Supplementary material for:

A Compact Water-Soluble Porphyrin Bearing an Iodoacetamido Bioconjugatable Site

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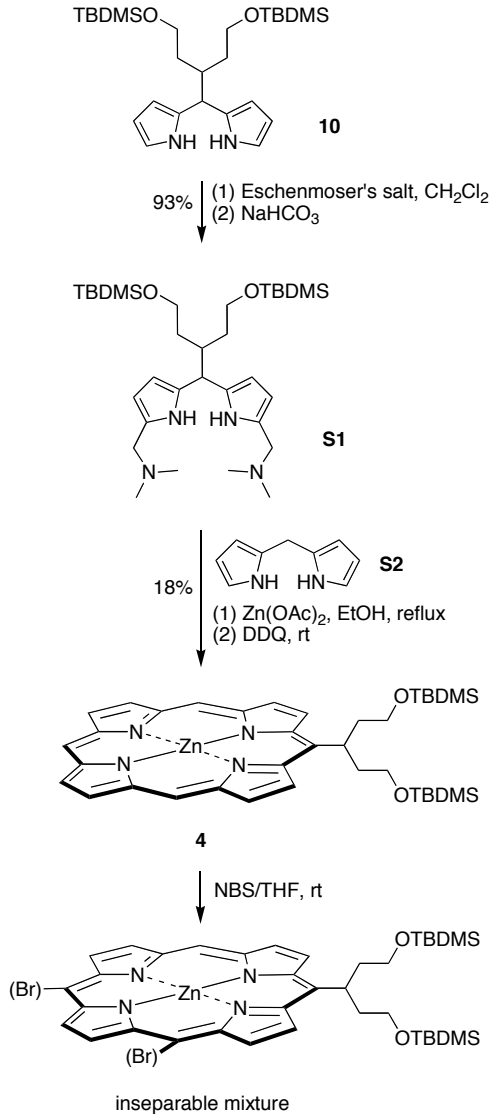
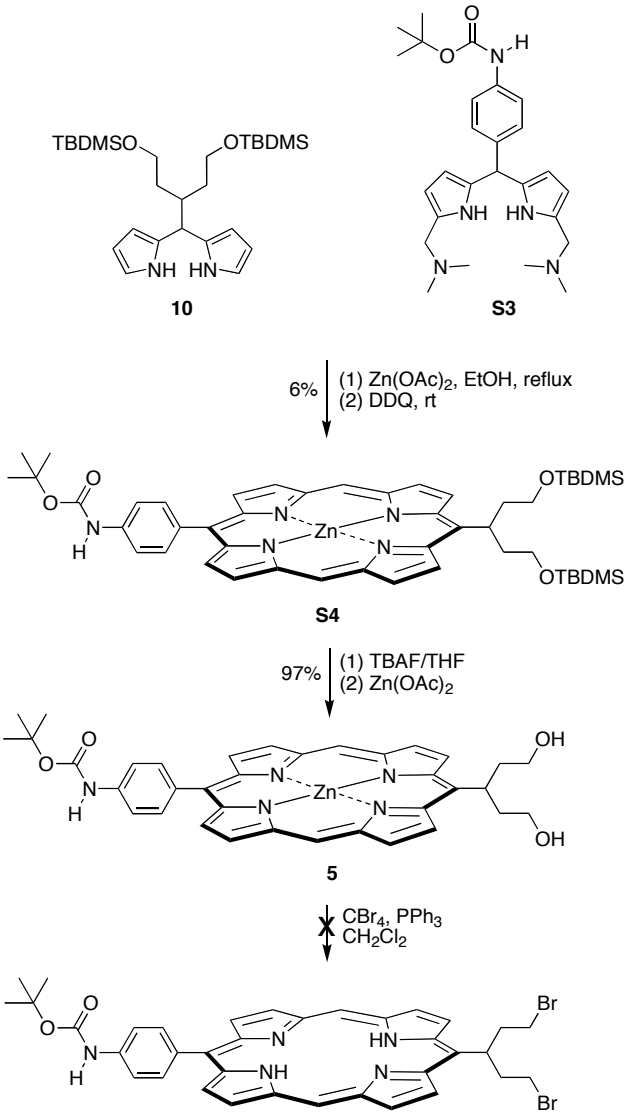
Route I. The swallowtail dipyrromethane (**10**) was synthesized from 2-bromoethanol according to a reported reaction sequence.[11] Treatment of **10** with 2.1 equiv of Eschenmoser's salt in CH_2Cl_2 followed by basic work-up afforded the 1,9-bis(*N,N*-dimethylaminomethyl) derivative **S1** in excellent yield (Scheme S1). Condensation of **S1** with dipyrromethane **S2**[35] in ethanol in the presence of $Zn(OAc)_2$, and subsequent oxidation of the resulting porphyrinogen with DDQ gave the monosubstituted swallowtail porphyrin **4** in 18% yield. Bromination of **4** with NBS under standard conditions[S1] yielded an inseparable mixture of products, which upon LD-MS and ^{1}H NMR analysis was found to contain a mixture of mono- and dibrominated porphyrins. Therefore, route I was abandoned and we turned our attention to route II.



