68.5, 68.4, 68.3, 66.8, 36.3, 28.6, 28.2; λ_{abs} (toluene) 416, 546, 580 nm; MALDI-MS obsd 1455.92, calcd 1455.63 [M$^+$]; ESI-MS obsd 1478.6191, calcd 1478.6224 [(M + Na)$^+$], M = C$_{75}$H$_{101}$N$_5$O$_{20}$Zn.

Zn(II)-5-(2,6-bis((1-*tert*-butyloxy-1-oxo-4,7,10,13,16,19-hexa-oxahenicosan-21-yl)oxy)phenyl)-15-(2-(*tert*-butyloxycarbonylamino)-ethyl)porphyrin (ZnP8-Bu/Boc). Following a reported method[6] with some modifications, a solution of **D6** (600 mg, 0.58 mmol) and **D13-Esch** (278 mg, 0.69 mmol) in ethanol (58 mL) at room temperature was treated with Zn(OAc)$_2$·2H$_2$O (1.27 g, 5.8 mmol) and then heated to 80 °C (oil bath). After 2 h, the reaction mixture was allowed to cool to room temperature. The reaction mixture was treated with DDQ (386 mg, 1.7 mmol), stirred at room temperature for 15 min, and then treated with triethyl-amine (406 μL, 2.9 mmol). The crude mixture was dried under high vacuum and then passed through a silica pad (3 cm × 3 cm; ethyl acetate then CH$_2$Cl$_2$/methanol 100 : 1 to 10 : 1) to give elution of black byproducts followed by a fraction containing the desired porphyrin (∼80% pure). The porphyrin fraction was concentrated and chromatographed [silica, CH$_2$Cl$_2$/ethyl acetate/methanol (6 : 6 : 1)] to give the desired product as a non-crystalline, red solid (72 mg, 7%): ^1H NMR (500 MHz, CDCl$_3$) δ 10.12 (s, 2H), 9.75 (d, J = 4.5 Hz, 2H), 9.44 (d, J = 4.5 Hz, 2H), 9.28 (d, J = 4.4 Hz, 2H), 8.99 (d,

J = 4.3 Hz, 2H), 7.72 (t, J = 8.5 Hz, 1H), 7.04 (d, J = 8.5 Hz, 2H), 5.34 (t, J = 6.9 Hz, 2H), 5.11–5.05 (m, 1H), 4.28 (q, J = 6.9 Hz, 2H), 3.98–3.93 (m, 4H), 3.54 (t, J = 6.6 Hz, 4H), 3.33–3.21 (m, 8H), 3.06–3.01 (m, 4H), 2.89 (t, J = 4.4 Hz, 8H), 2.61–2.56 (m, 4H), 2.38 (t, 4H), 2.27–2.21 (m, 4H), 1.62–1.60 (m, 8H), 1.56 (s, 9H), 1.41 (s, 18H), 1.34–1.29 (m, 4H), 1.28–1.22 (m, 4H); $^{13}C\{^1H\}$ NMR (125 MHz, CDCl$_3$) δ 171.0, 156.0, 151.1, 150.0, 149.2, 148.9, 148.2, 132.0, 131.8, 130.1, 129.4, 112.5, 106.3, 105.1, 80.6, 70.19, 70.18, 70.1, 69.9, 69.6, 69.5, 69.2, 68.9, 68.8, 68.5, 68.30, 68.26, 66.9, 36.3, 28.8, 28.2; λ_{abs} [MeCN/H$_2$O (95 : 5)] 411, 546, 578 nm; ESI-MS obsd 1408.6400, calcd 1408.6404 [(M + H)$^+$], M = C$_{71}$H$_{101}$N$_5$O$_{20}$Zn.

Zn(II)-5-(4-((2,5,8,11,14,17-hexaoxanonadecan-19-yl)oxy)phenyl-15-(4-(2-(trimethylsilyl)ethoxycarbonyl)phenyl)porphyrin (ZnP9-ETMS). Following a procedure[6] with modification, a sample of Zn(OAc)$_2$ (1.10 g, 5.00 mmol) was added to a solution of **D9-Esch** (240 mg, 0.50 mmol) and **D14** (258 mg, 0.50 mmol) in ethanol (50.0 mL). The resulting mixture was stirred and refluxed (oil bath) for 1.5 h. The reaction mixture was allowed to cool to room temperature. A sample of DDQ (340 mg, 1.50 mmol) was added, and the reaction mixture was stirred for 15 min. Triethylamine (700 μL, 5 mmol) was added, and the reaction mixture was stirred for 15 min. The mixture was concentrated under reduced pressure. Purification of the crude mixture by column chromatography [silica, CH$_2$Cl$_2$/ethyl acetate (2 : 1)] afforded reddish fractions (λ_{abs} 415–420 nm) that were set aside for further purification; all black fractions were discarded. Purification of the reddish fractions by column chromatography [silica, CH$_2$Cl$_2$/ethyl acetate (2 : 1)] afforded a dark-red solid (55.3 mg, 12%): ^1H NMR (500 MHz, CDCl$_3$) δ 10.24 (s, 2H), 9.39–9.38 (m, 4H), 9.13 (d, J = 4.4 Hz, 2H), 9.03 (d, J = 4.4 Hz, 2H), 8.43–8.41 (m, 2H), 8.31–8.30 (m, 2H), 8.13–8.11 (m, 2H), 7.27–7.25 (m, 2H, buried in CDCl$_3$), 4.61–4.57 (m, 2H), 4.32–4.26 (m, 2H), 3.89–3.87 (m, 2H), 3.68–3.64 (m, 2H), 3.57–3.55 (m, 2H), 3.53–3.47 (m, 4H), 3.44–3.39 (m, 4H), 3.37–3.35 (m, 2H), 3.29–3.27 (m, 2H), 3.12–3.10 (m, 2H), 2.98–2.96 (m, 2H), 2.85 (s, 3H), 1.34–1.28 (m, 2H), 0.20 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, CDCl$_3$) δ 168.4, 159.8, 151.7, 150.78, 150.76, 150.6, 148.8, 136.9, 136.5, 136.0, 133.9, 133.2, 133.0, 131.0, 129.0, 121.4, 119.6, 114.2, 107.5, 72.6, 72.0, 71.80, 71.76, 71.7, 71.62, 71.59, 71.52, 71.48, 71.2, 71.1, 69.0, 64.9, 59.8, 18.9, 0.00; λ_{abs} (toluene) 415, 540, 576 nm; MALDI-MS obsd 986.94, calcd 985.32 [(M + Na)$^+$]; ESI-MS obsd 963.3321, calcd 963.3337 [(M + H)$^+$], M = C$_{51}$H$_{58}$N$_4$O$_9$SiZn.

Porphyrin elaboration

Zn(II)-5-(2,6-bis(propargyloxy)phenyl)-5-(4-formylphenyl)por-phyrin (ZnP1-CHO). Following a method[19] with some modifica-tions, a sample of **ZnP1-acetal** (24.8 mg, 0.0331 mmol) was added to a solution of TFA (1 mL), 5% H$_2$SO$_4$ in water (504 μL), and acetic acid (2 mL). The mixture was heated to 80 °C (oil bath). After 1.5 h, the mixture was allowed to cool to room temperature. Then, CH$_2$Cl$_2$ (50 mL) and saturated aqueous NaHCO$_3$ (50 mL) were added. The organic phase was washed (saturated aqueous NaHCO$_3$ (50 mL × 3) and brine), dried (Na$_2$SO$_4$), and then concentrated to dryness under reduced pressure. The crude was dissolved in the mixed solvent CH$_2$Cl$_2$/MeOH (9 : 1) (18 mL), and then Zn(OAc)$_2$·2H$_2$O (373 mg, 1.70 mmol) was added. The mixture was stirred
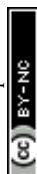
overnight at room temperature. The mixture was washed with saturated aqueous NaHCO$_3$ (50 mL × 3) and extracted with CH$_2$Cl$_2$ (50 mL). The organic extract was washed with brine, dried (Na$_2$SO$_4$), concentrated under reduced pressure, and recrystallized (hexane/CHCl$_3$) to give a red solid (19 mg, 87%): ^{1}H NMR (700 MHz, CD$_2$Cl$_2$) δ 10.37 (s, 1H), 10.29 (s, 2H), 9.44–9.43 (m, 4H), 9.07 (d, J = 4.3 Hz, 2H), 9.03 (d, J = 4.3 Hz, 2H), 8.43 (d, J = 7.5 Hz, 2H), 8.30 (d, J = 7.5 Hz, 2H), 7.85 (t, J = 8.8 Hz, 1H), 7.29 (d, J = 8.8 Hz, 2H), 4.43 (d, J = 2.4 Hz, 4H), 2.33 (t, J = 2.4 Hz, 2H); ^{13}C{^{1}H} NMR (175 MHz, CD$_2$Cl$_2$) δ 192.4, 158.5, 150.6, 149.6, 149.35, 149.26, 149.0, 135.5, 135.3, 132.1, 131.8, 131.6, 130.0, 127.8, 121.3, 118.3, 111.2, 106.7, 105.9, 78.4, 75.0, 56.3; λ_{abs} (toluene) 414, 539, 573 nm; MALDI-MS obsd 660.36, calcd 660.11 [M$^+$]; ESI-MS obsd 661.1202, calcd 661.1213 [(M + H)$^+$], M = C$_{39}$H$_{24}$N$_4$O$_3$Zn.

