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# A Facile Synthetic Method for Conversion of Chlorophyll-*a* to Bacteriochlorophyll-*c*

Shin-ichi Sasaki,† Tadashi Mizoguchi, and Hitoshi Tamiaki*

*Department of Bioscience and Biotechnology, Faculty of Science and Engineering, Ritsumeikan University, Kusatsu, Shiga 525-8577, Japan*

*tamiaki@se.ritsumei.ac.jp*

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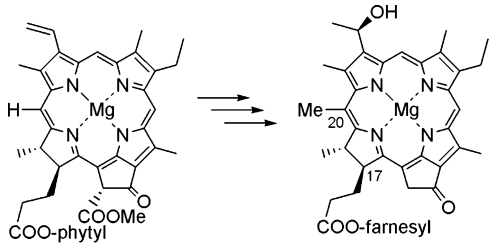
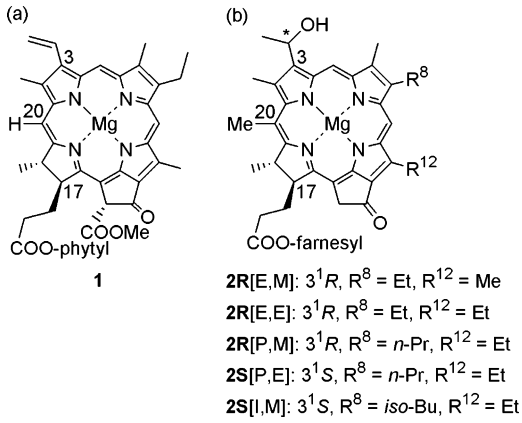



Chlorophyll-*a* Bacteriochlorophyll-*c*

A simple synthetic route for converting chlorophyll(Chl)-*a* to bacteriochlorophyll(BChl)-*c* is described. Methyl bacteriopheophorbide(MBPhe)-*d*, easily obtained from Chl-*a*, was selectively brominated at the 20-position with pyridinium tribromide, and the following Suzuki-coupling with methylboronic acid afforded ca. a 4:1 mixture of desired MBPhe-*c* (20-Me) and debrominated MBPhe-*d* (20-H) in quantitative yield. Separation of MBPhe-*c*, transesterification of the 17-propionate group (Me → farnesyl), and magnesium insertion successfully led to naturally occurring BChl-*c*.

Chlorophyll(Chl)-*a* (**1**, see Figure 1a) is a representative dye-pigment in oxygenic photosynthesis, while bacteriochlorophyll-(BChl)s-*c* (**2**, see Figure 1b) are found as main light-harvesting pigments in green photosynthetic bacteria.[1] Although the synthesis and self-assembling ability of BChl-*d* derivatives, 20-H analogues of BChl-*c*, have been extensively investigated, studies of BChl-*c* derivatives are relatively limited probably due to their lesser accessibility from natural sources.[2−4] Aiming at the introduction of 20-methyl group on an easily accessible chlorin precursor such as **3**,[5] we recently developed a direct methylation technique of Zn-**4** to Zn-**5** as shown in Scheme 1.[6] Since the enzymatic reaction has been performed in microgram scale due to the limited amount of the purified methyl transferase, His-tagged BchU,[6,7] we decided to investigate an alternative synthetic method of 20-methylation toward a Chl-*a* derivative to obtain one of the less abundant BChl-*c* homologues (**2R**[E,M]) in green sulfur bacteria, epimerically pure 3$^1$*R*-BChl-*c* possessing 8-ethyl and 12-methyl groups. Although the structural differences between **3** and **5** are only two functional groups at the 3- and 20-positions, traditional synthetic transformation required multiple steps with a low total yield due to the necessity of various protection/deprotection processes.[8] In light of recent progress in metal-catalyzed cross-coupling reactions,[9] here we report an improved synthetic route of converting natural Chl-*a* (**1**) to the corresponding BChl-*c* homologue (**2**).




