Tetrahedron 72 (2016) 3477–3489

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of methyl pyropheophorbide-*d* derivatives possessing the 3-acyl groups and their electronic absorption spectra

Hitoshi Tamiaki [a,*], Yuki Kimura [a,b], Hiroaki Watanabe [a], Tomohiro Miyatake [b]

[a] Graduate School of Life Sciences, Ritsumeikan University, Kusatsu, Shiga 525-8577, Japan
[b] Department of Materials Chemistry, Faculty of Science and Technology, Ryukoku University, Otsu, Shiga 520-2194, Japan

ARTICLE INFO

Article history:
Received 29 March 2016
Received in revised form 23 April 2016
Accepted 26 April 2016
Available online 27 April 2016

Keywords:
Chlorophyll
Conformation
π-Conjugation
Oxidation
Substitution effect

ABSTRACT

Methyl 3-acyl-pyropheophorbides-*a* were prepared by modification of naturally occurring chlorophyll-*a* through Grignard or Barbier reactions of the 3-formyl group and successive Ley–Griffith or Dess–Martin oxidations of the resulting secondary alcohols. The semi-synthetic 3-acyl-chlorins gave intense visible bands in dichloromethane and the absorption spectra were dependent on the 3^1-substituents. The larger π-conjugation of the 3-acyl group with the chlorin moiety shifted the visible absorption maxima to longer wavelengths.

1. Introduction

Light-harvesting antenna systems play important roles in the initial stage of photosynthesis. They absorb sunlight efficiently, stimulate rapid migration of the excited energy, and finally deliver it to a reaction center. In the photosynthetic antennas, a variety of pigments were used for absorbing light and transferring singlet excited energy. The former is dependent on their absorption spectra and the latter is controlled by the excited energy difference and configuration between the donor and acceptor.[1] These physical properties were regulated by the molecular structures of the pigments, their conformation, and their interaction with the environments including proteins and the other pigments.[2]

Typically, green sulfur bacteria utilize several antenna systems and harvesting light energy is transferred to a reaction center as follows.[3] Self-aggregates of bacteriochlorophylls(BChls)-*c*/*d*/*e* (see the left drawing of Fig. 1) surrounded by a lipid monolayer initially absorb sunlight in extramembranous antennas, called chlorosomes. The collected light energy is transferred to BChl-*a* (see the center drawing of Fig. 1) inside proteins embedded in the chlorosomal lipid layer, called baseplates. The singlet energy of excited BChl-*a* in baseplates is transferred to core antenna systems through FMO proteins and finally accepted by the reaction center. In the energy flow from the baseplates to reaction center, the same BChl-*a* molecules are utilized for the pigments. Their singlet excited energies were adjusted in the downhill fashion for efficient energy transfer. The absorption maxima at the longest wavelength of chlorophyllous pigments in photosynthetic apparatus are nearly equal to their singlet excited energy levels due to their small Stokes shifts, called site energies. The site energies of the composite BChl-*a* molecules are partially affected by their conformational changes mentioned above. Especially, the rotation of the C3–$C3^1$ bond changes the redmost (Qy) absorption maximum largely due to π-(de)conjugation of the 3-acetyl group with bacteriochlorin moiety.

In natural photosynthetic antenna systems, BChl-*a* molecules are interacted with protein residues to take various conformers around the 3-acetyl group.[4] Substitution with a bromine atom or methyl group at the 20-position of 3-acetyl-chlorin **1b** (R=Me, see the right drawing of Fig. 1) rotated the 3-acetyl group toward the perpendicular direction of the chlorin π-plane, due to the remote steric interaction through the 2-methyl group.[5] Here we report the systematic synthesis of 3-acyl-chlorins **1** by oxidation of secondary alcohols **2** prepared by addition of R to the 3-formyl group of methyl pyropheophorbide-*d* **1a** (R=H) and their visible absorption spectra in dichloromethane. The 3^1-substituents (R) of **1** affected the visible spectra including their Qy maxima due to the steric interaction between the 3-acyl and its neighboring

* Corresponding author. Fax: +81 77 561 3729; e-mail address: tamiaki@fc.ritsumei.ac.jp (H. Tamiaki).

http://dx.doi.org/10.1016/j.tet.2016.04.074
0040-4020/

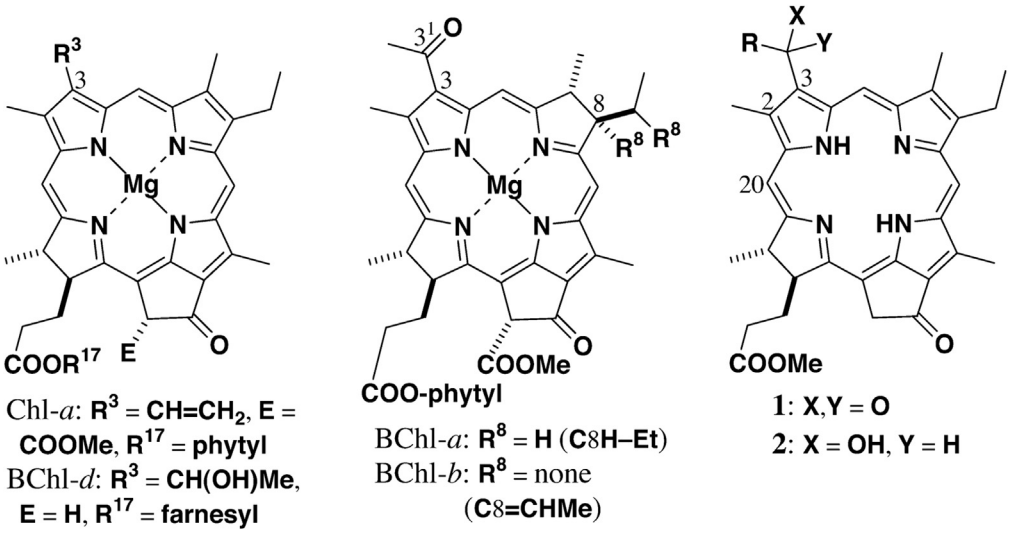


Fig. 1. Molecular structures of naturally occurring Chl-*a* (3-CH=CH_2, left), BChl-*d* [3-CH(OH)Me, left], and BChls-*a*/*b* (3-COMe, center) as well as synthetic Chl-*a* derivatives (right), methyl 3-carbonylated pyropheophorbides **1** (3-COR) and methyl bacteriopheophorbide-*d* analogs **2** [3-CH(OH)R].

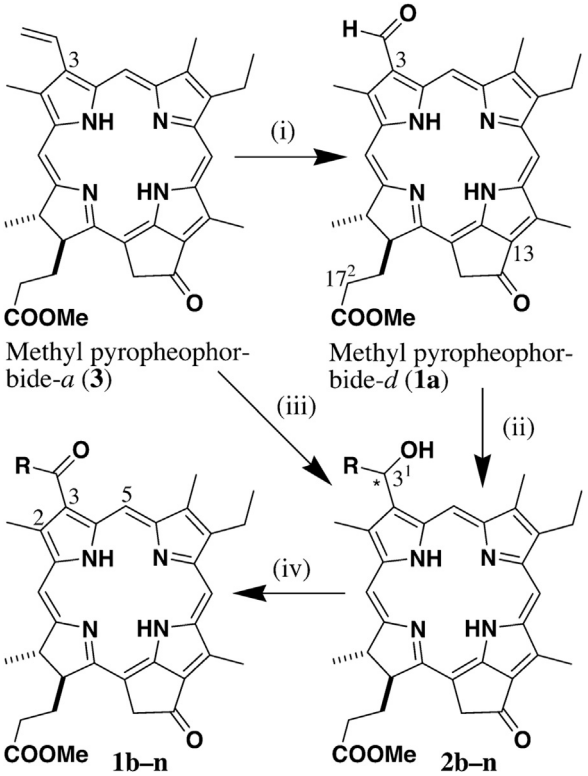
groups. The 3-acyl groups conjugated or deconjugated with the chlorin π-system to afford the red or blue shifts of absorption maxima, respectively. In the present paper, we focused on hydrocarbon moieties as the R group.

2. Results and discussion

2.1. Synthesis of methyl bacteriopheophorbide-*d* analogs possessing the secondary-alcoholic 3^1-hydroxy group

In photosynthetic green bacteria, the 3-vinyl group of chlorophyll biosynthetic precursors is hydrated to the 1-hydroxyethyl group by BchF or BchV enzyme to finally give BChl-*d*.[6] The in vitro enzymatic reactions were recently performed.[7] The 3-vinyl group of methyl pyropheophorbide-*a* (**3**), one of the chlorophyll(Chl)-*a* derivatives, was reported to be hydrated by acidic hydrobromination and successive hydrolysis to give methyl bacteriopheophorbide-*d* (**2b**), one of the BChl-*d* derivatives [see step (iii) of Scheme 1].[8,9] As shown in step (ii) of Scheme 1, **2b** had alternatively been prepared by Grignard reaction of methyl pyropheophorbide-*d* (**1a**),[10] one of the Chl-*d* (3-formylated Chl-*a*) derivatives, which was readily synthesized by the oxidation of the 3-vinyl group in **3** [step (i) of Scheme 1].[11] Of the three carbonyl groups in **1a**, the 3-formyl group was more reactive than the 13-keto and 17^2-ester carbonyl groups, so the regioselective Grignard reactions occurred at the 3-C=O[12–15] to give various secondary alcohols **2b**–**n** (Scheme 1).

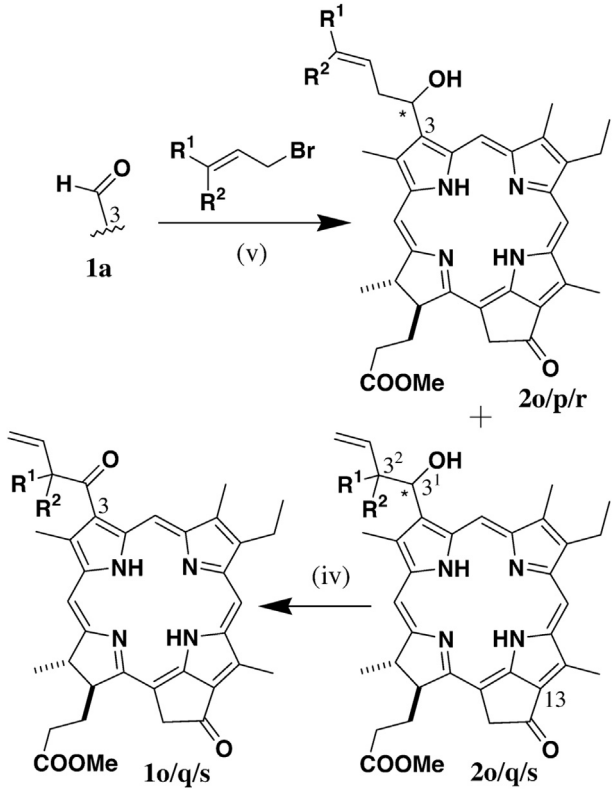
Under nitrogen atmosphere in the dark, commercially available Grignard reagents in an ethereal solution were dropwise added to an ice-chilled dry THF solution of aldehyde **1a**. The Grignard reaction was monitored by visible absorption spectra and the redmost Qy peak characteristic of **1a** at 695 nm decreased during the reaction progress. Just after the disappearance of **1a**, the reaction was quenched with an aqueous ammonium chloride solution at 0 °C. The reaction mixture was purified by silica gel flash column chromatography (FCC) to give **2c**–**n**, which were identified by their VIS, ^{1}H NMR, IR, and MS spectra. The isolated yields were suppressed in the order of R=Et (45%, **2c**), Pr (40%, **2d**), cycloPr (33%, **2f**), and iPr (<10%, **2e**), which was ascribable to the steric factor of the alkyl groups. The yields of alkenyl- **2g**–**j**, alkynyl- **2k**–**m** and aryl-adducts **2n** (see Section 4.2.1) were comparable to the above values observed in (cyclo)alkyl-adducts



Scheme 1. Synthesis of methyl 3-acyl-pyropheophorbides-*a* **1b**–**n** through Grignard reaction of **1a** and successive oxidation of the resulting alcohols **2b**–**n**: (i) OsO_4–$NaIO_4$/THF–H_2O; (ii) MeMgI/Et_2O for methyl bacteriopheophorbide-*d* (**2b**), EtMgBr/THF for **2c**, PrMgCl/Et_2O for **2d**, iPrMgCl/THF for **2e**, cycloPrMgBr/2-MeTHF for **2f**, and RMgBr/THF for **2g**–**n**, then aq. NH_4Cl; (iii) HBr/AcOH, H_2O, CH_2N_2/Et_2O for **2b**; (iv) Pr_4NRuO_4–MeN(O)$(CH_2CH_2)_2O$/CH_2Cl_2 or *o*-C_6H_4[–COOI$(OAc)_3$–]/CH_2Cl_2. R=Me (**b**), Et (**c**), Pr (**d**), iPr (**e**), cycloPr (**f**), CH=CH_2 (**g**), *cis*-CH=CHMe (**h**), *trans*-CH=CHMe (**i**), CMe=CH_2 (**j**), C≡CH (**k**), C≡CMe (**l**), C≡CPh (**m**), and Ph (**n**).

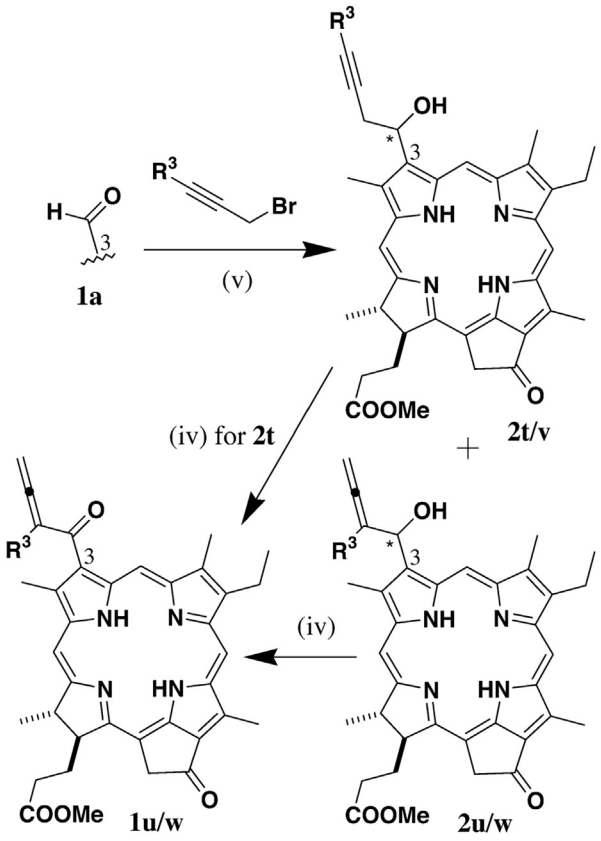
2c/**d**/**f**. It is noted that all the adducts **2b**–**n** were 3^1-epimeric mixtures (3^1R:3^1S=1:1) from their ^{1}H NMR analysis and used for the following oxidation (section 2.2) without their stereochemical separation.

When aldehyde **1a** was treated with allyl bromide in the presence of indium powder in aqueous THF at room temperature [see step (v) of Scheme 2],[16] allyl adduct **2o** (R^1=R^2=H) was obtained in a very good isolated yield (88%). Similar Barbier reactions of **1a** with crotyl (R^1=Me, R^2=H) and prenyl bromides (R^1=R^2=Me)[13] gave neither α-attacked products **2p** nor **2r**, but exclusively γ-attacked products **2q** (70%) and **2s** (43%). The isolated yields decreased with an increase of steric hindrance around the reactive γ-carbon of allyl-type bromides, which is consistent with the aforementioned reactions of **1a** with alkyl Grignard reagents. It is noteworthy that the yields of primary- **2o** and secondary-adducts **2q** by the Barbier reaction were larger than those of **2c**/**d** and **2e**/**f** by the Grignard reaction, respectively: 88% (**2o**)>45% (**2c**) and 40% (**2d**); 70% (**2q**)>33% (**2f**) and less than 10% (**2e**). Products **2o**/**s** were 1:1 3^1-epimeric mixtures, while **2q** was a 3^1- and 3^2-epimeric mixture; (3^1R,3^2R): (3^1S,3^2R): (3^1R,3^2S): (3^1S,3^2S)=1: 1: 1: 1 from its ^{1}H NMR analysis.



