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Synthesis of stereospecifically face-protected chlorophyll derivatives

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Abstract—A pair of zinc chlorins having a bridged moiety between the 3 and 13^2-positions on the front or back side of its π-face were synthesized, and their asymmetric coordination ability towards pyridine was determined in benzene.

Chlorophylls (Chls) are known to play important roles as main pigment molecules in the initial stage of photosynthesis.[1] In the crystal structures of pigment–protein complexes reported so far,[2] Chls are found to be fixed in proper locations by the fifth coordination of a protein residue (or others including water) to their central magnesium.[3] To investigate the coordination chemistry of Chls, we have recently developed zinc chlorins having a bridged moiety between 3- (or 8-) and 17-positions, which would restrict axial ligation to one side of the two macrocycle π-faces.[4] Since the linkage of the synthetic compounds was situated only above its front side,[5] an alternative route has been required to synthesize any strapped structure covering the back π-face. Here we report the synthesis of a pair of zinc chlorins having a bridge between the 3- and 13^2-positions on the front or back-face of chlorin macrocycle.

Two kinds of strapped zinc chlorins Zn-**1**/**2** and their acyclic reference compounds Zn-**3**/**4** were synthesized as shown in Scheme 1. Chlorin **5** possessing the 3-hydroxymethyl group was used as a starting material,[6] which was prepared by modifying a Chl-*a*/*a*′ mixture extracted and derived from the cyanobacterium, *Spirulina geitleri*. Esterification of the 3^1-hydroxy group with 5-hexenoic acid using EDC·HCl and DMAP,[7] and the following transesterification of the 13^2-methoxycarbonyl group with 8-nonen-1-ol by CMPI and DMAP in refluxing toluene[8,9] gave **6** having two vinyl groups at the terminals of the 3- and 13^2-substituents in 73% yield. To form a strapped bridge, ring-closing metathesis of **6** was performed using $Cl_2(PCy)_2Ru{=}CHPh$ as a catalyst[10] to give **7** in 77% yield.[11] Because the intramolecular cyclization formed an alkene linkage as its *cis*/*trans* mixture, the bridge of chlorin **7** was hydrogenated in the presence of PtO_2 to transform a dodecamethylene unit for simplicity. During these synthetic procedures, the ratio of 13^2S- (*a*′) and *R*-epimers (*a*) was retained constant at ca. 1:6. The free-base mixture 13^2S-**1** and 13^2R-**2** was separated by reversed-phase HPLC,[12] and zinc was inserted[13] to give desired Zn-**1**/**2**.[14] On the other hand, esterification of the 3^1-hydroxy group of **5** with acetic acid gave a mixture of **3** and **4**, which was zinc-metallated and separated by HPLC to give reference compounds Zn-**3**/**4**.

Figure 1a shows the absorption spectra of Zn-**1** and Zn-**2** in THF. The Q_y peak maximum (651.4 nm) of Zn-**1** (solid line) is slightly red-shifted compared to that (650.8 nm) of Zn-**2** (dotted line) by 0.6 nm (14 cm^{-1}). A similar difference between each diastereomer was also observed for free-base chlorins **1** and **2**. Because the small differences were almost the same as those in their reference compounds (Zn-)**3**/**4**, the bridging dodecamethylene unit of (Zn-)**1**/**2** caused a little strain on the chlorin macrocycle. The characteristics of the observed CD spectra of Zn-**1**/**2** in Figure 1b were quite similar to those of Zn-**3**/**4** or naturally occurring Chl-*a*′/*a* (see SI), indicating that the strapped compounds Zn-**1**/**2** still retain the structural and spectral characteristics of Chl-*a*′/*a*, and the bridging moiety is expected to just cover a π-face for single axial ligation. Their molecular modelling study by PM3/MM+ calculation[15] also supported the proposed structures of (Zn-)**1**/**2** in which the