Zn(II)-5-(2,6-bis((2,5,8,11-tetraoxatridecan-13-yl)oxy)phenyl)-15-(4-carboxyphenyl)porphyrin (ZnP2). Following a reported procedure,[21] a solution of **ZnP2-ETMS** (3.8 mg, 3.5 μmol) in THF (350 μL) was treated with TBAF (1 M in THF, 32 μL, 32 μmol) at 40 °C. The reaction mixture was stirred for 1 h and then concentrated under reduced pressure to remove residual THF. The crude product was dissolved in CH$_2$Cl$_2$ (50 mL), washed with water (3 × 50 mL) and brine (50 mL), dried (Na$_2$SO$_4$), concentrated under reduced pressure, and finally chromatographed [silica, CH$_2$Cl$_2$ to CH$_2$Cl$_2$/MeOH (15:1)] to afford a red solid (2.4 mg, 70%): ^{1}H NMR (700 MHz, CDCl$_3$) δ 10.20 (s, 2H), 9.39 (d, J = 4.2 Hz, 2H), 9.33 (d, J = 4.2 Hz, 2H), 9.04 (d, J = 4.2 Hz, 4H), 8.54 (d, J = 7.4 Hz, 2H), 8.37 (d, J = 7.4 Hz, 2H), 7.74 (t, J = 8.7 Hz, 1H), 7.06 (d, J = 8.7 Hz, 2H), 3.98 (t, J = 4.5 Hz, 4H), 2.92 (t, J = 4.2, 4H), 2.36 (s, 6H), 2.31 (t, J = 4.2, 4H), 2.14 (t, J = 4.2, 4H), 1.80 (dd, J = 4.9, 4.2 Hz, 4H), 1.68–1.64 (m, 8H), 1.45 (t, J = 4.9 Hz, 4H); ^{13}C{^{1}H} NMR (175 MHz, CDCl$_3$) δ 159.8, 151.0, 149.5, 149.1, 148.9, 134.8, 132.0, 131.8, 131.54, 131.48, 130.0, 128.3, 121.8, 117.9, 112.1, 105.9, 105.5, 70.6, 69.4, 68.9, 68.8, 68.7, 68.5, 68.4, 58.0; λ_{abs} (DMSO) 417, 548, 582 nm; MALDI-MS obsd 980.30, calcd 980.32 [M$^+$]; ESI-MS obsd 981.3253, calcd 981.3259 [(M + H)$^+$], M = C$_{51}$H$_{56}$N$_4$O$_{12}$Zn.

5-(2,6-Bis((2,5,8,11-tetraoxatridecan-13-yl)oxy)phenyl)-15-(4-(N-succinimidyloxycarbonyl)phenyl)porphyrin (P2-NHS). A solution of **ZnP2** (3.6 mg, 3.7 μmol) in CH$_2$Cl$_2$ (1.0 mL) was treated with TFA (100 μL) at room temperature for 5 min. The resulting solution was diluted with CH$_2$Cl$_2$ (10 mL), washed extensively (H$_2$O (20 mL), aqueous NaHCO$_3$ (20 mL × 2) and brine (20 mL × 2)), and then dried (Na$_2$SO$_4$). The organic layer was collected and dried under vacuum to give a dark red solid. The solid was dissolved in CH$_2$Cl$_2$ (290 μL) and then treated with DCC (6.0 mg, 29 μmol) and N-hydroxysuccinimide (3.3 mg, 29 μmol). The mixture was stirred at room temperature for 1 h and then filtered. The filtrate was purified by preparative TLC [silica, 5 cm × 20 cm × 0.5 mm; CH$_2$Cl$_2$/ethyl acetate/methanol (5:5:1)] to give the final product as a non-crystalline red solid (3.5 mg, 94%): ^{1}H NMR (700 MHz, CDCl$_3$) δ 10.28 (s, 2H), 9.42 (d, J = 4.4 Hz, 2H), 9.33 (d, J = 4.4 Hz, 2H), 9.02 (d, J = 4.4 Hz, 2H), 9.00 (d, J = 4.5 Hz, 2H), 8.61 (d, J = 7.8 Hz, 2H), 8.45 (d, J = 7.7 Hz, 2H), 7.75 (t, J = 8.7 Hz, 1H), 7.06 (d, J = 8.7 Hz, 2H), 4.02 (t, J = 4.9 Hz, 4H), 3.18–3.16 (m, 10H), 3.08–3.01 (m, 8H), 2.92

(t, J = 4.9 Hz, 4H), 2.66–2.63 (m, 4H), 2.31 (dd, J = 5.7, 4.3 Hz, 4H), 2.06–2.03 (m, 4H), 1.88 (dd, J = 5.6, 3.8 Hz, 4H), −3.13 (s, 2H); ^{13}C{^{1}H} NMR (175 MHz, CDCl$_3$) δ 170.4, 169.5, 162.3, 159.8, 148.9, 148.4, 145.9, 145.5, 145.2, 135.3, 131.94, 131.85, 131.3, 130.7, 130.3, 129.3, 124.5, 119.5, 116.8, 112.3, 105.9, 105.2, 71.7, 70.0, 69.7, 69.4, 69.3, 69.2, 68.8, 59.0, 26.0, 25.3; λ_{abs} (MeOH) 404, 500, 534, 574, 629 nm; MALDI-MS obsd 1038.47, calcd 1038.41 [(M + Na)$^+$]; ESI-MS obsd 1016.4278, calcd 1016.4288 [(M + H)$^+$], M = C$_{55}$H$_{61}$N$_5$O$_{14}$.

5-(2,6-Bis((2,5,8,11-tetraoxatridecan-13-yl)oxy)phenyl)-15-(4-carboxyphenyl)porphyrin (P2). Following a standard procedure,[22] a solution of **ZnP2-ETMS** (16.0 mg, 14.8 μmol) in CH$_2$Cl$_2$ (1.0 mL) was treated with TFA (1.0 mL) at room temperature. The reaction mixture was stirred for 5 h, then diluted with CH$_2$Cl$_2$ (20 mL), washed with water (3 × 15 mL), and dried (Na$_2$SO$_4$). The crude residue was purified by column chromatography [silica, CH$_2$Cl$_2$/MeOH (20:1)] to afford a red solid (12.4 mg, 91%): ^{1}H NMR (700 MHz, CDCl$_3$) δ 10.27 (s, 2H), 9.39 (d, J = 4.4 Hz, 2H), 9.35 (d, J = 4.4 Hz, 2H), 9.05 (t, J = 3.8 Hz, 4H), 8.58 (d, J = 7.3 Hz, 2H), 8.40 (d, J = 7.4 Hz, 2H), 7.76 (t, J = 8.7 Hz, 1H), 7.08 (d, J = 8.8 Hz, 2H), 4.05 (t, J = 4.8 Hz, 4H), 3.23–3.19 (m, 10H), 3.05 (t, J = 4.7 Hz, 4H), 2.96 (t, J = 4.9 Hz, 4H), 2.68 (t, J = 5.0 Hz, 4H), 2.34 (t, J = 5.0 Hz, 4H), 2.07 (t, J = 4.6 Hz, 4H), 1.90 (t, J = 4.7 Hz, 4H), −3.08 (s, 2H); ^{13}C{^{1}H} NMR (175 MHz, CDCl$_3$) δ 171.3, 159.9, 148.3, 147.1, 146.2, 145.5, 145.2, 135.0, 131.8, 131.7, 131.2, 130.7, 130.6, 129.4, 128.8, 119.6, 117.6, 112.1, 105.9, 105.0, 71.7, 70.7, 70.0, 69.7, 69.33, 69.27, 69.2, 68.8, 59.0; λ_{abs} (MeOH) 404, 500, 533, 574, 629 nm; MALDI-MS obsd 919.34, calcd 919.41 [(M + H)$^+$]; ESI-MS obsd 919.4095, calcd 919.4124 [(M + H)$^+$]; M = C$_{51}$H$_{58}$N$_4$O$_{12}$.

