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焦脱镁叶绿酸的区域和立体选择性的芳(芳酰)亚甲基化及其叶绿素类二氢卟吩衍生物的合成

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摘要 以焦脱镁叶绿酸-*a* 甲酯为起始原料, 利用其外接环酮的空气氧化反应, 在大环色基 N^{21}-N^{23} 轴的水溶性端向的不同位置上构建了甲酰基和邻位二酮结构. 通过交叉羟醛缩合反应, 在焦脱镁叶绿酸的外接环和12-位上区域和立体选择性地完成了芳(芳酰)亚甲基化, 合成出一系列未见报道的具有芳(芳酰)烯酮结构单元的叶绿素类二氢卟吩衍生物, 同时, 讨论了芳(芳酰)亚甲基化二氢卟吩的形成机理、立体异构以及紫外-可见光谱性质. 所有新合成化合物的结构均经UV-Vis、^{1}H NMR、MS 以及元素分析予以证实.

关键词 叶绿素; 二氢卟吩; 区域和立体选择性; 交叉羟醛缩合反应; 芳(芳酰)亚甲基化

Regio- and Stereoselective Aryl(aroyl)methylenenation of Pyropheophorbide and Syntheses of Chlorophyllous Chlorin Derivatives

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Abstract Using the pyropheophorbide-*a* methyl ester as the starting material, the formyl group and *α*-diketone moiety were introduced into the water-soluble end of the N^{21}-N^{23} axis of the macrocyclic chromophore at different positions by the allomerization on the exocyclic ring ketone. Based on the cross-aldol condensation, the regio- and stereoselective aryl(aroyl)methylenations of pyropheophorbide-*a* were accomplished on the exocyclic ring and at C12-position. A series of unreported chlorin derivatives that contain the aryl(aroyl)ketene unit were synthesized. In addition, the formation mechanism, stereoisomerism and the optical properties of the aryl(aroyl)methylenated products were discussed. The chemical structures of all newly synthesized compounds were characterized by elemental analysis, MS, UV-Vis and ^{1}H NMR spectra.

Keywords chlorophyll; chlorin; regio- and stereoselectities; cross-aldol reaction; aryl(aroyl)methylenenation

1 Introduction

Naturally occurring chlorophylls (*Chl*s) are a class of important macrocyclic compounds. As photosensitizers, *Chls* have widespread applications in the areas of photodynamic therapy (PDT), dye-sensitized solar cells (DSSCs) and artificial photosynthetic reaction centers.[1-4] The structural changes of these chlorins, derived from chlorophyll by various reactions, can remarkably affect their electronic absorption spectra, singlet excited energy level and self-assembly ability, which are considered as essential qualities in the practical application.[5-9] Therefore, the targeted functionalization around the chromophore periphery of the chlorophyllous chlorines is an important strategy for expanding their research fields.[10-12]

The *α*,*β*-unsaturated ketone is one of the most versatile reactive functional groups and many familiar name reactions, such as the Michael addition, Diels-Alder cycloaddition and Robinson annulation, are all associated with it. These reactions have been commonly used in organic synthesis, which provide valuable way for increasing the carbon chain and extending the conjugation length of the system. Such structural modification can be employed to

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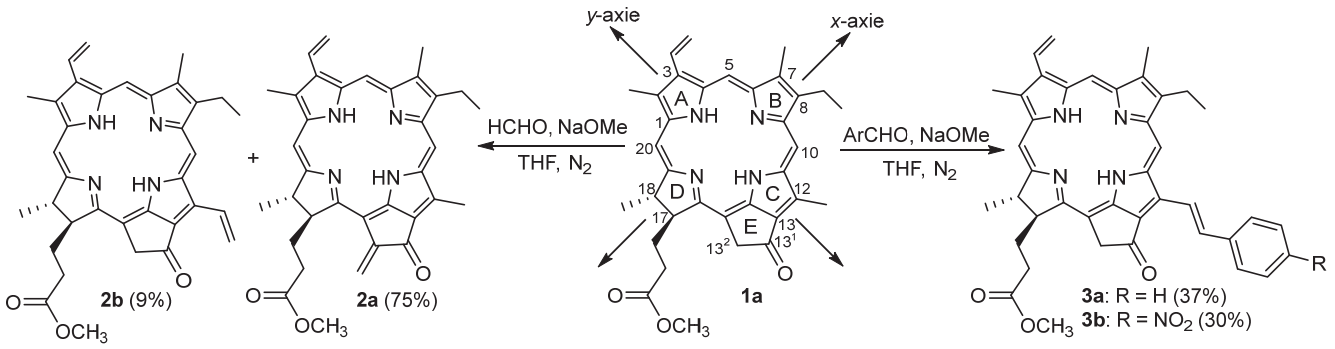
change or regulate the UV-vis spectra, and it is important for these chlorophyll chlorins because their electronic absorption spectra are considered as a significant quality in applications.[13] The cross-aldol reaction is one of the most powerful transformation for introducing enone structure. The basic skeleton of chlorophyll-*a* exactly contains an exocyclic ring with the ketone group, which can be used as electron donor to carry out the cross-aldol reaction. However, the relevant studies on this exocyclic ring are scarce except our early reports regarding the methylenenation of pyropheophorbide-*a* with paraformaldehyde.[14] Inspired by these preliminary works, our interest focused on directionally establishing an arylalkenyl or aroylalkenyl group at the water-soluble end of the N^{21}-N^{23} axis of chlorophyllous chlorin by condensation of the ketone group with various aromatic aldehydes. Herein, we report a regio- and stereoselective aryl(aroyl)alkenylation of these tetrapyrrole macrocyclic compounds by cross-aldol (Claisen-Schmidt) reaction, and synthesized a series of novel chlorins that possess the enone unit with aryl(aroyl) group.

In our approach, the methyl pyropheophorbide-*a* **1a** (MPP*a*), prepared from the accessiable *Spirulina pacifica*,[15] was used as the starting material for the synthesis of the chlorins that contain the *α*,*β*-unsaturated enone moiety (Scheme 1). Under the N_2 atmosphere, the cross-aldol reaction of **1a** with the paraformaldehyde, catalyzed by the sodium methoxide, occurred simultaneously on the *E*-ring and C12-position affording **2a** and **2b** in the isolated yield of 75% and 9%, respectively. These results showed that the C12-methyl group was also activated by the cyclic ketone, despite of its lower reactivity compared with the methylene at 13^2-position. Surprisingly, under the same condition the condensation of **1a** with arylaldehyde shows high regio- and stereoselectivity, which afforded the unique *E*-form of 12-arylvinyl (styryl) chlorins **3a**/**3b** with similar yields (37% and 30%), however, the 13^2-substituted product was not found. Note that all attempts of the arylalkenylation on the *E*-ring, including using different kinds of alkaline catalysts and reaction conditions, are failed.

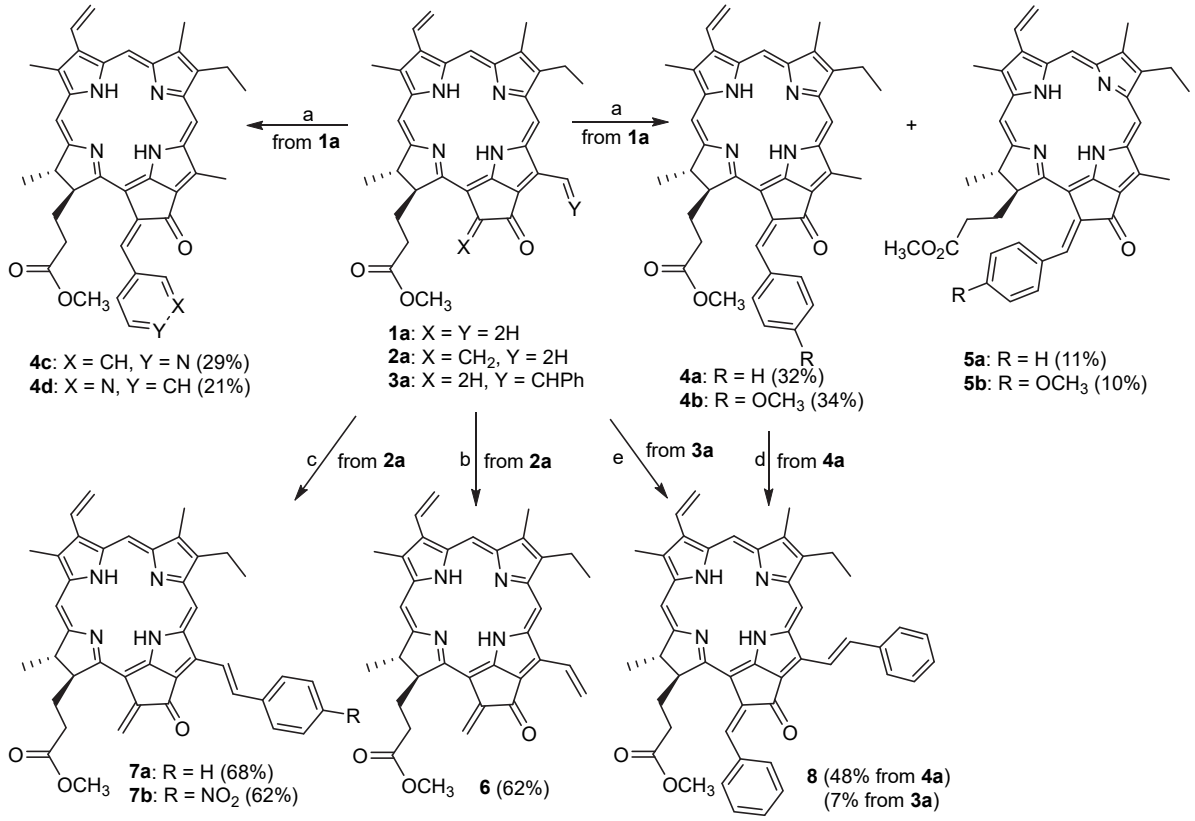
In order to increase the nucleophilic activity of the methylene group on the *E*-ring, the reaction was conducted in the refluxing toluene with the catalysis of sarcosine, which affords a mixture of chlorins **4a**～**4b** (32% and 34%) and **5a**～**5b** (11% and 10%), as a pair of *E*/*Z*-isomers in a ratio of about 3∶1. The proportion of two isomers depends upon the substituents on the aromatic aldehyde. When 3- or 4-pyridylaldehyde was chosen as the aldol accepter to react with MPP*a* **1a**, only the *E*-form of 13^2-arylmethylene-substituted chlorins **4c** and **4d** were obtained as the stereoselective products in the isolated yields of 21% and 29%. It is noteworthy that the arylmethylenenation of compound **1a** using sarcosine as catalyst at 110 ℃ only took place on the exocyclic ring, also showing the excellent regioselectivity of the cross-aldol reaction by basic catalysis.

