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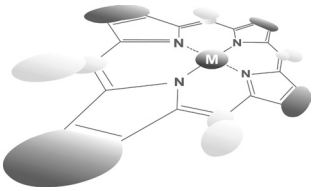

Ene-thiol reaction of C3-vinylated chlorophyll derivatives in the presence of oxygen: synthesis of C3-formyl-chlorins under mild conditions

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ABSTRACT: Reactions of thiol with the C3-vinyl group of various chlorophyll (Chl) derivatives were examined. The reactions resemble thiol-olefin co-oxidation, except that the vinyl C=C double bond was cleaved to afford a formyl group without any transition metal catalyst, and that the simple *anti*-Markovnikov adduct of thiol to olefin was obtained as a minor product. Peripheral substituents of Chl derivatives little affected the reaction, while the central metal atom of the chlorin macrocycle influenced the composition of the products. Oxygen and acid dissolved in the reaction mixture can facilitate the oxidation. Sufficiently mild conditions in this regioselective oxidation at the C3[1]-position are significant in bioorganic chemistry.

KEYWORDS: aldehyde, chlorophyll, co-oxidation, olefin, thiol.

INTRODUCTION

Ene-thiol reactions are classically found in chemistry but have recently been reevaluated. Electrophilic addition, Michael addition, and radical addition of thiol across a double bond are well known. Michael reaction between a cysteine thiol and a maleimide proceeds even in water, and the reaction is widely used for cross-linking and labeling of proteins [1]. Very recently, such ene-thiol reactions have been reinvestigated and highlighted as useful click-reactions beneficial for bio-conjugation and facile synthesis of supramolecules [2–4].

When oxygen is introduced into a system involving thiol and olefin, oxidation of the olefin takes place besides the formation of simple adducts. This thiol-olefin co-oxidation (TOCO reaction) has long been studied in relation to hydrocarbon fuel instability [5, 6]. Styrene ($PhCH{=}CH_2$) for instance reacted with thiophenol (PhSH) and oxygen (O_2) to give 1-phenyl-2-(phenylsulfinyl)-ethanol, $PhCH(OH)CH_2S(O)Ph$. Thiyl radical ($PhS^{\bullet}$) and molecular oxygen add to the double bond to afford a sulfanyl hydroperoxide [$PhCH(O–O^{\bullet})CH_2SPh$] in the early step of the co-oxidation. The unstable hydroperoxide transforms into the more stable sulfinyl ethanol. In contrast, Szmant and co-workers studied the mechanism of the reaction by NMR, and proposed that not a thiyl radical but a charge transfer complex formed by the thiol and the olefin played an essential role in the early step [7].

In the presence of oxygen, addition of a thiol across an ene double bond (Cα=Cβ) is accompanied by oxidation of the α-carbon atom and the sulfur atom at the β-position. The conventional TOCO reaction does not, however, involve cleavage of the double bond. The double bond cleavage, leading to formation of aldehydes

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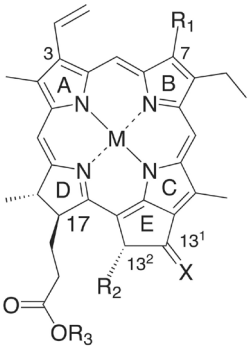
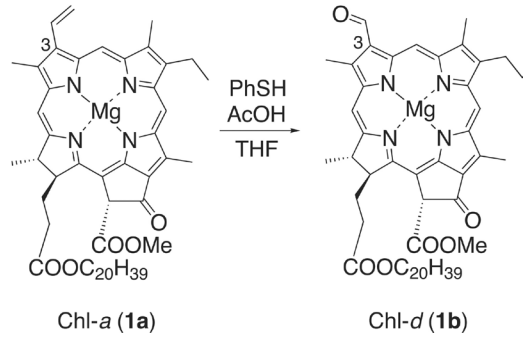


Substrate	M	R_1	R_2	R_3	X
1a (Chl-*a*)	Mg	CH_3	$COOCH_3$	$C_{20}H_{39}$	O
2a	H_2	CH_3	H	CH_3	O
3a (Pheo-*a*)	H_2	CH_3	$COOCH_3$	$C_{20}H_{39}$	O
4a	H_2	CH_3	H	$C_{20}H_{39}$	O
5a	H_2	CH_3	$COOCH_3$	CH_3	O
6a (Chl-*b*)	Mg	CHO	$COOCH_3$	$C_{20}H_{39}$	O
7a (Pheo-*b*)	H_2	CHO	$COOCH_3$	$C_{20}H_{39}$	O
8a	H_2	CH_3	H	CH_3	H_2
9a	Ni	CH_3	H	CH_3	O
10a	Zn	CH_3	H	CH_3	O

Fig. 1. Molecular structures of natural chlorophylls and their derivatives **1a–10a** possessing the C3-vinyl group as the substrates of the present oxidation

