Synthesis of Derivatives of Chlorines Related to Chlorophyll-*a* by Vilsmeier Reaction with Methyl Pyropheophorbide-*a*

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From methyl pyropheophorbide-*a* (MPP*a*, **1**), the vinyl group was converted into other functional groups including 2-dimethoxylethyl, 1-hydroxylalkyl, and alkylcarbonyl groups by addition and oxidization to form chlorin (**2~5b**). The nickel complexes (**6a~e**) were prepared by treatment with excess nickel acetate in MeOH by refluxing and were used directly for the next reaction without further separation. The Vilsmeier reactions of nickel chlorins with 3-(dimethylamino)acrolein/phosphoryl chloride (3-DMA/$POCl_3$) are carried out to give *meso*-20-fotmyl-vinylpyropheophorbide-*a* (**7a~9b**).

Keywords: Chlorin; Chlorophyll; Pyropheophorbide; Synthesis; Vilsmeier reaction.

INTRODUCTION

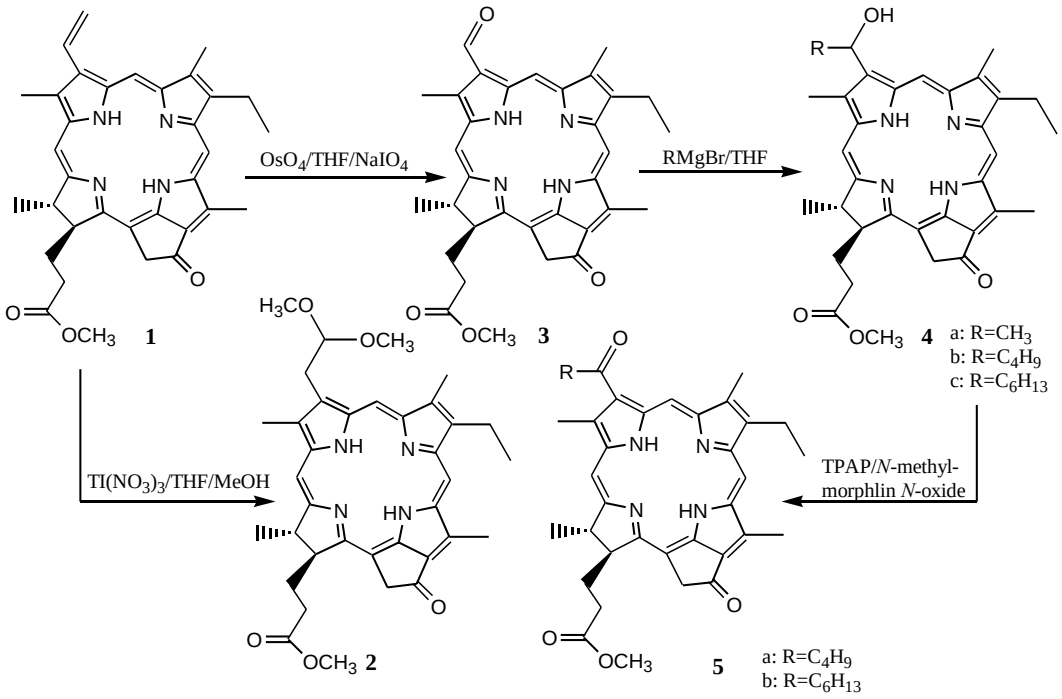
In the active field of photodynamic therapy (PDT), the design of new photosensitizers having well-defined structure with amphiphilic properties, high selectivity for tumor cells, quick elimination from healthy cells and strong absorption in the red region of the visible spectrum is an important challenge. The syntheses of many derivatives of tetrapyrrolic compounds such as purpurins and chlorines have been developed by introducing and modifying reactive functional groups on the periphery of the parent ring.[1-4] Aldehyde is highly reactive and formyl reacts with several regents to give a variety of compounds. The reaction of formyl-chlorin including chlorophylls-*b* and -*d* which are antenna pigments of photosynthesis has attracted much synthetic and biological interest. The reactivity of formyl groups conjugated with chlorin chromophore has already been investigated in ways such as reduction, reductive alkylation, reductive amination, oxidation, Wittig reaction and so on.[5-10] Formylvinyl group is another highly reactive functional group. The Vilsmeier formylation reaction, which was first introduced into porphyrin chemistry in 1966 by Inhoffen and coworkers, is a convenient method for constructing a formylvinyl group on the chlorine.[11-12] The introducing reactive functional on the chlorin chromophore is an important premise for a variety of syntheses of chlorins. The establishment of multifunctional structures on the parent ring such as aldehyde-ketone, aldehyde-aldehyde and α,β-unsaturated aldehyde or ketone structure should provide valuable information for developing new photosensitizers in photodynamic therapy.