Scheme S1

Route II. The required bioconjugatable group (iodoacetamide) can be introduced into the porphyrin through a protected amine. The amine can then be reacted with an actived iodoacetic acid (iodoacetic anhydride, or an isolated or in situ-formed activated ester) to yield the iodoacetamide. The known 1,9-bis(*N,N*-dimethylaminomethyl)-5-(*N*-Boc-4-aminophenyl) dipyrromethane[S2] (**S3**) was reacted with the swallowtail–dipyrromethane **10** under the conditions described in route I (ethanol, $Zn(OAc)_2$, reflux; then oxidation with DDQ at room temperature) to yield porphyrin **S4** in moderate yield (Scheme S2).

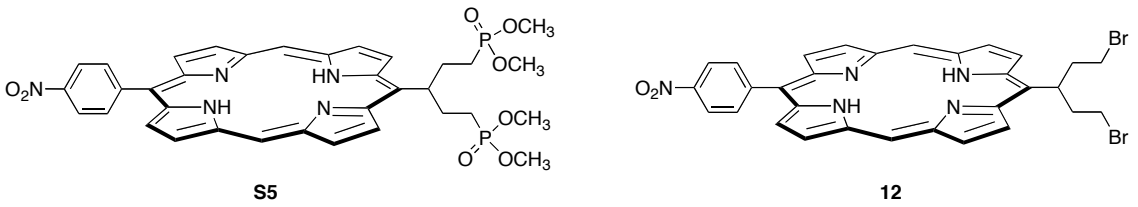


Scheme S2

Removal of the TBDMS protecting groups with TBAF afforded the porphyrin–diol **5**. LD-MS analysis of the crude reaction mixture revealed partial loss of both the zinc metal and the Boc protecting group, in accord with our previous findings.[11] Remetalation was possible by treatment of the crude product with zinc acetate. Following previously reported procedures,[11,38] the porphyrin–diol **5** was reacted with PPh_3/CBr_4 in CH_2Cl_2 to obtain the porphyrin–dibromide. None of the desired product was isolated from the resulting complex mixture. LD-MS analysis of the crude sample showed loss of the Boc protecting group. Furthermore, quantitative

demetalation had taken place, among other (unidentified) side-reactions. Therefore, we decided to introduce the amine functionality through a nitro substituent (a latent amino group), instead of searching for a different amine protecting group, which may be either as labile under the porphyrin manipulation conditions as the Boc group, or may be too robust, and thus cumbersome to remove.

Catalytic transfer hydrogenation. Despite the predominance of the putative ipso-substitution pathway during phosphonation of **12**, trace amounts of the desired *p*-nitrophenylporphyrin–swallowtail-diphosphonate (**S5**, Chart S1) could be isolated. Reduction of the nitro group to the amine was attempted employing both **S5** and **12** as substrates (Chart S1). A number of hydride sources (ammonium formate, hydrazine), solvents (ethanol, THF), reaction temperatures (room temperature, refluxing ethanol, refluxing THF), and reaction times (10 min, 30 min, 1 h to 12 h) were scanned (Table S1). Reduction of the nitro group to the amine was facile, and given enough time (2 h, as shown by TLC and LD-MS), quantitative. The reduction of **S5** was in all cases accompanied by the removal of two of the methyl esters, rendering the product water-soluble and difficult to purify. Quantitative removal of the four methyl esters was never observed.