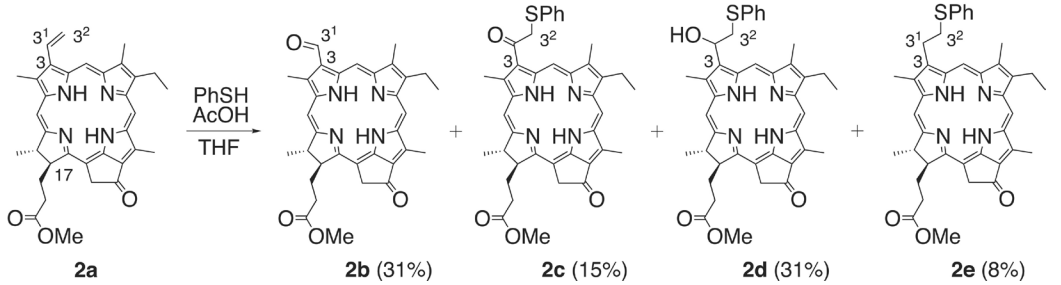


Scheme 1. *In vitro* conversion of Chl-*a* (**1a**) into Chl-*d* (**1b**) using thiophenol and acetic acid

or ketones, requires transition metal complexes such as Mn salen [8] and Fe porphyrin [9] in addition to the thiol and oxygen. β-Sulfanyl hydroperoxides were also assumed to be intermediates of these catalytic oxidations.

We have found that in the presence of a thiol the peripheral vinyl groups of chlorophyll-*a* (Chl-*a*, **1a**, see Fig. 1) and methyl pyropheophorbide-*a* (**2a**) were selectively converted into the formyl groups to afford Chl-*d* (**1b**) and methyl pyropheophorbide-*d* (**2b**), respectively, in substantial yields without aid of any metal catalysts (Schemes 1 and 2), which were preliminary reported [10, 11]. The reaction was carried out by simply mixing the pigments, thiophenol, and acetic acid in THF, followed by stirring the solution for several hours at room temperature. Because Chl-*a*, which is labile to strong oxidants, oxygen, and acids, was readily transformed into Chl-*d* in one-step under such mild conditions, we assume it to be a model reaction of Chl-*d* biosynthesis. Very recently, Belykh and Ashikhmina reported that a catalytic amount of alkyl thiol and oxygen gas enabled formylation of **2a** and chlorin-e_6 derivatives [12].

Molecular oxygen attracts much attention as an ideal oxidant due to its abundance, low cost, and safety, all of which benefit us from the viewpoint of green and sustainable chemistry. *N*-Hydroxyphthalimide is one of the catalysts that facilitate oxidation of organic substrates using molecular oxygen as an oxidant [13, 14]. Attack of phthalimide *N*-oxyl radical on an olefin and subsequent decomposition of the peroxide intermediate are assumed to be involved in the mechanism that converts olefins into ketones or aldehydes. Living organisms also use molecular oxygen in their metabolic processes, for instance, by using cytochrome P450 as a catalyst. Molecular oxygen coordinates to the heme iron of P450 to form the ferric peroxide [Fe(III)–OOH], followed by transformation into the oxo ferryl species [Fe(IV)=O] that oxidizes the substrates [15]. Thiol in the oxidation shown in Scheme 1 may also function as a catalyst to harness molecular oxygen. It is intriguing that no metal catalyst is needed to cleave the double bond of the vinyl group of Chl-*a*. This ene-thiol chemistry is worthy of investigation from the aspects of bioorganic chemistry as well as green chemistry.



Scheme 2. Reaction of the C3-vinyl double bond of Chl-*a* derivative **2a** with a thiol to give **2b–2e**. The values in parenthesis indicate the yields of **2b–2e** (using 10 μmol of **2a**, see Experimental section for the reaction conditions)

Here we report the effects of vinylated chlorin substrates, oxygen molecule, and additional acid species on the ene-thiol reaction, as a model for the enzymatic conversion of Chl-*a* into Chl-*d*. As substrates, we examined ten pigments including natural Chls and their synthetic derivatives with different peripheral substituents and central metals. All the substrates successfully underwent the oxidation of the vinyl group to give the corresponding aldehydes. The reaction also gave sulfanyl-adducts, but simple *anti*-Markovnikov-type adducts were obtained in lower yields. Thus, this reaction is in sharp contrast to the traditional TOCO reaction.