RESULTS AND DISCUSSION

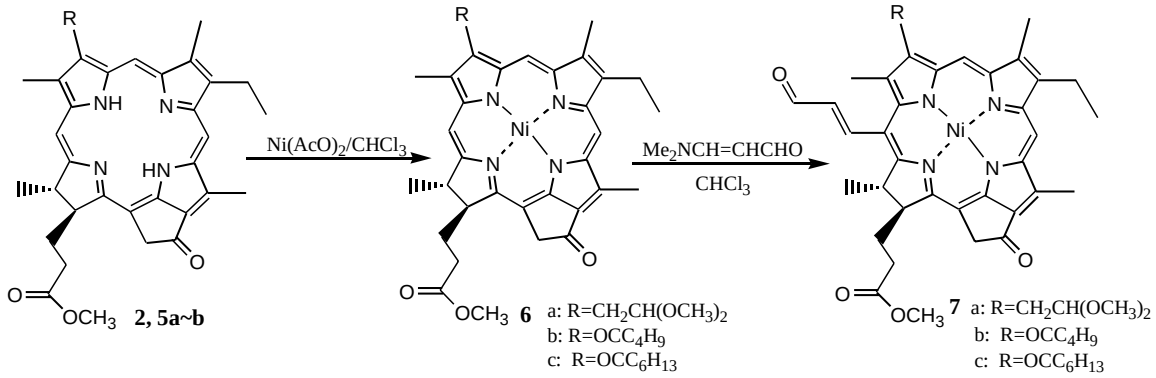
In our approach, methyl pyropheophorbide-*a* (MPP*a*) (**1**) was used as a starting material. To avoid the influence upon the Vilsmeier reaction the vinyl group at 3-position was converted into other functional groups by addition or oxidization. Treatment of starting material **1** with thallium(III) nitrate in tetrahydrofuran gave the bisdimethylacetal (**2**) in good yield.[13] MPP*a* **1** was oxidized with osmium(IV) oxide in tetrahydrofuran containing a catalytic amount of pyridine at 0 °C for 1 hour and was treated with sodium perioadate in aqueous tetrahydrofuran to give methyl 2-formyl-2-devinylpyropheophorbide-*a* (**3**).[14] The Grignard reaction of MPP*d* **3** with alkyl magnesium bromide in tetrahydrofuran afforded alcohol chlorin **4a**~**c** in moderate yield, and then their hydroxyl groups at the 3-position were converted into carbonyl groups by oxidation with tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide to yield diketo chlorin **5a** and **5b** in 68% and 62% yield, respectively.

Upon treatment with excess nickel acetate in MeOH by refluxing, chlorin **2**, **4a~b** and **5a~b** were converted into their nickel complexes **6a**~**e** which were directly used for the next reaction without separation or identification. The formylations of these nickel(II) complexes **6a~c** were performed by the Vilsmeier reaction with 3-(dimethylamino)acrolein (3-DMA) in the presence of phosphoryl chloride and basic hydrolysis and neutralization to afford the major product, nickel(II) 20-(2-formylvinyl)-substituted chlorin **7a**~**c** in an average 65% yield. In these reactions, many other green products besides major compounds were formed but in much lower