**1**

**2R**[E,M]: 3$^1$*R*, R$^8$ = Et, R$^{12}$ = Me
**2R**[E,E]: 3$^1$*R*, R$^8$ = Et, R$^{12}$ = Et
**2R**[P,M]: 3$^1$*R*, R$^8$ = *n*-Pr, R$^{12}$ = Et
**2S**[P,E]: 3$^1$*S*, R$^8$ = *n*-Pr, R$^{12}$ = Et
**2S**[I,M]: 3$^1$*S*, R$^8$ = *iso*-Bu, R$^{12}$ = Et

**FIGURE 1.** Chemical structures of (a) chlorophyll-*a* (**1**) and (b) homologues of bacteriochlorophyll-*c* (**2**) isolated from *Chlorobium tepidum*.

As to the synthetic study of BChl-*c* derivatives, Smith et al. examined various routes for obtaining **5** from Chl-*a* derivatives including **3**.[8] Among several candidates for the 20-selective introduction of a functional group, they reported the following procedure as a successful method: (i) protection of the reactive

* To whom correspondence should be addressed. Fax: +81-77-561-2659, Tel: +81-77-566-1111.
† Present address: Nagahama Institute of Bio-Science and Technology, Nagahama, Shiga 526-0829, Japan.

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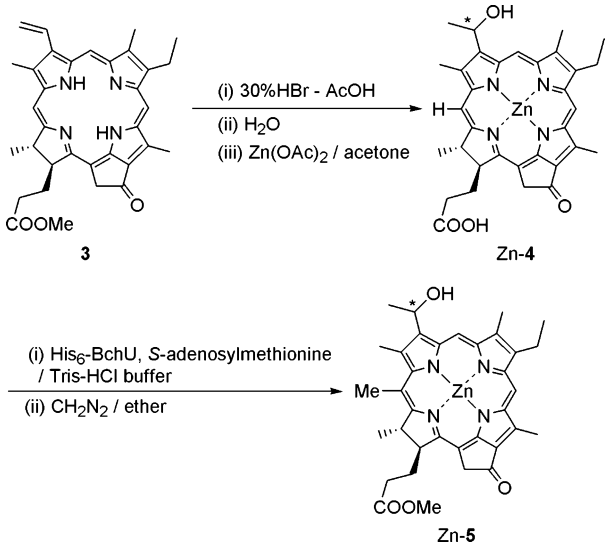
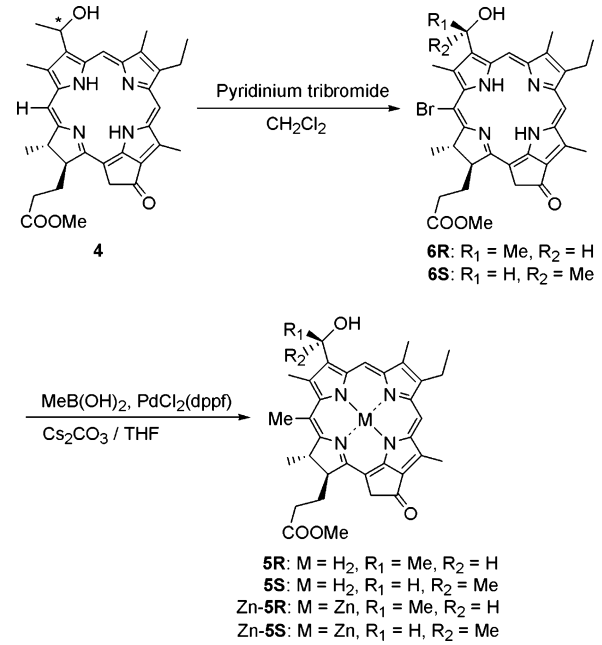
**SCHEME 1**




