Synthesis of 3^2-Phenyl-substituted Methyl *E/Z*-Pyropheophorbide-*a*'s from Methyl *E/Z*-Pyropehophorbide-*a* 13^1-Ketoximes

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Methyl *E/Z*-pyropheophorbide-*a* 13^1-ketoximes **2a**,**b** and their *O*-acetyl derivatives **3a**,**b** were oxidized with osmium(VIII) oxide to give aldehydes **4a**,**b** and **5a**,**b**, respectively. The Wittig reactions of the aldehyde chlorines **4a**,**b** and **5a**,**b** with benzyltriphenylphosphonium chloride were performed to form the corresponding methyl (3^1*E/Z*,13^1*E/Z*)-3^2-phenylpyropheophorbide-*a* 13^1-ketoximes **6aa**-**bb** and their *O*-acetyl derivatives **7aa**-**bb**; hydrolysis of these ketoximes **6aa**,**ba** and **6ab**,**bb** in formic acid produced methyl (*E/Z*)-3^2-phenylpyropheophorbide-*a*'s **8a**,**b**.

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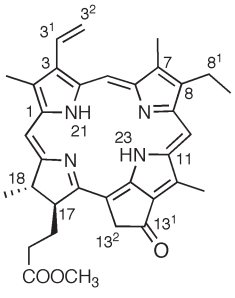
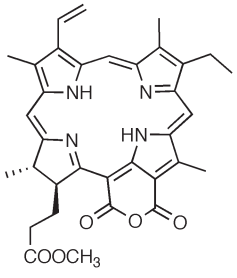
Photodynamic therapy (PDT) is an experimental cancer treatment modality that selectively destroys cancer cells by interaction of light with a photosensitizing dye presumably due to the formation of singlet oxygen [1]. In continuing efforts to develop new photosensitizers for photodynamic therapy, the designs and synthesis of chlorin derivatives having high selectivity for removal of tumor cells from healthy cells are important challenges in the PDT field. These compounds have a strong absorption in the red region of the uv-vis spectrum. Recently, interests have been arisen in natural chlorines and their derivatives having a five-membered *E*-ring of methyl pyropheophorbide-*a* (MPP-*a*) and a six-membered anhydride ring of methyl purpurin-18 [2-7] (Figure 1). The modifications of these naturally occurring chlorines have focused on developing new photosensitisers used in PDT. Particularly, substituents at the 3-position and in the additional ring play important parts, because the Qy bands of chlorin, the longest absorption band, are strongly affected by substitutents along the Qy axis (N^{21}-N^{23}) [8].



MPP-*a* (**1**)



Purpurin-18 methyl ester

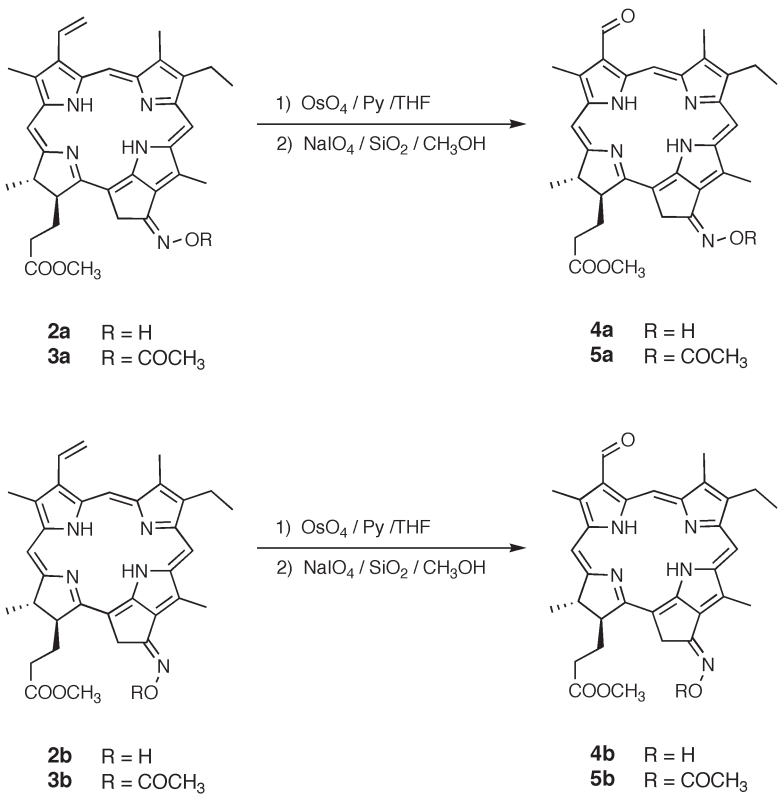
Figure 1

Hitherto, many chlorin derivatives were synthesized from MPP-*a* and exhibited special effective photosensitivity in PDT research [9]. These works suggested that construction of special structures along the Qy axis of the parent chlorin system would provide new photosensitizers for use in PDT. On the other hand, pheophobide-related compounds have been isolated from natural sources [10].

Recently, we reported that the carbonyl function in the *E*-ring of MPP-*a* (**1**) readily reacted with hydroxylamine hydrochloride in ethanol, containing sodium hydroxide, to give methyl (*E/Z*)-pyropheophorbide-*a* 13^1-ketoximes **2a**,**b** in 62 and 21% yield, respectively [11]. The acetylation of *E/Z*-ketoximes **2a**,**b** with acetyl chloride was carried out to afford (*E/Z*)-*O*-acetylketoximes **3a**,**b** in high yields. The present work deals with the synthesis of methyl (*E/Z*)-3^2-phenylpyropheophobide-*a*'s from (*E/Z*)-pyropheophorbide-*a* 13^1-ketoximes **2a**,**b**.