RESULTS

When Chl-*a* (**1a**), AcOH (1 equiv.), and PhSH (5 equiv.) were dissolved in THF, followed by stirring overnight in the air at room temperature, **1a** was converted into Chl-*d* (**1b**) successfully (Table 1). When **2a** was reacted under the same conditions, **2a** was fully consumed within 5 h and C3-formyl-chlorin **2b** was obtained in the same yield as that of **1a** to **1b**. Other natural and synthetic chlorins **3a–8a** (see Fig. 1) also gave their corresponding C3-formyl-chlorins **3b–8b** (see Table 1). The reaction proceeded smoothly, regardless of the esterifying group of the C17-propionate and the substituents at the $C13^1$- and $C13^2$-positions. During the oxidation, the major products were free from any degradation including hydrogen abstraction at peripheral substituents, ester hydrolysis, thioacetal formation, demetallation, and ring opening. The C3-vinyl groups of C7-formyl-chlorins, Chl-*b* (**6a**) and its free base Pheo-*b* (**7a**), were similarly transformed to give the corresponding C3,7-diformyl-chlorins **6b** and **7b**, respectively, under the above conditions. ^{1}H NMR spectrum of **6b** clearly showed two formyl proton signals at 11.37 and 11.43 ppm [16], demonstrating that the C7-formyl group was kept intact during the oxidation. The C7-formyl group retarded the oxidation: Chl-*b* (**6a**) took 7 h to complete the reaction, while the formylation of Chl-*a* (**1a**) was completed within 4 h, indicating that the C7-formyl-chlorins were less reactive for the present oxidation than the C7-methylated pigments. This tendency is consistent with the fact that demetallation of Zn-chlorins is retarded by electronic effects of the C7-formyl group [17].

Table 1. Oxidation of C3-vinylated Chl derivatives **na** to C3-formyl-chlorins **nb**[a]

Substrate		Yield (%)	Product		
	λ_{max}[b]			λ_{max}[b]	$\Delta\lambda$ (ΔE)[c]
1a (Chl-*a*)	666	31	**1b** (Chl-*d*) [11]	684	18 (395)
2a	668	31	**2b**	697	29 (623)
3a (Pheo-*a*)	668	22	**3b** (Pheo-*d*)	691	23 (498)
4a	667	17	**4b**	691	24 (521)
5a	668	25	**5b**	698	30 (643)
6a (Chl-*b*)	647	32	**6b**	667	20 (463)
7a (Pheo-*b*)	650	24	**7b**	678	28 (635)
8a	648	26	**8b**	667	19 (440)
9a	652	35	**9b**	680	28 (632)
10a	659	9	**10b**	688	29 (640)

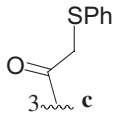
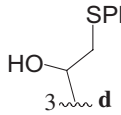
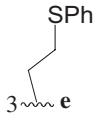
[a] Basic reaction conditions: 3-vinyl-chlorin (10 μmol), AcOH (1 equiv.), and PhSH (5 equiv.) in THF (3 mL), in the air, at room temperature. The yields were determined by ^{1}H NMR spectral analysis (see Experimental section). [b] In nm in $CHCl_3$. [c] $\Delta\lambda$ in nm and ΔE in cm^{-1}.

The central metal atom of the chlorin macrocycles greatly influenced their reactivity to this oxidation. Nickel and zinc atoms were inserted into the central cavity of the free base **2a** in a conventional way [18], and the obtained Ni- **9a** and Zn-complexes **10a** were subjected to the oxidation reaction as mentioned above. The Ni-complex **9a** also afforded the corresponding Ni-formyl-chlorin **9b** (35%). The value was comparable to those of Mg complex **1a** to **1b** and its free base **2a** to **2b**. On the other hand, the C=C double bond cleavage at the C3-moiety was strongly inhibited in the case of Zn-complex **10a** and C3-formyl-chlorin **10b** was obtained in only 9% yield. The suppression may arise from the difference in the redox property of the substrates.

Table 1 also shows the Q_y absorption maxima of **na** and **nb**. Compounds **2a–5a** possess the same π-system and gave the Q_y peaks at 667–668 nm. Conversion of the vinyl group to the formyl group induced large red-shift of these bands to 691–698 nm. The other substrates also experienced comparable red-shift by the conversion.

The reaction of **2a** afforded two other major products after purification with reversed-phase HPLC: retention time (t_R) = 21 and 30 min. The slowly eluting (t_R = 30 min) and less polar species is assigned to C3-[1-oxo-2-(phenylsulfanyl)ethyl] derivative **2c** (Scheme 2) from its ^{1}H NMR [δ = 4.86 ppm for singlet CH_2-3^2], visible (λ_{max} = 687 nm for Q_y peak), and MS data (*m*/*z* = 672 for $[M]^+$) [10]. The fast eluting (t_R = 21 min) and more polar species is assignable to a 3^1-epimeric mixture (1:1) of C3-[1-hydroxy-2-(phenylsulfanyl)ethyl] form **2d**: λ_{max} = 664 nm for Q_y peak and *m*/*z* = 674 for $[M]^+$. The molecular structure of alcohol **2d** was also confirmed by the authentic sample prepared by reduction of ketone **2c** with ^{t}BuNH$_2$BH$_3$ in CH_2Cl_2. It is noted that the simple *anti*-Markovnikov-type adduct, C3-[2-(phenylsulfanyl)-ethyl] form **2e**, was obtained in a lower yield (8%). This is in sharp contrast to the fact that conventional TOCO reaction simultaneously gave simple *anti*-Markovnikov-type adducts in substantial yields. The typical reaction of styrene with *p*-chlorothiophenol at 30 °C afforded both the sulfinyl alcohol (31%) and the simple adduct (69%) [7]. This is one of the characteristics of the present reaction of Chl derivatives. The reaction conditions employed seemed to be very oxidative for Chl

