Synthesis of Chlorophyll-*a* Skeleton Homologs Using Grignard Reaction with Methyl Pyropheophorbide-*a*

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From methyl pyropheophorbide-*a* (MPPa) (**1**), methyl 2-formylmethyl-2-devinyl-9-ethylenedioxy-9-deoxopyropheophorbide-*a* (**2**) and methyl 3-acetyl-9-ethylenedioxy-2-devinyl-9-deoxopyropheophorbide-*a* (**3**) were prepared. The Grignard reactions of **2** and **3** were performed using cycloalkyl magnesium bromides to afford cycloalkyl-substituted *sec*-alcohol **4** and *tert*-alcohols **9a**-**c**, respectively. By the deprotection of the ethylenedioxy group, these alcohols were respectively converted to exocyclic ketones **5** and **10a**-**c**, which were dehydrated to give chlorins **6** and **11a**-**c** having an alkenyl function at the 2-position. On the other hand, the oxidation and deprotection of the alcohol **4** gave a diketo chlorin **8**.

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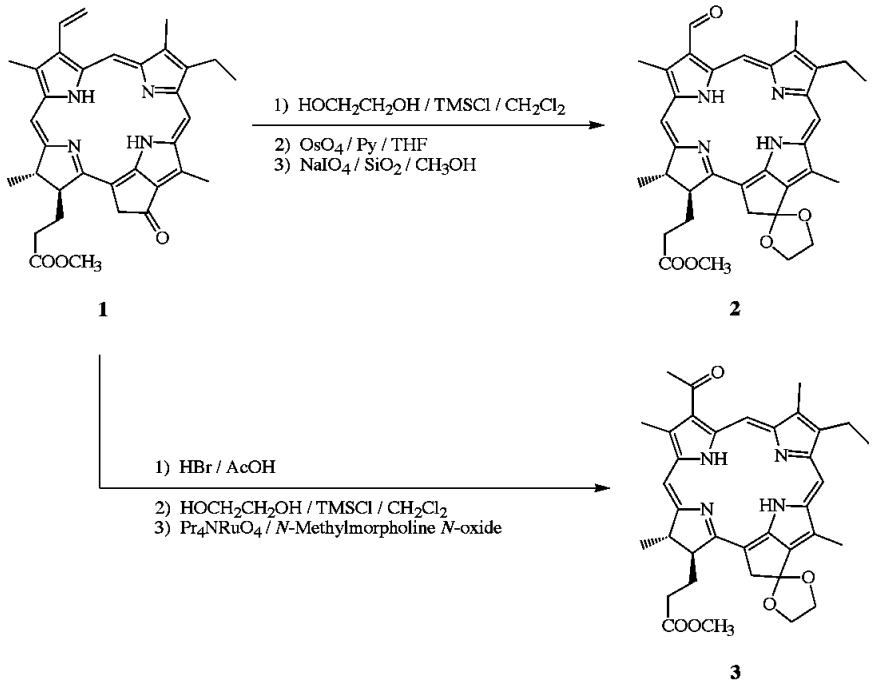
Photodynamic therapy (PDT) is a kind of medical treatments which employ the light, drugs, and/or tumorlocalizing photosensitizer, to bring about a cytotoxic or modifying effect to cancerous or other unwanted tissue [1,2]. The emphasis for development of new anticancer drugs associated with PDT has been concentrated on the molecular design, chemical synthesis, and biological examination of natural chlorins, which stand in marked contrast to symmetric porphyrin due to substantially stabilized S_1-energies, a strong Qy-absorption band, and unique redox reactivities. Recently, many studies have been carried out in order to construct chlorins based photosensitizers with a variety of substituents on the periphery of the parent ring. The experimental data has shown that the presence and position of the substituents in the parent molecule make a remarkable difference in the biological activities

Recently, in a congeneric series of the alkyl ether derivatives of pyropheophorbide-*a*, it was observed that the *in vitro* photodynamic efficacy increased by extending the length of the carbon chain, and different substituents in other carbon derivatives also play an important role in tumor uptake and tumor selectivity [3-6]. These studies suggested that constructions of special structures on the chlorin parent ring should provide valuable information for developing new photosensitizers in photodynamic therapy. As a part of our research program, a variety of cycloparaffin structures were selected as a substituted alkyl group to introduce to chlorin chromophore in consideration of their lengths and geometric space of alkyl carbon chain for improving their physicochemical properties.

In this approach, methyl pyropheophorbide-*a* (MPPa) (**1**) was used as a starting material. To avoid the influence of exocyclic carbonyl group on the following reactions, this group was protected first with ethylene glycol using trimethylsilyl chloride as catalyst to give acetal, which was oxidized with osmium(VIII) oxide in tetrahydrofuran containing catalytic pyridine at 0 °C followed by glycol cleavage with sodium periodate in aqueous tetrahydrofuran to give the aldehyde **2**. MPPa **1** reacted with 30% hydrobromic acid in acetic acid to form a chlorin alcohol. After protecting for the exocyclic carbonyl group, the alcohol was oxidized with tetrapropylammonium perruthenate and *N*-methylmorpholine *N*-oxide to generate 2-acetyl-substituted chlorin **3** [7] (Scheme 1).

