Synthesis of Porphyrins Bearing Multiple *meso*-Aminoalkyl Groups

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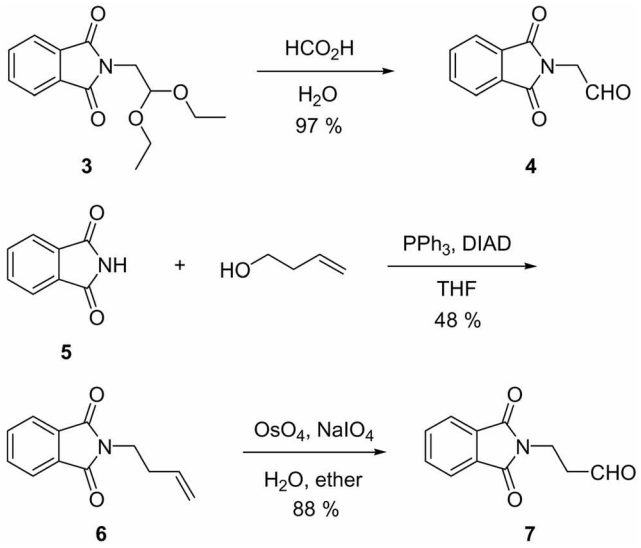
meso-Substituted porphyrins have been widely used as key components in constructing porphyrin-based model systems as well as molecular materials.[1,2] The design and synthesis of basic porphyrin building blocks for the construction of highly ordered systems often require incorporation of different peripheral substituents. The synthesis of porphyrins bearing specific patterns of functionality is still challenging task in spite of the ample presence of reported procedure.[1] The difficulties also arise from the separation and limited availablilty of suitable precursors. Although many sophisticated synthetic routes for designed porphyrins have been reported recently,[3,4] some of the porphyrin building blocks bearing specific peripheral substituents are not available yet. The molecular weight of the porphyrins lacking of any peripheral substituents has considerably lower molecular weight than the porphyrins bearing substituents at *meso*- or *β*-pyrrolic positions. Keeping the low molecular weight of porphyrins is sometimes important in medical application.[5] It has been demonstrated that lower molecular weight of porphyrins permits high charge density when electro-active surface is constructed for molecular information storage applications.[6] Most of the reported methods generally adopted acid-catalyzed condensation of dipyrromethanes with appropriate aldehydes for the construction of porphyrins. Generally, porphyrins bearing one carbon unit directly attached to the *meso*-positions have been synthesized by selective formylation followed by conversion to other functional groups.[7] Although selective Vilsmeier formylation resulted in high yields in some cases, the method is not applicable when the starting porphyrins have unsymmetrical multiple reaction sites. On the other hand, porphyrins bearing aminoalkyl group at *meso*-positions such as **1** or **2** are rare and only handful examples have been reported.[8,9] Directly attachment of basic functional groups at the *meso*-position with proper dimension would enable the construction of porphyrin-based supramolecular architectures more conveniently. With these regards, we here report a new synthetic method of porphyrins bearing aminoalkyl equivalents at multiple *meso*-positions. Also is reported the synthesis of amine-protected aldehydes which can be used as building blocks for the synthesis of *meso*-amine substituted porphyrins. The aldehydes and corresponding dipyrromethanes would provide the starting point for the desired porphyrin synthesis.

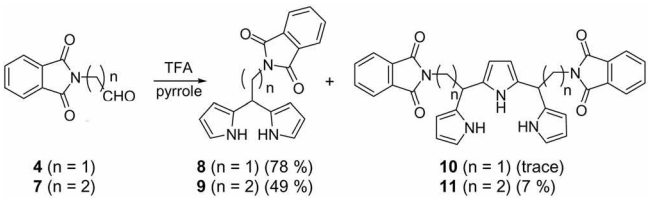
As shown in Scheme 1, phthalimido-aldehyde **4** was prepared from phthalimidoacetaldehyde diethyl acetal and compound **7** was synthesized by two steps starting from phthalimide and 3-buten-1-ol. The phthalimide was reacted with alcohol under Mitsunobu conditions,[10] followed by oxidative cleavage of double-bond afforded **7** in 88% yield.[11] Since the starting aldehydes **4** and **7** are in hand, the desired dipyrromethane derivatives then were prepared by condensation of **4** or **7** with pyrrole in neat excess pyrrole presence as shown in Scheme 2. Corresponding dipyrromethanes **8** and **9** were major products and small amount of tripyrrylmethane **10** and **11** were also isolated and characterized. The porphyrin synthesis was then attempted as shown in Scheme 3. The '2+2' condensation of dipyrromethane **8** with *p*-(*t*-butyl)benzaldehyde and dipyrromethane **12** in the presence of TFA[12] afforded the mixture of porphyrins **13**, **14**, and **16** in 7%, 6%, and 2% yields, respectively.

