Pergamon

Tetrahedron, Vol. 53, No. 31, pp. 10677-10688, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00699-6

Synthesis of Chlorophyll-*a* Homologs by Wittig and Knoevenagel Reactions with Methyl Pyropheophorbide-*d*

Hitoshi Tamiaki* and Mitsuru Kouraba

Department of Bioscience and Biotechnology, Faculty of Science and Engineering, Ritsumeikan University, Kusatsu, Shiga 525-77, Japan

Abstract: The formyl group at the 3-position of methyl pyropheophorbide-*d* reacted with phosphorous ylides and activated methylene compounds to give efficiently the corresponding 3-(2-substituted ethenyl)chlorins compounds as a product of Wittig and Knoevenagel reactions. The *trans*-isomers of the synthetic chlorins, methyl 3^2-substituted pyropheophorbide-*a* had visible bands absorbing longer wavelengths than the *cis*-isomers and the 3^2-unsubstituted chlorin, methyl pyropheophorbide-*a*. $3^2,3^2$-Disubstitution strongly affected the absorption bands compared with the bands of the 3^2-monosubstituted chlorins. The absorption, fluorescence and circular dichroism spectra were dependent upon the 3-substituents conjugated with the chlorin chromophore. © 1997 Elsevier Science Ltd.

INTRODUCTION

Aldehydes are highly reactive and the formyl group reacts with several reagents to give a variety of compounds. Reaction of formylchlorins including chlorophylls-*b* and *d* (see Fig. 1) which are antenna pigments of photosynthesis[1] has attracted much synthetic[2] and biological interest.[3] The reactivity of the 3-formyl group conjugated with chlorin chromophore in methyl pyropheophorbide-*d* (**1**, metal-free / 13^2-demethoxycarbonyl / 17^2-methyl ester form of chlorophyll-*d*) has already been investigated: reduction to alcohol,[4–8] reductive alkylation,[8] reductive amination,[9] oxidation to carboxylic acid,[7] Grignard reaction,[10] acetal formation,[11] and Wittig reaction.[4] Chlorins directly linked with a substituted ethenyl group at the 3-position are interesting in comparison with naturally occurring chlorophyll-*a* possessing the 3-vinyl (unsubstituted ethenyl) group, but few reports[4,12,13] are available on synthesis of such compounds to our knowledge. Moreover, these compounds should provide good models for intramolecular electron/energy transfer system at the initial stage of photosynthesis because the ethenyl group can determine the distance and geometry between the donor and acceptor moieties.[14]

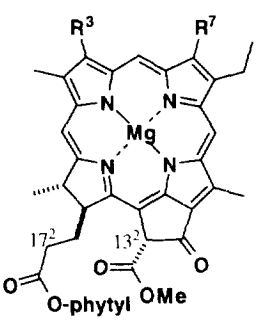
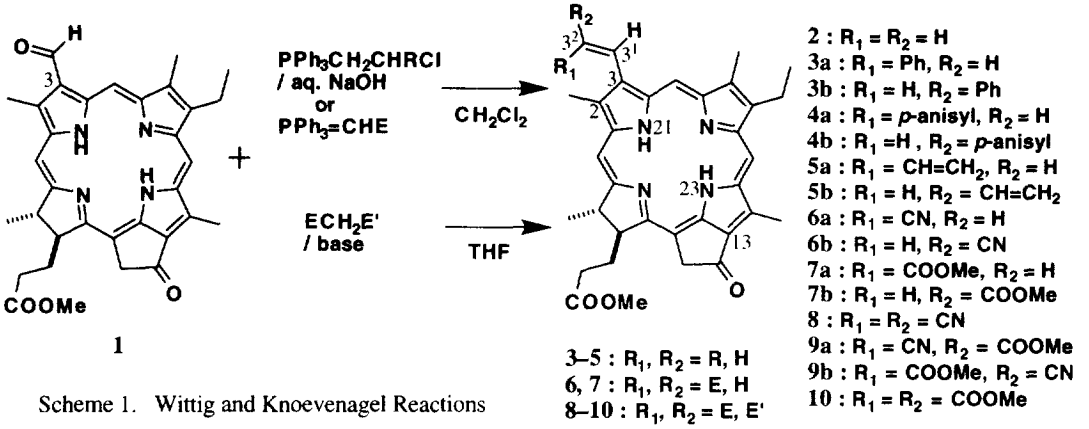


Fig. 1
Chlorophyll-*a* :
R^3 = CH=CH_2, R^7 = Me
Chlorophyll-*b* :
R^3 = CH=CH_2, R^7 = CHO
Chlorophyll-*d* :
R^3 = CHO, R^7 = Me



Scheme 1. Wittig and Knoevenagel Reactions

Here we report on the synthesis of methyl pyropheophorbide-*a* derivatives **3-10** possessing -CH=CR$_1$R$_2$ group at the 3-position by Wittig and Knoevenagel reactions of **1** (see Scheme 1), and the optical properties (visible, fluorescence and circular dichroism spectra) of the synthetic compounds which were affected by the 3^2-substituents (R$_1$ and R$_2$).

RESULTS AND DISCUSSION

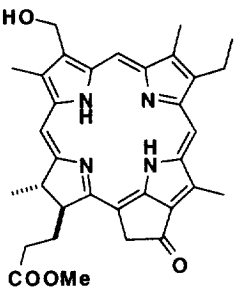
Wittig Reaction

The reaction of methyl pyropheophorbide-*d* (**1**) with reactive and unstable Wittig reagents including PPh$_3$=CH$_2$ was performed. After usual preparation of PPh$_3$=CH$_2$ from PPh$_3$CH$_3$I and LiOMe in dry THF, aldehyde **1** was added to give almost recovered **1** and trace of the desired methyl pyropheophorbide-*a* (**2**) as an isolable product. The formyl group of **1** was less reactive than benzaldehyde and the reactive Wittig reagent must be predominantly decomposed without the reaction with **1**. Fischer *et al.* also reported that Wittig reaction of **1** with excess PPh$_3$=CH$_2$ afforded **2** in only 16% yield.[6]

Therefore, the reaction of aldehyde **1** with *meta*-stable Wittig reagents was examined. Johnson *et al.* reported that Wittig reagent prepared from methyl 3-devinyl-3-[(triphenylphosphonium)methyl]pyropheophorbide-*a* reacted with **1** under dry conditions to give the corresponding vinyl compounds in 12% yield.[4] The aryl-substituted Wittig reagents PPh$_3$=CHAr are fairly stable and are known to be useful for preparation of β-ArCH=CH$_2$-substituted porphyrins by Wittig reaction with β-formylporphyrin.[15] Methyl pyropheophorbide-*d* (**1**) in dichloromethane reacted with PPh$_3$CH$_2$PhCl in the presence of aqueous NaOH solution. Wittig reaction of **1** with *in situ* prepared PPh$_3$=CHPh at room temperature for 30 min gave 3-(2-phenylethenyl)chlorin **3** in 84% yield and all the aldehyde **1** was consumed. Product **3** was a mixture of *cis*- (**3a**, 22%) and *trans*-isomers (**3b**, 62%), which were easily separated by recrystallization from dichloromethane and hexane. The *trans*-rich selectivity is consistent with the results of Wittig reaction of other aldehydes with PPh$_3$=CHPh: *cis* / *trans* = 3 / 7 in the preparation of stilbene. The stereo-structures were determined by ^{1}H NMR spectroscopy (1D and COSY/NOESY 2D spectra). The major isomer has the coupling constant $^3J(3^1\text{H-}3^2\text{H})$ = 17 Hz and the *J* of the minor isomer is 12 Hz, indicating that the major product is *trans*-isomer and the minor has *cis*-configuration.