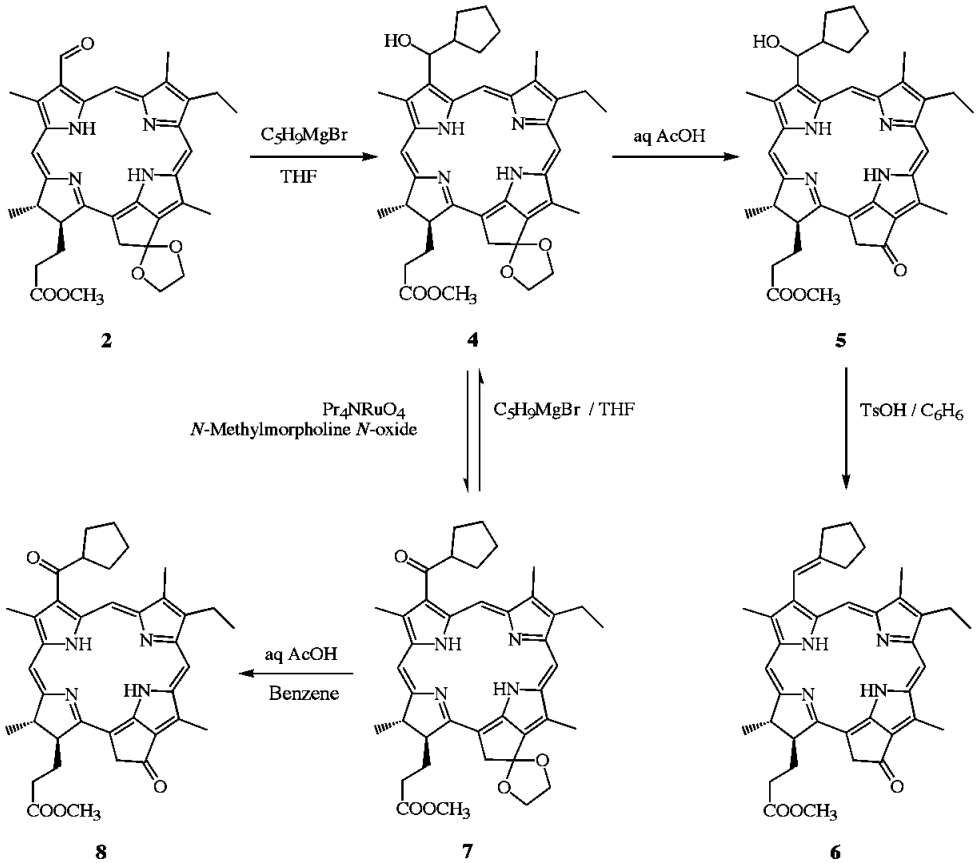
In order to introduce the cycloparaffin moiety on the chlorin parent ring, the aldehyde **2** was treated with cyclopentyl magnesium bromide in tetrahydrofuran at 0 °C to form a *sec*-alcohol **4**. The deprotection of **4** in 60% acetic acid at 45 °C completed to generate a ketol **5**, the cycloalkylidene-substituted pyropheophorbide-*a* **6** was also obtained by the dehydration of **5** in benzene in the presence of *p*-toluenesulfonic acid. The hydroxyl group at

Scheme 1



1 **2** **3**

Scheme 2



2 **4** **5** **8** **7** **6**

the 2-position of **4** was converted into carbonyl group by oxidation with tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide. Thus, the acetal-keto compound **7** was obtained in 60% yield. The deprotection of **7** gave a diketo chlorin **8** (Scheme 2).

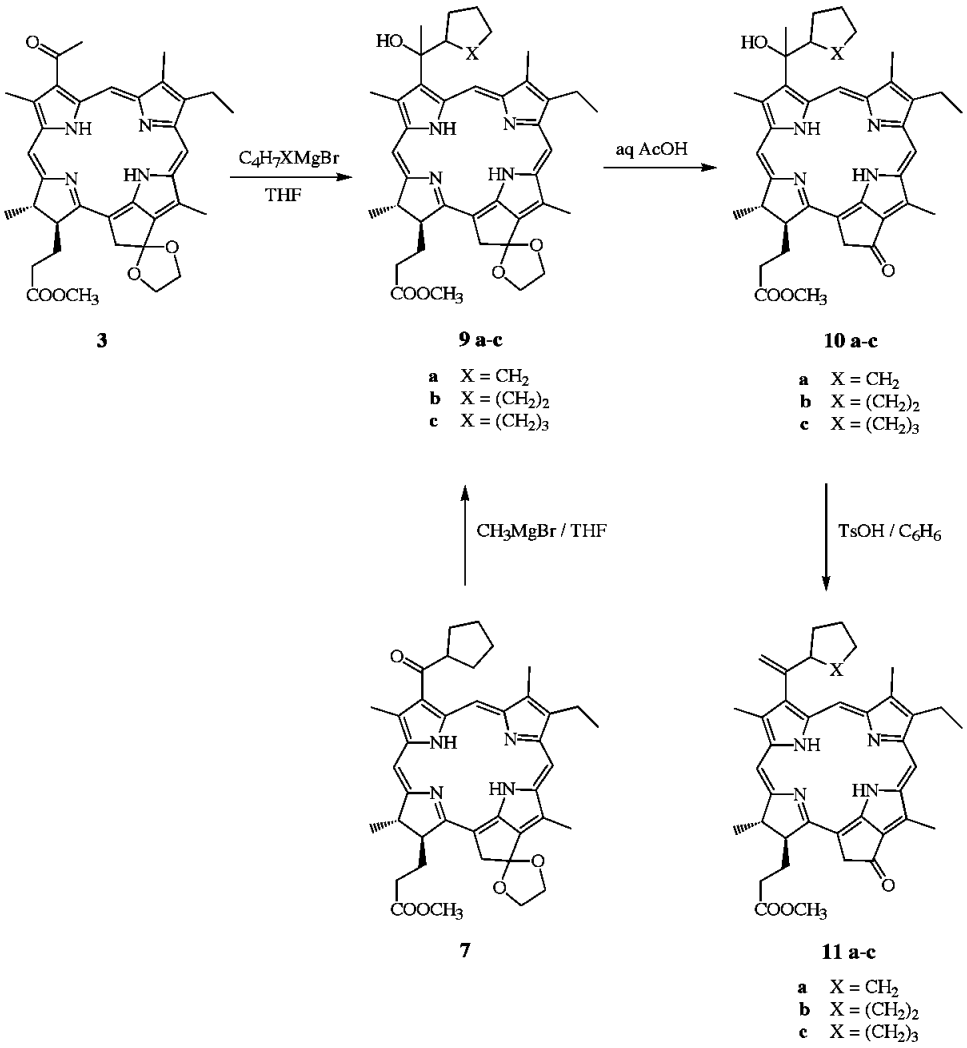
Similarly, the Grignard reactions of compound **3** with cycloalkyl magnesium bromides in tetrahydrofuran at room temperature afforded *tert*-alcohols **9a-c** in mild yields. The deprotection reactions of compounds **9a-c** were fulfilled under acidic condition to give keto alcohols **10a-c**, which were converted into 2a-cycloalkyl-substituted pyropheophorbide-*a*'s **11a-c** by heating in benzene under the acidic conditions (Scheme 3).