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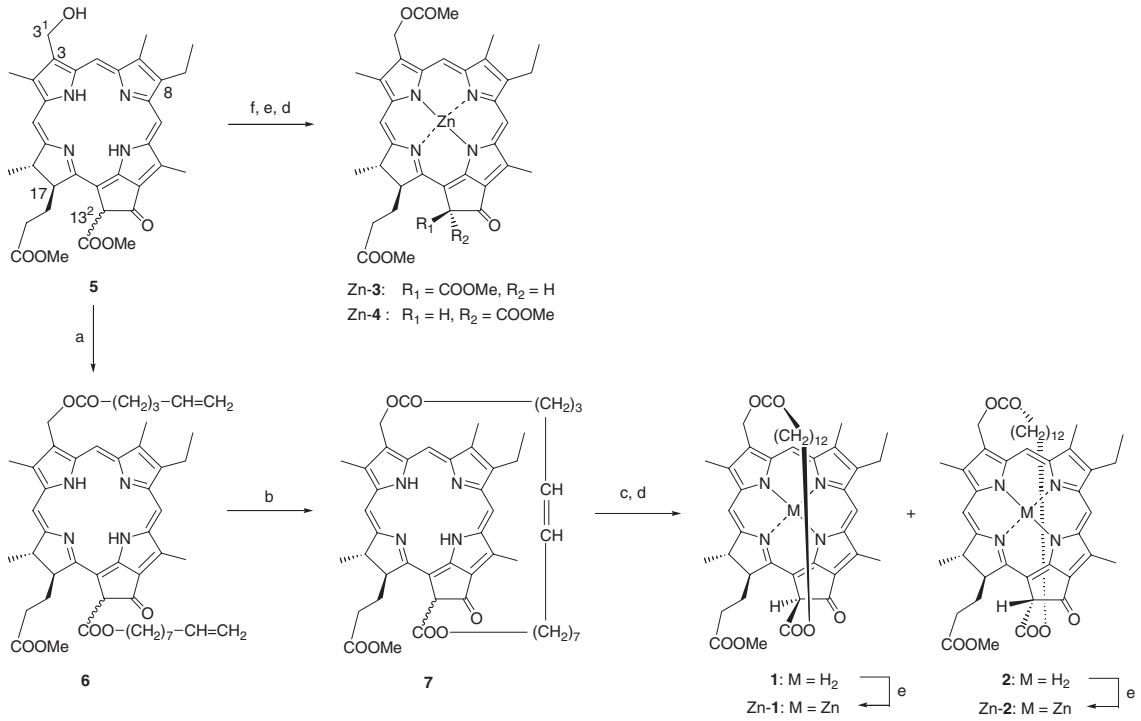

Scheme 1. Reagents and conditions: (a) (i) 5-hexenoic acid, EDC·HCl, DMAP, CH_2Cl_2, 77%, (ii) 8-nonen-1-ol, CMPI, DMAP, toluene, reflux, 96%, (b) $Cl_2(PCy)_2Ru{=}CHPh$, CH_2Cl_2, 77%, (c) $PtO_2{\cdot}2H_2O$, H_2, acetone, (d) HPLC separation, (e) $Zn(OAc)_2{\cdot}2H_2O$, CH_2Cl_2–MeOH, (f) CH_3COOH, EDC·HCl, DMAP, CH_2Cl_2, 67%.

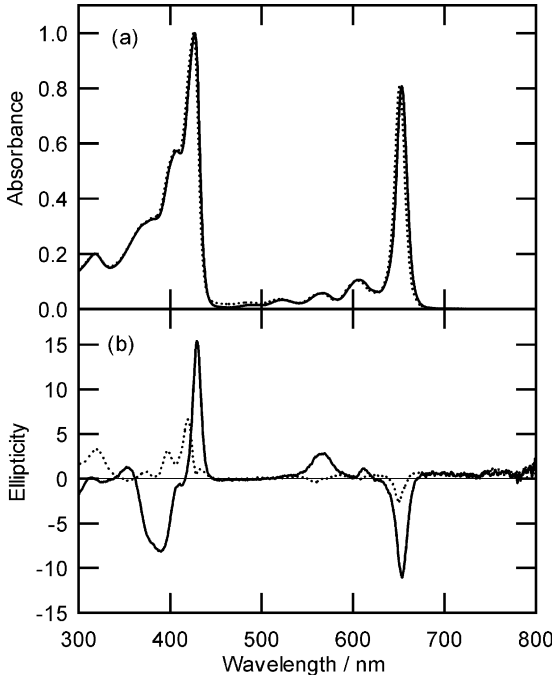

Figure 1. (a) Electronic absorption and (b) CD spectra of Zn-**1** (solid line) and Zn-**2** (dotted line) in THF.

front/back π-face was selectively protected by the dodecamethylene linkage and its movement between the front and back sides did not occur due to the steric restriction. Because the ^1H NMR spectra of (Zn-)**1**/**2** showed upfield-shifted signals of the linked methylene protons up to −2 ppm (see SI),[14] the bridge is considered to be located in a shielding region of a chlorin π-ring and thus would prevent coordination of an axial ligand from the protected face.

The 1:1 binding constants (K) of Zn-**1** and Zn-**2** with pyridine in benzene were determined by UV–vis titration method to be 2.5 and $2.6 \times 10^4\ M^{-1}$, respectively (see SI).[16] The closely similar K-values indicate little difference in asymmetric single and axial coordination of pyridine to Zn-**1** (from the back side) and Zn-**2** (from the front side). In acyclic compounds Zn-**3**/**4**, epimerization at the 13^2-position occurred under the same basic titration conditions.[9,17] This result shows that the dodecamethylene bridge fixed the stereochemistry at the 13^2-position and disturbed the epimerization.

In summary, we explored a synthetic route of face-protected chlorophyll derivatives that can control the direction of the fifth axial ligand. Little difference was observed in the formation of 1:1 complexes of Zn-**1**/**2** with pyridine from the back/front side. Synthesis of a series of strapped compounds and further investigation of face-selective coordination are in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.09.034. Supplementary data available via ScienceDirect: http://www.sciencedirect.com.