Zn(II)-5-(2,6-bis((1-tert-butyloxy-1-oxo-4,7,10,13,16,19-hexaoxahenicosan-21-yl)oxy)phenyl)-5-(4-carboxyphenyl)porphyrin (ZnP3-Bu). Following a reported procedure,[21] a solution of **ZnP3-Bu/ETMS** (20.4 mg, 13.7 μmol) in THF (1.4 mL) was treated with TBAF (1 M in THF, 28 μL, 28 μmol) at 35 °C (oil bath). The reaction mixture was stirred for 1.5 h, then allowed to cool to room temperature. The solvent was removed under reduced pressure. The crude product was purified by preparative TLC [silica, 1 mm, 20 × 20 cm, CH$_2$Cl$_2$/MeOH (20:1)] to give a red solid (16.2 mg, 85%): ^{1}H NMR (700 MHz, CD$_3$OD) δ 10.27 (s, 2H), 9.45 (d, J = 4.2 Hz, 2H), 9.38 (d, J = 4.2 Hz, 2H), 9.01 (d, J = 4.2 Hz, 2H), 8.98 (d, J = 4.2 Hz, 2H), 8.50 (d, J = 7.7 Hz, 2H), 8.37 (d, J = 7.7 Hz, 2H), 7.81 (t, J = 8.4 Hz, 1H), 7.17 (d, J = 8.4 Hz, 2H), 4.04–4.02 (m, 4H), 3.46 (t, J = 6.3 Hz, 4H), 3.30–3.26 (m, 8H), 3.20–3.19 (m, 4H), 3.09–3.08 (m, 4H), 2.94–2.93 (m, 4H), 2.89–2.88 (m, 4H), 2.58–2.57 (m, 4H), 2.31 (t, J = 6.3 Hz, 4H), 2.13–2.11 (m, 4H), 1.86–1.83 (m, 8H), 1.56–1.55 (m, 4H), 1.40 (s, 18H); ^{13}C{^{1}H} NMR (175 MHz, CD$_3$OD) δ 171.4, 159.9, 151.0, 149.6, 149.3, 149.0, 148.1, 134.5, 131.5, 131.4, 131.3, 131.0, 130.0, 127.5, 121.3, 117.9, 112.0, 105.4, 105.1, 80.3, 69.7, 69.5, 69.3, 68.94, 68.88, 68.7, 68.38, 68.36, 68.3, 68.2, 66.3, 35.6, 27.0; λ_{abs} (toluene) 417, 548, 582 nm; MALDI-MS obsd 1385.72, calcd 1385.57 [(M + H)$^+$]; ESI-MS obsd 1407.5413, calcd 1407.5489 [(M + Na)$^+$], M = C$_{71}$H$_{92}$N$_4$O$_{20}$Zn. Note: in a prior synthesis, attempted separation by column chromatography (silica)
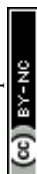
afforded the product and unknown species, hence the reliance here on preparative TLC for purification.

Zn(II)-5-(2,6-bis((1-*tert*-butyloxy-1-oxo-4,7,10,13,16,19-hexaoxahenicosan-21-yl)oxy)phenyl)-5-(4-(*N*-succinimidyloxycarbonyl)phenyl)porphyrin (ZnP3-Bu/NHS). Following a reported method[42] with some modifications, a solution of **ZnP3-Bu** (14.5 mg, 10.5 µmol) and *N*-hydroxysuccinimide (12.1 mg, 105 µmol) in CH$_2$Cl$_2$ was stirred at room temperature. After 5 min, DCC (8.7 mg, 42 µmol) and DMAP (1.3 mg, 1.1 µmol) were added. The reaction mixture was stirred at room temperature for 1 h, and then filtered to remove a white precipitate. The filtrate was concentrated under reduced pressure and then chromatographed [silica, CH$_2$Cl$_2$/ethyl acetate (1:2) to (1:4)] to afford a red solid (13.2 mg, 85%): ^{1}H NMR (500 MHz, CDCl$_3$) δ 10.19 (s, 2H), 9.39 (d, J = 4.4 Hz, 2H), 9.31 (d, J = 4.4 Hz, 2H), 9.03 (d, J = 4.4 Hz, 2H), 8.99 (d, J = 4.3 Hz, 2H), 8.59–8.56 (m, 2H), 8.42–8.40 (m, 2H), 7.73 (t, J = 8.5 Hz, 1H), 7.05 (d, J = 8.5 Hz, 2H), 3.98–3.96 (m, 4H), 3.51 (t, J = 6.6 Hz, 4H), 3.22 (dd, J = 6.0, 3.9 Hz, 4H), 3.14 (dd, J = 5.9, 3.9 Hz, 4H), 3.03 (s, 4H), 2.94–2.90 (m, 8H), 2.82 (dd, J = 5.8, 4.0 Hz, 4H), 2.65–2.64 (m, 4H), 2.37 (t, J = 6.6 Hz, 4H), 2.33–2.31 (m, 4H), 1.83–1.81 (m, 4H), 1.66–1.60 (m, 8H), 1.45–1.43 (m, 4H), 1.40 (s, 18H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 171.0, 169.6, 162.5, 159.9, 151.1, 150.9, 149.7, 149.2, 148.7, 135.3, 132.2, 131.9, 131.8, 131.4, 128.9, 123.9, 117.2, 112.5, 106.1, 105.7, 80.6, 70.09, 70.05, 70.0, 69.8, 69.6, 69.5, 69.2, 68.9, 68.8, 68.6, 68.52, 68.47, 66.8, 49.3, 36.3, 34.0, 28.2, 26.0, 25.7, 25.0; λ_{abs} (MeOH) 412, 544, 580 nm; MALDI-MS obsd 1481.96, calcd 1481.58 [M$^+$]; ESI-MS obsd 1504.5610, calcd 1504.5652 [(M + Na)$^+$], M = C$_{75}$H$_{95}$N$_5$O$_{22}$Zn.

5-(2,6-Bis((1-hydroxy-1-oxo-4,7,10,13,16,19-hexaoxahenicosan-21-yl)oxy)phenyl)-15-(4-(*N*-succinimidyloxycarbonyl)phenyl)porphyrin (P3-NHS). Following a reported method[22] with some modifications, a sample of **ZnP3-Bu/NHS** (11.0 mg, 7.4 µmol) in CH$_2$Cl$_2$ (370 µL) was treated with TFA (370 µL) at room temperature. The reaction mixture was stirred for 2 h at room temperature. The mixture was concentrated under reduced pressure. Given the high polarity and chromatographic tailing of the product, the mixture was purified by preparative TLC [silica, 0.25 mm, 20 × 20 cm, CH$_2$Cl$_2$/MeOH (9:1)] to afford a red solid (8.7 mg, 90%): ^{1}H NMR (700 MHz, CDCl$_3$) δ 10.29 (s, 2H), 9.43 (d, J = 4.5 Hz, 2H), 9.35 (d, J = 4.5 Hz, 2H), 9.02 (d, J = 4.4 Hz, 2H), 9.00 (d, J = 4.4 Hz, 2H), 8.61 (d, J = 7.7 Hz, 2H), 8.45 (d, J = 7.7 Hz, 2H), 7.75 (t, J = 8.7 Hz, 1H), 7.06 (d, J = 8.7 Hz, 2H), 4.02 (t, J = 4.6 Hz, 4H), 3.57 (t, J = 6.0 Hz, 4H), 3.45–3.43 (m, 12H), 3.38 (dd, J = 5.8, 3.6 Hz, 4H), 3.25 (t, J = 4.8 Hz, 4H), 3.05–3.00 (m, 8H), 2.95 (t, J = 4.7 Hz, 4H), 2.60 (t, J = 4.8 Hz, 4H), 2.41 (t, J = 6.0 Hz, 4H), 2.23 (t, J = 4.8 Hz, 4H), 1.99 (t, J = 4.5 Hz, 4H), 1.78 (t, J = 4.5 Hz, 3H), −3.14 (s, 2H); ^{13}C{^{1}H} NMR (175 MHz, CDCl$_3$) δ 174.3, 169.6, 162.3, 159.8, 148.8, 135.3, 132.03, 131.96, 131.3, 130.8, 130.4, 129.3, 124.6, 119.4, 116.8, 112.3, 105.9, 105.2, 70.7, 70.5, 70.4, 70.3, 70.12, 70.06, 69.9, 69.44, 69.36, 69.2, 69.04, 69.02, 68.8, 66.7, 35.2, 29.9, 26.0; λ_{abs} (MeOH) 405, 500, 534, 573, 629 nm; λ_{abs} (DMSO) 410, 503, 538, 575, 630 nm; MALDI-MS obsd 1307.96, calcd 1307.54 [M$^+$]; ESI-MS obsd 1308.5418, calcd 1308.5446 [(M + H)$^+$], M = C$_{67}$H$_{81}$N$_5$O$_{22}$.