When a basic solution of methyl (*E/Z*)-pyropheophorbide-*a* 13^1-ketoximes **2a**,**b** in tetrahydrofuran were stirred at 0 °C in the presence of osmium(VIII) oxide, followed by glycol cleavage with sodium metaperiodate, the corresponding methyl (*E/Z*)-3-formyl-3-devinylpyropheophorbide-*a* 13^1-ketoximes **4a**,**b** were obtained in 87 and 89% yield, respectively. In a similar manner, their *O*-acetyl derivatives **5a**,**b** were prepared in high yields (Scheme 1).

Scheme 1

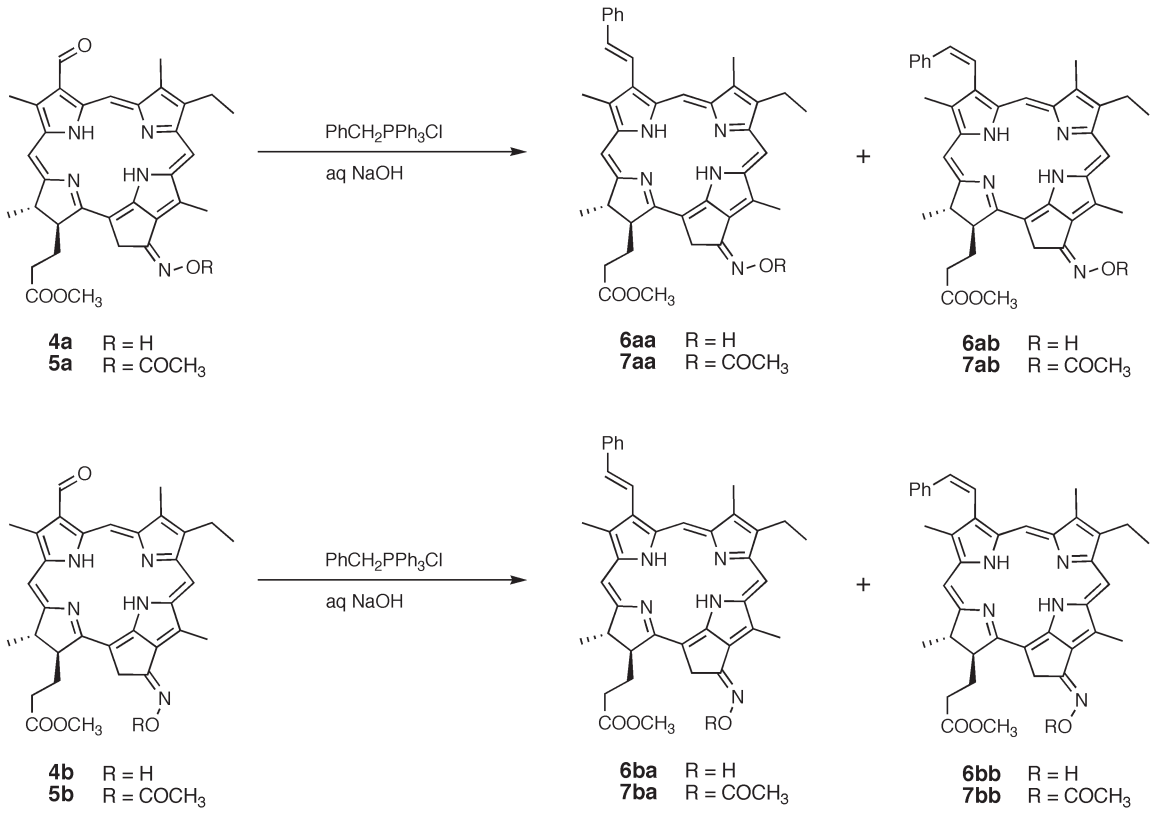


The aldehydes **4a** possessing *Z*-configuration in the 13^1-ketoxime reacted with benzyltriphenylphosphonium chloride in dichloromethane in the presence of an aqueous sodium hydroxide solution at room temperature to give (3^1*E*/*Z*,13^1*E*)-3-(2-phenylethenyl)chlorines, which were readily separated by chromatography to give 3^1*E*- **6aa** (61%) and 3^1*Z*-isomer **6ab** (23%). The 3^1*E*-rich selectivity is consistent with the results of the Wittig reaction of other aldehyde chlorines [12]. Similarly, *Z*-configurated ketoxime **5a** gave (3^1*E*)- (**7aa**) and (3^1*Z*)-3-(2-phenylethenyl)chorin (**7ab**) in 66 and 19% yield, respectively. On the other hand, the Wittig reactions of (*E*)-13^1-ketoximes **4b** and **5b** gave the corresponding (3^1*E*/*Z*,13^1*E*)-3-(2-phenylethenyl)chlorines which were also (3^1*E*)-isomers **6ba** (62%) and **7ba** (66%) and (3^1*Z*)-isomers **6bb** (17%) and **7bb** (19%) (Schme 2). (3^1*E*)- and (3^1*Z*)-3^1-phenylpyropheophobide-*a* 13^1-ketoximes **6aa**,**ba** and **6ab**,**bb** were heated in 88% formic acid at reflux for 2 hours to give the hydrolyzed products, methyl (*E*)- and (*Z*)-3^1-phenylpyropheophobide-*a*'s **8a**,**b** [12] instead of Beckmann rearrangement products (Scheme 3).

