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Self-Aggregation of Synthetic Bacteriochlorophyll-*d* Analogues Possessing a B-Ring Reduced Chlorin π-System

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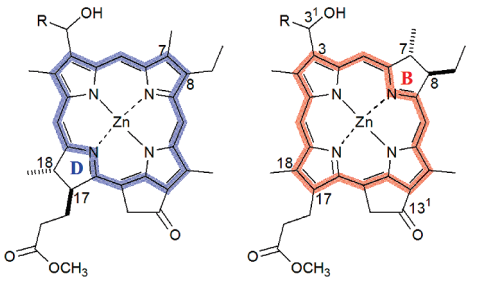

Zinc 3^1-hydroxy-13^1-oxo-chlorophyll derivatives **3** and **4** having a B-ring reduced chlorin π-system (C7═C8, C17═C18) were prepared as models of self-aggregative bacteriochlorophyll-*d*, which are regioisomers of **1** and **2** possessing a natural-type D-ring reduced chlorin π-system (C7═C8, C17−C18). 3^1-Epimerically pure forms of secondary alcohol **3** (3-CH(OH)CH_3) as well as primary alcohol **4** (3-CH_2OH) were effectively synthesized by modifying naturally available bacteriochlorophyll-*a*. Self-aggregation of **3** and **4** in an aqueous micellar solution was examined by UV−vis and CD spectroscopies and compared with that of their regioisomeric **1** and **2**.

A chlorin chromophore is characterized by the presence of one β,β'-dihydrogenated pyrrole in a fully π-conjugated cyclic tetrapyrrole (porphyrin), and widely found in photoactive chlorophyllous pigments, chlorophyll(Chl)s-*a*/*b*/*d* and bacteriochlorophyll(BChl)s-*c*/*d*/*e*.[1,2] All the naturally occurring Chls and BChls, except Chls-*c* possessing a porphyrin π-system,[1−3] have the same reduced pyrrole at the D-ring, where a propionate residue and a methyl group are attached in a trans-configuration at the 17- and 18-positions, respectively: 17*S*,18*S*-stereoisomer, see the molecular structure of BChl-*d* in Figure 1. This structural character is ascribable to their common biosynthetic precursors: enzymatic hydrogenation of (8-vinyl)protochlorophyllide-*a* occurs at the C17═C18 double bond on the D-ring to give (8-vinyl)-chlorophyllide-*a*.[4] Recently Pandey and his colleagues have reported synthesis of ring-B reduced chlorin **6** by selective oxidation of the D-ring in BChl-*a* derivative **5** (see Scheme 1).[5]

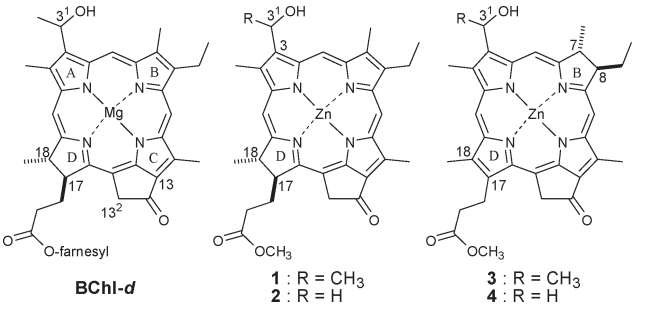

FIGURE 1. Molecular structures of natural BChl-*d* (left), its standard C17−C18 models **1**/**2** (center), and ring-B reduced C7−C8 analogues **3**/**4** (right).

Since such a new chlorin possessing a single bond between the C7 and C8 (C7−C8) is available by the specific oxidation of a bacteriochlorin moiety (C7−C8 and C17−C18), the chlorophyll chemistry has been expanded. We then designed self-aggregative compounds possessing the above new chlorin π-system and examined their *J*-aggregation, as shown in unique self-aggregation of BChl-*d* in natural photosynthesis.