Zn(II)-5-(2,6-bis((1-*tert*-butyloxy-1-oxo-4,7,10,13,16,19-hexaoxahenicosan-21-yl)oxy)phenyl)-15-(4-(3-hydroxy-3-oxopropyl)phenyl)porphyrin (ZnP4-Bu). Following a reported procedure,[21] a solution of **ZnP4-Bu/ETMS** (29.0 mg, 19.1 µmol) in THF (1.90 mL) was treated with TBAF (1 M in THF, 48 µL, 48 µmol) at 35 °C (oil bath). The reaction mixture was stirred for 1 h, then allowed to cool to room temperature. The solvent was removed under reduced pressure. Given the similarity with the homologue **ZnP3-Bu**, the crude product was purified by preparative TLC [silica, 1 mm, 20 × 20 cm, CH$_2$Cl$_2$/MeOH (20:1)] to give a red solid (23.8 mg, 88%): ^{1}H NMR (700 MHz, CDCl$_3$) δ 10.15 (s, 2H), 9.34 (d, J = 4.3 Hz, 2H), 9.30 (d, J = 4.3 Hz, 2H), 9.08 (d, J = 4.3 Hz, 2H), 9.01 (d, J = 4.3 Hz, 2H), 8.16 (d, J = 7.5 Hz, 2H), 7.72 (t, J = 8.6 Hz, 1H), 7.61 (d, J = 7.2 Hz, 2H), 7.04 (d, J = 8.7 Hz, 2H), 3.96–3.95 (m, 4H), 3.54 (t, J = 6.6 Hz, 4H), 3.28–3.25 (m, 6H), 3.17–3.16 (m, 4H), 2.95 (t, J = 4.9 Hz, 4H), 2.89 (t, J = 4.4 Hz, 4H), 2.83 (t, J = 5.0 Hz, 4H), 2.65 (t, J = 4.8 Hz, 4H), 2.40 (t, J = 6.6 Hz, 4H), 2.31–2.29 (m, 4H), 1.78–1.74 (m, 4H), 1.59–1.51 (m, 8H), 1.42 (s, 18H), 1.34 (q, J = 5.2 Hz, 4H); ^{13}C{^{1}H} NMR (175 MHz, CDCl$_3$) δ 171.1, 159.9, 150.9, 149.6, 149.4, 149.2, 141.4, 139.5, 135.0, 132.1, 131.9, 131.7, 131.2, 130.0, 126.6, 122.0, 119.5, 111.6, 106.1, 105.3, 80.7, 70.0, 69.9, 69.7, 69.6, 69.5, 69.1, 68.83, 68.77, 68.5, 68.4, 68.3, 66.8, 36.2, 28.2; λ_{abs} (MeOH) 411, 544, 575 nm; MALDI-MS obsd 1413.03, calcd 1413.60 [M$^+$]; ESI-MS obsd 1435.5778, calcd 1435.5802 [(M + Na)$^+$], M = C$_{73}$H$_{96}$N$_4$O$_{20}$Zn.

Zn(II)-5-(2,6-bis((1-*tert*-butyloxy-1-oxo-4,7,10,13,16,19-hexaoxahenicosan-21-yl)oxy)phenyl)-15-(4-(3-(*N*-succinimidyloxy)-3-oxopropyl)phenyl)porphyrin (ZnP4-Bu/NHS). Following a reported method[42] with some modifications, a solution of **ZnP4-Bu** (6.1 mg, 4.3 µmol) and *N*-hydroxysuccinimide (4.9 mg, 43 µmol) in CH$_2$Cl$_2$ was stirred at room temperature. After 5 min, DCC (8.9 mg, 43 µmol) was added. The reaction mixture was stirred at room temperature for 1 h, and then the resulting mixture was filtered to remove a white precipitate. The filtrate was concentrated under reduced pressure and then chromatographed [silica, CH$_2$Cl$_2$/ethyl acetate (1:2) to (1:4)] to afford a red solid (5.2 mg, 80%): ^{1}H NMR (700 MHz, CDCl$_3$) δ 10.15 (s, 2H), 9.34 (d, J = 4.3 Hz, 2H), 9.30 (d, J = 4.3 Hz, 2H), 9.07 (d, J = 4.3 Hz, 2H), 9.02 (d, J = 4.2 Hz, 2H), 8.18–8.17 (m, 2H), 7.73 (t, J = 8.6 Hz, 1H), 7.64 (d, J = 7.7 Hz, 2H), 7.05 (d, J = 8.6 Hz, 2H), 3.97 (dd, J = 5.2, 3.6 Hz, 4H), 3.51 (t, J = 6.6 Hz, 4H), 3.46 (t, J = 7.9 Hz, 2H), 3.30–3.28 (m, 2H), 3.22 (t, J = 4.9 Hz, 4H), 3.14 (dd, J = 5.9, 4.1 Hz, 4H), 2.99–2.86 (m, 12H), 2.80 (t, J = 5.0 Hz, 4H), 2.63–2.60 (m, 4H), 2.37 (t, J = 6.6 Hz, 4H), 2.28 (t, J = 4.9 Hz, 4H), 1.76 (dd, J = 5.7, 3.8 Hz, 4H), 1.59–1.57 (m, 8H), 1.40 (s, 18H), 1.38 (t, J = 5.4 Hz, 4H); ^{13}C{^{1}H} NMR (175 MHz, CDCl$_3$) δ 171.0, 169.3, 168.3, 160.0, 151.0, 149.6, 149.5, 149.2, 141.9, 138.2, 135.1, 132.1, 132.0, 131.7, 131.3, 130.1, 126.7, 122.1, 119.3, 111.8, 106.1, 105.4, 80.6, 70.08, 70.06, 69.9, 69.74, 69.67, 69.5, 69.2, 68.9, 68.8, 68.6, 68.5, 68.4, 66.8, 56.1, 36.3, 33.1, 30.6, 29.9, 28.2, 25.9; λ_{abs} (MeOH) 411, 545, 580 nm; MALDI-MS obsd 1509.12, calcd 1509.61 [M$^+$]; ESI-MS obsd 1532.5932, calcd 1532.5965 [(M + Na)$^+$], M = C$_{77}$H$_{99}$N$_5$O$_{22}$Zn.

5-(2,6-Bis((1-hydroxy-1-oxo-4,7,10,13,16,19-hexaoxahenicosan-21-yl)oxy)phenyl)-15-(4-(3-(*N*-succinimidyloxy)-3-oxopropyl)phenyl)porphyrin (P4-NHS). Following a reported method[22] with some modifications, a sample of **ZnP4-Bu/NHS** (3.2 mg,
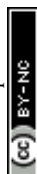
2.1 µmol) in CH_2Cl_2 (150 µL) was treated with TFA (150 µL) at room temperature. The reaction mixture was stirred for 2 h at room temperature. The mixture was concentrated under reduced pressure and then purified by reversed-phase HPLC [C18-silica, H_2O (0.1% TFA)/CH_3CN (0.1% TFA) (1 : 1 to 1 : 9)] to afford a red solid (2.4 mg, 85%): ^{1}H NMR (700 MHz, CD_2Cl_2) δ 10.30 (s, 2H), 9.43 (d, J = 4.5 Hz, 2H), 9.38 (d, J = 4.4 Hz, 2H), 9.10 (d, J = 4.5 Hz, 2H), 9.02 (d, J = 4.4 Hz, 2H), 7.77 (t, J = 8.7 Hz, 1H), 7.72 (d, J = 7.8 Hz, 2H), 7.11 (d, J = 8.7 Hz, 2H), 4.04–4.01 (m, 4H), 3.60 (t, J = 6.1 Hz, 4H), 3.49–3.43 (m, 14H), 3.38–3.36 (m, 4H), 3.30–3.27 (m, 2H), 3.25–3.23 (m, 4H), 3.02–2.99 (m, 4H), 2.96–2.94 (m, 4H), 2.93–2.85 (m, 4H), 2.60–2.58 (m, 4H), 2.45 (t, J = 6.1 Hz, 4H), 2.27–2.24 (m, 4H), 2.15–2.12 (m, 4H), 1.92–1.90 (m, 4H), −3.14 (s, 2H); ^{13}C{^{1}H} NMR (175 MHz, CD_2Cl_2) δ 174.5, 169.9, 168.9, 160.3, 148.6, 147.3, 145.8, 140.3, 139.5, 135.6, 132.2, 131.9, 131.4, 131.3, 131.1, 127.6, 119.9, 119.5, 112.0, 106.4, 105.2, 70.9, 70.84, 70.81, 70.58, 70.56, 70.4, 69.98, 69.96, 69.7, 69.6, 69.5, 69.2, 66.9, 35.3, 33.4, 31.0, 26.3; λ_{abs} (MeOH) 403, 500, 533, 573, 628 nm; λ_{abs} (DMSO) 408, 503, 536, 574, 630 nm; MALDI-MS obsd 1336.21, calcd 1336.58 [(M + H)[+]]; ESI-MS obsd 1336.5739, calcd 1336.5759 [(M + H)[+]], M = $C_{69}H_{85}N_5O_{22}$.