In compounds **6aa**-**bb** and **7aa**-**bb**, the stereochemistry at the 3^1-position was determined by the ^{1}H nmr spectroscopy in which the major isomers have the coupling constants ^3J (3^{1}H-3^{2}H), about 17 Hz, and the *J* values of the minor isomers are about 12 Hz. These *J* values indicate that the major products are *E*-isomers and the minor ones are *Z*-isomers. In addition, the =N-OH protons of the oximes **6aa**-**bb** were not found in their ^{1}H nmr spectra. In the uv-vis spectra, the λ_{max} of (3^1*E*,13^1*Z*)- **6aa**,**7aa** and (3^1*E*,13^1*E*)-isomers **6ba**,**7ba** showed a red shift compared with those of unsubstituted 3-vinyl ketoximes **2a**,**b** and *O*-acetyl ketoximes **3a**,**b** because the phenyl group at the 3^2-position are effectively conjugated with the chlorin chromophore through the C3^1-C3^2 double bond. In the spectra, the Qy and Soret bands were observed at 667 to 670 nm and 412 to 415 nm, respectively. The Qy absorptions in (3^1*Z*)-isomers evidently display a blue shift compared with those of (3^1*E*)-isomers in which Qy and Soret bands were observed at 674 to 676 nm and 415 to 418 nm, respectively. This is ascribable to the retarded conjugation between the phenyl group and the chlorin chromophor through the C3^1-C3^2 double bond because of steric repulsion between the (*Z*)-substituted phenyl group and 2-methyl group. The aldehyde chlorines **4a**,**b** and **5a**,**b** showed absorption bands at about 690 nm because the Qy bands were strongly affected by the formyl group at the 3-position.

In conclusion, methyl (*E*/*Z*)-3^2-phenylpyropheophorbide-*a*'s **8a**,**b** were obtained from MMP-*a* (**1**) *via* their 13^1-ketoximes. In this process, Beckmann rearrangement

Scheme 2



4a R = H
5a R = $COCH_3$

6aa R = H
7aa R = $COCH_3$

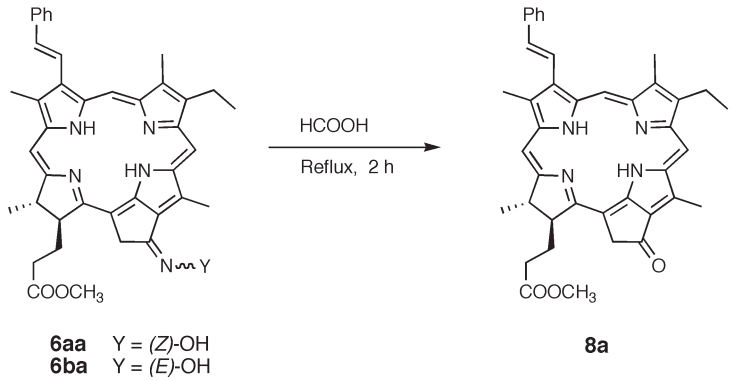
6ab R = H
7ab R = $COCH_3$

4b R = H
5b R = $COCH_3$

6ba R = H
7ba R = $COCH_3$

6bb R = H
7bb R = $COCH_3$

Scheme 3



6aa Y = *(Z)*-OH
6ba Y = *(E)*-OH

8a

6ab Y = *(Z)*-OH
6bb Y = *(E)*-OH

8b

products were not observed. The uv-vis spectroscopic characters were also discussed.

EXPERIMENTAL

The mps were obtained by a Shanghai Precision WRS-2A apparatus and are uncorrected. The ir spectra were measured with a Shimadzu FT IR 8300 spectrophotometer. The uv-vis spectra were taken on a Unicam SP 800 spectrophotometer. The ^{1}H nmr spectra were recorded with a Varian-300 spectrometer (300 MHz) using of TMS as an internal standard. The elemental analyses were performed on a Perkin-Elmer 240C microanalyzer. All chemical reagents were commercially available and purified by using standard methods. Solvents were dried in routine ways and redistilled. Methyl pyropheophorbide-*a* (**1**) was obtained according to Smith's method [13]. The ketoximes **2a**,**b** and the *O*-acetyl ketoxime **3a**,**b** were prepared as described in a previous work [11].

Oxidation of Ketoximes **2a**,**b** and *O*-Acetyl Ketoximes **3a**,**b**.

General Procedure.

A ketoxime **2a**,**b**;**3a**,**b** (0.35 mmol) was suspended in a solution of osmium(VIII) oxide (175 mg) in a mixture of tetrahydrofuran (35 mL) and pyridine (0.5 mL) at 0 °C. After stirring for 30 minutes at the same temperature, the mixture was stirred at room temperature for an additional hour. An excess of a solution of sodium hydrogensulfite (15 g) in a 50% mixture of methanol in water was added. The mixture was stirred for 20 minutes. After filtrating the brown osmium(VI) oxide precipitate, dichloromethane was added to the mixture. The organic layer was separated and dried over sodium sulfate. The solvent was removed to give solid material that was suspended in a mixture of tetrahydrofuran (15 mL) and silica gel (2.5 g). After addition of a solution of sodium metaperiodate (1 g) in water (15 mL), the color of the solution changed from green to bronze within 30 minutes. After adding dichloromethane (20 mL), the mixture was filtered through cotton wool and then the resultant crude material was chromatographed on silica gel with hexane – ethyl acetate (3:1) as eluent to give aldehydes **4a**,**b**;**5a**,**b**.