Scheme I



Scheme II

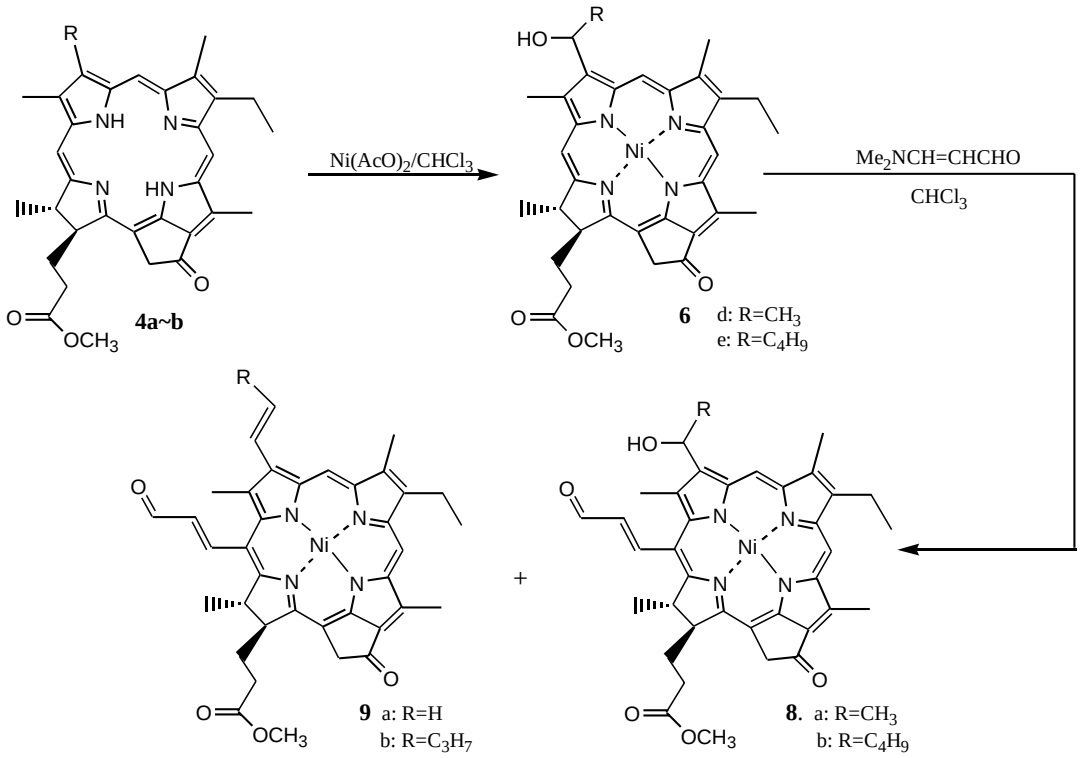


yield, and their separation and identification were very difficult.

The Vislmeier reactions of nickel complexes **6d** and **6e** were carried out with 3-(dimethylamino)acrolein (3-DMA) and phosphoryl chloride in the same conditions to give two major products, respectively; one was the expected formylmethylation product **8a~b** and the other was the vinyl-substituted product **9a~b** which underwent dehydration reaction at the 3-position. The dehydrated product **9b** possessed *E*-style structure in the carbon-carbon double bond at the 3-position according to the coupling constant between 3a-H and 3b-H (J = 16.2 Hz).

The Vilsmeier reaction is applicable only to active substrates for electrophilic substitution on aromatic rings, such as amines and phenols. Chlorin has an unsaturated porphyrins structure in which one of the macrocycle peripheral double bonds is reduced. The unusual chemical shift of the neighboring methine resonances is best explained by a picture of the macrocycle introduced by Woodward.[15-16] In this model, the four pyrrole rings are considered to remain to some extent autonomous aromatic subunits that borrow electron density from the methine positions. Removal of a peripheral double bond results in the loss of an aromatic subunit and an increase in the electron density at the neighboring methine position, which accounts for the high field shift of the signals for the neighboring methine protons. The chemical shift of metal-

Scheme III



loporphyrin appeared on the high field ($\Delta\delta > 0.5$) in comparison with free porphyrin because of the difference in self-aggregation.[17-18] The Vilsmeier reactions of compounds **6** take place on the δ-position due to its higher electron density. The ^{1}H NMR spectra of products **7** and **8** both showed two *meso*-hydrogen signals between δ 8.58-9.33. The single peak at about δ 8.00 was not discovered to indicate another *meso*-hydrogen at δ-position was substituted by a formylvinyl group.

EXPERIMENTAL SECTION

The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian-300 MHz spectrometer. Chemical shifts are given as δ values using tetramethylsilane as the internal standard and *J* values are given in Hz. The IR spectra were measured with a Shimadzu FTIR 8300 instrument. The mass spectra were measured with a JEOL 01SG-2 spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 C Microanalyzer.

All chemical reagents were commercially available and purified with standard methods before use. Solvents were dried in routine ways and redistilled. Methyl pyropheophorbide-*a* (MPP*a*, **1**) was obtained according to Smith's method.[19] The chlorin **2** and **3** were prepared according to references [13] and [14].

Methyl 3-(1-Hydroxylethyl)-3-devinylpyropheophorbide-*a* (4a)

To a solution of compound **3** (138 mg, 0.25 mmol) in THF (15 mL) at 0 °C was added 3 mL of methyl magnesium bromide in THF (1 mol/L). The mixture was then allowed to stir for 15 min until it was poured onto ice-cooled aq. NH_4Cl. The aqueous phase was extracted with ethyl ether. The combined organic layers were dried over Na_2SO_4. After evaporation of the solvent the residue was purified with a silica-gel column with hexane-ethyl acetate (3:1) to give **4** in 72% yield. The analytical data is identical with reference [20].

