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A general approach to L-tyrosine porphyrins

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Abstract—A novel and general approach has been developed to prepare L-tyrosine-containing porphyrins. The key intermediates, 2-*tert*-butoxycarbonylamino-3-(3-formyl-4-hexyloxy-phenyl)-propionic acid hexyl ester and 2-*tert*-butoxycarbonylamino-3-(3-formyl-4-methoxy-phenyl)-propionic acid methyl ester, were prepared by the Reimer–Tiemann reaction of Boc-protected L-tyrosine, which was followed by esterification and alkylation of the phenol hydroxide. A number of novel chiral L-tyrosine porphyrins were obtained from the reactions of 2-*tert*-butoxycarbonylamino-3-(3-formyl-4-alkoxy-phenyl)-propionic acid ester with different dipyrrolylmethanes and the reaction of 5-(4-trifluoromethylphenyl)pyrromethane afforded the highest yield. The tyrosine porphyrins could be readily deprotected to afford the corresponding diacid or diamine derivatives.

1. Introduction

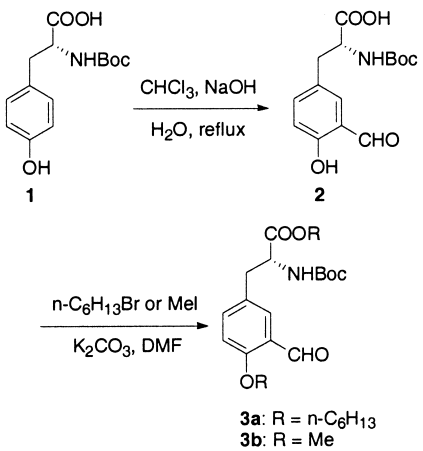
Porphyrins are one of the most useful frameworks for artificial receptors and catalysts because of their unique features, such as large rigid and planar conjugated structures, strong metal coordination activity, extensive modifiability, and plentiful photophysical properties.[1–5] A large number of achiral porphyrin derivatives have been synthesized for the purpose of molecular recognition and self-assembly.[6–12] In contrast, examples of chiral porphyrins as recognition or assembling blocks are remarkably limited.[13–16] We herein report one facile and general method to prepare chiral porphyrin derivatives by directly introducing two or four natural L-tyrosine units to the *meso* positions of porphyrins. Considering that the amino and acid groups of the new porphyrin derivatives may be readily modified, the chiral porphyrin derivatives developed in this paper are expected to be used as new building blocks for future chiral supramolecular design and synthesis.

2. Results and discussion

We recently initiated a new project of porphyrin-based molecular recognition, which requires that two chiral amino acid or short peptide units are connected to a porphyrin skeleton as closely as possible. Reported methods could not meet our requirement because in all the reported cases amino acid or peptide groups are connected by additional linkers.[14–16] Therefore, the possibility of synthesizing porphyrin derivatives from natural L-tyrosine was explored.

We chose the well-established Lindsey method, which involves the condensation of an aldehyde with a dipyrrolylphenylmethane, followed by an oxidation process, to synthesize tyrosine porphyrins. Thus, aldehyde **2** was first prepared according to a reported method,[17] which was then converted into compounds **3a**,**b**. The phenol hydroxy group was alkylated in order to improve the solubility of the resulting compounds in organic solvents (Scheme 1). ^{1}H NMR spectra exhibit one set of well-established signals, indicating that the alkylation of the phenol hydroxyl groups did not lead to the formation of *cis*/*trans* atropisomers.[18,19]

Since the formation of the porphyrin skeleton by the reactions of aldehydes and dipyrrolylphenylmethanes is usually of low yields, it is necessary to explore the effect of



Scheme 1. Synthesis of **3a**,**b**.

Keywords: porphyrin; L-tyrosine; synthesis; Reimer–Tiemann reaction.

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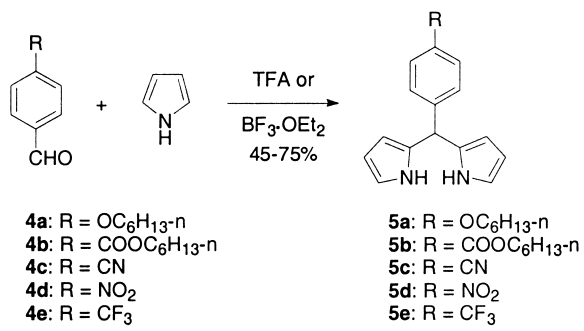