BChl-*d* is biosynthetically produced in green photosynthetic bacteria, and self-assembled to form excitonically well-delocalized *J*-aggregates in their light-harvesting antenna systems, called chlorosomes.[2] The structural characters in BChl-*d* are the presence of the 3^1-OH and the absence of the 13^2-$COOCH_3$ which are useful for the chlorosomal self-aggregation: coordination of 3^1-OH with central Mg and cooperative hydrogen bonding of the 3^1-OH with less sterically hindered 13-C═O.[6,7] Zinc chlorins **1** and **2** (center of Figure 1) are synthetic models of BChl-*d*, and readily self-aggregated in nonpolar organic solvents, aqueous solutions, and their solid states.[6,8] Various spectroscopic studies indicated that supramolecular structures of both **1** and **2** self-aggregates were quite similar to those of natural $(BChl\text{-}d)_n$. Here we report that synthesis of ring-B reduced **3** and **4** (right of Figure 1) as models of BChl-*d*, which were regioisomers of ring-D reduced **1** and **2**, respectively, and their self-aggregation

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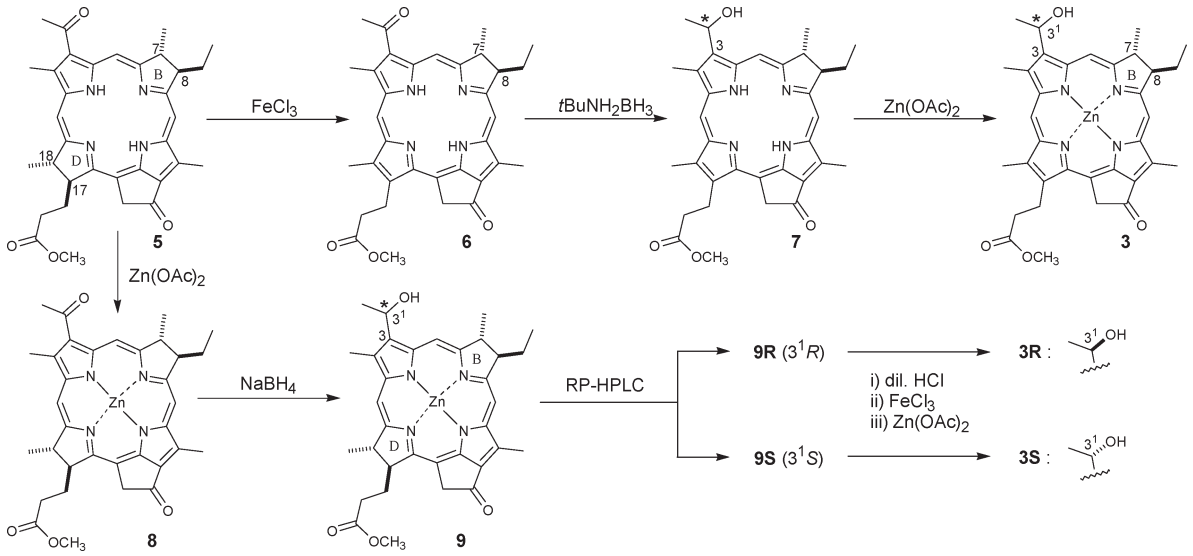
SCHEME 1. Synthesis of Secondary Alcohol 3 (a 3^1-epimeric 1:1 mixture), as Well as 3^1-Epimerically Pure 3*R* and 3*S*



behaviors in an aqueous micellar solution using nonionic surfactant, Triton X-100 (TX-100).

Ring-B reduced chlorin **6** was prepared from BChl-*a* derivative **5** according to the reported procedures,[5] then nonstereoselectively reduced by tBuNH$_2\cdot$BH$_3$ to give its corresponding 3-1-hydroxyethylated derivative **7** (91% yield, Scheme 1). Zinc metalation of **7** gave the desired zinc 3-(1-hydroxyethyl)-C7−C8-chlorin **3** as a 1:1 mixture of $3^1R/3^1S$-epimers (93%). To obtain epimerically pure (3^1R)-**3** (**3*R***) and (3^1S)-**3** (**3*S***), we tried to separate the 3^1-epimers by reverse-phase (RP) HPLC on an ODS column in a manner similar to the separation of 3^1-epimers of **1** (**1*R***/**1*S***) as reported previously.[9] The 3^1-epimeric separation of C7−C8-**3** was more difficult under both the analytical and preparative conditions than that of C17−C18-**1**, due to less dissolution of **3** in aqueous methanol as the eluted solvent. To increase the solubility, a small amount of pyridine was added to the elution, but RP-HPLC with methanol/water/pyridine = 80/19/1 still gave an incomplete separation of the 3^1-epimers (Figure S1A): the separation ratio (Rs) = 0.67.

