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A strategic approach for the synthesis of new porphyrin rings, attractive for heme model purpose

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Abstract—Novel complexes have been efficiently synthesized with a facile route using two different atropisomers of the same porphyrin. These compounds feature a tridentate binding site, a tyrosine molecule, and a proximal base, all bound to the porphyrin ring in different fashions, making them attractive for heme modeling purposes.

1. Introduction

Cytochrome *c* oxidase (C*c*O) is an important metalloenzyme of the respiratory chain in many aerobic organisms. It catalyses the four electron, four proton reduction, of oxygen to water, without releasing toxic, reactive intermediates (e.g., H_2O_2), conserving the energy required for the biosynthesis of ATP.[1] The catalytic active site of the enzyme consists of a heme (heme a_3) and a tricoordinated copper (Cu_B) in close proximity (~4.4–5.3 Å), depending on the protein and its oxidation state.[2] Recent X-ray crystallographic studies revealed that one of the copper-bound histidines (H240) is covalently connected to a tyrosine residue (Y244).[3] The presence of a phenol residue is proposed to act either as an electron and proton donor to the oxygen reduction cycle[3a,4] or to help the enzyme to adopt a favorable structural conformation.[5] Despite all the above detailed information derived from the natural enzyme, the precise role of Cu_B in mediating O_2 reduction remains unresolved. Therefore, in order to elucidate the mechanism of O_2 reduction, a number of synthetic heme-based binuclear complexes have been prepared.[6] Despite the large number of catalysts that have been synthesized so far, it is not clear which elements influence the selective reduction of O_2 to H_2O over H_2O_2.

2. Results and discussion

In this new synthetic approach, we have developed new complexes in which it is easy to modify possible factors that are responsible for the reduction of oxygen. These new compounds **1**–**4** are easily made, based on the two different atropisomers of the same porphyrin. All complexes have the same porphyrin base and differ in three ways: (i) the coordination environment of a second metallic center; (ii) the presence or absence of a proximal base; (iii) the existence, or not, of a tyrosine molecule as well as the mode by which the tyrosine is linked to the porphyrin. Finally, various physicochemical studies of these molecules can give an insight into whether one of the above features will influence the catalytic activity of these compounds.

Complex **1** is based on the α,α-atropisomer of porphyrin **11a** and has a tridentate ligand covalently attached on one site of the porphyrin ring and a tyrosine molecule on the opposite site. In compounds **2**–**4**, tyrosine and bis(2-(pyridin-2-yl)-ethyl)amine (BPEA) **5** are covalently linked to the porphyrin. The hydroxyl group of all compounds can be protected/deprotected in order to investigate the role of this tyrosine mimic. Moreover, in complexes **3** and **4** an axial pyridine ligand is covalently attached to the porphyrin in order to block the lower face of the porphyrin ring.

The synthesis of tridentate ligands is shown in Scheme 1. BPEA **5** and axial ligand **6** were prepared by the reaction of 2-vinylpyridine and ammonium chloride in 50 and 30%, respectively.[7] Reaction of commercially available protected tyrosine **7** and BPEA **5**, followed by deprotection of the 9-fluorenylmethoxycarbonyl (Fmoc) group afforded ligand **9** in good yield.[8]

After preparation of compounds **5** and **9**, a suitable trans-substituted porphyrin such as **11** was desired in order to proceed with the synthesis of superstructured porphyrins[9] (Scheme 2). Dipyrromethane **10** was synthesized by reacting 2,4,6-trimethyl-benzaldehyde, pyrrole, and trifluoroacetic acid in 70% yield. A mixture of two porphyrin atropisomers **11**