In order to synthesize chlorins having two alkyl and/or cycloalkyl functions at the 2-position, the Grignard reactions of the acetal-keto compound **7** were also carried out by using methyl magnesium bromide and cyclopentyl magnesium bromide in tetrahydrofuran at 0 °C, respectively. It was found that the reactions depended on the bulkiness of the Grignard reagent. When the methyl magnesium bromide was used, a normal additive product **9** was obtained. However, the reaction of **7** with cyclopentyl magnesium bromide showed that reduction took place to give the *sec*-alcohol **4** because the cyclopentyl group was more sterically bulky (in Scheme 2).

EXPERIMENTAL

The ir spectra were measured with a Shimadzu FT IR 8300 spectrophotometer. The uv-vis spectra were taken with a Unicam SP 800 spectrophotometer. The ^{1}H nmr spectra were recorded with a Varian 300 spectrometer. The elemental analyses were performed on a Perkin-Elmer 240 microanalyzer. All chemical reagents were commercially available and purified by using standard methods. Solvents were dried in routine ways and redistilled. Methyl pyropheophorbide-*a* (MPPa) (**1**) was obtained according to Smith's method [8]. The compounds **2** and **3** were also prepared as described in reference [7].

Scheme 3



Methyl 2-Cyclopentylhydroxymethyl-9-ethylenedioxyl-2-devinyl-9-deoxopyropheophorbide-*a* (**4**).

To a solution of compound **2** (149 mg, 0.250 mmol) in tetrahydrofuran (15 mL) was added 1 mol/L cyclopentyl magnesium bromide in tetrahydrofuran (0.35 mL) at 0 °C. After stirring for 25 minute, the mixture was poured into an ice-cooled aqueous ammonium chloride solution. The aqueous layer was extracted with diethyl ether. The combined organic layer was dried over sodium sulfate. After evaporation of the solvent, the residue was chromatographed on a silica gel column with hexane-ethyl acetate (3:1) to give **4** (113 mg, 68%) as a dark green solid (from chloroform-hexane); mp 224-227 °C; ir (potassium bromide): ν 1740 (C=O), 1608 (C=C), 1517 (chlorin skeleton), 1441, 1395, 1308, 1251, 1207, 1163, 1110 cm^{-1}; uv-vis (chloroform): λ (log ε) 305 (3.50), 413 (4.58), 528 (3.15), 567 (3.15), 598 (3.18), 648 nm (4.03); ^{1}H nmr (deuteriochloroform): δ -3.25 (1H, br.s, NH), -1.28 (1H, br.s, NH), 1.48-1.78 (9H, m, cyclopentyl-H), 1.68 (3H, t, J = 7.6 Hz, 4b-CH_3), 1.75 (3H, d, J = 7.2 Hz, 8-CH_3), 2.09-2.42 (2H, m, 7a-CH_2), 2.47-2.79 (2H, m, 7b-CH_2), 3.34 (3H, s, CH_3), 3.50 (3H, s, CH_3), 3.53 (3H, s, CH_3), 3.57 (3H, s, $COCH_3$), 3.76 (2H, q, J = 7.6 Hz, 4a-CH_2), 4.37-4.69 (6H, m, 7-,8-H, OCH_2CH_2O), 5.01 (1H, d, J = 18.2 Hz, 10-H_a), 5.09 (1H, d, J = 18.2 Hz, 10-H_b), 5.98 (1H, d, J = 9.9 Hz, 2a-CH), 8.77 (1H, s, meso-H), 9.61 (1H, s, meso-H), 10.00 (1H, s, meso-H).

Anal. Calcd for $C_{40}H_{48}N_4O_5$: C, 72.26; H, 7.28; N, 8.43. Found: C, 72.50; H, 7.52; N, 8.22.

Methyl 2-Cyclopentylhydroxymethyl-2-devinylpyropheophorbide-*a* (**5**).

A solution of compound **4** (110 mg, 0.165 mmol) in 60% acetic acid (25 mL) was stirred for 1 hour at 45 °C in the dark. The mixture was poured into an ice-cooled water and extracted with dichloromethane. After washing with water, the organic layer was dried over sodium sulfate. After removal of the solvent, the crude product was purified with a silica gel column with hexane-ethyl acetate (3:1) to give **5** (93 mg, 90%) as a dark green solid (from chloroform-hexane); mp 232-234 °C; ir (potassium bromide): ν 1744 (C=O), 1734 (C=O), 1608 (C=C), 1518 (chlorin skeleton), 1439, 1390, 1313, 1250, 1207, 1163, 1109 cm^{-1}; uv-vis (chloroform): λ (log ε) 410 (4.58), 505 (3.05), 536 (3.03), 604 (3.01), 660 nm (3.09); ^{1}H nmr (deuteriochloroform): δ -1.89 (1H, br.s, NH), 0.05 (1H, br.s, NH), 1.46-1.78 (9H, m, cyclopentyl-H), 1.63 (3H, d, J = 7.3 Hz, 8-CH_3), 1.73 (3H, t, J = 6.9 Hz, 4b-CH_3), 2.06-2.38 (2H, m, 7a-CH_2), 2.40-2.78 (2H, m, 7b-CH_2), 3.20 (3H, s, CH_3), 3.36 (3H, s, CH_3), 3.59 (3H, s, CH_3), 3.64 (3H, s, $COOCH_3$), 3.65 (2H, q, J = 6.9 Hz, 4a-CH_2), 4.18-4.29 (1H, m, 7-H), 4.30-4.49 (1H, m, 8-H), 5.08 (1H, d, J = 17.9 Hz, 10-H_a), 5.16 (1H, d, J = 17.9 Hz, 10-H_b), 5.82 (1H, d, J = 10.0 Hz, 2a-CH), 8.46 (1H, s, meso-H), 9.43 (1H, s, meso-H), 9.64 (1H, s, meso-H).