Moreover, the chemical shifts δ of 2-methyl protons in *cis*- and *trans*-isomers were different at 2.99 and 3.48 ppm, respectively. The high-field shift (-0.49 ppm in *cis* → *trans*) was ascribed to the ring current effect of the 3^2-phenyl group. Molecular modeling by MM+/PM3 calculation[16] showed that the 2-methyl group was located on the 3^2-phenyl π-ring in the *cis*-**3a** and was far from the 3^2-phenyl group in the *trans*-**3b**.

Under similar conditions, Wittig reaction of aldehyde **1** with *in situ* produced PPh_3=CH(*p*-anisyl) for 40 min afforded 3-CH=CH(*p*-anisyl) compound **4** in 81% yield without recovery of **1**. The product was a mixture of *cis* / *trans* isomers (= 1 / 2) which were also separated by recrystallization. The Wittig reagent PPh_3=CHCH=CH_2 prepared from PPh_3CH_2CH=CH_2Cl was less reactive with **1**, and 2-h reaction at room temperature gave 3-dienyl products **5** (44%) and **1** (42%). The separation of **5** from **1** in the reaction mixture by silica gel column chromatography and/or recrystallization was very difficult, probably because these compounds have similar polarities and crystal structures. The reaction mixture was reduced by *tert*-butylamine borane complex which was effective for selective reduction of the 3-formyl group.[8] After reduction, intact **5** (product of Wittig reaction) was easily separated from higher polar 3-hydroxymethyl compound **11** produced by selective reduction of the 3-formyl group of **1** by column chromatography. The dienyl product was also a mixture of *cis* / *trans* isomers (= 4 / 7). The isomers could not be separated by recrystallization but were separated by reverse-phase high performance liquid chromatography (HPLC). Under the same conditions, no Wittig reactions of **1** with PPh_3=CH(*p*-nitrophenyl) (from PPh_3CH_2(*p*-nitrophenyl)Br) and PPh_3=CHC≡CH (from PPh_3CH_2C≡CHBr) occurred.



11

Then, the reaction of aldehyde **1** with stable and less reactive Wittig reagents PPh_3=CHE (E = electron-withdrawing group) was employed. The Wittig reagent PPh_3=CHCN was prepared by treatment of PPh_3CH_2CNCl with an aqueous NaOH solution, and was isolated as a white solid. Aldehyde **1** reacted with PPh_3=CHCN in dichloromethane. After reflux for 8 h, 4% **1** remained and 3-CH=CHCN compound **6** was produced in 99% yield based on the consumed **1**. Product **6** was a mixture of *cis* / *trans* isomers (= 17 / 83). Under similar conditions (6-h reflux), the Wittig reaction of **1** with PPh_3=CHCOOMe afforded a single isomer of 3-CH=CHCOOMe compound **7** (85%) without any recovery of **1**. The sole isomer was determined to have *trans*-configuration by ^{1}H NMR spectra: $^3J(3^1H\text{-}3^2H)$ = 16 Hz. Wittig reactions of benzaldehyde with PPh_3=CHCN and PPh_3=CHCOOMe in reflux of dichloromethane gave cinnamonitrile and methyl cinnamate as an isolated product and the *cis* / *trans* ratios were 21 / 79 and 2 / 98, respectively. These results are consistent with *cis*-**6a** / *trans*-**6b** = 17 / 83 and *cis*-**7a** / *trans*-**7b** = 0 / 100. Reaction of **1** with a stable Wittig reagent, PPh_3=CHCOPh gave no vinyl compound even in prolonged reflux of the dichloromethane solution.

Knoevenagel Reaction

It has been reported that some formylchlorins and formylporphyrins reacted with activated methylene compounds (ECH_2E') by the action of a base to give chlorins and porphyrins possessing -CH=CEE', respectively.[17] Knoevenagel reaction seems useful for preparation of chlorins with a substituted vinyl group at the 3-position from methyl pyropheophorbide-*d* (**1**) as well as the Wittig reaction described above. The reaction of aldehyde **1** with ECH_2E' was thus examined. A tetrahydrofuran (THF) solution of **1**, malononitrile and triethylamine was stirred at room temperature. After the disappearance of **1** (4 h), the reaction mixture was

purified by silica gel column chromatography to give methyl 3^2,3^2-dicyanopyropheophorbide-*a* (**8**) in 76% yield. Knoevenagel reaction of **1** with dimethyl malonate in the presence of diethylamine (2-day reflux in THF) gave 3-vinyl compound **10** (29%) as a product and 3-formyl compound **1** (44%) as a recovered starting material. The longer reaction time (4 → 48 h) at higher temperature (20 → 66 °C) and lower conversion (100 → 56%) in the Knoevenagel reaction of dimethyl malonate compared with malononitrile are ascribed to the fact that dimethyl malonate is less reactive with formyl compounds than malononitrile because a methoxycarbonyl group is less electron-withdrawing than a cyano group, and also that dimethyl malonate is more sterically crowded around the reactive methylene group than malononitrile.

Methyl cyanoacetate, in the middle of malononitrile and dimethyl malonate reacted with formylchlorin **1** in the presence of triethylamine in THF. After 12 h stirring at room temperature, **1** was completely consumed and 78% 3-vinyl compound **9** was obtained. The reactivity of methyl cyanoacetate was intermediate between malononitrile and dimethyl malonate as expected. The product is an unsymmetrical trisubstituted ethylene and can take two conformers. Chromatography (TLC and HPLC) and ^{1}H NMR spectra of the product showed a single conformer. The structure of **9** was determined by comparison with ^{1}H NMR chemical shifts δ at the 3^1-position of similar compounds. The δ(3^1-H)s of *trans*-CH=CHCN **6b** and CH=C(CN)$_2$ **8** were 8.85 and 9.40 ppm, respectively, and substitution of CN group at the *cis*-position induced 0.55 ppm low-field shift of the δ(3^1-H). On the other hand, the δs of *trans*-CH=CHCOOMe **7b** and CH=C(COOMe)$_2$ **10** were 9.10 and 9.07 ppm, respectively, and *cis*-attachment of the COOMe group made the δ slight high-field shift (0.03 ppm). The δ(3^1-H)s of (*Z*)-CH=C(CN)COOMe **9a** (*cis*-CN / *trans*-COOMe) and (*E*)-CH=C(CN)COOMe **9b** (*cis*-COOMe / *trans*-CN) were estimated to be 9.65 and 8.82 ppm from calculation of the δ-values by *cis*-substitution of CN group to **7b** and of COOMe to **6b**, respectively. The δ of the single product **9** was observed at 9.80 ppm. Therefore, the configuration of the sole product should be (*Z*)-CH=C(CN)COOMe **9a** (*cis*-CN / *trans*-COOMe). A methoxycarbonyl group is more sterically bulky than a cyano group (*vide supra*) and steric repulsion between the 3^2-methoxycarbonyl group and the 2-methyl group should occur in the (*E*)-conformer. The steric effect showed that (*Z*)-**9a** was predominantly formed from Knoevenagel reaction of **1** and methyl cyanoacetate, and also that **10** possessing the COOMe group at the *cis*-position was less efficiently obtained from the reaction of **1** and dimethyl malonate. Reaction of **1** with ethyl acetoacetate and nitromethane gave no vinyl compounds of Knoevenagel reaction type even in the prolonged reflux of the THF solution.