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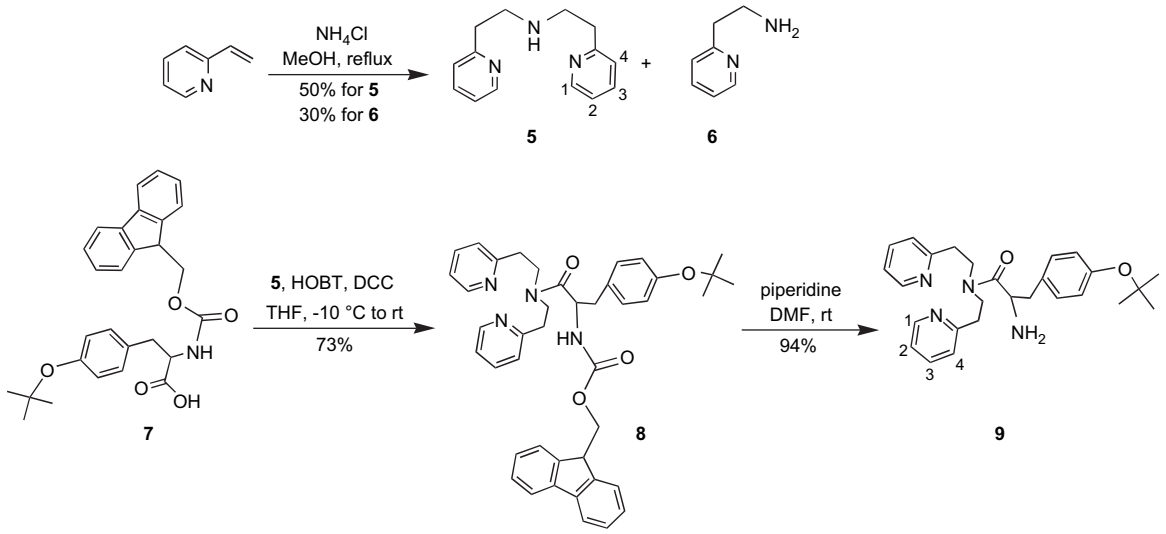


Scheme 1. Synthesis of ligands **5** and **9**.

was prepared in 20% yield by the reaction of dipyrromethane **10** with 2-nitrobenzaldehyde, in the presence of TFA, followed by oxidation of the resulting porphyrinogen with DDQ. The two atropisomers were separated by column chromatography. The α,α-atropisomer was used for the synthesis of **1**, while for **2** the α,β-atropisomer was required. Interestingly, compound **12a** can be selectively reduced by $SnCl_2$ in the presence of concentrated HCl in CH_2Cl_2 at 0 °C, to give α,α-monoaminoporphyrin **12a** in 65% yield. Acylation of **12a** with chloroacetyl chloride gave **13** (93%). Condensation of ligand **5** in the presence of DIPEA gave **14** (88%),[10] followed by reduction to give **15** in 94% yield. Then **15** was coupled with protected tyrosine molecule **7** in the presence of DCC, yielding **16** (75%). The synthesis of compound **1** is completed with deprotection of the Fmoc group in the presence of piperidine in DMF (92%), and deprotection of the *tert*-butyl group using TFA affording **1** in 90% yield.