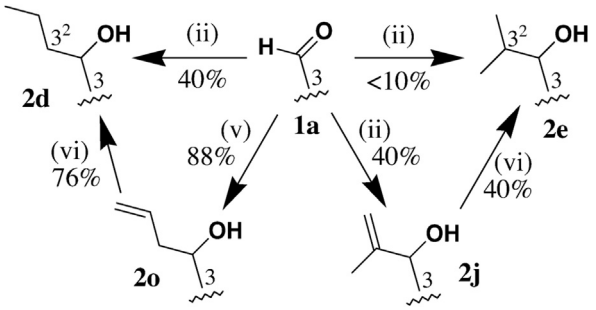
Scheme 2. Synthesis of methyl 3-acyl-pyropheophorbides-*a* **1o**/**q**/**s** through Barbier reaction of **1a** with allyl-type bromides and successive oxidation of the resulting alcohols **2o**/**q**/**s**: (iv) Pr_4NRuO_4–MeN(O)$(CH_2CH_2)_2O$/CH_2Cl_2 or *o*-C_6H_4[–COOI$(OAc)_3$–]/CH_2Cl_2; (v) In, THF–H_2O. R^1=R^2=H (**o**); R^1=Me, R^2=H (**p**/**q**), and R^1=R^2=Me (**r**/**s**).

Similarly as in allyl-type bromides, propargyl bromide (R^3=H in Scheme 3) was reacted with **1a** to give **2t** as an α-attacked product (49%) and **2u** as a γ-attacked product (26%). Substitution of a methyl group at the terminal position of propargyl bromide (R^3=Me) led to the preferential production of γ-attacked allene product **2w** (75%) over α-attacked alkyne product **2v** (9%). The regioselectivity is consistent with previous reports.[17] The characterizations of isomeric products **2t**/**u** and **2v**/**w** were performed by the combination of VIS, ^{1}H NMR, IR, and MS spectroscopy: especially ν_{max}=2120 cm^{-1} for C≡C of **2t** and 1956 cm^{-1} for C=C=C of **2u**.



Scheme 3. Synthesis of methyl 3-acyl-pyropheophorbides-*a* **1u**/**w** through Barbier reaction of **1a** with propargyl-type bromides and successive oxidation of the resulting alcohols **2t**/**u**/**w**: (iv) Pr_4NRuO_4–MeN(O)$(CH_2CH_2)_2O$/CH_2Cl_2 or *o*-C_6H_4[–COOI$(OAc)_3$–]/CH_2Cl_2; (v) In, THF–H_2O. R^3=H (**t**/**u**) and Me (**v**/**w**).

Propyl adduct **2d** was directly obtained by Grignard reaction of **1a** but the yield was low (40%). Since the Barbier reaction was cleaner than the Grignard reaction under the present conditions (vide supra), hydrogenation of **2o** was examined. Conventional hydrogenation of **2o** [step (vi) of Scheme 4] gave **2d** in a good isolated yield (76%) without any other reduction of 3^1-OH to 3^1-H and of 13-C=O to 13-CH–OH/13-CH_2. The overall yield of **1a** to **2d** via **2o** was estimated to be 67% and larger than the single-step yield of **1a** to **2d**. The former is more efficient for the preparation of **2d**.



Scheme 4. Synthesis of methyl 3^2-ethyl- (**2d**) or 3^2,3^2-dimethyl-bacteriopheophorbide-*d* (**2e**) through Grignard reaction of **1a** or Barbier reaction–hydrogenation from **1a**: (ii) PrMgCl/Et_2O for **2d**, iPrMgCl/THF for **2e**, and CH_2=CMeMgBr/THF for **2j**, then aq. NH_4Cl; (v) CH_2=$CHCH_2$Br, In, THF–H_2O; (vi) H_2, Pd-C/THF–Me_2CO. Isolated yields are shown.

Isopropyl adduct **2e** was poorly synthesized by Grignard reaction of **1a** with isopropylmagnesium chloride. In contrast, Grignard reaction of **1a** with less sterically demanding isopropenylmagnesium chloride gave its adduct **2j** in a larger yield (40%). 1,1-Disubstituted ethylene **2j** was successfully hydrogenated

to give **2e** similarly as in **2o**→**2d** (Scheme 4). The total yield of **1a** to **2e** via **2j** was 16%, which was more effective than the direct pathway of **1a** to **2e** (<10%).

Similar treatment of **2f** with hydrogen gas afforded no products and the starting material **2f** was recovered. The cyclopropane ring in **2f** was not hydrogenated under the present conditions and neither propylated **2d** nor isopropylated **2e** was obtained. Moreover, the hydrogenation conditions induced no isomerization of cyclopropylated **2f** to propenylated **2h**–**j**/**o** through the ring-opening.

2.2. Synthesis of methyl 3-acyl-pyropheophorbides-*a*

In all photosynthetic bacteria except heliobacteria, the 1-hydroxyethyl group at the 3-position of chlorophyll pigments is oxidized to the 3-acetyl group by BchC enzyme, leading to BChls-*a* and *b* (see the center drawing of Fig. 1) as the final biosynthetic products.[6] The recombinant BchC protein has been reported to be useful for such oxidation of some substrates in an aqueous buffer solution.[18] The secondary alcoholic moiety in methyl bacteriopheophorbide-*d* (**2b**) has already been oxidized to methyl 3-acetyl-pyropheophorbide-*a* (**1b**) by dimethyl sulfoxide–acetic anhydride (Albright-Goldman oxidation)[19] and tetrapropylammonium perruthenate–*N*-methylmorpholine *N*-oxide [Ley–Griffith (LG) oxidation][9,20,21] [see step (iv) of Scheme 1]. The latter LG-oxidation was convenient for preparation of 3-propionyl- and 3-butyryl-chlorins **1c** and **1d** and the very good yields of **2c**/**d** to **1c**/**d** were the same (88%) as that of **2b**–**1b** (see Table 1). Under the same conditions, the secondary alcohol **2e** bearing an isopropyl group was oxidized to give the corresponding ketone **1e** in a lower yield (36%). A large amount of undetermined products were obtained from the reaction mixture. The secondary isopropyl moiety at the 3^1-position of **2e** (or **1e**) would be altered during the LG-oxidation where the primary moieties (Me, Et, and Pr) were chemically stable. Next, Dess–Martin (DM) oxidation[22] was examined. Secondary alkylated **2e** was smoothly oxidized by DM periodinane, *o*-C_6H_4[-COOI(OAc)$_3$-], to afford **1e** in a good yield of 79%. The DM-oxidation was useful for preparation of primary alkylated **1b** and **1c**, whose yields were 50% and 60%, respectively, and a little bit smaller than that of **2e** to **1e**. Propylated **2d** was oxidized much less efficiently by the DM-reagent to give **1d** (25%). The suppression would be due to the production of some other compounds not yet identified.

Cyclopropylated **2f** was LG-oxidized effectively to yield **1f** (72%). The value was twice as large as that of **2e** to **1e** in spite of being the same secondary-alkylated alcohols. The double yield was ascribable to the chemical stability of cyclopropyl group in **2f** (or **1f**) under the LG-conditions. The locally steric crowdedness around the 3^1-carbon atom completely disturbed the DM-oxidation of **2f** to **1f**.

The LG-oxidation of vinylated **2g** was converted to **1g** (72%). Addition of one methyl group to the vinyl group partially decreased the LG-oxidation yields: 49% for **2h**/**i** to **1h**/**i** and 60% for **2j** to **1j**. In contrast, such further methylation increased the DM-oxidation yields: 51% (**2g**→**1g**)<64% (**2h**/**i**→**1h**/**i**)<80% (**2j**→**1j**). The ratios of *cis* and *trans* isomers **1h**/**i** and **2h**/**i** were not changed (3:7) during the present LG- and DM-oxidations. The stereochemistry at the 3^3-position did not influence either of the oxidations at the 3^1-position.

Ethynylated **2k** was smoothly oxidized under the LG- and DM-conditions to give **1k** in comparable yields of 77% and 60%, respectively. Methylation and phenylation at the terminal position of the ethynyl group did not largely affect the oxidation yields: 66%/63% (methylated **2l**→**1l**) and 75%/72% (phenylated **2m**→**1m**) for LG/DM-oxidations. Directly phenylated carbinol **2n** was transformed by DM-reagent to **1n** in a very good yield of 88%. The yield of LG-oxidation of **2n** to **1n** (69%) was slightly smaller than that of its DM-oxidation.

Allylated **2o** was oxidized by DM-reagent to afford **1o** in a very good yield of 87%, while the LG-oxidation of **2o** gave none of the desired product **1o** and showed no recovery of **2o**. The full disturbance showed that the allyl group of **2o** (or **1o**) was labile under the LG-conditions. Single methylation at the allyl position of **2o** as in **2q** led to the production of **1q** by the LG-oxidation (64%) as well as the DM-oxidation (70%). One more methylation to **2q** increased the yield of **2s**–**1s** by the LG-oxidation (80%) and completely suppressed the DM-oxidation to completely recover **1s**. The increase of the LG-oxidation yields with successive methylation at the allyl position was ascribable to their chemical stability under the LG-conditions: 0% (non-methylated **2o**→**1o**)<64% (mono-methylated **2q**→**1q**)<80% (di-methylated **2s**→**1s**). The decrease of the DM-oxidation yields by the same methylation was explained by the aforementioned sterically sensitive DM-oxidation: 87% (**2o**→**1o**)>70% (**2q**→**1q**)>0% (**2s**→**1s**). It is noted that isolated **1q** was a 1:1 3^2-epimeric mixture due to the achiral oxidations of a 3^1,3^2-diastereomeric mixture of **2q**.

A 65:35 mixture of propargylated **2t** and allenylated **2u** was treated with LG-reagents to give sole allenylated **1u** as the isolable oxidation product (11%): ν_{max}=1957 and 1933 cm^{-1} for C=C=C of **1u**. The lack of observable **1t** in the reaction mixture would be ascribable to the chemical unstability of propargyl group by the LG-oxidation. This is consistent with the above explanation that the allyl group was labile under the LG-conditions. The poor yield was improved by the DM-oxidation to an excellent yield (96%). The DM-oxidation of the above mixed **2t**/**u** cleanly proceeded to afford only **1u** without **1t**. During the oxidation, the propargyl moiety was fully isomerized to the allenyl moiety, as reported earlier.[23] The 3^2-methylated analog of allenylated **2u** as in **2w** was oxidized by the LG-reagents to **1w** (48%) and the DM-oxidation of **2w** occurred more efficiently to give **1w** in a good yield of 83%. Therefore, the LG- and/or DM-oxidations are useful for the preparation of **1b**–**o**, **1q**, **1s**, **1u**, and **1w**.

Table 1
Oxidation of methyl bacteriopheophorbide-*d* analogs **2** [3-CH(OH)R] to methyl 3-acyl-pyropheophorbides-*a* **1** (3-COR) [see step (iv) of Schemes 1–3]

R	Isolated yields/%	
	Ley–Griffith[a]	Dess–Martin[b]
Me (**b**)	88	50
Et (**c**)	88	60
Pr (**d**)	88	25
iPr (**e**)	36	79
cycloPr (**f**)	72	NR
CH=CH_2 (**g**)	72	51
cis/*trans*-CH=CHMe (**h**/**i**)[c]	49	64
CMe=CH_2 (**j**)	60	80
C≡CH (**k**)	77	60
C≡CMe (**l**)	66	63
C≡CPh (**m**)	75	72
Ph (**n**)	69	88
CH_2CH=CH_2 (**o**)	0	87
CHMeCH=CH_2 (**q**)	64	70
CMe_2CH=CH_2 (**s**)	80	NR
CH=C=CH_2 (**u**)/CH_2C≡CH (**t**)[d]	11/0	96/0
CMe=C=CH_2 (**w**)	48	83

[a] Ley–Griffith oxidation: Pr_4NRuO_4–MeN(O)$(CH_2CH_2)_2$O/CH_2Cl_2 (see Section 4.2.3).
[b] Dess–Martin oxidation: *o*-C_6H_4[-COOI(OAc)$_3$-]/CH_2Cl_2 (see Section 4.2.4). NR means no progress of the oxidation and full recovery of the starting alcohol.
[c] A 3:7 mixture of **2h** and **2i** was oxidized by both procedures to give a 3:7 mixture of **1h** and **1i** without isomerization.
[d] Full isomerization of propargyl to allenyl moiety was observed during the Dess–Martin oxidation: the change of isomeric ratios from **2t**/**2u**=65/35 to **1t**/**1u**=0/100.

2.3. Electronic absorption spectra of methyl 3-acyl-pyropheophorbides-*a*

All the chlorophyll derivatives prepared here were well dissolved in dichloromethane to give their monomeric species at ca. 10 μM. Methyl bacteriopheophorbide-*d* analogs **2** possessing 3-CH(OH)R gave almost the same visible absorption spectra in a diluted dichloromethane solution (see Fig. S1). The 3^1-substituents (R) were connected with a chlorin π-system through a methyne moiety and the homoconjugation slightly affected their spectra including absorption maxima (λ_{max}). The redmost Soret and Qx maxima were observed at 410–1 and 536–8 nm, respectively (see Table S1), while the Qy maxima were categorized into three types: λ_{max}=661–2 (**2b**–**e**/**o**/**q**/**s**/**t**/**v**, sp^3-carbon at the 3^2-position), 662–3 (**2f**–**j**/**n**/**u**/**w**, sp^2(-like)-C), and 665–6 nm (**2k**–**m**, sp-C).

Oxidation of secondary alcohols **2** to ketones **1** induced red-shifts of all the visible λ_{max}. The bathochromic shifts were ascribable to direct conjugation of the 3-acyl group with the chlorin π-system. The visible spectra were dependent on the 3^1-substituents which were π-conjugated with a chlorin moiety through the carbonyl group (see Fig. 2).

Addition of a methyl group at the terminal of the 3-acetyl group in **1b** to **1c** shifted redmost Soret, Qx, and Qy maxima to shorter wavelengths by 2–4 nm (see Table 2). Such substitution of the methyl with ethyl group at the 3^1-position enlarged the 3-acyl group. The larger the 3-acyl group became, the less it was conjugated with the chlorin π-system due to the steric repulsion with the 2-methyl group and the 5-hydrogen atom. One more methylation at the 3^3-position of **1c** to **1d** induced fewer but apparent blue shifts of both the Q maxima (1–2 nm) and that at the 3^2-position of **1c** to **1e** induced larger hypsochromic shifts of all the maxima (2–7 nm). These shifts supported the steric effect of the 3^1-substituents on their visible maxima: λ_{max}(Qy)=683 (3^1-methylated **1b**)>679 (ethylated **1c**)>678 (propylated **1d**)>672 nm (isopropylated **1e**).

Mono-methylation at the 3^2-position of 3^1-allylated **1o** to **1q** led to blue shifts of all the λ_{max} (2–6 nm) and additional methylation of **1q** to **1s** also made their blue shifts (4–7 nm). The blue shifts were due to the aforementioned steric effect around the 3^2-position: λ_{max}(Qy)=680 (3^1-primary-substituted **1o**)>674 (secondary **1q**)> 667 nm (tertiary **1s**). The Qy bands were sharpened and their bandwidths decreased in the same order: full widths at half maximum (FWHM)=667 (**1o**)>588 (**1q**)>398 (**1s**) > 376/363/352 cm^{-1} (**2o**/**2q**/**2s**). The narrowing proved a less π-conjugation of the 3-acyl group with chlorin moiety. A similar situation was observed in some other 3^2-methylations: FWHM=642 (**1c**)>608 cm^{-1} (**1e**) and 707 (**1g**)>503 cm^{-1} (**1j**).

