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# Synthesis of a chlorophyll-*a* derivative fused with an additional *exo*-five-membered ring and its optical properties

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## ABSTRACT

A C20-free chlorophyll-*a* derivative with an additional *exo*-five-membered ring was successfully prepared using an ethylene linkage at the C3- and C5-positions. A bromination at the C20-position was requisite for the cyclization of a 1-hydroxyethyl or vinyl group at the C3-position of methyl bacteriopheophorbide-*d* or methyl pyropheophorbide-*a*, respectively. By comparing optical properties of the cyclized product with those of its 3-ethyl uncyclized analog in a diluted dichloromethane solution, it was shown that the cyclization shifted the $Q_x$ and $B_x$ absorption maxima to longer wavelengths and reduced the Stokes shift.

Plants convert sunlight into chemical energy through photosynthesis. During the initial stage of photosynthesis, chlorophylls (Chls) play important roles in efficient light-absorbing processes in light-harvesting antennas, rapid excitation energy-transferring pathways from the antennas to a reaction center, and successive charge-separating process in the reaction center [1]. Naturally occurring Chls are cyclic tetrapyrrole pigments with different $\pi$-conjugated systems and have various substituents at their peripheral positions (Fig. 1) [2], where the A-, B-, C-, and D-rings are connected via methine moieties. Chls-*a*/*b*/*d*/*f* are present in several oxygenic phototrophs including green plants and cyanobacteria, which possess a chlorin $\pi$-system containing a partially reduced D-ring (*trans*-17,18-dihydroporphyrin) [3]. Chls-*c*, found in chromophytes, have a fully $\pi$-conjugated porphyrin skeleton (17,18-didehydrochlorin) [4], whereas bacteriochlorophyll(BChl)s-*a*/*b*/*g*, found in purple, green, and heliobacteria, have a bacteriochlorin $\pi$-skeleton possessing partially reduced B- and D-rings (the C7–C8 single bonded form of a chlorin) [5]. All photosynthetically active (B)Chls bear an additional five-membered ring (E-ring) fused to the C-ring with an ethylene linkage at the C13- and C15-positions. The E-ring always has an oxo group substituted at the $C13^1$-position.

Some fossil porphyrins, observed in sediment and oil shales, have a different five- membered ring fused to the A-ring by ethylene linkage at the C3- and C5-positions (Fig. 2, left) [6]. This five-membered ring is named F-ring in this paper. To the best of our knowledge, naturally occurring chlorins possessing such two *exo*-five-membered rings have not been found yet, and only one semi-synthetic chlorin molecule with both E- and F-rings has been reported [7]. Methyl bacteriopheophorbide-*c* having 3-(1-hydroxyethyl) and 20-methyl groups (Fig. 1, middle; $M=H_2$, $R^2=R^7=R^{20}=R=CH_3$, $R^3=CH(OH)CH_3$, $R^8=CH_2CH_3$, and E=H) was refluxed in benzene containing *p*-toluenesulfonic acid (*p*-TSA) to afford a product with the F-ring (Fig. 2, right). Under the same conditions, methyl bacteriopheophorbide-*d* without the 20-methyl group did not result in the corresponding cyclized product [7], and any 20-unsubstituted chlorins with the F-ring have not been reported yet.

In this communication, a Chl-*a* derivative with a chlorin $\pi$-skeleton possessing the F-ring and lacking the C20-substituent was first prepared via acidic cyclization of methyl 20-bromobacteriopheophorbide-*d* and subsequent debromination. Its optical properties in dichloromethane were also discussed, comparing with those of its 3-ethyl analog lacking the F-ring.

Chl-*a* was extracted from cyanobacterial cells using methanol [step (i) in Scheme 1], and was demetalated, transesterified, and demethoxycarbonylated to convert into methyl pyropheophorbide-*a* (**1a**) [step (ii)] [8,9]. The 3-vinyl group in **1a** was hydrated to the 3-(1-hydroxyethyl) group in methyl bacteriopheophorbide-*d* (**2a**) [step (iii)] [9,10], followed by regioselective bromination at the C20-position to give methyl 20-bromobacteriopheophorbide-*d* (**2b**) [step (iv)] [11].

Compound **2b** was dissolved in a 1:2 mixture of benzene and toluene and heated at 80 °C for 10 min under nitrogen, then *p*-TSA monohydrate (30 eq.) was added [step (v) in Scheme 2].

