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Modification of 3-Substituents in (Bacterio)Chlorophyll Derivatives to Prepare 3-Ethylated, Methylated, and Unsubstituted (Nickel) Pyropheophorbides and Their Optical Properties

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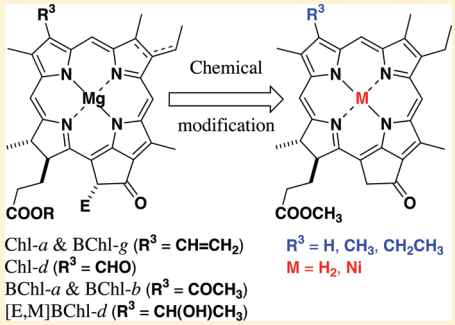
Supporting Information

ABSTRACT: Methyl mesopyropheophorbide-*a* possessing an ethyl group at the 3-position, its 3^1-demethyl analogue (3-methyl homologue), and its 3^1-deethyl analogue (3-unsubstituted chlorin) were prepared by modifying naturally occurring (bacterio)chlorophylls bearing 3-vinyl, formyl, acetyl, and 1-hydroxyethyl groups. These synthetic 3-(un)substituted chlorophyll derivatives and their nickel complexes are probable intermediates during degradation of (bacterio)chlorophylls to chemically stable porphyrinoids. The optical properties (visible absorption, circular dichroism, and fluorescence emission) of the catabolic candidates in a solution were measured, and the substitution effect was investigated.



INTRODUCTION

Chlorophylls (Chls) are one of the most important pigments in nature, especially in photosynthetic apparatus. Photosynthetically active chlorophylls are π-conjugated cyclic tetrapyrroles possessing an exo-five-membered ring.[1] A variety of functional groups are found at the peripheral positions of the core π-system, and the 3-substituents are effective in controlling their optical and electronic properties. For example, Chl-*d* possessing the 3-formyl group (see the left drawing of Figure 1, upper) gives visible absorption maxima λ_{max} to longer wavelengths than did Chl-*a* bearing the 3-vinyl group: λ_{max} = 661/616/430 (Chl-*a*) → 686/638/446 nm (Chl-*d*) in diethyl ether.[2] Since a formyl group is more electronegative than a vinyl group, Chl-*d* is reduced more easily and oxidized less readily than Chl-*a*: the first reduction/oxidation potentials = −1.12/0.81 (Chl-*a*) → −0.91/0.88 V (Chl-*d*) in acetonitrile vs NHE.[3] As a result, specific cyanobacteria producing Chl-*d* can utilize lights in the region at >700 nm more efficiently than conventional cyanobacteria biosynthesizing sole Chl-*a*. A similar substitution effect is observed in bacteriochlorophyll(BChl)-*b* possessing the 3-acetyl group and BChl-*g* bearing the 3-vinyl group (see the right drawings of Figure 1): λ_{max} = 767/565/405/365 (BChl-*g*) → 795/579/408/369 nm (BChl-*b*) in diethyl ether.[2]

The conformation of conjugatable substituents at the 3-position of (B)Chls affects their electronic absorption bands. In BChl-*a* (see the right drawing of Figure 1, upper), typically, the 3-acetyl group rotates around the C3−$C3^1$ single bond from its coplanar position with the bacteriochlorin π-system to give a blue-shifted absorption band.[4] Such a regulation is clearly observed in the peripheral light-harvesting antenna systems of purple photosynthetic bacteria. Moreover, (de)conjugation of the 3-trifluoroacetyl group in chlorophyll derivatives is useful for development of colorimetric chemosensors for amines and alcohols.[5]

As degradation products of (B)Chls, various deoxophyllo-erythroetioporphyrins (DPEPs) were found, and nickel complexes of DPEP homologues were identified in oil shale (Scheme 1).[6] Ethyl and methyl groups as well as a hydrogen atom at the 3-position of Ni-DPEPs would be transformed from the vinyl, formyl, acetyl, and 1-hydroxyethyl groups at the 3-position of naturally occurring (B)Chls. One of the transformation pathways was proposed as follows.[7] Chl-*a* is modified to pyropheophorbide-*a* through substitution of magnesium(II) ion at the central position with two protons (pheophytinization), removal of methoxycarbonyl group at the 13^2-position (pyrolysis), and hydrolysis of phytyl ester in the 17-propionate residue. Successive reduction of the 3-vinyl and 13-carbonyl groups, aromatization at the D-ring, decarboxylation at the 17^2-position, and nickel metalation affords Ni-DPEP bearing the 3-ethyl group.

Here, we report synthesis of methyl pyropheophorbide-*a* derivatives **1**−**3a** possessing ethyl and methyl groups as well as a hydrogen atom at the 3-position and their nickel complexes **1**−**3b** as models of degradation intermediates from (B)Chls (Figure 2). Modification of the 3-substituents provides possible pathways for (B)Chl degradation. Effects of the 3-substituents on the optical properties of synthetic chlorophyll derivatives **1**−**3** are also discussed. Investigation of catabolites of (B)Chls is useful to elucidate mechanisms of natural photosynthesis and create artificial photosynthetic systems. The present study

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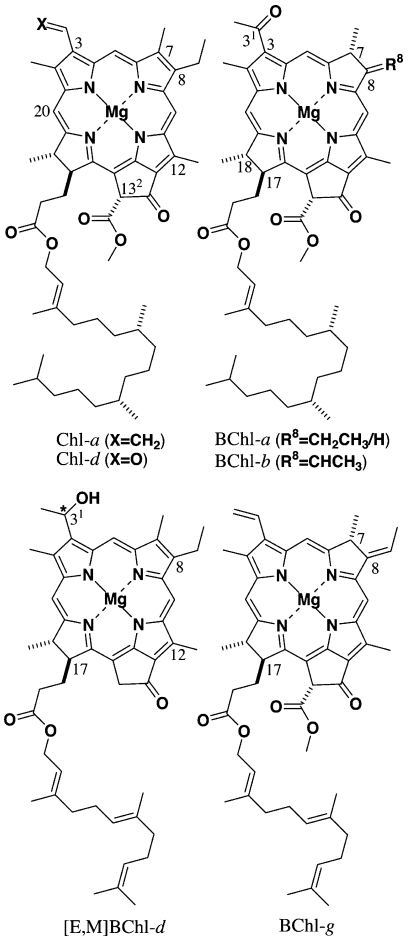
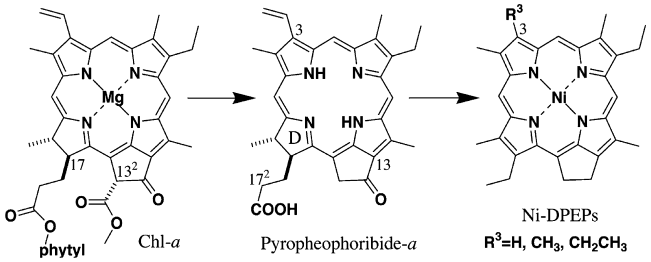
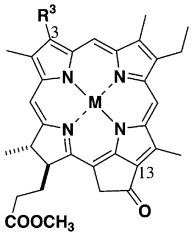


Figure 1. Naturally occurring (bacterio)chlorophylls [(B)Chls] possessing the 7,12-dimethyl and 8-ethyl groups as well as no substituent at the 20-position.

Scheme 1. Degradation of Chl-*a* to Ni-DEPEs





1a (M=H_2, R^3=CH_2CH_3), **1b** (M=Ni, R^3=CH_2CH_3)
2a (M=H_2, R^3=CH_3), **2b** (M=Ni, R^3=CH_3)
3a (M=H_2, R^3=H), **3b** (M=Ni, R^3=H)
4a (M=H_2, R^3=CH=CH_2), **4b** (M=Ni, R^3=CH=CH_2)
5a (M=H_2, R^3=CH(OH)CH_3), **5b** (M=Ni, R^3=CH(OH)CH_3)
6a (M=H_2, R^3=CHClCH_3)
7a (M=H_2, R^3=CH(OCOCF_3)CH_3)
8a (M=H_2, R^3=$COCH_3$)
9a (M=H_2, R^3=CHO)
10a (M=H_2, R^3=CH_2OH), **10b** (M=Ni, R^3=CH_2OH)
11a (M=H_2, R^3=CH_2Cl)
12a (M=H_2, R^3=CH_2OCOCF_3)
13a (M=H_2, R^3=COOH), **13b** (M=Ni, R^3=COOH)
14a (M=H_2, R^3=$COOCH_3$), **14b** (M=Ni, R^3=$COOCH_3$)

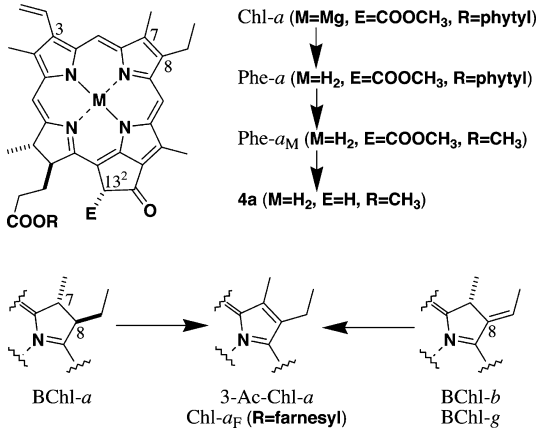
Figure 2. Methyl 3-substituted pyropheophorbides-*a* **1**−**14**: **a** for free base and **b** for nickel complex.

provides pathways from all the (B)Chls studied to the same set of the products with 3-H, CH_3, or CH_2CH_3.