Therefore, we chose an alternative route for preparing 3^1-epimerically pure **3*R*** and **3*S*** as follows (lower half of Scheme 1). As previously reported, zinc 3-(1-hydroxyethyl)-bacteriochlorin **9** (3^1R:3^1S = 1:1) was synthesized from **5**.[10] The 3^1-epimers were easily separated by RP-HPLC (Rs = 2.0, see Figure S1C, Supporting Information), affording the first elution (**9a**, 36.8 min) and the second (**9b**, 39.9 min). Each fraction was carefully demetalated under acidic conditions without any epimerization and successively dehydrogenated at C7H−C8H by DDQ (see Scheme S1, Supporting Information) to afford epimerically pure 3-(1-hydroxyethyl)-C17−C18-chlorins **11a** (modified from **9a**) and **11b** (from **9b**): **11** is the metal-free form of zinc complex **1**. The 3^1-stereochemistry of **11*R*** and **11*S*** had been unambiguously determined by X-ray crystallographic and chiral HPLC analyses:[11] the reported chiral normal phase (NP) HPLC gave the first eluted **11*S*** and the second **11*R***. Under the reported chiral NP-HPLC conditions, **11b** eluted first followed by **11a**, so that **9a** and **9b** were assigned as 9*R* and **9*S***, respectively. 3^1-Epimerically pure **9*R*** and 9*S* were demetalated, selectively dehydrogenated at C17H−C18H, and zinc inserted (steps i, ii, and iii in Scheme 1) to afford 3^1-epimerically pure **3*R*** and **3*S*** without any 3^1-epimerization (see the analytical RP-HPLC in Figure S2, Supporting Information). It is noteworthy that 3*R* was eluted first followed by **3*S*** under the present RP-HPLC conditions, using an ODS column, similar to the elution orders of **1** and **9** epimers (Figure S1, Supporting Information).

As the regioisomeric partner for primary alcohol **2**, we synthesized ring-B reduced model **4** by modifying **7** as follows (Scheme 2). Dehydration of the 1-(hydroxyethyl) group in **7** was carried out with treatment of mesyl chloride to afford 3-vinylchlorin **12** (73%). The resulting 3-vinyl group in **12** was oxidatively cleaved by treatment of OsO_4 and $NaIO_4$ to give 3-formylchlorin **13** (72%). After the selective reduction of the 3-formyl group in **13** giving **14** (90%), zinc insertion afforded the desired zinc 3-hydroxymethyl-C7−C8-chlorin **4** (94%).

UV−vis spectra of zinc chlorins **1**−**4** in THF (Figure 2A) showed that they were monomers in the Zn-coordinating solvent, as indicated by their sharp absorption bands as well as intense Soret and Qy bands at around 420 and 650 nm, respectively. Their energetically lowest Qy bands were in the order of **1** < **2** < **3** < **4** from blue to red (see Table S1, Supporting Information). The Qy maxima of primary alcohols **2** and **4** were located at longer wavelength than those of the corresponding secondary alcohols **1** and **3**, and also those of ring-B reduced **3** and **4** were at a longer wavelength than those of ring D-reduced **1** and **2**. Soret absorption maxima of **1**−**4** were situated at almost the same wavelength, but **3** and **4** had a shoulder at the red sides (see the red lines in Figure 2A). In THF, UV−vis spectra of 3^1-epimerically pure **3*R*** and **3*S*** were clearly the same, as observed in **1*R*** and **1*S*** (Table S1, Supporting Information).