The 3^2,3^3-dehydrogenation of **1c** to **1g** showed no shifts of the λ_{max}, which can be explained as follows. The 3^1-vinyl group of **1g** is able to be π-conjugated with the 3-carbonyl group to make a planar acryloyl group. The 3-acryloyl moiety in **1g** would interact with the neighboring moieties more largely than the 3-propionyl moiety in **1c**. Due to the larger steric repulsion, the former should be rotated around the C3–C3^1 bond to give a conformer less π-conjugated between the 3-acryloyl and chlorin components. Such lower coplanarization induces blue shifts of the visible maxima. The 3^1-vinyl group is partially π-conjugated with the chlorin moiety through the 3-C=O. Since a vinyl group is more electronegative than an ethyl group,[24] the 3-acryloyl moiety electron-withdraws in an inductive fashion from the chlorin π-system more than the 3-propionyl moiety. These electronic effects of the 3^1-vinyl group induced red shifts of the visible maxima. The conflicting blue and red shifts proposed above would make no changes in λ_{max} between **1c** and **1g**.

The *cis*-methylation at the terminal position of 3^1-vinyl group in **1g** to **1h** moved the Qy maximum to a longer wavelength by 2 nm. The sterically demanded *cis*-methyl group reduced the planarization of 3^1-vinylene group with 3-carbonyl groups. The less planar 3-isocrotonoyl substituent can allow its 3-carbonyl group to be more π-conjugated with the chlorin moiety to give the above red shift. The *trans*-methylation of **1g** to **1i** shifted all the λ_{max} hypsochromically. The *trans*-methyl group did not disturb the planarization of the 3-COCH=CH moiety to make the planar 3-substituent larger. The steric factor led to less coplanarization between the 3-crotonoyl group and chlorin π-system to afford the blue shifts.

The 3^2-methylation of acryloylated **1g** to methacryloylated **1j** made blue shifts of Q maxima. This is due to the same steric factor as in 3^1-ethylated **1c** to isopropylated **1e**. The shift values of 5 and 8 nm for Qx and Qy maxima, respectively, in **1g**→**1j** were almost identical to those (5 and 7 nm) in **1c**→**1e**. The substitution of the 3^1-vinyl group in acryloylated **1g** with the 3^1-phenyl group in benzoylated **1n** shifted all the λ_{max} to shorter wavelengths. This observation is also explained by the similar steric effect at the 3^2-position.

Addition of a methylene group to the 3^1-vinyl group in **1g** to 3^1-cyclopropylated **1f** shifted Soret and Q maxima to longer and shorter wavelengths, respectively. Substitution with a methylene group at the terminal positions of the 3^1-vinyl group in **1g** to 3^1-allylated **1u** gave similar shifts as in the above methylene addition. The complex shifts are not clearly explained but might be ascribable to steric and electronic effects. The 3^2-methylation of **1u** to **1w** caused blue shifts of all the λ_{max} (1–2 nm), which is consistent with hypsochromic shifts in the other 3^2-methylation (vide supra).

The 3^2,3^3-dehydrogenation of **1g** to **1k** showed large red shifts of all the λ_{max} (4–15 nm). A planar propioloyl group is sterically smaller than an acryloyl group, so the former is more coplanar with the chlorin π-system. The resulting larger π-conjugation between the two components made the bathochromic shifts. Additionally, the shifts were reinforced by an inductive electronic effect that an ethynyl group is more electronegative than a vinyl group: electronegativity=3.07 (−C≡CH)>2.79 (−CH=CH_2).[24] Substitution at the terminal position of the 3^1-ethynyl group in **1k** with a methyl group as in **1l** moved all the λ_{max} to longer wavelengths, and similar substitution with a phenyl group as in **1m** shifted them more bathochromically: λ_{max}(Qy)=694 (**1k**)<695 (**1l**)<698 nm (**1m**). These red shifts were due to the electronic effects including (hyper) conjugation and electronegativities of the 3^3-substituents: electronegativity=2.17 (−H)<2.47 (−Me)<2.72 (−Ph).[24] The Soret bands of **1k**–**m** possessing an ethynylene group were broader than those of any other 3-acyl-chlorins (Fig. 2), supporting larger π-conjugation of the 3-substituent with chlorin moiety in **1k**–**m**.

2.4. Conformation of 3-carbonyl group in methyl 3-acyl-pyrophoeophorbides-*a*

As mentioned in section 2.3, visible spectra of 3-acyl-chlorins were sensitive to the conformation of the 3-carbonyl group. The 3-C=O moiety was coplanar with the chlorin π-system to shift the absorption maxima bathochromically, while the former was perpendicular to the latter to shift them hypsochromically. The relationship among the conformation, π-conjugation, and λ_{max} was confirmed by ^{1}H NMR spectral and molecular modeling analyses.

In deuterated chloroform, ^{1}H NMR spectra of **1o**, **1q**, and **1s** were measured at ca. 10 mM and their chemical shifts (δ) were compared. The δ-values of their methyl resonance at the 2-position were changed by the 3^2-methylation more than those of any other methyl singlet peaks: δ(2-CH_3)=3.61 (3^2-non-methylated **1o**)>3.55 (mono-methylated **1q**)>3.33 ppm (di-methylated **1s**). The high-field shift was explained as follows. The 2-methyl group of **1s** was situated over the neighboring 3-carbonyl π-plane and inside its shielding zone to give the smaller δ-value. Therefore, the 3-carbonyl group was rotated around the C3–C3^1 bond toward its

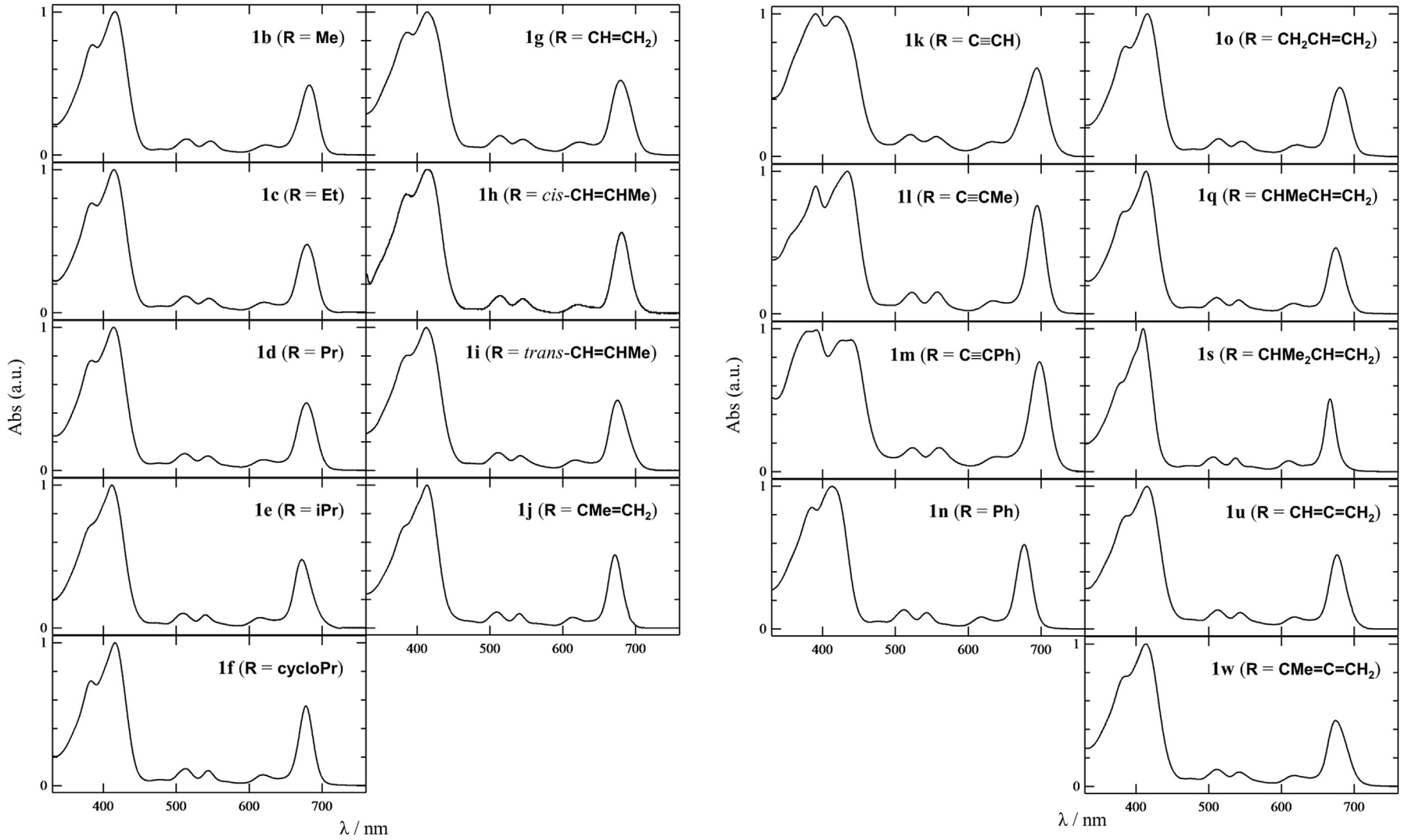


Fig. 2. Visible absorption spectra of methyl 3-acyl-pyropheophorbides-*a* **1** (3-COR) in dichloromethane. All the spectra are normalized at Soret maxima.

Table 2
Redmost Soret, Qx, and Qy maxima λ_{max} of methyl 3^1-(un)substituted pyropheophorbides-*d* **1** (3-COR) in dichloromethane, their intensities relative to the Soret band, and full widths at half maximum (FWHM) of their Qy bands

R	λ_{max}/nm (Relative intensity) [FWHM/cm^{-1}]		
	Soret	Qx	Qy
H (**1a**)	429	555 (0.16)	695 (0.85) [425]
Me (**1b**)	416	547 (0.10)	683 (0.49) [627]
Et (**1c**)	414	545 (0.10)	679 (0.48) [642]
Pr (**1d**)	414	543 (0.10)	678 (0.47) [649]
iPr (**1e**)	412	540 (0.09)	672 (0.48) [608]
cyclоPr (**1f**)	416	544 (0.10)	678 (0.56) [505]
CH=CH$_2$ (**1g**)	414	545 (0.11)	679 (0.52) [707]
cis-CH=CHMe (**1h**)	414	545 (0.10)	681 (0.56) [579]
trans-CH=CHMe (**1i**)	413	542 (0.10)	675 (0.49) [638]
CMe=CH$_2$ (**1j**)	414	540 (0.10)	671 (0.51) [503]
C≡CH (**1k**)	418	556 (0.14)	694 (0.62) [781]
C≡CMe (**1l**)	434	558 (0.15)	695 (0.76) [565]
C≡CPh (**1m**)	439	560 (0.18)	698 (0.83) [634]
Ph (**1n**)	413	543 (0.11)	677 (0.59) [546]
CH$_2$CH=CH$_2$ (**1o**)	416	545 (0.11)	680 (0.48) [667]
CHMeCH=CH$_2$ (**1q**)	414	541 (0.10)	674 (0.46) [588]
CMe$_2$CH=CH$_2$ (**1s**)	410	537 (0.09)	667 (0.51) [398]
CH=C=CH$_2$ (**1u**)	415	543 (0.12)	676 (0.52) [567]
CMe=C=CH$_2$ (**1w**)	414	542 (0.10)	674 (0.46) [669]

perpendicular conformation by the successive 3^2-methylation of **1o** to **1s** via **1q**. The conformational change reduced the π-conjugation of the 3-acyl group with chlorin moiety to give blue shifts of all the λ_{max}. Additionally, the molecular modeling based on MM+/PM3 calculation[25] supported their rotational conformers. The dihedral angles (Z) of C2(4)–C3–C3^1–O (see inset structure of Fig. 3) increased in the order of **1o** (1°), **1q** (15°), and **1s** (69°). Similar high-field shifts of the 2-methyl peak by the 3^2-methylation were observed in **1g** to **1j** and **1u** to **1w**: $\Delta\delta$(2-CH$_3$)=−0.12 ppm [= 3.41 (**1j**)−3.53 (**1g**)] and −0.09 ppm [=3.45 (**1w**)−3.54 (**1u**)]. It is noted that the estimated dihedral angles were correlated with the observed Qy maxima as shown in Fig. 3.

In 3-propioloyl-chlorin **1k** and its 3^3-substituted analogs **1 l**/**m**, the δ-values of their 2-methyl and 5-hydrogen signals were shifted to lower fields than the corresponding data in the other 3-acyl-chlorins: δ(2-CH$_3$)=3.83/79/87 (**1k**/**l**/**m**)>3.3–3.6 ppm (the others) and δ(5-H)=10.49/53/50 (**1k**/**l**/**m**)>9.1–9.8 ppm (the others). The low-field shifts were ascribable to the deshielding effect of the 3-C(=O)–C≡C π-circuit. When the 3-substituent is coplanar with the chlorin π-system, the deshielding is the most effective for the 2-CH$_3$ and 5-H. The observed large low-field shifts showed such coplanarization to afford red-shifted λ_{max}.

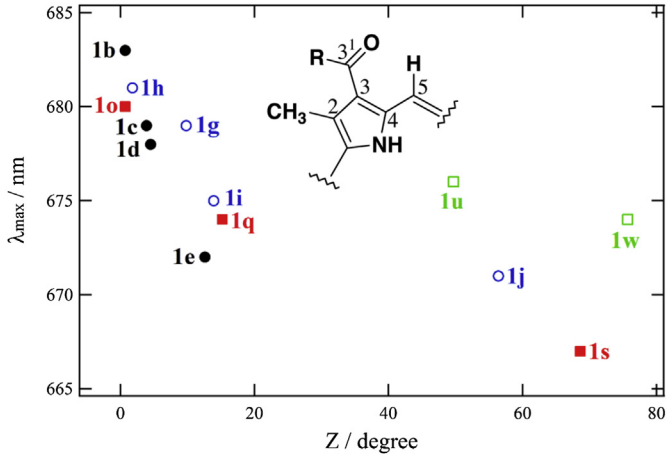


Fig. 3. Dependence of Qy absorption maxima (λ_{max}) of methyl 3-acyl-pyropheophorbides-*a*, **1b**–**e** (black filled circles), **1g**–**j** (blue open circles), **1o**/**q**/**s** (red filled squares), and **1u**/**w** (green open squares) in CH_2Cl_2 on their dihedral angles (Z) of C2(4)–C3–C3^1–O estimated by MM+/PM3 calculation.

3. Concluding remarks

The 3-formyl group of methyl pyropheophorbide-*d* (**1a**) was reacted with RMgX or allyl/propargyl-type bromides in the presence of indium to give methyl bacteriopheophorbide-*d* analogs **2** possessing various 3^1-substituents. Both the Grignard and Barbier reactions regioselectively occurred at the more reactive 3-CHO than the other carbonyl groups (13-C=O and 17^2-C=O). Under the present conditions (an aqueous THF solution), γ-adducts were preferable in the Barbier allylation. The isolated yields of some secondary alcohols diminished with an increase of the steric crowdedness around the reacting position of the alkyl and allyl(-type) substituents. Since the yields of the Barbier reactions were larger than those of the Grignard reactions, the former additions were useful for preparation of **2**. The secondary alcohols **2** were oxidized by Ley–Griffith and/or Dess–Martin reagents to afford the corresponding ketones **1** except for propargylated alcohol **2t**. The isolated yields of **1** were sensitive to the 3^1-substituents and most of **1** were obtained in good to excellent yields by either or both the oxidation procedures.