Methyl (*Z*)-3-Formyl-3-devinylpyropheophorbide-*a* 13^1-Ketoxime (**4a**).

This compound was obtained from the oxidation of compound **2a** as a dark green solid (172 mg, 87%); mp 211-213 °C; ir (potassium bromide) ν: 1738 (C=O), 1701 (C=O), 1620 (C=C), 1522 (chlorin skeleton), 1435, 1380, 1313, 1233, 1197, 1152, 1106 cm^{-1}; uv-vis (chloroform) λ_{max}: 317 (relative intensity 0.25), 416 (1.00), 518 (0.13), 554 (0.12), 691 nm (0.55); ^{1}H nmr (deuteriochloroform) δ: -2.62 (1H, br s, NH), 0.88 (1H, br s, NH), 1.60 (3H, t, *J* = 7.4 Hz, 8^1-CH_3), 1.71 (3H, d, *J* = 7.4 Hz, 18-CH_3), 2.14-2.82 (4H, m, 17-CH_2CH_2), 3.31 (3H, s, CH_3), 3.40 (3H, s, CH_3), 3.61 (3H, s, $COOCH_3$), 3.63 (3H, s, CH_3), 3.76 (2H, q, *J* = 7.4 Hz, 8-CH_2), 4.27-4.52 (1H, m, 17-H), 4.58-4.76 (1H, m, 18-H), 5.54 (1H, d, *J* = 18.7 Hz, 13^2-H_a), 5.68 (1H, d, *J* = 18.7 Hz, 13^2-H_b), 8.92 (1H, s, meso-H), 9.32 (1H, s, meso-H), 10.48 (1H, s, meso-H), 11.63 (1H, s, CHO).

Anal. Calcd for $C_{33}H_{35}N_5O_4$: C, 70.07; H, 6.24; N, 12.38. Found: C, 70.27; H, 6.47; N, 12.16.

Methyl (*E*)-3-Formyl-3-devinylpyropheophorbide-*a* 13^1-Ketoxime (**4b**).

This compound was obtained from the oxidation of compound **2b** as a dark green solid (176 mg, 89%); mp 204-206 °C; ir (potassium bromide) ν: 1737 (C=O), 1705 (C=O), 1621 (C=C), 1526 (chlorin skeleton), 1436, 1382, 1318, 1227, 1189, 1150, 1100 cm^{-1}; uv-vis (chloroform) λ_{max}: 420 (relative intensity 1.00), 519 (0.15), 554 (0.11), 636 (0.08), 689 nm (0.73); ^{1}H nmr (deuteriochloroform) δ: -2.58 (1H, br s, NH), 0.75 (1H, br s, NH), 1.69 (3H, t, *J* = 7.5 Hz, 8^1-CH_3), 1.84 (3H, d, *J* = 7.4 Hz, 18-CH_3), 2.08-2.81 (4H, m, 17-CH_2CH_2), 3.22 (3H, s, CH_3), 3.27 (3H, s, CH_3), 3.64 (3H, s, CH_3), 3.68 (3H, s, CH_3), 3.66 (2H, q, *J* = 7.5 Hz, 8-CH_2), 4.09-4.40 (1H, m, 17-H), 4.48-4.76 (1H, m, 18-H), 5.58 (1H, d, *J* = 19.0 Hz, 13^2-H_a), 5.69 (1H, d, *J* = 19.0 Hz, 13^2-H_b), 8.90 (1H, s, meso-H), 9.65 (1H, s, meso-H), 10.42 (1H, s, meso-H), 11.61 (1H, s, CHO).

Anal. Calcd for $C_{33}H_{35}N_5O_4$: C, 70.07; H, 6.24; N, 12.38. Found: C, 69.87; H, 6.39; N, 12.56.

Methyl (*Z*)-*O*-Acetyl-3-formyl-3-devinylpyropheophorbide-*a* 13^1-Ketoxime (**5a**).

This compound was obtained from the oxidation of compound **3a** as a dark green solid (185 mg, 87%); mp 189-192 °C; ir (potassium bromide) ν: 1738 (C=O), 1722 (C=O), 1701 (C=O), 1620 (C=C), 1527 (chlorin skeleton), 1429, 1384, 1310, 1197, 1160, 1101 cm^{-1}; uv-vis (chloroform) λ_{max}: 319 (relative intensity 0.28), 413 (1.00), 517 (0.12), 552 (0.11), 693 nm (0.57); ^{1}H nmr (deuteriochloroform) δ: -2.50 (1H, br s, NH), 0.36 (1H, br s, NH), 1.74 (3H, t, *J* = 7.4 Hz, 8^1-CH_3), 1.87 (3H, d, *J* = 7.3 Hz, 18-CH_3), 2.14-2.80 (4H, m, 17-CH_2CH_2), 2.56 (3H, s, $COCH_3$), 3.31 (3H, s, CH_3), 3.52 (3H, s, CH_3), 3.68 (3H, s, $COOCH_3$), 3.73 (3H, s, CH_3), 3.76 (2H, q, *J* = 7.3 Hz, 8-CH_2), 4.27-4.52 (1H, m, 17-H), 4.58-4.76 (1H, m, 18-H), 5.64 (1H, d, *J* = 18.6 Hz, 13^2-H_a), 5.70 (1H, d, *J* = 18.6 Hz, 13^2-H_b), 8.90 (1H, s, meso-H), 9.65 (1H, s, meso-H), 10.42 (1H, s, meso-H), 11.60 (1H, s, CHO).