Visible Spectra

In dichloromethane, *trans*-isomers **3b**, **4b** and **5b** showed almost the same visible spectra (see the solid line of Fig. 2A). The peaks λ_{max} of the *trans*-isomers are red-shifted compared to those of unsubstituted vinyl compound **2** because the R_2-group at the 3^2-position (see Scheme 1) conjugated with the chlorin chromophore through the 3^1-3^2 double bond.[12] The visible spectra of *cis*-isomers **3a** (R_2 = Ph) and **4a** (R_2 = *p*-anisyl) were the same and the λ_{max} of Q_y and Soret bands were 667 and 415 nm, respectively (see the broken line of Fig. 2A), but slightly different from those of **5a** (R_2 = CH=CH$_2$) with 665 and 414-nm peaks. The peaks of the *cis*-isomers were almost the same as those of **2** as shown in Fig. 2B. This similarity is ascribable to the combination of two adverse effects: i) less conjugation of the 3^1-3^2 double bond with the chlorin chromophore because of steric repulsion between the *cis*-substituents (= R_1-groups in Scheme 1) and 2-methyl group, and ii) more conjugation of the R_1-group with the chlorin chromophore through the 3^1-3^2 double bond. Molecular modeling calculation (*vide supra*) also supported the above explanation; typically the dihedral angles between the

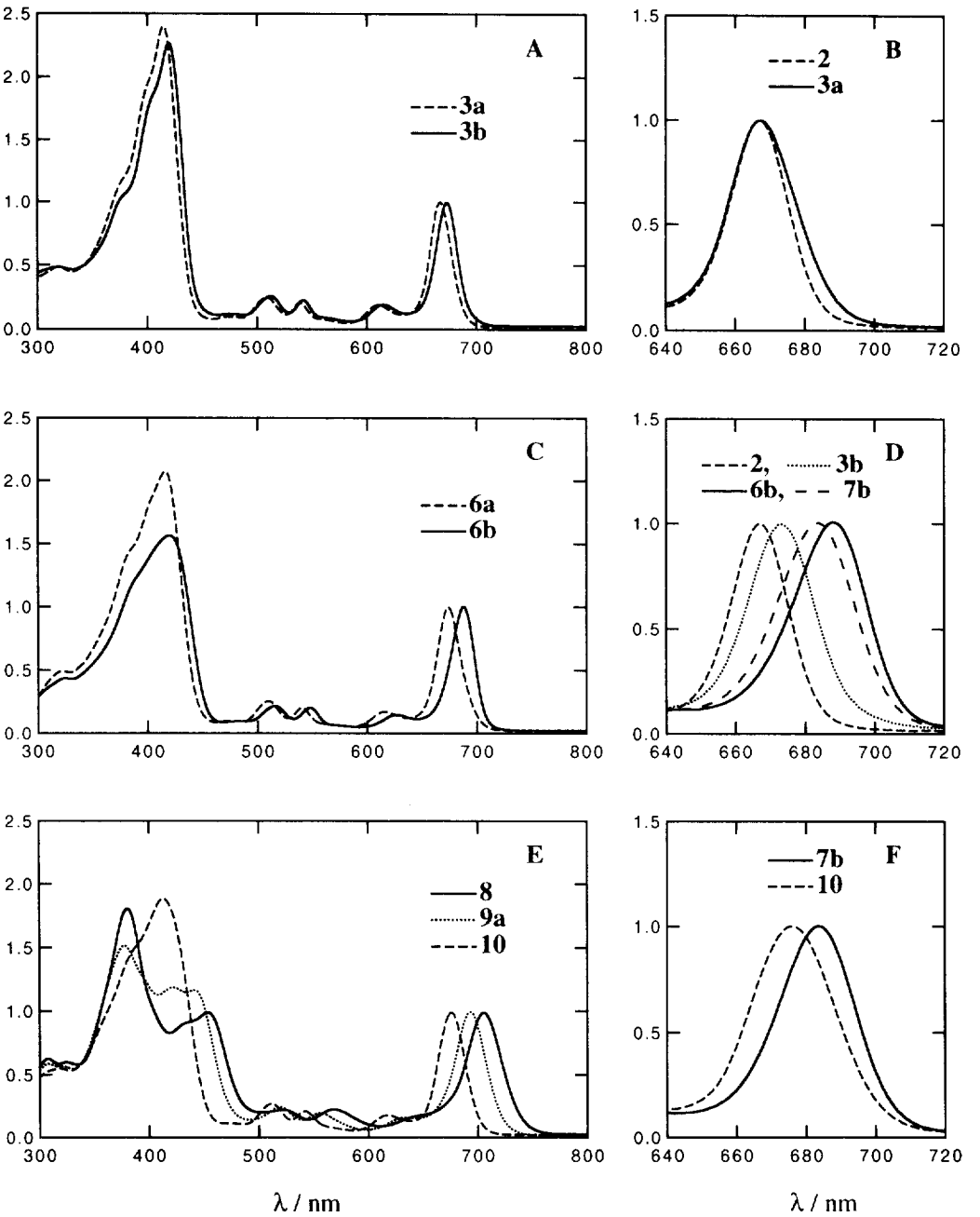


Fig. 2. Visible spectra in dichloromethane, normalized at Qy peak

chlorin and the 3-CH=CH- π-planes were 12 ° in **2**, 17 ° in *cis*-**3a** and 14 ° in *trans*-**3b** and the dihedral angles between the 3-CH=CH- and 3^2-phenyl π-planes were 13 ° in *cis*-**3a** and 1 ° in *trans*-**3b**.

Trans-**6b** (R_2 = CN) had visible bands absorbing longer wavelengths than *cis*-**6a** (see Fig. 2C). The red-shift in **6** was due to the steric effect as true in **3-5**. The order in the Q_y peaks, 667 nm in **2** (R_2=H) < 673 nm in *trans*-**3b** (R_2=Ph) < 684 nm in *trans*-**7b** (R_2=COOMe) < 689 nm in *trans*-**6b** (R_2=CN) as shown in Fig. 2D, can be explained by the electronic and conjugated effects of R_2 group. Substitution of such electron-withdrawing groups at the 3^2-position broadened the visible bands, i.e., increased the half-height widths Δ of visible bands; typically, Δ in Q_y bands were 20 nm in **2**, 23 nm in *trans*-**3b**, and 26 nm in *trans*-**6b** and *trans*-**7b**. The Soret / Q_y absorbance ratio was also reduced by the 3^2-*trans*-substitution of electron-withdrawing groups, 2.3 (**2**, **3b**) > 1.8 (**7b**) > 1.6 (**6b**).

2,2-Disubstituted ethenyl compounds **8-10** possessing two electron-withdrawing groups had different visible spectra from the 2-mono-substituted compounds **6**, **7** (Fig. 2E). The Q_y peak at 706 nm of **8** (R_1=R_2=CN) was red-shifted in comparison with 674 nm of *cis*-**6a** (R_1=CN, R_2=H) and 689 nm of *trans*-**6b** (R_1=H, R_2=CN). The Soret band of **8** was split to red-shifted 454- and blue-shifted 380-nm peaks. Such changes in visible spectra are due to the electronic effect of the two electron-withdrawing cyano groups, because the 3-CHO group of **1** induced a similar red-shift of Q_y band and also a similar split of Soret band in comparison with the 3-CH=CH_2 of **2**. Visible spectra of **9a** (R_1=CN, R_2=COOMe) showed similar shifts to **8** but the values of those in **9a** were lower than those in **8**. The lower shifts would be ascribable to decrease of the electron-withdrawing effect by CN/CN → CN/COOMe in **8** → **9a** as discussed above. *Cis*-substitition of COOMe (as in **10**) at the 3^2-position of *trans*-**7b** induced the blue-shift and broadening of visible bands: λ_{max} = 684 → 677 / 421 → 413 nm and Δ (Q_y) = 26 → 30 nm (Fig. 2F). These changes in visible spectra were explained by the fact that a less electron-withdrawing methoxycarbonyl group is more sterically bulky than a cyano group, and that greater destruction of conjugation of the chlorin chromophore with the ethenyl substituent occurred in *cis*-COOMe compound as in **10** than in *cis*-CN compounds (**8** and **9a**), consistent with the results in synthesis of **8-10** by Knoevenagel reaction. Molecular modeling calculation (*vide supra*) also supported this explanation; the dihedral angles between the chlorin and the 3-CH=C< π-planes were 17 ° in **8**, 18 ° in **9a** and 21 ° in **10**.