RESULTS AND DISCUSSION

Synthesis of Methyl Pyropheophorbides from Natural (B)Chls. Methyl pyropheophorbide-*a* (**4a**) was prepared by modifying naturally occurring Chl-*a* extracted from a cyanobacterium, *Spirulina geitleri*, which was commercially available as its dry cell powder (Scheme 2, upper).[8] Chl-*a*

Scheme 2. Modification of Naturally Occurring (B)Chls



was demetalated to pheophytin(Phe)-*a* by treatment of an acid (pheophytinization), the phytyl group in Phe-*a* was transesterified to the methyl group in methyl pheophorbide-*a* (Phe-a_M) by sulfuric acid in cooled methanol, and the methoxycarbonyl moiety at the 13^2-position of methyl pheophorbide-*a* was removed to **4a** by pyrolysis in refluxed 2,4,6-collidine.[8,9] BChl-*g* (C7H—C8═$CHCH_3$) from a cultured heliobacterium, *Heliobacterium modesticaldum*,[10] was readily isomerized by action of an acid to give farnesylated Chl-*a* (Chl-a_F; see Scheme 2, lower, right to center)[11] and Phe-*a* (C7═C8—CH_2CH_3),[12,13] which were transformed to **4a** similarly as mentioned above.

Purple photosynthetic bacteria were easily cultivated in an aqueous media, and BChl-*a* was extracted from cultured cells of *Rhodobacter sphaeroides*, *Rhodopseudomonas palustris*, and so on.[14] According to the same procedures from Chl-*a* to **4a**, BChl-*a* was converted to methyl pyrobacteriopheophorbide-*a*, and the resulting bacteriochlorin (7,8,17,18-tetrahydroporphyrin) was oxidized through 7,8-dehydrogenation to the corresponding chlorin (17,18-dihydroporphyrin), methyl 3-acetyl-3-devinyl-pyropheophorbide-*a* (**8a**), by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (see also Scheme 2, lower, left to center).[15] Compound **8a** was alternatively prepared by modification of BChl-*b* from a cultured purple bacterium, *Blastochloris viridis* (formerly named *Rhodopseudomonas viridis*). BChl-*b* possessing the 8-ethylidene group was readily demetalated (pheophytinized) and isomerized to the 3-acetyl analogue of Phe-*a* by action of an acid (see also Scheme 2, lower, right to center) as mentioned in BChl-*g* to Chl-a_F.[12,16] The obtained product was transformed to **8a** similarly as the preparation of **4a** from Phe-*a*.

Green sulfur bacteria gave BChl-*c*, *-d*, or *-e* molecules as the pigment of their main light-harvesting antennae.[17] A strain of *Prosthecochloris vibrioformis* (formerly named *Chlorobium vibrioforme*) species produced sole BChl-*d* homologues

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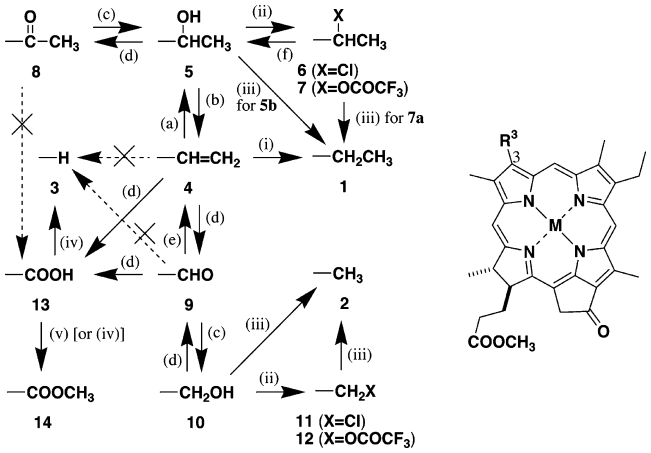
possessing various alkylated substituents at the 8- and 12-positions.[18] One of them is 8-ethyl-12-methyl-BChl-*d* ([E,M]-BChl-*d*) with a farnesyl ester in the 17-propionate residue (the left drawing of Figure 1, lower). The separated BChl-*d* molecule as a 3¹*R*-rich diastereomeric mixture was demetalated and transesterified to afford methyl bacteriopheophorbide-*d* (**5a**),[19] which corresponded to methyl 3-devinyl-3-(1-hydroxyethyl)pyropheophorbide-*a*. Compound **5a** was also synthesized from hydration of the 3-vinyl group in **4a**[8,20] as well as selective reduction of the 3-acetyl group in **8a** (Scheme 3).[15,21] Reversely, **5a** was dehydrated to **4a**[22] and oxidized to **8a**.[23]

Scheme 3. Transformation of 3-Substituents of Methyl Pyropheophorbides[a]



[a](i) H_2, Pd/C, acetone−THF; (ii) $SOCl_2$ (for X = Cl), $(CF_3CO)_2O$ (for X = $OCOCF_3$), CH_2Cl_2; (iii) H_2, $Pd(OH)_2$, acetone−THF; (iv) 2,4,6-collidine, reflux; (v) CH_2N_2/Et_2O, CH_2Cl_2; (a) hydration; (b) dehydration; (c) reduction; (d) oxidation; (e) Wittig reaction; (f) hydrolysis.

One of the cyanobacteria, *Acaryochlorin marina*, produced Chl-*d* as the main chlorophyllous pigment.[24] From its cultured cells, Chl-*d* was isolated and transformed to methyl pyropheophorbide-*d* (**9a**)[25] similarly as the synthesis of **4a** from Chl-*a*. Compound **9a** is the 3-formyl analogue of **4a**, methyl 3-devinyl-3-formyl-pyropheophorbide-*a*. The 3-vinyl group of **4a** was oxidatively cleaved to afford **9a** possessing the 3-formyl group by OsO_4−$NaIO_4$ (Lemieux−Johnson oxidation),[26−29] O_3 (ozonolysis),[30] and O_2−PhSH.[31] The 3-formyl group was reactive with various reagents. Typically, Wittig reaction of the CHO of **9a** with CH_2=PPh_3 gave **4a** bearing the 3-CH=CH_2,[30] and its Grignard reaction with CH_3MgI afforded **5a** bearing 3-CH(OH)CH_3.[32]

Synthesis of Methyl Mesopyropheophorbides-*a* (1). 3-Ethyl-chlorin **1a** has already been prepared by catalytic hydrogenation of **4a** (Scheme 3).[9] The 3-vinyl group of **4a** was selectively hydrogenated on palladium−charcoal (Pd/C), and acetone as the solvent was useful to avoid undesired reduction of the 13-carbonyl group. Treatment of **4a** in 1,2-dichloroethane with nickel acetate in methanol at 80 °C gave the corresponding nickel complex **4b**. Similar hydrogenation of **4b** afforded **1b** efficiently, while reduction of **4b** on Raney nickel in ethers had partially led to the additional hydrogenation of 13-C=O to 13-CH_2 and 2C=3C to 2CH−3CH.[33]

Treatment of 3-(1-hydroxyethyl)chlorin **5a** in acetone and THF with hydrogen gas on any catalysts including Pd/C and $Pd(OH)_2$ gave no product, and **5a** was recovered from the reaction mixture. Secondary alcohol **5a** was esterified with *p*-toluic chloride to give the *p*-toluate (95%), and its transformation to **1a** was unsuccessful under Markó−Lam deoxygenation conditions (SmI_2, HMPA/THF).[34] The thiocarbonate obtained from **5a** and PhOCSCl (97%) could not give **1a** under Barton−McCombie deoxygenation conditions (Bu_3SnH, AIBN/toluene).[35] After treatment of **5a** with thionyl chloride, the resulting chloride **6a** was hydrogenated on $Pd(OH)_2$ to give undesired decomposed products because of its lower chemical stability. The corresponding trifluoroacetate **7a** produced from **5a** (80%) was successfully reduced to **1a** (32%) after hydrogenation on $Pd(OH)_2$ in acetone−THF. The major isolated byproduct was **5a** prepared by hydrolysis of **7a**.

When nickel complex **5b** in acetone−THF was hydrogenated in the presence of $Pd(OH)_2$ at room temperature for 4 days, direct reduction to **1b** was apparently observed (1.7% isolated yield), and 98% of the starting material **5b** was recovered. The success in the direct hydrogenation of nickel complex (**5b** → **1b**) and the failure in that of free base (**5a** → **1a**) might be ascribable to the electron-withdrawing effect of the central nickel.

Synthesis of Methyl 3-Devinyl-3-methyl-pyropheophorbides-*a* (2). The 3-formyl group of **9a** was selectively reduced by $NaBH_4$,[36] $NaCNBH_3$,[27] Bu_4NBH_4,[30] and *t*-$BuNH_2BH_3$[28,29] to give 3-hydroxymethyl-chlorin **10a**. Catalytic hydrogenation of primary alcohol **10a** gave a trace amount of **2a**, and almost all of **10a** was recovered. The direct hydrogenation (deoxygenation) of primary alcohol **10a** but not secondary alcohol **5a** was observed, because the former was less sterically hindered and more reactive than the latter. Similar hydrogenation of nickel complex **10b** directly afforded **2b** in 5% yield (89% recovery of **10b**), which was three times larger than that in **5b** to **1b**. The enhancement is due to the higher reactivity in primary alcohol **10b** than in secondary alcohol **5b**.

Two other indirect hydrogenation from **10a** to **2a** proceeded through chloride **11a** and trifluoroacetate **12a** as mentioned in the transformation of secondary alcohol **5a**: **10a** → **11a** (83%) → **2a** (41%) and **10a** → **12a** (69%) → **2a** (24%). The best way to access 3-methyl-chlorin **2a** was the two-step path through chloride **11a**, and the total yield for deoxygenation of **10a** to **2a** was 34%.