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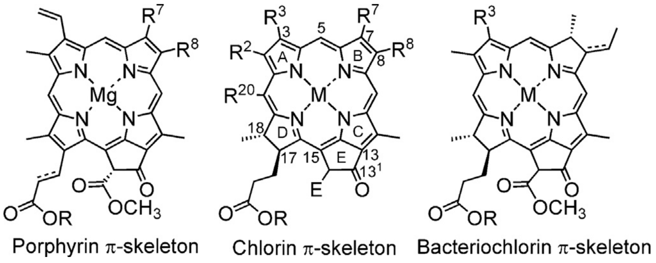


**Fig. 1.** Naturally occurring (B)Chls with different π-conjugated cyclic tetrapyrrole skeletons.

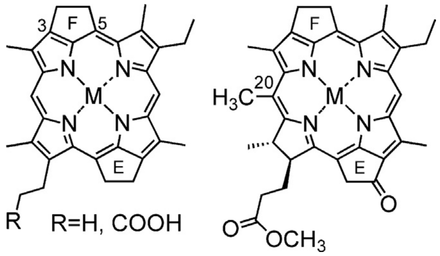
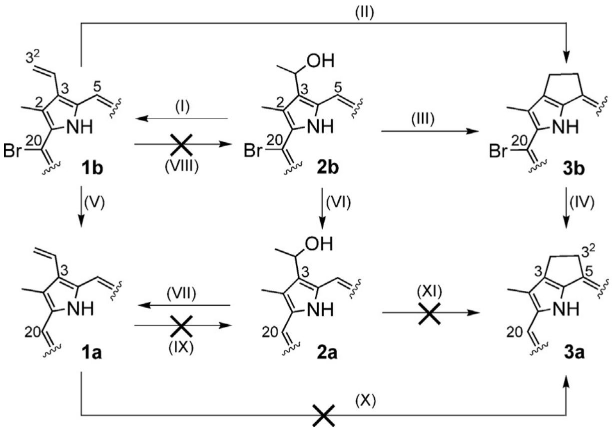


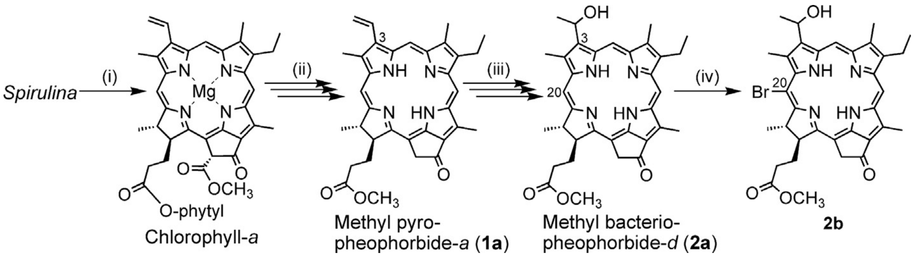
**Fig. 2.** Porphyrinoids possessing both the E- and F-rings: fossil porphyrins discovered from geological samples (left) and a synthetic chlorin prepared from bacteriochlorophyll-*c* (right).

After further refluxing for 17 h, the starting material disappeared, which was confirmed by TLC and MS spectral analyses. The reaction mixture was conventionally worked up and purified using silica gel column chromatography and recrystallization to give two products. The first eluted product was identified as **1a**, which was produced via dehydration of the C3-substituent and debromination at the C20-position of **2b** [12]. The second eluted product gave the same parent peak in the mass spectrum as in **1a**, but neither peaks of the vinyl group nor one of the three *meso*-proton signals were visible in the $^1$H NMR spectrum. Two methylene resonances newly appeared and were correlated with each other, and the *meso*-proton at the C5-position (not the C20-position) was missing from the 2D $^1$H NMR COSY/NOESY spectral analysis. Therefore, the other product was characterized as methyl 3-devinyl-3,5-ethylene-pyropheophorbide-*a* (**3a**), which was yielded by the ethylene linkage at the C3- and C5-positions and 20-debromination. The isolated yields of **1a** and **3a** were 6% and 34%, respectively. Notably, both products were 20-unsubstituted through acidic debromination at the C20-position as reported previously [12].