Methyl 3-(1-Hydroxylpentyl)-3-devinylpyropheophorbide-*a* (4b)

This compound **4b** was obtained from Grignard reaction of **3** using butyl magnesium bromide as a dark green solid. mp 224-227 °C (chloroform-*n*-hexane); Yield 68%; UV-vis ($CHCl_3$) λ_{max}: 289 (0.38), 410 (1.00), 505 (0.12), 536 (0.11), 604 (0.10), 661 (0.47) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ: -1.95 (br s, 1H, NH), 0.06 (br s, 1H, NH), 0.81 (t, *J*

= 6.6 Hz, 3H, 3e-H), 1.65 (t, *J* = 7.2 Hz, 3H, 8b-H), 1.78 (d, *J* = 7.2 Hz, 3H, 18-CH_3), 1.43-2.78 (m, 10H, 2b~d-H+17a+17b-H), 3.22 (s, 3H, CH_3), 3.35 (s, 3H, CH_3), 3.58 (s, 3H, OCH_3), 3.63 (s, 3H, CH_3), 3.66 (q, *J* = 7.2 Hz, 2H, 8a-H), 4.12-4.27 (m, 1H, 18-H), 4.32-4.46 (m, 1H, 17-H), 5.02 (d, *J* = 17.0 Hz, 1H, 13^2-H), 5.14 (d, *J* = 17.0 Hz, 1H, 13^2-H), 6.12-6.22 (m, 1H, 3a-H), 8.55, 9.43, 9.71 (s, each 1H, meso-H); IR (KBr) ν: 1740, 1732 (C=O), 1609 (C=C), 1553 (chlorin skeleton), 1468, 1366, 1287, 979 cm^{-1}. Anal. Calcd for $C_{37}H_{44}N_4O_4$: C 73.00, H 7.29, N 9.20. Found C 72.88, H 7.41, N 9.64.

Methyl 3-(1-Hydroxylheptyl)-3-devinylpyropheophorbide-*a* (4c)

This compound **4c** was obtained from Grignard reaction of **3** using hexyl magnesium bromide as a dark green solid. mp 212-214 °C (chloroform-*n*-hexane); Yield 61%; UV-vis ($CHCl_3$) λ_{max}: 288 (0.36), 411 (1.00), 505 (0.14), 536 (0.12), 605 (0.10), 661 (0.48) nm; ^{1}H NMR (300 MHz, $CDCI_3$) δ: -1.94 (br s, 1H, NH), 0.07 (br s, 1H, NH), 0.83 (t, *J* = 6.8 Hz, 3H, 3g-H), 1.68 (t, *J* = 7.4 Hz, 3H, 8b-H), 1.77 (d, *J* = 7.6 Hz, 3H, 18-CH_3), 1.38-2.89 (m, 14H, 2b~f-H+17a+17b-H), 3.20 (s, 3H, CH_3), 3.36 (s, 3H, CH_3), 3.60 (s, 3H, OCH_3), 3.64 (s, 3H, CH_3), 3.68 (q, *J* = 7.4 Hz, 2H, 8a-H), 4.10-4.28 (m, 1H, 18-H), 4.30-4.50 (m, 1H, 17-H), 5.03 (d, *J* = 17.3 Hz, 1H, 13^2-H), 5.14 (d, *J* = 17.3 Hz, 1H, 13^2-H), 6.11-6.25 (m, 1H, 3a-H), 8.57, 9.45, 9.72 (s, each 1H, meso-H); IR (KBr) ν: 1739, 1730 (C=O), 1610 (C=C), 1551 (chlorin skeleton), 1466, 1359, 1290, 982 cm^{-1}. Anal. Calcd for $C_{39}H_{48}N_4O_4$: C 73.56, H 7.60, N 8.80. Found C 72.39, H 7.41, N 8.99.

Methyl 3-Pentylcarbonyl-3-devinylpyropheophorbide-*a* (5a)