Anal. Calcd for $C_{35}H_{37}N_5O_5$: C, 69.17; H, 6.14; N, 11.52. Found: C, 69.37; H, 6.37; N, 11.36.

Methyl (*E*)-*O*-Acetyl-3-formyl-3-devinylpyropheophorbide-*a* 13^1-Ketoxime (**5b**).

This compound was obtained from the oxidation of compound **3b** as a dark green solid (181 mg, 85%); mp 186-188 °C; ir (potassium bromide) ν: 1739 (C=O), 1720 (C=O), 1706 (C=O), 1623 (C=C), 1530 (chlorin skeleton), 1422, 1384, 1312, 1197, 1157, 1093 cm^{-1}; uv-vis (chloroform) λ_{max}: 317 (relative intensity 0.28), 413 (1.00), 517 (0.12), 551 (0.11), 692 nm (0.54); ^{1}H nmr (deuteriochloroform) δ: -2.55 (1H, br s, NH), 0.42 (1H, br s, NH), 1.77 (3H, t, *J* = 7.5 Hz, 8^1-CH_3), 1.89 (3H, d, *J* = 7.4 Hz, 18-CH_3), 2.14-2.79 (4H, m, 17-CH_2CH_2), 2.57 (3H, s, $COCH_3$), 3.29 (3H, s, CH_3), 3.56 (3H, s, CH_3), 3.67 (3H, s, $COOCH_3$), 3.76 (3H, s, CH_3), 3.68 (2H, q, *J* = 7.3 Hz, 8-CH_2), 4.25-4.53 (1H, m, 17-H), 4.57-4.78 (1H, m, 18-H), 5.60 (1H, d, *J* = 18.6 Hz, 13^2-H_a), 5.68 (1H, d, *J* = 18.6 Hz, 13^2-H_b), 8.89 (1H, s, meso-H), 9.62 (1H, s, meso-H), 10.47 (1H, s, meso-H), 11.63 (1H, s, CHO).

Anal. Calcd for $C_{35}H_{37}N_5O_5$: C, 69.17; H, 6.14; N, 11.52. Found: C, 68.90; H, 6.40; N, 11.28.

Wittig Reaction of Aldehyde Chlorins **4a**,**b** and **5a**,**b**.

General Procedure.

The chlorin aldehyde **4a**,**b**;**5a**,**b** (0.19 mmol) and benzyltriphenylphosphonium chloride (78 mg, 0.20 mmol) were dissolved in

dichloromethane (50 mL). After adding a solution of sodium hydroxide (60 mg) in water (10 mL) under stirring, the solution was stirred at room temperature under nitrogen atmosphere. Disappearance of the aldehyde was monitored by visible spectra at about 691 and 416 nm. When the these absorption bands were no longer visible after 40 minutes for **4a**,**b** and 50 minutes for **5a**,**b**, the reaction mixture was poured into a mixture of ice water (20 mL) and dichloromethane (20 mL). The aqueous layer was extracted several times with dichloromethane and then the combined organic extracts were washed with 2% hydrochloric acid, 4% sodium hydrogencarbonate solution, followed with water. After drying over sodium sulfate, the solvent was evaporated *in vacuo* to dryness to afford a residue, which was purified by chromatography on a silica gel column with hexane - ethyl acetate (6:1) as eluent to give 3^2-phenyl-substituted ketoximes **6aa**-**bb**; **7aa**-**bb**.

Methyl (3^1E,13^1Z)-3^2-Phenylpyropheophorbide-*a* 13^1-Ketoxime (**6aa**) and Methyl (3^1Z,13^1Z)-3^2-Phenylpyropheophorbide-*a* 13^1-Ketoxime (**6ab**).

These compounds **6aa**,**ab** were obtained from the aldehyde **4a** and separated by chromatography.

6aa: a dark green solid (74 mg, 61%); mp 255-257 °C; ir (potassium bromide) ν: 1738 (C=O), 1640 (C=N), 1619 (C=C), 1530 (chlorin skeleton), 1417, 1374, 1322, 1190, 1160 cm^{-1}; uv-vis (chloroform) λ_{max}: 311 (relative intensity 0.18), 415 (1.00), 510 (0.14), 540 (0.07), 565 (0.04), 616 (0.07), 675 nm (0.49); ^1H nmr (deuteriochloroform) δ: -2.72 (1H, br s, NH), 0.72 (1H, br s, NH), 1.69 (3H, t, *J* = 7.4 Hz, 8^1-CH_3), 1.85 (3H, d, *J* = 7.4 Hz, 18-CH_3), 2.18-2.87 (4H, m, 17-CH_2CH_2), 3.34 (3H, s, CH_3), 3.35 (3H, s, CH_3), 3.54 (3H, s, $COOCH_3$), 3.63 (3H, s, CH_3), 3.74 (2H, q, *J* = 7.4 Hz, 8-CH_2), 4.36-4.58 (1H, m, 17-H), 4.62-4.78 (1H, m, 18-H), 5.59 (1H, d, *J* = 19.0 Hz, 13^2-H_a), 5.67 (1H, d, *J* = 19.0 Hz, 13^2-H_b), 7.50 (1H, d, *J* = 16.2 Hz, 3^2-H), 7.37-7.88 (5H, m, Ph), 8.45 (1H, d, *J* = 16.2 Hz, 3^1-H), 8.81 (1H, s, meso-H), 9.37 (1H, s, meso-H), 9.72 (1H, s, meso-H).