The condensation of the C13^2-methylenated **2a** with paraformaldehyde, catalyzed by the sodium methoxide, led to the formation of the dimethylenated chlorin **6** in 62% isolated yield (Scheme 2). The 12-methylenated **2b** can also be converted **6** by the cross-aldol reaction with paraformaldehyde at the catalysis of sodium methoxide or sarcosine. The condensation of chlorin **2a** with different arylaldehydes in the same alkaline media also occurred at 12-position to afford the diolefinated products **7a**～**7b** in higher yield. Based on the methods mentioned above, the second benzylmethylenation of **3a** or **4a** also proceed smoothly to give the dibenzylidene-substituted chlorin **8**. The yield of C12-arylmethylenation from **4a** in alkaline media was 48%, but the cross-aldol reaction of **3a** with benzaldehyde with the catalysis of sarcosine only gave the *E*-form isomer **8** in a rather low yield (7%).

The carbonyl groups in chlorin *α*-diketone **1b** and chlorin aldehyde **1c**, prepared by the allomerization reaction from **1a**,[11a,16] can further act as an electron acceptor to participate in the cross-aldol reaction. Meanwhile, the formyl group of **1c** can be readily converted to the acetyl croup by the Tiffeneau-Demjanov rearrangement with diazomethane to afford another chlorin diketon **1d**,[17] which may also be used as an electron donor for condensation with arylaldehyde (Scheme 3). These newly formed carbonyl groups are supposed to be another reactive site for acquiring different arylmethylenated and aroylmethylenated chlorins.

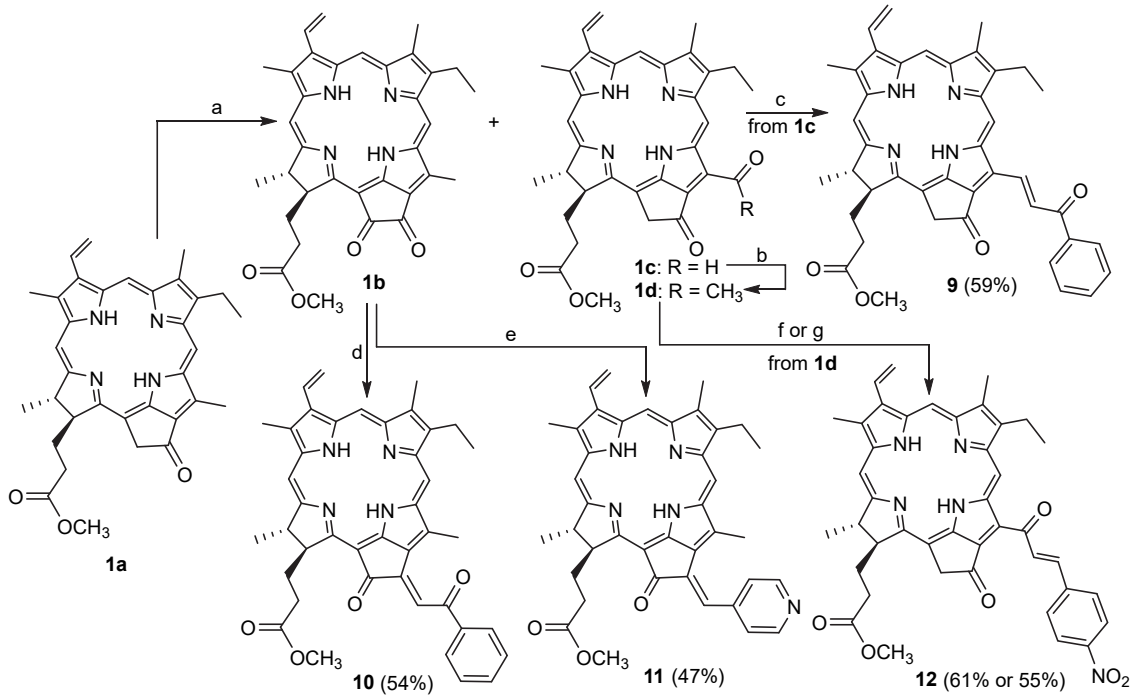


Scheme 1 Synthesis of (aryl)methylenated chlorins **2**～**3** from **1a** by cross-aldol reaction



Reaction conditions: (a) ArCHO, Sar, toluene, reflux; (b) CH_2O, NaOMe, THF, r.t., N_2; (c) ArCHO, NaOMe, THF, r.t., N_2; (d) C_6H_5CHO, NaOMe, THF, r.t., N_2; (e) C_6H_5CHO, Sar, toluene, reflux

Scheme 2 Synthesis of (aryl)methylenated chlorins **4**～**8** from chlorins **1a**～**3a** by cross-aldol reaction



Reaction conditions: (a) $LiOH/O_2/MeOH/H_2O$; (b) $CH_2N_2/Et_2O/THF/r.t$; (c) PhAc/NaOMe/MeOH/THF; (d) PhAc/Diox/BF_3•Et_2O; (e) 4-MePyr/AcOH/Ac_2O; (f) 4-NO_2CHO/Diox/BF_3•Et_2O; (g) 4-NO_2CHO/NaOMe/THF/r.t./N_2

Scheme 3 Synthesis of aroyl(aryl)methylenated chlorins **9**～**12** from chlorins **1b**～**1d** by cross-aldol reaction

As expected, the cross-aldol reaction of **1c** with acetophenone was completed in the mixture of methanol and tetrahydrofuran (THF) with the catalysis of sodium methoxide under N_2 atmosphere at room temperature, which stereoselectively gave the conjugated 1,6-diketone moiety-containing pyropheophorbide-*a* **9** with *E*-configuration in 59% isolated yield. But the attempt to perform the condensation of chlorin **1b** with acetophenone failed, because the *α*-diketone structure on the *E*-ring was particularly prone to ring opening due to its high sensitivity to alkaline surrounding. Thus, the corresponding phenylmethylenation could proceed only in acid condition. The chlorin *γ*-diketone **10** was obtained in moderate yield by the reaction with acetophenone in dioxane containing boron trifluoride diethyl etherate as Lewis acid catalyst. Owing to extreme electron-deficient characteristic of the *α*-diketone structure, **1b** can also undergo an aldol-like condensation with 4-methylpyridine upon treatment with acetic acid in refluxing acetic anhydride, affording 13^2-pyridylmethylen chlorin **11** in 47% isolated yield. The reaction of **1b** with different electron donors all regioselectively occurred at 13^1-position and stereoselectively generated the products with *E*-configuration. The aldol reaction of **1d** with 4-nitrobenzaldehyde under the same condition for preparing compound **10** selectively took place at the 12-methyl ketone instead of the 13^2-cyclic ketone to produce 12-benzoylmethylene substituted chlorin **12** in 61% isolated yield, or 55% isolated yield under the alkaline condition that is same in the synthesis of chlorin **6**.

2 Results and discussion

2.1 Regio- and stereoselectivity of aryl(aroyl)methylenenation for the synthesis of pyropheophorbide derivatives

The cross-aldol reaction of the chlorins related to chlorophyll is closely associated with the reactivity of the carbonyl groups on the periphery and the steric circumstances. Under alkaline condition, MPPa **1a** can form two enol anions $\mathbf{N_1}$ and $\mathbf{N_2}$ by losing the methylic proton at 12-position or the methylenic proton on the *E*-ring. Although the condensation of **1a** with formaldehyde may smoothly occur at both sites by the base catalysis, the current cross-aldol reaction with a bulky aromatic aldehyde under the same condition takes place only at the 12-position. This result shows that the reactivity of the enol anion $\mathbf{N_1}$ is insufficient to overcome the ambient stereohindrance caused by the approaching of the formyl group bearing an aromatic ring, while the corresponding reaction of enol anion $\mathbf{N_2}$ is subjected to lesser spatial obstacles to give C12-arylmethylenated products. Even increasing reaction temperature the expected arylmethylenation on the exocyclic ring was still unsuccessful, which was mainly due to the instability of chlorophyll derivatives in hot alkaline environment that result in an extremely complicated mixture[18] (Figure 1).

Unlike that of the enolization by capturing proton with sodium alkoxide, the enamination of chlorin **1a** starts from the nucleophilic addition of $C13^1$-carbonyl group with the catalysis of sarcosine. The dehydration of the resulted amino-alcohol intermediate $\mathbf{N_3}$ only forms enamine $\mathbf{N_4}$ rather than $\mathbf{N_5}$, because there is always a C—H bond at 13^2-position which keeps at the inverse orientation with the $C13^1$-hydroxyl group, and it is conducive to dehydrate in *trans*-elimination. In addition, the electronic effect from the terminal carboxyl group attached to the 13^1-position can also promote the $C13^2$-proton to leave in the enamination process. By comparison, the formation of enamine $\mathbf{N_5}$ requires higher energy to carry out the dehydration by vinylogy, besides the lack of the favorable *trans*-elimination conformation. Therefore, the enamine $\mathbf{N_5}$ was unavailable and the sarcosine-catalyzed cross aldol condensation exclusively occurred on the exocyclic ring (Figure 1).