(9) Tamiaki, H.; Takeuchi, S.; Tsudzuki, S.; Miyatake, T.; Tanikaga, R. *Tetrahedron* **1998**, *54*, 6699–6718.
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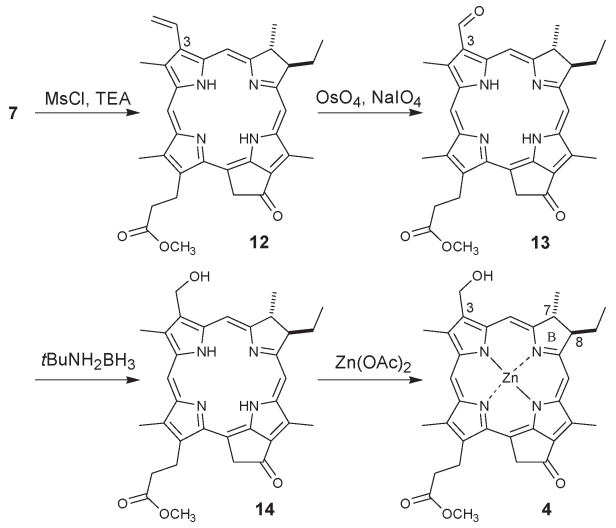
SCHEME 2. Synthesis of Primary Alcohol 4



CD spectra of monomeric zinc chlorins **1**−**4** (Figure 2B) were differentiated into two types as in ring-D reduced **1**/**2** (blue dotted/solid lines) and ring-B reduced **3**/**4** (red dotted/solid lines). Such mirror-like images indicated that π-conjugate systems of **1**/**2** and **3**/**4** were recognizable as pseudo-enantiomers.[5] CD spectra of 3^1-diastereomers **3*R*** and **3*S*** showed no difference from each other as expected.

In aq 0.025% v/v TX-100 solution, both the Soret and Qy bands of **1**−**4** were broadened and red-shifted (Figure 2C), indicating that chlorosome-like *J*-aggregation, through coordination and hydrogen bondings, occurred in the hydrophobic environments inside micelles. Self-aggregation behaviors of 3-hydroxymethyl-**2** (blue solid line) and 3-(1-hydroxyethyl)-**1** (blue dotted) have been well-characterized by various spectroscopic techniques: large red-shifts observed in **2** were attributed to the less steric hindrance around the 3^1-OH (Table S1, Supporting Information).[6,8,12] In contrast, Qy and Soret absorption bands of oligomers of zinc chlorins **3** (secondary) and **4** (primary) were nearly the same: no more steric effect was observed. CD spectra of all **1**−**4** (Figure 2D) showed intense signals around the newly appearing bands, which were significantly enlarged compared to those of monomers, indicating that there was strong excitonic coupling among the dyes by *J*-aggregation.

Self-aggregation behaviors of **3** and **4** possessing a new chlorin π-system (ring-B reduced) showed little difference as described above: primary **4** and secondary **3** had their oligomeric Qy maxima at nearly the same wavelengths. The minimal difference is explained by the 7,8-dihydro-form (ring-B reduced) and/or the 17,18-dehydro-form (ring-D oxidized). We have reported the corresponding zinc porphyrin (oxidized at both rings B and D) possessing a 3-CH(CH$_3$)OH (**15**, see Chart S1, Supporting Information) or a 3-CH$_2$OH group (3^1-demethyl-form of **15**), self-aggregated to give their oligomeric Qy maxima at nearly the same wavelength.[13] In the case of the bacteriochlorin π-system,

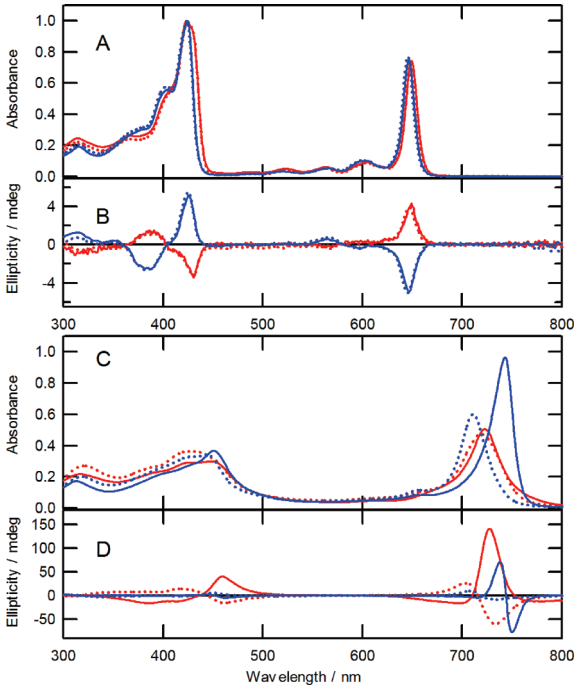


FIGURE 2. UV−vis (A/C) and CD spectra (B/D) of zinc chlorins **1**−**4** in THF (A/B) and aq 0.025% v/v TX-100 solution containing 1% v/v THF (C/D): blue dotted and solid lines, **1** and **2** respectively; red dotted and solid lines, **3** and **4**, respectively. Concentrations of the samples were approximately 10 μM.