A mixture of **4b** (128 mg, 0.21 mmol) and N-methylmorpholine N-oxide (40 mg) in dichloromethane (25 mL) was stirred for 15 minutes at room temperature under nitrogen. After adding tetrapropylammonium perruthenate (TPAP, 15 mg) was added, and the stirring was continued for an additional 1 hour. The mixture was washed with water and dried over sodium sulfate. The evaporation residue was chromatographed on silica gel initially with dichloromethane to remove excess *N*-methylmopholine N-oxide and then with 1% methanol-dichloromethane to give **7** (87 mg, 68%) as a dark green solid; mp 216-219 °C; UV-vis ($CHCl_3$) λ_{max}: 408 (1.00), 504 (0.11), 545 (0.09), 5.77 (0.08), 657 (0.24), 689 (0.59) nm; ^{1}H NMR (300 MHz, $CDCI_3$) δ: -2.18 (br s, 1H, NH), -0.12 (br s, 1H, NH), 0.87 (t, *J* = 6.9 Hz, 3H, 3e-H), 1.64 (t, *J* = 7.6 Hz, 3H, 8b-H), 1.78 (d, *J* = 7.2 Hz, 3H, 18-CH_3), 1.50-2.95 (m, 10H, 2b~d-H+17a+17b-H), 3.21 (s, 3H, CH_3), 3.36 (s, 3H, CH_3), 3.58 (s, 3H, OCH_3), 3.60 (s, 3H, CH_3), 3.66 (q, *J* = 7.6 Hz, 2H, 8a-H), 4.20-4.36 (m, 1H, 18-H), 4.40-4.58 (m, 1H, 17-H), 5.10 (d, *J* = 19.5 Hz, 1H, 13^2-H), 5.25 (d, *J* = 19.5 Hz, 1H, 13^2-H), 8.71, 9.45, 9.88 (s, each 1H, meso-H); IR (KBr) ν: 1740-1698 (C=O), 1619 (C=C), 1563 (chlorin skeleton), 1458, 1370, 1298, 958 cm^{-1}. Anal. Calcd for $C_{37}H_{42}N_4O_4$: C 73.24, H 6.98, N 9.23. Found C 73.50, H 7.76, N 9.47.

Methyl 3-Heptylcarbonyl-3-devinylpyropheophorbide-*a* (5b)

This compound **5b** was obtained from oxidation reaction of **4c** with N-methylmorpholine N-oxide and tetrapropylammonium perruthenate as a dark green solid. mp 202-204 °C (chloroform-*n*-hexane); Yield 62%; UV-vis ($CHCl_3$) λ_{max}: 409 (1.01), 508 (0.07), 579 (0.08), 654 (0.22), 689 (0.57) nm; ^{1}H NMR (300 MHz, $CDCI_3$) δ: -2.14 (br s, 1H, NH), -0.11 (br s, 1H, NH), 0.88 (t, *J* = 6.8 Hz, 3H, 3g-H), 1.65 (t, *J* = 7.5 Hz, 3H, 8b-H), 1.77 (d, *J* = 7.4 Hz, 3H, 18-CH_3), 1.49-2.98 (m, 14H, 2b~f-H+17a+17b-H), 3.20 (s, 3H, CH_3), 3.34 (s, 3H, CH_3), 3.57 (s, 3H, OCH_3), 3.62 (s, 3H, CH_3), 3.66 (q, *J* = 7.5 Hz, 2H, 8a-H), 4.20-4.40 (m, 1H, 18-H), 4.43-4.59 (m, 1H, 17-H), 5.10 (d, *J* = 19.5 Hz, 1H, 13^2-H), 5.18 (d, *J* = 19.5 Hz, 1H, 13^2-H), 8.72, 9.49, 9.91 (s, each 1H, meso-H); IR (KBr) ν: 1741-1698 (C=O), 1616 (C=C), 1560 (chlorin skeleton), 1460, 1371, 1284, 962 cm^{-1}. Anal. Calcd for $C_{39}H_{46}N_4O_4$: C 73.79, H 7.30, N 8.83. Found C 73.58, H 7.30, N 9.04.

The insertion of metal nickel(II) ion in chlorin (2, 4a~b and 5a~b) to form nickel chlorin (6a~e)
General procedure

To a saturated solution of $Ni(AcO)_2$ in methanol (10 mL) was added chlorin (0.2 mmol) in methylenechloride (20 mL). The mixture was then stirred at 50 °C for 12 hours. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was chromatographed on silica-gel with hexane-ethyl acetate (4:1) to give corresponding nickel complex **6a~e** in above 90% yield, which were directly used for the next Vilsmeier reaction without identification.