The longest absorption bands, Q_y bands of chlorin compounds were strongly affected by the substituents on the Q_y axis (N21-N23, see Scheme 1), i.e., functional groups at the 3- and 13-positions.[19] Q_y bands of the synthetic 3-ethenyl chlorins **3-10** were shifted by conjugation of the chlorin and ethenyl chromophores as well as by the electronic and steric effects of substituents at the 3^2-position. The 3^2-substitution changed the Q_y peaks to between 665 and 706 nm (14,200 and 15,000 cm^{-1}); typically there was an interval of about 10 nm (200 cm^{-1}) of the Q_y peaks as shown in Fig. 3A.

Fluorescence and Circular Dichroism Spectra

Fluorescence spectra of **3-10** excited at the Soret bands were observed at the region of lower energy than the Q_y band. All the spectra consisted of two bands with the strong peak at the high energy level and the broad band at the lower. The main emission peaks were red-shifted in the same order as the Q_y-absorption peaks (see Fig. 3B). The shifts from the main fluorescence peak to the visible Q_y peak of 3^2-mono-substituted chlorins **3-7** were almost the same (175±15 cm^{-1}) except for the value of **5a** (130 cm^{-1}), but were smaller than those of 3^2,3^2-disubstituted chlorins **8-10**. The main fluorescence bands of **8-10** were broader than those of **3-7**.

The relative fluorescence strengths calculated from the spectral area (cm^{-1} unit) were little changed by 3^2-substituents.

Circular dichroism (CD) spectra were observed in the region of absorption bands. Several peaks above 300-nm wavelength appeared in the region of the Q_y, Q_x and Soret bands. The negative peak at the Q_y band was more intense than the positive peaks at the Q_x band. The S-shaped band (++/-) was observed around the Soret band; in **8** and **9a** possessing split Soret bands, it was seen around the higher Soret peak (*ca.* 380 nm) at the lower wavelength. The negative CD peaks at the Q_y region were shifted as well as Q_y peaks of visible spectra (see Fig. 3C).

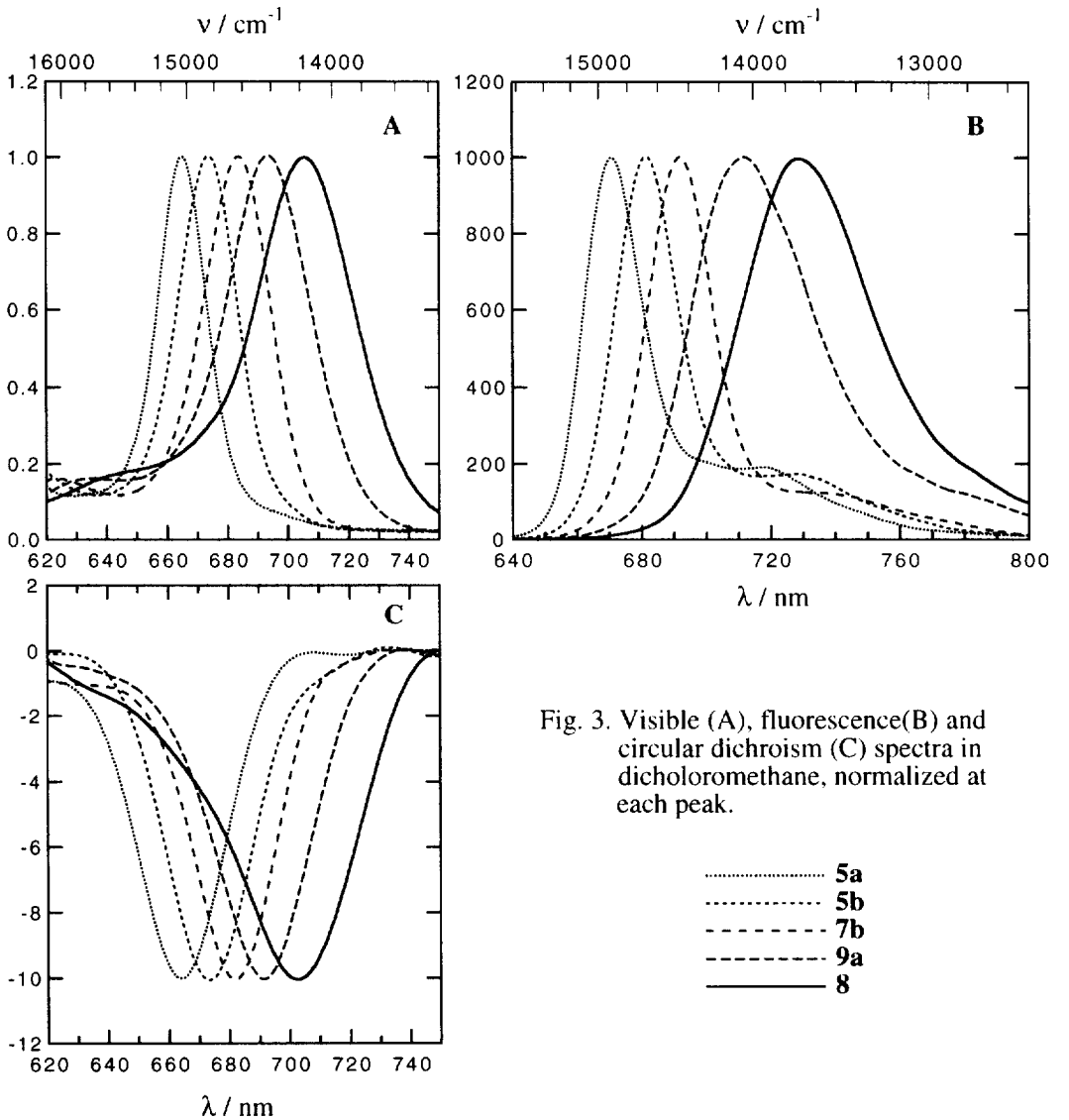


Fig. 3. Visible (A), fluorescence(B) and circular dichroism (C) spectra in dicholoromethane, normalized at each peak.

EXPERIMENTAL

Apparatus

Visible absorption and fluorescence emission spectra were measured with Hitachi U-3500 and F-4500 spectrophotometers, respectively. CD spectra were measured with a Jasco J-720W spectropolarimeter. All melting points were measured with a Yanagimoto micro melting apparatus and were uncorrected. ^{1}H-NMR spectra were measured with a Bruker AC-300 spectrometer; δs are expressed in parts per million relative to $CHCl_3$ (7.26 ppm) as an internal reference. Mass spectra were recorded on a JEOL HX-100 spectrometer; FAB-MS samples were dissolved in $CHCl_3$ and *m*-nitrobenzyl alcohol was used as the matrix. HPLC was done with a Shimadzu LC-10AS pump, a SPD-10AV visible detector and a C-R6A chromatopac.

Materials

Methyl pyropheophorbide-*d* (**1**) and methyl pyropheophorbide-*a* (**2**) were prepared according to the procedures reported by Tamiaki *et al.*[8,18] Dichloromethane (CH_2Cl_2) as a solvent for Wittig reaction was used without further purification of that commercially available and THF for Knoevenagel reaction was distilled from CaH_2 before use. Flash column chromatography (FCC) was performed with silica gel (Merck, Kieselgel 60, 9385). HPLC was performed with a packed ODS column (Gelpack, GL-OP100, Hitachi Chemical Co., 6 × 150 mm). CH_2Cl_2 for visible, fluorescence and CD spectra was purchased from Nacalai Tesque (Grade for UV-spectroscopy). Before measurements of visible, fluorescence and CD spectra, all compounds **1**-**10** were extra-purified by HPLC.