Table 2. Composition of the products of **2a** dependent upon the reaction conditions[a]

Atmosphere	Yield, %				
	 **a**	 **b**	 **c**	 **d**	 **e**
Air	0	20	13	47	9
O_2	0	43	27	9	0
Ar	6	31	19	16	3
Air (no AcOH)[b]	0	25	14	35	6

[a] Basic reaction conditions: 3-vinyl-chlorin **2a** (100 μmol), AcOH (1 equiv.), and PhSH (5 equiv.) in THF (10 mL), in the air, at room temperature. [b] **2a** (10 μmol).

derivatives, in spite of lacking any catalyst and flushing oxygen. A Markovnikov-type adduct was detected using *p*-toluenesulfonic acid as a coexisting acid [10], but was not obtained under the present conditions employing lower acidic AcOH. Preliminary analysis demonstrated essentially the same tendency for the composition of the reaction products **nb–ne** obtained from the other chlorin substrates **1a** and **3a–9a** (see Table S1).

Oxygen gas had an additional effect on the composition of the products (see Table 2). Introduction of oxygen into the reaction mixture of **2a** enhanced the two-fold formation of **2b** and **2c**, while production of **2d** was greatly inhibited. When Ar gas was bubbled into the solution before the reaction, a small amount of substrate **2a** remained unreacted even after stirring for 24 h.

DISCUSSION

The present oxidation reaction (Scheme 2) resembles a traditional TOCO reaction, but clear differences were noted: (1) the vinyl C=C double bond was cleaved to afford a formyl group without any transition metal catalysts or bubbling of oxygen gas, and (2) the simple *anti*-Markovnikov adduct **ne** (C3-CH_2CH_2SPh) was obtained in a lower yield. Compound **2a** is a good representative to examine reactivity of these Chl derivatives, because essentially the same major products were obtained as in the other derivatives. The vinyl group was selectively transformed, and less degradation of the pigments including hydrolysis of esters, demetalation, and ring opening was observed. The modification at the sole C3-vinyl group under sufficiently mild reaction conditions offers the possibility of wider application in organic synthesis and of the unveiling of unidentified reactions in bioorganic chemistry including Chl-*d* biosynthesis.

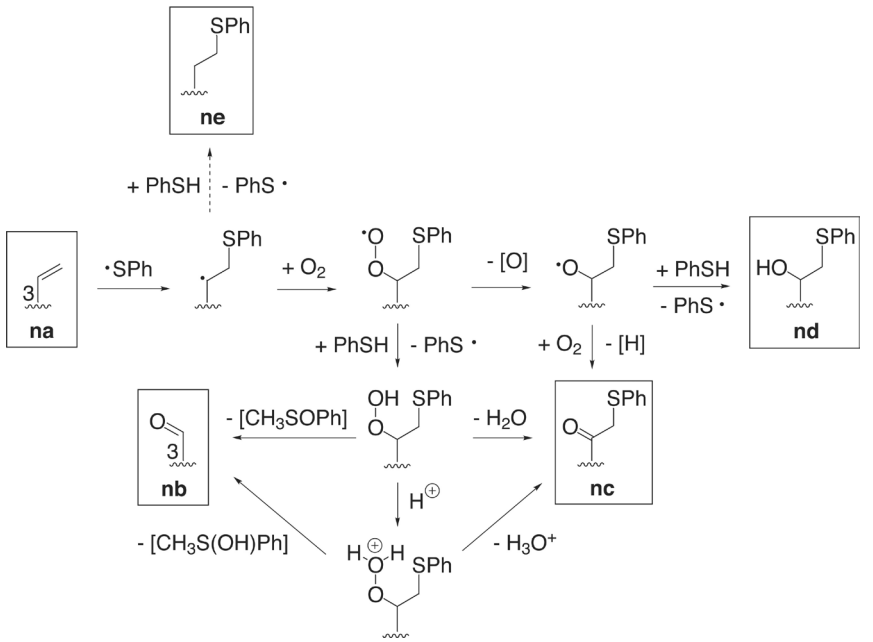
We assume that the oxidation examined here proceeds through a peroxide intermediate (Scheme 3) as in a TOCO reaction [10, 11]. Sequential addition of thiol and molecular oxygen to the C3-vinyl group of **na** can afford a peroxide species. Loss of an oxygen atom from the peroxide could lead to the formation of sulfanyl alcohol **nd**. Sulfanyl ketone **nc** could be obtained by additional abstraction of a hydrogen atom at the $C3^1$-position. It is proposed that the C3-formyl-chlorin **nb** is also derived from the peroxide intermediate. The reaction conditions are sufficiently oxidative even without flushing oxygen gas through the system. Attack of molecular oxygen to the $C3^1$-carbon centered radical (C3-CH$^{\bullet}$–CH_2SPh) would be much faster than abstraction of hydrogen from thiophenol that should provide the simple *anti*-Markovnikov adduct.