5-(2,6-Bis((1-hydroxy-1-oxo-4,7,10,13,16,19-hexaoxahenicosan-21-yl)oxy)phenyl)-15-(4-carboxyphenyl)porphyrin (P3). A solution of **ZnP3-Bu/ETMS** (15 mg, 10 µmol) in CH_2Cl_2 (1.0 mL) was treated with TFA (1.0 mL) at room temperature. The reaction mixture was stirred for 2 h and then diluted with CH_2Cl_2 (10 mL). Saturated aqueous $NaHCO_3$ was added to the reaction mixture until pH = 9. The aqueous phase was washed once with CH_2Cl_2. The aqueous phase was acidified with aqueous 1 M HCl until pH = 2, and then extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extract was washed with brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give a red solid (7.6 mg, 63%): ^{1}H NMR (700 MHz, CD_2Cl_2) δ 10.29 (s, 2H), 9.41–9.36 (m, 4H), 9.05–9.01 (m, 4H), 8.48–8.46 (m, 2H), 8.35 (d, J = 7.3 Hz, 2H), 7.77 (t, J = 8.7 Hz, 1H), 7.10 (d, J = 8.7 Hz, 2H), 4.04 (t, J = 4.7 Hz, 4H), 3.59 (t, J = 6.0 Hz, 5H), 3.50–3.40 (m, 12H), 3.34 (dd, J = 5.8, 3.5 Hz, 4H), 3.20 (t, J = 4.7 Hz, 4H), 2.96–2.92 (m, 8H), 2.51 (t, J = 4.7 Hz, 4H), 2.45 (t, J = 6.2 Hz, 4H), 2.15 (t, J = 4.7 Hz, 4H), 2.07 (dd, J = 5.6, 3.7 Hz, 4H), 1.80 (dd, J = 5.7, 3.7 Hz, 4H), −3.14 (s, 2H); ^{13}C{^{1}H} NMR (175 MHz, CD_2Cl_2) δ 174.6, 170.1, 159.7, 148.1, 146.7, 146.1, 145.4, 145.1, 134.9, 131.8, 131.7, 130.9, 130.6, 130.4, 129.8, 129.2, 128.6, 119.2, 117.5, 111.9, 105.8, 104.9, 70.23, 70.18, 70.1, 70.0, 69.9, 69.7, 69.3, 69.2, 69.0, 68.9, 68.8, 68.6; λ_{abs} (DMSO) 409, 503, 538, 575, 630 nm; MALDI-MS obsd 1211.42, calcd 1211.52 [(M + H)[+]]; ESI-MS obsd 606.2670, calcd 606.2678 [(M + 2H)[2+]]; M = $C_{63}H_{78}N_4O_{20}$.

5-(2,6-Bis((1-hydroxy-1-oxo-4,7,10,13,16,19-hexaoxahenicosan-21-yl)oxy)phenyl)-15-(4-(3-hydroxy-3-oxopropyl)phenyl)porphyrin (P4). A solution of **ZnP4-Bu/ETMS** (15.2 mg, 10.0 µmol) in CH_2Cl_2 (1.0 mL) was treated with TFA (1.0 mL) at room temperature. The reaction mixture was stirred for 6 h and then diluted with CH_2Cl_2 (10 mL). Saturated aqueous $NaHCO_3$ was added to the reaction mixture until pH = 9. The aqueous phase was washed once with CH_2Cl_2. The aqueous phase was acidified with aqueous 2 M HCl until pH = 2, and then extracted with CH_2Cl_2 (2 × 10 mL).

The combined organic extract was washed with brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give a red solid (11.0 mg, 89%): ^{1}H NMR (700 MHz, CD_2Cl_2) δ 10.19 (s, 2H), 9.32 (d, J = 4.4 Hz, 2H), 9.28 (d, J = 4.5 Hz, 2H), 8.99 (d, J = 4.4 Hz, 2H), 8.92 (d, J = 4.4 Hz, 2H), 8.12–8.09 (m, 2H), 7.68 (t, J = 8.7 Hz, 1H), 7.60–7.57 (m, 2H), 7.00 (d, J = 8.7 Hz, 2H), 3.95–3.92 (m, 4H), 3.53 (t, J = 6.0 Hz, 4H), 3.40–3.38 (m, 4H), 3.36–3.34 (m, 4H), 3.33–3.30 (m, 4H), 3.26–3.21 (m, 6H), 3.06–3.02 (m, 4H), 2.91 (t, J = 7.1 Hz, 2H), 2.87–2.84 (m, 4H), 2.76–2.73 (m, 4H), 2.39 (t, J = 6.0 Hz, 4H), 2.24–2.21 (m, 4H), 1.90–1.88 (m, 4H), 1.86–1.83 (m, 4H), 1.56–1.53 (m, 4H), −3.23 (s, 2H); ^{13}C{^{1}H} NMR (175 MHz, CD_2Cl_2) δ 178.5, 175.7, 160.3, 148.6, 147.3, 145.7, 140.6, 139.9, 135.5, 132.2, 131.9, 131.4, 131.3, 131.1, 127.6, 119.9, 119.7, 112.0, 106.3, 105.2, 70.89, 70.87, 70.7, 70.6, 70.5, 70.2, 69.8, 69.68, 69.66, 69.34, 69.27, 69.1, 66.8, 35.4, 30.3; λ_{abs} (MeOH) 404, 500, 533, 573, 628 nm; λ_{abs} (DMSO) 408, 503, 536, 574, 631 mm; MALDI-MS obsd 1239.31, calcd 1239.56 [(M + H)[+]]; ESI-MS obsd 1238.5513, calcd 1238.5522 [M[+]]; M = $C_{65}H_{82}N_4O_{20}$.

5-(2,6-Bis((1-hydroxy-1-oxo-4,7,10,13,16,19-hexaoxahenicosan-21-yl)oxy)phenyl)-15-(4-aminophenyl)porphyrin (P7). A solution of **ZnP7-Bu/Boc** (12.6 mg, 8.64 µmol) in CH_2Cl_2 (580 µL) was treated with TFA (290 µL) at room temperature for 2 h. The reaction was monitored by LC-MS. The reaction mixture was concentrated under reduced pressure and then passed through a C18-silica pad (1 cm × 1 cm) by eluting with H_2O (to remove the remaining TFA) followed by acetonitrile. The collected solution was dried under vacuum to give a red solid (7.6 mg, 75%): ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.22 (s, 2H), 9.36 (d, J = 4.4 Hz, 2H), 9.32 (d, J = 4.4 Hz, 2H), 9.13 (d, J = 4.4 Hz, 2H), 8.98 (d, J = 4.4 Hz, 2H), 8.01 (d, J = 7.5 Hz, 2H), 7.72 (t, J = 8.7 Hz, 1H), 7.06–7.02 (m, 4H), 4.01–3.99 (m, 4H), 3.54 (t, J = 6.0 Hz, 4H), 3.39–3.36 (m, 12H), 3.29 (dd, J = 5.8, 3.7 Hz, 4H), 3.12 (dd, J = 5.7, 3.8 Hz, 4H), 2.93 (t, J = 4.6 Hz, 4H), 2.85 (dd, J = 5.7, 3.8 Hz, 4H), −3.07 (s, 2H); ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$) δ 159.8, 148.2, 147.3, 146.3, 145.1, 136.0, 131.8, 131.6, 131.22, 131.20, 130.8, 130.6, 120.0, 119.7, 114.0, 111.1, 105.8, 104.7, 70.3, 70.1, 69.9, 69.6, 69.35, 69.27, 69.2, 69.1, 68.9, 68.8, 68.7, 67.2, 35.8; λ_{abs} (DMSO) 410, 505, 543, 577, 634; MALDI-MS obsd 1204.22, calcd 1204.53 [(M + Na)[+]]; ESI-MS obsd 1204.5290, calcd 1204.5312 [(M + Na)[+]], M = $C_{62}H_{79}N_5O_{18}$.