**SCHEME 2**




3-vinyl group as the 3-(2-chloroethyl) group, (ii) introduction of the methylthiomethyl group at the 20-position on the copper (II) complex, and (iii) reduction toward the 20-methyl group, demetalation, deprotection, and hydration of the 3-vinyl to 3-(1-hydroxyethyl) group.[8d] Since the reaction scheme was reported to be ca. 10 steps with 3% yield, we investigated cross-coupling methylations leading to a more direct synthetic route for converting 20-H to 20-Me group. In the first stage, selective 20-bromination of 3-(1-hydroxyethyl)chlorin **4**[3a,8b] was examined (Scheme 2) because it is necessary to avoid the bromination of the 3-vinyl group and also because the hydration of this group is a required step for the synthesis of BChl-*c*. Although the bromination of **4** using $HBr-H_2O_2$ in aqueous THF did not work well in contrast to the successful 20-bromination of 1-hydroxymethyl-chlorin,[10] it was found that treatment of **4** ($3^1R/S$ = 1/1) with pyridinium tribromide in $CH_2Cl_2$[11] proceeded smoothly to give **6** in 87% yield as a 1:1 $3^1R/S$ mixture. Among three kinds of cross-coupling methylations examined, Suzuki-coupling using $MeB(OH)_2$ as a methyl source and $PdCl_2$(dppf) as a catalyst in the presence of $Cs_2CO_3$ in THF gave a better result than the following two types of Pd-catalyzed conditions. Negishi-coupling using $ZnMe_2$ and $PdCl_2$(dppe) in 1,4-dioxane[12] gave a complex mixture containing unmethylated Zn-**6**. Methylation of **4** using $(AlMe_3)\cdot$DABCO, $Pd_2(dba)_3$, and phosphine ligand in THF[13] gave **5** up to 10% which can be ascribable to the presence of enolizable protons in **4**. Thus, reaction conditions of Suzuki-coupling were optimized, and the results are summarized in Table 1. Although the debromination **6** to **4** was inevitable,[14] this byproduct was less produced by increasing the ratio of $MeB(OH)_2$ to $PdCl_2$(dppf), and all the reactions were essentially quantitative to afford only a mixture of **4** and **5** after

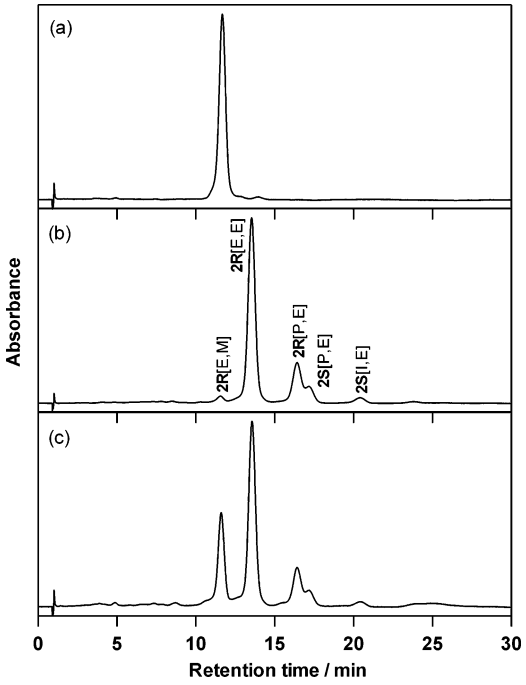



**FIGURE 2.** HPLC charts of (a) synthetic epimerically pure **2R**[E,M], (b) natural bacteriochlorophyll-*c* mixtures extracted from *Chlorobium tepidum*, and (c) cochromatography of synthetic **2R**[E,M] with natural extracts. Absorbance was monitored at 435 nm.

**TABLE 1. Palladium Catalyzed Cross-Coupling Methylation of 20-Bromo-chlorin 6**[a]

| entry | $MeB(OH)_3$ (equiv) | $PdCl_2$(dppf) (equiv) | ratio of products (**4**:**5**)[b] |
|---|---|---|---|
| 1 | 10 | 1 | 1:2.7 |
| 2 | 10 | 0.1 | 1:4.0 |
| 3 | 100 | 0.05 | 1:4.2 |
| 4 | 100 | 0.01 | c |

[a] All reactions were conducted in refluxed THF in the presence of $Cs_2CO_3$. [b] Determined by $^1H$ NMR. [c] Reaction did not proceed probably due to the deactivation of the small amount of catalyst.