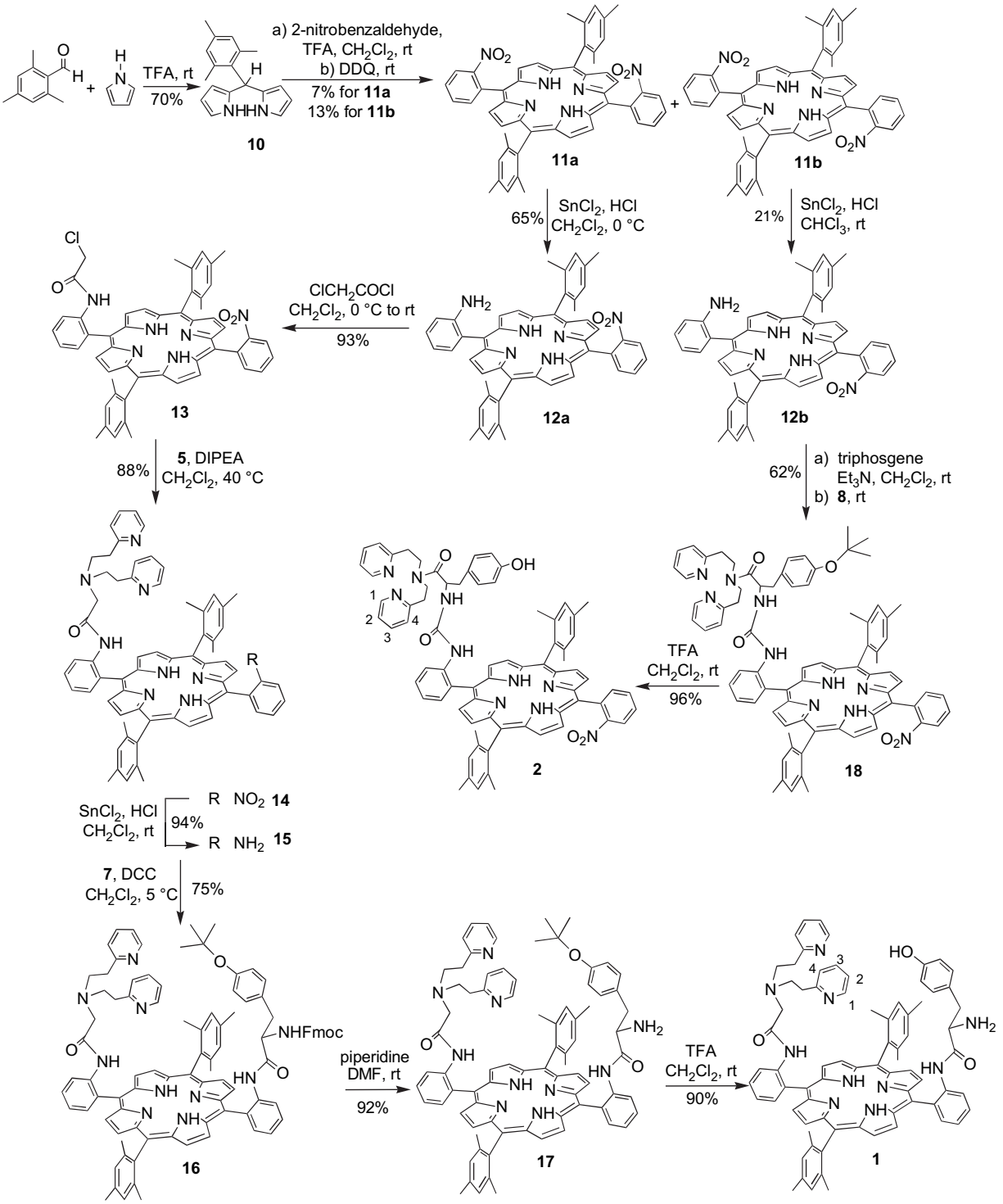
For the preparation of porphyrin **2**, the α,β-atropisomer **11b** was selectively reduced with $SnCl_2$ in the presence of concentrated HCl in $CHCl_3$ at room temperature yielding **12b** (21%). Urea-substituted porphyrin **18** was synthesized by a useful method introduced by Collman and co-workers in which the amino group of the monoaminoporphyrin **12b** is converted to isocyanate under mild conditions using triphosgene.[11] The intermediate porphyrin can then be reacted with a nucleophile, such as amine **9**, to form **18** in 62% yield. The reason that ligand **9** is attached on the porphyrin ring via urea link is because the affinity of dioxygen might be stronger compared to an amide link, as observed for other oxyhemoglobin models.[12] Finally, compound **2** was obtained by deprotection of the *tert*-butyl group, using TFA in 96% yield.

The synthesis of complexes **3** and **4** is shown in Scheme 3 and they both bear groups attached to the porphyrin via urea linkers. A tridentate ligand is directly attached to a tyrosine molecule and a proximal base. The only difference between them is the coordinating base that will be used later as a fifth ligand for the iron atoms of porphyrin. Thus, two different substituted pyridine molecules were used in order to investigate which one will better coordinate to the iron.