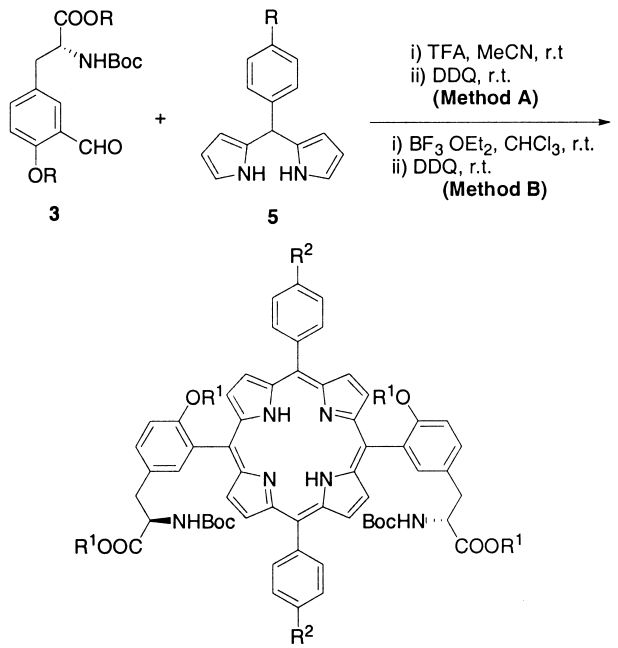
4a: R = OC_6H_{13}-n
4b: R = $COOC_6H_{13}$-n
4c: R = CN
4d: R = NO_2
4e: R = CF_3

5a: R = OC_6H_{13}-n
5b: R = $COOC_6H_{13}$-n
5c: R = CN
5d: R = NO_2
5e: R = CF_3

Scheme 2. Synthesis of **5a**–**e**.

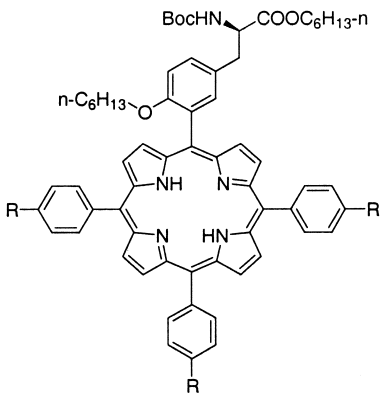
different substituents at the benzene *p*-position on the yields of the corresponding reactions to prepare porphyrin derivatives and find the most suitable dipyrrolylmethane intermediates. Therefore, a series of dipyrrolylmethanes **5a**–**e** were synthesized from the reactions of aldehydes **4a**–**e** and pyrrole in the presence of trifluoroacetic acid (TFA) or boron trifluoride (Scheme 2).

Several different condensation conditions were explored in order to find the optimal conditions for the reactions of compounds **3** and **5**. Using toluenesulfonic acid and propionic acid as catalysts at high temperature was not suitable for any of the present reactions: no expected porphyrin derivatives could be obtained from the reactions with these two acids as catalysts.[20,21] Trifluoroacetic acid (Method A) and boron trifluoride (Method B) could catalyze the reactions, but the yields of the reactions were substantially dependent on the substituents of compounds **5a**–**e**. The reaction conditions and yields obtained from these compounds are shown in Scheme 3.

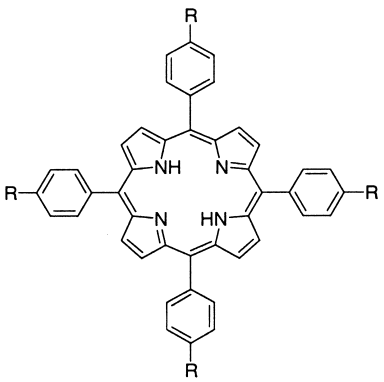


6a: R^1 = C_6H_{13}-n, R^2 = $COOC_6H_{13}$-n, 6% (**A**)
6b: R^1 = C_6H_{13}-n, R^2 = CN, 16% (**A**)
6c: R^1 = C_6H_{13}-n, R^2 = NO_2, 11% (**A**), 8% (**B**)
6d: R^1 = C_6H_{13}-n, R^2 = CF_3, 6% (**A**), 15% (**B**)
6e: R^1 = CH_3, R_2 = CF_3, 32% (**B**)

Scheme 3. Synthesis of porphyrins **6**.