Synthesis of Methyl 3-Devinyl-pyropheophorbides-*a* (3). The vinyl and formyl groups as the peripheral substituent of ferric(III) chlorins were reported to be removed by heating in melted resorcinol at 170−200 °C.[37] Heating of vinyl-chlorin **4a** in resorcinol at a higher temperature than 200 °C gave no desired devinyl-chlorin **3a** as an isolable product. Decarbonylation of 3-formyl-chlorin **9a** by $RhCl(PPh_3)_3$ in benzonitrile[38] could not be observed. Direct removal of such vinyl and formyl groups on free base pyropheophorbide chlorin π-systems did not proceed under the examined conditions.

The carboxy groups on some porphyrinoids were removed by pyrolysis in resorcinol as well as biphenyl above 200 °C.[39] Pyrolysis of 3-carboxy-chlorin **13a** was examined. Under refluxed conditions in 1,2,4-trichlorobenzene (bp = 214 °C) and quinoline (238 °C), 3-unsubstituted chlorin **3a** could not be detected in the reaction mixture of **13a**. Pyrolysis of **13a** in refluxed 2,4,6-collidine (171−172 °C) for 4 days was performed to successfully give **3a** in 9% isolated yield. Starting material **13a** (67%) was recovered, and 3-methoxycarbonyl-chlorin **14a** (3%) was produced as the byproduct. The formation of **14a** would be ascribable to an intramolecular

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disproportionated methylation: two 3-COOH/17^2-COOCH$_3$ (**13a**) → 3-COOCH$_3$/17^2-COOCH$_3$ (**14a**) + 3-COOH/17^2-COOH. The production of **3a** was indirect transformation of **4a**/**9a** to **3a** through **13a**: 3-CH=CH$_2$ → 3-COOH[40] → 3-H and 3-CHO → 3-COOH[41] → 3-H. It is noted that oxidation of **5a** (3-CH(OH)CH$_3$) and **8a** (3-COCH$_3$) to **13a** (3-COOH) could not be observed under haloform reaction conditions (KI, I$_2$, NaOH/aq dioxane).[42]

Nickel metalation of **13a** to **13b** smoothly proceeded under the conditions slightly modified from the conversion of **4a** to **4b**. In the reaction, methanol as the cosolvent must be replaced with acetone, to exclude methyl esterification at the 3-carboxy group of **13a**. Nickel complex **13b** was pyrolyzed similarly to afford **3b** (4.5%), **14b** (0.5%), and **13b** (79%) as isolable compounds after purification with flash column chromatography. The conversion yield (21%) in decarboxylation of nickel complex **13b** → **3b** (based on consumed **13b**) was comparable to that in free base **13a** → **3a** (27%).

Optical Properties of Synthetic Methyl Pyropheophorbides 1−3. Visible spectrum of 3-ethyl-chlorin **1a** in dichloromethane gives sharp bands at λ_{max} = 656 and 410 nm (black line of Figure 3A), indicating that **1a** is monomeric at a low concentration (ca. 10 μM). The former and latter absorption bands are called Qy and Soret (B) bands, respectively. Relatively less intense bands are observed between the Qy and Soret maxima, which include two vibronic components of the main Qy band and three vibronic Qx bands from longer to shorter wavelengths: Qy(0,0), Qy(0,1), Qy(0,2), Qx(0,0), Qx(0,1), and Qx(0,2) maxima are situated at 656, 601, ca. 550, 535, 504, ca. 470 nm. Visible spectrum of 3-methyl-chlorin **2a** in dichloromethane (red line of Figure 3A) is almost the same as that of **1a**, but their close comparison shows slightly blue shifts (<1 nm) of the maxima in all the Qy bands by substitution of the 3-ethyl with 3-methyl groups (**1a** → **2a**). The small substitution effect might be explained by an electron-withdrawing factor. Electron-withdrawing substituents at the 3-position generally induce bathochromic shifts of Qy bands.[2] The substituent constants (σ_p) in Hammet rule show that an ethyl group (−0.15) is slightly more electron-withdrawing than a methyl group (−0.17).

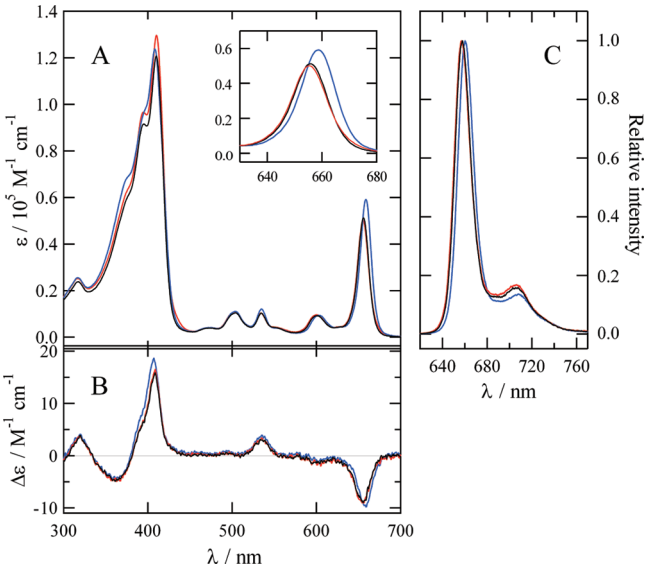

Figure 3. Visible absorption (A), circular dichroism (B), and fluorescence emission spectra (excited at Soret maxima) (C) of methyl 3-(un)substituted pyropheophorbides-*a* **1**−**3a** in dichloromethane: **1a** (3-CH$_2$CH$_3$, black line), **2a** (3-CH$_3$, red line) and **3a** (3-H, blue line).

In a diluted dichloromethane solution, the Qy maxima of 3-unsubstituted chlorin **3a** were shifted to a longer wavelength and/or enhanced with a larger extinction coefficient than those of 3-alkylated chlorins **1a**/**2a** (see Figure 3A): λ_{max}[Qy(0,0)] = 656/655 → 659 nm and ε[Qy(0,0)] = 51 000/50 000 → 59 000 M^{-1} cm^{-1} for **1a**/**2a** → **3a**. Considering the lack of changes of Qy band widths and Qx maxima, the red shifts by removal of such alkyl groups are also ascribable to electron-donating alkyl substituents on the molecular *y*-axis (the C3−C13 line): the σ_p-value of H is 0 (see Figure S1, Supporting Information). Compared with the Soret bands of **1a**/**2a**, the Soret maximum of **3a** was slightly blue-shifted: λ_{max}(Soret) = 410/410 → 408 nm for **1a**/**2a** → **3a**. It is noted that all the free bases **1**−**3a** gave no concentration effect for their visible spectra to be monomeric in dichloromethane at 1 to 100 μM.

Circular dichroism (CD) spectra of **1**−**3a** were measured in dichloromethane (Figure 3B). The spectral shapes were closely similar, and small shifts were observed as in visible absorption spectra. Dealkylation at the 3-substituents induces a red-shift of the CD negative peak at Qy(0,0), no shift of the positive peak at Qx(0,0) and a blue shift of the most intense positive peak at the Soret region. In nickel complexes **1**−**3b**, similar substitution effects were observed in visible and CD spectra (see Figure S2, Supporting Information). The CD intensities of nickel chlorins were larger than those of free bases because of the distortion of π-planes by insertion of nickel at the core position.[43]

Free bases **1**−**3a** are emissive in a diluted dichloromethane solution. Their fluorescence emission spectra were measured by excitation at the Soret maxima and gave almost the same shapes (Figure 3C). The main emission maxima λ_{em}(0,0) were shifted as in Qy(0,0) maxima: λ_{em}(0,0) = 658, 657, and 660 nm for **1**−**3a**. All the Stokes shifts were small to be 40 cm^{-1}, which was similar to the values for monomeric chlorophyll derivatives (see also Figure S1, Supporting Information). The relative intensities of the vibronic emission band were comparable to those of the corresponding vibronic Qy absorption bands: I_{em}(1,0)/I_{em}(0,0) = 0.16, 0.17, and 0.14, and ε[Qy(0,1)]/ε[Qy(0,0)] = 0.18, 0.19, and 0.16 for **1**−**3a**. Quantum yields and lifetimes of fluorescence emission in **1**−**3a** gradually increased with a decrease of steric factor in the 3-substituents (Table 1).

Table 1. Quantum Yields Φ and Lifetimes τ (ns) of Fluorescence Emission of 1−3a in Dichloromethane[a]

compound	Φ	τ (ns)
1a (3-CH$_2$CH$_3$)	0.20	5.7
2a (3-CH$_3$)	0.23	5.8
3a (3-H)	0.25	6.2

[a]Excited at Soret maxima at room temperature.