After our preliminary report [10], the formylation of **2a** and chlorin-e_6 derivatives (*ca*. 50% yields) using a catalytic amount of alkyl thiol (5~7 mole%) and oxygen gas (4~5 L/h, 1 h) was described [12]. We could not obtain such C3-formyl-chlorins in the presence of an alkyl thiol under the atmospheric conditions where Chl-*d* biosynthesis took place [10]. A large amount of oxygen in the system may activate reactivity of alkyl thiol and successfully enable the formylation. The fact that such an alkyl thiol catalyzes the formylation might suggest that the thiol moiety of cysteine residue can participate in the enzymatic transformation from Chl-*a* to Chl-*d*. We speculate that a postulated Chl-*d* synthase facilitates monooxygenation using molecular oxygen and preferentially decomposes the peroxide intermediate into the formyl-chlorin.

Not only formyl-chlorins [19, 20] but sulfanylated chlorins await future application. Supramolecular devices including artificial photosynthesis may be fabricated by conjugation of a pigment with a biomolecule by formation of a thioether linkage between a thiol and a vinyl group. It is also expected that the sulfanylated chlorins function as photosensitizing drugs of photodynamic therapy and as their synthetic intermediates.

EXPERIMENTAL

Chl-*a* (**1a**) and Chl-*b* (**6a**) were extracted from Spirulina and spinach, respectively, and were used as materials to prepare compounds **2a–5a** and **7a–10a** as described previously [18, 21–23]. Reagents were



Scheme 3. Hypothetical synthetic pathway of the reaction of the C3-vinyl double bond of Chl derivatives **na** with a thiol. A thiyl radical (PhS•) attacked the C3-vinyl group, followed by addition of a molecular oxygen. The resulting hydroperoxide oxidatively decomposed into C3-formyl-chlorins **nb**, C3-[1-oxo-2-(phenylsulfanyl)ethyl] derivatives **nc**, and the C3-[1-hydroxy-2-(phenylsulfanyl)ethyl] derivatives **nd**, and C3-[2-(phenylsulfanyl)ethyl] derivatives **ne**

purchased from Kanto Chemical Co., Inc., and were used as provided. The oxidation reactions of the 3-vinylated Chl derivatives were carried out as reported earlier [10, 11]. The typical reaction of **2a** is described below.

Compound **2a** (10 μmol) was dissolved in dry tetrahydrofuran (THF, 3 mL) and the solution was chilled in an ice water bath. Thiophenol (PhSH, 5 equiv.) was added to this solution and stirred for 45 min. Then, acetic acid (AcOH, 1 equiv.) was added to the mixture, and stirred for 24 h at room temperature. The mixture was neutralized by 5% aq. $NaHCO_3$, and the pigments were extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to dryness. The residue was analyzed by ^{1}H NMR (Varian VNMR-500), MALDI-TOF-MS (Bruker autoflex II), and UV-vis (JASCO V-550). The composition of **2a**–**2e** in the reaction mixture was calculated based on the ^{1}H NMR data (Fig. 2). Areas of proton signals specific for respective compounds (C3-moieties, CH-5, CH-10, and CH-20) were divided by the total area of the $C13^2$-protons and the results were averaged from triplicate experiments.

The major products (**2b**, 37 min; **2c**, 30 min; **2d**, 21 min) were isolated from the mixtures using a reversed-phase HPLC [column, Nomura Chemical Develosil ODS-HG5 (20ϕ × 150 mm); eluent, methanol; pump, JASCO PU-2089; detector, JASCO MD-2018; flow rate, 3 mL/min; room temperature] and analyzed by their ^{1}H NMR, HRMS (Bruker micrOTOF II), and UV-vis spectra. The data of **2b** were identical to the reported data [10, 21]. The NMR and UV-vis spectra of novel compounds **2c**, **2d** and **2e** were similar to those of known