The synthesis of these molecules was achieved by reduction of α,β-dinitroporphyrin **11b** to obtain diaminoporphyrin **19** in 99% yield. Therefore, selective reaction of amine **6** or 3-(2-aminoethyl)pyridine hydrobromide with porphyrin **19** afforded compounds **20** and **21** in 35 and 48% yield, respectively. According to the above reaction, the isocyanate was generated in situ by reacting diaminoporphyrin **19** with 1/3 of an equivalent of triphosgene in the presence of Et_3N at room temperature in dry dichloromethane. When the pyridine amine **6** was added 2 equiv of Et_3N was needed to neutralize the HCl generated, but in case of 3-(2-aminoethyl)pyridine hydrobromide, 4 equiv was used. Compounds **20** and **21** were also prepared following an alternative route. Porphyrin **11b** was selectively reduced to give **12b** and then reacted with **6** or 3(2-aminoethyl)pyridine hydrobromide. Finally, the nitro group was reduced to afford the desired molecules **20** and **21**. Following this route the overall yield was much lower compared to the overall yield obtained when reduced porphyrin **11b** selectively reacted with the substituted pyridines. The overall yield following the above route (selective reduction) was 16% for **20** and 17% for **21**, while the overall yield of the route that was finally followed (selective reaction) was 35 and 48%, respectively. Subsequently, reaction of aminoporphyrins **20** and **21** with triphosgene in the presence of Et_3N and addition of amine **9** afforded urea-linked porphyrins **22** and **23**. Finally, the compounds were obtained by deprotection of the *tert*-butyl group with TFA to produce **3** and **4** in 97% yield.

Structural information from the above compounds in solution was obtained by comparison of the ^1H NMR spectra of the free ligands and final molecules. In the first simple approach, a comparison of the chemical shifts was performed between ligands **5** and **1** (Table 1).

Protons H_1–H_4 of compound **1** are found to be shifted upfield in comparison to BPEA **5**, with values varying from $\Delta\delta$=2.6 ppm for H_4 to $\Delta\delta$=0.3 ppm for H_2. This upfield shift observed is due to the porphyrin ring current, which means that the tridentate ligand is well situated on top of the porphyrin plane. On the other hand, comparison of chemical

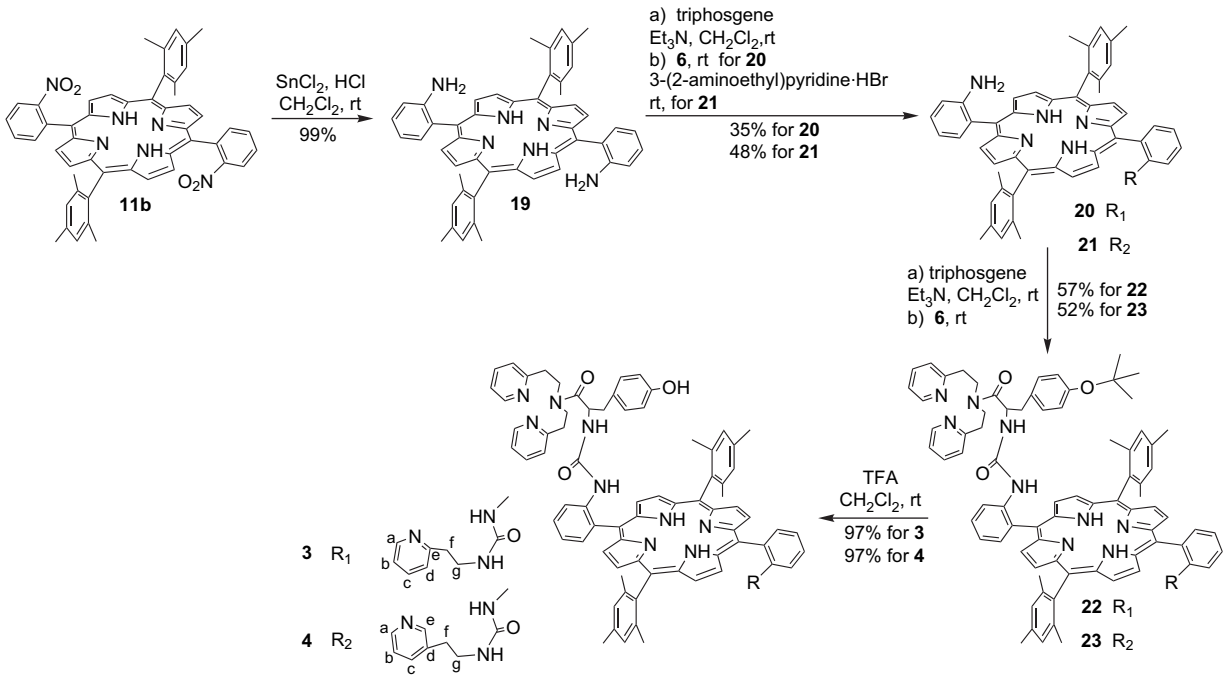


Scheme 2. Synthesis of compounds **1** and **2**.