Although the enamine $\mathbf{N_4}$ may attack the arylaldehyde from both of the chromophore plane via route-a and route-b, the nucleophilic addition along route-a was blocked by the long chain of propionate residue at 17-position from its protruding orientation. Namely, the two planar reactants can only efficiently close to each other in route-b. Therefore, the nucleophilic addition of the enamine $\mathbf{N_4}$ to aromatic aldehyde has four possible ways ($\mathbf{A_1}$～$\mathbf{A_4}$), which depend on the relative orientation of the molecular plane and functional group. $\mathbf{A_3}$ and $\mathbf{A_4}$ in *endo*-facial approach are difficult to achieve due to the overlap of two planes, and $\mathbf{A_1}$ and $\mathbf{A_2}$ in *exo*-facial approach are

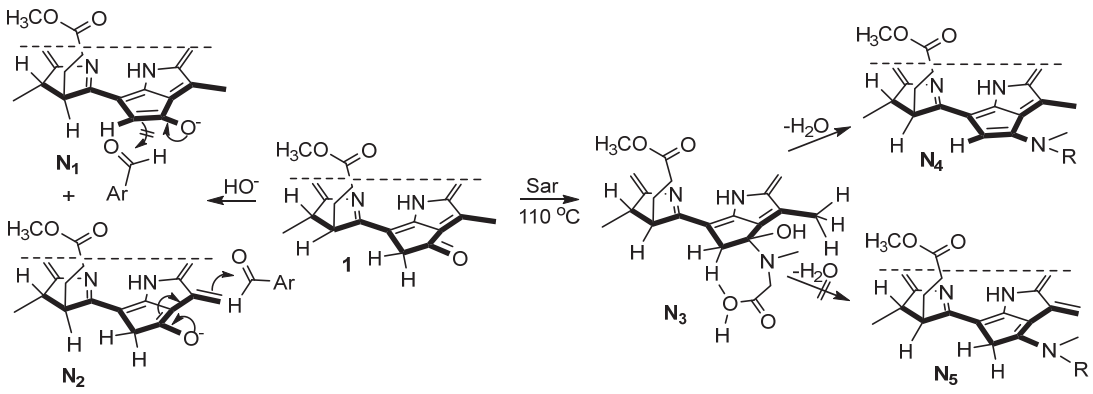


Figure 1 Region-selectivities of the cross-aldol reaction of **1a** with aromatic aldehyde under different conditions

practicable because the chromophore and aromatic ring are distantly separated. According to the orientation of the aldehyde group, the nucleophilic addition of **1a** with aromatic aldehyde should produce two aldol products $\mathbf{B_1}$ and $\mathbf{B_2}$. After converting the corresponding conformational isomers $\mathbf{C_1}$ and $\mathbf{C_2}$ by rotation around the $C13^2$—$C13^2$a bond, the dehydration in *trans*-elimination was accomplished to form the *Z*- and *E*-type 13^2-arylmethylene substituted chlorins **4a**～**4c** and **5a**～**5b**.

According to the favorable ways ($\mathbf{A_1}$ and $\mathbf{A_2}$) of nucleophilic addition and favorable conformation for dehydration in *trans*-elimination ($\mathbf{B_1}$, $\mathbf{C_1}$ and $\mathbf{B_2}$, $\mathbf{C_2}$), the *Z*-type $C13^2$-arylmethylenated chlorin **4** should be the main product. Obviously, the *exo*-addition process will encounter more crowded stereostructure than that in the *endo*-addition process, which has been verified by the proportion of the *E*/*Z* isomers in this cross-aldol reaction. In the case of using pyridinecarboxaldehyde, only the *Z*-type aldol products were isolated and no any *E*-type isomer was observed, which are mainly caused by the repulsion between the nitrogen atom at 13^1-position and the nitrogen atom in the pyridine ring that restricts the approaching way of $\mathbf{A_1}$ (Figure 2).

2.2 Stereo structures and optical properties of the arylmethylenated chlorins

The ^{1}H NMR spectra of the arylmethylenated chlorins left no ambiguity in their structures as cross-Aldol condensation products. The 13^2-aryl-substituted **4a**～**4c** and **5a**～**5b** all clearly showed a low-field shifted singlet signal within the range from δ 8.09 to 8.23, which are ascribable to the arylidene protons on the *E*-ring. A set of mutually coupled absorption peaks corresponding to four to five protons, appearing between δ 6.99～8.21 for **4(5)a**～**4(5)b** and δ 7.53～9.18 for **4c**～**4d**, demonstrated the presence of aromatic rings. In the meantime, the original AB-type signals with large-coupling constant, belonging to the two *gem*-protons on the exocyclic ring, disappeared completely. Except for these changes, the other peripheral proton signals of the chlorins basically remained about the same, which precisely indicated that the arylmethylene moiety was really established at 13^2-position.

The forceful evidence for the arylmethylenations of chlorins **3b** and **7a**～**7b** at 12-position came from the disappearance of the singlet signal assigned to the C12-methyl groups and the emergence of a set of new arylmethylenic absorption peaks in their ^{1}H NMR spectra, while other less altered chemical shifts implied that the original macrocyclic structure was still intact. The two vinylic proton signals with large-coupling constant (*e.g.*, **3b**, δ 9.02 and 8.39, J=15.9 Hz; **7a**, δ 9.17 and 8.30, J=15.4 Hz; **7b**, δ 9.20 and 8.29, J=15.6 Hz) revealed that this C12-disubstituted double bond was *E*-configuration, suggesting the excellent stereoselectivity of the cross-aldol reaction at 12-position. The ^{1}H NMR spectra of diarylmethylenated chlorin **8** exhibited all sorts of the characteristic absorption peaks, and characterized the *E*-type configuration on the *E*-ring that is similar to chlorins **4a** and the *E*-type configuration at 12-position resembled to chlorins **3b** (*e.g.*, 13^2a-H, singlet, δ 8.27; 12a-H, doublet, δ 9.22, J=15.9 Hz, 12b-H, δ 8.57, J=15.9 Hz, 12b-H).

The stereoisomerism of chlorins **4a**～**4d** and **5a**～**5b**, arising from the different orientation of the aromatic ring attached to the $C13^2$-methylene group, gave rise to two sets of absorption peaks which were one-to-one correspondence between the *E*- and *Z*-isomers. Compared to starting material **1a**, the resonance frequency of the other protons in chlorins **4a**～**4d** with *Z*-configuration slightly fluctuated except the disappeared and new-formed ones linked with the exocyclic ring. However, all the chemical shifts, which are ascribable to the protons related to the D-ring of the *E*-isomers **5a**～**5b**, obviously moved to the high-field. Among them, the C17-proton signals even appeared at δ 3.57 for **5a** and 3.49 for **5b**, respectively, and they were in sharp contrast with the ones in *Z*-isomers (δ 4.79 for **4a**; 4.78 for **4b**; 4.78 for **4c**; 4.79 for **4d**). The ethylidenic absorption peaks of the propionate residue at 17-position in **4a**～**4b** were situated in δ 2.02～2.83, while ones of its corresponding isomers **5a**～**5b** appeared among the interval from δ 1.52 to 1.88. The C18-CH_3 signals of these *E*/*Z* isomers also demonstrated obvious difference (*e.g.*, $\Delta\delta$ 0.18 for **4a** and **5a**; $\Delta\delta$ 0.10 for **4b** and **5b**) (Figure 3).

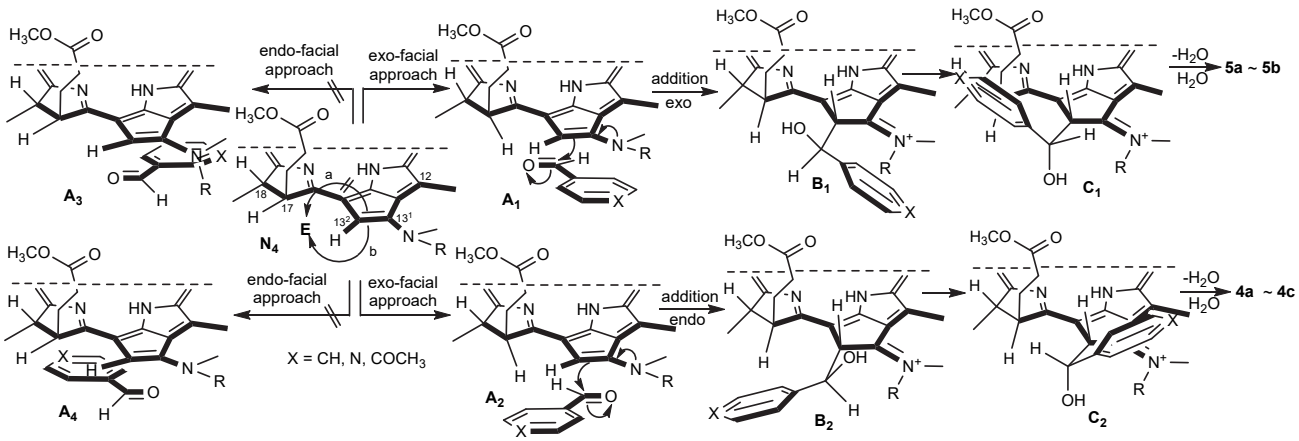


Figure 2 Stereoselectivity based on Lewis acid catalyzed cross-aldol reaction of MPPa **1a** with aromatic aldehyde