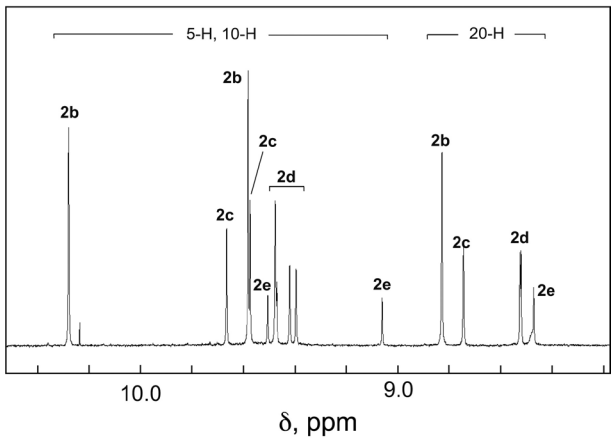


Fig. 2. A partial ^{1}H NMR spectrum of a reaction mixture recorded after 24-h oxidation. Compound **2a** was fully consumed and products **2b–2e** were observed. Characteristic signals of the respective products are indicated

analogs (*e.g.* C3-acetyl, C3-hyrdoxymethyl, and C3-ethyl chlorins) [21, 23, 24], and were listed below.

Since the introduction of oxygen or argon gas into the above reaction mixture involving 10 μmol of **2a** gave scattered results for the composition of products, the gases were bubbled into a relatively large scale of **2a** (100 μmol and THF, 10 mL) before 24-h stirring to give less variable data.

Methyl 3-devinyl-3-[1-oxo-2-(phenylsulfanyl)ethyl]-pyropheophorbide-*a* (2c). UV-vis ($CHCl_3$): λ_{max}, nm 687 (relative intensity, 0.53), 628 (0.08), 550 (0.12),

516 (0.12), 419 (1.00), 390 (0.87). ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si): δ_H, ppm -2.03 (1H, s, pyrrole-N*H*) (another NH was too broad to be observed), 1.71 (3H, t, J = 8 Hz, CH_3-8^2), 1.84 (3H, d, J = 7 Hz, CH_3-18^1), 2.26–2.36, 2.52–2.79 (4H, m, CH_2-17^1, 17^2), 3.18 (3H, s, CH_3-7^1), 3.56 (3H, s, CH_3-2^1), 3.61 (3H, s, CH_3-17^5), 3.71 (3H, s, CH_3-12^1), 3.72 (2H, q, J = 8 Hz, CH_2-8^1), 4.37 (1H, dt, J = 8, 2 Hz, C*H*-17), 4.56 (1H, dq, J = 2, 7 Hz, C*H*-18), 4.86 (2H, s, CH_2-3^2), 5.18, 5.33 (2H, 2d, J = 20 Hz, CH_2-13^2), 7.18–7.22 (3H, m, C*H*-3′, 4′, 5′ of phenyl), 7.38–7.42 (2H, m, C*H*-2′, 6′ of phenyl), 8.75 (1H, s, C*H*-20), 9.60 (1H, s, C*H*-10), 9.67 (1H, s, C*H*-5). HRMS (APCI): *m/z* 673.2846 (calcd. for $[M + H]^+$ 673.2849).

Methyl 3-devinyl-3-[1-hydroxy-2-(phenylsulfanyl)-ethyl]pyropheophorbide-*a* (2d). UV-vis ($CHCl_3$): λ_{max}, nm 664 (relative intensity, 0.51), 608 (0.09), 540 (0.10), 508 (0.10), 412 (1.00). ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si): δ_H, ppm -1.83 (1H, s, pyrrole-N*H*) (another NH was too broad to be observed), 1.70 (3H, t, J = 8 Hz, CH_3-8^2), 1.80/1.81 (3H, d, J = 7 Hz, CH_3-18^1), 2.22–2.36, 2.52–2.75 (4H, m, CH_2-17^1, 17^2), 3.13/3.14 (3H, s, CH_3-7^1), 3.36/3.38 (3H, s, CH_3-2^1), 3.61 (3H, s, CH_3-17^5), 3.68 (3H, s, CH_3-12^1), 3.68 (2H, q, J = 8 Hz, CH_2-8^1), 3.78–3.94 (2H, m, CH_2-3^2), 4.30 (1H, m, C*H*-17), 4.48 (1H, br-q, J = 7 Hz, C*H*-18), 5.12, 5.27 (2H, 2d, J = 20 Hz, CH_2-13^2), 6.24 (1H, m, C*H*-3^1), 7.32–7.37 (1H, m, C*H*-4′ of phenyl), 7.40–7.44 (2H, m, C*H*-3′, 5′ of phenyl), 7.62–7.66 (2H, m, C*H*-2′, 6′ of phenyl), 8.53/8.54 (1H, s, C*H*-20), 9.44/9.46 (1H, s, C*H*-5), 9.54 (1H, s, C*H*-10) (the 3^1-OH signal was not detected due to proton exchange with trace water). HRMS (APCI): *m/z* 675.3001 (calcd. for $[M + H]^+$ 675.3006). Alternative preparation of **2d** was conducted by reduction of compound **2c** using *tert*-butylamine borane complex in the previously described manner [16, 17].