Anal. Calcd for $C_{40}H_{41}N_5O_3$: C, 75.09; H, 6.46; N, 10.95. Found: C, 75.34; H, 6.20; N, 11.08.

6ab: a dark green solid (28 mg, 23%); mp 148-151 °C; ir (potassium bromide) ν: 1740 (C=O), 1644 (C=N), 1620 (C=C), 1536 (chlorin skeleton), 1410, 1364, 1316, 1194, 1155 cm^{-1}; uv-vis (chloroform) λ_{max}: 312 (relative intensity 0.17), 412 (1.00), 507 (0.13), 535 (0.06), 560 (0.05), 613 (0.07), 669 nm (0.42); ^1H nmr (deuteriochloroform) δ: -2.64 (1H, br s, NH), 0.76 (1H, br s, NH), 1.71 (3H, t, *J* = 7.6 Hz, 8^1-CH_3), 1.86 (3H, d, *J* = 7.4 Hz, 18-CH_3), 2.11-2.19 (4H, m, 17-CH_2CH_2), 3.12 (3H, s, CH_3), 3.22 (3H, s, CH_3), 3.62 (3H, s, $COOCH_3$), 3.71 (3H, s, CH_3), 3.72 (2H, q, *J* = 7.6 Hz, 8-CH_2), 4.40-4.81 (2H, m, 17-H + 18-H), 5.50 (1H, d, *J* = 18.2 Hz, 13^2-H_a), 5.60 (1H, d, *J* = 18.2 Hz, 13^2-H_b), 6.90-7.10 (2H, m, Ph), 7.46 (1H, d, *J* = 12.0 Hz, 3^2-H), 7.77 (1H, d, *J* = 12.0 Hz, 3^1-H), 7.38-7.95 (3H, m, Ph), 8.68 (1H, s, meso-H), 9.48 (1H, s, meso-H), 9.58 (1H, s, meso-H).

Anal. Calcd for $C_{40}H_{41}N_5O_3$: C, 75.09; H, 6.46; N, 10.95. Found: C, 75.28; H, 6.70; N, 10.70.

Methyl (3^1E,13^1E)-3^2-Phenylpyropheophorbide-*a* 13^1-Ketoxime (**6ba**) and Methyl (3^1Z,13^1E)-3^2-Phenylpyropheophorbide-*a* 13^1-Ketoxime (**6bb**).

These compounds **6ba**,**bb** were obtained from the aldehyde **4b** and separated by chromatography.

6ba: a dark green solid (75 mg, 62%); mp 240-242 °C; ir (potassium bromide) ν: 1739 (C=O), 1640 (C=N), 1620 (C=C), 1517 (chlorin skeleton), 1417, 1374, 1308, 1120, 1117 cm^{-1}; uv-vis (chloroform) λ_{max}: 311 (relative intensity 0.22), 418 (1.00), 509 (0.11), 540 (0.08), 617 (0.08), 674 nm (0.43); ^1H nmr (deuteriochloroform) δ: -2.70 (1H, br s, NH), -0.65 (1H, br s, NH), 1.69 (3H, t, *J* = 7.3 Hz, 8^1-CH_3), 1.86 (3H, d, *J* = 7.4 Hz, 18-CH_3), 2.19-2.91 (4H, m, 17-CH_2CH_2), 3.34 (3H, s, CH_3), 3.35 (3H, s, CH_3), 3.54 (3H, s, $COOCH_3$), 3.63 (3H, s, CH_3), 3.72 (2H, q, *J* = 7.3 Hz, 8-CH_2), 4.37-4.54 (1H, m, 17-H), 4.58-4.73 (1H, m, 18-H), 5.51 (1H, d, *J* = 19.1 Hz, 13^2-H_a), 5.69 (1H, d, *J* = 19.1 Hz, 13^2-H_b), 7.20-7.89 (5H, m, Ph), 7.47 (1H, d, *J* = 16.3 Hz, 3^2-H), 8.45 (1H, d, *J* = 16.3 Hz, 3^1-H), 8.81 (1H, s, meso-H), 9.37 (1H, s, meso-H), 9.72 (1H, s, meso-H).

Anal. Calcd for $C_{40}H_{41}N_5O_3$: C, 75.09; H, 6.46; N, 10.95. Found: C, 75.29; H, 6.29; N, 10.78.