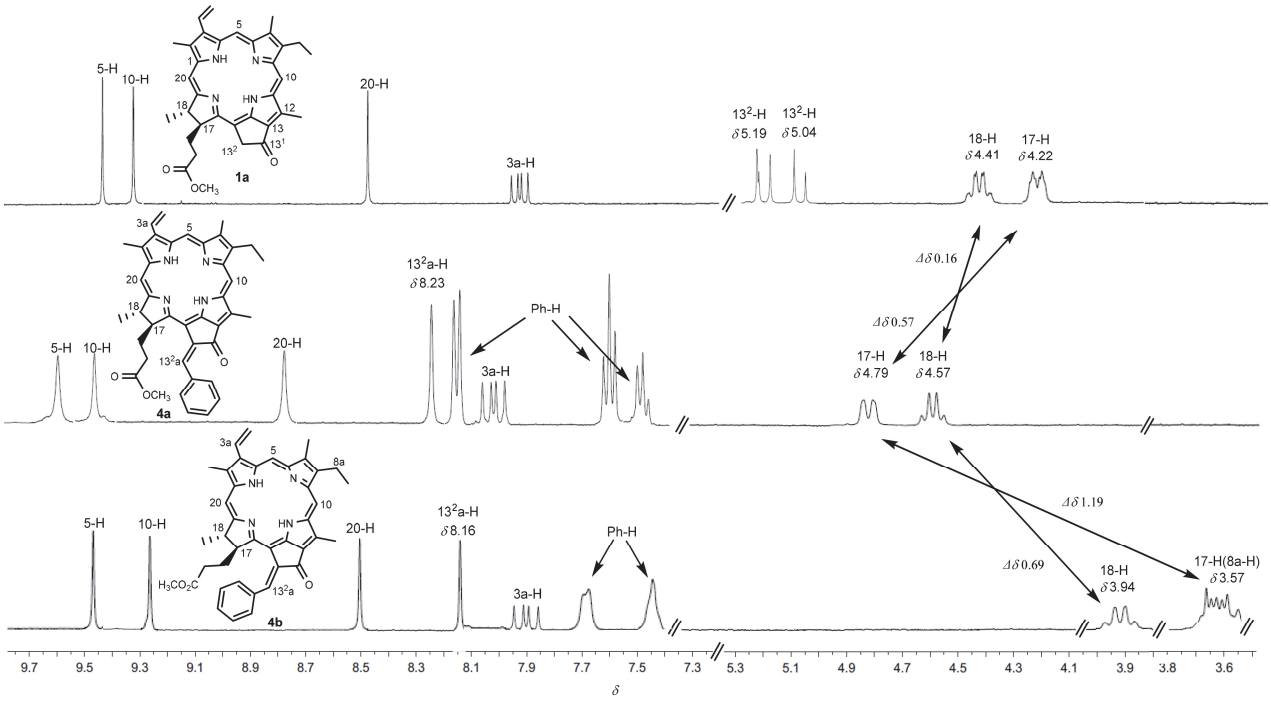


Figure 3 Comparison of the ^{1}H NMR spectra ($CDCl_3$, 400 MHz) in the region of δ 3.5～9.7 for chlorins **1a**, **4a**, and **5a**

Such large discrepancies between these *E*/*Z* isomers quite possibly resulted from the ring current effect of the aromatic rings, attached to the 13^{2}a-position. Taking **4a** and **5a** for instance, the benzylidene group in *Z*-form cross-aldol product **4a** can exert a deshielding effect to the protons jointed at 17- and 18-positions, resulting in their chemical shifts moved to more low-field than the ones of **1a**. In the *E*-isomer **5a**, the C17-H and 18-CH_3 are located just above the aromatic ring (Figures 3 and 4), and thus the relevant proton signals substantially shifted to high-field due to the shielding effect from the benzylidene group linked to the *E*-ring. Compared to the C17-proton, the 18-CH_3 is relatively far away from the aromatic ring, and so its resonance signal moved to high field in a lesser extent.

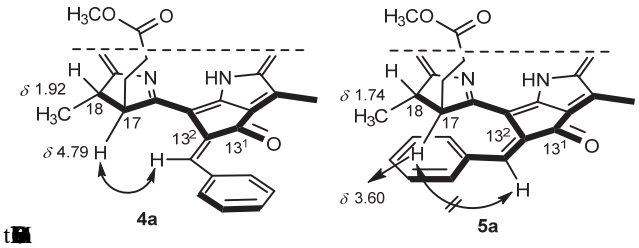


Figure 4 NOE interactions between the C17-H and C13^{2}b-H observed in 2D/NOESY ^{1}H NMR spectra of **4a** and **5a**

Meanwhile, additional ^{1}H 2D NOESY experiments for **4a**～**4b** and **5a**～**5b** were also used to confirm these stereochemical assignments. For example, the NOESY spectra for **4a** with *Z*-configuration revealed a NOE enhancement between the 17-H and the methylenic proton on the *E*-ring, while the relative NOE correlation for the *E*-isomer **5a** was not found based on its 2D spectra, further ascertaining the steric configurations of these *E*/*Z*-isomers (Figure 4). The ^{1}H 2D NOESY spectrum of **4b** and **5b** also reflected the same correlation result.

All UV-vis spectra give three typical electronic absorption bands of chlorins that contain the basic skeleton of chlorophyll. Specifically, the intense Qy, Qx and Soret bands are situated at 709～675, 640～510, and 446～396 nm, respectively. The absorption wavelength of Qy band, determined by transition dipole moments along the molecular *y*-axes (Scheme 1) is an important parameter for the application of chlorophyll.[19-20] Therefore, improvement of π-electron system by the structural modification around the exocyclic ring has already become a main strategy for acquiring tetrapyrrolic macrocycle compounds with excellent optical property.[21]

In the Uv-Vis spectra of the arylmethylenated chlorins (Figure 5), the absorption wavelength and intensity of the Soret and Qy band were intensively changed along with the reaction sites. Compared with **1a**, the arylmethylenation at 12-position in **7a**～**7b** induced a conspicuous bathochromic shifts of the Qy peaks by 32～38 nm due to the extension of the conjugated systems of the macrocyclic chromophores, while the C13^2-arylmethylenated chlorins **4a**～**4d** and **5a**～**5b** only exhibited a bathochromic shift of 10～11 nm for their maximum absorption wavelengths. The Qy peaks of the C12- and C13^2-methylenated chlorins, obtained in our previous works,[22] were situated at 675 and 682 nm, respectively. The ΔQy caused by the transformations (**2a**→**3a**, **6**→**7a**) at 12-position from vinyl to phenylvinyl group reached up to 13 and 21 nm, respectively, but the difference of the Qy peaks between the 13^2-methylenated chlorins and 13^2-phenylmethylenated chlorins (**2a**→**4a**, **2a**→**5a**) was only 3～4 nm.

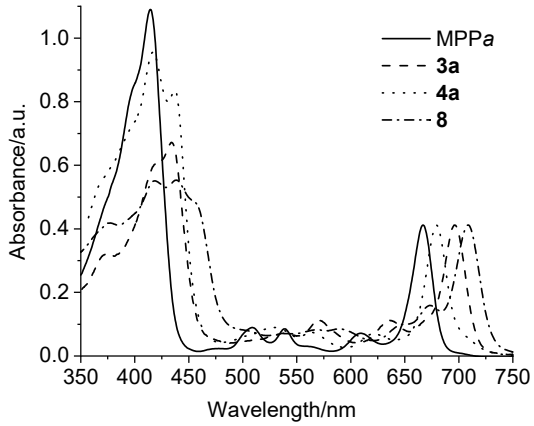


Figure 5 UV-Vis spectra of **1a**, arylmethylenated chlorins **3a**, **4a** and diarylmethylenated chlorin **8** in CH_2Cl_2

These results indicated that the introduction of the conjugated group at 12-position effectively contributes to the red-shift for the longest absorption band. By comparison with the 12-position, the 13^2-position is relatively far from the molecular *y*-axes, and its bonding orientation deviates more significantly from the Qy axes. Another probably factor is that the rigidity of exocyclic ring and ambient crowded space restrict the formation of the coplane between the 13^2-substituted group and chlorin chromophore. The UV-vis spectra of **4a** with *E*-configuration and **5a** with *Z*-configuration are very similar, and their Qy absorptions are nearly identical (ΔQy＝1 nm), which can further explain that the C13^2a-benzene ring does not form efficient conjugation with the macrocyclic chromophore. The maximum absorption wavelength of diarylalkenyl-substituted chlorin **8** even appeared at 709 nm, which was largely due to the wider extension in the system by two cross-aldol condensations at 12- and 13^2-positions with aromatic aldehyde

Similar to the arylmethylenenation, the aroylmethylenenation on chlorin periphery was also extended the macrocyclic conjugate system, resulting in the significant shift of the Qy peaks towards the long wavelengths. For instance, the Qy peak of the C12a-aroylmethylenenated product (chlorin **9**) is 5 nm longer than that of 12-styryl-substituted chlorin **3a**. The C13^1-benzoylmethylenenation of diketone **1b** (**1b**～**10**) also caused a change in its Qy absorption band from 679 nm to 684 nm. In addition, the ΔQy between chlorins **9** and **12** was 7 nm, which demonstrated that the connecting position of the enone structure with macrocycle similarly influences their electronic spectrum.

3 Conclusions

In summary, an efficient and practical method for the preparation of novel chlorophyll derivatives, which contain different enone units, has been developed. The regio- and stereoselective aryl(aroyl)methylenenation of chlorins with basic skeleton of chlorophyll were accomplished on the exocyclic ring or at 12-position based on cross-aldol condensation. The introduction of arylmethylene or aroylmethylene group causes remarkable bathochromic shift in the Qy peak maxima, which can also regioselectively establish new functional structure that is amenable to many common chemical reaction. This method of forming *α*,*β*-unsaturated carbonyl group on the periphery of chlorophyll provides a more extensive synthetic route for acquiring novel macrocycle compound with potential application prospect.

4 Experimental sections

4.1 General

The UV-vis spectra were taken with a Unicam SP 800 spectrophotometer. The ^{1}H NMR spectra were recorded with a Varian 400 spectrometer. Mass spectra were recorded by a JMX-DX300. The elemental analyses were performed on a Perkin-Elmer 240 microanalyzer. Methyl pyropheophorbide-*a* **1a** was obtained according to Smith's method.[14] All chemical reagents were purchased from Merck, Fluka and Aldrich chemical companies and purified by using standard methods.