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11. Ten mole percent of the commercially available Grubbs' catalyst was added to a 2 mM solution of **6** in CH_2Cl_2, and the mixture was stirred for 4 h at room temperature.
12. Retention times of HPLC were 21 (minor) and 23.5 min (Cosmosil ODS: 5C18-ARII 10 mm $\phi \times 250$ mm, MeOH, 2 ml min^{-1}). The minor component showed NOE between 13^2-H and 17-H protons in the NMR spectrum, which was assigned to be **1** (13^2R form). The NMR spectrum of the major component, in contrast, showed NOE between 13^2-H and 17-CH_2 protons, and thus was assigned to be **2** (13^2S form), see SI.
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14. Spectral data. Zn-**1**: vis (benzene) λ_{max} 654 (ε, 73,000), 606 (10,200), 553 (5700), 512 (5300), 425 nm (85,000); ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 9.61$, 9.46, 8.47 (each 1H, s, 5-, 10-, 20-H), 6.45, 6.25 (each 1H, d, $J = 12$ Hz, 3-CH_2), 6.04 (1H, s, 13^2-H), 4.45 (1H, q, $J = 7$ Hz, 18-H), 4.24 (1H, m, 17-H), 3.77 (2H, q, $J = 8$ Hz, 8-CH_2), 3.67, 3.58, 3.39, 3.30 (s, each 3H, 2-, 7-, 12-CH_3, 17^2-$COOCH_3$), 1.71 (3H, t, $J = 8$ Hz, 8^1-CH_3), 1.63 (3H, d, $J = 8$ Hz, 18-CH_3), 4.12, 3.93, 2.59, 2.48, 2.32, 2.29, 2.26, 2.26, 2.06, 2.01, 0.83, 0.81, 0.30, 0.22, 0.10, 0.10, 0.08, −0.07, −0.30, −0.51, −0.88, −0.94, −1.22, −1.22, −1.46, −1.55, −1.72, −2.03 (each 1H, m, 17-CH_2CH_2, $(CH_2)_{12}$); ^{13}C NMR (150 MHz, $CDCl_3$) $\delta = 190.4$, 173.7, 173.2, 170.1, 169.2, 162.3, 157.1, 153.9, 151.5, 147.5, 147.4, 145.6, 144.4, 138.6, 136.5, 135.6, 134.0, 131.0, 107.2, 105.9, 100.1, 93.4, 66.7, 66.4, 56.9, 51.6, 50.7, 49.5, 34.6, 31.1, 30.3, 29.7, 28.9, 28.25, 28.17, 28.0, 27.75, 27.65, 27.1, 26.0, 22.8, 19.4, 17.5, 14.1, 12.8, 11.4, 10.9; MS (FAB) m/z 852 (M^+). Zn-**2**: vis (benzene) λ_{max} 653 (ε, 70,500), 605 (9300), 560 (4400), 515 (3800), 425 nm (83,000); ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 9.61$, 9.44, 8.46 (each 1H, s, 5-, 10-, 20-H), 6.45, 6.23 (each 1H, d, $J = 12$ Hz, 3-CH_2), 5.97 (1H, s, 13^2-H), 4.42 (1H, dq, $J = 2$, 7 Hz, 18-H), 4.26 (1H, m, 17-H), 3.77 (2H, q, $J = 8$ Hz, 8-CH_2), 3.64, 3.39, 3.30, 3.28 (each 3H, s, 2-, 7-, 12-CH_3, 17^2-$COOCH_3$), 1.78 (3H, d, $J = 7$ Hz, 18-CH_3), 1.72 (3H, t, $J = 8$ Hz, 8^1-CH_3), 4.24, 3.84, 2.53, 2.49, 2.45, 2.45, 2.29, 2.16, 1.60, 1.46, 1.38, 1.30, 1.11, 1.11, 1.08, 0.88, 0.88, 0.83, −0.32, −0.44, −1.05, −1.13, −1.20, −1.20, −1.40, −1.47, −1.57, −1.87 (each 1H, m, 17-CH_2CH_2, $(CH_2)_{12}$); ^{13}C NMR (150 MHz, $CDCl_3$) $\delta = 190.8$, 173.7, 173.6, 168.9, 168.8, 161.5, 156.4, 153.7, 151.6, 147.6, 147.3, 145.6, 144.3, 138.9, 136.2, 135.2, 134.0, 130.8, 107.0, 105.1, 99.7, 92.7, 65.5, 65.3, 56.7, 51.6, 49.5, 48.6, 34.7, 30.7, 29.7, 29.5, 28.4, 28.0, 27.8, 27.6, 27.5, 27.2, 25.6, 25.4, 23.4, 19.5, 17.5, 14.1, 12.6, 11.4, 10.9; MS (FAB) m/z 852 (M^+).
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