3-Substituted Pyropheophorbides as Proposed Catabolites of (B)Chls. 3-Ethylated, 3-methylated, and 3-unsubstituted porphyrins have been found in nature[6] and are proposed to be prepared by degradation of naturally occurring (B)Chls.[7] Most of them are metal complexes containing nickel(II), copper(II), and oxo-vanadium(IV). There are open questions about their degradation pathways, but pyropheophorbides are probable intermediates (see Scheme 1). Most

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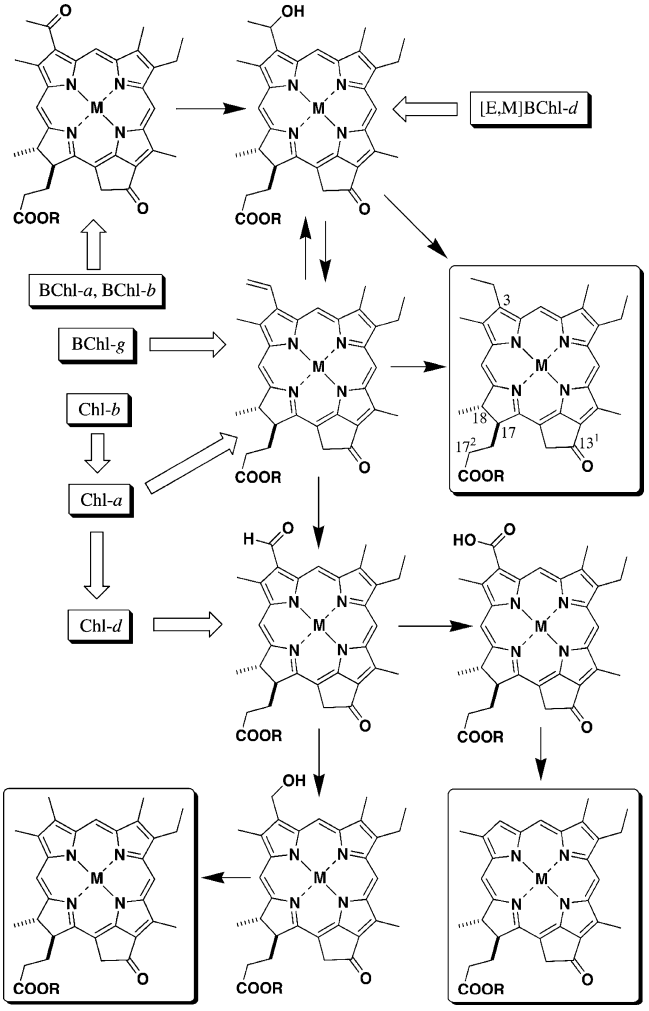
(B)Chls are readily transformed to 3-substituted pyropheophorbides-*a* (M = H_2, R = H in Scheme 4), based on the present modification of the 3-substituents in methyl pyropheophorbides (M = H_2, Ni, R = CH_3 in Scheme 3). It is not clear whether such 3-substitution takes place before or after metalation, 13^1-deoxygenation, 17^2-decarboxylation, and 17,18-dehydrogenation. The 3-vinyl groups of Chls-*a*/*b*/*c*/*f* and BChl-*g*, the 3-formyl group of Chl-*d*, the 3-acetyl group of BChls-*a*/*b*, and the 3-(1-hydroxyethyl) group of BChls-*c*/*d*/*e* are altered to chemically stable 3-ethyl- and methyl-porphyrinoids as well as their 3-unsubstituted analogues. The reactive functional groups at the 3-position of (B)Chls are converted into less reactive alkyl groups and hydrogen atom during their degradation. The three types of 3-(un)substituted pyropheophorbides are more chemically inactive and are proposed to be catabolites of natural (B)Chls.

Scheme 4. Proposed Degradation Pathways of Natural (B)Chls to 3-Ethylated, Methylated, and Unsubstituted (Metallo)Pyropheophorbides



EXPERIMENTAL SECTION

All the synthetic procedures were done in the dark. Nickel methyl pyropheophorbide-*a* (**4b**),[44] methyl bacteriopheophorbide-*d* (**5a**),[15,20] methyl 3-devinyl-3-hydroxymethyl-pyropheophorbide-*a* (**10a**, methyl 3^1-demethyl-bacteriopheophorbide-*d*),[28] and methyl 3-carboxy-3-devinyl-pyropheophoribide-*a* (**13a**)[41] were prepared according to reported procedures. ^{1}H, ^{13}C, and ^{19}F NMR spectra were measured at 600, 150.5, and 564.7 MHz, respectively, and COSY, NOESY, HMBC, and HMQC techniques were used to assign the NMR peak. Flash column chromatography (FCC) was perforemd on silica gel (Merck, Kieselgel 60, 40−63 μm, 230−400 mesh). Commercially available dichloromethane, tetrahydrofuran, acetone, methanol, and 1,2-dichloroethane (Nacalai Tesque, extra pure reagent) were used as the reaction solvents. Solvents for optical spectroscopy were purchased from Nacalai Tesque as reagents prepared specially for spectroscopy and used without further purification. All the optical properties in solution were measured as described previously.[45]

Chlorination. To 3^1-hydroxychlorin **5a**/**10a** (0.1 mmol) in CH_2Cl_2 (10 mL) was added dropwise thionyl chloride (15 μL, 0.2 mmol) at 0 °C, and the mixture was stirred at room temperature under N_2 for 1 h. The reaction was quenched with aqueous saturated $NaHCO_3$ solution, and the reaction mixture was extracted with CH_2Cl_2, washed with aqueous saturated $NaHCO_3$ solution, and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by FCC (CH_2Cl_2−Et_2O) to give the corresponding 3^1-chlorochlorin **11a** (5% Et_2O as an eluent). In the case of 3-(1-chloroethyl)-chlorin **6a**, the reaction mixture was directly distilled in vacuo, and the crude product was used for the further reaction without purification because of its chemical instability.

Trifluoroacetylation. To 3^1-hydroxychlorin **5a**/**10a** (0.1 mmol) in CH_2Cl_2 (6 mL) was added dropwise trifluoroacetic anhydride (56 μL, 0.4 mmol) at 0 °C, and the mixture was stirred at room temperature under N_2 for 1 h. The reaction was quenched with aqueous saturated $NaHCO_3$ solution, and the reaction mixture was extracted with CH_2Cl_2, washed with aqueous saturated $NaHCO_3$ solution, and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by FCC (CH_2Cl_2−Et_2O) to give the corresponding trifluoroacetate **7a**/**12a** (5−10% Et_2O as an eluent).

Hydrogenation. To palladium(II) hydroxide (3 mg) in THF (1 mL) was added 3^1-substituted chlorin **5**−**7**/**10**−**12** (50 μmol) in THF (2 mL) and acetone (1 mL), and the mixture was stirred at room temperature under H_2 for 1−4 days. After removal of $Pd(OH)_2$ by filtration, the solvents were evaporated, and the residue was purified by FCC (CH_2Cl_2−Et_2O) to give the corresponding 3-alkyl-chlorin **1**/**2** as the fast-moving band (10% Et_2O as an eluent) and the starting material as the slow-moving band.

Nickel Metalation. To free base chlorin (0.1 mmol) in 1,2-dichloroethane (10 mL) was added a methanol solution saturated with nickel(II) acetate tetrahydrate (5 mL), and the mixture was stirred at 80 °C under N_2 for several hours. The reaction mixture was cooled down to room temperature, quenched with aqueous saturated $NaHCO_3$ solution, extracted with CH_2Cl_2, washed with aqueous saturated $NaHCO_3$ solution, and dried over Na_2SO_4. After evaporation of the solvents, the residue was purified by FCC (CH_2Cl_2−Et_2O) to give the corresponding nickel complex (5−15% Et_2O as an eluent). In the case of 3-carboxy-chlorin, acetone instead of methanol was used as the reaction cosolvent, and methanol (10%) instead of diethyl ether was necessary for the additional FCC eluent.

Decarboxylation. A solution of 3-carboxychlorin **13** (0.2 mmol) in 2,4,6-collidine (100 mL) was stirred at 180 °C under N_2 for 4 days. The reaction mixture was cooled to 80 °C, and the solvent was removed under a reduced pressure. The residue was dissolved in CH_2Cl_2, washed with an aqueous 0.1 M HCl solution, and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by FCC (CH_2Cl_2) to give the products as the fast-moving band (addition of 3−5% Et_2O as an eluent) and the starting material **13** as the slow-moving band (10% CH_3OH). The separated products were further purified by FCC (hexane/Et_2O = 1:2) to afford 3-unsubstituted chlorin **3** as the first fraction and 3-methoxycarbonyl-chlorin **14** as the second.

The latter methyl ester **14** obtained as a byproduct was alternatively prepared as follows. To 3-carboxychlorin **13** (50 μmol) in CH_2Cl_2 (5 mL) and CH_3OH (5 mL) was added an excess amount of ethereal diazomethane (10 mL), and the mixture was stirred at room temperature for a few hours. After evaporation of the solvents, the

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residue was purified by FCC (CH_2Cl_2/Et_2O = 95:5) to give the corresponding methyl ester **14**.