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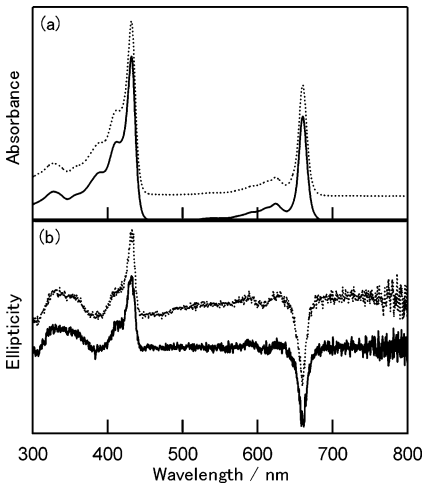
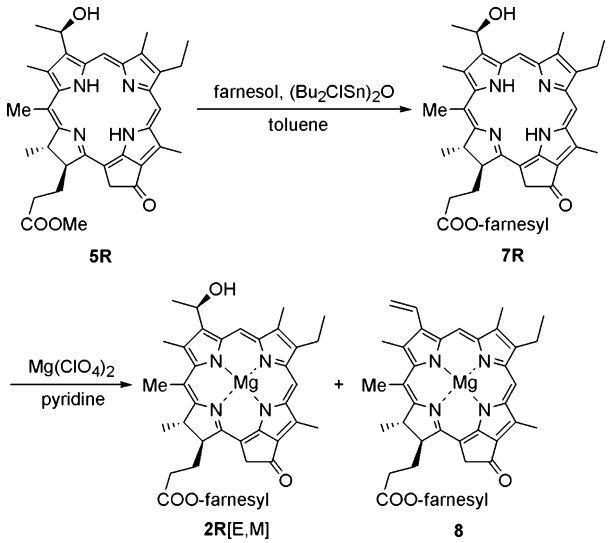



**FIGURE 3.** (a) Absorption and (b) CD spectra of synthetic epimerically pure **2R**[E,M] (solid line) and natural product (dotted line). Each sample was measured in $Et_2O$ at *ca.* $1 \times 10^{-5}$ M.

**SCHEME 3**




consuming **6**. Regarding the yield of **6** to **5** as 80% (entry 2), the present scheme from **3** to **5** could be much improved compared to the reported procedure,[8d] because reaction steps were shortened to one-third and the yield was increased 20-fold (from the previous 3% for ten steps to the present 86% × 87% × 80% = 60% for three steps).

To complete the synthesis of natural compound **2R**[E,M], $3^1$*R*-epimerically pure compound **6R** was subjected to the Suzuki-coupling, and the obtained 20-H/Me mixture was separated in zinc-metalated forms by reversed-phase HPLC.[15] After demetalation to **5R**, transesterification of the 17-propionate was performed with excess farnesol and $(Bu_2ClSn)_2O$[16] to give **7R**[17] in 88% yield (Scheme 3). Under the ester-exchange conditions, the secondary hydroxy group at the $3^1$-position did not react, presumably due to the steric hindrance.[18] Magnesium insertion was done by treating with excess $Mg(ClO_4)_2$ in pyridine, and undesired dehydration of the 3-(1-hydroxyethyl) group partially occurred to form magnesium 3-vinyl-chlorin **8**. The reaction mixture was purified by HPLC, and finally pure **2R**[E,M] was identified by comparison with the authentic sample from naturally occurring BChls-*c*. Extracts from a green sulfur bacteria, *Chlorobium tepidum*, contain several BChl-*c* homologues as represented in Figure 2b. Thus the absoption and CD spectra (Figure 3) as well as the HPLC peak (Figure 2c) of synthetically derived **2R**[E,M] are shown to be coincident with those of the natural component. It is noteworthy that no racemization occurred during the conversion from **6R** to **2R**[E,M].

In conclusion, we have developed a simple and efficient synthetic route for converting natural Chl-*a* (**1**) to BChl-*c* (**2**). Sequential procedures demonstrated in this study should be useful for the synthesis of natural BChl-*c* analogues possessing various 17-propionate terminals.[1b,19]

## Experimental Section

Proton peaks were assigned by $^1H-^1H$ COSY and NOESY spectra, and carbon peaks except for quaternary peaks were assigned by DEPT and $^{13}C-^1H$ COSY spectra. Methyl bacteriopyropheophorbide-*d* (**4**) was prepared from methyl pyropheophorbide-*a* (**3**)[5] by slight modifications of the previously reported procedure in 86% yield.[3a]