secondary alcohol **9**[10] and its 3^1-demethyl form of **9**[14] showed a large difference in their oligomeric Qy bands: the latter primary alcohol showed a significant red-shift in the oligomeric Qy band. These results indicated that the 17,18-dehydrogenation as in **3**/**4** suppresses the steric effect around the 3^1-OH moiety on the chlorosomal *J*-aggregation, compared to the 7,8-hydrogenation.

Diastereomeric control by the 3^1-epimers in **1*R*** and **1*S*** has been well studied: the stereochemical difference at the 3^1-chiral center in **1** greatly influenced their self-aggregation behaviors (Figure S3, Supporting Information).[6,9,15] We examined self-aggregation of **3*R*** and **3*S*** and found a similar diastereomeric control by the 3^1-configuration (Figure S3, Supporting Information). A common feature in **1** and **3** was that the UV−vis spectrum of each 3^1R form in the self-aggregates was similar to that of the corresponding diastereomeric mixture (Figure 2).

Experimental Section

Methyl 17,18-Didehydro-7,8-*trans*-dihydrobacteriopheophorbide-*d* (7). To a CH_2Cl_2 (25 mL) solution of **6** (40.3 mg, 71 μmol) was added tBuNH$_2\cdot$BH$_3$ (101.5 mg, 1.17 mmol), then the mixture was stirred for 4 h. The reaction mixture was poured into aq 5% HCl, extracted with CH_2Cl_2, washed with water twice, dried over Na_2SO_4, and evaporated to dryness. The residue was purified with FCC (5% acetone−CH_2Cl_2) and recrystallized from CH_2Cl_2 and hexane to give pure **7** as a black solid (36.9 mg, 91%): VIS (CH_2Cl_2) 668 (rel intensity, 0.55), 612 (0.09), 539 (0.09), 513 (0.15), 411 nm (1.0); ^{1}H NMR ($CDCl_3$, $3^1R/S$ = 1:1) δ 9.02/8.98 (1H, s, 5-H), 8.90/89 (1H, s, 20-H), 8.61 (1H, s, 10-H),

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6.38 (1H, m, 3-CH), 4.93 (2H, m, 13^1-CH_2), 4.48 (1H, m, 7-H), 4.23 (1H, m, 8-H), 3.72 (3H, s, 17^2-CO_2CH_3), $3.53_4/53_1$ (3H, s, 12-CH_3), 3.46/45 (3H, s, 2-CH_3), 3.28 (2H, m, 17-CH_2), 2.89/88 (3H, s, 18-CH_3), 2.68 (2H, m, 17^1-CH_2), 2.47, 2.18 (each 1H, m, 8-CH_2), 2.17/16 (3H, d, J = 7 Hz, 3^1-CH_3), 1.95/94 (3H, d, J = 7 Hz, 7-CH_3), 1.20/19 (3H, t, J = 7 Hz, 8^1-CH_3), −0.68, −1.69 (each 1H, br s, NH × 2); ^{13}C NMR ($CDCl_3$, $3^1R/S$ = 1:1) δ 195.8/7, 173.2, 171.9, 166.0, 153.7, $145.8_0/7_5$, 144.9, 142.2, 139.7, 138.9/8, $138.4_1/3_6$, 138.2/1, 137.4, 135.0/134.9, 133.2/1, 121.2, 115.0/114.9 (C), $96.5_9/5_1$, 96.4, 94.0/93.9, 65.6/5, 55.7, 49.2 (CH), $48.3_3/2_8$, 35.6, 30.3, $21.5_4/4_9$ (CH_2), 51.7, 25.4/3, 23.2/1, 11.6, 11.3, 11.2/1, 10.6 (CH_3); HRMS (FAB) m/z 566.2900 (M^+), calcd for $C_{34}H_{38}N_4O_4$ 566.2893.