Anal. Calcd for $C_{38}H_{44}N_4O_4$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.77; H, 7.35; N, 9.22.

Methyl 2-Cyclopentylidene-2-devinylpyropheophorbide-*a* (**6**).

A solution of compound **5** (100 mg, 0.161 mmol) in benzene (25 mL) was stirred for 1 hour at 90 °C in the presence of *p*-toluenesulfonic acid (3 mg). After adding water (20 mL) and dichloromethane (25 mL) to the reaction mixture, the organic layer was separated and dried over sodium sulfate. The evaporation residue was chromatographed on a silica gel column with chloroform-hexane (3:1) to give **6** (72 mg, 74%) as a dark green solid (from chloroform-hexane); mp 207-209 °C; ir (potassium bromide): ν 1734 (C=O), 1727 (C=O), 1608 (C=C), 1516 (chlorin skeleton), 1444, 1397, 1310, 1248, 1210, 1161, 1118 cm^{-1}; uv-vis (chloroform): λ (log ε) 414 (5.34), 509 (3.24), 539 (3.18), 609 (3.13), 665 nm (4.40); ^{1}H nmr (deuteriochloroform): δ -1.78 (1H, br.s, NH), 0.05 (1H, br.s, NH), 1.46-1.78 (9H, m, cyclopentyl-H), 1.68 (3H, t, J = 7.6 Hz, 4b-CH_3), 1.81 (3H, d, J = 7.3 Hz, 8-CH_3), 2.04-2.15 (2H, m, 7a-CH_2), 3.26 (3H, s, CH_3), 3.57 (3H, s, CH_3), 3.59 (3H, s, CH_3), 3.69 (3H, s, $COOCH_3$), 3.66 (2H, q, J = 7.6 Hz, 4a-CH_2), 4.20-4.31 (1H, m, 7-H), 4.33-4.52 (1H, m, 8-H), 5.15 (1H, d, J = 20.1 Hz, 10-H_a), 5.30 (1H, d, J = 20.1 Hz, 10-H_b), 7.85 (1H, d, J = 10.1 Hz, 2a-CH), 8.72 (1H, s, meso-H), 9.59 (1H, s, meso-H), 9.79 (1H, s, meso-H).

Anal. Calcd for $C_{38}H_{42}N_4O_3$: C, 75.72; H, 7.02; N, 9.30. Found: C, 75.87; H, 7.22; N, 9.12.

Methyl 2-Cyclopentylcarbonyl-9-ethylenedioxy-2-devinyl-9-deoxopyropheophorbide-*a* (**7**).

A mixture of **4** (120 mg, 0.181 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 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*-methylmorpholine *N*-oxide and then with 1% methanol-dichloromethane to give **7** (73 mg, 61%) as a dark green solid (from chloroform-hexane); mp 196-198 °C; ir (potassium bromide): ν 1742 (C=O), 1736 (C=O), 1608 (C=C), 1510 (chlorin skeleton), 1444, 1389, 1309, 1251, 1211, 1168, 1108 cm^{-1}; uv-vis (chloroform): λ (log ε) 404 (5.22), 505 (3.13), 541 (2.98), 610 (2.97), 662 nm (3.55); ^{1}H nmr (deuteriochloroform): δ -3.07 (1H, br.s, NH), -1.27 (1H, br.s, NH), 1.68-2.03 (4H, m, cyclopentyl-H), 1.73 (3H, t, J = 7.6 Hz, 4b-CH_3), 1.82 (3H, d, J = 7.3 Hz, 8-CH_3), 2.15-2.44 (7H, m, cyclopentyl-H + 7a-H), 2.25-2.78 (2H, m, 7b-CH_2), 3.36 (3H, s, CH_3), 3.58 (3H, s, CH_3), 3.62 (3H, s, CH_3), 3.65 (3H, s, $COOCH_3$), 3.81 (2H, q, J = 7.6 Hz, 4a-CH_2), 3.82-4.67 (6H, m, 7-,8-H + OCH_2CH_2O), 5.06 (1H, d, J = 18.8 Hz, 10-H_a), 5.15 (1H, d, J = 18.8 Hz, 10-H_b), 8.93 (1H, s, meso-H), 9.65 (1H, s, meso-H), 9.98 (1H, s, meso-H).

Anal. Calcd for $C_{40}H_{46}N_4O_5$: C, 72.48; H, 7.00; N, 8.45. Found: C, 72.65; H, 6.81; N, 8.75.

Methyl 2-Cyclopentylcarbonyl-2-devinylpyropheophorbide-*a* (**8**).