S5 **12**

Chart S1

Catalytic transfer hydrogenation of **12** was carried out in THF with use of ammonium formate as the hydrogen source and palladium supported on carbon (5 wt%) as the catalyst. The conditions that were screened for this substrate are given in Table S1.

Table S1. Survey of conditions for catalytic transfer hydrogenation.

Reactant	Reducing agent	Solvent	Temperature	Time	Yield
S5	$(NH_4)HCO_2$	EtOH	reflux	1 h	-[a]
S5	$(NH_4)HCO_2$	THF	r.t	12 h	0
S5	$(NH_4)HCO_2$	THF	reflux	1 h	-[a]
S5	N_2H_4	THF	r.t	12 h	-[a]
12	$(NH_4)HCO_2$	THF	reflux	1 h	~ 60[b, c]
12	$(NH_4)HCO_2$	THF	reflux	2 h	quant.[c]
12	cyclohexene	THF	reflux	1 h	0

All reactions were conducted in the presence of 0.5 equiv Pd/C (5%). Reactions were monitored by TLC and LD-MS analysis of the crude reaction mixture. [a]Two of the four phosphonate methyl esters were hydrolyzed. [b]Determined by TLC and ^{1}H NMR analysis of the crude product after aqueous-organic work-up. [c]Some debrominated porphyrin was observed upon LD-MS analysis of the purified product.

Experimental Section.

1,9-Bis(*N*,*N*-dimethylaminomethyl)-5-[1,5-bis(*tert*-butyldimethylsilyloxy)pent-3-yl]dipyrromethane (S1). Following a standard procedure,[S3] a solution of dipyrromethane **10** (476 mg, 1.00 mmol) in CH_2Cl_2 (10 mL) was cooled in an ice-water bath and treated with Eschenmoser's salt (389 mg, 2.10 mmol). The reaction mixture was allowed to warm to room temperature. Stirring was continued for 1 h. The mixture was poured into CH_2Cl_2, and was washed with saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated to afford a yellow oil that was used without further purification (548 mg, 93%): IR (film, ν_{max} cm^{-1}) 1590, 1645, 1662, 2931, 3351; ^1H NMR δ 0.05 (s, 12H), 0.90 (s, 18H), 1.34–1.40 (m, 2H), 1.67–1.76 (m, 2H), 2.16 (s, 12), 2.18–2.26 (m, 1H), 3.28–3.42 (m, 4H), 3.59–3.68 (m, 4H), 4.17 (d, J = 5.1 Hz, 1H), 5.90–5.91 (m, 4H), 8.28 (s, 2H); ^{13}C NMR δ –5.07, 18.61, 26.28, 34.94, 35.79, 41.25, 42.23, 56.89, 62.07, 106.49, 107.33, 128.30, 131.90; λ_{abs} 355 nm.

Zn(II)-5-[1,5-Bis(*tert*-butyldimethylsilyloxy)pent-3-yl]porphyrin (4). Following a standard procedure,[S3] a solution of **S1** (75.1 mg, 0.127 mmol) and dipyrromethane **S2** (19.0 mg, 0.127 mmol) in ethanol (13 mL) was treated with $Zn(OAc)_2$ (233 mg, 1.27 mmol). The mixture was refluxed for 2 h open to the air. The reaction mixture was allowed to cool to room temperature, and then DDQ (87.0 mg, 0.383 mmol) was added. Stirring was continued for 15 min. The sample was concentrated and chromatographed (silica, CH_2Cl_2) to give a purple solid (16 mg, 18%): ^1H NMR δ –0.14 (s, 12H), 0.88 (s, 18H), 3.09–3.15 (m, 2H), 3.34–3.39 (m, 2H), 3.66–3.71 (m, 4H), 5.98 (m, 1H), 9.07 (s, 2H), 9.13–9.15 (m, 2H), 9.44–9.45 (m, 2H), 9.65 (s, 2H), 9.93–10.08 (m, 4H); LD-MS obsd 702.6, also 645.5 [trace, $(M - Zn)^+$]; FAB-MS obsd 702.2807, calcd 702.2764 ($C_{37}H_{50}N_4O_2Si_2Zn$); λ_{abs} 401, 532 nm; λ_{em} (λ_{exc} 401 nm) 571, 623 nm.