4.2 Synthesis of methyl 13^2-methylenepyropheophorbide-*a* (**2a**) and methyl 12-vinyl-12-demethylpyropheophorbide-*a* (**2b**)

Methyl pyropheophorbide-*a* **1a** (98 mg, 0.178 mmol) and paraformaldehyde (100 mg) were dissolved in THF (15 mL), and a solution of sodium methoxide in methanol (1 mol/L, 0.6 mL) was added under N_2 atmosphere, then the reaction mixture was stirred at room temperature under N_2 atmosphere for 5 h, monitoring the progress spectroscopically. The pH value of the reaction mixture was adjusted to 4～5 by adding diluted hydrochloric acid and extracted with dichloromethane (10 mL×3). The combined organic layers were washed with water, dried over sodium sulfate, and evaporated in vacuum. The residue was dissolved in methanol containing 5% H_2SO_4 (30 mL) and allowed to stir at room temperature under N_2 atmosphere overnight to recover the 17^3-methyl ester structure. The mixture was diluted with water and extracted with dichloromethane (10 mL×3). The combined organic layers were washed with water, dried over sodium sulfate, and evaporated in vacuum. The residue was separated on silica gel (eluent: dichloromethane-acetone, gradient 0.5%～2% acetone) to give 75 mg of **2a** (0.134 mmol, 75%) as orange solid and 9 mg of **2b** (0.016 mmol, 9%) as dark green solid. **2a**: Their analytical data are consistent with ones in the literature.[18,22]

4.3 Synthesis of methyl 12-styryl-12-demethylpyropheophorbide-*a* (**3a**)

This compound as a green solid was obtained from compound **1a** by reacting with benzaldehyde in the yield of 37% according to the method for preparing compound **2a**～**2b**. m.p. 261.0～261.9 ℃; UV-vis ($CHCl_3$) λ_{max} (relative intensity): 419 (0.97), 433 (1.00), 542 (0.12), 571 (0.18), 637 (0.17), 696 (0.61) nm; ^{1}H NMR (600 MHz, $CDCl_3$) *δ*: 9.10, 9.02, 8.37 (each s, each 1H, *meso*-H), 8.95 (d, *J*＝15.8 Hz, 1H, *trans*-12a-H), 8.17 (d, *J*＝15.8 Hz, 1H,

trans-12b-H), 7.93～7.87 (m, 2H, Ph-H), 7.81 (dd, *J*=17.8, 11.5 Hz, 1H, 3a-H), 7.54 (t, *J*=7.5 Hz, 2H, Ph-H), 7.45～7.39 (m, 1H, Ph-H), 6.18 (dd, *J*=17.8, 1.2 Hz, 1H, *trans*-3b-H), 6.08 (dd, *J*=11.5, 1.2 Hz, 1H, *cis*-3b-H), 5.17 (d, *J*=18.9 Hz, 1H, 13^2-H), 5.03 (d, *J*=18.8 Hz, 1H, 13^2-H), 4.39 (qd, *J*=7.6, 2.1 Hz, 1H, 17-H), 4.21 (dt, *J*=9.3, 2.8 Hz, 1H, 18-H), 3.66, 3.28, 3.04 (each s, each 3H, CH_3+OCH_3), 3.43 (q, *J*=7.3 Hz, 2H, 8a-CH_2), 2.72～2.64, 2.60～2.55, 2.35～2.24 (each m, total 4H, 17a+17b-CH_2), 1.84 (d, *J*=7.5 Hz, 3H, 18-CH_3), 1.57 (t, *J*=7.8 Hz, 3H, 8a-CH_3), 0.70 (br s, 1H, NH), −1.27 (br s, 1H, NH); ^{13}C NMR (101 MHz, Chloroform-*d*) *δ*: 194.24, 173.59, 171.90, 159.88, 155.54, 150.69, 150.24, 144.46, 141.97, 137.79, 136.79, 136.72, 136.64, 135.65, 135.42, 131.67, 129.37, 128.85, 128.79, 128.28, 127.37, 126.32, 122.11, 118.47, 105.96, 102.38, 96.62, 92.93, 51.81, 51.48, 49.98, 47.69, 31.15, 29.71, 23.01, 19.02, 17.21, 11.96, 10.94; HRMS (ESI) calcd for $C_{41}H_{41}N_4O_3$ $(M+H)^+$ 637.3173, found 637.3162. Anal. calcd for $C_{41}H_{40}N_4O_3$: C 77.33, H 6.33, N 8.80; found C 77.22, H 6.41, N 8.87.

4.4 Synthesis of methyl 12-(4-nitrostyryl)-12-demethylpyropheophorbide-*a* (**3b**)

This compound as a green solid was obtained from compound **1a** by reacting with 4-nitrobenzaldehyde in the yield of 30% according to the method for preparing compound **2a**～**2b**. m.p. 243.2～244.3 ℃; UV-vis ($CHCl_3$) λ_{max} (relative intensity): 418 (0.65), 438 (0.891), 538 (0.11), 579 (0.19), 640 (0.20), 701 (0.65) nm; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.36 (s, 1H, 10-H), 9.19 (s, 1H, 5-H), 8.95 (d, *J*=15.8 Hz, 1H, 12^1-H), 8.40 (s, 1H, 20-H), 8.28 (d, *J*=15.8 Hz, 1H, 12^2-H), 7.92 (dd, *J*=17.8, 11.6 Hz, 1H, 3^1-H), 7.80 (d, *J*=8.2 Hz, 2H, ph-H), 7.45 (d, *J*=8.2 Hz, 2H, ph-H), 6.26 (dd, *J*=17.8, 1.4 Hz, 1H, 3^2-H), 6.15 (dd, *J*=11.5, 1.4 Hz, 1H, 3^2-H), 5.24 (d, *J*=19.8 Hz, 1H, 13^2-H), 5.09 (d, *J*=19.8 Hz, 1H, 13^2-H), 4.41 (q, *J*=7.9 Hz, 1H, 18-H), 4.24 (d, *J*=8.7 Hz, 1H, 17-H), 3.62 (q, *J*=7.6 Hz, 2H, 8^1-CH_2), 3.63, 3.33, 3.18 (each s, each 3H, CH_3+OCH_3), 2.75～2.52, 2.38～2.16 (each m, total 4H, 17^1+17^2-CH_2), 1.81 (d, *J*=7.3 Hz, 3H, 18-CH_3), 1.67 (t, *J*=7.6 Hz, 3H, 8^2-CH_3), −1.02 (s, 1H, NH); ^{13}C NMR (101 MHz, Chloroform-*d*) *δ*: 194.54, 173.47, 172.40, 160.16, 156.37, 151.44, 150.69, 145.19, 142.34, 137.37, 137.25, 136.37, 136.31, 136.03, 135.77, 133.85, 132.08, 129.56, 128.99, 128.95, 128.95, 128.54, 128.54, 126.87, 122.66, 119.40, 106.38, 103.10, 96.98, 93.26, 51.70, 51.46, 50.02, 47.73, 30.97, 27.22, 22.97, 19.41, 17.32, 12.01, 11.22; MS (ESI) *m/z*: 682.4 $(M+H)^+$. Anal. calcd for $C_{41}H_{39}N_5O_5$: C 72.23, H 5.77, N 10.27; found C 72.15, H 5.89, N 10.45.

4.5 Synthesis of (*Z*)-methyl 13^2-benzylidenepyropheophorbide-*a* (**4a**) and (*E*)-methyl 13^2-benzylidenepyropheophorbide-*a* (**5a**)

Methyl pyropheophorbide-*a* **1a** (22 mg, 0.040 mmol) and newly-distilled benzaldehyde (8.5 mg, 0.08 mmol) were dissolved in toluene (10 mL), and sarcosine (50 mg) was added under N_2 atmosphere, then the reaction mixture was refluxed at 115 ℃ under N_2 atmosphere for 4 h, monitoring the progress spectroscopically. The pH value of the reaction mixture was adjusted to about 3 by adding diluted hydrochloric acid and extracted with dichloromethane (15 mL×2). The combined organic layers were washed with water, dried over sodium sulfate, and evaporated in vacuum. The obtained mixture was treated with CH_2N_2 for short time (approximately 2 min). After evaporation in vacuum, the residue was purified on chromatography on a silica gel column with hexane-ethyl acetate (*V*∶*V*=5∶1) as eluent to give 8.2 mg of **4a** (0.013 mmol, 32%) as an orange-red solid and 2.8 mg of **5a** (0.004 mmol, 11%) as an orange-red solid.

4a: m.p. >300 ℃; UV-vis ($CHCl_3$) λ_{max} (relative intensity): 410 (0.89), 439 (0.99), 446 (1.00), 546 (0.10), 587 (0.06), 632 (0.06), 679 (0.50) nm; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.57, 9.44, 8.75 (each s, each 1H, *meso*-H), 8.23 (s, 1H, 13^2a-H), 8.12 (d, *J*=7.5 Hz, 2H, Ph-H), 7.99 (dd, *J*=17.9, 11.2 Hz, 1H, 3a-H), 7.57 (t, *J*=7.5 Hz, 2H, Ph-H), 7.47 (t, *J*=7.5 Hz, 1H, Ph-H), 6.28 (d, *J*=17.9 Hz, 1H, *trans*-3b-H), 6.17 (d, *J*=11.2 Hz, 1H, *cis*-3b-H), 4.80 (d, *J*=8.1 Hz, 1H, 17-H), 4.67 (q, *J*=7.3 Hz, 1H, 18-H), 3.66 (q, *J*=7.6 Hz, 2H, 8a-CH_2), 3.67, 3.55, 3.43, 3.21 (each s, each 3H, CH_3+OCH_3), 2.83～2.76, 2.68～2.60, 2.38～2.32, 2.13～2.03 (each m, total 4H, 17a+17b-CH_2), 1.92 (d, *J*=7.3 Hz, 3H, 18-CH_3), 1.67 (t, *J*=7.6 Hz, 3H, 8a-CH_3), −0.26, −1.86 (each br s, each 1H, NH); ^{13}C NMR (101 MHz, Chloroform-*d*) *δ*: 187.17, 173.42, 161.54, 154.82, 150.57, 147.80, 144.78, 142.97, 142.28, 138.27, 136.84, 136.11, 135.98, 135.84, 135.63, 133.16, 131.38, 131.01, 129.49, 129.10, 128.68, 128.31, 127.78, 122.45, 109.71, 104.25, 97.98, 93.87, 51.73, 51.48, 49.90, 31.26, 29.75, 23.83, 19.37, 17.46, 12.17, 11.84, 11.15; HRMS (ESI) calcd for $C_{41}H_{41}$-N_4O_3 $(M+H)^+$ 637.3173, found 637.3162. Anal. calcd for $C_{41}H_{40}N_4O_3$: C 77.33, H 6.33, N 8.80; found C 77.45, H 6.42, N 8.71.

