Synthesis of Chlorin-enediyne Dyads by Palladium-catalyzed Coupling Reaction

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Methyl 9-ethylenedioxypyropheophorbide-d was prepared from methyl pyropheophorbide-a by protection of cyclic ketone with ethylene glycol, and oxidation with OsO_4 in vinyl group at 2-position. The terminal alkyne was introduced into chlorin chromophore by Grignard reaction, and the enediyne moiety was constructed by a palladium-catalyzed coupling reaction with (*Z*)-chloroenynes.

Keywords enediyne, chlorin, chlorin-enediyne dyads, photodynamic therapy, anticancer agent

Introduction

Photodynamic therapy (PDT) is a kind of medical treatment which employs the light, drugs and/or tumor-localizing photosensitizer, to bring about a cytotoxic or modifying effect to cancerous or otherwise unwanted tissue.[1,2] The emphasis for development of new anticancer drugs associated with PDT has been concentrated on the molecular design, chemical synthesis and biological action studies of porphyrin derivatives.[3-5] The local photosensitized activation following accumulation of photo-senstizer in the tumors suggested that construction of some special chemical devices on chlorin, which possess anticancer activity such as nitrogen mustard and 5-fluorouracil, should provide valuable information for the dual functionalized anticancer drugs between chemotherapentic and photodynamic therapy.

The conjugated enynes and enediynes as structural moieties were found in several natural products, in particular, the (*Z*)-enediyne is present in a novel class of antitumor antibiotics (esperamycins, calicheamycins, dynemycin, neocarzinostatin and C 1027 chromophore).[6] These antitumor antibiotics possessing the charateristic *cis*-hex-3-ene-1,5-dinyl subunit have attracted considerable attention due to the generation of a phenylene biradical which is responsible for DNA strand scission.[8] Introducing ene-diyne congeners retaining the impressive DNA cleaving properties into porphyrin pigment is of great importance for the potential application in chemotherapy and photodynamic therapy as dual function anticancer drug. As a part of our research program to establish new methodologies for preparing photosenstizer bearing anticancer structure as initial models, herein we report the first synthesis of open chain chlorin-enediynes dyads to combine the properties of enediynes into PDT.

Results and discussion

In our studies, methyl pyropheophorbide-a (MPPa) (**1**) was used as the starting material. At first, the ketone group in E-ring of (**1**) was protected with ethylene glycol using trimethylsily chloride as catalyst to give acetal **2** in 75% yield. The aldehyde **4** was obtained in 84% from **2** by oxidation with OsO_4 in THF containing catalytic pyridine at 0 ℃ and followed by glycol cleavage with sodium periodate in aqueous THF. To introduce the terminal alkyne structure, a Grignard reaction of **4** with ethynyl magnesium bromide in THF at 0 ℃ afforded the propargylal alcohol **5** (Scheme 1). Deprotection of **5** with 20% aqueous acetic acid afforded ketone **6**, which was converted into zinc chlorin **7** by refluxing with excess $Zn(OAc)_2$ in MeOH in quantitative yield (Scheme 3). The purpose of preparing zinc complex is to prevent transmetalation with metal ions during the following reaction.

The coupling reaction of (*Z*)-dichloroethene with terminal alkyne was carried out by the use of tetrakis -(triphenylphosphine)palladium and copper iodide as catalyst in benzene containing *n*-butylamine to lead to high yields of (*Z*)-chlorenynes (**a**)[7](Scheme 2).