General Procedures

Preparation of Phosphonium Salts and Ylides. Xylene solutions of *p*-methoxybenzyl chloride or *p*-nitrobenzyl bromide, and triphenylphosphine were refluxed and the precipitates formed after cooling were filtered, washed with xylene and dried to give PPh_3CH_2(*p*-anisyl)Cl (mp 246-247 °C) or PPh_3CH_2(*p*-nitrophenyl)Br (mp 275-275.5 °C), respectively.[20] Slow addition of 48% HBr and successively propargyl bromide to a dioxane solution of triphenylphosphine with stirring gave precipitates after slight heating and standing overnight, which were filtered, washed with xylene and dried to give $PPh_3CH_2C{\equiv}CHBr$ (mp 179-180 °C).[21] PPh_3CH_2PhCl and $PPh_3CH_2CH{=}CH_2Cl$ were commercially available and used for preparation of Wittig reagents without further purification.

A nitromethane solution of chloroacetonitrile and triphenylphosphine was refluxed and the precipitates after standing at room temperature were filtered and dried to give PPh_3CH_2CNCl. Addition of 4% aq. NaOH to an aqueous solution of resulting salt PPh_3CH_2CNCl gave precipitates, which were filtered and washed with water and dried to give $PPh_3{=}CHCN$ (mp 128-130 °C).[22] An aqueous 10% Na_2CO_3 solution of commercially available $PPh_3CH_2COPhBr$ was stirred to give precipitates and recrystallization from benzene and petroleum ether afforded $PPh_3{=}CHCOPh$ (mp 183-185 °C).[23] $PPh_3{=}CHCOOMe$ was commercially available and used without further purification.

Wittig Reaction. Aldehyde **1** (11.0 mg, 20 μmol) and Ph_3CH_2RCl (1.1 eq., 22 μmol) was dissolved in 7 mL CH_2Cl_2 and a solution of NaOH (7 mg) in H_2O (3 mL) was added with stirring. The solution was stirred at room temperature under N_2 and the decrease of **1** was monitored by visible spectra (694, 428 and 388-nm peaks). After the decrease of these peaks was stopped (30 min for R = Ph, 40 min for R = *p*-anisyl, 120 min for R = vinyl), the reaction mixture was poured into ice water and CH_2Cl_2. The aqueous phase was

extracted with several portions of CH_2Cl_2 and the combined CH_2Cl_2 phases were washed with aqueous aq. 2% HCl, aq. 4% $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated *in vacuo* to dryness. The residue was purified with FCC with 4-6% Et_2O-CH_2Cl_2. The elute was evaporated *in vacuo* and the residue was recrystallized from CH_2Cl_2 and hexane to give methyl *trans*-3^2-substituted pyropheophorbides-*a* **3b** and **4b** as the first major crop; the residue after concentration of the mother liquid was recrystallized from CH_2Cl_2-hexane to give methyl *cis*-3^2-substituted pyropheophorbides-*a* **3a** and **4a** as the second minor crop.

In the case of R = vinyl (use of 1.7 eq. of phosphonium salt and 2.5 fold concentrated aq. NaOH), the residue after the work-up of the reaction mixture was dissolved in 20 mL of CH_2Cl_2, to which was added *tert*-butylamine borane complex (8.5 mg) with stirring. After stirring for 30 min under N_2, 2% aqueous HCl was added to the reaction mixture, and stirred vigorously for another 20 min. The reaction mixture was poured into CH_2Cl_2. After the same work-up as described above, FCC afforded intact product **5** (6% Et_2O-CH_2Cl_2) and selectively reduced compound **11** (10-15% Et_2O-CH_2Cl_2). A mixture of the *cis* / *trans* conformers was separated by HPLC (MeOH, 1.5 ml / min, injection of a MeOH solution with a minimum of THF) to give *cis*-**5a** for a 26-min band and *trans*-**5b** for 30-min.

A CH_2Cl_2 solution (17 mL) of **1** (11.0 mg, 20 μmol) and PPh_3=CHE (3.7 eq. for E = CN and 1.5 eq. for E = COOMe) was refluxed under N_2. After the decrease of **1** was stopped (8 h for E = CN and 6 h for E = COOMe), the reaction mixture was worked up as described above to give 3-CH=CHE chlorins **6** and **7**. In E = COOMe, only *trans*-**7b** was produced. In E = CN, *cis* / *trans* mixture was separated by HPLC (MeOH, 1.5 ml / min, injection of a MeOH solution with a minimum of THF); the retention time of *cis*-**6a** was 28 min and that of *trans*-**6b** = 34 min.

Knoevenagel Reaction. Formylchlorin **1** (11.0 mg, 20 μmol) was dissolved in 30 mL THF, to which was added activated methylene compounds ECH_2E' (65 eq. for E=E'=CN, 210 eq. for E=CN/E'=COOMe, 140 eq. for E=E'=COOMe) and amine (15 eq. of Et_3N for E=E'=CN, 70 eq. of Et_3N for E=CN/E'=COOMe, 90 eq. of Et_2NH for E=E'=COOMe) with stirring. The solution was stirred at room temperature or refluxed under N_2 and decrease of **1** was monitored by visible spectra (*vide supra*). After the decrease of **1** was stopped (4-h stirring for malononitrile, 12-h stirring for methyl cyanoacetate, 48-h reflux for dimethyl malonate), the reaction mixture was poured into ice water. After the work-up described above, the residue was purified with FCC with 5-8% Et_2O-CH_2Cl_2. The elute was evaporated *in vacuo* and the residue was recrystallized from CH_2Cl_2 and hexane to give methyl 3^2,3^2-disubstituted pyropheophorbide-*a* **8**-**10**.

Spectral Data

Methyl *cis*-3^2-Phenylpyropheophorbide-*a* (3a). 22% yield (all the yields described below were based on the consumed **1**); black solids; mp 138-140 °C; Vis (CH_2Cl_2) λ_{max}=667 (relative intensity, 0.41), 612 (0.07), 540 (0.08), 510 (0.10), 415 (1.00), 397 (0.81, sh), 374 nm (0.49, sh); ^{1}H-NMR ($CDCl_3$) δ=9.48 (1H, s, 10-H), 9.25 (1H, s, 5-H), 8.46 (1H, s, 20-H), 7.67 (1H, d, *J*=12 Hz, 3^1-H), 7.41 (1H, d, *J*=12 Hz, 3^2-H), 7.25 (1H, d, *J*=7 Hz, Ph-2,6-H), 7.03 (1H, t, *J*=7 Hz, Ph-4-H), 7.00 (2H, t, *J*=7 Hz, Ph-3,5-H), 5.27, 5.11 (1H+1H, d, *J*=20 Hz, 13^2-H_2), 4.46 (1H, dq, *J*=2, 7 Hz, 18-H), 4.30 (1H, dt, *J*=8, 2 Hz, 17-H), 3.73 (2H, q, *J*= 8 Hz, 8-CH_2), 3.67 (3H, s, 12-CH_3), 3.62 (3H, s, CO_2CH_3), 3.11 (3H, s, 7-CH_3), 2.99 (3H, s, 2-CH_3), 2.53-2.70, 2.21-2.43 (2H+2H, m, 17-CH_2CH_2), 1.81 (3H, d, *J*=7 Hz, 18-CH_3), 1.67 (3H, t, *J*=8 Hz, 8^1-CH_3), -1.59 (1H, s, NH^{24}). MS (FAB) found: *m/z* 624. Calcd for $C_{40}H_{40}N_4O_3$; M^+, 624.