7a: R = $COOC_6H_{13}$-n
7b: R = NO_2
7c: R = CF_3



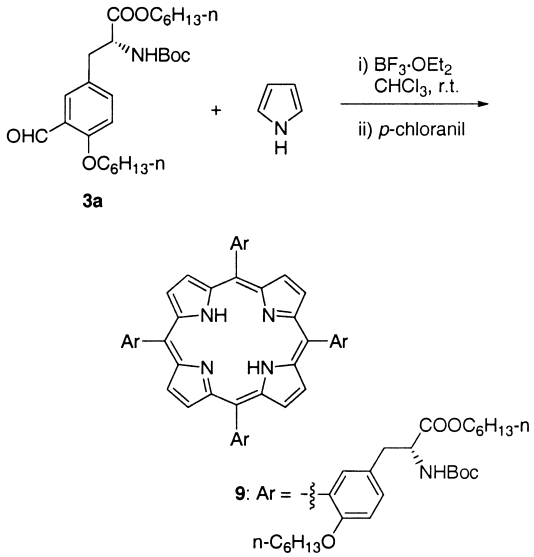
8: R = $COOC_6H_{13}$-n

The highest yield (32%) of the porphyrin derivative was obtained from the reaction of compounds **3b** and **5e** by using Method B. Most other reactions afforded moderate yields of the expected porphyrins (6–16%). Generally, the existence of electron-withdrawing groups in intermediates **5** is helpful for the formation of porphyrins **6**, since it was found that, under the similar conditions, the reaction of **3a**,**b** with **5a**, which bears the electron donating hexyloxy group, only led to the formation of trace amounts of the expected porphyrin products, as indicated by the MS spectra. Rearrangement products **7a**–**c** and **8** were also separated from the reactions of compound **3a** and the corresponding dipyrrolylmethanes **5**.[22–24]

Porphyrin **9**, which bears four tyrosine units, was also generated albeit in the relatively low yield of 6% for the reaction of compound **3b** with pyrrole in the presence of boron trifluoride (Scheme 4). The product has been fully characterized by ^{1}H NMR spectroscopy, and electron spray mass spectrometry.

De-protection of porphyrin **6e** was explored as a typical example. With trifluoroacetic acid as the de-protection reagent, compound **10** was obtained in quantitative yield. With lithium hydroxide, diacid **11** was obtained in 86% yield. In principle, these tyrosine porphyrins may be further modified, to produce different chiral porphyrin derivatives.

The formation of the porphyrin skeletons is usually affected by the existence of strong Lewis acids. The Boc protecting



Scheme 4.

group of the tyrosine amino might be unstable during the reactions. This may be partly responsible for the reduced yields of some of the tyrosine porphyrins. Therefore, the reactions of simple methyl ester of L-tyrosine **12** with intermediates **5** were also explored. However, no expected tyrosine porphyrin products could be obtained under the above conditions, indicating that the protection of the amino group is necessary. Treatment of tyrosine derivatives with the acid group unprotected with **5** in the presence of trifluoroacetic acid or boron trifluoride led to formation of the expected porphyrin products in remarkably low yields (ca. 2%). These results indicate that protection of the amino and acid group in the starting materials are necessary for efficient formation of the porphyrin skeleton.

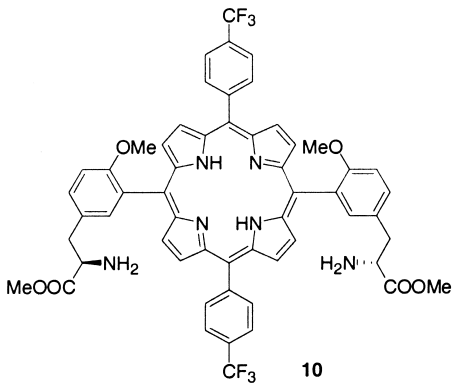
3. Conclusion

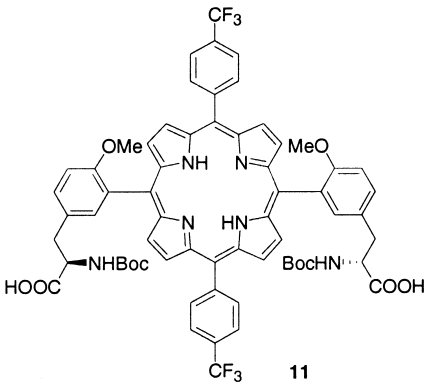
We have developed one general and efficient method to prepare L-tyrosine porphyrin derivatives, starting from various aldehyde derivatives of the amino- and acid-protected tyrosines. The effects of the substituents and reaction conditions on the yields of the reactions have been investigated. Considering the ready availability of the corresponding tyrosine intermediates and the simple reaction conditions used in this work, it is expected that the new porphyrin derivatives developed here may be used as starting materials for further new chiral porphyrin systems. Further work of molecular recognition based on the tyrosine porphyrins reported in this paper is being carried out.