Zn(II)-5-[1,5-Bis(*tert*-butyldimethylsilyloxy)pent-3-yl]-15-(4-*N*-*tert*-butyloxycarbonylaminophenyl)porphyrin (S4). Following a standard procedure,[S3] a solution of **S3** (804 mg, 1.78 mmol) and **10** (849 mg, 1.78 mmol) in ethanol (177 mL) was treated with $Zn(OAc)_2$ (3.27 g, 17.8 mmol). The mixture was refluxed for 2 h open to the air. The reaction mixture was allowed to cool to room temperature. DDQ was added (1.22 g, 5.37 mmol), and stirring was continued for 15 min at room temperature. The ethanol was evaporated, and the residue was chromatographed (silica, CH_2Cl_2) to give a purple solid (92.4 mg, 6%): ^1H NMR δ –0.19 (s, 12H), 0.84 (s, 18H), 1.62 (s, 9H), 3.03–3.12 (m, 2H), 3.28–3.32 (m, 2H), 3.56–3.65 (m, 2H), 5.93 (m, 1H), 7.76 (br, 2H), 8.12–8.15 (m, 2H), 9.11 (app s, 2H), 9.36–9.37 (m, 2H), 9.47 (app s, 2H), 9.90–9.91 (m, 1H), 10.03–10.04 (m, 1H), 10.22–10.23 (m, 2H); LD-MS obsd 893.3; FAB-MS obsd 893.3745, calcd 893.3710 ($C_{48}H_{63}N_5O_4Si_2Zn$); λ_{abs} 409, 537 nm; λ_{em} (λ_{exc} 409 nm) 580, 632 nm.

Zn(II)-5-(4-*N*-*tert*-Butyloxycarbonylaminophenyl)-15-(1,5-dihydroxypent-3-yl) porphyrin (5). A solution of **S4** (89.5 mg, 0.100 mmol) was treated with TBAF (3.0 mL of a 1 M solution, water content ~5 wt%). The reaction was allowed to proceed for 5 h at room temperature. The sample was poured into ethyl acetate. The solution was washed with water. The aqueous layer was extracted with ethyl acetate. The organic extract was washed three times with water. The organic layer was concentrated and treated with $Zn(OAc)_2$ (200 mg, 1.09 mmol) for 10 min. Chromatography [neutral alumina, CH_2Cl_2 / MeOH (0→10%)] afforded a bright red solid (64.5 mg, 97%): ^1H NMR δ 1.66 (s, 9H), 3.04–3.11 (m, 2H), 3.31–3.35 (m, 2H), 3.46–3.54 (m, 2H), 3.66–3.74 (m, 2H), 5.83 (m, 1H), 7.83–7.86 (m, 2H), 8.10–8.13 (m, 2H), 9.02 (s, 2H), 9.34–9.35 (m, 2H), 9.44–9.46 (m, 2H), 9.88–9.90 (m, 1H), 9.94–9.96 (m, 1H), 10.18 (s, 2H);

LD-MS 665.8 (M^+), 564.0 [$(M - Boc)^+$]; FAB-MS obsd 665.1998, calcd 665.1980 ($C_{36}H_{35}N_5O_4Zn$); λ_{abs} [CH_2Cl_2 / MeOH (95:5)] 413, 545 nm; λ_{em} (λ_{exc} 413 nm) 588, 640 nm.

References.

(S1) M. Taniguchi, M. N. Kim, D. Ra and J. S. Lindsey, *J. Org. Chem.,* 2005, **70**, 275–285.

(S2) I. Schmidt, J. Jiao, P. Thamyongkit, D. S. Sharada, D. F. Bocian and J. S. Lindsey, *J. Org. Chem.,* 2006, **71**, 3033–3050.

(S3) D. Fan, M. Taniguchi, Z. Yao, S. Dhanalekshmi and J. S. Lindsey, *Tetrahedron,* 2005, **61**, 10291–10302.