A solution of compound **7** (70 mg, 0.106 mg) in 60% acetic acid (25 mL) was stirred for 1 hour at 45 °C in the dark. The mixture was poured into an ice-cooled water and extracted with dichloromethane. After washing with water, the organic layer was dried over sodium sulfate. The crude product was chromatographed on silica gel column with hexane-ethyl acetate (3:1) to give **8** (59 mg, 90%) as a dark green solid (from chloroform-hexane); mp 213-215 °C; ir (potassium bromide): ν 1745 (C=O), 1731 (C=O), 1727 (C=O), 1606 (C=C), 1519 (chlorin skeleton), 1438, 1388, 1303, 1249, 1211, 1166, 1107 cm^{-1}; uv-vis (chloroform): λ (log ε) 326 (3.56), 413 (5.41), 513 (3.19), 547 (3.13), 623 (3.05), 682 nm (4.09); ^{1}H nmr (deuteriochloroform): δ -2.00 (1H, br.s, NH), -0.06 (1H, br.s, NH), 1.68 (3H, t, J = 7.7 Hz, 4b-CH_3), 1.70-2.09 (4H, m, cyclopentyl-H), 1.81 (3H, d, J = 7.2 Hz, 8-CH_3), 2.12-2.39 (7H, m, cyclopentyl-H + 7a-CH_2), 2.47-2.77 (2H, m, 7b-CH_2), 3.23 (3H, s, CH_3), 3.54 (3H, s, CH_3), 3.59 (3H, s,

CH_3), 3.67 (3H, s, $COOCH_3$), 3.71 (2H, q, *J* = 7.7 Hz, 4a-CH_2), 4.21-4.38 (1H, m, 7-H), 4.51-4.59 (1H, m, 8-H), 5.14 (1H, d, *J* = 20.0 Hz, 10-H_a), 5.29 (1H, d, *J* = 20.0 Hz, 10-H_b), 8.69 (1H, s, meso-H), 9.58 (1H, s, meso-H), 9.61 (1H, s, meso-H).

Anal. Calcd for $C_{38}H_{42}N_4O_4$: C, 73.76; H, 6.84; N, 9.06. Found: C, 73.87; H, 6.62; N, 9.22.

Grignard Reaction of Methyl 2-Acetyl-2-devinylpyropheophorbide-*a* (**3**).

General Procedure.

To a solution of compound **3** (152 mg, 0.25 mmol) in tetrahydrofuran (15 mL) at 0 °C was added 1 mol/L cyclopenyl magnesium bromide in tetrahydrofuran (0.35 mL). After stirring for 25 minutes, the mixture was poured into an ice-cooled ammonium chloride solution and extracted with diethyl ether. The organic layer was dried over sodium sulfate. After evaporation of the solvent, the residue was chromatographed on a silica gel column with hexane-ethyl acetate (3:1) to give methyl 2-(1-cycloalkyl-1-hydroxyethyl)-9-ethylenedioxy-2-devinyl-9-deoxopyropheophorbide-*a*'s **9a**-**c**.

Methyl 2-(1-Cyclopentyl-1-hydroxyethyl)-9-ethylenedioxy-2-devinyl-9-deoxopyropheophorbide-*a* (**9a**).

This compound **9a** was obtained from the reaction using cyclopentyl magnesium bromide as a dark green solid (115 mg, 68%) (from chloroform-hexane); mp 225-228 °C; ir (potassium bromide): ν 1739 (C=O), 1610 (C=C), 1520 (chlorin skeleton), 1448, 1391, 1310, 1250, 1217, 1162, 1118 cm^{-1}; uv-vis (chloroform): λ (log ε) 399 (5.37), 499 (3.11), 538 (2.96), 607 (2.96), 646 nm (3.57); ^1H nmr (deuteriochloroform): δ -1.57 (1H, br.s, NH), 0.39 (1H, br.s, NH), 1.58-2.02 (9H, m, cyclopentyl-H), 1.67 (3H, t, *J* = 7.6 Hz, 4b-CH_3), 1.73 (3H, d, *J* = 7.2 Hz, 8-CH_3), 2.04-2.41 (2H, m, 7a-CH_2), 2.34 (3H, s, 2a-CH_3), 2.44-2.80 (2H, m, 7b-CH_2), 3.32 (3H, s, CH_3), 3.51 (3H, s, CH_3), 3.53 (3H, s, CH_3), 3.57 (3H, s, $COOCH_3$), 3.74 (2H, q, *J* = 7.6 Hz, 4a-CH_2), 4.38-4.68 (6H, m, 7-,8-H + OCH_2CH_2O), 4.98 (1H, d, *J* = 19.8 Hz, 10-H_a), 5.07 (1H, d, *J* = 19.8 Hz, 10-H_b), 8.78 (1H, s, meso-H), 9.59 (1H, s, meso-H), 10.58 (1H, s, meso-H).

Anal. Calcd for $C_{41}H_{50}N_4O_5$: C, 72.54; H, 7.42; N, 8.25. Found: C, 72.77; H, 7.52; N, 8.42.

Methyl 2-(1-Cyclohexyl-1-hydroxyethyl)-9-ethylenedioxy-2-devinyl-9-deoxopyropheophorbide-*a* (**9b**).

This compound **9b** was obtained from the reaction using cyclohexyl magnesium bromide as a dark green solid (121 mg, 70%) (from chloroform-hexane); mp 219-222 °C; ir (potassium bromide): ν 1740 (C=O), 1609 (C=C), 1519 (chlorin skeleton), 1441, 1395, 1309, 1250, 1211, 1162, 1110 cm^{-1}; uv-vis (chloroform): λ (log ε) 398 (5.36), 498 (3.16), 538 (2.97), 606 (2.97), 646 nm (3.58); ^1H nmr (deuteriochloroform): δ -1.56 (1H, br.s, NH), 0.39 (1H, br.s, NH), 1.59-2.03 (11H, m, cyclohexyl-H), 1.67 (3H, t, *J* = 7.6 Hz, 4b-CH_2), 1.73 (3H, d, *J* = 7.2 Hz, 8-CH_3), 2.04-2.43 (2H, m, 7a-CH_2), 2.34 (3H, s, 2a-CH_3), 2.42-2.81 (2H, m, 7b-CH_2), 3.33 (3H, s, CH_3), 3.51 (3H, s, CH_3), 3.54 (3H, s, CH_3), 3.56 (3H, s, $COOCH_3$), 3.77 (2H, q, *J* = 7.6 Hz, 4a-CH_2), 4.33-4.66 (6H, m, 7-,8-H + OCH_2CH_2O), 4.98 (1H, d, *J* = 19.2 Hz, 10-H_a), 5.07 (1H, d, *J* = 19.2 Hz, 10-H_b), 8.79 (1H, s, meso-H), 9.60 (1H, s, meso-H), 10.55 (1H, s, meso-H).