shifts of free ligand **9** and porphyrin **2** showed a slight upfield shift. This indicates that the tridentate ligand is not suspended over the porphyrin plane. However, the structures shown in Schemes 2 and 3 are not a good representation of **2**–**4**. This is due to the small $\Delta\delta$ values of the phenol protons between free ligand **9** and porphyrins **18**, **22**, and **23**. Moreover, in order to investigate the stereo orientation of the proximal base attached on **3** and **4**, the non-porphyrin analogs **24** and **25** were synthesized and their chemical shifts were compared (Scheme 4 and Table 2).[13]

Compounds **24** and **25** were synthesized following Collman's isocyanate method.[11] Reaction of aniline with triphosgene in the presence of triethylamine in dry dichloromethane, followed by the addition of **6** or 3-(2-aminoethyl)pyridine hydrobromide and stirring for 1 h at room temperature, afforded **24** and **25** in 78 and 76% yield, respectively.

In porphyrin **3**, protons H_{a-d} and $H_{f,g}$ are shifted upfield in comparison to **24** with a maximum value of $\Delta\delta$=0.9 ppm for H_a. This indicates that the proximal base is situated close



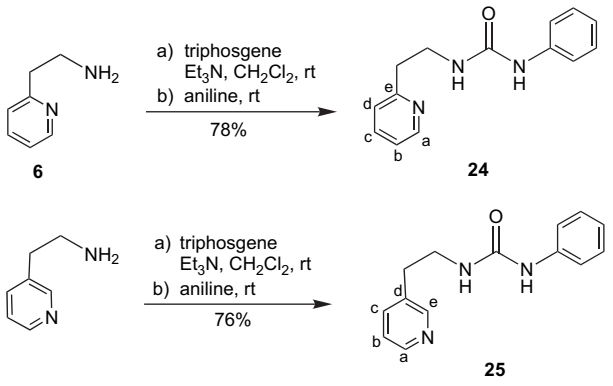
Scheme 3. Synthesis of porphyrins **3** and **4**.

Table 1. Chemical shifts of pyridine protons

	H_1	H_2	H_3	H_4
5	8.37	6.96	7.43	7.02
1	7.91	6.68	6.43	4.45
9	8.49	7.08	7.55	7.00, 7.14
2	8.38	6.81	7.24	6.76

All chemical shifts are in parts per million; ^{1}H NMR 500 MHz, 300 K.

to the porphyrin ring. In addition, for compounds **4** and **25** there is a more pronounced upfield trend for all protons with a maximum value of $\Delta\delta$=1.2 ppm for H_e, implying that



Scheme 4. Synthesis of pyridine analogs **24** and **25**.

Table 2. Chemical shifts of proximal base protons

	H_a	H_b	H_c	H_d	H_e	H_f	H_g
24	8.44	7.14	7.62	7.19	—	3.03	3.68
3	7.53	6.42	6.91	6.51	—	2.43	3.08
25	8.41	7.23	7.61	—	8.41	2.85	3.46
4	7.42	6.11	6.42	—	7.20	1.68	2.69

All chemical shifts are in parts per million; ^{1}H NMR 500 MHz, 300 K.

3-pyridine base is oriented closer under the porphyrin ring compared to 2-pyridine.

3. Conclusion

In conclusion, a new series of porphyrins **1**–**4** have been efficiently synthesized, featuring covalently attached tridentate ligand sites, a tyrosine molecule, and a proximal base. Urea and amide linkers have been used to build-up the superstructures, in order to examine whether different linkers can affect binding and reduction of oxygen. Furthermore, protection or deprotection of tyrosine molecule can be used as a switch to probe the role of tyrosine in these compounds. Finally a preliminary structural investigation has been attempted comparing the ^{1}H NMR chemical shifts of free and bound ligands.