The Vilsmeier reaction of nickel chlorin (6a~e)
General procedure
Nickel(II) 3-(2,2-dimethoxylethyl)-20-formylvinyl-3-devinylpyropheophorbide-*a* methyl ester (7a)

Phosphorus oxychloride (0.4 mL, 4.0 mmol) was added dropwise to a solution of 3-(dimethylamino)acrolein (0.4 mL, 4.0 mmol) in dichloromethane (4.0 mL), and the mixture

was stirred at 0 °C for 15 minutes. This mixture was then added to a solution of nickel chlorin **6a** (94 mg, 0.14 mmol) in dichloromethane (20 mL) with continuous stirring at 0 °C. The final mixture was then warmed up to room temperature and stirred for 18 hours. Saturated aqueous sodium carbonate (100 mL) was then added, and the solution was stirred overnight. The mixture was extracted with dichloromethane; the combined organic layers were washed with water (3 × 200 mL) and dried over anhydrous sodium sulfate, and the solvent was removed under vacuum. The resulting residue was chromatographed on silica gel with hexane-ethyl acetate (3:1) to give **7a** as a dark green solid (79 mg, 78%); mp 156-157 °C; UV-vis ($CHCl_3$) λ_{max}: 413 (1.00), 605 (0.27), 692 (0.62) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.40 (t, *J* = 7.4 Hz, 3H, 8b-H), 1.43 (d, *J* = 7.6 Hz, 3H, 18-CH_3), 1.82-2.46 (m, 4H, 17a+17b-H), 2.74 (s, 3H, CH_3), 2.90 (s, 3H, CH_3), 3.24 (s, 3H, CH_3), 3.22-3.48 (m, 1H, 17-H), 3.57 (s, 6H, 2 × OCH_3), 3.72 (q, *J* = 7.2 Hz, 2H, 8a-H), 3.90 (s, 3H, OCH_3), 4.15 (d, *J* = 5.7, 1.9 Hz, 3a-H), 4.35-4.48 (m, 1H, 18-H), 4.42 (d, *J* = 19.3 Hz, 1H, 13^2-H), 4.45 (t, *J* = 5.7 Hz, 3b-H), 4.60 (d, *J* = 19.3 Hz, 1H, 13^2-H), 5.79 (dd, *J* = 15.4, 7.8 Hz, 1H, 20b-H), 8.36 (d, *J* = 15.4 Hz, 20a-H), 8.58, 8.88 (s, each 1H, meso-H), 9.69 (d, *J* = 7.8 Hz, 20c-H); IR (KBr) ν: 1739-1670 (C=O), 1625 (C=C), 1573 (chlorin skeleton), 1450, 1368, 1298, 984 cm^{-1}. Anal. Calcd for $C_{39}H_{42}N_4NiO_6$: C 64.93, H 5.87, N 7.77. Found C 64.73, H 5.69, N 7.52.

Nickel(II) 3-pentylcarbonyl-20-formylvinyl-3-devinyl-pyropheophorbide-*a* methyl ester (7b)

This compound was obtained from the nickel complex **6b** as a green solid (70%); mp 143-145 °C; UV-vis ($CHCl_3$) λ_{max}: 416 (1.00), 436 (0.97), 605 (0.26), 712 (0.72) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.86 (t, *J* = 7.0 Hz, 3d-CH_3), 1.43 (t, *J* = 7.5 Hz, 3H, 8b-H), 1.42-1.79 (m, 4H, 3c~d-H), 1.46 (d, *J* = 7.4 Hz, 3H, 18-CH_3), 1.88-2.48 (m, 6H, 3b-H+17a+17b-H), 2.95 (s, 3H, CH_3), 3.06 (s, 3H, CH_3), 3.30 (s, 3H, CH_3), 3.24-3.55 (m, 1H, 17-H), 3.59 (s, 3H, OCH_3), 3.78 (q, *J* = 7.5 Hz, 2H, 8a-H), 4.43-4.60 (m, 1H, 18-H), 4.47 (d, *J* = 19.8 Hz, 1H, 13^2-H), 4.68 (d, *J* = 19.8 Hz, 1H, 13^2-H), 5.76 (dd, *J* = 15.8, 7.6 Hz, 1H, 20b-H), 8.44 (d, *J* = 15.8 Hz, 20a-H), 8.97, 9.26 (s, each 1H, meso-H), 9.72 (d, *J* = 7.6 Hz, 20c-H); IR (KBr) ν: 1738-1669 (C=O), 1640 (C=C), 1568 (chlorin skeleton), 1440, 1344, 1270, 987 cm^{-1}. Anal. Calcd for $C_{40}H_{42}N_4NiO_5$: C 66.96, H 5.90, N 7.81. Found C 66.76, H 5.73, N 7.70.