Anal. Calcd for $C_{42}H_{52}N_4O_5$: C, 72.80; H, 7.57; N, 8.09. Found: C, 72.87; H, 7.42; N, 8.27.

Methyl 2-(1-Cycloheptyl-1-hydroxyethyl)-9-ethylenedioxy-2-devinyl-9-deoxopyropheophorbide-*a* (**9c**).

This compound **9c** was obtained from the reaction using cycloheptyl magnesium bromide as a dark green solid (113 mg, 64%) (from chloroform-hexane); mp 212-215 °C; ir (potassium bromide): ν 1737 (C=O), 1612 (C=C), 1513 (chlorin skeleton), 1438, 1389, 1310, 1248, 1207, 1167, 1115 cm^{-1}; uv-vis (chloroform): λ (log ε) 398 (5.39), 499 (3.11), 539 (2.96), 607 (2.97), 646 nm (3.57); ^1H nmr (deuteriochloroform): δ -1.56 (1H, br.s, NH), 0.41 (1H, br.s, NH), 1.54-2.05 (13H, m, cycloheptylyl-H), 1.68 (3H, t, *J* = 7.5 Hz, 4b-CH_3), 1.74 (3H, d, *J* = 7.3 Hz, 8-CH_3), 2.07-2.37 (2H, m, 7a-CH_2), 2.31 (3H, s, 2a-CH_3), 2.42-2.76 (2H, m, 7b-CH_2), 3.32 (3H, s, CH_3), 3.51 (3H, s, CH_3), 3.53 (3H, s, CH_3), 3.56 (3H, s, $COOCH_3$), 3.77 (2H, q, *J* = 7.5 Hz, 4a-CH_2), 4.29-4.62 (6H, m, 7-,8-H + OCH_2CH_2O), 4.98 (1H, d, *J* = 19.1 Hz, 10-H_a), 5.07 (1H, d, *J* = 19.1 Hz, 10-H_b), 8.78 (1H, s, meso-H), 9.60 (1H, s, meso-H), 10.53 (1H, s, meso-H).

Anal. Calcd for $C_{43}H_{54}N_4O_5$: C, 73.06; H, 7.70; N, 7.93. Found: C, 73.29; H, 7.52; N, 7.72.

Hydrolysis of Methyl 2-(1-Cycloalkyl-1-hydroxyethyl)-9-ethylenedioxy-2-devinyl-9-deoxopyropheophorbide-*a*'s **9a**-**c**.

General Procedure.

A solution of compound **9a**-**c** (110 mg) in 60% acetic acid (25 mL) was stirred for 1 hour at 45 °C in the dark. The mixture was poured into an ice-cooled water and extracted with dichloromethane. After washing with water, the organic layer was dried over sodium sulfate. The evaporation residue was chromatographed on a silica gel column with hexane-ethyl acetate (3:1) to give methyl 2-(1-cycloalkyl-1-hydroxyethyl)-2-devinylpyropheophorbide-a **10a**-**c**.

Methyl 2-(1-Cyclopentyl-1-hydroxyethyl)-2-devinylpyropheophorbide-*a* (**10a**).

This compound **10a** was obtained from the hydrolysis of compound **9a** as a dark green solid (91 mg, 88%) (from chloroform-hexane); mp 225-227 °C; ir (potassium bromide): ν 1744 (C=O), 1731 (C=O), 1609 (C=C), 1515 (chlorin skeleton), 1443, 1400, 1313, 1260, 1204, 1170, 1108 cm^{-1}; uv-vis (chloroform): λ (log ε) 410 (5.06), 469 (2.93), 506 (3.11), 536 (3.05), 606 (3.03), 660 nm (3.80); ^1H nmr (deuteriochloroform): δ -1.87 (1H, br.s, NH), 0.40 (1H, br.s, NH), 1.53-2.02 (9H, m, cyclopentyl-H), 1.64 (3H, t, *J* = 7.5 Hz, 4b-CH_3), 1.71 (3H, d, *J* = 7.2 Hz, 8-CH_3), 2.09-2.29 (2H, m, 7a-CH_2), 2.28 (3H, s, 2a-CH_3), 2.35-2.61 (2H, m, 7b-CH_2), 3.17 (3H, s, CH_3), 3.45 (3H, s, CH_3), 3.53 (3H, s, CH_3), 3.57 (3H, s, $COOCH_3$), 3.65 (2H, q, *J* = 7.5 Hz, 4a-CH_2), 4.15-4.21 (1H, m, 7-H), 4.30-4.46 (1H, m, 8-H), 5.01 (1H, d, *J* = 20.0 Hz, 10-H_a), 5.17 (1H, d, *J* = 20.0 Hz, 10-H_b), 8.46 (1H, s, meso-H), 9.40 (1H, s, meso-H), 10.19 (1H, s, meso-H).

Anal. Calcd for $C_{39}H_{46}N_4O_4$: C, 73.79; H, 7.30; N, 8.83. Found: C, 73.67; H, 7.52; N, 8.69.

Methyl 2-(1-Cyclohexyl-1-hydroxyethyl)-2-devinylpyropheophorbide-*a* (**10b**).