5a: m.p. >300 ℃; UV-vis ($CHCl_3$) λ_{max} (relative intensity): 410 (0.89), 436 (0.99), 446 (1.00), 545 (0.11), 584 (0.07), 629 (0.07), 678 (0.52) nm; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.48, 9.27, 8.56 (each s, each 1H, *meso*-H), 8.16 (s, 1H, 13^2a-H), 7.88 (dd, *J*=17.9, 11.2 Hz, 1H, 3a-H), 7.69～7.75 (m, 2H, Ph-H), 7.42～7.53 (m, 3H, Ph-H), 6.21 (dd, *J*=17.9, 1.0 Hz, 1H, *trans*-3b-H), 6.10 (dd, *J*=11.5, 1.0 Hz, 1H, *cis*-3b-H), 3.94 (q, *J*=7.3 Hz, 1H, 18-H), 3.57 (d, *J*=7.7 Hz, 1H, 17-H), 3.60 (q, *J*=7.6 Hz, 2H, 8a-CH_2), 3.72, 3.42, 3.33, 3.13 (each s, each 3H, CH_3+OCH_3), 1.88～1.72, 1.71～1.52, (each m, total 4H, 17a+17b-CH_2), 1.74 (d, *J*=7.3 Hz, 3H, 18-CH_3), 1.65 (t, *J*=7.6 Hz, 3H, 8a-CH_3), 0.20, −1.70 (each br s, each 1H, NH); ^{13}C NMR (101 MHz, Chloroform-*d*) *δ*: 187.38, 173.39, 154.83, 149.96, 144.82, 142.96, 142.27, 138.26, 136.32, 136.13, 135.96, 133.21, 131.47, 130.99, 129.27, 129.14, 129.07, 128.64, 128.31, 127.76, 122.57, 122.53, 104.68, 104.32, 98.20, 98.04, 93.72, 52.73, 51.45, 49.65, 31.11, 29.74, 23.95, 19.42, 17.45, 12.28, 12.08, 11.18; HRMS (ESI) calcd for $C_{41}H_{41}N_4O_3$ $(M+H)^+$ 637.3173, found 637.3164. Anal. calcd for $C_{41}H_{40}N_4O_3$: C 77.33, H 6.33, N

8.80; found C 77.44, H 6.20, N 8.91.

4.6 Synthesis of (*Z*)-methyl 13²-(4-methoxybenzylidene)-pyropheophorbide-*a* (**4b**) and (*E*)-methyl 13²-(4-methoxybenzylidene)-pyropheophorbide-*a* (**5b**)

These compounds were obtained from compound **1a** by reacting with 4-methoxybenzaldehyde in the yield of 34% and 10% according to the method for preparing compound **4a** and **5a**.

4b as a green solid: m.p. >300 ℃; UV-vis ($CHCl_3$) λ_{max} (relative intensity): 396 (0.87), 419 (0.99), 446 (2.123), 546 (0.10), 584 (0.07), 633 (0.06), 679 (0.52) nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.52, 9.34, 8.67 (each s, each 1H, *meso*-H), 8.21 (d, J=8.4 Hz, 2H, Ph-H), 8.15 (s, 1H, 13²a-H), 7.95 (dd, J=17.8, 11.2 Hz, 1H, 3a-H), 7.10 (d, J=8.4 Hz, 2H, Ph-H), 6.26 (d, J=17.8 Hz, 1H, *trans*-3b-H), 6.14 (d, J=11.6 Hz, 1H, *cis*-3b-H), 4.78 (d, J=7.9 Hz, 1H, 17-H), 4.54 (q, J=7.2 Hz, 1H, 18-H), 3.61 (q, J=7.6 Hz, 2H, 8a-CH_2), 3.95, 3.64, 3.56, 3.41, 3.13 (each s, each 3H, CH_3+OCH_3), 2.80～2.73, 2.66～2.58, 2.37～2.29, 2.11～2.02 (each m, total 4H, 17a+17b-CH_2), 1.91 (d, J=7.2 Hz, 3H, 18-CH_3), 1.65 (t, J=7.6 Hz, 3H, 8a-CH_3), −0.21, −1.85 (each br s, each 1H, NH); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 187.59, 173.48, 160.17, 144.87, 141.82, 140.81, 136.16, 135.66, 133.27, 131.44, 130.38, 129.71, 129.32, 129.22, 129.15, 128.53, 122.54, 122.46, 114.47, 113.30, 110.59, 107.28, 104.70, 104.35, 98.20, 97.93, 93.89, 93.69, 55.49, 51.76, 49.96, 32.02, 23.83, 22.79, 19.47, 17.52, 14.22, 11.88, 11.23; HRMS (ESI) calcd for $C_{42}H_{43}N_4O_4$ $(M+H)^+$ 667.3279, found 667.3273. Anal. calcd for $C_{41}H_{42}N_4O_4$: C 75.65, H 6.35, N 8.40; found C 75.55, H 6.29, N 8.29.

5b as a green solid: m.p. >300 ℃; UV-vis ($CHCl_3$) λ_{max} (relative intensity): 396 (0.84), 419 (0.93), 443 (2.245), 534 (0.13), 569 (0.09), 631 (0.05), 678 (0.51) nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.54, 9.36, 8.53 (each s, each 1H, *meso*-H), 8.09 (s, 1H, 13²a-H), 7.96 (dd, J=17.8, 11.6 Hz, 1H, 3a-H), 7.69 (d, J=8.4 Hz, 2H, Ph-H), 6.99 (br s, 2H, Ph-H), 6.26 (dd, J = 17.8, 1.0 Hz, 1H, *trans*-3b-H), 6.21 (dd, J=11.6, 1.0 Hz, 1H, *cis*-3b-H), 3.98 (q, J=7.3 Hz, 1H, 18-H), 3.49 (dd, J=8.6, 2.4 Hz, 1H, 17-H), 3.66 (q, J=7.6 Hz, 2H, 8a-CH_2), 3.90, 3.70, 3.41, 3.37, 3.21 (each s, each 3H, CH_3+OCH_3), 1.86～1.73, 1.66～1.53 (each m, total 4H, 17a+17b-CH_2), 1.81 (d, J=7.3 Hz, 3H, 18-CH_3), 1.68 (t, J=7.6 Hz, 3H, 8a-CH_3), 0.26, −1.62 (each br s, each 1H, NH); ^{13}C NMR (101 MHz, Chloroform-*d*) δ: 187.61, 173.41, 160.10, 144.77, 141.75, 141.13, 140.75, 136.72, 136.07, 135.75, 133.50, 133.24, 131.38, 130.30, 129.93, 129.29, 129.05, 128.47, 122.47, 122.38, 114.39, 113.25, 107.21, 104.61, 104.24, 98.10, 93.64, 55.45, 52.84, 51.45, 49.74, 31.19, 23.96, 19.39, 17.47, 12.26, 12.09, 11.15; HRMS (ESI) calcd for $C_{42}H_{43}N_4O_4$ $(M+H^+)$ 667.3279, found 667.3274. Anal. calcd for $C_{42}H_{42}N_4O_4$: C 75.65, H 6.35, N 8.40; found C 75.73, H 6.44, N 8.51.

4.7 Synthesis of (*Z*)-methyl 13²-(4-pyridylidene)-pyropheophorbide-*a* (**4c**)

This compound as a green solid was obtained from compound **1a** by reacting with 4-pyridinecarboxaldehyde in the yield of 29% according to the method for preparing compound **4a** and **5a**. m.p. >300 ℃; UV-vis ($CHCl_3$) λ_{max} (relative intensity): 419 (1.00), 439 (0.65), 537 (0.18), 583 (0.09), 630 (0.09), 679 (0.33) nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.62, 9.51, 8.75 (each s, each 1H, *meso*-H), 8.80 (d, J=5.2 Hz, 2H, Py-H), 8.21 (s, 1H, 13²a-H), 8.11 (d, J=5.2 Hz, 2H, Py-H), 8.02 (dd, J=18.0, 11.2 Hz, 1H, 3a-H), 6.33 (d, J=18.0 Hz, 1H, *trans*-3b-H), 6.21 (d, J=11.2 Hz, 1H, *cis*-3b-H), 4.78 (d, J=10.0 Hz, 1H, 17-H), 4.60 (q, J=7.2 Hz, 1H, 18-H), 3.72 (q, J=7.6 Hz, 2H, 8a-CH_2), 3.72, 3.65, 3.46, 3.26 (each s, each 3H, CH_3+OCH_3), 2.85～2.70, 2.47～2.27, 2.08～1.95 (each m, total 4H, 17a+17b-CH_2), 1.90 (d, J=7.2 Hz, 3H, 18-CH_3), 1.71 (t, J=7.6 Hz, 3H, 8a-CH_3), −0.05, −1.88 (each br s, each 1H, NH); MS (ESI) *m/z*: 638.4 $(M+H)^+$. Anal. calcd for $C_{40}H_{39}N_5O_3$: C 75.33, H 6.16, N 10.98; found C 75.41, H 6.23, N 11.07.