5-(2,6-Bis((1-hydroxy-1-oxo-4,7,10,13,16,19-hexaoxahenicosan-21-yl)oxy)phenyl)-15-(4-isothiocyanatophenyl)porphyrin (P7-NCS). Following a reported method[76] with some modifications, a sample of **P7** (6.8 mg, 5.8 µmol) in CH_2Cl_2 (1.5 mL) was treated with 1,1′-thiocarbonyldi-2(1H)-pyridone (2.7 mg, 12 µmol) at room temperature for 2 h. The mixture was concentrated under reduced pressure. Given the high polarity and chromatographic tailing of the product, the mixture was purified by preparative TLC [silica, 0.25 mm, 20 × 20 cm, CH_2Cl_2/MeOH (9 : 1)] to give a red solid (5.6 mg, 80%): ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.28 (s, 2H), 9.39 (d, J = 4.5 Hz, 2H), 9.36 (d, J = 4.5 Hz, 2H), 9.01 (d, J = 4.4 Hz, 2H), 8.99 (d, J = 4.5 Hz, 2H), 7.73 (t, J = 8.7 Hz, 1H), 7.68–7.65 (m, 2H), 7.05 (d, J = 8.7 Hz, 2H), 4.01 (t, J = 4.5 Hz, 4H), 3.45 (t, J = 6.1 Hz, 4H), 3.38 (dd, J = 5.9, 3.5 Hz, 4H), 3.36–3.30 (m, 12H), 3.16 (dd, J = 5.8, 3.6 Hz, 4H), 2.95 (t, J = 4.6 Hz, 4H), 2.91 (dd, J = 5.7, 3.7 Hz, 4H), 2.56–2.48 (m, 4H), 2.27 (t, J = 6.2 Hz, 4H), 2.18–2.12 (m, 4H),
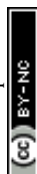
1.96–1.90 (m, 4H), 1.75–1.69 (m, 4H), −3.17 (s, 2H); $^{13}C\{^1H\}$ NMR (175 MHz, CDCl$_3$) δ 177.4, 159.8, 148.3, 146.3, 145.5, 145.2, 140.9, 136.6, 135.8, 132.0, 131.9, 131.3, 131.2, 130.8, 130.5, 124.5, 119.3, 117.2, 112.1, 105.8, 105.1, 70.7, 69.9, 69.85, 69.78, 69.73, 69.68, 69.4, 69.3, 69.23, 69.20, 69.0, 68.85, 68.82, 68.6, 68.1, 37.0, 29.8; λ_{abs} (DMSO) 411, 504, 539, 576, 632; MALDI-MS obsd 1245.84, calcd 1246.49 [(M + Na)$^+$]; ESI-MS obsd 1246.4856, calcd 1246.4877 [(M + Na)$^+$], M = C$_{63}$H$_{77}$N$_5$O$_{18}$.

5-(2,6-Bis((1-hydroxy-1-oxo-4,7,10,13,16,19-hexaoxahenicosan-21-yl)oxy)phenyl)-15-(2-aminoethyl)porphyrin (P8). A solution of **ZnP8-Bu/Boc** (5.4 mg, 3.8 μmol) in CH$_2$Cl$_2$ (225 μL) was treated with TFA (25 μL) at room temperature for 3 h. The reaction was monitored by LC-MS. The reaction mixture was concentrated and then passed through a C18-silica pad (1 cm × 1 cm) by eluting with H$_2$O (to remove the remaining TFA) followed by acetonitrile. The collected solution was dried under vacuum to give the desired product as a non-crystalline red solid (3.9 mg, 90%): ^1H NMR (500 MHz, CDCl$_3$) δ 10.13 (s, 2H), 9.85 (d, J = 4.6 Hz, 2H), 9.40 (d, J = 4.6 Hz, 2H), 9.27 (d, J = 4.6 Hz, 2H), 8.96 (d, J = 4.5 Hz, 2H), 7.72 (t, J = 8.5 Hz, 1H), 7.01 (d, J = 8.6 Hz, 2H), 5.55 (t, J = 8.3 Hz, 2H), 4.08–4.02 (m, 2H), 4.00 (t, J = 4.3 Hz, 4H), 3.88 (t, J = 6.0 Hz, 4H), 3.62–3.56 (m, 4H), 3.51–3.45 (m, 4H), 3.35–3.27 (m, 4H), 3.18–3.10 (m, 4H), 2.93 (t, J = 4.3 Hz, 4H), 2.82–2.70 (m, 8H), 2.20 (t, J = 4.8 Hz, 4H), 1.57–1.39 (m, 8H), 0.95–0.82 (m, 4H), 0.81–0.63 (m, 4H), −3.16 (s, 2H). This crude sample was used in the next step without further purification.

5-(2,6-Bis((1-hydroxy-1-oxo-4,7,10,13,16,19-hexaoxahenicosan-21-yl)oxy)phenyl)-15-(2-isothiocyanatoethyl)porphyrin (P8-NCS). Following a reported method[76] with some modifications, a solution of **P8** (3.9 mg, 3.4 μmol) in CH$_2$Cl$_2$ (500 μL) was treated overnight with 1,1′-thiocarbonyldi-2(1H)-pyridone (2.3 mg, 10 μmol) at room temperature. The resulting reaction mixture was purified by preparative thin layer chromatography [silica, 20 cm × 20 cm × 0.5 mm; CH$_2$Cl$_2$/methanol (9:1, R_f = 0.45)] to give the desired product as a non-crystalline, dark-red solid (2.6 mg, 64%): ^1H NMR (500 MHz, CDCl$_3$) δ 10.26 (s, 2H), 9.58 (d, J = 4.6 Hz, 2H), 9.50 (d, J = 4.6 Hz, 2H), 9.35 (d, J = 4.6 Hz, 2H), 8.99 (d, J = 4.6 Hz, 2H), 7.74 (t, J = 8.5 Hz, 1H), 7.05 (d, J = 8.6 Hz, 2H), 5.43 (t, J = 7.3 Hz, 2H), 4.64 (t, J = 7.3 Hz, 2H), 4.09–3.96 (m, 4H), 3.52–3.31 (m, 16H), 3.18–3.11 (m, 4H), 3.02–2.93 (m, 4H), 2.90–2.82 (m, 4H), 2.50–2.42 (m, 4H), 2.35–2.25 (m, 4H), 2.11–2.03 (m, 8H), 1.95–1.87 (m, 4H), 1.67–1.58 (m, 4H), −3.15 (d, J = 21.3 Hz, 2H); λ_{abs} [MeCN/H$_2$O (95:5)] 402, 500, 532, 574, 627; MALDI-MS obsd 1199.7, calcd 1198.5 [(M + Na)$^+$]; ESI-MS obsd 1176.5075, calcd 1176.5057 [(M + H)$^+$], M = C$_{59}$H$_{77}$N$_5$O$_{18}$S.