Methyl *trans*-3^2-Phenylpyropheophorbide-*a* (3b). 62% yield; purple solids; mp 277-278 °C (lit.[12] 256-259 °C); Vis (CH_2Cl_2) λ_{max}=673 (0.43), 616 (0.07), 543 (0.09), 513 (0.11), 420 (1.00), 400 (0.81, sh), 373 nm (0.46, sh); ^{1}H-NMR ($CDCl_3$) δ=9.52 (1H, s, 10-H), 9.45 (1H, s, 5-H), 8.58 (1H, s, 20-

H), 8.38 (1H, d, J=17 Hz, 3^1-H), 7.88 (2H, d, J=7 Hz, Ph-2,6-H), 7.64 (1H, d, J=17 Hz, 3^2-H), 7.56 (2H, t, J=7 Hz, Ph-3,5-H), 7.47 (1H, t, J=7 Hz, Ph-4-H), 5.27, 5.11 (1H+1H, d, J=20 Hz, 13^2-H_2), 4.50 (1H, dq, J=2, 7 Hz, 18-H), 4.30 (1H, dt, J=8, 2 Hz, 17-H), 3.70 (2H, q, J=8 Hz, 8-CH_2), 3.68 (3H, s, 12-CH_3), 3.62 (3H, s, CO_2CH_3), 3.48 (3H, s, 2-CH_3), 3.25 (3H, s, 7-CH_3), 2.50-2.78, 2.21-2.39 (2H+2H, m, 17-CH_2CH_2), 1.83 (3H, d, J=7 Hz, 18-CH_3), 1.70 (3H, t, J=8 Hz, 8^1-CH_3), 0.52 (1H, br, NH), -1.63 (1H, s, NH). MS (FAB) found: m/z 625. Calcd for $C_{40}H_{41}N_4O_3$; MH^+, 625. Anal found: C; 76.66, H; 6.33, N; 8.94. Calcd for $C_{40}H_{40}N_4O_3$: C; 76.90, H; 6.45, N; 8.97.

Methyl *cis*-3^2-*p*-Anisylpyropheophorbide-*a* (4a). 27% yield; black solids; mp 162-165 °C; Vis (CH_2Cl_2) λ_{max}=667 (0.41), 612 (0.07), 540 (0.08), 509 (0.10), 415 (1.00), 397 (0.79, sh), 373 nm (0.49, sh); ^{1}H-NMR ($CDCl_3$) δ=9.52 (1H, s, 10-H), 9.27 (1H, s, 5-H), 8.46 (1H, s, 20-H), 7.55 (1H, d, J=12 Hz, 3^1-H), 7.34 (1H, d, J=12 Hz, 3^2-H), 7.19 (2H, d, J=9 Hz, Ph-2,6-H), 6.53 (2H, t, J=9 Hz, Ph-3,5-H), 5.27, 5.11 (1H+1H, d, J=20 Hz, 13^2-H_2), 4.47 (1H, dq, J=2, 7 Hz, 18-H), 4.28 (1H, dt, J=8, 2 Hz, 17-H), 3.70 (2H, q, J=8 Hz, 8-CH_2), 3.67 (3H, s, 12-CH_3), 3.62, 3.61 (3H+3H, s, OCH_3, CO_2CH_3), 3.12 (3H, s, 7-CH_3), 3.02 (3H, s, 2-CH_3), 2.50-2.75, 2.20-2.42 (2H+2H, m, 17-CH_2CH_2), 1.82 (3H, d, J=7 Hz, 18-CH_3), 1.68 (3H, t, J=8 Hz, 8^1-CH_3), -1.58 (1H, s, NH^{24}). MS (FAB) found: m/z 654. Calcd for $C_{41}H_{42}N_4O_4$; M^+, 654.

Methyl *trans*-3^2-*p*-Anisylpyropheophorbide-*a* (4b). 54% yield; purple solids; mp 262-266 °C; Vis (CH_2Cl_2) λ_{max}=674 (0.46), 615 (0.08), 543 (0.09), 513 (0.11), 421 (1.00), 401 (0.78, sh), 375 nm (0.45, sh); ^{1}H-NMR ($CDCl_3$) δ=9.51 (1H, s, 10-H), 9.45 (1H, s, 5-H), 8.56 (1H, s, 20-H), 8.26 (1H, d, J=16 Hz, 3^1-H), 7.84 (2H, d, J=9 Hz, Ph-2,6-H), 7.60 (1H, d, J=16 Hz, 3^2-H), 7.11 (2H, t, J=9 Hz, Ph-3,5-H), 5.24, 5.14 (1H+1H, d, J=20 Hz, 13^2-H_2), 4.46 (1H, dq, J=2, 7 Hz, 18-H), 4.11 (1H, dt, J=8, 2 Hz, 17-H), 3.95 (3H, s, OCH_3), 3.70 (2H, q, J=8 Hz, 8-CH_2), 3.68 (3H, s, 12-CH_3), 3.61 (3H, s, CO_2CH_3), 3.47 (3H, s, 2-CH_3), 3.25 (3H, s, 7-CH_3), 2.50-2.80, 2.10-2.40 (2H+2H, m, 17-CH_2CH_2), 1.82 (3H, d, J=7 Hz, 18-CH_3), 1.73 (3H, t, J=8 Hz, 8^1-CH_3), -1.94 (1H, s, NH^{24}). MS (FAB) found: m/z 655. Calcd for $C_{41}H_{43}N_4O_4$; MH^+, 655.

Methyl *cis*-3^2-Vinylpyropheophorbide-*a* (5a). 27% yield; black solids; Vis (CH_2Cl_2) λ_{max}=665 (0.43), 609 (0.08), 538 (0.08), 508 (0.10), 414 (1.00), 395 (0.81, sh), 373 nm (0.52, sh); ^{1}H-NMR ($CDCl_3$) δ=9.51 (1H, s, 10-H), 9.22 (1H, s, 5-H), 8.53 (1H, s, 20-H), 7.51 (1H, d, J=11 Hz, 3^1-H), 7.05 (1H, d, J=11 Hz, 3^2-H), 6.65 (1H, dt, J=16, 11 Hz, 3^3-H), 5.61 (1H, d, J=16 Hz, *cis*-3^4-H), 5.29 (1H, d, J=11 Hz, *trans*-3^4-H), 5.27, 5.11 (1H+1H, d, J=20 Hz, 13^2-H_2), 4.45 (1H, dq, J=2, 7 Hz, 18-H), 4.30 (1H, dt, J=8, 2 Hz, 17-H), 3.69 (2H, q, J=8 Hz, 8-CH_2), 3.68 (3H, s, 12-CH_3), 3.61 (3H, s, CO_2CH_3), 3.26, 3.20 (3H+3H, s, 2-, 7-CH_3), 2.50-2.80, 2.20-2.40 (2H+2H, m, 17-CH_2CH_2), 1.81 (3H, d, J=7 Hz, 18-CH_3), 1.69 (3H, t, J=8 Hz, 8^1-CH_3), -1.62 (1H, s, NH^{24}). MS (FAB) found: m/z 575. Calcd for $C_{36}H_{39}N_4O_3$; MH^+, 575.