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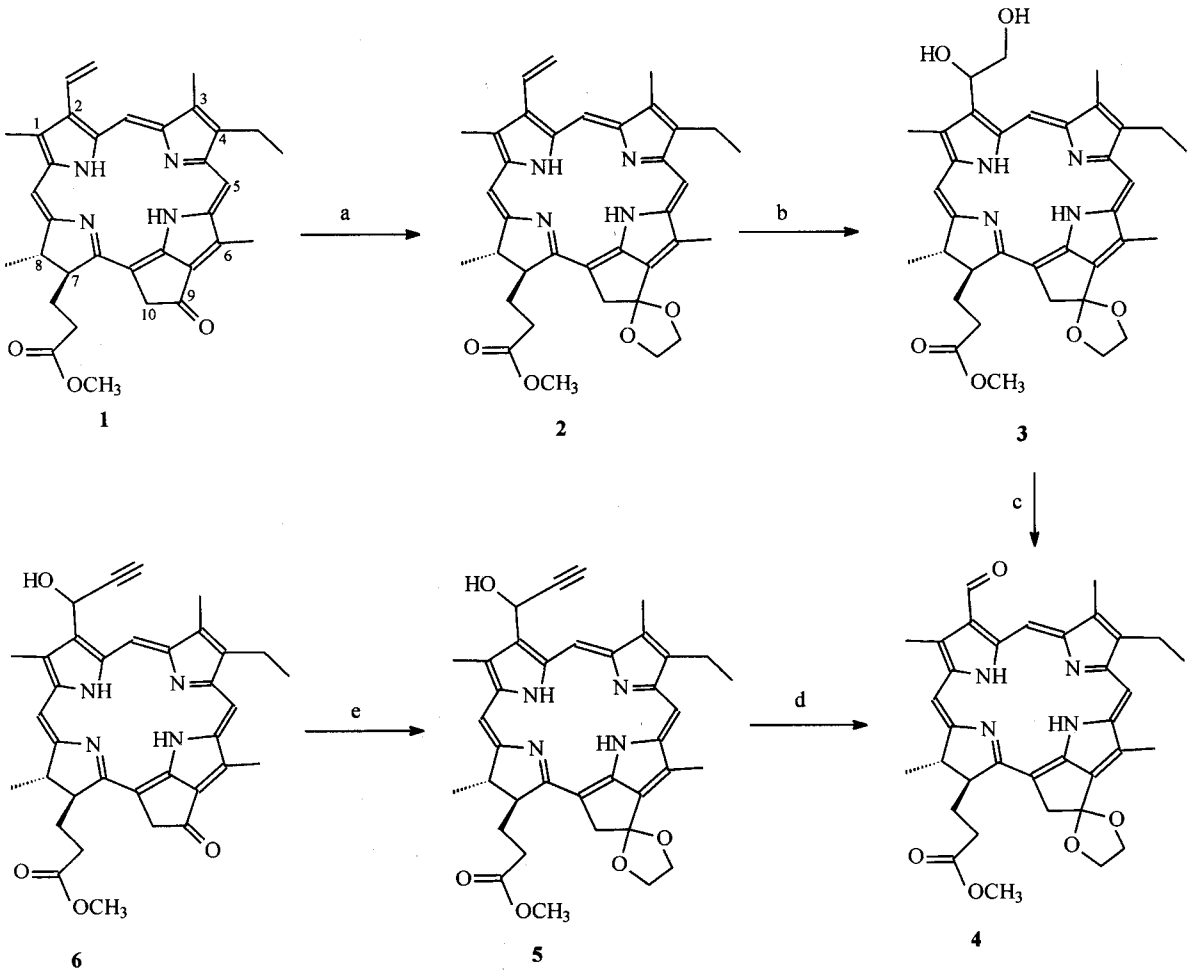
Received August 30, 2002; revised December 3, 2002; accepted February 10, 2003.

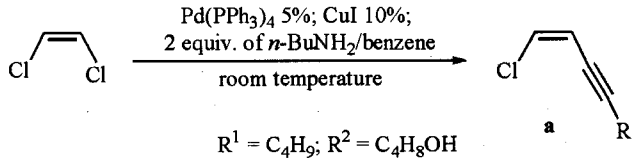
Project supported by the Ministry of the Science and Technology of China as a cooperative Project between China and Korea (2002).

Scheme 1



a) $HOCH_2CH_2OH/TMS/CH_2Cl_2$; b) $OsO_4/C_5H_5N/THF$;
c) $NaIO_4/MeOH/SiO_2$; d) $BrMgC{\equiv}CH/THF$; e) $H_2O/AcOH$

Scheme 2



Further palladium-catalyzed coupling reaction of **7** was performed with (*Z*)-chloroenynes (**a**) in benzene containing *n*-butylamine to produce zinc chlorin-enediyne dayds (**8**) in moderate yield. After zinc-chlorins **8** were demetalated with 30% TFA in CH_2Cl_2, the alchol chlorin-enediyne dyads **9** were oxidized using tetrapropylammonium perruthenate and *N*-methyl-morpholine *N*-oxide to generate di-keto chlorinenediynes (**10**) in 61% yield (Scheme 3).

In summary, we have developed a new approach for the preparation of a versatile chlorin-alkyn building block **6** via Grignard reaction. The utility of this terminal alkyne has been demonstrated by preparing new chlorin-enediynes dyads. This synthesis has great significance and potential for searching the dual functionalized anticancer drugs in chemotherapeutic and photodynamic therapy.