Zinc Methyl 17,18-Didehydro-7,8-*trans*-dihydrobacteriopheophorbide-*d* (3). To a CH_2Cl_2 (20 mL) solution of **7** (16.4 mg, 29 μmol) was added a methanol solution (2 mL) saturated with zinc acetate dehydrate, then the mixture was stirred for 4 h. The reaction mixture was poured into water, washed with aq 4% $NaHCO_3$ and water, dried over Na_2SO_4, and evaporated to dryness. The residue was recrystallized from CH_2Cl_2 and hexane to give pure **3** as a green solid (16.9 mg, 93%): VIS (THF) 648 (rel intensity, 0.74), 605 (0.09), 564 (0.05), 523 (0.04), 424 nm (1.0); ^{1}H NMR (3% pyridine-d_5−$CDCl_3$, $3^1R/S$ = 1:1) δ 9.05/04 (1H, s, 5-H), 8.82/80 (1H, s, 20-H), 8.54 (1H, s, 10-H), 6.31 (1H, m, 3-CH), 5.34 (2H, m, 13^1-CH_2), 4.52−4.33 (2H, m, 7-H, 3^1-OH), 4.19 (1H, m, 8-H), 3.72 (3H, s, 17^2-CO_2CH_3), 3.68 (2H, m, 17-CH_2), 3.57 (3H, s, 12-CH_3), $3.41_4/40_7$ (3H, s, 2-CH_3), 3.08/06 (3H, s, 18-CH_3), 2.84 (2H, m, 17^1-CH_2), 2.39, 2.10 (each 1H, m, 8-CH_2), 2.14/13 (3H, d, J = 7 Hz, 3^1-CH_3), 1.80/78 (3H, d, J = 7 Hz, 7-CH_3), 1.03/01 (3H, t, J = 7 Hz, 8^1-CH_3); ^{13}C NMR (3% pyridine-d_5−$CDCl_3$, $3^1R/S$ = 1:1) δ 196.6, 173.2, 168.8, 162.0, 156.3, 153.6, 152.3/2, 149.7, 148.0, 141.6, 140.7, 138.2, 137.7, 136.5, 135.8, 126.6, 115.9 (C), 98.0/97.9, 96.6, 93.9/8, 65.8/7, 55.5, $47.5_1/4_7$ (CH), 49.9, 36.6, 30.3, 22.4 (CH_2), 51.6, 25.8, $23.3_2/2_7$, 12.3, $11.6_2/5_9$, 11.0, 10.6 (CH_3); HRMS (FAB) m/z 628.2026 (M^+), calcd for $C_{34}H_{36}N_4O_4Zn$ 628.2028.

Methyl 17,18-Didehydro-7,8-*trans*-dihydropyropheophorbide-*a* (12). To a CH_2Cl_2 (5 mL) solution of **7** (31.1 mg, 55 μmol) was added MsCl (35.0 mg, 0.31 mmol), then the mixture was stirred. After 2 h of stirring, Et_3N (42.6 mg, 0.42 mmol) was added, then the mixture was stirred overnight. The reaction mixture was poured into water, extracted with CH_2Cl_2, washed with water twice, dried over Na_2SO_4, and evaporated to dryness. The residue was purified with FCC (5% Et_2O−CH_2Cl_2) and recrystallized from CH_2Cl_2 and hexane to give pure **12** as a black solid (21.9 mg, 73%): VIS (CH_2Cl_2) 675 (rel intensity, 0.52), 616 (0.09), 542 (0.9), 514 (0.15), 412 nm (1.0); ^{1}H NMR ($CDCl_3$) δ 9.07 (1H, s, 20-H), 8.67 (1H, s, 5-H), 8.62 (1H, s, 10-H), 7.92 (1H, dd, J = 12, 18 Hz, 3-CH), 6.23 (1H, d, J = 18 Hz, 3^1-CH *trans* to 3-CH), 6.13 (1H, d, J = 12 Hz, 3^1-CH *cis* to 3-CH), 5.28, 5.22 (each 1H, d, J = 19 Hz, 13^1-CH_2), 4.45 (1H, dq, J = 3, 7 Hz, 7-H), 4.22 (1H, m, 8-H), 3.74 (3H, s, 17^2-CO_2CH_3), 3.67 (2H, br t, J = 8 Hz, 17-CH_2), 3.53 (3H, s, 12-CH_3), 3.43 (3H, s, 2-CH_3), 3.09 (3H, s, 18-CH_3), 2.82 (2H, br t, J = 8 Hz, 17^1-CH_2), 2.47, 2.15 (each 1H, m, 8-CH_2), 1.91 (3H, d, J = 7 Hz, 7-CH_3), 1.14 (3H, t, J = 7 Hz, 8^1-CH_3), −0.52, −1.65 (each 1H, br s, NH × 2); ^{13}C NMR ($CDCl_3$) δ 196.0, 173.1, 172.1, 166.0, 154.3, 146.4, 145.1, 142.3, 140.3, 139.7, 139.2, 137.7, 135.1, 133.4, 132.9, 121.6, 115.4 (C), 129.1, 97.3, 96.6, 93.1, 55.5, 48.9 (CH), 122.0, 48.8, 36.0, 30.2, 22.3 (CH_2), 51.8, 23.2, 12.2, 11.6, 11.2, 10.9 (CH_3); MS (FAB) m/z 548 (M^+), calcd for $C_{34}H_{36}N_4O_3$ 548.