Condensation of **9** with **12** and *p*-(*t*-butyl)benzaldehyde under the same condition resulted in the formation of **13**, **15** and **17** in 9%, 14% and 18% yields, respectively. Porphyrin **14** and **15** were major products as expected and scrambling of dipyrromethane was not observed.

The reductive cleavage of phthalimide to amine was not successful due to the difficulty in isolation of pure products. Thus metalation was carried out first as shown in Scheme 4. Treatment of **14** or **16** with $Ni(OAc)_2$ in refuluxing DMF afforded Ni(II)-complexes **Ni(II)-14** and **Ni(II)-16** in quan-



Scheme 1



Scheme 2

titative yields. Then reductive cleavage of the corresponding Ni(II)-complexes yielded desired aminoalkyl porphyrins **1** and **2** in high yields.[13]

The UV-Vis spectra of the porphyrin **14-17** taken in chloroform at room temperature, showed typical absorption pattern of *meso*-substituted porphyrins (Figure 1). One interesting observation was that the molar absorptivity of each porphyrins exhibited gradual decrease depending on the number of amino group present.

In conclusion, a convenient synthesis of porphyrins bearing *meso*-alkylamino substituents at multiple *meso*-positions has been accomplished. The synthesis utilized the methodology of the one-flask pyrrole-aldedyde condensations. The rational routes described here afforded the porphyrins bearing *meso*-aminoalkyl substituents in controlled manner. The ability to prepare such porphyrins may be useful in the construction of a variety of porphyin-based model systems and further applications in the biominetic and material chemistry.

Experimental

Proton NMR spectra (400 MHz, Bruker DPX-400) were recorded using TMS as the internal standard. High and Low resolution FAB mass spectra were obtained on an AUTO SPEC M-363 high-resolution mass spctrometer. Column chromatography was performed over silica gel (Merck, 230-400 mesh). All other reagents were obtained from Aldrich and used as received unless noted otherwise.

Phthalimidoacetaldehyde (4): Compound **3** (2.0 g, 7.60 mmol) was added to the solution of formic acid (15 mL) and distilled water (1 mL). The resulting mixture was stirred at room temperature for overnight. Then the solution was washed with aq. $NaHCO_3$ and water. The solution was dried (anhydrous Na_2SO_4) and the solvent was removed under reduced pressure to afford compound **4** (1.40 g, 97%). ^{1}H NMR ($CDCl_3$) δ 4.56 (2H, s), 7.73-7.80 (2H, m), 7.87-7.93 (2H, m), 9.66 (1H, s); ^{13}C NMR ($CDCl_3$) δ 47.37, 123.70, 131.95, 134.35, 167.52, 193.45; CI MS calcd for $C_{10}H_7NO_3$ *m/z* 189.04, found 207.08 ($M + NH_4^+$).