Zn(II)-5-(4-((2,5,8,11,14,17-hexaoxanonadecan-19-yl)oxy)phenyl-15-(4-carboxyphenyl)porphyrin (P9). A solution of **ZnP9-ETMS** (17.0 mg, 17.6 μmol) in CH$_2$Cl$_2$ (880 μL) was treated dropwise with TFA (880 μL) and then stirred overnight at room temperature. The resulting dark-green reaction mixture was diluted with CH$_2$Cl$_2$ (20.0 mL). The organic solution was washed with 5% NaHSO$_4$ (20.0 mL) and saturated aqueous NH$_4$Cl (20.0 mL) to give a reddish solution. Each aqueous solution was extracted with CH$_2$Cl$_2$ (2 × 15.0 mL). The combined organic extract was dried (Na$_2$SO$_4$) and then concentrated under reduced pressure. Column chromatography [silica, CH$_2$Cl$_2$/MeOH (9:1)] afforded

a dark-red solid (11.0 mg, 78%): ^1H NMR (500 MHz, CDCl$_3$) δ 10.21 (s, 2H), 9.33–9.32 (m, 4H), 9.09 (d, J = 4.4 Hz, 2H), 9.02 (d, J = 4.4 Hz, 2H), 8.62–8.60 (m, 2H), 8.41–8.40 (m, 2H), 8.17–8.14 (m, 2H), 7.37–7.35 (m, 2H), 4.46–4.45 (m, 2H), 4.10–4.08 (m, 2H), 3.92–3.89 (m, 2H), 3.84–3.82 (m, 2H), 3.80–3.75 (m, 4H), 3.74–3.72 (m, 4H), 3.71–3.70 (m, 2H), 3.69–3.67 (m, 2H), 3.66–3.65 (m, 2H), 3.56–3.55 (m, 2H), 3.38 (s, 3H), −3.15 (s, 2H), −CO$_2$H signal is not observed; $^{13}C\{^1H\}$ NMR (125 MHz, CDCl$_3$) δ 170.9, 158.8, 147.5, 147.0, 146.5, 145.2, 145.1, 135.9, 135.0, 133.8, 131.9, 131.6, 131.2, 130.4, 128.9, 128.8, 119.5, 117.1, 113.3, 105.4, 71.9, 71.0, 70.8, 70.71, 70.66, 70.62, 70.60, 70.58, 70.5, 70.4, 69.9, 67.8, 59.0; λ_{abs} (toluene) 411, 504, 539, 578, 634 nm; MALDI-MS obsd 801.43, calcd 801.35 [(M + H)$^+$]; ESI-MS obsd 801.3478, calcd 801.3494 [(M + H)$^+$], M = C$_{46}$H$_{48}$N$_4$O$_9$.

Statistical syntheses of porphyrins

5-(2,6-Bis((1-tert-butyloxy-1-oxo-4,7,10,13,16,19-hexaoxahenicosan-21-yl)oxy)phenyl)-5-(4-carboxyphenyl)porphyrin (P3-Bu). Following a reported method[69] for statistical condensations with some modifications, a solution of **A1** (75.1 mg, 0.500 mmol), dipyrromethane (146 mg, 1.00 mmol), and **A6** (461 mg, 0.500 mmol) in CH$_2$Cl$_2$ (50.0 mL) was stirred at room temperature. After 5 min, TFA (134 μL, 1.75 mmol) was added, and the reaction mixture was stirred at room temperature for 30 min. Then, DDQ (341 mg, 1.50 mmol) was added. The resulting mixture was stirred at room temperature for 15 min, and then triethylamine was added (350 μL, 2.50 mmol). After stirring for 15 min, the solution was concentrated under reduced pressure, and the crude product was chromatographed [silica, CH$_2$Cl$_2$/MeOH (15:1)]. Three porphyrin bands were observed, whereupon the most mobile band and second-most mobile band were collected together. A second column [silica, CH$_2$Cl$_2$/MeOH (25:1)] was used to obtain in pure form the second band, which upon concentration afforded a red solid (65.9 mg, 10%): ^1H NMR (700 MHz, CDCl$_3$) δ 10.18 (s, 2H), 9.36–9.19 (m, 4H), 9.03 (d, J = 4.4 Hz, 2H), 9.00 (d, J = 4.4 Hz, 2H), 8.58–8.50 (m, 2H), 8.31 (d, J = 7.3 Hz, 2H), 7.74 (t, J = 8.7 Hz, 1H), 7.08 (d, J = 8.7 Hz, 2H), 4.04 (t, J = 4.8 Hz, 4H), 3.67–3.65 (m, 4H), 3.55–3.50 (m, 12H), 3.44 (dd, J = 5.8, 4.0 Hz, 4H), 3.31 (t, J = 4.9 Hz, 4H), 3.09 (t, J = 4.9 Hz, 4H), 2.95 (t, J = 4.9 Hz, 4H), 2.70 (t, J = 4.9 Hz, 4H), 2.47 (t, J = 6.5 Hz, 4H), 2.36 (t, J = 4.9 Hz, 4H), 2.08 (t, J = 4.6 Hz, 4H), 1.91 (t, J = 4.6 Hz, 4H), 1.42 (s, 18H), −3.10 (s, 2H); $^{13}C\{^1H\}$ NMR (175 MHz, CDCl$_3$) δ 171.1, 159.9, 148.3, 146.3, 145.6, 145.4, 145.1, 134.8, 131.8, 131.6, 131.1, 130.7, 128.7, 119.6, 118.2, 111.9, 105.9, 104.9, 80.7, 70.7, 70.50, 70.47, 70.41, 70.38, 70.2, 70.0, 69.62, 69.58, 69.3, 69.23, 69.16, 68.8, 67.0, 36.3, 28.2; λ_{abs} (MeOH) 404, 500, 533, 574, 629 nm; MALDI-MS obsd 1323.39, calcd 1323.65 [(M + H)$^+$]; ESI-MS obsd 1345.6317, calcd 1345.6354 [(M + Na)$^+$], M = C$_{71}$H$_{94}$N$_4$O$_{20}$.

5-(2,6-Bis((1-tert-butyloxy-1-oxo-4,7,10,13,16,19-hexaoxahenicosan-21-yl)oxy)phenyl)-5-(4-(N-succinimidyloxycarbonyl)phenyl)porphyrin (P3-Bu/NHS). Following a reported method[42] with some modifications, a solution of **P3-Bu** (24.3 mg, 18.4 μmol) and N-hydroxysuccinimide (21.2 mg, 184 μmol) in CH$_2$Cl$_2$ was

stirred at room temperature. After 5 min, DCC (38.0 mg, 184 μmol) was added. The reaction mixture was stirred at room temperature for 1 h, and then the resulting mixture was filtered to remove a white precipitate. The filtrate was concentrated under reduced pressure and then chromatographed [silica, CH_2Cl_2/ethyl acetate (1:1) to (1:3)] to afford a red solid (23.5 mg, 90%): ^{1}H NMR (700 MHz, CDCl$_3$) δ 10.29 (s, 2H), 9.43 (d, J = 4.4 Hz, 2H), 9.34 (d, J = 4.5 Hz, 2H), 9.02 (d, J = 4.4 Hz, 2H), 9.00 (d, J = 4.4 Hz, 2H), 8.61 (d, J = 8.1 Hz, 2H), 8.46 (d, J = 8.0 Hz, 2H), 7.75 (t, J = 8.7 Hz, 1H), 7.07 (d, J = 8.7 Hz, 2H), 4.02 (t, J = 4.9 Hz, 4H), 3.66 (t, J = 6.6 Hz, 4H), 3.55–3.48 (m, 12H), 3.43 (dd, J = 5.9, 4.0 Hz, 4H), 3.31–3.28 (m, 4H), 3.10–2.97 (m, 8H), 2.93 (t, J = 4.9 Hz, 4H), 2.70–2.67 (m, 4H), 2.46 (t, J = 6.6 Hz, 4H), 2.35–2.32 (m, 4H), 2.08–2.05 (m, 4H), 1.92–1.89 (m, 4H), 1.42 (s, 18H), −3.13 (s, 2H); ^{13}C{^{1}H} NMR (175 MHz, CDCl$_3$) δ 171.4, 171.0, 169.5, 162.3, 159.8, 148.8, 148.3, 145.9, 145.5, 145.2, 135.3, 131.95, 131.86, 131.2, 130.7, 130.3, 129.3, 124.5, 119.5, 116.7, 112.3, 105.9, 105.2, 80.6, 70.54, 70.50, 70.46, 70.4, 70.3, 70.1, 69.6, 69.34, 69.26, 69.1, 68.8, 67.0, 36.3, 28.2, 25.9, 25.3; λ_{abs} (MeOH) 405, 500, 534, 573, 629 nm; MALDI-MS obsd 1420.23, calcd 1420.67 [(M + H)$^+$]; ESI-MS obsd 1420.6659, calcd 1420.6698 [(M + H)$^+$], M = $C_{75}H_{97}N_5O_{22}$.

5-(2,6-Bis((1-hydroxy-1-oxo-4,7,10,13,16,19-hexaoxahenicosan-21-yl)oxy)phenyl)-15-(4-(*N*-succinimidyloxycarbonyl)phenyl)porphyrin (P3-NHS). A solution of **P3-Bu/NHS** (22.0 mg, 15.5 μmol) in CH_2Cl_2 (1.1 mL) was treated with TFA (550 μL) at room temperature. The reaction mixture was stirred for 2 h at room temperature and then diluted with CH_2Cl_2 (20.0 mL). The organic solution was washed water (3 × 20.0 mL), dried (Na$_2$SO$_4$), and concentrated under reduced pressure. The crude product was loaded on a C18-silica pad (2 cm × 1 cm) and washed with water (40 mL) followed by acetonitrile (8 mL) to give an eluant that upon concentration afforded a red solid (19.7 mg, 97%) with identical characterization data (^{1}H NMR, ^{13}C{^{1}H} NMR, MALDI-MS) as above.