Methyl 3^1-Trifluoroacetoxy-mesopyropheophorbide-*a* (7a). Trifluoroacetylation of **5a** (57 mg, 0.10 mmol) gave **7a** as dark green solid (53 mg, 80 μmol, 80%): mp 82−86 °C; VIS (CH_2Cl_2) λ_{max}/nm 665 (relative intensity, 0.50), 608 (0.07), 536 (0.08), 506 (0.09), 410 (1.00), 319 (0.18); ^{1}H NMR ($CDCl_3$) δ/ppm (3^1*R*:*S* = 1:1) 9.60 (1H, s, 5-H), 9.55/54 (1H, s, 10-H), $8.64_2/63_6$ (1H, s, 20-H), 7.48/46 (1H, q, *J* = 7 Hz, 3-CH), $5.28_4/28_2$, $5.14_9/14_8$ (each 1H, d, *J* = 19 Hz, 13^1-CH_2), 4.52 (1H, dq, *J* = 2, 8 Hz, 18-H), 4.34−4.31 (1H, m, 17-H), 3.72/71 (2H, q, *J* = 8 Hz, 8-CH_2), 3.67/66 (3H, s, 12-CH_3), $3.61_7/61_4$ (3H, s, 17^2-$COOCH_3$), $3.50_0/49_9$ (3H, s, 2-CH_3), 3.30/29 (3H, s, 7-CH_3), 2.73−2.67, 2.60−2.53, 2.33−2.23 (1H+1H+2H, m, 17-CH_2CH_2), $2.38_3/2.38_2$ (3H, d, *J* = 7 Hz, 3^1-CH_3), 1.83 (3H, d, *J* = 8 Hz, 18-CH_3), 1.71 (3H, t, *J* = 8 Hz, 8^1-CH_3), 0.10, −1.89 (each 1H, br, NH × 2); ^{13}C NMR δ/ppm (3^1*R*:*S* = 1:1) 196.3 (C13^1), 173.6 (C17^3), 171.3 (C19), 160.9 (C16), 157.2 (q, $^2J_{CF}$ = 43 Hz, C3^3), 154.8 (C6), 151.3 (C9), 149.1 (C14), 145.3 (C8), 140.3/140.2 (C1), 138.4 (C11), 136.6 (C7), $134.4_6/134.4_3$ (C3), 133.9/133.8 (C4), 133.1/133.0 (C2), 131.0 (C13), 129.2 (C12), 114.8 (q, $^1J_{CF}$ = 288 Hz, C3^4), 106.7 (C15), 104.4 (C10), 97.7 (C5), 93.6 (C20), $72.4_8/72.4_5$ (C3^1), 51.9, 51.8 (C17, C17^5), 50.1 (C18), 48.2 (C13^3), 31.7/31.0, 30.9/29.9 (C17^1, C17^2), 23.3_6, 23.3_2 (C3^2, C18^1), 19.7 (C8^1), 17.6 (C8^2), 12.2 (C12^1), $11.5_3/11.5_1$ (C2^1), $11.2_3/11.2_2$ (C7^1); ^{19}F-NMR ($CDCl_3$) δ/ppm (3^1*R*:*S* = 1:1) −73.72/73; MS (TOF) found *m*/*z* 662, calcd for $C_{36}H_{37}N_4O_5F_3$ M$^+$, 662; HRMS (FAB) *m*/*z* 663.2769, calcd for $C_{36}H_{38}N_4O_5F_3$ MH$^+$, 663.2789.

Methyl Mesopyropheophorbide-*a* (1a). Hydrogenation of **7a** (33 mg, 50 μmol) gave **1a** as black solid (8.8 mg, 16 μmol, 32%): VIS (CH_2Cl_2) λ_{max}/nm 656 (ε, 5.1 × 10^4), 601 (9.3 × 10^3), 535 (1.0 × 10^4), 504 (1.0 × 10^4), 410 (1.21 × 10^5), 395 (9.2 × 10^4), 317 (2.4 × 10^4); ^{1}H NMR ($CDCl_3$) δ/ppm 9.48 (1H, s, 10-H), 9.21 (1H, s, 5-H), 8.45 (1H, s, 20-H), 5.24, 5.09 (each 1H, d, *J* = 19 Hz, 13^1-CH_2), 4.45 (1H, dq, *J* = 2, 8 Hz, 18-H), 4.27 (1H, dt, *J* = 2, 9 Hz, 17-H), 3.83 (2H, q, *J* = 8 Hz, 3-CH_2), 3.69 (2H, q, *J* = 8 Hz, 8-CH_2), 3.67 (3H, s, 12-CH_3), 3.60 (3H, s, 17^2-$COOCH_3$), 3.29 (3H, s, 2-CH_3), 3.25 (3H, s, 7-CH_3), 2.71−2.65 (1H, m, 17^1-CH), 2.57−2.50 (1H, m, 17-CH), 2.34−2.23 (2H, m, 17-CHCH), 1.80 (3H, d, *J* = 8 Hz, 18-CH_3), 1.73 (3H, t, *J* = 8 Hz, 3^1-CH_3), 1.70 (3H, t, *J* = 8 Hz, 8^1-CH_3), 0.64, −1.60 (each 1H, s, NH × 2) [see also the ^{1}H NMR spectral data in ref 9]; MS (TOF) found *m*/*z* 550, calcd for $C_{34}H_{38}N_4O_3$ M$^+$, 550.

Nickel Methyl Bacteriopheophorbide-*d* (5b). Nickel metalation of **5a** (57 mg, 0.10 mmol) gave **5b** as dark green solid (54 mg, 87 μmol, 87%): mp 114−119 °C; VIS (CH_2Cl_2) λ_{max}/nm 642 (relative intensity, 0.87), 598 (0.17), 537 (0.08), 498 (0.07), 417 (1.00), 396 (0.82); ^{1}H NMR ($CDCl_3$) δ/ppm (3^1*R*:*S* = 1:1) 9.40/32 (1H, s, 5-H), 9.11/09 (1H, s, 10-H), 8.08/06 (1H, s, 20-H), 6.16/14 (1H, dq, *J* = 2, 7 Hz, 3-CH), 4.70/69, 4.61/57 (each 1H, d, *J* = 19 Hz, 13^1-CH_2), 4.20/18 (each 1H, dq, *J* = 1, 8 Hz, 18-H), 3.84 (1H, m, 17-H), 3.51/48 (2H, dq, *J* = 11, 8 Hz, 8-CH_2), 3.63/62 (3H, s, 17^2-$COOCH_3$), 3.37/36 (3H, s, 12-CH_3), 3.16/13, 3.12/11 (each 3H, s, 2-, 7-CH_3), 2.72/69 (1H, br, 3^1-OH), 2.43−2.38, 2.27−2.21, 2.12−2.02, 2.00−1.88 (each 1H, m, 17-CH_2CH_2), 2.06/03 (3H, d, *J* = 7 Hz, 3^1-CH_3), 1.57/56 (3H, t, *J* = 8 Hz, 18-CH_3), 1.47/45 (each 3H, d, *J* = 8 Hz, 8^1-CH_3); ^{13}C NMR ($CDCl_3$) δ/ppm 195.7 (C13^1), 173.5 (C17^3), 162.0/161.9 (C19), $156.2_3/156.2_1$ (C14), 148.5 (C16), 148.0/147.9 (C1), 144.8/144.7 (C3), 144.2 (C6), 143.7 (C8), 139.8/139.5 (C2), 139.6 (C11), 139.2 (C9), 135.0/134.6 (C4), 134.4 (C12), $133.5_8/133.5_2$ (C7), 132.5 (C13), 106.3 (C10), $104.8_8/104.8_3$ (C15), 100.8/100.3 (C5), 93.0/92.9 (C20), 65.8/65.5 (C3^1), 51.9 (C17^5), 49.1 (C17), 48.6/48.5 (C18), 47.1 (C13^2), 30.7, 29.8 (C17^1, C17^2), 26.0/25.6 (C3^2), $22.3_5/22.3_1$ (C18^1), 19.5 (C8^1), 17.3 (C8^2), $12.5_2/12.5_0$ (C12^1), 11.6/11.4, 11.2 (C2^1, C7^1); MS (TOF) found *m*/*z* 623, calcd for $C_{34}H_{37}N_4O_4Ni$ MH$^+$, 623; HRMS (FAB) *m*/*z* 622.2105, calcd for $C_{34}H_{36}N_4O_4Ni$ M$^+$, 622.2090.

Nickel Methyl Mesopyropheophorbide-*a* (1b). Hydrogenation of **5b** (31 mg, 50 μmol) gave **1b** (0.5 mg, 0.85 mmol, 1.7%) and starting **5b** (31 mg, 49 μmol, 98%). Nickel metalation of **1a** and hydrogenation of **4b** over Pd/C in acetone (by the same procedures[9] as in **4a** to **1a**) gave **1b** as dark green solid in 82 and 90% yield, respectively: mp 185−188 °C; VIS (CH_2Cl_2) λ_{max}/nm 639 (ε, 6.0 × 10^4), 595 (1.1 × 10^4), 536 (4.3 × 10^3), 496 (3.3 × 10^3), 417 (5.9 × 10^4), 391 (5.1 × 10^4); ^{1}H NMR ($CDCl_3$) δ/ppm 9.25 (1H, s, 10-H), 8.89 (1H, s, 5-H), 8.09 (1H, s, 20-H), 4.83, 4.78 (each 1H, d, *J* = 19 Hz, 13^1-CH_2), 4.25 (1H, dq, *J* = 1, 7 Hz, 18-H), 3.96 (1H, ddd, *J* = 1, 4, 8 Hz, 17-H), 3.60 (3H, s, 17^2-$COOCH_3$), 3.61−3.50 (each 2H, m, 3-, 8-CH_2), 3.46 (3H, s, 12-CH_3), 3.12 (3H, s, 7-CH_3), 3.02 (3H, s, 2-CH_3), 2.45−2.40 (1H, m, 17^1-CH), 2.28−2.18 (2H, m, 17-CHCH), 2.13−2.07 (1H, m, 17-CH), 1.60_1, 1.59_8 (each 3H, t, *J* = 8 Hz, 3^1-, 8^1-CH_3), 1.54 (3H, d, *J* = 7 Hz, 18-CH_3) [see also the ^{1}H NMR spectral data in ref 46]; MS (TOF) found *m*/*z* 606, calcd for $C_{34}H_{36}N_4O_3Ni$ M$^+$, 606.