Methyl 3-devinyl-3-[2-(phenylsulfanyl)ethyl]pyropheophorbide-*a* (2e). UV-vis ($CHCl_3$): λ_{max}, nm 661 (relative intensity, 0.48), 605 (0.08), 537 (0.09), 505 (0.09), 412 (1.00). ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si): δ_H, ppm -1.70, 0.49 (2H, 2s, pyrrole-N*H* × 2), 1.70 (3H, t, J = 8 Hz, CH_3-8^2), 1.80 (3H, d, J = 7 Hz, CH_3-18^1), 2.22–2.36, 2.51–2.73 (4H, m, CH_2-17^1, 17^2), 3.19 (3H, s, CH_3-7^1), 3.29 (3H, s, CH_3-2^1), 3.60 (3H, s, CH_3-17^5), 3.68 (3H, s, CH_3-12^1), 3.70 (2H, q, J = 8 Hz, CH_2-8^1), 3.64, 4.14 (4H, m, CH_2-3^1, 3^2), 4.28 (1H, dt, J = 7, 2 Hz, C*H*-17), 4.47 (1H, dq, J = 2, 7 Hz, C*H*-18), 5.10, 5.30 (2H, 2d, J = 20 Hz, CH_2-13^2), 7.36 (1H, t, J = 7 Hz, C*H*-4′ of phenyl), 7.42 (2H, t, J = 7 Hz, C*H*-3′, 5′ of phenyl), 7.64 (2H, d, J = 7 Hz, C*H*-2′, 6′ of phenyl), 8.48 (1H, s, C*H*-20), 9.10 (1H, s, C*H*-5), 9.51 (1H, s, C*H*-10). HRMS (APCI): *m/z* 659.3078 (calcd. for $[M + H]^+$ 659.3056). Alternatively, **2e** was synthesized by radical addition of PhSH initiated by AIBN; detail of this reaction will be presented elsewhere carriage return.

The other 3-formyl-chlorins **1b** and **3b–10b** were prepared similarly as mentioned above. NMR spectra of trace compounds were obtained by liquid MAS technique using the "Nano probe" (Varian). NMR spectra of metal complexes **1**, **9** and **10** were measured in $CDCl_3$ containing 10% CD_3OD to prevent aggregation. ^{1}H NMR, HRMS, and UV-vis data of novel compounds **4b**, **7b** and **8b** were analyzed based on spectral data of known analogs [10, 11, 16, 21–34], and are listed below. Spectral data of the other products are listed in Supplementary material. Preparation of 3-vinyl-chlorins **1a**–**3a** [25, 26], **4a** [27], **5a**–**6a** [25, 26], **7a** [26], **8a** [23, 28], **9a** [29], and **10a** [30] as well as 3-formyl-chlorins **1b** [11, 31], **2b** [10, 21], **3b** [31], **5b** [32, 33], **6b** [16], **9b** [29], and **10b** [34] were confirmed by the literature data.

Pyropheophytin-*d* (4b). Compound **4a** (10 μmol) was reacted with PhSH (5 equiv.) and AcOH (1 equiv.) in dry THF (3 mL) for 24 h at room temperature, as mentioned above. The desired product **4b** was isolated from the reaction mixture using a normal-phase HPLC (t_R = 15.5 min; column, Senshu-Pak 5251N (20ϕ × 250 mm); eluent, hexane/2-propanol/methanol = 100/8/4; pump, JASCO PU-2089; detector, JASCO MD-2018; flow rate, 5 mL/min; room temperature) and analyzed by ^{1}H NMR, HRMS, and UV-vis spectroscopies. UV-vis ($CHCl_3$): λ_{max}, nm 691 (relative intensity, 0.76), 629 (0.07), 549 (0.14), 517 (0.15), 420 (1.00), 385 (0.84). ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si): δ_H, ppm -2.02 (1H, s, pyrrole-N*H*) (another NH was too broad to be observed). 0.77, 0.78 (6H, 2d, J = 7 Hz, P15-(CH_3)$_2$), 0.84 (6H, d, J = 7 Hz, P7, P11-CH_3), 1.62 (3H, s, P3-CH_3), 1.74 (3H, t, J = 8 Hz, CH_3-8^2), 1.84 (3H, d, J = 7 Hz, CH_3-18^1), 2.2–2.8 (4H, m, CH_2-17^1, 17^2), 3.76 (2H, q, J = 8 Hz, CH_2-8^1), 3.35, 3.74, 3.79 (9H, 3s, CH_3-2^1, 7^1, 12^1), 4.39 (1H, m, C*H*-17), 4.48–4.62 (3H, m, P1-H_2 + C*H*-18), 5.21 (1H, t, J = 6 Hz, P2-*H*), 5.19, 5.35 (2H, 2d, J = 20 Hz, CH_2-13^2), 8.85 (1H, s, C*H*-20), 9.65, 10.35 (2H, 2s, C*H*-5, 10), 11.58 (1H, s, C*H*O-3^1). (Some protons of phytyl group were not clearly assigned.) HRMS (APCI): *m/z* 815.5473 (calcd. for $[M + H]^+$ 815.5475).