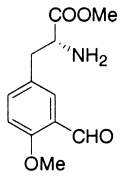
4. Experimental

4.1. General

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer with Me_4Si as internal standard. Mass spectra were record on a Finnigan Mat-MD800 (EI), a Kratos Concept-1H (ESI) or Bruker Daltonics FTMS-7 (MALDI-TOF) mass spectrometer.







Elemental analysis was carried out at the SIOC analytical center. Unless stated otherwise, all reagents and chemical were obtained from commercial sources and used without further purification. Pyrrole was distilled from calcium hydride, dichloromethane and chloroform from calcium hydride or phosphorus pentoxide, acetonitrile from phosphorus pentoxide. Silica gel (300–400 mesh) was used for column chromatography. Compounds **1**,[25] **4a**,[26] **5a**,[27] **5c**,[28] **5d**,[29] and **5e**[30] were prepared according to reported methods.

4.1.1. 2-*tert*-Butoxycarbonylamino-3-(3-formyl-4-hexyloxy-phenyl)-propionic acid hexyl ester 3a. A mixture of compound **2** (1.69 g, 5.47 mmol), potassium carbonate (1.51 g, 10.9 mmol) and 1-bromohexane (1.54 mL, 10.9 mmol) in DMF (50 mL) was heated at 80°C with stirring for 1 h and then cooled to room temperature. The solid was then filtered off and DMF was evaporated under reduced pressure. The residue was triturated in ethyl acetate (100 mL) and the solution was washed with water (20 mL), brine (20 mL) and dried over $MgSO_4$. After the solvent was removed in vacuo, the residue was purified with column chromatography (*n*-hexane/ethyl acetate, 10:1), to afford compound **3a** (1.62 g, 66%) as yellow liquid. ^{1}H NMR ($CDCl_3$): δ 10.48 (s, 1H), 7.59 (s, 1H), 7.34 (d, J=8.7 Hz, 1H), 6.92 (d, J=8.7 Hz, 1H), 5.03 (d, J=7.8 Hz, 1H), 4.55–4.52 (m, 1H), 4.13–4.03 (m, 4H), 3.10–3.02 (m, 2H), 2.0–0.7 (m, 31H). IR (neat): 945, 1310, 1690, 1710, 1720,

3250 cm^{-1}. EI-MS: *m/z* 478 $[M+H]^+$. Anal. calcd for $C_{27}H_{43}NO_6$: C, 67.90; H, 9.07; N, 2.93. Found: C, 67.95; H, 8.81; N, 2.82.

4.1.2. 2-*tert*-Butoxycarbonylamino-3-(3-formyl-4-methoxy-phenyl)-propionic acid methyl ester 3b. A mixture of **2** (1.40 g, 4.60 mmol), potassium carbonate (1.38 g, 10.0 mmol) and iodomethane (0.68 mL, 10.9 mmol) in DMF (30 mL) was stirred at room temperature for 24 h. The solid was then filtered off and the solvent evaporated under reduced pressure. The residue was triturated in ethyl acetate (100 mL) and the solution was washed with water (20 mL), brine (20 mL) and dried over $MgSO_4$. After the solution was concentrated, the residue was purified with a column chromatography (*n*-hexane/ethyl acetate, 3:1). Compound **3b** was obtained as yellow liquid (1.08 g, 70%). ^1H NMR ($CDCl_3$): δ 10.43 (s, 1H), 7.58 (s, 1H), 7.35 (d, *J*=8.7 Hz, 1H), 6.97 (d, *J*=8.7 Hz, 1H), 5.04 (d, *J*=5.5 Hz, 1H), 4.70–4.50 (m, 1H), 3.91 (s, 3H), 3.71 (s, 3H), 3.11–3.00 (m, 2H), 1.41 (s, 9H). IR (neat): 940, 1215, 1692, 1715, 1720, 3240 cm^{-1}. EI-MS: *m/z* 337 $[M]^+$. Anal. calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.62; H, 6.90; N, 3.99.