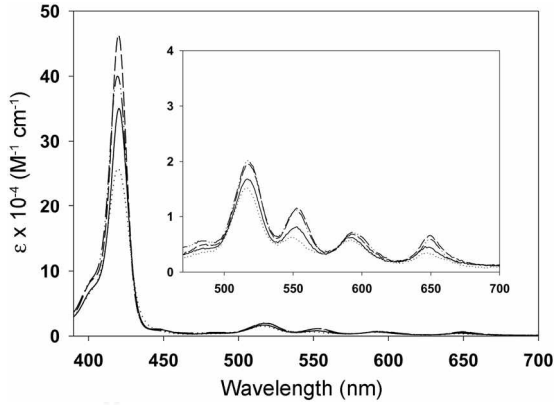
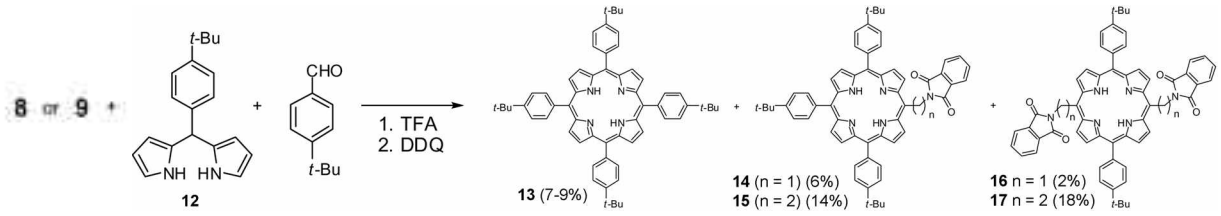
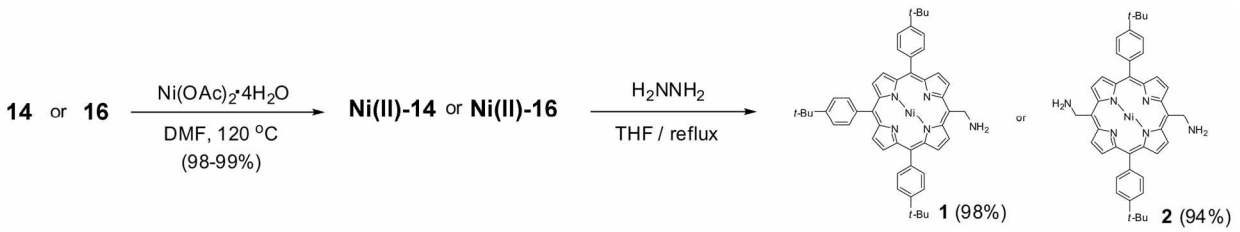


Figure 1. UV-vis spectra of **14** (—), **16** (····), **15** (----), and **17** (–·–) (3.0×10^{-6} M) in $CHCl_3$.

Compound (6): A mixture of 3-buten-1-ol (1 mL, 11.8 mmol), phthalimide (2.61 g, 17.7 mmol) and triphenylphosphine (4.64 g, 17.7 mmol) in anhydrous THF (40 mL) was stirred for several minutes. Then, isopropyl azodicarboxylate (3.5 mL, 17.8 mmol) was added dropwise keeping the temperature at 0 °C. Then, the mixture was allowed to stir at room temperature overnight. The solution was combined with CH_2Cl_2 (50 mL) and washed with water (50 mL). The solvent was removed and remaining solid was purified by column chromatography on silica (CH_2Cl_2/hexanes = 8/2). Yield 1.14 g (48%); mp 46-47 °C; ^{1}H NMR ($CDCl_3$) δ 2.42-2.49 (2H, m), 3.78 (2H, t, J = 7.13 Hz), 5.00-5.10 (2H, m), 5.73-5.84 (1H, m), 7.70-7.74 (2H, m), 7.82-



Scheme 3



Scheme 4

7.86 (2H, m); ^{13}C NMR ($CDCl_3$) δ 32.84, 37.33, 117.56, 123.21, 132.10, 133.89, 134.48, 168.36; EI MS calcd for $C_{12}H_{11}NO_2$ *m/z* 201.08, found 201.10.

Phthalimidopropylaldehyde (7): Compound **6** (0.54 g, 2.67 mmol) was dissolved in the mixture of diethyl ether and water (1/1, 20 mL) and osmium tetroxide (0.03 g, 0.13 mmol) was added in one portion. The mixture was stirred for 10 min at room temperature, then sodium periodate (1.32 g, 6.18 mmol) was added in four portions. The mixture was stirred overnight at room temperature. The mixture was then combined with water (100 mL) and extracted with diethyl ether. The organic layer was dried and compound **7** (0.48 g, 88%) was obtained by evaporation of the solvent under reduced pressure. mp 115-116 °C; ^{1}H NMR ($CDCl_3$) δ 2.88 (2H, dd, J = 1.35, 6.99 Hz), 4.04 (2H, t, J = 6.99 Hz), 7.70-7.76 (2H, m), 7.82-7.87 (2H, m), 9.83 (1H, t, J = 1.35 Hz); ^{13}C NMR ($CDCl_3$) δ 31.68, 42.38, 123.40, 131.96, 134.14, 168.03, 199.44; CI MS calcd for $C_{11}H_9NO_3$ *m/z* 203.19, found 203.67.