4. Experimental section

4.1. General

^{1}H and ^{13}C NMR spectra were recorded unless otherwise specified, as deuteriochloroform solutions using the solvent peak as internal standard on a Bruker AMX-500 MHz spectrometer. UV–vis spectra were recorded on a Shimadzu Multispec-1501 instrument. All electrospray mass spectrometric experiments were performed using an LCQ Advantage (ThermoElectron, San Jose, CA) mass spectrometer. High-resolution mass spectra were performed on a MS/MS ZABSpec TOF spectrometer at the University of Rennes I (C.R.M.P.O.). Thin layer chromatography was preformed on silica gel 60 F_{254} plates. Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 70–230 mesh ASTM). All dry solvents used were dried by the appropriate technique. Organic extracts were dried over magnesium sulfate unless indicated otherwise.

Evaporation of the solvents was accomplished on a rotary evaporator.

4.1.1. Synthesis of ligands 5 and 6. A solution of 2-vinylpyridine (25.4 mL, 0.23 mmol) and ammonium chloride (24.6 g, 0.46 mmol) in water (70 mL) and methanol (10 mL) was heated for 8 h under reflux. Then the reaction mixture was cooled at 0 °C and basified with 30% w/w aqueous NaOH solution (60 mL). The water layer was then washed with chloroform (5×20 mL). The combined organic extracts were dried over sodium sulfate, filtered, and the solvent was evaporated to obtain a yellow oil. The resulting mixture was then distilled under reduced pressure (~0.07 Torr) to give first at 100–120 °C 2-(pyridin-2-yl)ethanamine **6** (8.43 g, 30%) as a colorless oil and then at 130–150 °C bis(2-(pyridin-2-yl)ethyl)amine (BPEA) **5** (26.1 g, 50%) as a pale yellow oil. Compound **5**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.37 (m, 2H), 7.43 (td, J_1=7.5 Hz, J_2=2 Hz, 2H), 7.02 (d, J=8 Hz, 2H), 6.96 (td, J_1=5 Hz, J_2=1 Hz, 2H), 2.94 (t, J=6.5 Hz, 4H), 2.85 (t, J=6.5 Hz, 4H), 1.64 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.6 (C), 149.6 (CH), 136.6 (CH), 123.6 (CH), 121.5 (CH), 49.6 (CH_2), 38.8 (CH_2). R_f (CH_2Cl_2/MeOH/Et_3N 9:1:0.3): 0.37. Anal. Calcd for $C_{14}H_{17}N_3$: C, 73.98; H, 7.54; N, 18.49. Found: C, 73.91; H, 7.58; N, 18.88. Compound **6**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.40 (d, J=5.0 Hz, 1H), 7.46 (td, J_1=7.5 Hz, J_2=2.0 Hz, 1H), 7.03 (d, J=7.5 Hz, 1H), 6.98 (m, 1H), 2.97 (t, J=7.0 Hz, 2H), 2.79 (t, J=7.0 Hz, 2H), 1.24 (br s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.4 (C), 149.7 (CH), 136.6 (CH), 123.7 (CH), 121.5 (CH), 42.4 (CH_2), 42.3 (CH_2). R_f (CH_2Cl_2/MeOH/Et_3N 9:1:0.3): 0.48. Anal. Calcd for $C_7H_{10}N_2$: C, 68.82; H, 8.25; N, 22.93. Found: C, 68.89; H, 8.21; N, 22.97.