Methyl *trans*-3^2-Vinylpyropheophorbide-*a* (5b). 48% yield; black solids; Vis (CH_2Cl_2) λ_{max}=674 (0.42), 616 (0.07), 542 (0.08), 513 (0.09), 419 (1.00), 400 (0.80, sh), 375 nm (0.47, sh); ^{1}H-NMR ($CDCl_3$) δ=9.51 (1H, s, 10-H), 9.38 (1H, s, 5-H), 8.56 (1H, s, 20-H), 7.91 (1H, d, J=16 Hz, 3^1-H), 7.36 (1H, dd, J=10, 16 Hz, 3^2-H), 7.01 (1H, dt, J=17, 10 Hz, 3^3-H), 5.67 (1H, d, J=17 Hz, *cis*-3^4-H), 5.50 (1H, d, J=10 Hz, *trans*-3^4-H), 5.27, 5.11 (1H+1H, d, J=20 Hz, 13^2-H_2), 4.48 (1H, dq, J=2, 7 Hz, 18-H), 4.29 (1H, dt, J=8, 2 Hz, 17-H), 3.70 (2H, q, J=8 Hz, 8-CH_2), 3.68 (3H, s, 12-CH_3), 3.61 (3H, s, CO_2CH_3), 3.49, 3.44 (3H+3H, s, 2-, 7-CH_3), 2.50-2.80, 2.20-2.40 (2H+2H, m, 17-CH_2CH_2), 1.81 (3H, d, J=7 Hz, 18-CH_3), 1.70 (3H, t, J=8 Hz, 8^1-CH_3), -1.66 (1H, s, NH^{24}). MS (FAB) found: m/z 575. Calcd for $C_{36}H_{39}N_4O_3$; MH^+, 575

Methyl *cis*-3^2-Cyanopyropheophorbide-*a* (6a). 17% yield; black solids; Vis (CH_2Cl_2) λ_{max}=674 (0.48), 617 (0.08), 541 (0.09), 510 (0.12), 416 (1.00), 381 nm (0.69, sh). ^{1}H-NMR ($CDCl_3$) δ=9.58 (1H, s, 10-H), 9.21 (1H, s, 5-H), 8.70 (1H, s, 20-H), 8.66 (1H, d, J=12 Hz, 3^1-H), 6.35 (1H, d, J=12 Hz, 3^2-H),

5.31, 5.15 (1H+1H, d, *J*=20 Hz, 13^2-H_2), 4.53 (1H, dq, *J*=2, 7 Hz, 18-H), 4.34 (1H, dt, *J*=8, 2 Hz, 17-H), 3.72 (2H, q, *J*=7 Hz, 8-CH_2), 3.70 (3H, s, 12-CH_3), 3.61 (3H, s, CO_2CH_3), 3.49 (3H, s, 2-CH_3), 3.27 (3H, s, 7-CH_3), 2.50-2.80, 2.20-2.40 (2H+2H, m, 17-CH_2CH_2), 1.83 (3H, d, *J*=7 Hz, 18-CH_3), 1.71 (3H, t, *J*=8 Hz, 8^1-CH_3), -1.77 (1H, s, NH^{24}). MS (FAB) found: *m/z* 574. Calcd for $C_{35}H_{36}N_5O_3$; MH^+, 574.

Methyl *trans*-3^2-Cyanopyropheophorbide-*a* (6b). 82% yield; dark blue solids; mp 285-287 °C; Vis (CH_2Cl_2) λ_{max}=689 (0.64), 626 (0.08), 548 (0.12), 515 (0.13), 420 (1.00), 385 nm (0.78, sh); ^{1}H-NMR ($CDCl_3$) δ=9.62 (1H, s, 10-H), 9.38 (1H, s, 5-H), 8.85 (1H, d, *J*=17 Hz, 3^1-H), 8.37 (1H, s, 20-H), 6.48 (1H, d, *J*=17 Hz, 3^2-H), 5.33, 5.17 (1H+1H, d, *J*=20 Hz, 13^2-H_2), 4.55 (1H, dq, *J*=2, 7 Hz, 18-H), 4.37 (1H, dt, *J*=7, 2 Hz, 17-H), 3.72 (2H, q, *J*=7 Hz, 8-CH_2), 3.71 (3H, s, 12-CH_3), 3.62 (3H, s, CO_2CH_3), 3.52 (3H, s, 2-CH_3), 3.30 (3H, s, 7-CH_3), 2.50-2.80, 2.20-2.40 (2H+2H, m, 17-CH_2CH_2), 1.83 (3H, d, *J*=7 Hz, 18-CH_3), 1.72 (3H, t, *J*=7 Hz, 8^1-CH_3), -1.97 (1H, s, NH^{24}). MS (FAB) found: *m/z* 573. Calcd for $C_{35}H_{35}N_5O_3$; M^+, 573.

Methyl *trans*-3^2-Methoxycarbonylpyropheophorbide-*a* (7b). 85% yield; black solids; mp 248-250°C; Vis (CH_2Cl_2) λ_{max}=684 (0.56), 624 (0.08), 547 (0.11), 515 (0.13), 421 (1.00), 385 nm (0.73, sh); ^{1}H-NMR ($CDCl_3$) δ=9.53 (1H, s, 10-H), 9.43 (1H, s, 5-H), 9.10 (1H, d, *J*=16 Hz, 3^1-H), 8.67 (1H, s, 20-H), 7.03 (1H, d, *J*=16 Hz, 3^2-H), 5.30, 5.16 (1H+1H, d, *J*=20 Hz, 13^2-H_2), 4.54 (1H, dq, *J*=2, 7 Hz, 18-H), 4.35 (1H, dt, *J*=8, 2 Hz, 17-H), 4.05 (3H, s, 3^2-CO_2CH_3), 3.68 (2H, q, *J*=7 Hz, 8-CH_2), 3.67 (3H, s, 12-CH_3), 3.62 (3H, s, 17^2-CO_2CH_3), 3.50 (3H, s, 2-CH_3), 3.26 (3H, s, 7-CH_3), 2.49-2.80, 2.20-2.39 (2H+2H, m, 17-CH_2CH_2), 1.83 (3H, d, *J*=7 Hz, 18-CH_3), 1.70 (3H, t, *J*=8 Hz, 8^1-CH_3), 0.08 (1H, br, s), -1.93 (1H, s, NH). MS (FAB) found: *m/z* 606. Calcd for $C_{36}H_{38}N_4O_5$; M^+, 606.

Methyl 3^2,3^2-Dicyanopyropheophorbide-*a* (8). 76% yield; black solids; mp 205-207 °C; Vis (CH_2Cl_2) λ_{max}=706 (0.54), 638 (0.08, sh), 569 (0.11), 522 (0.11), 454 (0.54), 431 (0.49, sh), 380 nm (1.00); ^{1}H-NMR ($CDCl_3$) δ=9.65 (1H, s, 10-H), 9.40 (1H, s, 3^1-H), 9.30 (1H, s, 5-H), 8.83 (1H, s, 20-H), 5.31, 5.22 (1H+1H, d, *J*=20 Hz, 13^2-H_2), 4.58 (1H, dq, *J*=2, 7 Hz, 18-H), 4.37 (1H, dt, *J*=8, 2 Hz, 17-H), 3.75 (2H, q, *J*=8 Hz, 8-CH_2), 3.72 (3H, s, 12-CH_3), 3.62 (3H, s, CO_2CH_3), 3.58 (3H, s, 2-CH_3), 3.33 (3H, s, 7-CH_3), 2.52-2.79, 2.21-2.38 (2H+2H, m, 17-CH_2CH_2), 1.85 (3H, d, *J*=7 Hz, 18-CH_3), 1.73 (3H, t, *J*=8 Hz, 8^1-CH_3), -0.06 (1H, br, s), -1.94 (1H, s, NH). MS (FAB) found: *m/z* 599. Calcd for $C_{36}H_{35}N_6O_3$; MH^+, 599. Anal found: C; 72.01, H; 5.59, N; 13.90. Calcd for $C_{36}H_{34}N_6O_3$: C; 72.22, H; 5.72, N; 14.04.