6bb: a dark green solid (21 mg, 17%); mp 137-139 °C; ir (potassium bromide) ν: 1738 (C=O), 1640 (C=N), 1620 (C=C), 1528 (chlorin skeleton), 1417, 1381, 1185, 1119 cm^{-1}; uv-vis (chloroform) λ_{max}: 311 (relative intensity 0.20), 414 (1.00), 507 (0.14), 536 (0.07), 612 (0.08), 667 nm (0.44); ^1H nmr (deuteriochloroform) δ: -2.68 (1H, br s, NH), -0.60 (1H, br s, NH), 1.70 (3H, t, *J* = 7.4 Hz, 8^1-CH_3), 1.84 (3H, d, *J* = 7.4 Hz, 18-CH_3), 2.20-2.90 (4H, m, 17-CH_2CH_2), 3.12 (3H, s, CH_3), 3.24 (3H, s, CH_3), 3.50 (3H, s, $COOCH_3$), 3.64 (3H, s, CH_3), 3.66 (2H, q, *J* = 7.4 Hz, 8-CH_2), 4.40-4.56 (1H, m, 17-H), 4.58-4.72 (1H, m, 18-H), 5.57 (1H, d, *J* = 19.5 Hz, 13^2-H_a), 5.71 (1H, d, *J* = 19.5 Hz, 13^2-H_b), 6.81-6.98 (5H, m, Ph), 7.46 (1H, d, *J* = 12.1 Hz, 3^2-H), 7.81 (1H, d, *J* = 12.1 Hz, 3^1-H), 8.76 (1H, s, meso-H), 9.51 (1H, s, meso-H), 9.59 (1H, s, meso-H).

Anal. Calcd for $C_{40}H_{41}N_5O_3$: C, 75.09; H, 6.46; N, 10.95. Found: C, 75.34; H, 6.30; N, 11.20.

Methyl (3^1E,13^1Z)-*O*-Acetyl-3^2-phenylpyropheophorbide-*a* 13^1-Ketoxime (**7aa**) and Methyl (3^1Z,13^1Z)-*O*-Acetyl-3^2-phenylpyropheophorbide-*a* 13^1-Ketoxime (**7ab**).

These compounds **7aa**,**ab** were obtained from the aldehyde **5a** and separated by chromatography.

7aa: a dark green solid (86 mg, 66%); mp 250-252 °C; ir (potassium bromide) ν: 1739 (C=O), 1728 (C=O), 1644 (C=N), 1622 (C=C), 1521 (chlorin skeleton), 1420, 1380, 1300, 1195, 1123 cm^{-1}; uv-vis (chloroform) λ_{max}: 418 (relative intensity 1.00), 510 (0.13), 541 (0.09), 616 (0.09), 674 nm (0.45); ^1H nmr (deuteriochloroform) δ: -2.46 (1H, br s, NH), -1.68 (1H, br s, NH), 1.69 (3H, t, *J* = 7.1 Hz, 8^1-CH_3), 1.83 (3H, d, *J* = 7.5 Hz, 18-CH_3), 2.12-2.88 (4H, m, 17-CH_2CH_2), 2.54 (3H, s, $COCH_3$), 3.19 (3H, s, CH_3), 3.41 (3H, s, CH_3), 3.60 (3H, s, $COOCH_3$), 3.71 (2H, q, *J* = 7.1 Hz, 8-CH_2), 3.72 (3H, s, CH_3), 4.20-4.56 (2H, m, 17-H + 18-H), 5.54 (1H, d, *J* = 18.2 Hz, 13^2-H_a), 5.66 (1H, d, *J* = 18.2 Hz, 13^2-H_b), 7.32-7.92 (6H, m, 3^2-H + Ph), 8.30 (1H, d, *J* = 16.5 Hz, 3^1-H), 8.78 (1H, s, meso-H), 9.55 (1H, s, meso-H), 9.59 (1H, s, meso-H).

Anal. Calcd for $C_{42}H_{43}N_5O_4$: C, 73.99; H, 6.36; N, 10.27. Found: C, 73.69; H, 6.20; N, 10.08.

7ab: a dark green solid (25 mg, 19%); mp 148-151 °C; ir (potassium bromide) ν: 1739 (C=O), 1728 (C=O), 1644 (C=N), 1622 (C=C), 1521 (chlorin skeleton), 1420, 1380, 1300, 1195, 1123 cm^{-1}; uv-vis (chloroform) λ_{max}: 313 (relative intensity 0.19), 414 (1.00), 507 (0.13), 537 (0.08), 613 (0.08), 670 nm (0.44); ^1H nmr (deuteriochloroform) δ: -2.42 (1H, br s, NH), -1.66 (1H, br s, NH), 1.70 (3H, t, *J* = 7.4 Hz, 8^1-CH_3), 1.82 (3H, d, *J* = 7.6 Hz, 18-CH_3), 2.18-2.84 (4H, m, 17-CH_2CH_2), 2.53 (3H, s, $COCH_3$), 3.10 (3H, s, CH_3), 3.18 (3H, s, CH_3), 3.61 (3H,

s, $COOCH_3$), 3.63 (2H, q, J = 7.4 Hz, 8-CH_2), 3.73 (3H, s, CH_3), 4.27-4.52 (1H, m, 17-H), 4.58-4.76 (1H, m, 18-H), 5.58 (1H, d, J = 19.0 Hz, 13^2-H_a), 5.70 (1H, d, J = 19.0 Hz, 13^2-H_b), 7.32-7.92 (6H, m, 3^2-H + Ph), 8.30 (1H, d, J = 16.5 Hz, 3^1-H), 8.78 (1H, s, meso-H), 9.55 (1H, s, meso-H), 9.59 (1H, s, meso-H).

Anal. Calcd for $C_{42}H_{43}N_5O_4$: C, 73.99; H, 6.36; N, 10.27. Found: C, 73.74; H, 6.10; N, 10.44.