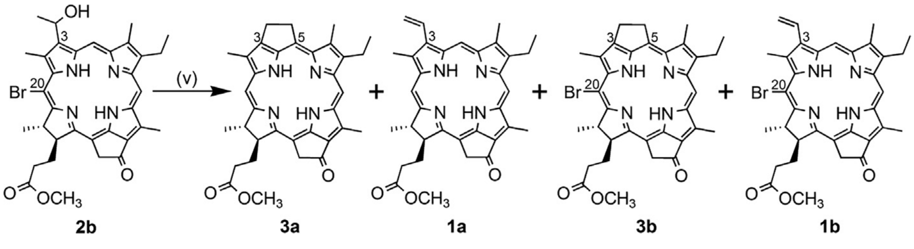
To investigate the cyclization pathway, all products from the reaction were analyzed. In the first step, methyl 20-bromopyropheophorbide-*a* (**1b**) was detected, which was prepared by dehydration at the 3-(1-hydroxyethyl) group of **2b** [step (I) in Scheme 3] [12]. Subsequently, methyl 20-bromo-3-devinyl-3,5-ethylene-pyropheophorbide-*a* (**3b**) was observed [step (II)] together with **1a** and **3a** as the above final products. Under the aforementioned acidic conditions, **1a** gave no product [steps (IX) and (X)], whereas **1b** gave **3a** as the cyclized and debrominated product [steps (II) and (IV)] and **1a** as the debrominated product [step (V)]. Considering that no hydration from **1b** to **2b** proceeded under the present reaction conditions [step (VIII)], **1b** was directly cyclized to **3b** [step (II)] [13]. However, the direct cyclization of **2b** to **3b** has not been ruled out yet [step (III)].



**Scheme 3.** Synthetic route of **2b** to **1a** and **3a**.



**Scheme 1.** Synthesis of methyl 20-bromobacteriopheophorbide-*d* (**2b**): (i) $CH_3OH$; (ii) (a) $H_2SO_4$, (b) $H_2SO_4/CH_3OH$, (c) collidine, reflux; (iii) (a) HBr/AcOH, (b) $H_2O$, (c) $CH_2N_2/Et_2O$; (iv) $C_5H_5NH^+Br_3^-/CH_2Cl_2$.



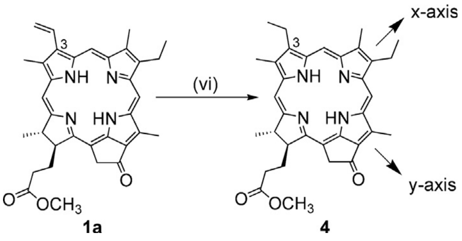
**Scheme 2.** Acidic dehydration, cyclization, and/or debromination of **2b**: (v) *p*-TSA·$H_2O$/benzene, toluene, 80 °C.

In the cyclization reaction route, the C$3^2$-cationic species was produced from the 3-vinyl group of **1b** (or the 3-(1-hydroxyethyl) group of **2b**) under the acidic conditions, and then the C$3^2$-cation electrophilically attacked the C5-atom, followed by deprotonation at the C5-position to produce the cyclized product **3b** (see Scheme S1 of SI). Finally, the protonation of **3b** at the C20-position and the removal of the bromonium cation produced **3a**. It is noted that the debromination in the last stage is important for the desired cyclization.

20-Unsubstituted **1a** and **2a** gave no cyclized products, whereas 20-brominated **1b** and **2b** did afford their cyclized products. Consequently, the 20-bromo atom was requisite for the present cyclization, which is consistent with the previous cyclization in the 20-methyl analog mentioned above [7]. The presence of the C20-substituents would direct the C3-substituents toward the C5-position through their steric interaction with the 2-methyl group [14,15]. The regioselective 20-bromination of 3-vinyl-chlorin **1a** to **1b** is problematic owing to the presence of the highly reactive 3-vinyl group [12,16]; however, **2a** bearing the less reactive 3-(1-hydroxyethyl) group was readily 20-brominated to **2b** [11,12]. Therefore, **3a** was synthesized as desired from **1a** via **2a**/**b**, whose total isolated yield was 27%.

To investigate the effect of ethylene linkage at the C3- and C5-positions of the F-ring on optical properties, methyl mesopyropheophorbide-*a* (**4**), lacking the F-ring by cleavage of the C$3^2$–C5 bond of **3a**, was prepared for the hydrogenation of the 3-vinyl group in **1a** as the reference compound [step (vi) in Scheme 4] [9,12].