Visible absorption spectra of **1** in a diluted dichloromethane solution were dependent on the 3^1-substituents. Sterically demanded 3-acyl groups shifted their absorption maxima to shorter wavelengths. The more π-conjugation of the 3-carbonyl group with the chlorin moiety induced their bathochromic shifts. Therefore, the singlet excited energies of the present chlorophyll derivatives would be controlled by the conformation of the 3-acyl group. The substitution effect mimics the regulation of the site energy of (bacterio)chlorophylls in photosynthetic proteins. Less sterically crowded 3-propioloyl-chlorins **1k**–**m** gave broadened Soret bands as well as red-shifted absorption bands, due to the coplanarization of the 3-propioloyl with chlorin π-planes. Especially, the redmost Qy maximum of 3^3-phenyl substituted **1m** was situated at 698 nm, which was longer than that of methyl pyropheophorbide-*d* (**1a**) possessing the 3-formyl group (695 nm) and the same as that of its derivative bearing a strongly electron-withdrawing trifluoroacetyl group at the 3-position.[26]

4. Experimental

4.1. General

All melting points were measured with a Yanagimoto micro melting apparatus and were uncorrected. Electronic absorption spectra were measured with a Hitachi U-3500 spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL AL-400 (400 MHz) spectrometer; residual $CHCl_3$ (δ=7.26 ppm) was used as an internal reference. FT-IR spectra were recorded on a Shimadzu FTIR-8600 spectrometer. High resolution mass spectra (HRMS) were recorded on a Bruker micrOTOF II spectrometer: atmospheric pressure chemical ionization (APCI) and positive mode in an acetonitrile solution. TLC or FCC was performed with silica gel (Merck, Kieselgel 60 F_{254} or Kieselgel 60, 40–63 μm, 230–400 mesh). High performance liquid chromatography (HPLC) was performed on a packed octadecylated column (Nacalai Tesque, Cosmosil 5C_{18}AR-II, 10ϕ×250 mm) with a Shimadzu LC-10ADvp pump and SPD-M10Avp photodiode-array detector.

All the reactions were done in the dark. Methyl pyropheophorbide-*d* (**1a**),[11,27] methyl 3-acetyl-3-devinyl-pyropheophorbide-*a* (**1b**),[9,11] and methyl bacteriopheophorbide-*d* (**2b**),[9,11] were prepared according to reported procedures.

Grignard reagents in THF were purchased from Sigma–Aldrich except for propyl magnesium chloride in diethyl ether and cyclopropyl magnesium bromide in 2-methyltetrahydrofuran. Bromides and indium powder (99.5%) were obtained from Wako Pure Chemical Ind. Tetrapropylammonium perruthenate, *N*-methylmorpholine *N*-oxide, Dess–Martin periodinane, and 10% palladium charcoal were purchased from Tokyo Chemical Ind. Dry THF was prepared by distillation from calcium hydride. Dichloromethane for oxidation as well as THF and acetone for reduction were treated with alumina just before use. Other commercially available organic solvents (Nacalai Tesque) as well as distilled water from a Yamato AutoStill WG250 system were used as the reaction media. All the other reaction reagents were obtained from commercial suppliers and utilized as supplied.

Dichloromethane for optical spectroscopy was purchased from Nacalai Tesque as a reagent prepared specially for spectroscopy and used without further purification.

4.2. Synthetic procedures

4.2.1. Grignard reaction [step (ii) of Scheme 1].[12] To a dry THF solution (30 ml) of aldehyde **1a** (82.5 mg, 150 μmol) was dropwise added a solution of Grignard reagent (about 10 equiv) at 0 °C with stirring under nitrogen. When the Qy absorption maximum of the solution at 695 nm was hypsochromically shifted to around 665 nm, the reaction was quenched by addition of an ice-chilled aqueous 1% ammonium chloride solution (4 ml). The reaction mixture was diluted with water and extracted with dichloromethane. The separated organic phase was washed with water and an aqueous 4% sodium hydrogen carbonate solution and dried over sodium sulfate. After all the solvents were evaporated, the residue was purified by FCC (5% Et_2O–CH_2Cl_2) and recrystallization (CH_2Cl_2–hexane) to give methyl bacteriopheophorbide-*d* analogs **2c**–**n** as a 3^1-epimeric mixture (3^1R:3^1S=1:1). The isolated yields were 45% for **2c** (R=Et), 40% for **2d** (R=Pr), <10% for **2e** (R=iPr), 33% for **2f** (R=cycloPr), 33% for **2g** (R=CH=CH_2), 29% for **2h**/**i** (*R*=3:7 *cis*/*trans*-CH=CH_2), 40% for **2j** (R=CMe=CH_2), 23% for **2k** (R=C≡CH), 45% for **2l** (R=C≡CMe), 29% for **2m** (R=C≡CPh), and 43% for **2n** (R=Ph).

4.2.2. Barbier reaction [step (v) of Schemes 2 and 3].[13] To a dry THF solution (20 ml) of aldehyde **1a** (50.0 mg, 90.9 μmol) were added distilled water (10 ml), indium powder (100 mg. 0.9 mmol), and bromide (0.22 ml, ca. 2 mmol). The mixture was stirred at room temperature under nitrogen for 2 h. When the Qy absorption maximum of the solution was blue-shifted from 695 to 662 nm, the reaction mixture was filtered over Celite to remove insoluble indium solid. The filtrate was diluted with water and extracted with dichloromethane. The separated organic phase was washed with water several times and dried over sodium sulfate. The same purification as mentioned in section 4.2.1 gave methyl bacteriopheophorbide-*d* analogs **2o**/**q**/**s**–**w** as a 3^1-epimeric mixture (3^1R:3^1S=1:1). Additionally, **2q** was a 3^2-epimeric mixture (3^2R:3^2S=1:1). The isolated yields were 88% for **2o** (R^1=R^2=H), 0/70% for **2p**/**q** (R^1=Me, R^2=H), 0/43% for **2r**/**s** (R^1=R^2=Me), 49/26% for **2t**/**u** (R^3=H), and 9/75% for **2v**/**w** (R^3=Me). Isomeric separations of **2t** (propargyl) with **2u** (allenyl) and of **2v** (yne) with **2w** (1,2-diene) were performed by HPLC (see Section 4.1, eluent: MeOH, 1.0 ml/min): retention times=21.6 (**2t**), 25.5 (**2u**), 24.7 (**2v**), and 26.6 min (**2w**).

4.2.3. Ley–Griffith oxidation [step (iv) of Schemes 1–3].[9,20] To a dichloromethane solution (10 ml) of secondary alcohol **2** (15 μmol) were added *N*-methylmorpholine *N*-oxide (4.0 mg, 34 μmol) and tetrapropylammonium perruthenate (2.0 mg, 5.7 μmol). The solution was stirred at room temperature under nitrogen for 10–150 min. When the disappearance of the starting alcohol was confirmed by visible spectral change (a red-shift of Qy maximum) or TLC, the reaction was quenched by addition of water (4 ml). The same work-up as in Section 4.2.1 gave the corresponding ketone **1**. The isolated yields are summarized in Table 1.

4.2.4. Dess–Martin oxidation [step (iv) of Schemes 1–3]. To a dichloromethane solution (10 ml) of secondary alcohol **2** (20 μmol) was added Dess–Martin periodinane (17 mg, 40 μmol) with stirring at room temperature under nitrogen for 30–120 min. The same work-up as in Section 4.2.1 gave the corresponding ketone **1**. The isolated yields are summarized in Table 1. Stereoisomeric separation of *cis*-**1h** with *trans*-**1i** was performed by HPLC (see Section 4.1, eluent: THF:H_2O=6:4, 1.0 ml/min): retention times=29.6 (**1h**) and 27.2 min (**1i**).

4.2.5. Hydrogenation [step (vi) of Scheme 4]. Olefins **2o**/**j** (50 μmol) were dissolved in THF (10 ml) and acetone (5 ml), to which was added 10% palladium charcoal (15 mg). The mixture was stirred under hydrogen at room temperature for 5 h. The same work-up as in Section 4.2.1 gave the corresponding reduction products **2d**/**e**.

4.3. Data of methyl bacteriopheophorbide-*d* analogs 2c–o/q/s–w

*4.3.1. Methyl 3^2-methyl-bacteriopheophorbide-d (**2c**) [3-C*H(OH) Et].* Black solid; mp 137–139 °C; VIS (CH_2Cl_2) λ_{max}=661 (relative intensity, 0.47), 605 (0.08), 536 (0.09), 505 (0.09), 410 nm (1.00); ^{1}H NMR ($CDCl_3$) δ=9.70/69 (1H, s, 10-H), 9.51 (1H, s, 5-H), 8.53/52 (1H, s, 20-H), 6.13 (1H, br t, *J*=7 Hz, 3-CH), 5.28/23, 5.10 (each 1H, d, *J*=20 Hz, 13^1-CH_2), 4.47 (1H, br q, *J*=7 Hz, 18-H), 4.28 (1H, br d, *J*=7 Hz, 17-H), 3.70 (2H, q, *J*=8 Hz, 8-CH_2), 3.67 (3H, s, 12-CH_3), 3.61 (3H, s, 17^2-$COOCH_3$), 3.412/407 (3H, s, 2-CH_3), 3.25 (3H, s, 7-CH_3), 2.72–2.47, 2.33–2.22 (4H+2H, m, 3^1-CH_2, 17-CH_2CH_2), 1.81/80 (3H, d, *J*=7 Hz, 18-CH_3), 1.70 (3H, t, *J*=7 Hz, 8^1-CH_3), 1.13 (3H, t, *J*=7 Hz, 3^2-CH_3), 0.36, −1.78 (each 1H, s, NH×2); IR (film) ν=3450 (O–H), 1736 (17^2-C=O), 1699 cm^{-1} (13-C=O); HRMS (APCI) found: *m*/*z* 581.3124, calcd for $C_{35}H_{41}N_4O_4$: MH^+, 581.3122; see also its spectral data in Ref. 13.

*4.3.2. Methyl 3^2-ethyl-bacteriopheophorbide-d (**2d**) [3-C*H(OH) Pr].* Black solid; mp 106–108 °C; VIS (CH_2Cl_2) λ_{max}=661 (relative intensity, 0.47), 605 (0.07), 536 (0.08), 505 (0.08), 410 nm (1.00); ^{1}H NMR ($CDCl_3$) δ=9.69/68 (1H, s, 10-H), 9.52 (1H, s, 5-H), 8.52 (1H, s, 20-H), 6.24 (1H, br t, *J*=7 Hz, 3-CH), 5.251/246, 5.09 (each 1H, d, *J*=20 Hz, 13^1-CH_2), 4.48 (1H, dq, *J*=2, 7 Hz, 18-H), 4.29 (1H, br d, *J*=7 Hz, 17-H), 3.71 (2H, q, *J*=8 Hz, 8-CH_2), 3.68 (3H, s, 12-CH_3), 3.61 (3H, s, 17^2-$COOCH_3$), 3.418/416 (3H, s, 2-CH_3), 3.26 (3H, s, 7-CH_3), 2.76–2.23 (7H, m, 3^1-OH, 3^1-CH_2, 17-CH_2CH_2), 1.814/807 (3H, d, *J*=7 Hz, 18-CH_3), 1.72 (3H, t, *J*=8 Hz, 8^1-CH_3), 1.78–1.68, 1.57–1.47 (each 1H, m, 3^2-CH_2), 1.05 (3H, t, *J*=7 Hz, 3^3-CH_3), 0.42/01, −1.74 (each 1H, s, NH×2); IR (film) ν=3450 (O–H), 1736 (17^2-C=O), 1697 cm^{-1} (13-C=O); HRMS (APCI) found: *m*/*z* 595.3280, calcd for $C_{36}H_{43}N_4O_4$: MH^+, 595.3280; see also its spectral data in Ref. 21.

*4.3.3. Methyl 3^2,3^2-dimethyl-bacteriophophorbide-d (**2e**) [3-C*H(OH)iPr].* Black solid; mp 110–112 °C; VIS (CH_2Cl_2) λ_{max}=662 (relative intensity, 0.47), 605 (0.07), 537 (0.09), 505 (0.09), 410 nm (1.00); ^{1}H NMR ($CDCl_3$) δ=9.68 (1H, s, 10-H), 9.49 (1H, s, 5-H), 8.52/51 (1H, s, 20-H), 5.79 (1H, d, *J*=9 Hz, 3-CH), 5.25/24, 5.09/08 (each 1H, d, *J*=20 Hz, 13^1-CH_2), 4.49 (1H, dq, *J*=2, 7 Hz, 18-H), 4.31 (1H, dt, *J*=8, 2 Hz, 17-H), 3.69 (2H, q, *J*=8 Hz, 8-CH_2), 3.65 (3H, s, 12-CH_3), 3.61 (3H, s, 17^2-$COOCH_3$), 3.42 (3H, s, 2-CH_3), 3.26 (3H, s, 7-CH_3), 2.94–2.90 (1H, m, 3^1-CH), 2.71–2.51, 2.36–2.20 (each 2H, m, 17-CH_2CH_2), 1.80/79 (3H, d, *J*=7 Hz, 18-CH_3), 1.69 (3H, t, *J*=8 Hz, 8^1-CH_3), 1.51, 0.91 (each 3H, d, *J*=7 Hz, 3^2-CH_3×2), 0.08, −1.94 (each 1H,

s, NH×2); IR (film) ν=3430 (O–H), 1736 (17^2-C=O), 1695 cm^{-1} (13-C=O); HRMS (APCI) found: m/z 595.3279, calcd for $C_{36}H_{43}N_4O_4$: MH^+, 595.3280; see also its spectral data in Ref. 13.

*4.3.4. Methyl 3^2,3^2-ethylene-bacteriopheophorbide-d (**2f**) [3-C*H(OH)cycloPr].* Black solid; mp 121–123 °C; VIS (CH_2Cl_2) λ_{max}=663 (relative intensity, 0.49), 606 (0.08), 537 (0.10), 506 (0.10), 410 nm (1.00); ^{1}H NMR ($CDCl_3$) δ=9.69/67 (1H, s, 10-H), 9.45 (1H, s, 5-H), 8.52/51 (1H, s, 20-H), 5.51/50 (1H, d, J=9 Hz, 3-CH), 5.24/19, 5.10/05 (each 1H, d, J=20 Hz, 13^1-CH_2), 4.45 (1H, dq, J=2, 7.5 Hz, 18-H), 4.25 (1H, m, 17-H), 3.67 (2H, q, J=8 Hz, 8-CH_2), 3.63 (3H, s, 12-CH_3), 3.604/598 (3H, s, 17^2-$COOCH_3$), 3.416/407 (3H, s, 2-CH_3), 3.24 (3H, s, 7-CH_3), 2.77/76 (1H, br, 3^1-OH), 2.71–2.61, 2.58–2.48, 2.31–2.21 (1H+1H+2H, m, 17-CH_2CH_2), 2.13–2.03 (1H, m, 3^1-CH), 1.78/77 (3H, d, J=7.5 Hz, 18-CH_3), 1.67 (3H, t, J=8 Hz, 8^1-CH_3), 0.98–0.84, 0.70–0.63, 0.60–0.53 (2H+1H+1H, m, 3^2-CH_2×2), 0.32, −1.81 (each 1H, s, NH×2); IR (film) ν=3440 (O–H), 1736 (17^2-C=O), 1694 cm^{-1} (13-C=O); HRMS (APCI) found: m/z 593.3124, calcd for $C_{36}H_{41}N_4O_4$: MH^+, 593.3122.