Methyl 3-Chloromethyl-3-devinyl-pyropheophorbide-*a* (11a). Chlorination of **10a** (55 mg, 0.10 mmol) gave **11a** as dark purple solid (47 mg, 83 μmol, 83%): mp >300 °C; VIS (CH_2Cl_2) λ_{max}/nm 675 (ε, 6.3 × 10^4), 616 (8.0 × 10^3), 540 (1.1 × 10^4), 511 (1.2 × 10^4), 415 (1.05 × 10^5), 321 (2.2 × 10^4); ^{1}H NMR ($CDCl_3$) δ/ppm 9.55(1H, s, 10-H), 9.38 (1H, s, 5-H), 8.61 (1H, s, 20-H), 5.85 (2H, s, 3-CH_2), 5.28, 5.14 (each 1H, d, *J* = 19 Hz, 13^1-CH_2), 4.50 (1H, dq, *J* = 2, 7 Hz, 18-H), 4.32 (1H, dt, *J* = 8, 2 Hz, 17-H), 3.71 (2H, q, *J* = 8 Hz, 8-CH_2), 3.69 (3H, s, 12-CH_3), 3.61 (3H, s, 17^2-$COOCH_3$), 3.43 (3H, s, 2-CH_3), 3.29 (3H, s, 7-CH_3), 2.73−2.68 (1H, m, 17-CH), 2.59−2.54 (1H, m, 17^1-CH), 2.33−2.23 (2H, m, 17-CHCH), 1.82 (3H, d, *J* = 7 Hz, 18-CH_3), 1.71 (3H, t, *J* = 8 Hz, 8^1-CH_3), 0.27, −1.84 (each 1H, s, NH × 2); ^{13}C NMR ($CDCl_3$) δ/ppm 196.3 (C13^1), 173.6 (C17^3), 171.4 (C19), 160.7 (C16), 155.0 (C6), 151.3 (C9), 149.0 (C14), 145.3 (C8), 141.6 (C1), 138.4 (C11), 136.5 (C7), 135.2, 134.4, 133.6 (C2, C3, C4), 131.0, 129.0 (C12, C13), 106.7 (C15), 104.3 (C10), 96.4 (C5), 93.7 (C20), $51.9_2/51.8_5$ (C17, C17^5), 50.0 (C18), 48.2 (C13^2), 36.3 (C3^1), 31.0, 30.0 (C17^1, C17^2), 23.3 (C18^1), 19.6 (C8^1), 17.6 (C8^2), 12.2 (C12^1), 11.4 (C7^1), 11.4 (C2^1); HRMS (FAB) *m*/*z* 571.2472, calcd for $C_{33}H_{36}N_4O_3Cl$ MH$^+$, 571.2476.

Methyl 3-Devinyl-3-trifluoroacetoxymethyl-pyropheophorbide-*a* (12a). Trifluoroacetylation of **10a** (55 mg, 0.10 mmol) gave **12a** as dark green solid (45 mg, 69 μmol, 69%): mp >300 °C; VIS (CH_2Cl_2) λ_{max}/nm 668 (relative intensity, 0.55), 609 (0.07), 537 (0.09), 506 (0.10), 411 (1.00), 378 (0.60), 319 (0.19); ^{1}H NMR ($CDCl_3$) δ/ppm 9.59 (1H, s, 10-H), 9.42 (1H, s, 5-H), 8.67 (1H, s, 20-H), 6.66 (2H, s, 3-CH_2), 5.30, 5.16 (each 1H, d, *J* = 19 Hz, 13^1-CH_2), 4.53 (1H, dq, *J* = 2, 7 Hz, 18-H), 4.34 (1H, dt, *J* = 9, 2 Hz, 17-H), 3.72 (2H, q, *J* = 8 Hz, 8-CH_2), 3.70 (3H, s, 12-CH_3), 3.61 (3H, s, 17^2-$COOCH_3$), 3.50 (3H, s, 2-CH_3), 3.28 (3H, s, 7-CH_3), 2.74−2.68 (1H, m, 17-CH), 2.60−2.54 (1H, m, 17^1-CH), 2.34−2.25 (2H, m, 17-CHCH), 1.82 (3H, d, *J* = 7 Hz, 18-CH_3), 1.72 (3H, t, *J* = 8 Hz, 8^1-CH_3), 0.14, −1.90 (each 1H, br, NH × 2); ^{13}C NMR ($CDCl_3$) δ/ppm 196.3 (C13^1), 173.6 (C17^3), 171.2 (C19), 160.9 (C16), 157.8 (q, $^2J_{CF}$ = 43 Hz, C3^3), 154.9 (C6), 151.5 (C9), 149.0 (C14), 145.3 (C8), 140.2 (C1), 138.6 (C11), 136.7 (C7), 136.2 (C2), 135.3 (C3), 131.2 (C12), 129.4 (C13), 129.1 (C4), 114.8 (q, $^1J_{CF}$ = 284 Hz, C3^4), 106.8 (C15), 104.3 (C10), 96.8 (C5), 94.0 (C20), 60.9 (C3^1), 52.0 (C17), 51.9 (C17^5), 50.0 (C18), 48.3 (C13^2), 31.0, 30.0 (C17^1, C17 ^{2}), 23.4 (C18^1), 19.6 (C8^1), 17.6 (C8^2), 12.3 (C12^1), 11.5 (C2^1), 11.3 (C7^1); ^{19}F-NMR ($CDCl_3$) δ/ppm −73.54; MS (TOF) found *m*/*z* 648, calcd for $C_{35}H_{35}N_4O_5F_3$ M$^+$, 648; HRMS (FAB) *m*/*z* 648.2581, calcd for $C_{35}H_{35}N_4O_5F_3$ M$^+$, 648.2560.

Methyl 3-Devinyl-3-methyl-pyropheophorbide-*a* (2a). Hydrogenation of chloride **11a** (29 mg, 50 μmol) and trifluoroacetate **12a** (32 mg, 50 μmol) gave **2a** (11 mg, 21 μmol and 6.4 mg, 12 μmol) as black solid in 41 and 24% yield, respectively: mp 237−241 °C; VIS (CH_2Cl_2) λ_{max}/nm 655 (ε, 5.0 × 10^4), 600 (9.6 × 10^3), 534 (1.0 × 10^4), 503 (1.1 × 10^4), 410 (1.30 × 10^5), 394 (9.7 × 10^4), 316 (2.5 × 10^4); ^{1}H NMR ($CDCl_3$) δ/ppm 9.40 (1H, s, 10-H), 9.09 (1H, s, 5-H), 8.41 (1H, s, 20-H), 5.22, 5.08 (each 1H, d, *J* = 19 Hz, 13^1-CH_2), 4.44 (1H, dq, *J* = 2, 8 Hz, 18-H), 4.25 (1H, dt, *J* = 9, 2 Hz, 17-H), 3.64 (2H, q, *J* = 8 Hz, 8-CH_2), 3.63 (3H, s, 12-CH_3), 3.62 (3H, s, 17^2-$COOCH_3$), 3.30 (3H, s, 3-CH_3), 3.25 (3H, s, 2-CH_3), 3.20 (3H, s, 7-CH_3), 2.71−2.65 (1H, m, 17-CH), 2.58−2.52 (1H, m, 17^1-CH), 2.32−2.26 (2H, m, 17-CHCH), 1.80 (3H, d, *J* = 8 Hz, 18-CH_3), 1.67 (3H, t, *J* = 8 Hz, 8^1-CH_3), 0.66, −1.57 (each 1H, br, NH × 2); ^{13}C NMR ($CDCl_3$) δ/ppm 196.4 (C13^1), 173.7 (C17^3), 172.0 (C19),

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159.9 (C16), 155.5 (C6), 150.5 (C9), 149.3 (C14), 145.2 (C8), 142.6 (C1), 138.2 (C4), 137.5 (C11), 135.7 (C7), 135.5 (C3), 132.0 (C2), 130.2 (C12), 127.9 (C13), 105.9 (C15), 104.3 (C10), 96.0 (C5), 92.4 (C20), 51.8 ($C17^5$), 51.5 (C17), 50.2 (C18), 48.1 ($C13^2$), 31.1, 30.0 ($C17^1$, $C17^2$), 23.2 ($C18^1$), 19.6 ($C8^1$), 17.6 ($C8^2$), 12.1 ($C12^1$), 11.4, 11.3, 11.2 ($C2^1$, $C3^1$, $C7^1$); MS (TOF) found m/z 536, calcd for $C_{33}H_{36}N_4O_3$ M^+, 536; HRMS (FAB) found m/z 536.2783, calcd for calcd for $C_{33}H_{36}N_4O_3$ M^+, 536.2787.

Nickel Methyl 3-Devinyl-hydroxymethyl-pyropheophorbide-*a* (10b). Nickel metalation of **10a** (55 mg, 0.10 mmol) gave **10b** as dark green solid (58 mg, 95 μmol, 95%): its spectral data were cited in ref 43.

Nickel 3-Devinyl-3-methyl-pyropheophorbide-*a* (2b). Hydrogenation of **10b** (30 mg, 50 μmol) gave **2b** (1.5 mg, 2.5 μmol, 5%) and starting **10b** (27 mg, 45 μmol, 89%). Nickel metalation of **2a** (54 mg, 0.10 mmol) gave **2b** as dark green solid (49 mg, 83 μmol, 83%): mp 228−231 °C; VIS (CH_2Cl_2) λ_{max}/nm 639 (ε, 5.8×10^4), 594 (1.1×10^4), 536 (4.3×10^3), 494 (3.5×10^3), 417 (6.1×10^4), 391 (5.1×10^4); ^{1}H NMR ($CDCl_3$) δ/ppm 9.21 (1H, s, 10-H), 8.83 (1H, s, 5-H), 8.05 (1H, s, 20-H), 4.82, 4.76 (each 1H, d, J = 19 Hz, 13^1-CH_2), 4.24 (1H, dq, J = 1, 7 Hz, 18-H), 3.95 (1H, ddd, J = 1, 5, 6 Hz, 17-H), 3.60 (3H, s, CH_3, 17^2-$COOCH_3$), 3.54, 3.50 (each 1H, q, J = 14, 7 Hz, 8-CH_2), 3.44 (3H, s, 12-CH_3), 3.09, 3.08 (each 3H, s, 3-, 7-CH_3), 3.00 (3H, s, 2-CH_3), 2.45−2.40 (1H, m, 17^1-CH), 2.29−2.18 (2H, m, 17-CHCH), 2.12−2.06 (1H, m, 17-CH), 1.58 (3H, t, J = 7 Hz, 8^1-CH_3), 1.53 (3H, d, J = 7 Hz, 8^1-CH_3); ^{13}C NMR δ/ppm 195.6 ($C13^1$), 173.5 ($C17^3$), 162.7 (C19), 156.6 (C14), 149.2 (C1), 148.3 (C16), 144.9 (C6), 144.0 (C8), 142.8 (C4), 139.4 (C9), 139.1 (C3), 138.9 (C13), 135.4 (C2), 134.0 (C11), 132.9 (C7), 132.4 (C12), 106.7 (C10), 105.2 (C15), 98.7 (C5), 92.9 (C20), 51.8 ($C17^5$), 49.0 (C17), 48.9 (C18), 47.3 ($C13^2$), 30.7, 29.9 ($C17^1$, $C17^2$), 22.3 ($C18^1$), 19.5 ($C8^1$), 17.4 ($C8^2$), 12.6 ($C12^1$), 11.4, 11.4, 11.0 ($C2^1$, $C3^1$, $C7^1$); MS (TOF) found m/z 593, calcd for $C_{33}H_{35}N_4O_3Ni$ MH^+, 593; HRMS (FAB) found m/z 592.1958, calcd for $C_{33}H_{34}N_4O_3Ni$ M^+, 592.1984.