Methyl (3^1E,13^1E)-*O*-Acetyl-3^2-phenylpyropheophorbide-*a* 13^1-Ketoxime (**7ba**) and Methyl (3^1Z,13^1E)-*O*-Ascetyl-3^2-phenylpyropheophorbide-*a* 13^1-Ketoxime (**7bb**).

These compounds **7ba**,**bb** were obtained from the aldehyde **5b** and separated by chromatography.

7ba: a dark green solid (86 mg, 66%); mp 228-230 °C; ir (potassium bromide) ν: 1739 (C=O), 1328 (C=O), 1643 (C=N), 1618 (C=C), 1522 (chlorin skeleton), 1409, 1365, 1311, 1123, 1109 cm^{-1}; uv-vis (chloroform) λ_{max}: 417 (relative intensity 1.00), 510 (0.15), 540 (0.09), 618 (0.10), 676 nm (0.50); ^{1}H nmr (deuteriochloroform) δ: -2.47 (1H, br s, NH), -0.60 (1H, br s, NH), 1.68 (3H, t, J = 7.2 Hz, 8^1-CH_3), 1.83 (3H, d, J = 7.1 Hz, 18-CH_3), 2.15-2.92 (4H, m, 17-CH_2CH_2), 2.53 (3H, s, $COCH_3$), 3.19 (3H, s, CH_3), 3.41 (3H, s, CH_3), 3.59 (3H, s, $COOCH_3$), 3.65 (3H, s, CH_3), 3.68 (2H, q, J = 7.2 Hz, 8-CH_2), 4.28-4.41 (1H, m, 17-H), 4.45-4.69 (1H, m, 18-H), 5.50 (1H, d, J = 18.8 Hz, 13^2-H_a), 5.64 (1H, d, J = 18.8 Hz, 13^2-H_b), 7.21-7.79 (6H, m, 3^2-H + Ph), 8.20 (1H, d, J = 16.6 Hz, 3^1-H), 8.69 (1H, s, meso-H), 9.43 (1H, s, meso-H), 9.47 (1H, s, meso-H).

Anal. Calcd for $C_{42}H_{43}N_5O_4$: C, 73.99; H, 6.36; N, 10.27. Found: C, 73.69; H, 6.45; N, 10.45.

7bb: a dark green solid (25 mg, 19%); mp 126-129 °C; ir (potassium bromide) ν: 1740 (C=O), 1727 (C=O), 1644 (C=N), 1623 (C=C), 1518 (chlorin skeleton), 1420, 1380, 1175, 1122 cm^{-1}; uv-vis (chloroform) λ_{max}: 318 (relative intensity 0.21), 415 (1.00), 508 (0.14), 538 (0.10), 613 (0.10), 669 nm (0.45); ^{1}H nmr (deuteriochloroform) δ: -2.44 (1H, br s, NH), -0.60 (1H, br s, NH), 1.70 (3H, t, J = 7.2 Hz, 8^1-CH_3), 1.82 (3H, d, J = 7.1 Hz, 18-CH_3), 2.18-2.88 (4H, m, 17-CH_2CH_2), 2.55 (3H, s, $COCH_3$), 3.17 (3H, s, CH_3), 3.59 (3H, s, CH_3), 3.60 (3H, s, $COOCH_3$), 3.64 (2H, q, J = 7.1 Hz, 8-CH_2), 3.71 (3H, s, CH_3), 4.38-4.42 (1H, m, 17-H), 4.48-4.65 (1H, m, 18-H), 5.52 (1H, d, J = 18.8 Hz, 13^2-H_a), 5.70 (1H, d, J = 18.8 Hz, 13^2-H_b), 6.85-6.98 (5H, m, Ph), 7.43 (1H, d, J = 12.0 Hz, 3^2-H), 7.77 (1H, d, J = 12.0 Hz, 3^1-H), 8.63 (1H, s, meso-H), 9.58 (1H, s, meso-H), 9.62 (1H, s, meso-H).

Anal. Calcd for $C_{42}H_{43}N_5O_4$: C, 73.99; H, 6.36; N, 10.27. Found: C, 74.20; H, 6.12; N, 10.04.

Hydrolysis of the Ketoximes **6aa**-**bb**.

General Procedure.

A ketoxime **6aa**-**bb** (128 mg, 0.20 mmol) was dissolved in 88% formic acid (30 mL). The solution was refluxed for 2 hours under nitrogen atmosphere and then the mixture was poured into a mixture of ice water (30 mL) and dichloromethane (30 mL). The aqueous layer was extracted several times with dichloromethane. The combined organic phase was washed with 4% sodium hydrogencarbonate and water. After drying over sodium sulfate, the solvent was evaporated to give a residue, which was chromatographed on a silica gel column with hexane - ethyl acetate (3:1) to give the corresponding methyl 3^2-phenylpyropheophorbide-*a*'s **8a**,**b** [12].

Methyl (*E*)-3^2-Phenylpyropheophorbide-*a* (**8a**).

This compound was obtained from the ketoxime **6aa** and **6ba** in 68 and 60% yield, respectively, as a dark green solid; mp 254-257 °C (lit [12] mp 277-278 °C, lit [14] mp 256-259 °C).

Methyl (*Z*)-3^2-Phenylpyropheophorbide-*a* (**8b**).

This compound was obtained from the ketoxime **6ba** and **6bb** in 65 and 62% yield, respectively, as a dark green solid; mp 136-139 °C (lit [12] mp 138-140 °C).

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