*4.3.5. Methyl 3^2-methylene-bacteriopheophorbide-d (**2g**) [3-C*H(OH)CH=CH_2].* Black solid; mp 132–135 °C; VIS (CH_2Cl_2) λ_{max}=663 (relative intensity, 0.50), 606 (0.07), 536 (0.09), 506 (0.09), 410 nm (1.00); ^{1}H NMR ($CDCl_3$) δ=9.68/67 (1H, s, 10-H), 9.52 (1H, s, 5-H), 8.55/54 (1H, s, 20-H), 6.76–6.67 (2H, m, 3-CHCH), 5.72 (1H, d, J=16 Hz, 3^2=CH *trans* to $C3^2$–H), 5.44 (1H, s, J=9 Hz, 3^2=CH *cis* to $C3^2$–H), 5.26/25, 5.11/10 (each, 1H, d, J=20 Hz, 13^1-CH_2), 4.48 (1H, br q, J=7 Hz, 18-H), 4.29 (1H, br d, J=7 Hz, 17-H), 3.70 (2H, q, J=7.5 Hz, 8-CH_2), 3.67 (3H, s, 12-CH_3), 3.61/60 (3H, s, 17^2-$COOCH_3$), 3.42/41 (3H, s, 2-CH_3), 3.24 (3H, s, 7-CH_3), 2.76 (1H, br s, OH), 2.72–2.64, 2.61–2.50, 2.34–2.22 (1H+1H+2H, m, 17-CH_2CH_2), 1.81/79 (3H, d, J=7 Hz, 18-CH_3), 1.69 (3H, t, J=7.5 Hz, 8^1-CH_3), 0.33, −1.81 (each 1H, s, NH×2); IR (film) ν=3450 (O–H), 1736 (17^2-C=O), 1690 cm^{-1} (13-C=O); HRMS (APCI) found: m/z 579.2966, calcd for $C_{35}H_{39}N_4O_4$: MH^+, 579.2966.

*4.3.6. Methyl 3^2-cis/trans-ethylidene-bacteriopheophorbide-d (**2h**/**i**) [3-C*H(OH)-cis/trans-CH=CHMe=3/7].* Black solid; mp 115–117 °C; VIS (CH_2Cl_2) λ_{max}=662 (relative intensity, 0.47), 606 (0.08), 536 (0.10), 506 (0.10), 410 nm (1.00); ^{1}H NMR ($CDCl_3$) δ=9.674/645 (1H-*trans*, s, 10-H), 9.654/631 (1H-*cis*, s, 10-H), 9.432 (1H-*trans*, s, 5-H), 9.427 (1H-*cis*, s, 5-H), 8.51 (1H-*trans*, s, 20-H), 8.50 (1H-*cis*, s, 20-H), 7.04/02 (1H-*cis*, d, J=8 Hz, 3-CH), 6.66/64 (1H-*trans*, d, J=8 Hz, 3-CH), 6.56–6.47 (1H-*cis*, m, 3^1-CH), 6.43–6.34 (1H-*trans*, m, 3^1-CH), 6.09 (1H-*trans*, dq, J=15, 7 Hz, 3^2=CH), 5.78 (1H-*cis*, dq, J=11, 7 Hz, 3^2=CH), 5.22/20, 5.07/06 (each 1H-*trans*, d, J=20 Hz, 13^1-CH_2), 5.21, 5.07 (each 1H-*cis*, d, J=20 Hz, 13^1-CH_2), 4.45 (1H, q, J=7 Hz, 18-H), 4.24 (1H, m, 17-H), 3.67 (2H, q, J=8 Hz, 8-CH_2), 3.62 (3H, s, 17^2-$COOCH_3$), 3.610 (3H-*cis*, s, 12-CH_3), 3.607 (3H-*trans*, s, 12-CH_3), 3.44/43 (3H-*cis*, s, 2-CH_3), 3.39/38 (3H-*trans*, s, 2-CH_3), 3.234 (3H-*cis*, s, 7-CH_3), 3.227 (3H-*trans*, s, 7-CH_3), 2.80–2.47, 2.36–2.17 (3H+2H, m, 3^1-OH, 17-CH_2CH_2), 2.09–1.97, 1.83–1.73 (3H, m, 3^3-CH_3), 1.79 (3H-*trans*, d, J=7 Hz, 18-CH_3), 1.76 (3H-*cis*, d, J=7 Hz, 18-CH_3), 1.68 (3H, t, J=8 Hz, 8^1-CH_3), 0.28, −1.85 (each 1H, s, NH×2); IR (film) ν=3440 (O–H), 1736 (17^2-C=O), 1694 cm^{-1} (13-C=O); HRMS (APCI) found: m/z 593.3123, calcd for $C_{36}H_{41}N_4O_4$: MH^+, 593.3122.

*4.3.7. Methyl 3^2-methyl-3^2-methylene-bacteriopheophorbide-d (**2j**) [3-C*H(OH)CMe=CH_2].* Black solid; mp 131–133 °C; VIS (CH_2Cl_2) λ_{max}=663 (relative intensity, 0.50), 606 (0.08), 537 (0.09), 506 (0.09), 410 nm (1.00); ^{1}H NMR ($CDCl_3$) δ=9.76/75 (1H, s, 10-H), 9.53/52 (1H, s, 5-H), 8.56/55 (1H, s, 20-H), 6.59 (1H, br, 3-CH), 5.85, 5.32 (each 1H, br s, 3^2=CH_2), 5.27/26, 5.11 (each 1H, d, J=20 Hz, 13^1-CH_2), 4.49/48 (1H, dq, J=2, 7 Hz, 18-H), 4.30/29 (1H, dt, J=9, 2 Hz, 17-H), 3.70 (2H, q, J=8 Hz, 8-CH_2), 3.68 (3H, s, 12-CH_3), 3.608/606 (3H, s, 17^2-$COOCH_3$), 3.43/42 (3H, s, 2-CH_3), 3.22 (3H, s, 7-CH_3), 2.773/765 (1H, d, J=3 Hz, OH), 2.71–2.65, 2.61–2.50, 2.35–2.22 (1H+1H+2H, m, 17-CH_2CH_2), 1.82 (3H, s, 3^2-CH_3), 1.81/80 (3H, d, J=7 Hz, 18-CH_3), 1.69 (3H, t, J=8 Hz, 8^1-CH_3), 0.38, −1.79 (each 1H, s, NH×2); IR (film) ν=3450 (O–H), 1736 (17^2-C=O), 1695 cm^{-1} (13-C=O); HRMS (APCI) found: m/z 593.3122, calcd for $C_{36}H_{41}N_4O_4$: MH^+, 593.3122.

*4.3.8. Methyl 3^2-methylidyne-bacteriopheophorbide-d (**2k**) [3-C*H(OH)C≡CH].* Black solid; mp 158–160 °C; VIS (CH_2Cl_2) λ_{max}=665 (relative intensity, 0.51), 607 (0.08), 537 (0.09), 507 (0.10), 411 nm (1.00); ^{1}H NMR ($CDCl_3$) δ=9.80/75 (1H, s, 10-H), 9.36 (1H, s, 5-H), 8.56/55 (1H, s, 20-H), 6.95/92 (1H, br, 3-CH), 5.14/12, 5.01/00 (each 1H, d, J=20 Hz, 13^1-CH_2), 4.43 (1H, br q, J=7 Hz, 18-H), 4.15 (1H, br t, J=7 Hz, 17-H), 3.65 (2H, q, J=7.5 Hz, 8-CH_2), 3.62 (3H, s, 12-CH_3), 3.56 (3H, s, 17^2-$COOCH_3$), 3.52/50 (3H, s, 2-CH_3), 3.26 (3H, s, 7-CH_3), 2.941/938 (1H, d, J=1 Hz, 3^2≡CH), 2.63–2.50, 2.31–2.13 (each 2H, m, 17-CH_2CH_2), 1.76/74 (3H, d, J=7 Hz, 18-CH_3), 1.66 (3H, t, J=7.5 Hz, 8^1-CH_3), 0.00, −2.01 (each 1H, s, NH×2); IR (film) ν=3430 (O–H), 2115 (C≡C), 1734 (17^2-C=O), 1690 cm^{-1} (13-C=O); HRMS (APCI) found: m/z 577.2809, calcd for $C_{35}H_{37}N_4O_4$: MH^+, 577.2809; see also its spectral data in Ref. 28.

*4.3.9. Methyl 3^2-ethylidyne-bacteriopheophorbide-d (**2l**) [3-C*H(OH) C≡CMe].* Black solid; mp 125–127 °C; VIS (CH_2Cl_2) λ_{max}=666 (relative intensity, 0.53), 609 (0.07), 537 (0.09), 507 (0.09), 410 nm (1.00); ^{1}H NMR ($CDCl_3$) δ=9.85/81 (1H, s, 10-H), 9.43/42 (1H, s, 5-H), 8.56/55 (1H, s, 20-H), 6.90/88 (1H, s, 3-CH), 5.22/17, 5.08/03 (each 1H, d, J=20 Hz, 13^1-CH_2), 4.41 (1H, m, 18-H), 4.23 (1H, m, 17-H), 3.67 (2H, q, J=8 Hz, 8-CH_2), 3.62 (3H, s, 12-CH_3), 3.61 (3H, s, 17^2-$COOCH_3$), 3.50/48 (3H, s, 2-CH_3), 3.27 (3H, s, 7-CH_3), 2.92 (1H, s, 3^1-OH), 2.71–2.59, 2.58–2.53, 2.33–2.17 (1H+1H+2H, m, 17-CH_2CH_2), 2.01 (3H, s, 3^3-CH_3), 1.78/76 (3H, d, J=7 Hz, 18-CH_3), 1.68 (3H, t, J=7 Hz, 8^1-CH_3), 0.25, −1.92 (each 1H, s, NH×2); IR (film) ν=3440 (O–H), 2226 (C≡C), 1736 (17^2-C=O), 1694 cm^{-1} (13-C=O); HRMS (APCI) found: m/z 591.2966, calcd for $C_{36}H_{39}N_4O_4$: MH^+, 591.2964.

*4.3.10. Methyl 3^2-phenylmethylidyne-bacteriopheophorbide-d (**2m**) [3-C*H(OH)C≡CPh].* Black solid; mp 140–141 °C; VIS (CH_2Cl_2) λ_{max}=666 (relative intensity, 0.54), 608 (0.08), 537 (0.10), 506 (0.10), 411 nm (1.00); ^{1}H NMR ($CDCl_3$) δ=9.93/92 (1H, s, 10-H), 9.52 (1H, s, 5-H), 8.62/61 (1H, s, 20-H), 7.52–7.50 (2H, m, *o*-H of 3^3-Ph), 7.31–7.30 (3H, m, *m*-, *p*-H of 3^3-Ph), 7.18/17 (1H, s, 3-CH), 5.27/22, 5.12/07 (each 1H, d, J=20 Hz, 13^1-CH_2), 4.41 (1H, dq, J=2, 7 Hz, 18-H), 4.18 (1H, br t, J=9 Hz, 17-H), 3.70 (2H, q, J=8 Hz, 8-CH_2), 3.66 (3H, s, 12-CH_3), 3.612/607 (3H, s, 17^2-$COOCH_3$), 3.573/565 (3H, s, 2-CH_3), 3.253/248 (3H, s, 7-CH_3), 2.96 (1H, s, 3^1-OH), 2.74–2.65, 2.59–2.51, 2.36–2.24 (1H+1H+2H, m, 17-CH_2CH_2), 1.82/80 (3H, d, J=7 Hz, 18-CH_3), 1.71 (3H, t, J=7 Hz, 8^1-CH_3), 0.25, −1.82 (each 1H, s, NH×2); IR (film) ν=3420 (O–H), 2233 (C≡C), 1736 (17^2-C=O), 1697 cm^{-1} (13-C=O); HRMS (APCI) found: m/z 653.3123, calcd for $C_{41}H_{41}N_4O_4$: MH^+, 653.3122.

*4.3.11. Methyl 3^1-demethyl-3^1-phenyl-bacteriopheophorbide-d (**2n**) [3-C*H(OH)Ph].* Black solid; mp 138–140 °C; VIS (CH_2Cl_2) λ_{max}=663 (relative intensity, 0.50), 607 (0.08), 537 (0.09), 507 (0.10), 411 nm (1.00); ^{1}H NMR ($CDCl_3$) δ=9.67 (1H, s, 10-H), 9.49 (1H, s, 5-H), 8.50 (1H, s, 20-H), 7.73/72 (2H, d, J=8 Hz, *o*-H of 3^1-Ph), 7.36 (2H, t, J=8 Hz, *m*-H of 3^1-Ph), 7.36/32 (1H, s, 3-CH), 7.28 (1H, t, J=8 Hz, *p*-H of 3^1-Ph), 5.14/11, 5.02/01 (each 1H, d, J=20 Hz, 13^1-CH_2), 4.41 (1H, m, 18-H), 4.18 (1H, br t, J=9 Hz, 17-H), 3.63/62 (3H, s, 12-CH_3), 3.61 (2H, q, J=8 Hz, 8-CH_2), 3.56/55 (3H, s, 17^2-$COOCH_3$), 3.38/37 (3H, s, 2-CH_3), 3.10/08 (3H, s, 7-CH_3), 2.63–2.49, 2.28–2.14 (each 2H, m, 17-CH_2CH_2), 1.76/74 (3H, d, J=7 Hz, 18-CH_3), 1.64/63 (3H, t, J=8 Hz, 8^1-CH_3), 0.08, −1.94/96 (each 1H, s, NH×2); IR (film) ν=3450 (O–H),

1736 (17^2-C=O), 1690 cm^{-1} (13-C=O); HRMS (APCI) found: *m/z* 629.3122, calcd for $C_{39}H_{41}N_4O_4$: MH^+, 629.3122.

*4.3.12. Methyl 3^2-vinyl-bacteriopheophorbide-d (**2o**) [3-C*H(OH)CH$_2$CH=CH$_2$].* Black solid; mp 96–98 °C (lit.[13] 97–99 °C); VIS (CH_2Cl_2) λ_{max}=661 (relative intensity, 0.47), 605 (0.08), 536 (0.10), 505 (0.10), 410 nm (1.00); ^{1}H NMR ($CDCl_3$) δ=9.69/68 (1H, s, 10-H), 9.50 (1H, s, 5-H), 8.524/517 (1H, s, 20-H), 6.26 (1H, m, 3-CH), 6.08–5.96 (1H, m, 3^2-CH), 5.33–5.28 (1H, m, 3^3=CH *trans* to C3^3–H), 5.24–5.18 (1H, m, 3^3=CH *cis* to C3^3–H), 5.27/22, 5.12/07 (each 1H, d, *J*=20 Hz, 13^1-CH_2), 4.49/48 (1H, q, *J*=8 Hz, 18-H), 4.28 (1H, m, 17-H), 3.70 (2H, q, *J*=8 Hz, 8-CH_2), 3.66 (3H, s, 12-CH_3), 3.62/61 (3H, s, 17^2-$COOCH_3$), 3.41/40 (3H, s, 2-CH_3), 3.25 (3H, s, 7-CH_3), 3.22–3.14 (2H, m, 3^1-CH_2), 2.83 (1H, br s, OH), 2.72–2.63, 2.61–2.51, 2.33–2.23 (1H+1H+2H, m, 17-CH_2CH_2), 1.81/79 (3H, d, *J*=8 Hz, 18-CH_3), 1.69 (3H, t, *J*=8 Hz, 8^1-CH_3), 0.35, −1.79 (each 1H, s, NH×2); IR (film) ν=3450 (O–H), 1736 (17^2-C=O), 1692 cm^{-1} (13-C=O); HRMS (APCI) found: *m/z* 593.3121, calcd for $C_{36}H_{41}N_4O_4$: MH^+, 593.3122; see also its spectral data in Ref. 16.