5-(*N*-Phthalimidomethyl)dipyrromethane (8): To the solution of **4** (0.30 g, 1.60 mmol) in pyrrole (4 mL) was added trifluoroacetic acid (62 μL, 0.80 mmol). The mixture was stirred for 30 min at room temperature. Then the reaction was quenched by addition of aqueous NaOH solution (0.1 N, 50 mL). The organic layer was combined with CH_2Cl_2 (50 mL), washed with water (50 mL) and the solvent was removed in vacuo. The residual solid was purified by column chromatography on silica (CH_2Cl_2/EtOAc = 9/1) to afford **8** (0.38 g, 78%). mp 169-170 °C; ^{1}H NMR ($CDCl_3$) δ 4.20 (2H, d, J = 8.33 Hz), 4.75 (1H, t, J = 8.33 Hz), 6.08-6.11 (4H, m), 6.67 (2H, dd, J = 2.50, 4.33 Hz), 7.67-7.71 (2H, m), 7.76-7.80 (2H, m), 8.03 (2H, br s); ^{13}C NMR ($CDCl_3$) δ 36.26, 41.31, 106.32, 108.51, 117.74, 123.29, 129.46, 131.86, 133.97, 168.14; FAB MS calcd for $C_{18}H_{15}N_3O_2$ *m/z* 305.12, found 305.07.

5-(*N*-Phthalimidoethyl)dipyrromethane (9) and 5,10-di(*N*-phthalimidoethyl)tripyrromethane (11): **7** (0.34 g, 1.70 mmol), pyrrole (4 mL) and TFA (65 μL, 0.84 mmol) was treated identically as for the synthesis of (**8**). Yield for (**9**) (0.27 g, 49%); Yield for (**11**) (0.03 g, 7%). Spectroscopic data for **9**: mp 102-103 °C; ^{1}H NMR ($CDCl_3$) δ 2.35 (2H, q, J = 6.95 Hz), 3.77 (2H, t, J = 6.43 Hz), 4.07 (1H, t, J = 7.42 Hz), 6.04-6.05 (2H, m), 6.10-6.13 (2H, m), 6.66-6.68 (2H, m), 7.69-7.75 (2H, m), 7.80-7.84 (2H, m), 8.37 (2H, br s); ^{13}C NMR ($CDCl_3$) δ 34.37, 35.73, 36.87, 105.93, 108.64, 117.59, 123.64, 132.43, 132.97, 134.46, 169.21; FAB MS calcd for $C_{17}H_{17}N_3O_2$ *m/z* 319.13, found 319.09; for **11**: ^{1}H NMR ($CDCl_3$) δ 2.21-2.35 (4H, m), 3.72 (4H, t, J = 6.66 Hz), 3.94-4.00 (2H, m), 5.88 (2H, t, J = 2.72 Hz), 5.99-6.00 (2H, m), 6.06-6.10 (2H, m), 6.64-6.67 (2H, m), 7.66-7.72 (4H, m), 7.76-7.81 (4H, m), 8.36 (1H, br s), 8.52 (2H, br s); ^{13}C NMR ($CDCl_3$) δ 33.81, 33.85, 35.40, 35.44, 36.42, 105.27, 105.67, 105.80, 108.21, 108.23, 116.98, 123.21, 123.22, 131.75, 131.86, 132.03, 132.69, 132.76, 133.99, 168.69, 168.72; FAB MS calcd for $C_{34}H_{29}N_3O_4$ *m/z* 571.22, found 571.21.