**Methyl 20-Bromobacteriopheophorbide-*d* (6).** To a solution of **4** ($3^1$*R/S* = 1:1, 101 mg, 0.18 mmol) in $CH_2Cl_2$ (50 mL) was added pyridinium tribromide (75 mg, 0.23 mmol), and the mixture was stirred for 30 min at room temperature. The mixture was poured into 2% aqueous HCl and extracted with $CH_2Cl_2$. The extract was washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The crude product was purified by silica gel chromatography ($Et_2O-CH_2Cl_2$, 1:9) to give **6** (100 mg, 87%) as a 1:1 $3^1$*R/S* mixture. The epimeric mixture was separated by HPLC (Cosmosil 5SL-II, 10 mm $\phi \times 250$ mm, acetone/1,2-dichloroethane 1:19, 2 mL/min, $t_R$ = 19 and 21 min for **6R** and **6S**, respectively). **6R**: mp 144−146 °C; vis ($CH_2Cl_2$) $\lambda_{max}$ 673 ($\epsilon$, 53800), 550 (15600), 518 (8840), 414 nm (114000); $^1H$ NMR ($CDCl_3$, 600 MHz) $\delta$ = 9.83 (1H, s, 5-H), 9.08 (1H, s, 10-H), 6.34 (1H, q, $J$ = 7 Hz, 3-CH), 4.92, 4.74 (each 1H, d, $J$ = 19 Hz, $13^1$-$CH_2$), 4.70 (1H, q, $J$ = 7 Hz, 18-H), 3.92 (1H, dd, $J$ = 3, 10 Hz, 17-H), 3.66 (3H, s, $COOCH_3$), 3.58 (2H, q, $J$ = 7 Hz, 8-$CH_2$), 3.57 (3H, s, 2-$CH_3$), 3.33 (3H, s, 12-$CH_3$), 3.20 (3H, s, 7-$CH_3$), 3.05 (1H, br, OH), 2.57, 2.20 (each 1H, m, $17^1$-$CH_2$), 2.09, 1.76 (each 1H, m, 17-$CH_2$), 2.07 (3H, d, $J$ = 7 Hz, $3^1$-$CH_3$), 1.63 (3H, d, $J$ = 7 Hz, $8^1$-$CH_3$), 1.35 (3H, t, $J$ = 7 Hz, 18-$CH_3$), 0.20, −2.39 (each 1H, s, NH); $^{13}C$ NMR ($CDCl_3$, 150 MHz) $\delta$ = 196.1 ($C13^1$), 173.4, 171.0, 160.6, 152.8, 151.7, 147.3, 144.2, 143.1, 139.1, 137.6, 137.1, 132.2, 132.2, 130.9, 129.3, 106.0, 94.6 (C1, 2, 3, 4, 6, 7, 8, 9, 11, 12, 13,

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14, 15, 16, 17,[3] 19, 20), 103.1 (C10), 99.1 (C5), 65.3 ($C3^1$), 51.7, 51.5, 51.5 (C17, 17,[5] 18), 48.1 ($C13^2$), 31.0 ($C17^2$), 29.7 ($C17^1$), 25.4 ($C3^2$), 20.6 ($C18^1$), 19.3 ($C8^1$), 17.3 (*C*2,[1] $8^2$),11.8 ($C12^1$), 11.2 ($C7^1$); HRMS (FAB) *m*/*z* 645.2058 ($MH^+$), calcd for $C_{34}H_{38}BrN_4O_4$ 645.2076. **6S**: mp 144−146 °C; vis ($CH_2Cl_2$) $\lambda_{max}$ 673 (relative intensity, 47%), 550 (14), 518 (8), 414 nm (100); $^1$H NMR ($CDCl_3$, 600 MHz) $\delta$ = 10.09 (1H, s, 5-H), 9.02 (1H, s, 10-H), 6.31 (1H, q, $J$ = 7 Hz, 3-CH), 4.80, 4.56 (each 1H, d, $J$ = 19 Hz, $13^1$-$CH_2$), 4.68 (1H, q, $J$ = 7 Hz, 18-H), 3.82 (1H, dd, $J$ = 3, 10 Hz, 17-H), 3.72 (3H, s, $COOCH_3$), 3.64 (2H, q, $J$ = 8 Hz, 8-$CH_2$), 3.56 (3H, s, 2-$CH_3$), 3.36 (1H, br, OH), 3.33 (3H, s, 12-$CH_3$), 3.26 (3H, s, 7-$CH_3$), 2.65, 2.35 (each 1H, m, $17^1$-$CH_2$), 2.14 (3H, d, $J$ = 7 Hz, $3^1$-$CH_3$), 2.10, 1.76 (each 1H, m, 17-$CH_2$), 1.64 (3H, d, $J$ = 8 Hz, $8^1$-$CH_3$), 1.27 (3H, t, $J$ = 7 Hz, 18-$CH_3$), −0.11, −2.55 (each 1H, s, NH); $^{13}$C NMR ($CDCl_3$, 150 MHz) $\delta$ = 196.3 ($C13^1$), 173.5, 170.9, 160.4, 152.8, 151.7, 147.0, 144.2, 143.7, 139.0, 137.5, 137.1, 132.1, 131.5, 130.6, 129.2, 105.7, 94.6 (C1, 2, 3, 4, 6, 7, 8, 9, 11, 12, 13, 14, 15, 16, 17,[3] 19, 20), 103.1 (C10), 100.1 (C5), 65.8 ($C3^1$), 51.8, 51.6, 51.3 (C17, 17,[5] 18), 48.1 ($C13^2$), 31.2 ($C17^2$), 30.0 ($C17^1$), 25.9 ($C3^2$), 20.6 ($C18^1$), 19.4 ($C8^1$), 17.3, 17.1 (*C*2,[1] $8^2$),-11.8 ($C12^1$), 11.3 ($C7^1$); HRMS (FAB) *m*/*z* 645.2088 ($MH^+$), calcd for $C_{34}H_{38}BrN_4O_4$ 645.2076.