4.1.2. Synthesis of ligand 9. Piperidine (9.5 mL, 96 mmol) was added to a solution of **8** (0.4 g, 0.6 mmol) in DMF (20 mL) at room temperature. The resulting solution was stirred for an hour and the reaction was monitored by thin layer chromatography (CH_2Cl_2/MeOH 9:1). The solvent was then removed under vacuum and the mixture was dissolved in CH_2Cl_2 (40 mL) and extracted with water (2×20 mL), dried over sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by chromatography (2–20% methanol in dichloromethane). The product was eluted with 10% methanol in dichloromethane to give **9** as a pale yellow oil (253 mg, 94%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.49 (m, 2H), 7.55 (m, 2H), 7.14 (d, J=7.5 Hz, 1H), 7.08 (m, 4H), 7.00 (d, J=8.0 Hz, 1H), 6.85 (d, J=8.5 Hz, 2H), 3.82 (m, 2H), 3.46 (m, 2H), 3.23 (m, 1H), 3.00 (m, 1H), 2.89 (m, 3H), 2.84–2.70 (m, 2H), 2.62 (br s, 2H), 1.25 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.4 (C), 159.5 (C), 158.4 (C), 154.4 (C), 150.1 (CH), 149.6 (CH), 136.9 (CH), 133.1 (C), 130.2 (CH), 124.6 (CH), 124.0 (CH), 123.9 (CH), 122.1 (CH), 121.9 (CH), 78.6 (C), 53.2 (CH), 47.5 (CH_2), 46.8 (CH_2), 42.4 (CH_2), 37.8 (CH_2), 36.4 (CH_2), 29.2 (CH_3). R_f (CH_2Cl_2/MeOH 9:1): 0.29. MS (EI): m/z=469.9 $[M+Na]^+$ (100%) for $C_{27}H_{34}N_4O_2$. Anal. Calcd for $C_{27}H_{34}N_4O_2$: C, 72.62; H, 7.67; N, 12.55. Found: C, 72.69; H, 7.73; N, 12.51.

4.1.3. Synthesis of porphyrin 14. To a solution of porphyrin **13** (45 mg, 0.05 mmol) in dry CH_2Cl_2 (3 mL) were added *N*,*N*-diisopropylethylamine (0.6 mL, 3.5 mmol) and BPEA **5** (0.57 g, 2.5 mmol). The resulting mixture was stirred for 18 h at 40 °C under argon. Then CH_2Cl_2 (30 mL) was added to the mixture and washed with water (4×30 mL). The organic layer was dried over magnesium sulfate, filtered, concentrated, and the residue was chromatographed on a silica gel column (CH_2Cl_2/ethanol 50:3) to obtain **14** as a purple solid (45 mg, 88%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.59 (s, 1H), 8.86 (d, J=8 Hz, 1H), 8.77 (d, J=4.5 Hz, 2H), 8.66 (d, J=4.5 Hz, 2H), 8.63 (m, 4H), 8.50 (d, J=8.5 Hz, 1H), 8.20 (d, J=7 Hz, 1H), 8.00 (t, J=7 Hz, 1H), 7.94 (m, 2H), 7.85 (m, 3H), 7.46 (t, J=7.5 Hz, 1H), 7.20 (s, 2H), 7.15 (s, 2H), 6.47 (m, 2H), 5.91 (t, J=7.5 Hz, 2H), 3.67 (d, J=7.5 Hz, 2H), 2.70 (s, 2H), 2.58 (s, 6H), 1.70 (s, 6H), 1.41 (s, 6H), 1.37 (m, 4H), 0.50 (br s, 4H), −2.40 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3 (C), 158.0 (C), 152.2 (C), 148.7 (CH), 139.9 (C), 139.4 (C), 139.0 (C), 138.4 (C), 138.1 (C), 137.8 (CH), 136.8 (C), 135.7 (CH), 135.2 (CH), 131.7 (C), 131.5 (CH), 130.1 (CH), 128.2 (CH), 124.4 (CH), 123.0 (CH), 122.1 (CH), 120.9 (CH), 120.6 (CH), 119.6 (C), 114.8 (C), 114.4 (C), 58.9 (CH_2), 54.7 (CH_2), 35.3 (CH_2), 22.0 (CH_3), 21.8 (CH_3), 21.7 (CH_3). R_f (CH_2Cl_2/MeOH 9:1): 0.57. MS (EI): m/z=1026.3 $[M+H]^+$ (100%) for $C_{66}H_{59}N_9O_3$. Anal. Calcd for $C_{66}H_{59}N_9O_3$: C, 77.24; H, 5.79; N, 12.28. Found: C, 77.18; H, 5.82; N, 12.27. UV–vis: λ_{abs} (CH_2Cl_2) (ε, $mM^{-1}\,cm^{-1}$) 419 (304.6), 514 (16.5), 548 (4.8), 590 (4.9), 647 (2.4).