This compound **10b** was obtained from the hydrolysis of compound **9b** as a dark green solid (84 mg, 90%) (from chloroform-hexane); mp 222-224 °C; ir (potassium bromide): ν 1740 (C=O), 1730 (C=O), 1615 (C=C), 1517 (chlorin skeleton), 1445, 1391, 1311, 1259, 1211, 1162, 1118 cm^{-1}; uv-vis (chloroform): λ (log ε) 410 (5.11), 470 (2.92), 505 (3.09), 537 (3.09), 605 (3.05),

660 nm (3.80); ^{1}H nmr (deuteriochloroform): δ -1.83 (1H, br.s, NH), 0.39 (1H, br.s, NH), 1.53-2.04 (11H, m, cyclohexyl-H), 1.65 (3H, t, *J* = 7.5 Hz, 4b-CH_3), 1.72 (3H, d, *J* = 7.2 Hz, 8-CH_3), 2.09-2.32 (2H, m, 7a-CH_2), 2.27 (3H, s, 2a-CH_3), 2.38-2.64 (2H, m, 7b-CH_2), 3.18 (3H, s, CH_3), 3.42 (3H, s, CH_3), 3.53 (3H, s, CH_3), 3.59 (3H, s, $COOCH_3$), 3.66 (2H, q, *J* = 7.5 Hz, 4a-CH_2), 4.17-4.22 (1H, m, 7-H), 4.32-4.44 (1H, m, 8-H), 5.01 (1H, d, *J* = 20.0 Hz, 10-H_a), 5.17 (1H, d, *J* = 20.0 Hz, 10-H_b), 8.46 (1H, s, meso-H), 9.43 (1H, s, meso-H), 10.17 (1H, s, meso-H).

Anal. Calcd for $C_{40}H_{48}N_4O_4$: C, 74.04; H, 7.46; N, 8.64. Found: C, 74.27; H, 7.59; N, 8.44.

Methyl 2-(1-Cycloheptyl-1-hydroxyethyl)-2-devinylpyropheophorbide-*a* (**10c**).

This compound **10c** was obtained from the hydrolysis of compound **9c** as a dark green solid (88 mg, 85%) (from chloroform-hexane); mp 216-129 °C; ir (potassium bromide): ν 1745 (C=O), 1730 (C=O), 1606 (C=C), 1518 (chlorin skeleton), 1444, 1388, 1315, 1263, 1199, 1172, 1111 cm^{-1}; uv-vis (chloroform): λ (log ε) 410 (5.16), 469 (2.93), 505 (3.09), 536 (3.06), 605 (3.03), 660 nm (3.80); ^{1}H nmr (deuteriochloroform): δ -1.83 (1H, br.s, NH), 0.39 (1H, br.s, NH), 1.53-2.07 (13H, m, cycloheptyl-H), 1.62 (3H, t, *J* = 7.6 Hz, 4b-CH_3), 1.72 (3H, d, *J* = 7.2 Hz, 8-CH_3), 2.09-2.35 (2H, m, 7a-CH_2), 2.37-2.64 (2H, m, 7b-CH_2), 3.17 (3H, s, CH_3), 3.42 (3H, s, CH_3), 3.53 (3H, s, CH_3), 3.60 (3H, s, $COOCH_3$), 3.64 (2H, q, *J* = 7.5 Hz, 4a-CH_2), 4.17-4.25 (1H, m, 7-H), 4.35-4.46 (1H, m, 8-H), 5.01 (1H, d, *J* = 19.9 Hz, 10-H_a), 5.17 (1H, d, *J* = 19.9 Hz, 10-H_b), 8.46 (1H, s, meso-H), 9.52 (1H, s, meso-H), 10.13 (1H, s, meso-H).

Anal. Calcd for $C_{41}H_{50}N_4O_4$: C, 74.29; H, 7.60; N, 8.45. Found: C, 74.57; H, 7.52; N, 8.22.

Dehydration of Methyl 2-(1-Cycloalkyl-1-hydroxyethyl)-2-devinylpyropheophorbide-*a*'s **10a**-**c**.

General Procedure.

A solution of compound **10a**-**c** (110 mg) in benzene (25 mL) was stirred for 1 hour at 90 °C in the presence of *p*-toluenesulfonic acid (3 mg). After adding water (20 mL) and dichloromethane (25 mL), the organic layer was separated and dried over sodium sulfate. The evaporation residue was chromatographed on a silica gel column with hexane-ethyl acetate (5:1) to give methyl 2a-cycloalkylpyropheophorbide-*a*'s **11a**-**c**.

Methyl 2a-Cyclopentylpyropheophorbide-*a* (**11a**).

This compound **11a** was obtained from the dehydration of **10a** as a dark green solid (75 mg, 70%) (from chloroform-hexane); mp 210-213 °C; ir (potassium bromide): ν 1745 (C=O), 1729 (C=O), 1610 (C=C), 1520 (chlorin skeleton), 1448, 1392, 1318, 1263, 1202, 1166, 1106 cm^{-1}; uv-vis (chloroform): λ (log ε) 410 (5.23), 507 (3.50), 538 (3.50), 607 (3.50), 661 nm (3.74); ^{1}H nmr (deuteriochloroform): δ -1.68 (1H, br.s, NH), 0.41 (1H, br.s, NH), 1.55-1.84 (9H, m, cyclopentyl-H), 1.68 (3H, t, *J* = 7.5 Hz, 4b-CH_3), 1.78 (3H, d, *J* = 7.2 Hz, 8-CH_3), 2.02-2.39 (2H, m, 7a-CH_2), 2.34-2.63 (2H, m, 7b-CH_2), 3.19 (3H, s, CH_3), 3.26 (3H, s, CH_3), 3.59 (3H, s, CH_3), 3.65 (3H, s, $COOCH_3$), 3.67 (2H, q, *J* = 7.5 Hz, 4a-CH_2), 4.22-4.36 (1H, m, 7-H), 4.37-4.53 (1H, m, 8-H), 5.09 (1H, d, *J* = 20.0 Hz, 10-H_a), 5.25 (1H, d, *J* = 20.0 Hz, 10-H_b), 5.52 (1H, d, *J* = 1.3 Hz, 2b-CH_a), 5.97 (1H, d, *J* = 1.3 Hz, 2b-CH_b), 8.49 (1H, s, meso-H), 9.18 (1H, s, meso-H), 9.49 (1H, s, meso-H).