Methyl *cis*-3^2-Cyano-*trans*-3^2-methoxycarbonylpyropheophorbide-*a* (9a). 78% yield; black solids; mp 212-215 °C; Vis (CH_2Cl_2) λ_{max}=694 (0.65), 629 (0.09, sh), 557 (0.12), 519 (0.15), 441 (0.77), 422 (0.78), 378 nm (1.00); ^{1}H-NMR ($CDCl_3$) δ=9.80 (1H, s, 3^1-H), 9.57 (1H, s, 10-H), 9.29 (1H, s, 5-H), 8.77 (1H, s, 20-H), 5.29, 5.19 (1H+1H, d, *J*=20 Hz, 13^2-H_2), 4.55 (1H, dq, *J*=2, 7 Hz, 18-H), 4.36 (1H, dt, *J*=7, 2 Hz, 17-H), 3.73 (2H, q, *J*=8 Hz, 8-CH_2), 4.18 (3H, s, 3^2-CO_2CH_3), 3.69 (3H, s, 12-CH_3), 3.62 (3H, s, 17^2-CO_2CH_3), 3.55 (3H, s, 2-CH_3), 3.27 (3H, s, 7-CH_3), 2.52-2.78, 2.21-2.38 (2H+2H, m, 17-CH_2CH_2), 1.84 (3H, d, *J*=7 Hz, 18-CH_3), 1.72 (3H, t, *J*=8 Hz, 8^1-CH_3), 0.01 (1H, br, s), -1.90 (1H, s, NH). MS (FAB) found: *m/z* 632. Calcd for $C_{37}H_{38}N_5O_5$; MH^+, 632.

Methyl 3^2,3^2-Dimethoxycarbonylpyropheophorbide-*a* (10). 52% yield; black solids; 135-140 °C; Vis (CH_2Cl_2) λ_{max}=677 (0.52), 619 (0.08), 542 (0.11), 512 (0.14), 413 (1.00), 381 nm (0.79, sh); ^{1}H-NMR ($CDCl_3$) δ=9.58 (1H, s, 10-H), 9.26 (1H, s, 5-H) 9.07 (1H, s, 3^1-H), 8.64 (1H, s, 20-H), 5.31, 5.22 (1H+1H, d, *J*=20 Hz, 13^2-H_2), 4.53 (1H, dq, *J*=2, 7 Hz, 18-H), 4.33 (1H, dt, *J*=8, 2 Hz, 17-H), 3.75 (2H, q, *J*=8 Hz, 8-CH_2), 4.09 (3H, s, *trans*-3^2-CO_2CH_3), 3.71 (3H, s, 12-CH_3), 3.62 (3H, s, 17^2-CO_2CH_3), 3.38 (3H, s, 2-CH_3), 3.29 (3H, s, 7-CH_3), 3.26 (3H, s, *cis*-3^2-CO_2CH_3), 2.50-2.80, 2.20-2.45 (2H+2H, m, 17-CH_2CH_2), 1.82 (3H, d, *J*=7 Hz, 18-CH_3), 1.71 (3H, t, *J*=8 Hz, 8^1-CH_3), -1.85 (1H, s, NH^{24}). MS (FAB) found: *m/z* 665. Calcd for $C_{38}H_{41}N_4O_7$; MH^+, 665.

ACKNOWLEDGMENTS

We thank Mr. Naoya Umesaki for his experimental assistance. This work was partially supported by a Grant-in-Aid for Scientific Research (No. 07454192) from the Ministry of Education, Science, Sports and Culture, Japan.

REFERENCES AND NOTES

1. Miyashita, H.; Ikemoto, H.; Kurano, N.; Adachi, K.; Chihara, M.; Miyachi, S. *Nature* **1996**, 383, 402.
2. Scheumann, V.; Helfrich, M.; Schoch, S.; Rüdiger, W. *Z. Naturforsch.* **1996**, 51c, 185–194; Oba, T.; Masada, Y.; Tamiaki, H. *Bull. Chem. Soc. Jpn.* **1997**, 70, in press.
3. Ito, H.; Ohtsuka, T.; Tanaka, A. *J. Biol. Chem.* **1996**, 271, 1475–1479.
4. Johnson, D. G; Svec, W. A.; Wasielewski, M. R. *Isr. J. Chem.* **1988**, 28, 193–203.
5. Bible, K. C.; Buytendorp, M.; Zierath, P. D.; Rinehart, K. L. *Proc. Natl. Acad. Sci. USA* **1988**, 85, 4582–4586.
6. Fischer, R.; Engel, N.; Henseler, A.; Gossauer, A. *Helv. Chim. Acta* **1994**, 77, 1046–1050.
7. Osuka, A.; Wada, Y.; Shinoda, S. *Tetrahedron* **1996**, 52, 4311–4326.
8. Tamiaki, H.; Amakawa, M.; Shimono, Y.; Tanikaga, R.; Holzwarth, A. R.; Schaffner, K. *Photochem. Photobiol.* **1996**, 63, 92–99.
9. Tamiaki, H.; Holzwarth, A. R.; Schaffner, K. *Photosynth. Res.* **1994**, 41, 245–251.
10. Tamiaki, H.; Shimono, Y.; Rattray, A. G. M.; Tanikaga, R. *Bioorg. Med. Chem. Lett.* **1996**, 6, 2085–2086.
11. Falk, H.; Hoornaert, G.; Isenring, H.-P.; Eschenmoser, A. *Helv. Chim. Acta* **1975**, 58, 2347–2357; Osuka, A.; Marumo, S.; Wada, Y.; Yamazaki, I.; Yamazaki, T.; Shirakawa, Y.; Nishimura, Y. *Bull. Chem. Soc. Jpn.* **1995**, 68, 2909–2915.
12. Morris, I. K.; Snow, K. M.; Smith, N. W.; Smith, K. M. *J. Org. Chem.* **1990**, 55, 1231–1236.
13. Jiang, X.; Pandey, R. K.; Smith, K. M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1607–1615.
14. Wiederrecht, G. P.; Niemczyk, M. P.; Svec, W. A.; Wasielewski, M. R. *J. Am. Chem. Soc.* **1996**, 118, 81–88.
15. Burrell, A. K.; Officer, D. L.; Reid, D. C. W. *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 900–902.
16. Kureishi, Y; Tamiaki, H. *J. Porphyrins Phthalocyanines* **1997**, submitted.
17. Ward, B.; Chang, C. K.; Young, R. *J. Am. Chem. Soc.* **1984**, 106, 3943–3950; Griffiths, G. F.; Kenner, G. W.; McCombie, S. W.; Smith, K. M.; Sutton, M. J. *Tetrahedron* **1976**, 32, 275–283.
18. Tamiaki, H.; Miyata, S.; Kureishi, Y.; Tanikaga, R. *Tetrahedron* **1996**, 52, 12421–12432.
19. Tamiaki, H.; Miyatake, T.; Tanikaga, R. *Tetrahedron Lett.* **1997**, 38, 267–270.
20. McDonald, R. N.; Campbell, T. W. *J. Org. Chem.* **1959**, 24, 1969–1975.
21. Schweizer, E. E.; Goff, S. D.; Murray, W. P. *J. Org. Chem.* **1977**, 42, 200–205.
22. Trippett, S.; Walker, D. M. *J. Chem. Soc.* **1959**, 3874–3876.
23. Ramirez, F.; Dershowitz, S. *J. Org. Chem.* **1957**, 22, 41–45.
24. Another NH was too broad to be observed.

(*Received in Japan* 31 *March* 1997; *accepted* 10 *June* 1997)