The UV–visible absorption spectra of **3a** and **4** in dichloromethane are shown in Fig. 3A. Compound **3a** gave its $Q_y(0,0)/(0,1)$ and $Q_x(0,0)/(0,1)$ maxima at 655/600 and 551/517 nm, respectively, and showed slightly blue-shifted $Q_y$ bands and largely red-shifted $Q_x$ bands as compared with those of **4**. The main Soret (B) band of **3a** is more intense than that of **4**. The enhancement is ascribed to the large red-shift of the $B_x$ band and the smaller shift of the $B_y$ band by the cyclization of **3a** to **4**. This interpretation is supported by the difference absorption spectrum (Fig. S1).



**Scheme 4.** Synthesis of **4**: (vi) $H_2$, Pd–C/acetone.

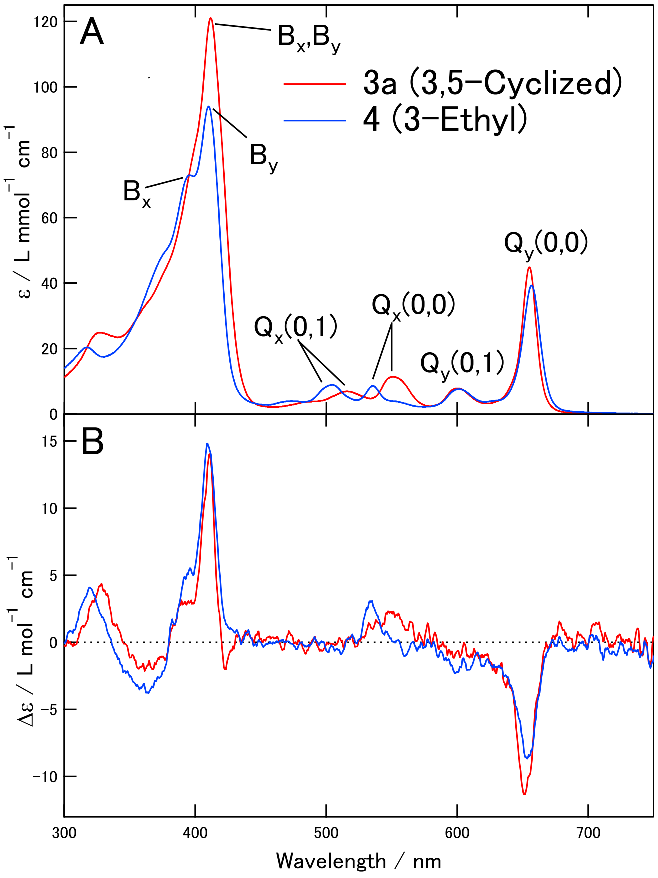


**Fig. 3.** UV–visible absorption (A) and CD spectra (B) of **3a** (red line) and **4** (blue line) in $CH_2Cl_2$.

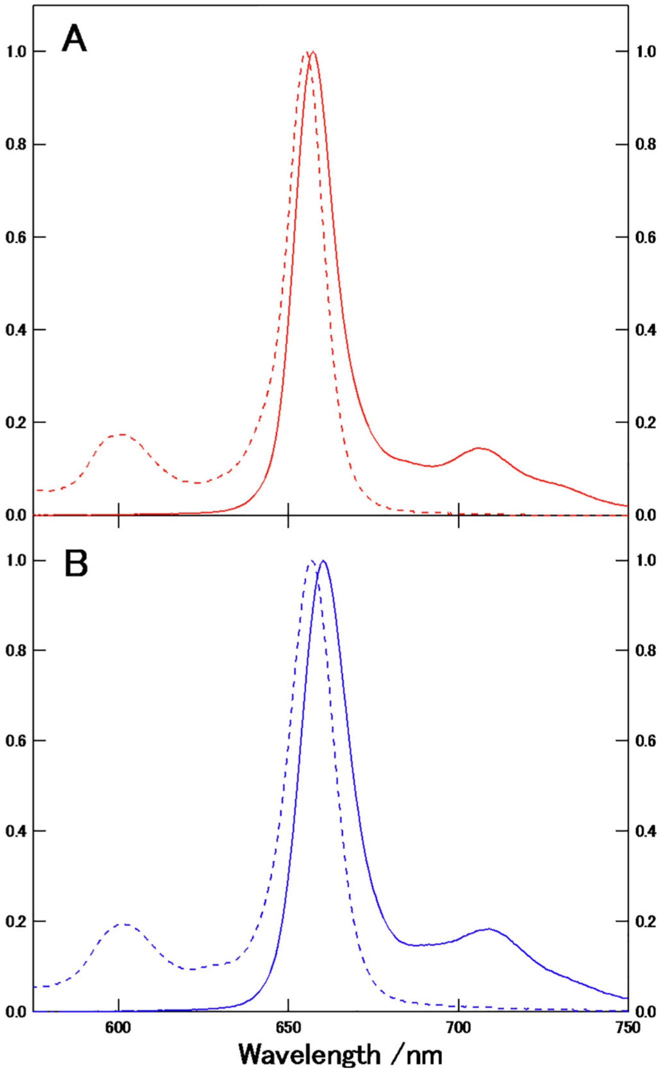


**Fig. 4.** Normalized visible absorption (dashed line) and fluorescence emission spectra (excited at Soret maxima, solid line) of **3a** (A) and **4** (B) in aerated $CH_2Cl_2$ at room temperature.

**Table 1**
Optical properties of **3a** and **4** in $CH_2Cl_2$.[a]

| Compound | $\lambda_{abs}$/nm | | | $\lambda_{em}$/nm | $\Delta$/cm$^{-1}$ | $\Phi_{em}$/% | $\lambda_{em}$/ns |
|---|---|---|---|---|---|---|---|
| | Soret $B_x/B_y$ | $Q_x$ (0,1)/(0,0) | $Q_y$ (0,1)/(0,0) | main/minor | | | |
| **3a** | 411.8[b] | 516.6/551.2 | 600.2/655.0 | 657.2/705.3 | 50 | 16 | 8.4 |
| **4** | 394.8/410.2 | 504.4/535.6 | 601.6/656.8 | 660.1/709.0 | 80 | 18 | 6.1 |

[a] $\lambda_{abs}$, absorption maximum; $\lambda_{em}$, fluorescence emission maximum (excited at Soret maximum); Δ, Stokes shift = $[1/\lambda_{abs}(Q_y(0,0)) - 1/\lambda_{em}(\text{main})] \times 10^7$; $\Phi_{em}$, fluorescence quantum yield (excited at Soret maxima); $\lambda_{em}$, fluorescence emission lifetime (excited at 403 nm).

[b] Not resolved.