4.1.3. 4-[Bis-(1*H*-pyrrol-2-yl)-methyl]-benzoic acid hexyl ester 5b. A solution of compound **4b** (0.56 g, 2.40 mmol) and pyrrole (6.78 mL, 0.10 mol) was degassed by bubbling with N_2 for 10 min. Then trifluoroacetic acid (18 μL, 0.24 mmol) was added. The solution was stirred for 15 min at room temperature, diluted with dichloromethane (100 mL), then washed with 0.1 M aqueous sodium hydroxide (20 mL), washed with water (10 mL), brine (10 mL), and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by chromatography (chloroform as the eluent), to afford **5b** as a yellow liquid (0.61 g, 72%). ^1H NMR ($CDCl_3$): δ 7.94–8.02 (m, 4H), 7.26 (d, *J*=9.9 Hz, 2H), 6.71–6.70 (m, 2H), 6.16 (d, d, *J*=3.0 Hz, *J*=2.4 Hz, 2H), 5.95–5.80 (m, 2H), 5.52 (s, 1H), 4.29 (t, *J*=6.4 Hz, 2H), 2.0–0.7 (m, 11H). IR (neat): 1715, 3240 cm^{-1}. EI-MS: *m/z* 350 $[M]^+$. Anal. calcd for $C_{22}H_{26}N_2O_2$: C, 75.39; H, 7.48; N, 7.99. Found: C, 75.47; H, 7.51; N, 8.20.

4.1.4. Porphyrin 6a. *Method A*. A solution of compound **5b** (0.89 g, 2.54 mmol) and compound **3a** (1.21 g, 2.54 mmol) in acetonitrile (180 mL) was purged with nitrogen for 30 min. Then trifluoroacetic acid (50 μL, 0.65 mmol) was added. The solution was stirred at room temperature for 5 h. Then a solution of 2,3-dichloro-4,5-dicyanoquinone (DDQ) (0.58 g, 2.55 mmol) in THF (20 mL) was added and the mixture was stirred over night. The solvent was removed and the residue was triturated with chloroform (150 mL). The solution was washed with 1 M aqueous sodium carbonate solution (30 mL), water (30 mL), brine (30 mL), and dried over $MgSO_4$. After the solvent was removed, the residue was subjected to column chromatography (dichloromethane/diethyl ether, 200:1), to give **6a** (124 mg, 6%) as a purple solid. The product was further purified by recrystallization from dichloromethane for microanalysis. Mp 285°C. ^1H NMR ($CDCl_3$): δ 8.85–8.75 (m, 8H), 8.45–8.41 (d, d, *J*=5.2, 3.9 Hz, 4H), 8.27 (d, *J*=5.1 Hz, 4H), 7.76 (s, 2H), 7.53–7.49 (d, *J*=3.8 Hz, 2H), 7.26–7.23 (m, 2H), 5.31 (d, *J*=7.8 Hz, 2H), 4.74–4.70 (m, 2H), 4.51 (t, *J*=6.6 Hz, 4H), 4.16–3.92 (m, 4H), 3.86 (t, *J*=6.3 Hz, 4H), 3.40–3.15 (m, 4H), 2.00–0.20 (m, 84H), −2.76 (s, 2H). IR (KBr): 1691, 1705, 1730, 3315, 3400 cm^{-1}. ESI-MS: *m/z* 1614 $[M]^+$. Anal. calcd for $C_{98}H_{128}N_6O_{14}$: C, 72.92; H, 7.99; N, 5.21. Found: C, 72.66; H, 8.02; N, 4.98.

4.1.5. Porphyrin 6b. *Method A*. Purple solid. Yield: 16%. Mp 290°C. ^1H NMR ($CDCl_3$): δ 8.90–8.75 (m, 4H), 8.69 (d, *J*=4.8 Hz, 4H), 8.40–8.25 (m, 4H), 8.10–8.00 (d, *J*=7.8 Hz, 4H), 7.75 (d, *J*=2.1 Hz, 2H), 7.54–7.45 (d, d, *J*=4.5, 2.1 Hz, 2H), 7.27 (d, *J*=4.5 Hz, 2H), 5.28 (d, *J*=5.9 Hz, 2H), 4.80–4.60 (m, 2H), 4.20–3.95 (m, 4H), 3.86 (t, *J*=6.2 Hz, 4H), 3.40–3.10 (m, 4H), 2.00–0.20 (m, 62H), −2.76 (s, 2H). IR (KBr): 1690, 1742, 2220, 3140, 3452 cm^{-1}. ESI-MS: *m/z* 1409 $[M+H]^+$. Anal. calcd for $C_{86}H_{102}N_8O_{10}$: C, 73.37; H, 7.30; N, 7.96. Found: C, 73.08; H, 7.52; N, 7.73.