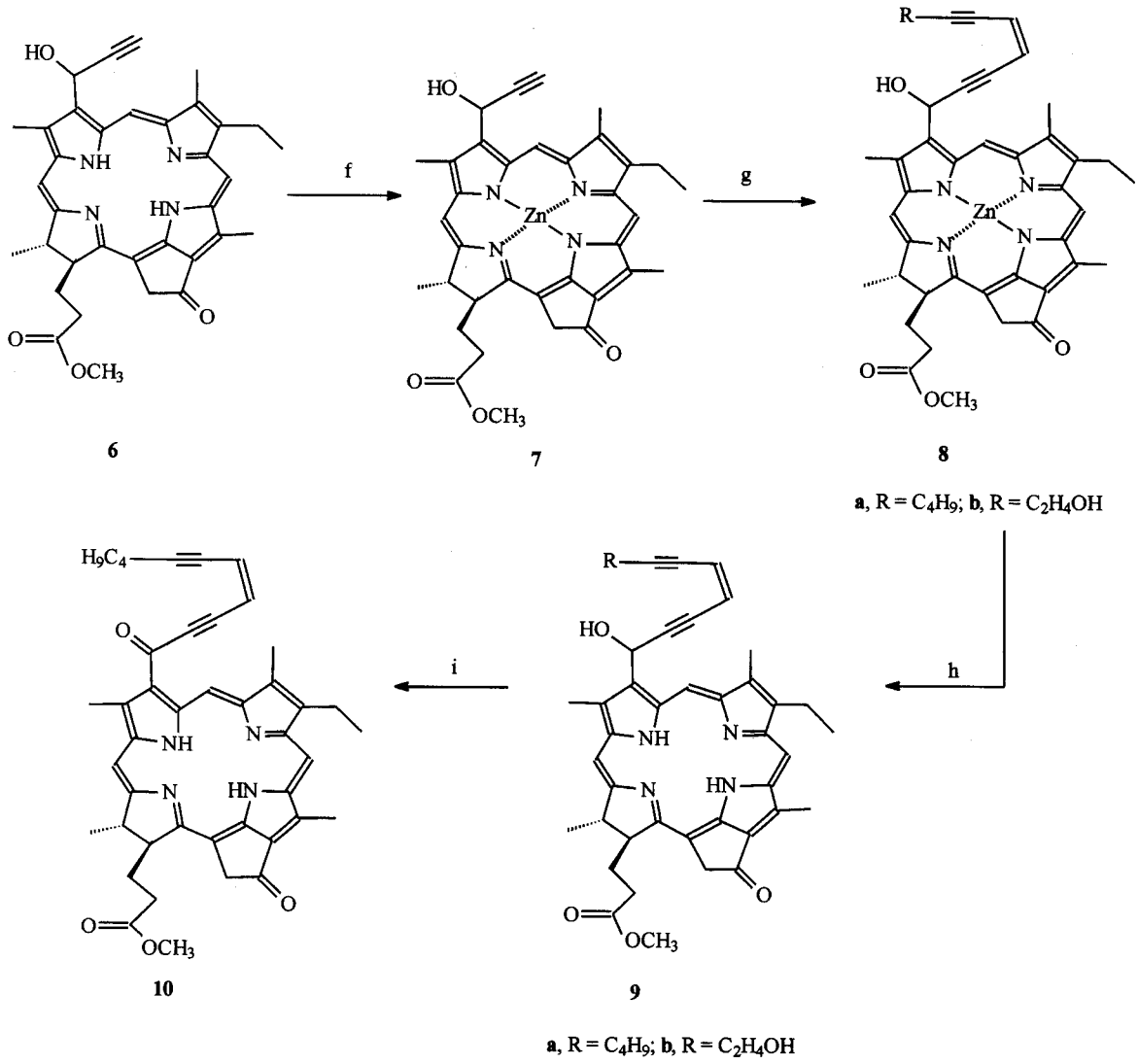
Experimental

Instruments and materials

The ^1H NMR spectra were recorded on a Varian-300 MHz spectrometer. Chemical shifts are given as δ values using tetramethylsilane as the internal standard and *J* values are given in Hz. The IR spectra were measured with a Shimadzu FTIR 8300 instrument. The mass spectra were measured with a JEOL 01SG-2 spectrometer. Elemental analyses were performed on a Perkin- Elmer 240 C Microanalyzer.

All chemical reagents were commercially available and purified with standard methods before use. Solvents were dried in routine ways and redistilled. Methyl pyropheophorbide-a (MPPa, **1**) was prepared according to Smith's method.[9]

Scheme 3



9-Ethylenedioxyl-9-deoxo-phropheophorbid-a methyl ester (**2**)