Anal. Calcd for $C_{39}H_{44}N_4O_3$: C, 75.94; H, 7.19; N, 9.08. Found: C, 75.77; H, 7.49; N, 9.22.

Methyl 2a-Cyclohexylpyropheophorbide-*a* (**11b**).

This compound **11b** was obtained from the dehydration of **10b** as a dark green solid (70 mg, 72%) (from chloroform-hexane); mp 201-233 °C; ir (potassium bromide): ν 1741 (C=O), 1730 (C=O), 1609 (C=C), 1517 (chlorin skeleton), 1438, 1393, 1317, 1250, 1218, 1163, 1109 cm^{-1}; uv-vis (chloroform): λ (log ε) 410 (5.28), 508 (3.51), 538 (3.50), 606 (3.48), 661 nm (3.73); ^{1}H nmr (deuteriochloroform): δ -1.67 (1H, br.s, NH), 0.42 (1H, br.s, NH), 1.57-1.85 (11H, m, cyclohexyl-H), 1.68 (3H, t, *J* = 7.5 Hz, 4b-CH_3), 1.79 (3H, d, *J* = 7.2 Hz, 8-CH_3), 2.05-2.38 (2H, m, 7a-CH_2), 2.37-2.64 (2H, m, 7b-CH_2), 3.19 (3H, s, CH_3), 3.26 (3H, s, CH_3), 3.59 (3H, s, CH_3), 3.65 (3H, s, $COOCH_3$), 3.66 (2H, q, *J* = 7.5 Hz, 4a-CH_2), 4.20-4.34 (1H, m, 7-H), 4.38-4.52 (1H, m, 8-H), 5.09 (1H, d, *J* = 20.0 Hz, 10-H_a), 5.25 (1H, d, *J* = 20.0 Hz, 10-H_b), 5.52 (1H, d, *J* = 1.3 Hz, 2b-CH_a), 5.93 (1H, d, *J* = 1.3 Hz, 2b-CH_b), 8.49 (1H, s, meso-H), 9.17 (1H, s, meso-H), 9.49 (1H, s, meso-H).

Anal. Calcd for $C_{40}H_{46}N_4O_3$: C, 76.16; H, 7.35; N, 8.88. Found: C, 76.37; H, 7.52; N, 9.02.

Methyl 2a-Cycloheptylpyropheophorbide-*a* (**11c**).

This compound **11c** was obtained from the dehydration of **10c** as a dark green solid (79 mg, 74%) (from chloroform-hexane); mp 199-202 °C; ir (potassium bromide): ν 1746 (C=O), 1729 (C=O), 1608 (C=C), 1520 (chlorin skeleton), 1448, 1401, 1316, 1256, 1217, 1175, 1109 cm^{-1}; uv-vis (chloroform): λ (log ε) 410 (5.24), 507 (3.51), 539 (3.49), 607 (3.49), 661 nm (3.73); ^{1}H nmr (deuteriochloroform): δ -1.68 (1H, br.s, NH), 0.44 (1H, br.s, NH), 1.52-1.87 (13H, m, cycloheptyl-H), 1.68 (3H, t, *J* = 7.5 Hz, 4b-CH_3), 1.79 (3H, d, *J* = 7.2 Hz, 8-CH_3), 2.03-2.37 (2H, m, 7a-CH_2), 2.36-2.67 (2H, m, 7b-CH_2), 3.19 (3H, s, CH_3), 3.27 (3H, s, CH_3), 3.59 (3H, s, CH_3), 3.65 (3H, s, $COOCH_3$), 3.67 (2H, q, *J* = 7.5 Hz, 4a-CH_2), 4.21-4.35 (1H, m, 7-H), 4.35-4.53 (1H, m, 8-H), 5.09 (1H, d, *J* = 20.0 Hz, 10-H_a), 5.25 (1H, d, *J* = 20.0 Hz, 10-H_b), 5.52 (1H, d, *J* = 1.3 Hz, 2b-CH_a), 6.00 (1H, d, *J* = 1.3 Hz, 2b-H_b), 8.50 (1H, s, meso-H), 9.19 (1H, s, meso-H), 9.48 (1H, s, meso-H).

Anal. Calcd for $C_{41}H_{48}N_4O_3$: C, 76.36; H, 7.50; N, 8.69. Found: C, 76.55; H, 7.59; N, 8.45.

Grignard Reactions of Compound **7**.

a) Reaction with Methyl Magnesium Bromide: To a solution of compound **7** (146 mg, 0.22 mmol) in tetrahydrofuran (15 mL) at 25 °C was added 1 mol/L methyl magnesium bromide in tetrahydrofuran (0.3 mL). After stirring for 30 minutes, the mixture was poured into an ice-cooled ammonium chloride solution and extracted with diethyl ether. The organic layer was dried over sodium sulfate. After evaporation of the solvent, the residue was chromatographed on a silica gel column with hexane-ethyl acetate (3:1) to give **9** (89 mg, 60%).

b) Reaction with Cyclopentyl Magnesium Bromide: To a solution of compound **7** (133 mg, 0.20 mmol) in tetrahydrofuran (12 mL) at 25 °C was added 1 mol/L cyclopentyl magnesium bromide in tetrahydrofuran (0.3 mL). After stirring for 30 minutes, the mixture was workwd up, as described above, to give **4** (64 mg, 48%).

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