Nickel(II) 3-heptylcarbonyl-20-formylvinyl-3-devinyl-pyropheophorbide-*a* methyl ester (7c)

This compound was obtained from the nickel complex **6c** as a green solid (70%); mp 152-153 °C; UV-vis ($CHCl_3$) λ_{max}: 417 (1.00), 435 (0.96), 606 (0.26), 712 (0.73) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.84 (t, *J* = 7.2 Hz, 3g-CH_3), 1.41 (t, *J* = 7.5 Hz, 3H, 8b-H), 1.39-1.80 (m, 8H, 3c~e-H), 1.43 (d, *J* = 7.4 Hz, 3H, 18-CH_3), 1.82-2.49 (m, 6H, 3b-H+17a+17b-H), 2.96 (s, 3H, CH_3), 3.04 (s, 3H, CH_3), 3.31 (s, 3H, CH_3), 3.22-3.57 (m, 1H, 17-H), 3.59 (s, 3H, OCH_3), 3.74 (q, *J* = 7.5 Hz, 2H, 8a-H), 4.42-4.61 (m, 1H, 18-H), 4.46 (d, *J* = 19.8 Hz, 1H, 13^2-H), 4.70 (d, *J* = 19.8 Hz, 1H, 13^2-H), 5.77 (dd, *J* = 15.8, 7.6 Hz, 1H, 20b-H), 8.46 (d, *J* = 15.8 Hz, 20a-H), 8.96, 9.28 (s, each 1H, meso-H), 9.74 (d, *J* = 7.6 Hz, 20c-H); IR (KBr) ν: 1739-1666 (C=O), 1638 (C=C), 1566 (chlorin skeleton), 1442, 1340, 1274, 982 cm^{-1}. Anal. Calcd for $C_{42}H_{46}N_4NiO_5$: C 67.66, H 6.22, N 7.52. Found C 67.48, H 6.03, N 7.79.

Nickel(II) 3-(1-hydroxylethyl)-20-formylvinyl-3-devinyl-pyropheophorbide-*a* methyl ester (8a) and Nickel(II) 20-formylvinylpyropheophorbide-*a* methyl ester (9a)

These two compounds were obtained from the nickel complex **6d** as a green solid in 42% and 26% yield, respectively. **8a**: mp 168-171 °C; UV-vis ($CHCl_3$) λ_{max}: 413 (0.99), 432 (1.00), 605 (0.26), 687 (0.67) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.40 (t, *J* = 7.5 Hz, 3H, 8b-H), 1.42 (d, *J* = 6.5 Hz, 3H, 18-CH_3), 1.79 (d, *J* = 6.5 Hz, 3a-CH_3), 1.89-2.51 (m, 4H, 17a+17b-H), 2.93 (s, 3H, CH_3), 2.79 (s, 3H, CH_3), 3.26 (s, 3H, CH_3), 3.26-3.48 (m, 1H, 17-H), 3.56 (s, 3H, OCH_3), 3.72 (q, *J* = 7.5 Hz, 2H, 8a-H), 4.30-4.48 (m, 1H, 18-H), 4.39 (d, *J* = 19.8 Hz, 1H, 13^2-H), 4.61 (d, *J* = 19.8 Hz, 1H, 13^2-H), 5.71 (dd, *J* = 16.0, 8.0 Hz, 1H, 20b-H), 8.39 (d, *J* = 16.0 Hz, 20a-H), 8.92, 9.31 (s, each 1H, meso-H), 9.69 (d, *J* = 8.0 Hz, 20c-H); IR (KBr) ν: 1740-1670 (C=O), 1645 (C=C), 1566 (chlorin skeleton), 1460, 1333, 1256, 989 cm^{-1}. Anal. Calcd for $C_{37}H_{38}N_4NiO_5$: C 65.60, H 5.65, N 8.27. Found C 65.34, H 5.41, N 8.04. **9a**: mp 147-150 °C; UV-vis ($CHCl_3$) λ_{max}: 409 (1.00), 604 (0.19), 694 (0.67) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.42 (d, *J* = 7.1 Hz, 3H, 8b-H), 1.45 (t, *J* = 7.3 Hz, 3H, 18-CH_3), 1.82-2.45 (m, 4H, 17a+17b-H), 2.81 (s, 3H, CH_3), 2.91 (s, 3H, CH_3), 3.25 (s, 3H, CH_3), 3.54 (q, *J* = 7.5 Hz, 2H, 8a-H), 3.57 (s, 3H, OCH_3), 3.60-3.78 (m, 1H, 17-H), 4.32-4.50 (m, 1H, 18-H), 4.45 (d, *J* = 20.0 Hz, 1H, 13^2-H), 4.62 (d, *J*=20.0 Hz, 1H, 13^2-H), 5.71-5.93 (m, 3H, 3b-H+20b-H), 7.38-7.50 (m, 1H, 3a-H), 8.40 (d, *J* = 15.6 Hz, 1H, 20a-H), 8.74, 8.92 (s, each 1H, meso-H), 9.70 (d, *J* = 7.8 Hz, 1H, 20c-H); IR (KBr) ν: 1740-1668 (C=O), 1645 (C=C), 1570 (chlorin skeleton), 1455, 1323, 1241, 992 cm^{-1}. Anal. Calcd for $C_{37}H_{36}N_4NiO_4$: C 67.39, H 5.50, N 8.50. Found C 67.18, H 5.35, N 8.29.