**Farnesyl Bacteriopheophorbide-*c* (7R).** To a solution of **6R** (32 mg, 0.050 mmol) in THF (10 mL) were added methyl boronic acid (60 mg, 1.0 mmol), $Cs_2CO_3$ (163 mg, 0.50 mmol), and $PdCl_2$-(dppf) (8.2 mg, 0.010 mmol), and the mixture was refluxed for 2 h. Completion of the reaction was monitored by vis and MS spectra. The mixture was poured into 2% aqueous HCl and extracted with $CH_2Cl_2$. The extract was washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The crude product was purified by silica gel chromatography ($Et_2O$−$CH_2Cl_2$, 1:9 to MeOH−$CH_2$-$Cl_2$, 2:98) to give a free-base chlorin mixture (**5R:4R** = 3.8:1). The mixture was zinc-metalated, separated by HPLC (Cosmosil 5C18-AR-II, 10 mm $\phi$ × 250 mm, $H_2O$−MeOH 1:19, 2 mL/min, $t_R$ = 41 and 45 min for **4R** and **5R**, respectively), and then shaken with diluted aqueous HCl in $CH_2Cl_2$ for demetalation. The spectral data of the obtained **5R** was coincident with that of the reported data.[8b] To a solution of **5R** (7.0 mg, 0.012 mmol) in toluene (10 mL) was added farnesol (53 mg, 0.24 mmol) and $(Bu_2ClSn)_2O$ (2.0 mg, 3.6 $\mu$mol), and the mixture was refluxed for 3 h. The mixture was cooled to room temperature and subjected to silica gel chromatography ($Et_2O$−$CH_2Cl_2$, 0:10 to 1:9) to give **7R** (8.2 mg, 88%) as a black solid: mp 86−88 °C; vis ($CH_2Cl_2$) $\lambda_{max}$ 670 (relative intensity, 49%), 551 (15), 519 (10), 415 nm (100); $^1$H NMR ($CDCl_3$, 600 MHz) $\delta$ = 9.88 (1H, s, 5-H), 9.43 (1H, s, 10-H), 6.47 (1H, q, $J$ = 7 Hz, 3-CH), 5.22 (1H, t, $J$ = 7 Hz, $17^5$-CH), 5.20, 5.21 (each 1H, d, $J$ = 19 Hz, $13^1$-$CH_2$), 5.03 (2H, t, $J$ = 7 Hz, $17^9$-, $17^{13}$-CH), 4.57 (1H, q, $J$ = 7 Hz, 18-H), 4.51 (2H, m, $17^4$-$CH_2$), 4.16 (1H, dd, $J$ = 4, 9 Hz, 17-H), 3.86 (3H, s, 20-$CH_3$), 3.69 (2H, q, $J$ = 8 Hz, 8-$CH_2$), 3.63 (3H, s, 12-$CH_3$), 3.48 (3H, s, 2-$CH_3$), 3.27 (3H, s, 7-$CH_3$), 2.65 (1H, br-s, OH), 2.52, 2.17 (each 1H, m, 17-$CH_2$), 2.46, 2.14 (each 1H, m, $17^1$-$CH_2$), 2.12 (3H, d, $J$ = 7 Hz, $3^1$-$CH_3$), 2.04−1.90 (8H, m, $17^7$-, $17^8$-, $17^{11}$-, $17^{12}$-$CH_2$), 1.69 (3H, d, $J$ = 8 Hz, $8^1$-$CH_3$), 1.62 (6H, s, $17^7$-, *trans*-$17^{15}$-$CH_3$), 1.54 (3H, s, *cis*-$17^{15}$-$CH_3$), 1.52 (3H, s, $17^{11}$-$CH_3$), 1.47 (3H, t, $J$ = 7 Hz, 18-$CH_3$), 1.04, −1.91 (each 1H, s, NH); $^{13}$C NMR ($CDCl_3$, 150 MHz) $\delta$ = 196.4 ($C13^1$), 173.1, 172.4, 159.4, 152.8, 151.6, 147.6, 144.2, 142.6, 142.1, 140.5, 139.3, 136.7, 135.4, 132.7, 131.4, 131.3, 131.1, 128.5, 106.0, 105.7 (C1, 2, 3, 4, 6, 7, 8, 9, 11, 12, 13, 14, 15, 16, 17,[3] 19, 20, $C_F$3, 7, 11), 124.2 ($C_F$10), 123.5 ($C_F$6), 117.9 ($C_F$2), 102.3 (C10), 97.5 (C5), 65.7 ($C3^1$), 61.4 ($C_F$1), 51.6 (C17), 48.8 ($C13^2$), 48.4 (C18), 39.6 ($C_F$8), 39.4 ($C_F$4), 31.2 ($C17^2$), 30.1 ($C17^1$), 26.6 ($C_F$9), 26.1 ($C_F$5), 25.6 (C3,[2] $C_F$12), 21.0 ($C18^1$), 20.5 ($C20^1$), 19.5 ($C8^1$), 17.6 ($C8^2$), 17.4 ($C_F11^1$), 16.7 (*C*$2^1$), 16.4 ($C_F3^1$), 15.9 ($C_F7^1$), 12.1 ($C12^1$), 11.3 ($C7^1$); HRMS (FAB) *m*/*z* 771.4857 ($MH^+$), calcd for $C_{49}H_{63}N_4O_4$ 771.4849.