4.8 Synthesis of (*Z*)-methyl 13²-(3-pyridylidene)-pyropheophorbide-*a* (**4d**)

This compound as a green solid was obtained from compound **1a** by reacting with 4-pyridinecarboxaldehyde in the yield of 21% according to the method for preparing compound **4a** and **5a**. m.p. >300 ℃; UV-vis ($CHCl_3$) λ_{max} (relative intensity): 407 (0.88), 433 (0.96), 444 (1.00), 545 (0.11), 586 (0.05), 634 (0.05), 678 (0.48) nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.45, 9.36, 8.71 (each s, each 1H, *meso*-H), 9.18 (s, 1H, Py-H), 8.68 (br s, 2H, Py-H), 8.20 (s, 1H, 13²a-H), 7.97 (dd, J=18.0, 11.2 Hz, 1H, 3a-H), 7.53 (dd, J=8.0, 3.2 Hz, 1H, Py-H), 6.28 (d, J=16.8 Hz, 1H, *trans*-3b-H), 6.15 (d, J=11.6 Hz, 1H, *cis*-3b-H), 4.79 (d, J=8.8 Hz, 1H, 17-H), 4.57 (q, J=7.6 Hz, 1H, 18-H), 3.60 (q, J=7.6 Hz, 2H, 8a-CH_2), 3.63, 3.61, 3.43, 3.17 (each s, each 3H, CH_3+OCH_3), 2.83～2.70, 2.44～2.33, 2.22～1.92 (each m, total 4H, 17a+17b-CH_2), 1.92 (d, J=7.6 Hz, 3H, 18-CH_3), 1.65 (t, J=7.6 Hz, 3H, 8a-CH_3), −0.19, −1.93 (each br s, each 1H, NH); MS (ESI) *m/z*: 638.3 $(M+H)^+$. Anal. calcd for $C_{40}H_{39}N_5O_3$: C 75.33, H 6.16, N 10.98; found C 75.25, H 6.20, N 10.85.

4.9 Synthesis of methyl 12-vinyl-13²-methylene-12-demethyl pyropheophorbide-*a* (**6**)

Compound **2a** (20 mg, 0.036 mmol) and paraformaldehyde (20 mg) were dissolved in anhydrous THF (5 mL), and a solution of sodium methoxide in methanol (1 mol/L, 0.2 mL) was added under N_2 atmosphere, then the reaction mixture was stirred at room temperature under N_2 atmosphere for 6 h monitoring the progress spectroscopically. The pH value of the reaction mixture was adjusted to 4～5 by adding diluted hydrochloric acid and extracted with dichloromethane (30 mL×3). The combined organic layers were washed with water, dried over sodium sulfate, and evaporated in vacuum. The residue was dissolved in 100 mL of methanol containing 5% H_2SO_4 and allowed to stir

at room temperature under N_2 atmosphere overnight. The mixture was diluted with water and extracted with dichloromethane. The combined organic layers were washed with water, dried over sodium sulfate, and evaporated in vacuum. The residue was separated on silica gel (eluent: dichloromethane-acetone, gradient 0.5%～2% acetone) to give 13 mg **6** (0.022 mmol, 62%) as dark green solid. Its analytical data is consistent with ones in the literature [14, 23].

4.10 Synthesis of (*Z*)-methyl 12-styryl-13^2-methylene-12-demethylpyropheophorbide-*a* (**7a**)

This compound as a green solid was obtained from compound **2a** by reacting with benzaldehyde in the yield of 68% according to the method for preparing compound **6**. m.p. ＞300 ℃; UV-vis ($CHCl_3$) λ_{max} (relative intensity): 398 (0.73), 440 (1.00), 587 (0.20), 642 (0.20), 702 (0.80) nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.33, 9.22, 8.55 (each s, each 1H, *meso*-H), 9.17 (d, J=15.4 Hz, 1H, 12a-H), 8.30 (d, J=15.4 Hz, 1H, 12b-H), 7.94 (d, J=7.5 Hz, 1H, Ph-H), 7.90 (dd, J=17.9, 11.5 Hz, 1H, 3a-H), 7.55 (t, J=7.5 Hz, 2H, Ph-H), 7.42 (t, J=7.5 Hz, 1H, Ph-H), 6.88 (s, 1H, 13^{2}a-H), 6.55 (s, 1H, 13^{2}a-H), 6.24 (d, J=17.9 Hz, 1H, *trans*-3b-H), 6.14 (d, J=11.5 Hz, 1H, *cis*-3b-H), 4.61 (d, J=8.6 Hz, 1H, 17-H), 4.49 (q, J=7.3 Hz, 1H, 18-H), 3.52 (q, J=7.6 Hz, 2H, 8a-CH_2), 3.67, 3.34, 3.12 (each s, each 3H, CH_3+OCH_3), 2.74～2.62, 2.42～2.34, 2.07～1.97 (each m, total 4H, 17a+17b-CH_2), 1.87 (d, J=7.2 Hz, 3H, 18-CH_3), 1.61 (t, J=7.6 Hz, 3H, 8a-CH_3), 0.65, −1.44 (each br s, each 1H, NH); HRMS (ESI) calcd for $C_{42}H_{40}N_4NaO_3$ $(M+H)^+$ 671.2993, found 671.3212. Anal. calcd for $C_{40}H_{40}N_4O_3$: C 77.75, H 6.21, N 8.64; found C 77.85, H 6.31, N 8.75.

4.11 Synthesis of (*Z*)-methyl 12-(4-nitrostyryl)-13^2-methylene-12-demethylpyropheophorbide-*a* (**7b**)

This compound as a green solid was obtained from compound **2a** by reacting with 4-nitrobenzaldehyde in the yield of 62% according to the method for preparing compound **6**. m.p. ＞300 ℃; UV-vis ($CHCl_3$) λ_{max} (relative intensity): 435 (1.00), 504 (0.12), 587 (0.15), 670 (0.29), 706 (0.74) nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.49, 9.29, 8.59 (each s, each 1H, *meso*-H), 9.20 (d, J=15.6 Hz, 1H, 12a-H), 8.29 (d, J=15.6 Hz, 1H, 12b-H), 7.92 (d, J=7.5 Hz, 2H, Ph-H), 7.84 (dd, J=17.9, 11.5 Hz, 1H, 3a-H), 7.08 d, J=7.5 Hz, 2H, Ph-H), 6.87 (s, 1H, 13^{2}a-H), 6.55 (s, 1H, 13^{2}a-H), 6.26 (d, J=17.9 Hz, 1H, *trans*-3b-H), 6.15 (d, J=11.5 Hz, 1H, *cis*-3b-H), 4.62 (d, J=8.0 Hz, 1H, 17-H), 4.50 (q, J=7.6 Hz, 1H, 18-H), 3.62 (q, J=7.6 Hz, 2H, 8a-CH_2), 3.94, 3.67, 3.37 (each s, each 3H, CH_3+OCH_3), 2.75～2.62, 2.44～2.33, 2.08～1.98 (each m, total 4H, 17a+17b-CH_2), 1.86 (d, J=7.2 Hz, 3H, 18-CH_3), 1.67 (t, J=7.6 Hz, 3H, 8a-CH_3), 0.45, −1.43 (each br s, each 1H, NH); MS (ESI) *m/z*: 694.4 $(M+H)^+$. Anal. calcd for $C_{42}H_{39}N_5O_4$: C 72.71, H 5.67, N 10.09; found C 72.69, H 5.52, N 10.21.

4.12 Synthesis of (12*Z*, 13^2*Z*)-methyl 12-styryl-13^2-benzylidene-12-demethylpyropheophorbide-*a* (8)

This compound as a green solid was obtained from compound **4a** by reacting with benzaldehyde in the yield of 48% according to the method for preparing compound **6** or from compound **3a** by reacting with benzaldehyde in the yield of 7% according to the method for preparing compound **4a** and **5a**. m.p. 295.0～296.0 ℃; UV-vis ($CHCl_3$) λ_{max} (relative intensity): 419 (1.00), 482 (0.05), 514 (0.06), 550 (0.19), 655 (0.08), 709 (0.36) nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.76, 9.38, 8.65 (each s, each 1H, *meso*-H), 9.22 (d, J=15.9 Hz, 1H, 12a-H), 8.57 (d, J=15.6 Hz, 1H, 12b-H), 8.27 (s, 1H, 13^{2}a-H), 8.13 (d, J=7.5 Hz, 2H, Ph-H), 8.09 (d, J=8.1 Hz, 2H, Ph-H), 7.93 (dd, J=17.6, 11.2 Hz, 1H, 3a-H), 7.60 (t, J=7.5 Hz, 2H, Ph-H), 7.53 (d, J=7.5 Hz, 2H, Ph-H), 7.49 (d, J=7.5 Hz, 1H, Ph-H), 7.43 (d, J=7.5 Hz, 1H, Ph-H), 6.30 (d, J=17.6 Hz, 1H, *trans*-3b-H), 6.19 (d, J=11.2 Hz, 1H, *cis*-3b-H), 4.77 (d, J=9.4 Hz, 1H, 17-H), 4.52 (q, J=7.2 Hz, 1H, 18-H), 3.73 (q, J=7.5 Hz, 2H, 8a-CH_2), 3.56, 3.41, 3.24 (each s, each 3H, CH_3+OCH_3), 2.75～2.63, 2.68～2.57, 2.42～2.27, 2.11～1.98 (each m, total 4H, 17a+17b-CH_2), 1.91 (d, J=7.2 Hz, 18-CH_3), 1.71 (t, J=7.5 Hz, 3H, 8a-CH_3), −0.17, −1.35 (each br s, each 1H, NH); ^{13}C NMR (101 MHz, Chloroform-*d*) δ: 185.39, 173.39, 170.81, 150.61, 147.14, 144.76, 141.73, 138.35, 137.85, 137.77, 136.64, 136.11, 136.00, 135.65, 133.35, 131.75, 131.17, 128.93, 128.73, 128.34, 127.86, 127.52, 125.94, 125.04, 122.40, 118.57, 110.87, 109.73, 103.18, 97.70, 94.86, 94.05, 93.89, 51.71, 51.32, 49.92, 31.33, 29.45, 23.71, 19.27, 17.28, 12.07, 11.10; HRMS (ESI) calcd for $C_{48}H_{45}N_4O_3$ $(M+H)^+$ 725.3486, found 725.3471. Anal. calcd for $C_{48}H_{44}N_4O_3$: C 79.53, H 6.12, N 7.73; found C 79.44, H 6.24, N 7.85.