5,10,15,20-Tetrakis(*p-tert*-butylphenyl)porphyrin (13), 10,15,20-tris(*p-tert*-butylphenyl)-5-(*N*-phthalimidomethyl)porphyrin (14) and 10,20-bis(*p-tert*-butylphenyl)-5,15-bis(*N*-phthalimidomethyl)porphyrin (16): Compound **8** (0.22 g, 0.71 mmol), compound **12** (0.20 g, 0.71 mmol), 4-*tert*-butylbenzaldehyde (240 μL, 1.44 mmol) and NaCl (0.046 g, 0.79 mmol) were dissolved in CH_2Cl_2 (71 mL) and TFA (55 μL, 0.71 mmol) was added with stirring at room temperature. The solution was stirred for 30 min and then DDQ (0.49 g, 2.15 mmol) was added and stirred for 1 hr. The mixture was extracted with CH_2Cl_2 and dried. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica (from CH_2Cl_2/Hexanes = 2/1 to CH_2Cl_2) to give three porphyrins **13**, **14** and **16**. Spectroscopic data for **13** (22 mg, 7%): ^{1}H NMR ($CDCl_3$) δ –2.74 (2H, s), 1.61 (36H, s), 7.75-7.77 (8H, m), 8.14-8.16 (8H, m), 8.87 (8H, s); UV-Vis ($CHCl_3$) λ_{max} (ε) 421 (610300), 449 (55700), 519 (27200), 555 (19300), 594 (11800), 651 (11900); MALDI-TOF MS calcd for $C_{60}H_{62}N_4$ *m/z* 838.50, found 838.39; for **14** (34 mg, 6%); ^{1}H NMR ($CDCl_3$) δ –2.77 (2H, s), 1.60 (9H, s), 1.62 (18H, s), 7.29 (2H, s), 7.58-7.61 (2H, m), 7.70-7.76 (8H, m), 8.11-8.13 (6H, m), 8.82 (4H, q, J = 4.75 Hz), 9.01 (2H, d, J = 4.93 Hz), 9.94 (2H, d, J=5.00 Hz); UV-Vis ($CHCl_3$) λ_{max} (ε) 420 (349700), 517 (16833), 553 (8167), 592 (6233), 646 (4600); MALDI-TOF MS calcd for $C_{59}H_{55}N_5O_2$ *m/z* 865.44, found 865.72; for **16** (6 mg, 2%); ^{1}H NMR ($CDCl_3$) δ –2.85 (2H, s), 1.62 (18H, s), 7.18 (4H, s), 7.54-7.57 (4H, m), 7.67-7.70 (4H, m), 7.72-7.75 (4H, m), 8.08-8.11 (4H, m), 8.95 (4H, d, J = 4.93 Hz), 9.89 (4H, d, J = 4.97 Hz); ^{13}C NMR ($CDCl_3$) δ 31.72, 34.92, 41.76, 110.82, 120.42, 123.24, 123.41, 128.82, 131.94, 132.40, 133.92, 134.30, 139.36, 150.58, 168.14; UV-Vis ($CHCl_3$) λ_{max} (ε) 420 (257767), 517 (15200), 550 (6300), 592 (5800), 646 (3467); MALDI-TOF MS calcd for $C_{58}H_{48}N_6O_2$ *m/z* 892.37, found 892.54.

10,15,20-tris(*p-tert*-butylphenyl)-5-(*N*-phthalimidoethyl)porphyrin (15) and 10,20-bis(*p-tert*-butylphenyl)-5,15-bis(*N*-phthalimidoethyl)porphyrin (17): Compound **9** (0.32 g, 1.00 mmol), compound **12** (0.28 g, 1.01 mmol), 4-*tert*-butylbenzaldehyde (333 μL, 2.00 mmol), NaCl (0.58 mg, 1.00 mmol) and TFA (77 μL, 1.00 mmol) was treated identically as for **14-16**. The residue was purified by column chromatography on silica (from CH_2Cl_2/hexanes = 2/1 to CH_2Cl_2) to give three porphyrins **13**, **15**, and **17**. Spectroscopic data for **15** (125 mg, 14%): ^{1}H NMR ($CDCl_3$) δ –2.76 (2H, s), 1.60 (9H, s), 1.63 (18H, s), 4.82-4.88 (2H, m), 5.30-5.36 (2H, m), 7.74-7.81 (8H, m), 7.93-7.97 (2H, m), 8.11-8.15 (6H, m), 8.84 (4H, s), 9.02 (2H, d, J = 4.87 Hz), 9.75 (2H, d, J = 4.85 Hz); UV-Vis ($CHCl_3$) λ_{max} (ε) 420 (463500), 518 (19467), 553 (11433), 593 (6833), 649 (6600); MALDI-TOF MS calcd for $C_{60}H_{57}N_5O_2$ *m/z* 879.45, found 879.56; for **17** (84 mg, 18%); ^{1}H NMR ($CDCl_3$) δ –2.77 (2H, s), 1.65 (18H, s), 4.79-4.85 (4H, m), 5.26-5.32 (4H, m), 7.77-7.82 (8H, m), 7.93-7.97 (4H, m), 8.11-8.14 (4H, m), 9.00 (4H, d, J = 4.85 Hz), 9.72 (4H, d, J = 4.88 Hz); UV-Vis ($CHCl_3$) λ_{max} (ε) 419 (399300), 517 (20167) 552 (11233), 593 (7200), 649 (5900); MALDI-TOF MS calcd for $C_{60}H_{52}N_6O_4$ *m/z* 920.41, found 920.55.