4.1.6. Porphyrin 6c. *Method A*. Purple solid. Yield: 11%. Mp 287°C. ^1H NMR ($CDCl_3$): δ 8.95–8.83 (m, 4H), 8.73 (d, *J*=4.8 Hz, 4H), 8.65 (d, d, *J*=4.3, 2.2 Hz, 4H), 8.41–8.36 (d, d, *J*=4.3, 2.5 Hz, 4H), 7.78 (d, *J*=1.5 Hz, 2H), 7.57–7.52 (m, 2H), 7.27 (d, *J*=9.0 Hz, 2H), 5.32 (d, *J*=6.1 Hz, 2H), 4.80–4.70 (m, 2H), 4.20–3.95 (m, 4H), 3.89 (t, *J*=6.2 Hz, 4H), 3.40–3.15 (m, 4H), 1.70–0.20 (m, 62H), −2.73 (s, 2H). IR (KBr): 1345, 1432, 1535, 1680, 1740, 3146, 3460 cm^{-1}. MALDI-TOF-MS: *m/z* 1447 $[M]^+$. Anal. calcd for $C_{84}H_{102}N_8O_{14}$: C, 69.69; H, 7.10; N, 7.74. Found: C, 69.50; H, 7.28; N, 7.54.

4.1.7. Porphyrin 6d. *Method A*. Purple solid. Yield: 6%. Mp 294°C. ^1H NMR ($CDCl_3$): δ 8.89–8.83 (m, 4H), 8.76 (d, *J*=4.2 Hz, 4H), 8.35 (d, *J*=6.6 Hz, 4H), 8.07–8.02 (m, 4H), 7.79 (d, *J*=1.8 Hz, 2H), 7.57–7.53 (d, d, *J*=8.8, 2.0 Hz, 2H), 7.28 (d, *J*=8.7 Hz, 2H), 5.34 (d, *J*=7.5 Hz, 2H), 4.77–4.74 (m, 2H), 4.16–3.95 (m, 4H), 3.90 (t, *J*=6.3 Hz, 4H), 3.36–3.27 (m, 4H), 1.70–0.20 (m, 62H), −2.73 (s, 2H). IR (KBr): 1215, 1678, 1736, 3156, 3458 cm^{-1}. ESI-MS: *m/z* 1495 $[M+H]^+$. Anal. calcd for $C_{86}H_{102}N_6F_6O_{10}$: C, 69.15; H, 6.88; N, 5.63. Found: C, 69.47; H, 7.08; N, 5.35.

4.1.8. Porphyrin 7a and 8. *Method B*. A solution of compound **3a** (0.39 g, 0.81 mmol) and compound **5b** (0.28 g, 0.80 mmol) in chloroform (80 mL) was purged with nitrogen for 15 min. Boron trifluoride etherate (106 μL, 2.5 M stock solution in chloroform, 0.27 mmol) was added. The solution was stirred for 1 h at room temperature, and then DDQ (0.14 g, 0.61 mmol) was added. The mixture was stirred for additional 1 h at room temperature. The solvent was removed under reduced pressure. After work-up, the residue was subjected to column chromatography (*n*-hexane/dichloromethane, 1:10), to give **7a** (65 mg, 15%) and **8** (100 mg, 19%) as purple solid. No expected tyrosine porphyrin product was purified.

Compound **7a**. Purple solid. Mp 245°C. ^1H NMR ($CDCl_3$): δ 8.94–8.78 (m, 8H), 8.48–8.44 (m, 6H), 8.33–8.26 (m, 6H), 7.79 (d, *J*=2.1 Hz, 1H), 7.55–7.50 (d, d, *J*=7.5, 2.0 Hz, 1H), 7.30–7.22 (m, 1H), 5.35–5.27 (d, *J*=6.0 Hz, 1H), 4.75–4.69 (m, 1H), 4.53 (t, *J*=6.7 Hz, 6H), 4.13–3.97 (m, 2H), 3.90–3.85 (t, *J*=6.3 Hz, 2H), 3.39–3.19 (m, 2H), 2.0–0.25 (m, 64H), −2.76 (s, 2H). IR (KBr): 1678, 1724, 1743,

3142, 3548 cm^{-1}. ESI-MS: *m/z* 1370 $[M+H]^+$. Anal. calcd for $C_{85}H_{103}N_5O_{11}$: C, 74.48; H, 7.57; N, 5.11. Found: C, 74.79; H, 7.95; N, 4.76.

Compound **8**. Purple solid. Mp 288°C. ^1H NMR ($CDCl_3$): δ 8.84 (s, 8H), 8.46 (d, J=7.8 Hz, 8H), 8.31 (d, J=8.1 Hz, 8H), 4.52 (t, J=6.9 Hz, 8H), 2.0–0.5 (m, 44H), −2.81 (s, 2H). IR (KBr): 1727, 3440 cm^{-1}. ESI-MS: *m/z* 1127 $[M]^+$. Anal. calcd for $C_{72}H_{78}N_4O_8$: C, 76.70; H, 6.97; N, 4.97. Found: C, 76.41; H, 7.17; N, 4.64.