*4.3.13. Methyl 3^2-methyl-3^2-vinyl-bacteriopheophorbide-d (**2q**) [3-C*H(OH)C*HMeCH=CH$_2$].* Black solid; mp 114–116 °C; VIS (CH_2Cl_2) λ_{max}=662 (relative intensity, 0.48), 605 (0.08), 537 (0.09), 506 (0.09), 411 nm (1.00); ^{1}H NMR ($CDCl_3$) δ=9.71/70/68/67 (1H, s, 10-H), 9.51/50/49/49 (1H, s, 5-H), 8.54/53/51/50 (1H, s, 20-H), 6.24/6.24/5.87/5.86 (1H, ddd, *J*=17, 10, 7 Hz, 3^2-CH), 6.01/5.84 (1H, d, *J*=8 Hz, 3-CH), 5.60/57/03/02 (1H, d, *J*=17 Hz, 3^3=CH *trans* to C3^3–H), 5.47/4.89 (1H, d, *J*=10 Hz, 3^3=CH *cis* to C3^3–H), 5.26/25/25/23, 5.12/11/10/09 (each 1H, d, *J*=20 Hz, 13^1-CH_2), 4.48/47 (1H, q, *J*=8 Hz, 18-H), 4.28–4.27 (1H, m, 17-H), 3.71/70 (2H, q, *J*=8 Hz, 8-CH_2), 3.67/66 (3H, s, 12-CH_3), 3.62 (3H, s, 17^2-$COOCH_3$), 3.43/43/42/39 (3H, s, 2-CH_3), 3.26/25 (3H, s, 7-CH_3), 3.50–3.40 (1H, m, 3^1-CH), 2.98/75 (1H, br s, OH), 2.70–2.62, 2.60–2.52, 2.31–2.25 (1H+1H+2H, m, 17-CH_2CH_2), 1.80/79 (3H, d, *J*=8 Hz, 18-CH_3), 1.67 (3H, t, *J*=8 Hz, 8^1-CH_3), 1.53/1.52/0.97/0.97 (3H, d, *J*=8 Hz, 3^2-CH_3), 0.33, −1.76/77/79/80 (each 1H, s, NH×2); IR (film) ν=3450 (O–H), 1736 (17^2-C=O), 1697 cm^{-1} (13-C=O); HRMS (APCI) found: *m/z* 607.3283, calcd for $C_{37}H_{43}N_4O_4$: MH^+, 607.3283; see also its spectral data in Ref. 13.

*4.3.14. Methyl 3^2,3^2-dimethyl-3^2-vinyl-bacteriopheophorbide-d (**2s**) [3-C*H(OH)CMe$_2$CH=CH$_2$].* Black solid; mp 135–137 °C; VIS (CH_2Cl_2) λ_{max}=662 (relative intensity, 0.49), 606 (0.08), 538 (0.10), 506 (0.09), 410 nm (1.00); ^{1}H NMR ($CDCl_3$) δ=9.8 (1H, br, 10-H), 9.54 (1H, s, 5-H), 8.53 (1H, s, 20-H), 6.31/30 (1H, dd, *J*=18, 11 Hz, 3^2-CH), 6.03 (1H, br, 3-CH), 5.31, 5.10 (each 1H, d, *J*=20 Hz, 13^1-CH_2), 5.31 (1H, m, 3^3=CH *trans* to C3^3–H), 5.27 (1H, m, 3^3=CH *cis* to C3^3–H), 4.48 (1H, dq, *J*=2, 7 Hz, 18-H), 4.29 (1H, dt, *J*=8, 2 Hz, 17-H), 3.71 (2H, q, *J*=7.5 Hz, 8-CH_2), 3.67 (3H, s, 12-CH_3), 3.603/600 (3H, s, 17^2-$COOCH_3$), 3.42 (3H, br, 2-CH_3), 3.24 (3H, s, 7-CH_3), 2.77–2.65, 2.60–2.51, 2.36–2.24 (1H+1H+2H, m, 17-CH_2CH_2), 1.810/805 (3H, d, *J*=7 Hz, 18-CH_3), 1.71 (3H, t, *J*=7.5 Hz, 8^1-CH_3), 1.41, 1.38 (each 3H, s, 3^2-CH_3×2), 0.37, −1.76 (each 1H, s, NH×2); IR (film) ν=3450 (O–H), 1736 (17^2-C=O), 1692 cm^{-1} (13-C=O); HRMS (APCI) found: *m/z* 621.3435, calcd for $C_{38}H_{45}N_4O_4$: MH^+, 621.3435; see also its spectral data in Ref. 13.

*4.3.15. Methyl 3^2-ethynyl-bacteriopheophorbide-d (**2t**) [3-C*H(OH)CH$_2$C≡CH].* Black solid; mp 86–88 °C; VIS (CH_2Cl_2) λ_{max}=662 (relative intensity, 0.52), 606 (0.08), 536 (0.09), 505 (0.09), 410 nm (1.00); ^{1}H NMR ($CDCl_3$) δ=9.70/69 (1H, s, 10-H), 9.52/51 (1H, s, 5-H), 8.55/54 (1H, s, 20-H), 6.41/40 (1H, t, *J*=8 Hz, 3-CH), 5.26/24, 5.11/10 (each 1H, d, *J*=20 Hz, 13^1-CH_2), 4.47 (1H, q, *J*=8 Hz, 18-H), 4.30–4.27 (1H, m, 17-H), 3.67 (2H, q, *J*=8 Hz, 8-CH_2), 3.67 (3H, s, 12-CH_3), 3.61 (3H, s, 17^2-$COOCH_3$), 3.45/44 (3H, s, 2-CH_3), 3.26 (3H, s, 7-CH_3), 3.51–3.46, 3.26–3.22 (each 1H, m, 3^1-CH_2), 3.13/12 (1H, br s, OH), 2.72–2.65, 2.62–2.53, 2.32–2.25 (1H+1H+2H, m, 17-CH_2CH_2), 2.16/15 (1H, t, *J*=3 Hz, 3^3≡CH), 1.80/79 (3H, d, *J*=8 Hz, 18-CH_3), 1.70 (3H, t, *J*=8 Hz, 8^1-CH_3), 0.35, −1.84 (each 1H, s, NH×2); IR (film) ν=3440 (O–H), 2120 (C≡C), 1735 (17^2-C=O), 1690 cm^{-1} (13-C=O); HRMS (APCI) found: *m/z* 591.2964, calcd for $C_{36}H_{39}N_4O_4$: MH^+, 591.2964; see also its spectral data in Ref. 15.

*4.3.16. Methyl 3^2-vinylidene-bacteriopheophorbide-d (**2u**) [3-C*H(OH)CH=C=CH$_2$].* Black solid; mp 102–104 °C; VIS (CH_2Cl_2) λ_{max}=663 (relative intensity, 0.51), 606 (0.07), 537 (0.08), 506 (0.08), 410 nm (1.00); ^{1}H NMR ($CDCl_3$) δ=9.67/66 (1H, s, 10-H), 9.52 (1H, s, 5-H), 8.55 (1H, s, 20-H), 6.82 (1H, br, 3-CH), 6.09/08 (1H, ddd, *J*=6, 4, 2 Hz, 3^1-CH), 5.26, 5.11 (each 1H, d, *J*=20 Hz, 13^1-CH_2), 5.13–5.08 (1H, m, 3^3=CH), 5.01/00 (1H, ddd, *J*=11, 6, 2 Hz, 3^3=CH), 4.48 (1H, q, *J*=8 Hz, 18-H), 4.29 (1H, br d, *J*=8 Hz, 17-H), 3.70 (2H, q, *J*=8 Hz, 8-CH_2), 3.68 (3H, s, 12-CH_3), 3.60 (3H, s, 17^2-$COOCH_3$), 3.43 (3H, s, 2-CH_3), 3.25 (3H, s, 7-CH_3), 2.88 (1H, br s, OH), 2.72–2.65, 2.62–2.53, 2.33–2.17 (1H+1H+2H, m, 17-CH_2CH_2), 1.80 (3H, d, *J*=8 Hz, 18-CH_3), 1.70/69 (3H, t, *J*=8 Hz, 8^1-CH_3), 0.35, −1.80 (each 1H, s, NH×2); IR (film) ν=3420 (O–H), 1956 (C=C=C), 1736 (17^2-C=O), 1692 cm^{-1} (13-C=O); HRMS (APCI) found: *m/z* 591.2966, calcd for $C_{36}H_{39}N_4O_4$: MH^+, 591.2964.

*4.3.17. Methyl 3^2-(1-propynyl)bacteriopheophorbide-d (**2v**) [3-C*H(OH)CH$_2$C≡CMe].* Black solid; mp 86–88 °C; VIS (CH_2Cl_2) λ_{max}=662 (relative intensity, 0.48), 606 (0.08), 536 (0.09), 506 (0.09), 410 nm (1.00); ^{1}H NMR ($CDCl_3$) δ=9.65/64 (1H, s, 10-H), 9.43/42 (1H, s, 5-H), 8.52/51 (1H, s, 20-H), 6.29/27 (1H, t, *J*=8 Hz, 3-CH), 5.22/18, 5.07/06 (each 1H, d, *J*=20 Hz, 13^1-CH_2), 4.45 (1H, q, *J*=8 Hz, 18-H), 4.26–4.22 (1H, m, 17-H), 3.66 (2H, q, *J*=8 Hz, 8-CH_2), 3.62 (6H, s, 12-CH_3, 17^2-$COOCH_3$), 3.42/41 (3H, s, 2-CH_3), 3.23 (3H, s, 7-CH_3), 3.38–3.34, 3.14–3.09 (each 1H, m, 3^1-CH_2), 3.17 (1H, br s, OH), 2.79–2.65, 2.62–2.50, 2.30–2.23 (1H+1H+2H, m, 17-CH_2CH_2), 1.82 (3H, t, *J*=3 Hz, 3^4-CH_3), 1.78/77 (3H, d, *J*=8 Hz, 18^1-CH_3), 1.67 (3H, t, *J*=8 Hz, 8^1-CH_3), 0.33, −1.80 (each 1H, s, NH×2); IR (film) ν=3420 (O–H), 1736 (17^2-C=O), 1697 cm^{-1} (13-C=O); HRMS (APCI) found: *m/z* 605.3123, calcd for $C_{37}H_{41}N_4O_4$: MH^+, 605.3122.

*4.3.18. Methyl 3^2-methyl-3^2-vinylidene-bacteriopheophorbide-d (**2w**) [3-C*H(OH)CMe=C=CH$_2$].* Black solid; mp 86–88 °C; VIS (CH_2Cl_2) λ_{max}=663 (relative intensity, 0.51), 606 (0.08), 537 (0.09), 506 (0.09), 410 nm (1.00); ^{1}H NMR ($CDCl_3$) δ=9.68/67 (1H, s, 10-H), 9.50 (1H, s, 5-H), 8.55/54 (1H, s, 20-H), 6.60 (1H, br, 3-CH), 5.28, 5.22 (each 1H, dq, *J*=10, 3 Hz, 3^3=CH_2), 5.26/25, 5.105/101 (each 1H, d, *J*=20 Hz, 13^1-CH_2), 4.48 (1H, dq, *J*=2, 7 Hz, 18-H), 4.31–4.26 (1H, m, 17-H), 3.69 (2H, q, *J*=8 Hz, 8-CH_2), 3.66 (3H, s, 12-CH_3), 3.613/610 (3H, s, 17^2-$COOCH_3$), 3.431/427 (3H, s, 2-CH_3), 3.24 (3H, s, 7-CH_3), 3.02 (1H, br, OH), 2.73–2.64, 2.61–2.51, 2.34–2.23 (1H+1H+2H, m, 17-CH_2CH_2), 1.81/80 (3H, d, *J*=7 Hz, 18^1-CH_3), 1.75 (3H, br t, *J*=3 Hz, 3^2-CH_3), 1.69 (3H, t, *J*=8 Hz, 8^1-CH_3), 0.34, −1.80 (each 1H, s, NH×2); IR (film) ν=3440 (O–H), 1961 (C=C=C), 1736 (17^2-C=O), 1697 cm^{-1} (13-C=O); HRMS (APCI) found: *m/z* 605.3122, calcd for $C_{37}H_{41}N_4O_4$: MH^+, 605.3122.

4.4. Data of methyl 3-acyl-pyropheophorbides-*a* 1c–o/q/s/u/w

*4.4.1. Methyl 3-devinyl-3-propionyl-pyropheophorbide-a (**1c**) [3-COEt].* Black solid; mp 230–234 °C; VIS (CH_2Cl_2) λ_{max}=679 (relative intensity, 0.48), 621 (0.07), 545 (0.10), 513 (0.12), 414 (1.00), 384 nm (0.77); ^{1}H NMR ($CDCl_3$, 45 °C) δ=9.86 (1H, s, 10-H), 9.62 (1H, s, 5-H), 8.74 (1H, s, 20-H), 5.31, 5.16 (each 1H, d, *J*=20 Hz, 13^1-CH_2), 4.56 (1H, dq, *J*=2, 7 Hz, 18-H), 4.36 (1H, dt, *J*=8, 2 Hz, 17-H), 3.74 (2H, q, *J*=7.5 Hz, 8-CH_2), 3.72 (3H, s, 12-CH_3), 3.62 (2H, q,

J=7 Hz, 3^1-CH_2), 3.61 (3H, s, 17^2-$COOCH_3$), 3.60 (3H, s, 2-CH_3), 3.29 (3H, s, 7-CH_3), 2.79–2.66, 2.63–2.53, 2.38–2.26, (1H+1H+2H, m, 17-CH_2CH_2), 1.84 (3H, d, J=7 Hz, 18-CH_3), 1.73 (3H, t, J=7.5 Hz, 8^1-CH_3), 1.60 (3H, t, J=7 Hz, 3^2-CH_3), 0.06, −1.95 (each 1H, s, NH×2); IR (film) ν=1736 (17^2-C=O), 1695 (13-C=O), 1674 cm^{-1} (3-C=O); HRMS (APCI) found: m/z 579.2966, calcd for $C_{35}H_{39}N_4O_4$: MH^+, 579.2966.

*4.4.2. Methyl 3-butyryl-3-devinyl-pyropheophorbide-a (**1d**) [3-COPr].* Black solid; mp 105–107 °C; VIS (CH_2Cl_2) λ_{max}=678 (relative intensity, 0.47), 620 (0.07), 543 (0.10), 512 (0.12), 414 (1.00), 384 nm (0.77); ^{1}H NMR ($CDCl_3$, 45 °C) δ=9.81 (1H, s, 10-H), 9.60 (1H, s, 5-H), 8.74 (1H, s, 20-H), 5.32, 5.17 (each 1H, d, J=20 Hz, 13^1-CH_2), 4.55 (1H, dq, J=2, 7 Hz, 18-H), 4.36 (1H, dt, J=8, 2 Hz, 17-H), 3.72 (2H, q, J=8 Hz, 8-CH_2), 3.71 (3H, s, 12-CH_3), 3.61 (3H, s, 17^2-$COOCH_3$), 3.60 (3H, s, 2-CH_3), 3.57 (2H, t, J=7 Hz, 3^1-CH_2), 3.28 (3H, s, 7-CH_3), 2.77–2.68, 2.63–2.55, 2.36–2.26 (1H+1H+2H, m, 17-CH_2CH_2), 2.14 (2H, sextet, J=7 Hz, 3^2-CH_2), 1.84 (3H, d, J=7 Hz, 18-CH_3), 1.71 (3H, t, J=8 Hz, 8^1-CH_3), 1.23 (3H, t, J=7 Hz, 3^3-CH_3), 0.07, −1.99 (each 1H, s, NH×2); IR (film) ν=1736 (17^2-C=O), 1699 (13-C=O), 1670 cm^{-1} (3-C=O); HRMS (APCI) found: m/z 593.3122, calcd for $C_{36}H_{41}N_4O_4$: MH^+, 593.3124; see also its spectral data in Ref. 21.