5-(2,6-Bis((1-*tert*-butyloxy-1-oxo-4,7,10,13,16,19-hexaoxahenicosan-21-yl)oxy)phenyl)-15-(4-(3-hydroxy-3-oxopropyl)phenyl)-porphyrin (P4-Bu). Following a reported method[69] for statistical condensations with some modifications, a solution of **A2** (89.1 mg, 0.500 mmol), dipyrromethane (146 mg, 1.00 mmol), and **A6** (461 mg, 0.500 mmol) in CH_2Cl_2 (50.0 mL) was stirred at room temperature. After 5 min, TFA (134 μL, 1.75 mmol) was added, and the reaction mixture was stirred at room temperature for 30 min. Then, DDQ (341 mg, 1.50 mmol) was added. The resulting mixture was stirred at room temperature for 15 min, and then triethylamine was added (350 μL, 2.50 mmol). After stirring for 15 min, the solution was concentrated under reduced pressure, and the crude product was chromatographed [silica, CH_2Cl_2/MeOH (20:1)]. Three porphyrin bands were observed, whereupon the most mobile band and second-most mobile band were collected together. A second column [silica, CH_2Cl_2/MeOH (25:1)] was used to obtain in pure form the second band, which upon concentration afforded a red solid (75.0 mg, 11%): ^{1}H NMR (700 MHz, CDCl$_3$) δ 10.20 (s, 2H), 9.32 (d, J = 4.5 Hz, 2H), 9.30 (d, J = 4.5 Hz, 2H), 9.08 (d, J = 4.4 Hz, 2H), 9.00 (d, J = 4.4 Hz, 2H), 7.73 (t, J = 8.7 Hz, 1H), 7.67 (d, J = 7.3 Hz, 2H), 7.06 (d, J = 8.7 Hz, 2H), 4.02 (t, J = 4.8 Hz, 4H), 3.65 (t, J = 6.4 Hz, 4H), 3.53–3.47

(m, 12H), 3.41 (dd, J = 5.9, 3.9 Hz, 4H), 3.33 (t, J = 7.9 Hz, 2H), 3.25 (dd, J = 5.8, 4.2 Hz, 4H), 3.01 (dd, J = 5.7, 4.1 Hz, 4H), 2.94–2.92 (m, 6H), 2.57 (t, J = 5.0 Hz, 4H), 2.47 (t, J = 6.5 Hz, 4H), 2.20 (t, J = 5.0 Hz, 4H), 2.00 (t, J = 4.7 Hz, 4H), 1.76 (t, J = 4.7 Hz, 4H), 1.42 (s, 18H), −3.09 (s, 2H); ^{13}C{^{1}H} NMR (175 MHz, CDCl$_3$) δ 171.1, 159.8, 148.2, 146.9, 145.2, 145.1, 141.3, 139.2, 135.0, 131.7, 131.3, 131.1, 130.9, 130.6, 127.2, 119.7, 119.4, 111.4, 105.9, 104.7, 80.7, 70.7, 70.44, 70.40, 70.35, 70.33, 70.2, 69.9, 69.5, 69.4, 69.2, 69.10, 69.08, 68.8, 66.9, 37.5, 36.3, 31.7, 28.2; λ_{abs} (MeOH) 404, 500, 532, 574, 629 nm; MALDI-MS obsd 1351.34, calcd 1351.68 [(M + H)$^+$]; ESI-MS obsd 1373.6636, calcd 1373.6667 [(M + Na)$^+$], M = $C_{73}H_{98}N_4O_{20}$.

5-(2,6-Bis((1-*tert*-butyloxy-1-oxo-4,7,10,13,16,19-hexaoxaheni-cosan-21-yl)oxy)phenyl)-15-(4-(3-(*N*-succinimidyloxy)-3-oxopropyl)phenyl)porphyrin (P4-Bu/NHS). Following a reported method[42] with some modifications, a solution of **P4-Bu** (24.3 mg, 18.4 μmol) and *N*-hydroxysuccinimide (21.2 mg, 184 μmol) in CH_2Cl_2 was stirred at room temperature. After 5 min, DCC (38.0 mg, 184 μmol) was added. The reaction mixture was stirred at room temperature for 1 h, and then the resulting mixture was filtered to remove a white precipitate. The filtrate was concentrated under reduced pressure and then chromatographed [silica, CH_2Cl_2/ethyl acetate (1:1) to (1:3)] to afford a red solid (23.5 mg, 89%): ^{1}H NMR (700 MHz, CDCl$_3$) δ 10.25 (s, 2H), 9.38 (d, J = 4.4 Hz, 2H), 9.32 (d, J = 4.4 Hz, 2H), 9.09 (d, J = 4.4 Hz, 2H), 9.00 (d, J = 4.4 Hz, 2H), 8.23 (d, J = 7.7 Hz, 2H), 7.74 (t, J = 8.7 Hz, 1H), 7.69 (d, J = 7.4 Hz, 2H), 7.06 (d, J = 8.7 Hz, 2H), 4.01 (t, J = 4.8 Hz, 4H), 3.65 (t, J = 6.6 Hz, 4H), 3.54–3.44 (m, 14H), 3.41 (dd, J = 5.8, 4.0 Hz, 4H), 3.30–3.26 (m, 6H), 3.05 (dd, J = 5.7, 4.2 Hz, 4H), 2.96–2.91 (m, 8H), 2.65–2.62 (m, 4H), 2.46 (t, J = 6.6 Hz, 4H), 2.29 (dd, J = 5.8, 4.1 Hz, 4H), 2.07–2.04 (m, 4H), 1.88 (dd, J = 5.7, 3.6 Hz, 4H), 1.42 (s, 18H), −3.11 (s, 2H); ^{13}C{^{1}H} NMR (175 MHz, CDCl$_3$) δ 171.2, 171.0, 169.3, 168.3, 159.7, 148.2, 146.8, 145.3, 145.1, 140.1, 138.7, 135.2, 131.7, 131.4, 131.1, 131.0, 130.6, 127.1, 119.7, 118.9, 111.5, 105.9, 104.8, 80.6, 70.54, 70.50, 70.45, 70.4, 70.3, 70.0, 69.63, 69.61, 69.3, 69.23, 69.18, 68.8, 67.0, 36.4, 33.0, 30.6, 28.2, 25.8, 25.2; λ_{abs} (MeOH) 404, 500, 533, 573, 628 nm; MALDI-MS obsd 1448.25, calcd 1448.70 [(M + H)$^+$]; ESI-MS obsd 1448.6966, calcd 1448.7011 [(M + H)$^+$], M = $C_{77}H_{101}N_5O_{22}$.

5-(2,6-Bis((1-hydroxy-1-oxo-4,7,10,13,16,19-hexaoxahenicosan-21-yl)oxy)phenyl)-15-(4-(3-(*N*-succinimidyloxy)-3-oxopropyl)phenyl)-porphyrin (P4-NHS). A solution of **P4-Bu/NHS** (31.8 mg, 22.0 μmol) in CH_2Cl_2 (1.5 mL) was treated with TFA (750 μL) at room temperature. The reaction mixture was stirred for 2 h at room temperature and then diluted with CH_2Cl_2 (20.0 mL). The organic solution was washed with water (3 × 25.0 mL), dried (Na$_2$SO$_4$), and concentrated under reduced pressure. The crude product was loaded on a C18-silica pad (2 cm × 1 cm) and washed with water (40 mL) followed by acetonitrile (8 mL) to give an eluant that upon concentration afforded a red solid (27.6 mg, 94%) with identical characterization data (^{1}H NMR, ^{13}C{^{1}H} NMR, MALDI-MS) as above.

Conflicts of interest

The authors declare competing financial interests.
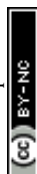
Data availability

Crystallographic data for **ZnP1-acetal** has been deposited at the CCDC under 2321456. Crystallographic data for **D7** has been deposited at the CCDC under 2415855. ^{1}H NMR and ^{13}C{^{1}H} NMR spectra for new compounds; and absorption spectra of selected compounds in solution. All other data are contained in the paper.

Acknowledgements

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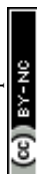
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