Methyl 3-Devinyl-pyropheophorbide-*a* (3a). Pyrolysis of **13a** (113 mg, 0.20 mmol) gave 3-unsubstituted chlorin **3a** (9.4 mg, 18 μmol, 9%) and 3-methoxycarbonyl-chlorin **14a** (3.5 mg, 6 μmol, 3%) as well as starting **13a** (76 mg, 134 μmol, 67%). **3a**: black solid; mp 105−109 °C (lit.,[37] 172−173 °C); VIS (CH_2Cl_2) λ_{max}/nm 659 (ε, 5.9×10^4), 603 (9.4×10^3), 535 (1.2×10^4), 504 (1.1×10^4), 408 (1.24×10^5), 316 (2.6×10^4); ^{1}H NMR ($CDCl_3$) δ/ppm 9.49 (1H, s, 10-H), 9.21 (1H, br-d, J = 1 Hz, 5-H), 8.71 (1H, br, 3-H), 8.54 (1H, s, 20-H), 5.28, 5.13 (each 1H, d, J = 19 Hz, 13^1-CH_2), 4.49 (1H, dq, J = 2, 8 Hz, 18-H), 4.31 (1H, dt, J = 8, 2 Hz, 17-H), 3.67_3 (2H, q, J = 8 Hz, 8-CH_2), 3.66_6 (3H, s, 12-CH_3), 3.62 (3H, s, 17^2-$COOCH_3$), 3.41 (3H, d, J = 1 Hz, 2-CH_3), 3.22 (3H, s, 7-CH_3), 2.73−2.67 (1H, m, 17-CH), 2.59−2.54 (1H, m, 17^1-CH), 2.33−2.25 (2H, m, 17-CHCH), 1.82 (3H, d, J = 8 Hz, 18-CH_3), 1.69 (3H, t, J = 8 Hz, 8^1-CH_3), 0.31, −1.80 (each 1H, br, NH × 2); ^{13}C NMR ($CDCl_3$) δ/ppm 196.4 ($C13^1$), 173.7 ($C17^3$), 171.4 (C19), 160.2 (C16), 155.4 (C6), 150.9 (C9), 148.9 (C14), 145.1 (C8), 142.6 (C1), 138.0 (C11), 137.3 (C4), 136.1 (C7), 135.7 (C2), 130.6 (C13), 128.4 (C3), 128.1 (C12), 106.1 (C15), 104.0 (C10), 99.5 (C5), 93.1 (C20), 51.8_5, 51.8_3 (C17, $C17^5$), 50.0 (C18), 48.2 ($C13^2$), 31.0 ($C17^1$), 30.4 ($C17^2$), 23.2 ($C18^1$), 19.6 ($C8^1$), 17.6 ($C8^2$), 13.4 ($C2^1$), 12.2 ($C12^1$), 11.3 ($C7^1$); HRMS (FAB) found m/z 522.2630, calcd for $C_{32}H_{34}N_4O_3$ M^+, 522.2631.

Methyl 3-Devinyl-3-methoxycarbonyl-pyropheophorbide-*a* (14a). Methyl-esterification of **13a** (28 mg, 50 μmol) gave **14a** as dark brown solid (21 mg, 36 μmol, 71%): its spectral data were cited in ref 41.

Nickel Methyl 3-Carboxy-3-devinyl-pyropheophorbide-*a* (13b). Nickel metalation of **13a** (57 mg, 0.10 mmol) gave **13b** as dark green solid (51 mg, 82 μmol, 82%): mp 187−192 °C; VIS (CH_2Cl_2) λ_{max}/nm 664 (relative intensity 0.97), 618 (0.19, sh), 554, (0.09), 506 (0.08), 429 (1.00), 408 (0.80), 381 (0.71); ^{1}H NMR gave broad peaks in usual deuterated solvents; HRMS (TOF) found m/z 622, calcd for $C_{33}H_{32}N_4O_5Ni$ M^+, 622; HRMS (FAB) found m/z 623.1797, calcd for $C_{33}H_{33}N_4O_5Ni$ MH^+, 623.1799.

Nickel Methyl 3-Devinyl-pyropheophorbide-*a* (3b). Pyrolysis of **13b** (125 mg, 0.20 mmol) gave 3-unsubstituted chlorin **3b** (5.2 mg, 9 μmol, 4.5%) and 3-methoxycarbonyl-chlorin **14b** (0.6 mg, 1 μmol, 0.5%) as well as starting **13b** (93 mg, 150 μmol, 75%). Nickel metalation of **3a** (52 mg, 0.10 mmol) gave **3b** as dark green solid (46 mg, 79 μmol, 79%): mp 157−161 °C; VIS (CH_2Cl_2) λ_{max}/nm 640 (ε, 5.7×10^4), 595 (9.3×10^3), 539 (3.8×10^3), 496 (3.1×10^3), 417 (5.9×10^4), 393 (4.5×10^4); ^{1}H NMR ($CDCl_3$) δ/ppm 9.30 (1H, s, 10-H), 8.90 (1H, s, 5-H), 8.41 (1H, br-q, J = 1 Hz, 3-H), 8.17 (1H, s, 20-H), 4.86, 4.81 (each 1H, d, J = 19 Hz, 13^1-CH_2), 4.29 (1H, dq, J = 1, 7 Hz, 18-H), 4.00 (1H, ddd, J = 1, 5, 8 Hz, 17-H), 3.60 (3H, s, 17^2-$COOCH_3$), 3.60, 3.57 (each 1H, dq, J = 14, 7 Hz, 8-CH_2), 3.48 (3H, s, 12-CH_3), 3.16 (3H, d, J = 1 Hz, 2-CH_3), 3.11 (3H, s, 7-CH_3), 2.48−2.41 (1H, m, 17^1-CH), 2.30−2.20 (2H, m, 17-CHCH), 2.15−2.08 (1H, m, 17-CH), 1.60 (3H, t, J = 7 Hz, 8^1-CH_3), 1.55 (3H, d, J = 7 Hz, 18-CH_3); ^{13}C NMR ($CDCl_3$) δ/ppm 195.7 ($C13^1$), 173.4 ($C17^3$), 162.3 (C19), 156.5 (C14), 149.1 (C1), 148.8 (C16), 144.6 (C6), 144.0 (C8), 141.8 (C4), 139.8 (C12), 139.3 (C2, C9), 134.6 (C11), 133.4 (C7), 132.9 (C13), 131.8 (C3), 106.5 (C10), 105.2 (C15), 101.9 (C5), 93.5 (C20), 51.9 ($C17^5$), 49.2 (C17), 48.8 (C18), 47.4 ($C13^2$), 30.7, 29.9 ($C17^1$, $C17^2$), 22.5 ($C18^1$), 19.6 ($C8^1$), 17.4 ($C8^2$), 13.6 ($C2^1$), 12.7 ($C12^1$), 11.1 ($C7^1$); MS (TOF) found m/z 579, calcd for $C_{32}H_{33}N_4O_3Ni$ MH^+, 579; HRMS (FAB) found m/z 579.1878, calcd for calcd for $C_{32}H_{33}N_4O_3Ni$ MH^+, 579.1901.