4.1.4. Synthesis of porphyrin 18. A mixture of α,β-monoaminoporphyrin **12b** (89 mg, 0.2 mmol), triethylamine (56 μL, 0.4 mmol), and triphosgene (20 mg, 0.07 mmol) in dry dichloromethane (150 mL) was stirred for 1 h under argon at room temperature, after which ligand **9** (89 mg, 0.2 mmol) was added and the stirring continued overnight. The reaction was monitored by thin layer chromatography (4% methanol in dichloromethane). The residue was purified by column chromatography (1–3% methanol in dichloromethane). The desired porphyrin was eluted with 2% methanol in dichloromethane to give a purple solid (153 mg, 62%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.74–8.67 (m, 6H), 8.59 (m, 2H), 8.48 (dd, J_1=8.0 Hz, J_2=1.5 Hz, 1H), 8.44 (d, J=8.5 Hz, 1H), 8.30 (m, 2H), 8.22 (d, J=7.0 Hz, 1H), 7.96 (m, 3H), 7.77 (t, J=8.0 Hz, 1H), 7.42 (t, J=7.5 Hz, 1H), 7.35 (m, 2H), 7.27 (m, 2H), 7.24 (m, 2H), 6.88 (m, 4H), 6.77 (d, J=7.0 Hz, 2H), 6.64 (d, J=7.5 Hz, 2H), 5.98 (s, 1H), 4.64 (m, 1H), 4.50 (d, J=7.5 Hz, 1H), 3.41 (m, 1H), 3.18 (m, 1H), 3.09 (m, 2H), 2.68 (m, 2H), 2.61 (m, 6H), 2.45 (m, 4H), 1.87 (s, 3H), 1.84 (s, 3H), 1.82 (s, 6H), 1.16 (s, 9H), −2.54 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.0 (C), 159.1 (C), 158.1 (C), 154.5 (C), 154.3 (C), 152.0 (C), 149.7 (CH), 149.4 (CH), 140.0 (C), 139.9 (C), 139.7 (C), 139.6 (C), 138.3 (C), 137.5 (CH), 136.9 (C), 136.8 (CH), 136.7 (CH), 135.3 (CH), 131.8 (C), 131.4 (C), 131.3 (CH), 130.2 (CH), 130.0 (CH), 129.9 (CH), 128.3 (CH), 128.2 (CH), 124.5 (CH), 124.4 (CH), 123.8 (CH), 123.7 (CH), 122.0 (CH), 121.9 (CH), 121.7 (CH), 120.7 (CH), 119.6 (C), 119.5 (C), 114.5 (C), 114.1 (C), 78.6 (C), 51.5 (CH), 48.0 (CH_2), 46.9 (CH_2), 39.8 (CH_2), 37.5 (CH_2), 36.1 (CH_2), 29.1 (CH_3), 22.3 (CH_3), 22.2 (CH_3), 21.9 (CH_3). R_f (CH_2Cl_2/MeOH 95:5): 0.32. MS (EI): m/z=1232.0 $[M+H]^+$ (100%) for $C_{78}H_{74}N_{10}O_5$. Anal. Calcd for $C_{78}H_{74}N_{10}O_5$: C, 76.07; H, 6.06; N, 11.37. Found: C,

76.10; H, 6.01; N, 11.32. UV–vis: λ_{abs} (CH_2Cl_2) (ε, $mM^{-1}\,cm^{-1}$) 420 (280.9), 515 (14.6), 549 (4.3), 591 (4.4), 647 (2.1).

Acknowledgements

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Supplementary data

Experimental procedures, characterization, ^{1}H NMR, and ^{13}C NMR spectra, for all new compounds. For synthesis of compounds **10**, **11a**, **11b**, **12a**, **12b**, and **19**, see Ref. 9. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.01.036.

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13. ^{1}H NMR chemical shifts of pyridine analogs **24** and **25** are provided in the Supplementary data.