4.13 Synthesis of (*Z*)-methyl 12-benzoylidene-12-demethylpyropheophorbide-*a* (9)

This compound as a green solid was obtained from compound **1d**[18] by reacting with benzaldehyde in the yield of 59% according to the method for preparing compound **6**. m.p. ＞300 ℃; UV-vis ($CHCl_3$) λ_{max} (relative intensity): 417 (1.00), 531 (0.07), 591 (0.20), 665 (0.18), 701 (0.45) nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.09, 8.83, 8.23 (each s, 3H, *meso*-H), 9.42 (d, J=14.9 Hz, 1H, 12a-H), 8.93 (d, J=14.9 Hz, 1H, 12b-H), 8.47 (d, J=7.7 Hz, 1H, Ph-H), 7.95 (d, J=7.4 Hz, 1H, Ph-H), 7.70-7.63 (m, 1H, Ph-H), 7.58 (d, J=7.4 Hz, 1H, Ph-H), 7.46 (d, J=7.7 Hz, 1H, Ph-H), 7.74 (dd, J=18.0, 11.6 Hz, 1H, 3a-H), 6.17 (d, J=18.0 Hz, 1H, *trans*-3b-H), 6.09 (d, J=11.6 Hz, 1H, *cis*-3b-H), 5.12 (d, J=19.7 Hz, 1H, 13^2-H), 4.95 (d, J=19.7 Hz, 1H, 13^2-H), 4.33 (q, J=7.4 Hz, 1H, 18-H), 4.13 (d, J=8.9 Hz, 1H, 17-H), 3.42 (q, J=7.5 Hz, 2H, 8a-CH_2), 3.64, 3.21, 2.99 (each s, each 3H, CH_3+OCH_3), 2.69～2.51, 2.37～2.19 (each m, total 4H, 17a-17b-CH_2), 1.82 (d, J=7.4 Hz, 18-CH_3), 1.55 (t, J=7.5 Hz, 3H, 8a-CH_3), 0.70, −0.51 (each br s, each 1H, NH); MS (ESI) *m/z*: 665.4 $(M+H)^+$. Anal. calcd for $C_{42}H_{40}N_4O_4$: C 75.88, H 6.06, N 8.43; found C 75.96, H 6.13, N 8.35.

4.14 Synthesis of (*E*)-methyl 13^2-*oxo*-13^1-benzoylidene-13^1-deoxopyropheophorbide-*a* (**10**)

Chlorin **1b** (9.4 mg, 0.018 mmol) and newly-distilled acetophenone (4 mg, 0.033 mmol) were dissolved in dried dioxane (10 mL), and 0.1 mL of BF_3•OEt_2 was added under N_2 atmosphere, then the reaction mixture was stirred at room temperature under N_2 atmosphere for 4 h, monitoring the progress spectroscopically. The pH value of the reaction mixture was adjusted to about 3 by adding diluted hydrochloric acid and extracted with dichloromethane (15 mL×2). The combined organic layers were washed with water, dried over sodium sulfate, and evaporated in vacuum. After evaporation in vacuum, the residue was purified on chromatography on a silica gel column with hexane/ethyl acetate (*V*∶*V*=5∶1) as eluent to give 6.4 mg of **10** (0.010 mmol, 54%) as a yellow solid. m.p. >300 ℃; UV-vis ($CHCl_3$) λ_{max} (relative intensity): 399 (1.00), 428 (0.10), 510 (0.09), 628 (0.18), 684 (0.36) nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.67, 9.33, 8.80 (each s, each 1H, *meso*-H), 8.15 (s, 1H, 13^{1}a-H), 8.04 (dd, *J*=17.8, 11.5 Hz, 1H, 3a-H), 7.84 (d, *J*=7.4 Hz, 2H, Ph-H), 7.59 (t, *J*=7.4 Hz, 1H, Ph-H), 7.52 (t, *J*=7.2 Hz, 1H, Ph-H), 6.24 (d, *J*=17.8 Hz, 1H, *trans*-3b-H), 6.12 (d, *J*=11.5 Hz, 1H, *cis*-3b-H), 5.10 (d, *J*=8.5 Hz, 1H, 17-H), 4.55 (q, *J*=7.3 Hz, 1H, 18-H), 3.59 (q, *J*=7.6 Hz, 2H, 8a-CH_2), 3.59, 3.42, 3.21, 2.93 (each s, each 3H, CH_3+OCH_3), 2.87～2.77, 273～267, 2.29～2.39 (each m, total 4H, 17a+17b-CH_2), 1.84 (d, *J*=7.3 Hz, 3H, 18-CH_3), 1.61 (t, *J*=7.6 Hz, 3H, 8a-CH_3), 0.37, −1.76 (each br s, each 1H, NH); MS (ESI) *m/z*: 665.4 $(M+H)^+$. Anal. calcd for $C_{42}H_{40}N_4O_4$: C 75.88, H 6.06, N 8.43; found C 75.75, H 6.11, N 8.55.

4.15 Synthesis of (*E*)-methyl 13^2-*oxo*-13^1-(4-pyridylidene)-13^1-deoxopyropheophorbide-*a* (**11**)

Chlorin **1b** (12 mg, 0.021 mmol) and 4-methylpyridine (4.6 mg, 0.43 mmol) were dissolved in acetic anhydride (10 mL), and 1 mL of acetic acid was added under N_2 atmosphere, then the reaction mixture was refluxed under N_2 atmosphere for 8 h, monitoring the progress spectroscopically. The reaction mixture was evaporated to remove the solvent, dissolved with dichloromethane (30 mL), washed with diluted hydrochloric acid, and then washed with H_2O (50 mL×2). The organic layer obtained was dried over sodium sulfate. After evaporation in vacuum, the residue was purified on chromatography on a silica gel column with hexane/ethyl acetate (*V*∶*V*=5∶1) as eluent to give 6.4 mg of **11** (0.010 mmol, 47%) as a yellow solid. m.p. >300 ℃; UV-vis ($CHCl_3$) λ_{max} (relative intensity): 406 (0.95), 414 (1.00), 516 (0.12), 555 (0.16), 684 (0.82) nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.81, 9.53, 8.01 (each s, each 1H, *meso*-H), 8.87 (br s, 3H, 13^{1}a-H+Py-H), 7.75 (d, *J*=3.2 Hz, 2H, Py-H), 8.11 (dd, *J*=18.0, 11.6 Hz, 1H, 3a-H), 6.31 (d, *J*=18.0 Hz, 1H, *trans*-3b-H), 6.20 (d, *J*=11.6 Hz, 1H, *cis*-3b-H), 5.11 (d, *J*=8.0 Hz, 1H, 17-H), 4.58 (q, *J*=7.4 Hz, 1H, 18-H), 3.72 (q, *J*=7.6 Hz, 2H, 8a-CH_2), 3.57, 3.48, 3.32, 3.02 (each s, each 3H, CH_3+OCH_3), 2.77～2.65, 2.39～2.25 (each m, total 4H, 17a+17b-CH_2), 1.85 (d, *J*=7.4 Hz, 3H, 18-CH_3), 1.70 (t, *J*=7.6 Hz, 3H, 8a-CH_3), 0.40, −1.62 (each br s, each 1H, NH); MS (ESI) *m/z*: 638.3 $(M+H)^+$. Anal. calcd for $C_{40}H_{39}N_5O_3$: C 75.33, H 6.16, N 10.98; found C 75.44, H 6.11, N 10.85.

4.16 Synthesis of (*E*)-methyl 12-(4-nitrostyrylformyl)-12-demethylpyropheophorbide-*a* (**12**)

This compounds as a green solid was obtained from compound **1d** by reacting with 4-nitrobenzaldehyde in the yield of 61% according to the method for preparing compound **10** or by reacting with benzaldehyde in the yield of 55% under alkalic condition like synthesizing chlorin **6**. m.p. >300 ℃; UV-vis ($CHCl_3$) λ_{max} (relative intensity): 411 (1.00), 588 (0.22), 628 (0.20), 636 (0.22), 694 (0.38) nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.24, 8.74, 8.12 (each s, each 1H, *meso*-H), 9.29 (d, *J*=15.6 Hz, 1H, 12a-H), 8.00 (d, *J*=15.6 Hz, 1H, 12b-H), 7.90 (d, *J*=7.8 Hz, 2H, Ph-H), 7.84 (d, *J*=7.8 Hz, 2H, Ph-H), 7.72 (dd, *J*=17.9, 11.5 Hz, 1H, 3a-H), 6.19 (d, *J*=17.9 Hz, 1H, *trans*-3b-H), 6.12 (d, *J*=11.5 Hz, 1H, *cis*-3b-H), 5.16 (d, *J*=20.0 Hz, 1H, 13^2-H), 4.99 (d, *J*=20.0 Hz, 1H, 13^2-H), 4.22 (q, *J*=7.2 Hz, 1H, 18-H), 4.05 (d, *J*=9.0 Hz, 1H, 17-H), 3.52 (q, *J*=7.5 Hz, 2H, 8a-CH_2), 3.64, 3.20, 3.01 (each s, each 3H, CH_3+OCH_3), 2.66～2.56, 2.37～2.16 (each m, total 4H, 17a+17b-CH_2), 1.75 (d, *J*=7.2 Hz, 3H, 18-CH_3), 1.63 (t, *J*=7.5 Hz, 3H, 8a-CH_3), 0.80, 0.37 (each br s, each 1H, NH); MS (ESI) *m/z*: 10.4 $(M+H)^+$; Anal. calcd for $C_{42}H_{39}N_5O_6$: C 71.07, H 5.54, N 9.87; found C 71.19, H 5.62, N 10.01.

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