3-Devinyl-3-formyl-pheophytin-*b* (7b). Compound **7a** (10 μmol) was reacted with PhSH (5 equiv.) and AcOH (1 equiv.) in dry THF (3 mL) for 24 h at room temperature, as mentioned above. The desired product **7b** was isolated from the reaction mixture using a normal-phase HPLC (t_R = 30.0 min; column, Senshu-Pak 5251N (20ϕ × 250 mm); eluent, hexane/2-propanol/methanol = 100/8/4; pump, JASCO PU-2089; detector, JASCO MD-2018; flow rate, 5 mL/min; room temperature) and analyzed by ^{1}H NMR, HRMS, and UV-vis spectroscopies. UV-vis ($CHCl_3$): λ_{max}, nm 678 (relative intensity, 0.29), 536 (0.11), 454 (1.00). ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si): δ_H, ppm -1.87 (1H, s, pyrrole-N*H*) (another NH was too broad to be observed). 0.78, 0.80 (6H, 2d, J = 6 Hz, P15-(CH_3)$_2$), 0.84 (6H, d, J = 6 Hz, P7, P11-CH_3), 1.58 (1H, m, P15-*H*), 1.58 (3H, s, P3-CH_3), 1.84–1.90 (6H, m, CH_3-8^2, 18^1), 2.2–2.7 (4H, m, CH_2-17^1, 17^2), 3.76, 3.76, 3.93 (9H, 3s, CH_3-2^1, 12^1, 13^2-COOCH_3), 4.15 (2H, q, J = 8 Hz, CH_2-8^1), 4.29 (1H, m, C*H*-17), 4.55 (1H, dq, J = 2, 8 Hz, C*H*-18), 4.40–4.53 (2H, m, P1-H_2), 5.14 (1H, t, J = 7 Hz, P2-*H*), 6.32 (1H, s, C*H*-13^2), 9.82

(1H, s, C*H*-20), 9.85, 10.99 (2H, 2s, C*H*-5, 10), 11.27, 11.67 (2H, 2s, C*H*O-3[1], 7[1]). (Some protons of phytyl group were not clearly assigned.) HRMS (APCI): *m/z* 887.5377 (calcd. for $[M + H]^+$ 887.5323).

Methyl 13[1]-deoxo-mesopyropheophorbide-*d* (8b). Compound **8a** (10 μmol) was reacted with PhSH (5 equiv.) and AcOH (1 equiv.) in dry THF (3 mL) for 24 h at room temperature, as mentioned above. The desired product **8b** was isolated from the reaction mixture by silica-gel column chromatography (dichloroethane/diethyl ether = 100/3) and analyzed by ^{1}H NMR, HRMS, and UV-vis spectroscopies. UV-vis ($CHCl_3$): λ_{max}, nm 667 (relative intensity, 0.34), 612 (0.06), 552 (0.08), 515 (0.12), 419 (1.00), 334 (0.26), 311 (0.24). ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si): δ_H, ppm -2.62, -1.15 (2H, 2s, pyrrole-N*H* × 2), 1.74 (3H, t, *J* = 8 Hz, CH_3-8[2]), 1.84 (3H, d, *J* = 8 Hz, CH_3-18[1]), 2.22–2.36, 2.58–2.84 (4H, m, CH_2-17[1], 17[2]), 3.42, 3.46, 3.59, 3.84 (12H, 4s, CH_3-2[1], 7[1], 12[1], 17[5]), 3.81 (2H, q, *J* = 8 Hz, CH_2-8[1]), 3.98–4.11 (2H, m, CH_2-13[1]), 4.44 (1H, dt, *J* = 8, 2 Hz, C*H*-17), 4.60 (1H, dq, *J* = 2, 8 Hz, C*H*-18), 4.78, 4.90 (2H, ddd, *J* = 3, 7, 16 Hz, CH_2-13[2]), 8.96 (1H, s, C*H*-20), 9.39, 10.47 (2H, 2s, C*H*-5, 10), 11.66 (1H, s, C*H*O-3[1]). HRMS (APCI): *m/z* 537.2874 (calcd. for $[M + H]^+$ 537.2866).

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Supporting information

Spectral data of by-products are given in the supplementary material. This material is available free of charge *via* the Internet at http://www.worldscinet.com/jpp/jpp.shtml.

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