4.1.9. Porphyrin 6e. *Method B*. Purple solid. Yield: 32%. Mp >300°C. ^1H NMR ($CDCl_3$): δ 9.00–8.75 (m, 8H), 8.50–8.25 (m, 4H), 8.10–8.02 (d, d, 4H), 7.79 (d, 2H), 7.58–7.53 (d, d, 2H), 7.28 (d, 2H), 5.33 (d, J=8.1 Hz, 2H), 4.77–4.74 (m, 2H), 3.70–3.50 (m, 12H), 3.36–3.20 (m, 4H), 1.40 (s, 18H), −2.73 (s, 2H). IR (KBr): 1217, 1324, 1670, 1735, 3150, 3450 cm^{-1}. ESI-MS: *m/z* $[M]^+$. Anal. calcd for $C_{66}H_{62}N_6F_6O_{10}$: C, 65.34; H, 5.15; N, 6.93. Found: C, 65.17; H, 5.36; N, 6.78.

4.1.10. Porphyrins 7b. *Method B*. Purple solid. Yield: 18%. Mp 278°C. ^1H NMR ($CDCl_3$): δ 8.98–8.74 (m, 8H), 8.69–8.64 (m, 6H), 8.42–8.37 (m, 6H), 7.80 (br, 1H), 7.55 (d, J=8.1 Hz, 1H), 7.27 (d, J=8.4 Hz, 1H), 5.30 (d, J=4.2 Hz, 1H), 4.76–4.71 (m, 1H), 4.13–3.98 (m, 2H), 3.89 (t, J=6.4 Hz, 2H), 3.40–3.18 (m, 2H), 1.60–0.20 (m, 31H), −2.77 (s, 2H). IR (KBr): 1345, 1534, 1670, 1726, 1745, 3135, 3460 cm^{-1}. ESI-MS: *m/z* 1120 $[M]^+$. Anal. calcd for $C_{64}H_{64}N_8O_{11}$: C, 68.56; H, 5.75; N, 9.99. Found: C, 68.37; H, 5.84; N, 9.68.

4.1.11. Porphyrins 7c. *Method B*. Purple solid. Yield: 30%. Mp 296°C. ^1H NMR ($CDCl_3$): δ 8.90–8.75 (m, 8H), 8.37–8.30 (m, 6H), 8.07–8.03 (m, 6H), 7.79 (d, J=6.4 Hz, 1H), 7.57–7.51 (m, 1H), 7.29–7.24 (m, 1H), 5.32–5.28 (d, J=4.0 Hz, 1H), 4.74–4.71 (m, 1H), 4.13–4.00 (m, 2H), 3.87 (t, J=6.3 Hz, 2H), 3.34–3.21 (m, 2H), 1.60–0.20 (m, 31H), −2.77 (s, 2H). IR (KBr): 1067, 1324, 1745, 3160, 3456 cm^{-1}. ESI-MS: *m/z* 1191 $[M+H]^+$. Anal. calcd for $C_{67}H_{64}N_5O_5F_9$: C, 67.61; H, 5.42; N, 5.88. Found: C, 67.69; H, 5.73; N, 5.32.

4.1.12. Porphyrin 9. A solution of compound **3a** (0.75 g, 1.58 mmol) and pyrrole (0.11 mL, 1.58 mmol) in chloroform (160 mL) was purged with nitrogen for 5 min. Boron trifluoride etherate (0.21 mL, 2.5 M stock solution in chloroform, 0.53 mmol) was added. The solution was stirred for 1 h at room temperature. Then *p*-chloranil (0.29 g, 0.12 mmol) was added and the mixture was refluxing for 1 h. Triethylamine (73 μL, 0.53 mmol) was added. The solvent was removed under reduced pressure. After work-up as above for Method B, the residue was subjected to chromatography (dichloromethane/ethyl acetate, 25:1), to give compound **9** (50 mg, 6%) as a purple solid. Mp 265°C. ^1H NMR ($CDCl_3$): δ 8.73–8.69 (m, 8H), 7.78–7.71 (m, 4H), 7.52–7.47 (m, 4H), 7.25–7.20 (m, 4H), 5.27 (d, J=8.1 Hz, 4H), 4.80–4.69 (m, 4H), 4.17–3.90 (m, 8H), 3.84–3.77 (m, 8H), 3.41–3.10 (m, 8H), 1.8–0.2 (m, 124H), −2.72 (s, 2H). IR (KBr): 1668, 1743, 3145, 3456 cm^{-1}. ESI-MS: *m/z* 2102 $[M+H]^+$. Anal. calcd for $C_{124}H_{178}N_8O_{20}$: C, 70.89; H, 8.54; N, 5.33. Found: C, 70.44; H, 8.52; N, 4.76.