Methyl 17,18-Didehydro-7,8-*trans*-dihydropyropheophorbide-*d* (13). To a THF solution (30 mL) of **12** (29.6 mg, 54 μmol) was added OsO_4 (ca. 5 mg, ca. 20 μmol), then the mixture was stirred. After 5 min of stirring, a 10% v/v aq acetic acid solution (4 mL) of $NaIO_4$ (195 mg, 0.91 mmol) was added and the mixture was stirred for 7 h. The reaction mixture was poured into water, extracted with CH_2Cl_2, washed with aq 10% NaOAc, aq 4% $NaHCO_3$, and water, dried over Na_2SO_4, and evaporated to dryness. The residue was purified with FCC (3% acetone−CH_2Cl_2) and recrystallized from CH_2Cl_2 and hexane to give pure **13** as a black solid (21.4 mg, 72%): VIS (CH_2Cl_2) 699 (rel intensity, 0.62), 647 (0.11), 556 (0.15), 524 (0.12), 420 nm (1.0); ^{1}H NMR ($CDCl_3$) δ 11.33 (1H, s, 3-CHO), 9.56 (1H, s, 5-H), 9.24 (1H, s, 20-H), 8.67 (1H, s, 10-H), 5.20, 5.13 (each 1H, d, J = 19 Hz, 13^1-CH_2), 4.53 (1H, dq, J = 3, 7 Hz, 7-H), 4.26 (1H, m, 8-H), 3.73 (3H, s, 17^2-CO_2CH_3), 3.66 (3H, s, 2-CH_3), 3.60 (2H, m, 17-CH_2), 3.53 (3H, s, 12-CH_3), 3.08 (3H, s, 18-CH_3), 2.78 (2H, br t, J = 8 Hz, 17^1-CH_2), 2.50, 2.19 (each 1H, m, 8-CH_2), 1.96 (3H, d, J = 7 Hz, 7-CH_3), 1.16 (3H, t, J = 7 Hz, 8^1-CH_3), −0.80, −1.68 (each 1H, br s, NH × 2); ^{13}C NMR ($CDCl_3$) δ 195.3, 172.8, 171.2, 167.7, 151.2, 147.1, 146.0, 145.8, 145.1, 139.9, 139.6, 138.4, 135.0, 134.9, 127.4, 125.1, 115.2 (C), 187.7, 100.7, 96.4, 95.0, 56.0, 48.2 (CH), 48.7, 35.8, 30.0, 22.0 (CH_2), 51.8, 23.2, 11.7, 11.1, 11.0, 10.9 (CH_3); HRMS (FAB) m/z 550.2575 (M^+), calcd for $C_{33}H_{34}N_4O_4$ 550.2580.

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Supporting Information Available: Syntheses of **14** and **4**, RP-HPLC chromatograms of **1**, **3**, and **9**, preparation and stereochemical determination of **3R** and **3S**, UV−vis and CD spectra of **3R** and **3S**, data list for the absorption maxima of the monomeric and oligomeric forms of compounds **1**−**4**, and 1D/2D ^{1}H and 1D ^{13}C NMR spectra of synthetic compounds. This material is available free of charge via the Internet at http://pubs.acs.org.