Nickel Methyl 3-Devinyl-3-methoxycarbonyl-pyropheophorbide-*a* (14b). Nickel metalation of **14a** (58 mg, 0.10 mmol) gave **14b** as dark green solid (58 mg, 91 μmol, 91%), and alternatively, methyl-esterification of **13b** (31 mg, 50 μmol) gave **14b** (29 mg, 46 μmol, 92%): mp 203−207 °C; VIS (CH_2Cl_2) λ_{max}/nm 662 (relative intensity 1.01), 617, (0.17), 551 (0.07), 510 (0.06), 428 (1.00), 409 (0.78), 380 (0.65); ^{1}H NMR ($CDCl_3$) δ/ppm 10.09 (1H, s, 5-H), 9.31 (1H, s, 10-H), 8.34 (1H, s, 20-H), 4.89, 4.81 (each 1H, d, J = 19 Hz, 13^1-CH_2), 4.32 (1H, dq, J = 1, 7 Hz, 18-H), 4.26 (3H, s, 3-$COOCH_3$), 4.03 (1H, ddd, J = 1, 5, 8 Hz, 17-H), 3.61 (3H, s, 17^2-$COOCH_3$), 3.58, 3.55 (each 1H, dq, J = 15, 8 Hz, 8-CH_2), 3.48 (3H, s, 12-CH_3), 3.44 (3H, s, 2-CH_3), 3.14 (3H, s, 7-CH_3), 2.48−2.43, 2.32−2.27 (each 1H, m, 17^1-CH), 2.26−2.20, 2.13−2.07 (each 1H, m, 17-CH), 1.59 (3H, t, J = 8 Hz, 8^1-CH_3), 1.54 (3H, d, J = 7 Hz, 18-CH_3); ^{13}C NMR ($CDCl_3$) δ/ppm 195.5 ($C13^1$), 173.4 ($C17^3$), 166.2 ($C3^1$), 160.8 (C19), 156.2 (C14), 150.0 (C16), 145.5 (C6), 144.3 (C1), 143.8_5, 143.8_1 (C3, C8), 141.0, (C12), 140.4 (C9), 139.3 (C2), 135.9 (C11), 135.4 (C7), 133.8 (C13), 128.9 (C4), 105.9 (C10), 105.4 (C15), 103.1 (C5), 94.5 (C20), 52.1 ($C3^3$), 51.9 ($C17^5$), 49.6 (C17), 48.6 (C18), 47.4 ($C13^2$), 30.7, 29.7 ($C17^1$, $C17^2$), 22.4 ($C18^2$), 19.5 ($C8^1$), 17.3 ($C8^2$), 13.6 ($C2^1$), 12.7 ($C12^1$), 11.2 ($C7^1$); MS (TOF) found m/z 636, calcd for $C_{34}H_{34}N_4O_5Ni$ M^+, 636; HRMS (FAB) found m/z 637.1974, calcd for calcd for $C_{34}H_{35}N_4O_5Ni$ MH^+, 637.1956.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Relation of σ_p with λ_{abs}[Qy(0,0)] and λ_{em}(0,0) of **1**−**3a**, visible and CD spectra of **1**−**3b**, as well as ^{1}H/^{13}C NMR spectra of **1**−**3a**/**b** and their synthetic intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Tamiaki, H.; Shibata, R.; Mizoguchi, T. *Photochem. Photobiol.* **2007**, *83*, 152.
(2) Tamiaki, H.; Kunieda, M. In *Handbook of Porphyrin Science*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; World Scientific Publishing: Singapore, 2011; Vol. *11*, Chapter 51, pp 223−290.
(3) Kobayashi, M.; Ohashi, S.; Iwamoto, K.; Shiraiwa, Y.; Kato, Y.; Watanabe, T. *Biochim. Biophys. Acta* **2007**, *1767*, 596.
(4) (a) Cogdell, R. J.; Gall, A.; Köhler, J. *Q. Rev. Biophys.* **2006**, *39*, 227. (b) Tamiaki, H.; Kotegawa, Y.; Mizutani, K. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6037.
(5) (a) Sasaki, S.; Kotegawa, Y.; Tamiaki, H. *Tetrahedron Lett.* **2006**, *47*, 4849. (b) Takano, K.; Sasaki, S.; Citterio, D.; Tamiaki, H.; Suzuki, K. *Analyst* **2010**, *135*, 2334.
(6) Verne-Mismer, J.; Ocampo, R.; Bauder, C.; Callot, H. J.; Albrecht, P. *Energy Fuels* **1990**, *4*, 639.
(7) Keely, B. J.; Prowse, W. G.; Maxwell, J. R. *Energy Fuels* **1990**, *4*, 628.
(8) Tamiaki, H.; Takeuchi, S.; Tsudzuki, S.; Miyatake, T.; Tanikaga, R. *Tetrahedron* **1998**, *54*, 6699.
(9) Smith, K. M.; Goff, D. A.; Simpson, D. J. *J. Am. Chem. Soc.* **1985**, *107*, 4946.
(10) Mizoguchi, T.; Oh-oka, H.; Tamiaki, H. *Photochem. Photobiol.* **2005**, *81*, 666.
(11) Kobayashi, M.; Hamano, T.; Akiyama, M.; Watanabe, T.; Inoue, K.; Oh-oka, H.; Amesz, J.; Yamamura, M.; Kise, H. *Anal. Chim. Acta* **1998**, *365*, 199.
(12) Kunieda, M.; Mizoguchi, T.; Tamiaki, H. *Tetrahedron* **2004**, *60*, 11349.
(13) Mizoguchi, T.; Oh-oka, H.; Tamiaki, H. *Photochem. Photobiol.* **2005**, *81*, 666.
(14) Mizoguchi, T.; Harada, J.; Tamiaki, H. *FEBS Lett.* **2006**, *580*, 6644.
(15) Tamiaki, H.; Kouraba, M.; Takeda, K.; Kondo, S.; Tanikaga, R. *Tetrahedron: Asymmetry* **1998**, *9*, 2101.
(16) Kobayashi, M.; Yamamura, M.; Akutsu, S.; Miyake, J.; Hara, M.; Akiyama, M.; Kise, H. *Anal. Chim. Acta* **1998**, *361*, 285.
(17) Saga, Y.; Shibata, Y.; Tamiaki, H. *J. Photochem. Photobiol., C* **2010**, *11*, 15.
(18) (a) Mizoguchi, T.; Saga, Y.; Tamiaki, H. *Photochem. Photobiol. Sci.* **2002**, *1*, 780. (b) Saga, Y.; Oh-oka, H.; Hayashi, T.; Tamiaki, H. *Anal. Sci.* **2003**, *19*, 1575.
(19) Smith, K. M.; Goff, D. A. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1099.
(20) Smith, K. M.; Bisset, G. M. F.; Bushell, M. J. *J. Org. Chem.* **1980**, *45*, 2218.
(21) Tamiaki, H.; Miyatake, T.; Tanikaga, R. *Tetrahedron Lett.* **1997**, *38*, 267.
(22) Yagai, S.; Tamiaki, H. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3135−3144.
(23) Tamiaki, H.; Yagai, S.; Miyatake, T. *Bioorg. Med. Chem.* **1998**, *6*, 2171.
(24) Miyashita, H.; Ikemoto, H.; Kurano, N.; Adachi, K.; Chihara, M.; Miyachi, S. *Nature* **1996**, *383*, 402.
(25) Mizoguchi, T.; Shoji, A.; Kunieda, M.; Miyashita, H.; Tsuchiya, T.; Mimuro, M.; Tamiaki, H. *Photochem. Photobiol. Sci.* **2006**, *5*, 291.
(26) Falk, H.; Hoornaert, G.; Isenring, H.-P.; Eschenmoser, A. *Helv. Chim. Acta* **1975**, *58*, 2347.
(27) Johnson, D. G.; Svec, W. A.; Wasielewski, M. R. *Isr. J. Chem.* **1988**, *28*, 193.
(28) Tamiaki, H.; Amakawa, M.; Shimono, Y.; Tanikaga, R.; Holzwarth, A. R.; Schaffner, K. *Photochem. Photobiol.* **1996**, *63*, 92.
(29) Tamiaki, H.; Miyata, S.; Kureishi, Y.; Tanikaga, R. *Tetrahedron* **1996**, *52*, 12421.
(30) Fischer, R.; Engel, N.; Henseler, A.; Gossauer, A. *Helv. Chim. Acta* **1994**, *77*, 1046.
(31) Oba, T.; Uda, Y.; Matsuda, K.; Fukusumi, T.; Ito, S.; Hiratani, K.; Tamiaki, H. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2489.
(32) Tamiaki, H.; Shimono, Y.; Rattray, A. G. M.; Tanikaga, R. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2085.
(33) Smith, K. M.; Goff, D. A. *J. Am. Chem. Soc.* **1985**, *107*, 4954.
(34) Lam, K.; Markó, I. E. *Org. Lett.* **2008**, *10*, 2773.
(35) Fürstner, A.; Stelzer, F.; Rumbo, A.; Krause, H. *Chem.—Eur. J.* **2002**, *8*, 1856.
(36) Bible, K. C.; Buytendorp, M.; Zierath, P. D.; Rinehart, K. L. *Proc. Natl. Acad. Sci. U. S. A.* **1988**, *85*, 4582.
(37) Fischer, H.; Wunderer, A. *Justus Liebigs Ann. Chem.* **1938**, *533*, 230.
(38) Brückner, C.; Hyland, M. A.; Sternberg, E. D.; MacAlpine, J. K.; Rettig, S. J.; Patrick, B. O.; Dolphin, D. *Inorg. Chim. Acta* **2005**, *358*, 2943.
(39) (a) Conant, J. B.; Hyde, J. F.; Moyer, W. W.; Dietz, E. M. *J. Am. Chem. Soc.* **1931**, *53*, 359. (b) Clezy, P. S.; Barrett, J. *Biochem. J.* **1961**, *78*, 798.
(40) Gust, D.; Moore, T. A.; Moore, A. L.; Liddell, P. A. *Methods Enzymol.* **1992**, *213*, 87.
(41) Osuka, A.; Wada, Y.; Shinoda, S. *Tetrahedron* **1996**, *52*, 4311.
(42) Scopton, A.; Kelly, T. R. *J. Org. Chem.* **2005**, *70*, 10004.
(43) Tamiaki, H.; Amakawa, M.; Holzwarth, A. R.; Schaffner, K. *Photosynth. Res.* **2002**, *71*, 59.
(44) Morishita, H.; Tamiaki, H. *Spectrochim. Acta, Part A* **2009**, *72*, 274.
(45) Shibata, R.; Mizoguchi, T.; Inazu, T.; Tamiaki, H. *Photochem. Photobiol. Sci.* **2007**, *6*, 749.
(46) Abraham, R. J.; Medforth, C. J.; Smith, K. M.; Goff, D. A.; Simpson, D. J. *J. Am. Chem. Soc.* **1987**, *109*, 4786.