Nickel(II) 3-(1-hydroxylpentyl)-3-devinyl-20-formylvinyl-pyropheophorbide-*a* methyl ester (8b) and Nickel(II) (*E*)-3-propyl-20-formylvinylpyropheophorbide-*a* methyl ester (9b)

These two compounds were obtained from the nickel complex **6e** as a green solid in 48% and 16% yield, respectively. **8b**: mp 176-179 °C; UV-vis ($CHCl_3$) λ_{max}: 413 (0.99), 432 (1.00), 605 (0.26), 687 (0.67) nm; ^{1}H NMR (300 MHz, $CDCI_3$) δ: 0.88 (t, *J* = 6.9 Hz, 3H, 3e-CH_3), 1.40 (t, *J* = 7.3 Hz, 3H, 8b-H), 1.44 (d, *J* = 7.0 Hz, 3H, 18-CH_3), 1.45-1.83 (m, 4H, 3c~d-H), 1.81-2.55 (m, 6H, 3b-H+17a+17b-H), 2.95 (s, 3H, CH_3), 2.81 (s, 3H, CH_3), 3.26 (s, 3H, CH_3), 3.30-3.51 (m, 1H, 17-H), 3.56 (s, 3H, OCH_3), 3.70 (q, *J* = 7.3 Hz, 2H, 8a-H), 4.27-4.47 (m, 1H, 18-H), 4.40 (d, *J* = 19.5 Hz, 1H, 13^2-H), 4.62 (d, *J* = 19.5 Hz, 1H, 13^2-H), 5.72 (dd, *J* = 15.8, 7.8 Hz, 1H, 20b-H), 8.40 (d, *J* = 15.8 Hz, 1H, 20a-H), 8.93, 9.33 (s, each 1H, meso-H), 9.70 (d, *J* = 7.8 Hz, 1H, 20c-H); IR (KBr) ν: 1739-1671 (C=O), 1648 (C=C), 1570 (chlorin skeleton), 1455, 1327, 1236, 992 cm^{-1}. Anal. Calcd for $C_{40}H_{44}N_4NiO_5$: C 66.77, H 6.16, N 7.79. Found C 66.58, H 5.88, N 7.57. **9b**: mp 138-141 °C; UV-vis ($CHCl_3$) λ_{max}: 414 (1.00), 529 (0.22), 645 (0.30), 693 (0.70) nm; ^{1}H NMR (300 MHz, $CDCI_3$) δ: 0.92 (t, *J* = 6.9 Hz, 3H, 3e-CH_3), 1.40 (d, *J* = 7.4 Hz, 3H, 8b-H), 1.44 (t, *J* = 7.4 Hz, 3H, 18-CH_3), 1.40-1.79 (m, 4H, 3c~d-H), 1.85-2.68 (m, 4H, 17a+17b-H), 2.77 (s, 3H, CH_3), 2.90 (s, 3H, CH_3), 3.24 (s, 3H, CH_3), 3.70 (q, *J* = 7.4 Hz, 2H, 8a-H), 3.57 (s, 3H, OCH_3), 3.29-3.48 (m, 1H, 17-H), 4.34-4.49 (m, 1H, 18-H), 4.40 (d, *J* = 19.8 Hz, 1H, 13^2-H), 4.61 (d, *J* = 19.8 Hz, 1H, 13^2-H), 5.77 (dd, *J* = 15.6, 7.8 Hz, 1H, 20b-H), 6.26 (dt, *J* = 16.2, 7.0 Hz, 1H, 3b-H), 7.08 (d, *J* = 16.2 Hz, 1H, 3a-H), 8.37 (d, *J* = 15.6 Hz, 1H, 20a-H), 8.66, 8.89 (s, each 1H, meso-H), 9.70 (d, *J* = 7.8 Hz, 1H, 20c-H); IR (KBr) ν: 1739-1671 (C=O), 1648 (C=C), 1566 (chlorin skeleton), 1445, 1338, 1252, 990 cm^{-1}. Anal. Calcd for $C_{40}H_{42}N_4NiO_4$: C 68.49, H 6.03, N 7.99. Found C 68.20, H 5.89, N 8.12.

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