4.1.13. Porphyrin 10. A solution of compound **6e** (0.12 g, 0.10 mmol) in a mixture of trifluoroacetic acid (5 mL) and dichloromethane (5 mL) was stirred at room temperature for 4 h. Dichloromethane (50 mL) was added and the solution was washed with water (3×15 mL), aqueous sodium carbonate solution (1N, 10 mL), water (10 mL), brine (10 mL), and dried with $MgSO_4$. After the solvent was removed under reduced pressure, the residue was purified with column chromatography (dichloromethane/methanol, 50:1), to give porphyrin **10** (98 mg, 98%) as purple solid. Mp 236–238°C. ^1H NMR ($CDCl_3$): δ 8.95–8.87 (m, 4H), 8.87–8.70 (m, 4H), 8.33 (d, 4H, J=8.4 Hz), 8.04 (d, 4H, J=7.8 Hz), 7.78 (d, 2H, J=1.5 Hz), 7.50 (d, J=7.6 Hz, 2H), 7.25 (d, J=7.4 Hz, 2H), 4.10–4.00 (m, 4H), 3.90 (t, J=5.4 Hz, 4H), 3.80–3.70 (br, 2H), 3.20–3.00 (m, 4H), 1.80–0.50 (m, 48H), −2.76 (s, 2H). IR (KBr): 1745, 3300 cm^{-1}. ESI-MS: *m/z* 1013 $[M+H]^+$. Anal. calcd for $C_{56}H_{46}F_6N_6O_6$: C, 66.40; H, 4.58; N, 8.30. Found: C, 64.06; H, 4.98; N, 8.12.

4.1.14. Porphyrin 11. A mixture of compound **6e** (0.10 g, 0.08 mmol) and lithium hydroxide monohydrate (28 mg, 0.67 mmol) in a mixture of tetrahydrofuran (20 mL) and water (2 mL) was stirred for 1 h. Hydrochloric acid (1N) was added to make pH=6.5. The solvent was removed under reduced pressure and the solid was washed with water completely, dried, and then purified by column chromatography (dichloromethane/methanol, 50:1), to afford compound **11** (85 mg, 86%) as purple solid. Mp 220–222°C. ^1H NMR (DMSO-d_6): δ 9.00–8.75 (m, 8H), 8.50–8.25 (m, 4H), 8.10–8.02 (d, d, J=6.8 Hz, J=3.2 Hz, 4H), 7.79 (d, J=2.0 Hz, 2H), 7.58–7.53 (d, d, J=7.6, 1.9 Hz, 2H), 7.28 (d, J=7.8 Hz, 2H), 5.33 (d, J=8.1 Hz, 2H), 4.77–4.74 (m, 2H), 3.70–3.50 (m, 12H), 3.36–3.20 (m, 4H), 1.40 (s, 18H), −2.73 (s, 2H). IR (KBr): 1676, 1760, 3000 cm^{-1}. ESI-MS: *m/z* 1185 $[M]^+$. Anal. calcd for $C_{64}H_{58}F_6N_6O_{10}$: C, 64.86; H, 4.93; N, 7.09. Found: C, 64.56; H, 5.05; N, 6.95.

4.1.15. 2-Amino-3-(3-formyl-4-methoxy-phenyl)-propionic acid methyl ester 12. A solution of compound **3b** (50 mM) in trifluoroacetic acid was stirred at room temperature for 2 h. The acid was removed under reduced pressure and the residue was triturated with dichloromethane. After work-up, the crude product was purified by flash chromatography (dichloromethane/methane 20:1), to afford compound **12** as a white solid (95%). Mp 145–147°C. ^1H NMR ($CDCl_3$): δ 10.34 (s, 1H), 7.58 (s, 1H), 7.30 (d, J=6. 8 Hz, 1H), 6.92 (d, J=6.9 Hz, 1H), 3.90 (m, 1H), 3.79 (s, 3H), 3.68 (s, 3H), 3.10–3.02 (m, 2H). IR (KBr): 1710, 1745, 3200 cm^{-1}. EI-MS: *m/z* 237 $[M]^+$. Anal. calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.52; H, 6.58; N, 6.09.

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