*4.4.3. Methyl 3-devinyl-3-isobutyryl-pyropheophorbide-a (**1e**) [3-COiPr].* Black solid; mp 115–117 °C; VIS (CH_2Cl_2) λ_{max}=672 (relative intensity, 0.48), 615 (0.07), 540 (0.09), 509 (0.10), 412 nm (1.00); ^{1}H NMR ($CDCl_3$) δ=9.60 (1H, s, 10-H), 9.55 (1H, s, 5-H), 8.71 (1H, s, 20-H), 5.32, 5.17 (each 1H, d, J=20 Hz, 13^1-CH_2), 4.55 (1H, dq, J=2, 8 Hz, 18-H), 4.37 (1H, dt, J=8, 2 Hz, 17-H), 4.04 (1H, septet, J=7 Hz, 3^1-CH), 3.72 (2H, q, J=7 Hz, 8-CH_2), 3.71 (3H, s, 12-CH_3), 3.61 (3H, s, 17^2-$COOCH_3$), 3.54 (3H, s, 2-CH_3), 3.26 (3H, s, 7-CH_3), 2.77–2.55, 2.35–2.25 (each 2H, m, 17-CH_2CH_2), 1.84 (3H, d, J=8 Hz, 18-CH_3), 1.71 (3H, t, J=7 Hz, 8^1-CH_3), 1.54, 1.53 (each 3H, d, J=7 Hz, 3^2-CH_3×2), 0.07, −1.97 (each 1H, s, NH×2); IR (film) ν=1736 (17^2-C=O), 1697 (13-C=O), 1653 cm^{-1} (3-C=O); HRMS (APCI) found: m/z 593.3121, calcd for $C_{36}H_{41}N_4O_4$: MH^+, 593.3122.

*4.4.4. Methyl 3-cyclopropylcarbonyl-3-devinyl-pyropheophorbide-a (**1f**) [3-COcycloPr].* Black solid; mp 169–171 °C; VIS (CH_2Cl_2) λ_{max}=678 (relative intensity, 0.56), 619 (0.08), 544 (0.10), 513 (0.12), 416 (1.00), 383 nm (0.73); ^{1}H NMR ($CDCl_3$, 45 °C) δ=9.87 (1H, s, 10-H), 9.57 (1H, s, 5-H), 8.74 (1H, s, 20-H), 5.32, 5.17 (each 1H, d, J=20 Hz, 13^1-CH_2), 4.55 (1H, dq, J=2, 7 Hz, 18-H), 4.36 (1H, dt, J=8, 2 Hz, 17-H), 3.71 (2H, q, J=7.5 Hz, 8-CH_2), 3.70 (3H, s, 12-CH_3), 3.64 (3H, s, 17^2-$COOCH_3$), 3.62 (3H, s, 2-CH_3), 3.26 (3H, s, 7-CH_3), 3.21–3.15 (1H, m, 3^1-CH), 2.77–2.69, 2.64–2.55, 2.36–2.27 (1H+1H+2H, m, 17-CH_2CH_2), 1.84 (3H, d, J=7 Hz, 18-CH_3), 1.70 (3H, t, J=7.5 Hz, 8^1-CH_3), 1.89–1.81, 1.51–1.47 (each 2H, m, 3^2-CH_2×2), 0.04, −1.99 (each 1H, s, NH×2); IR (film) ν=1736 (17^2-C=O), 1697 (13-C=O), 1655 cm^{-1} (3-C=O); HRMS (APCI) found: m/z 591.2968, calcd for $C_{36}H_{39}N_4O_4$: MH^+, 591.2964.

*4.4.5. Methyl 3-acryloyl-3-devinyl-pyropheophorbide-a (**1g**) [3-COCH=CH$_2$].* Black solid; mp 138–140 °C; VIS (CH_2Cl_2) λ_{max}=679 (relative intensity, 0.52), 623 (0.09), 545 (0.11), 514 (0.13), 414 (1.00), 387 nm (0.86); ^{1}H NMR ($CDCl_3$, 45 °C) δ=9.62 (2H, s, 5-, 10-H), 8.74 (1H, s, 20-H), 7.47 (1H, dd, J=17, 10 Hz, 3^1-CH), 6.53 (1H, d, J=17 Hz, 3^2=CH *trans* to C3^2–H), 6.34 (1H, d, J=10 Hz, 3^2=CH *cis* to C3^2–H), 5.33, 5.18 (each 1H, d, J=20 Hz, 13^1-CH_2), 4.56 (1H, br q, J=8 Hz, 18-H), 4.37 (1H, dt, J=8, 2 Hz, 17-H), 3.73 (2H, q, J=8 Hz, 8-CH_2), 3.72 (3H, s, 12-CH_3), 3.61 (3H, s, 17^2-$COOCH_3$), 3.53 (3H, s, 2-CH_3), 3.24 (3H, s, 7-CH_3), 2.78–2.68, 2.64–2.54, 2.36–2.26 (1H+1H+2H, m, 17-CH_2CH_2), 1.84 (3H, d, J=8 Hz, 18-CH_3), 1.71 (3H, t, J=8 Hz, 8^1-CH_3), 0.03, −1.96 (each 1H, s, NH×2); IR (film) ν=1736 (17^2-C=O), 1698 (13-C=O), 1655 cm^{-1} (3-C=O); HRMS (APCI) found: m/z 577.2809, calcd for $C_{35}H_{37}N_4O_4$: MH^+, 577.2809; see also its spectral data in Ref. 29.

*4.4.6. Methyl 3-devinyl-3-isocrotonoyl/3-crotonoyl-3-devinyl-pyropheophorbide-a (**1h/i**) [3-CO-cis/trans-CH=CHMe=3/7].* Black solid; mp 100–102 °C; VIS (CH_2Cl_2) λ_{max}=675 (relative intensity, 0.46), 617 (0.08), 542 (0.10), 511 (0.12), 413 nm (1.00); ^{1}H NMR ($CDCl_3$) δ(*cis*/*trans*)=9.82/54 (1H, s, 5-H), 9.59 (1H, s, 10-H), 8.73/70 (1H, s, 20-H), 7.26/18 (1H, dq, J=2/1, 11/16 Hz, 3^1-CH), 6.76/7.09 (1H, dq, J=7.5/6, 11/16 Hz, 3^2=CH), 5.31, 5.16 (each 1H, d, J=20 Hz, 13^1-CH_2), 4.54 (1H, dq, J=2, 8 Hz, 18-H), 4.35 (1H, dt, J=8, 2 Hz, 17-H), 3.71 (2H, q, J=8 Hz, 8-CH_2), 3.70 (3H, s, 12-CH_3), 3.60 (3H, s, 17^2-$COOCH_3$), 3.58/49 (3H, s, 2-CH_3), 3.25/22 (3H, s, 7-CH_3), 2.76–2.67, 2.62–2.52, 2.36–2.24 (1H+1H+2H, m, 17-CH_2CH_2), 2.41/12 (1H, dd, J=7.5/6, 2/1 Hz, 3^3-CH_3), 1.83 (3H, d, J=7 Hz, 18-CH_3), 1.70/69 (3H, t, J=8 Hz, 8^1-CH_3), 0.07, −2.00/−1.98 (each 1H, s, NH×2); IR (film) ν=1736 (17^2-C=O), 1695 (13-C=O), 1655 cm^{-1} (3-C=O); HRMS (APCI) found: m/z 591.2967, calcd for $C_{36}H_{38}N_4O_4$: MH^+, 591.2966.

*4.4.7. Methyl 3-devinyl-3-methacryloyl-pyropheophorbide-a (**1j**) [3-COCMe=CH$_2$].* Black solid; mp 133–135 °C; VIS (CH_2Cl_2) λ_{max}=671 (relative intensity, 0.51), 614 (0.07), 540 (0.10), 510 (0.11), 414 nm (1.00); ^{1}H NMR ($CDCl_3$) δ=9.58 (1H, s, 10-H), 9.34 (1H, s, 5-H), 8.70 (1H, s, 20-H), 6.28, 5.92 (each 1H, s, 3^2=CH_2), 5.32, 5.17 (each 1H, d, J=20 Hz, 13^1-CH_2), 4.55 (1H, dq, J=2, 8 Hz, 18-H), 4.37 (1H, dt, J=8, 2 Hz, 17-H), 3.70 (2H, q, J=8 Hz, 8-CH_2), 3.70 (3H, s, 12-CH_3), 3.62 (3H, s, 17^2-$COOCH_3$), 3.41 (3H, s, 2-CH_3), 3.20 (3H, s, 7-CH_3), 2.77–2.68, 2.63–2.54, 2.36–2.21 (1H+1H+2H, m, 17-CH_2CH_2), 2.49 (3H, s, 3^2-CH_3), 1.84 (3H, d, J=8 Hz, 18-CH_3), 1.69 (3H, t, J=8 Hz, 8^1-CH_3), 0.09, −1.96 (each 1H, s, NH×2); IR (film) ν=1738 (17^2-C=O), 1701 (13-C=O), 1653 cm^{-1} (3-C=O); HRMS (APCI) found: m/z 591.2966, calcd for $C_{36}H_{39}N_4O_4$: MH^+, 591.2964.

*4.4.8. Methyl 3-devinyl-3-propioloyl-pyropheophorbide-a (**1k**) [3-COC≡CH].* Black solid; mp 162–164 °C; VIS (CH_2Cl_2) λ_{max}=694 (relative intensity, 0.62), 634 (0.10), 556 (0.14), 521 (0.15), 418 (0.98), 390 nm (1.00); ^{1}H NMR ($CDCl_3$) δ=10.49 (1H, s, 5-H), 9.55 (1H, s, 10-H), 8.86 (1H, s, 20-H), 5.34, 5.19 (each 1H, d, J=20 Hz, 13^1-CH_2), 4.58 (1H, dq, J=2, 7 Hz, 18-H), 4.38 (1H, dt, J=8, 2 Hz, 17-H), 3.94 (1H, s, 3^2≡CH), 3.83 (3H, s, 2-CH_3), 3.70 (3H, s, 12-CH_3), 3.67 (2H, q, J=7.5 Hz, 8-CH_2), 3.62 (3H, s, 17^2-$COOCH_3$), 3.26 (3H, s, 7-CH_3), 2.79–2.70, 2.62–2.55, 2.36–2.27 (1H+1H+2H, m, 17-CH_2CH_2), 1.85 (3H, d, J=7 Hz, 18-CH_3), 1.69 (3H, t, J=7.5 Hz, 8^1-CH_3), −0.18, −2.13 (each 1H, s, NH×2); IR (film) ν=2092 (C≡C), 1736 (17^2-C=O), 1703 cm^{-1} (13-C=O); HRMS (APCI) found: m/z 575.2653, calcd for $C_{35}H_{35}N_4O_4$: MH^+, 575.2654; see also its spectral data in Ref. 30.

*4.4.9. Methyl 3-(2-butynoyl)-3-devinyl-pyropheophorbide-a (**1l**) [3-COC≡CMe].* Black solid; mp 101–103 °C; VIS (CH_2Cl_2) λ_{max}=695 (relative intensity, 0.76), 634 (0.09), 558 (0.15), 523 (0.15), 434 (1.00), 391 nm (0.90); ^{1}H NMR ($CDCl_3$) δ=10.53 (1H, s, 5-H), 9.58 (1H, s, 10-H), 8.84 (1H, s, 20-H), 5.34, 5.19 (each 1H, d, J=20 Hz, 13^1-CH_2), 4.57 (1H, dq, J=2, 7 Hz, 18-H), 4.37 (1H, dt, J=8, 2 Hz, 17-H), 3.79 (3H, s, 2-CH_3), 3.72 (2H, q, J=8 Hz, 8-CH_2), 3.71 (3H, s, 12-CH_3), 3.62 (3H, s, 17^2-$COOCH_3$), 3.29 (3H, s, 7-CH_3), 2.78–2.70, 2.64–2.57, 2.38–2.27 (1H+1H+2H, m, 17-CH_2CH_2), 2.43 (3H, s, 3^3-CH_3), 1.84 (3H, d, J=7 Hz, 18-CH_3), 1.71 (3H, t, J=8 Hz, 8^1-CH_3), −0.07, −2.10 (each 1H, s, NH×2); IR (film) ν=2224 (C≡C), 1736 (17^2-C=O), 1699 cm^{-1} (13-C=O); HRMS (APCI) found: m/z 589.2811, calcd for $C_{36}H_{37}N_4O_4$: MH^+, 589.2809.

*4.4.10. Methyl 3-devinyl-3-(3-phenylpropynoyl)pyropheophorbide-a (**1m**) [3-COC≡CPh].* Black solid; mp 118–120 °C; VIS (CH_2Cl_2) λ_{max}=698 (relative intensity, 0.77), 639 (0.11), 560 (0.17), 524 (0.17),

439 (0.93), 427 (0.93), 391 (1.00), 380 nm (0.99); ^{1}H NMR ($CDCl_3$) δ=10.50 (1H, s, 5-H), 9.55 (1H, s, 10-H), 8.86 (1H, s, 20-H), 7.84 (2H, d, J=7 Hz, *o*-H of 3^3-Ph), 7.60–7.50 (3H, m, *m*-, *p*-H of 3^3-Ph), 5.34, 5.19 (each 1H, d, J=20 Hz, 13^1-CH_2), 4.58 (1H, dq, J=2, 7 Hz, 18-H), 4.39 (1H, dt, J=8, 2 Hz, 17-H), 3.87 (3H, s, 2-CH_3), 3.70 (3H, s, 12-CH_3), 3.68 (2H, q, J=8 Hz, 8-CH_2), 3.62 (3H, s, 17^2-$COOCH_3$), 3.19 (3H, s, 7-CH_3), 2.83–2.71, 2.65–2.56, 2.36–2.30 (1H+1H+2H, m, 17-CH_2CH_2), 1.86 (3H, d, J=7 Hz, 18-CH_3), 1.69 (3H, t, J=8 Hz, 8^1-CH_3), −0.13, −2.08 (each 1H, s, NH×2); IR (film) ν=2220 (C≡C), 1736 (17^2-C=O), 1697 cm^{-1} (13-C=O); HRMS (APCI) found: m/z 651.2968, calcd for $C_{41}H_{39}N_4O_4$: MH^+, 651.2966.

*4.4.11. Methyl 3-benzoyl-3-devinyl-pyropheophorbide-a (**1n**) [3-COPh].* Black solid; mp 143–145 °C; VIS (CH_2Cl_2) λ_{max}=677 (relative intensity, 0.59), 618 (0.08), 543 (0.11), 512 (0.13), 413 (1.00), 385 nm (0.85); ^{1}H NMR ($CDCl_3$) δ=9.61 (1H, s, 10-H), 9.34 (1H, s, 5-H), 8.75 (1H, s, 20-H), 8.14 (2H, dd, J=7, 2 Hz, *o*-H of 3^1-Ph), 7.74 (1H, tt, J=7, 2 Hz, *p*-H of 3^1-Ph), 7.58 (2H, t, J=7 Hz, *m*-H of 3^1-Ph), 5.33, 5.18 (each 1H, d, J=20 Hz, 13^1-CH_2), 4.55 (1H, br q, J=7.5 Hz, 18-H), 4.39 (1H, br d, J=8 Hz, 17-H), 3.69 (2H, q, J=8 Hz, 8-CH_2), 3.72 (3H, s, 12-CH_3), 3.62 (3H, s, 17^2-$COOCH_3$), 3.60 (3H, s, 2-CH_3), 3.29 (3H, s, 7-CH_3), 2.80–2.62, 2.62–2.43, 2.35–2.26 (1H+1H+2H, m, 17-CH_2CH_2), 1.86 (3H, d, J=7.5 Hz, 18-CH_3), 1.68 (3H, t, J=8 Hz, 8^1-CH_3), 0.05, −1.91 (each 1H, s, NH×2); IR (film) ν=1736 (17^2-C=O), 1697 (13-C=O), 1651 cm^{-1} (3-C=O); HRMS (APCI) found: m/z 627.2966, calcd for $C_{39}H_{39}N_4O_4$: MH^+, 627.2966.