**Bacteriochlorophyll-*c* (2R[E,M]).** To a solution of **7R** (4.0 mg, 5.2 $\mu$mol) in pyridine (5 mL) was added $Mg(ClO_4)_2$ (223 mg, 1.0 mmol), and the mixture was stirred for 30 min at 80 °C. The mixture was concentrated, diluted with $CH_2Cl_2$, washed with phosphate buffer (pH = 6.8) and water, and concentrated. The residue was purified by HPLC (Cosmosil 5C18-AR-II, 10 mm $\phi$ × 250 mm, MeOH 2 mL/min) to give titled compound **2R**[E,M] ($t_R$ = 8 min), byproduct **8** ($t_R$ = 14 min), and unreacted **7R** ($t_R$ = 20 min). **2R**[E,M]: vis ($Et_2O$) $\lambda_{max}$ 660 (relative intensity, 63%), 624 (11), 431 nm (100); HRMS (FAB) *m*/*z* 793.4528 ($MH^+$), calcd for $C_{49}H_{61}MgN_4O_4$ 793.4543. **8**: vis ($Et_2O$) $\lambda_{max}$ 666 (relative intensity, 58%), 626 (11), 435 nm (100); HRMS (FAB) *m*/*z* 775.4430 ($MH^+$), calcd for $C_{49}H_{59}MgN_4O_3$ 775.4438.

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**Supporting Information Available:** $^1$H and $^{13}$C NMR spectra of **6R, 6S**, and **7** in $CDCl_3$ (Figures S1−S6). This material is available free of charge via the Internet at http://pubs.acs.org.

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