From the CD spectra of **3a** and **4** (Fig. 3B), the cyclization moved the negative peak at the $Q_y(0,0)$ region to a slightly shorter wavelength and the positive peak at the $Q_x(0,0)$ region to a much longer wavelength, which are consistent with the aforementioned UV–visible absorption spectral shifts. Thus, we inferred that the electronic transition moment along the molecular x-axis (see Scheme 4) was considerably perturbed via the cyclization, resulting in significantly bathochromic shifts of $Q_x$ and $B_x$ bands.

Upon excitation at the Soret maxima, both **3a** and **4** strongly emitted red light in aerated dichloromethane at room temperature. Their fluorescence emission spectra were obtained with mirror images of the $Q_y$ bands (Fig. 4). Both emission spectra were similar, which was also comparable to their $Q_y$ absorption spectra. The Stokes shift of **3a** was smaller than that of **4** (see also Table 1). The suppression indicates that the molecular structural difference between the ground and excited states of **3a** is smaller than that of **4** because of a limited molecular distortion in the chlorin skeleton by the cyclization. Additionally, the cyclization slightly reduced the fluorescence quantum yield and increased the fluorescence lifetime (Table 1).

In summary, the hydration of **1a**, regioselective bromination at the C20-position, and heating in a mixture of benzene and toluene containing an excess amount of *p*-TSA successfully gave a C20-unsubstituted and 3,5-ethylene-linked Chl-*a* derivative **3a**, which is the first prepared chlorin possessing the F-ring and lacking any C20-substituent. The cyclization proceeded via attack of the $C3^2$-cationic species to the C5-position, for which the 20-bromo atom was critical. Cyclization by the linkage at the C3- and C5-positions, as in **4** to **3a**, red-shifted $Q_x$ and $B_x$ bands and decreased the Stokes shift. Synthetic cyclized chlorin **3a** may be useful as a standard compound to investigate the degradation process of natural Chls. Moreover, further investigation of various Chl-*a* derivatives with an *exo*-five-membered ring fused to the cyclic tetrapyrrole skeleton would enhance the development of Chl chemistry.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.07.025.

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