*4.4.12. Methyl 3-(3-butenoyl)-3-devinyl-pyropheophorbide-a (**1o**) [3-COCH$_2$CH=CH$_2$].* Black solid; mp 98–100 °C; VIS (CH_2Cl_2) λ_{max}=680 (relative intensity, 0.48), 621 (0.08), 545 (0.11), 514 (0.12), 416 (1.00), 386 nm (0.77); ^{1}H NMR ($CDCl_3$, 45 °C) δ=9.88 (1H, s, 10-H), 9.60 (1H, s, 5-H), 8.76 (1H, s, 20-H), 6.41 (1H, ddt, J=17, 10, 7 Hz, 3^2-CH), 5.461/457 (1H, dd, J=17, 2 Hz, 3^3=CH *trans* to C3^3–H), 5.412/407 (1H, dd, J=10, 2 Hz, 3^3=CH *cis* to C3^3–H), 5.33, 5.18 (each 1H, d, J=20 Hz, 13^1-CH_2), 4.56 (1H, dq, J=2, 8 Hz, 18-H), 4.38 (2H, d, J=7 Hz, 3^1-CH_2), 4.37–4.36 (1H, m, 17-H), 3.72 (2H, q, J=8 Hz, 8-CH_2), 3.71 (3H, s, 12-CH_3), 3.63 (3H, s, 17^2-$COOCH_3$), 3.61 (3H, s, 2-CH_3), 3.28 (3H, s, 7-CH_3), 2.77–2.69, 2.63–2.55, 2.36–2.26 (1H+1H+2H, m, 17-CH_2CH_2), 1.84 (3H, d, J=8 Hz, 18-CH_3), 1.71 (3H, t, J=8 Hz, 8^1-CH_3), −0.02, −2.01 (each 1H, s, NH×2); IR (film) ν=1736 (17^2-C=O), 1697 (13-C=O), 1676 cm^{-1} (3-C=O); HRMS (APCI) found: m/z 591.2966, calcd for $C_{36}H_{39}N_4O_4$: MH^+, 591.2964.

*4.4.13. Methyl 3-devinyl-3-(2-methyl-3-butenoyl)pyropheophorbide-a (**1q**) [3-COC*HMeCH=CH$_2$].* Black solid; mp 103–105 °C; VIS (CH_2Cl_2) λ_{max}=674 (relative intensity, 0.46), 616 (0.07), 541 (0.10), 511 (0.12), 414 nm (1.00); ^{1}H NMR ($CDCl_3$) δ=9.550/545 (1H, s, 5-H), 9.53 (1H, s, 10-H), 8.73 (1H, s, 20-H), 6.29/27 (1H, ddd, J=17, 10, 7 Hz, 3^2-CH), 5.35/34 (1H, d, J=17 Hz, 3^3=CH *trans* to C3^3–H), 5.25/24 (1H, d, J=10 Hz, 3^3=CH *cis* to C3^3–H), 5.31, 5.17 (each 1H, d, J=20 Hz, 13^1-CH_2), 4.67 (1H, quintet, J=7 Hz, 3^1-CH), 4.55 (1H, dq, J=2, 8 Hz, 18-H), 4.36 (1H, dt, J=8, 2 Hz, 17-H), 3.68 (2H, q, J=8 Hz, 8-CH_2), 3.67 (3H, s, 12-CH_3), 3.62 (3H, s, 17^2-$COOCH_3$), 3.55 (3H, s, 2-CH_3), 3.23 (3H, s, 7-CH_3), 2.76–2.67, 2.63–2.55, 2.36–2.25 (1H+1H+2H, m, 17-CH_2CH_2), 1.85 (3H, d, J=8 Hz, 18-CH_3), 1.70 (3H, d, J=7 Hz, 3^2-CH_3), 1.69 (3H, t, J=7 Hz, 8^1-CH_3), 0.09, −2.03 (each 1H, s, NH×2); IR (film) ν=1736 (17^2-C=O), 1697 (13-C=O), 1674 cm^{-1} (3-C=O); HRMS (APCI) found: m/z 605.3128, calcd for $C_{37}H_{41}N_4O_4$: MH^+, 605.3128.

*4.4.14. Methyl 3-devinyl-3-(2,2-dimethyl-3-butenoyl)pyropheophorbide-a (**1s**) [3-COCMe$_2$CH=CH$_2$].* Black solid; mp 135–137 °C; VIS (CH_2Cl_2) λ_{max}=667 (relative intensity, 0.51), 610 (0.07), 537 (0.09), 507 (0.10), 410 nm (1.00); ^{1}H NMR ($CDCl_3$, 45 °C) δ=9.55 (1H, s, 10-H), 9.07 (1H, s, 5-H), 8.61 (1H, s, 20-H), 6.39 (1H, dd, J=17, 10 Hz, 3^2-CH), 5.40 (1H, d, J=17 Hz, 3^3=CH *trans* to C3^3–H), 5.35 (1H, d, J=10 Hz, 3^3=CH *cis* to C3^3–H), 5.31, 5.15 (each 1H, d, J=20 Hz, 13^1-CH_2), 4.52 (1H, dq, J=2, 7 Hz, 18-H), 4.35 (1H, dt, J=8, 2 Hz, 17-H), 3.69 (2H, q, J=7 Hz, 8-CH_2), 3.68 (3H, s, 12-CH_3), 3.62 (3H, s, 17^2-$COOCH_3$), 3.33 (3H, s, 2-CH_3), 3.17 (3H, s, 7-CH_3), 2.77–2.67, 2.62–2.54, 2.36–2.25 (1H+1H+2H, m, 17-CH_2CH_2), 1.83 (3H, d, J=7 Hz, 18-CH_3), 1.70 (3H, t, J=7 Hz, 8^1-CH_3), 1.68 (6H, s, 3^2-CH_3×2), 0.12, −1.98 (each 1H, s, NH×2); IR (film) ν=1736 (17^2-C=O), 1701 (13-C=O), 1676 cm^{-1} (3-C=O); HRMS (APCI) found: m/z 619.3279, calcd for $C_{38}H_{43}N_4O_4$: MH^+, 619.3279.

*4.4.15. Methyl 3-(2,3-butadienoyl)-3-devinyl-pyropheophorbide-a (**1u**) [3-COCH=C=CH$_2$].* Black solid; mp 103–105 °C; VIS (CH_2Cl_2) λ_{max}=676 (relative intensity, 0.52), 617 (0.08), 543 (0.12), 512 (0.13), 415 nm (1.00); ^{1}H NMR ($CDCl_3$) δ=9.60 (2H, s, 5-, 10-H), 8.71 (1H, s, 20-H), 6.89 (1H, t, J=6 Hz, 3^1-CH), 5.32, 5.17 (each 1H, d, J=20 Hz, 13^1-CH_2), 5.09 (2H, d, J=6 Hz, 3^3=CH_2), 4.55 (1H, dq, J=2, 8 Hz, 18-H), 4.36 (1H, dt, J=8, 2 Hz, 17-H), 3.72 (2H, q, J=8 Hz, 8-CH_2), 3.71 (3H, s, 12-CH_3), 3.62 (3H, s, 17^2-$COOCH_3$), 3.54 (3H, s, 2-CH_3), 3.25 (3H, s, 7-CH_3), 2.76–2.67, 2.63–2.55, 2.36–2.25 (1H+1H+2H, m, 17-CH_2CH_2), 1.84 (3H, d, J=8 Hz, 18-CH_3), 1.71 (3H, t, J=8 Hz, 8^1-CH_3), 0.07, −2.00 (each 1H, s, NH×2); IR (film) ν=1957, 1933 (C=C=C), 1736 (17^2-C=O), 1697 (13-C=O), 1647 cm^{-1} (3-C=O); HRMS (APCI) found: m/z 589.2808, calcd for $C_{36}H_{37}N_4O_4$: MH^+, 589.2809.

*4.4.16. Methyl 3-devinyl-3-(2-methyl-2,3-butadienoyl)pyropheophorbide-a (**1w**) [3-COCMe=C=CH$_2$].* Black solid; mp 102–104 °C; VIS (CH_2Cl_2) λ_{max}=674 (relative intensity, 0.46), 618 (0.08), 542 (0.10), 511 (0.12), 414 nm (1.00); ^{1}H NMR ($CDCl_3$) δ=9.58 (1H, s, 10-H), 9.40 (1H, s, 5-H), 8.65 (1H, s, 20-H), 5.31, 5.16 (each 1H, d, J=20 Hz, 13^1-CH_2), 4.75, 4.74 (each 1H, dq, J=15, 3 Hz, 3^3=CH_2), 4.53 (1H, dq, J=2, 8 Hz, 18-H), 4.35 (1H, dt, J=8, 2 Hz, 17-H), 3.72 (2H, q, J=8 Hz, 8-CH_2), 3.70 (3H, s, 12-CH_3), 3.62 (3H, s, 17^2-$COOCH_3$), 3.45 (3H, s, 2-CH_3), 3.23 (3H, s, 7-CH_3), 2.77–2.65, 2.63–2.52, 2.35–2.24 (1H+1H+2H, m, 17-CH_2CH_2), 2.42 (3H, t, J=3 Hz, 3^2-CH_3), 1.84 (3H, d, J=8 Hz, 18-CH_3), 1.70 (3H, t, J=8 Hz, 8^1-CH_3), 0.08, −1.97 (each 1H, s, NH×2); IR (film) ν=1957, 1932 (C=C=C), 1736 (17^2-C=O), 1697 (13-C=O), 1647 cm^{-1} (3-C=O); HRMS (APCI) found: m/z 603.2966, calcd for $C_{37}H_{39}N_4O_4$: MH^+, 603.2966.

Acknowledgements

We thank Mr. Shin-ichiro Nitta of Ritsumeikan University for his experimental assistance. This work was partially supported by a Grant-in-Aid for Scientific Research on Innovative Areas 'Artificial Photosynthesis (AnApple)' (No. 24107002) from the Japan Society for the Promotion of Science (JSPS).

Supplementary data

Supplementary data (visible spectra and maxima of **2**) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.04.074.

References and notes

1. Orf, G. S.; Tank, M.; Vogl, K.; Niedzwiedzki, D. M.; Bryant, D. A.; Blankenship, R. E. *Biochim. Biophys. Acta* **2013**, *1827*, 493–501; (a) Blankenship, R. E. *Molecular Mechanisms of Photosynthesis*, 2nd ed.; Wiley Blackwell: West Sussex, UK, 2014.
2. Cogdell, R.; Gall, A.; Köhler, J. *Q. Rev. Biophys.* **2006**, *39*, 227–324.
3. Orf, G. S.; Blankenship, R. E. *Photosynth. Res.* **2013**, *116*, 315–331; (a) Pšenčík, J.; Butcher, S. J.; Tuma, R. *Adv. Photosynth. Respir* **2014**, *39*, 77–109; (b) Tsukatani, Y.; Mizoguchi, T.; Thweatt, J.; Tank, M.; Bryant, D. A.; Tamiaki, H. *Photosynth. Res.* **2016**, http://dx.doi.org/10.1007/s11120-016-0228-z in press.
4. Gudowska-Nowak, E.; Newton, M. D.; Fajer, J. *J. Phys. Chem.* **1990**, *94*, 5795–5801.
5. Tamiaki, H.; Kotegawa, Y.; Mizutani, K. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6037–6040.

6. Chew, A. G. M.; Bryant, D. A. *Annu. Rev. Microbiol.* **2007**, *61*, 113–129; (a) Bryant, D. A.; Liu, Z. *Adv. Botanical Res.* **2013**, *66*, 99–150.
7. Harada, J.; Teramura, M.; Mizoguchi, T.; Tsukatani, Y.; Yamamoto, K.; Tamiaki, H. *Mol. Microbiol.* **2015**, *98*, 1184–1198; (a) Teramura, M.; Harada, J.; Tamiaki, H. *Photosynth. Res.* **2016**, http://dx.doi.org/10.1007/s11120-016-0220-7 in press.
8. Smith, K. M.; Bisset, G. M. F.; Bushell, M. J. *J. Org. Chem.* **1980**, *45*, 2218–2224.
9. Tamiaki, H.; Ariki, N.; Sugiyama, H.; Taira, Y.; Kinoshita, Y.; Miyatake, T. *Tetrahedron* **2013**, *69*, 8412–8421.
10. Tamiaki, H.; Shimono, Y.; Rattray, A. G. M.; Tanikaga, R. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2085–2086 ;the isolated yield of **2b** was 75% based on the consumed **1a**.
11. Tamiaki, H.; Machida, S.; Mizutani, K. *J. Org. Chem.* **2012**, *77*, 4751–4758.
12. Tamiaki, H.; Kitamoto, H.; Nishikawa, A.; Hibino, T.; Shibata, R. *Bioorg. Med. Chem.* **2004**, *12*, 1657–1666.
13. Tamiaki, H.; Kotegawa, Y.; Nitta, S.; Sasaki, S.; Mizutani, K. *Tetrahedron* **2009**, *65*, 628–637.
14. Wang, J.-J.; Lee, K.-I.; Kim, M.-H.; Shim, Y. K. *Bull. Korean Chem. Soc.* **2004**, *25*, 1449–1450; (a) Wang, J.-J.; Wu, X.-R.; Shim, Y. K. *Chin. J. Chem.* **2005**, *23*, 76–80; (b) Wang, J.-J.; Li, J.-Z.; Li, F.-G. *J. Iran. Chem. Soc.* **2011**, *8*, 1139–1145.
15. Yin, J.-G.; Wang, Z.; Yang, Z.; Jin, Y.-X.; Wang, J.-J. *Chin. J. Org. Chem.* **2012**, *32*, 1936–1943.
16. Yagai, S.; Tamiaki, H. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3135–3144.
17. Isaac, M. B.; Chan, T.-H. *J. Chem. Soc., Chem. Commun.* **1995**, 1003–1004; (a) Kwon, J. S.; Pae, A. N.; Choi, K. I.; Koh, H. Y.; Kim, Y.; Cho, Y. S. *Tetrahedron Lett.* **2001**, *42*, 1957–1959; (b) Augé, J.; Lubin-Germain, N.; Uziel, J. *Synthesis* **2007**, 1739–1764.
18. Lange, C.; Kiesel, S.; Peters, S.; Virus, S.; Scheer, H.; Jahn, D.; Moser, J. *J. Biol. Chem.* **2015**, *290*, 19697–19709.
19. Inhoffen, H. H.; Jäger, P.; Mählhop, R.; Mengler, C.-D. *Justus Liebigs Ann. Chem.* **1967**, *704*, 188–207.
20. Tamiaki, H.; Yagai, S.; Miyatake, T. *Bioorg. Med. Chem.* **1998**, *6*, 2171–2178.
21. Wang, J.-J.; Ji, J.-Y.; Han, G.-F.; Wu, X.-R.; Wang, L.-M.; Shim, Y. K. *Acta Chim. Sin.* **2004**, *62*, 302–311.
22. Felpin, F.-X.; Lebreton, J. *J. Org. Chem.* **2002**, *67*, 9192–9199.
23. Liu, J.; Ma, S. *Tetrahedron Lett.* **2013**, *69*, 10161–10167.
24. Inamoto, N.; Masuda, S. *Chem. Lett.* **1982**, 1003–1006.
25. Kureishi, Y.; Tamiaki, H. *J. Porphyr. Phthalocyanines* **1998**, *2*, 159–169.
26. Sasaki, S.; Kotegawa, Y.; Tamiaki, H. *Tetrahedron Lett.* **2006**, *47*, 4849–4852.
27. Tamiaki, H.; Amakawa, M.; Shimono, Y.; Tanikaga, R.; Holzwarth, A. R.; Schaffner, K. *Photochem. Photobiol.* **1996**, *63*, 92–99.
28. Wang, J.-J.; Han, G.-F.; Yin, J.-G.; Wu, X.-R.; Zhao, Y.; Gong, B.-A.; Shim, Y. K. *Chin. J. Chem.* **2003**, *21*, 674–679.
29. Wang, J.-J.; Li, F.-G.; Li, Y.-W. *Chin. J. Org. Chem.* **2011**, *31*, 68–74.
30. Yin, J.-G.; Wang, J.-J.; Shim, Y. K. *Chem. J. Chin. Univ.* **2005**, *26*, 1474–1476.