10,15,20-tris(*p-tert*-butylphenyl)-5-(*N*-phthalimidomethyl)porphyrinato Nickel(II) [Ni(II)-14]: Porphyrin **14** (0.034 g, 0.04 mmol) and $Ni(OAc)_2{\cdot}4H_2O$ (0.10 g, 0.4 mmol) were dissolved in 15 mL of DMF. The resulting solution was heated at 120 °C for 2 hr. The solution was diluted with CH_2Cl_2, and washed with water (100 mL). The organic layer was evaporated under reduced pressure to give **Ni(II)-14** (0.036 g, 99%); ^{1}H NMR ($CDCl_3$) δ 1.53-1.55 (27H, m), 6.98 (2H, s), 7.47-7.51 (2H, m) 7.53-7.57 (2H, m), 7.63-7.68 (6H, m), 7.85-7.91 (6H, m), 8.68-8.72 (4H, m), 8.90 (2H, d, J = 5.10 Hz), 9.78 (2H, d, J = 5.10 Hz); MALDI-TOF MS calcd for $C_{59}H_{53}N_5NiO_2$ m/z 921.36, found 921.37.

10,20-bis(*p-tert*-butylphenyl)-5,15-bis(*N*-phthalimidomethyl)porphyrinato Nickel (II) [Ni(II)-16]: The procedure used for the preparation of **Ni(II)-14** was repeated with porphryin **16** (0.022 g, 0.025 mmol) and $Ni(OAc)_2{\cdot}4H_2O$ (0.11 g, 0.45 mmol) to obtain **Ni(II)-16** (0.023 g, 98%); ^{1}H NMR ($CDCl_3$) δ 1.54 (18H, s), 6.89 (4H, S), 7.41-7.48 (4H, m), 7.49-7.54 (4H, m), 7.64-7.67 (4H, m), 7.85-7.87 (4H, m), 8.83 (4H, d, J = 5.09 Hz), 9.70 (4H, d, J = 5.13 Hz); MALDI-TOF MS calcd for $C_{58}H_{46}N_6NiO_4$ m/z 948.29, found 949.73.

5-(Aminomethyl)-10,15,20-tris(*p-tert*-butylphenyl)porphyrinato Nickel(II) (1): An excess amount of hydrazine monohydrate (0.5 mL) was added to a solution of **Ni·14** (0.036 g, 0.039 mmol) in THF (10 mL). The resulting mixture was heated at reflux for 17 hr. The solution was diluted with CH_2Cl_2 and washed with 0.2 N NaOH (50 mL) and water (50 mL). The solution was evaporated under reduced pressure to give **1** (0.03 g, 98%); ^{1}H NMR ($CDCl_3$) δ 1.54-1.56 (27H, m), 5.10-5.11 (4H, m), 4.71 (2H, s), 7.65-7.70 (6H, m), 7.89-7.93 (6H, m), 8.73 (4H, S), 8.88 (2H, d, J = 4.99 Hz), 9.33 (2H, d, J = 4.96 Hz); MALDI-TOF MS calcd for $C_{51}H_{51}N_5Ni$ m/z 791.35, found 793.32.

5,15-Bis(aminomethyl)-10,20-bis(*p-tert*-butylphenyl)-porphyrinato Nickel (II) (2): The procedure used for the preparation of **1** was repeated with porphryin **Ni·16** (0.013 g, 0.014 mmol) and hydrazine monohydrate (0.5 mL) to obtain **2** (9 mg, 94%); ^{1}H NMR ($CDCl_3$) δ 1.55 (18H, s), 5.11 (4H, br S), 5.74 (4H, S), 7.69-7.71 (4H, m), 7.89-7.92 (4H, m), 8.86 (4H, d, J = 5.02 Hz), 9.34 (4H, d, J = 5.01 Hz); MALDI-TOF MS calcd for $C_{42}H_{42}N_6Ni$ m/z 688.28, found 688.25.

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