To a stirred solution of compound **1** (0.3 mmol) in dry dichlorimethane (20 mL) was added ethylene glycol (4 mL) and trimethylsilyl chloride (1 mL). The mixture was stirred at room temperature for 24 h and then poured into ice-cooled aqueous NH_4OH. The organic layer was separated, washed, dried and evaporated to dryness. The residue was chromatographed on alumina (Crade III) with dichloromethane as eluent to give **2** in 75% yield, UV-vis ($CHCl_3$) λ_{max}: 400 (1.00), 500 (0.15), 550 (0.05), 598 (0.07), 652 (0.35) nm; ^1H NMR (300 MHz, $CDCl_3$) δ: -3.06 (brs, 1H, NH), -1.22 (brs, 1H, NH), 1.76 (t, J = 7.8 Hz, 3H, 4b-H), 1.81 (d, J = 7.2 Hz, 3H, 8-CH_3), 2.20—2.80 (m, 4H, 7a + 7b-H), 3.40, 3.55, 3.60, 3.64, (s, each 3H, OCH_3 + CH_3), 3.84 (q, J = 7.8 Hz, 2H, 4a-H), 3.82—4.42 (m, 1H, 7-H), 4.50—4.98 (m, 5H, 8-H + OCH_2CH_2-O), 5.10 (d, J = 20 Hz, 1H, 10-H), 5.14 (d, J = 20 Hz, 1H, 10-H), 6.08—6.32 (m, 2H, 2b-H), 8.06—8.21 (m, 1H, 2a-H), 8.89, 9.68, 9.82 (s, each 1H, meso-H); IR (KBr) ν: 2976 —2878 (C—H), 1736 (C=O), 1620 (C=C) cm^{-1}. Anal. calcd for $C_{36}H_{40}N_4O_4$: C 72.94, H 6.82, N 9.45; found C 72.84, H 6.74, N 9.36.

2-Formyl-9-ethylenedioxyl-2-devinyl-9-deoxo-pyropheophorbid-a methyl ester (**4**)

The compound **2** (0.35 mmol) was suspended in a solution of osmium (VIII) oxide (175 mg) in THF (35 mL) with pyridine (0.5 mL) at 0 ℃. The mixture was stirred for 30 min in dark before the ice bath was removed, allowing the mixture to stir at room temperature for additional 1 h. An excess of $NaHSO_3$ (15 g), dissolved in

50% MeOH/water was added, and the mixture was stirred for 20 min, until the brown Os_2O_3 precipitate was filtered off. After partition between CH_2Cl_2 and water, the organic layer was dried over anhydrous Na_2SO_4, and the solvent were evaporated to give compound **3**. The crude compound was suspended with silica gel (2.5 g) in THF (15 mL) before a solution of sodium metaperiodate (1 g) in water (15 mL) was added. A color change from green to copper, completed within 30 min, indicating the end of the reaction. After addition of CH_2Cl_2(20 mL), the mixture was filtered through cotton wool and then the resultant crude product was chromatographed on silic-gel column [eluent: Hex-EA (4:1, *V/V*)] to give **4** in 84% yield. UV-vis ($CHCl_3$) λ_{max}: 401 (1.00), 507 (0.05), 537 (0.11), 608 (0.05), 672 (0.24) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ: −1.82 (brs, 1H, NH), 0.29 (brs, 1H, NH), 1.68 (t, J = 7.8 Hz, 3H, 4b-H), 1.78 (d, J = 7.6 Hz, 3H, 8-CH_3), 2.18—2.85 (m, 4H, 7a + 7b-H), 3.33, 3.51, 3.56, 3.76, (s, each 3H, OCH_3 + CH_3), 3.88 (q, J = 7.8 Hz, 2H, 4a-H), 4.22—4.43 (m, 1H, 7-H), 4.45—4.79 (m, 5H, 8-H + OCH_2CH_2-O), 5.02 (d, J = 20 Hz, 1H, 10-H), 5.14 (d, J = 20 Hz, 1H, 10-H), 8.92, 9.50, 10.49 (s, each 1H, *meso*-H), 11.62 (s, 1H, CHO); IR (KBr) ν: 2970—2878 (C—H), 1714, 1728 (2C = O), 1600 (C = C) cm^{-1}. Anal. calcd for $C_{35}H_{38}N_4O_5$: C 70.67, H 6.45, N 9.42; found C 70.77, H 6.57, N 9.26.

2-(1-Hydroxylpropynyl)-9-ethylenedioxyl-2-devinyl-9-deoxo-pyropheophorbide-a methyl ester (**5**)

To a solution of compound **4** (0.25 mmol) in THF (15 mL) at 0 ℃ was added 3 mL of ethynyl magnesium bromide in THF (1 mol/L). The mixture was then allowed to stir for 15 min until it was poured to ice-cooled aq. NH_4Cl. The aqueous phase was extracted with ethyl ether. The combined organic layers were dried over Na_2SO_4. After evaporation of the solvent, the residue was purified with a silica-gel column [eluent: Hex-EA (3:1, *V/V*)] to give **5** in 68% yield. UV-vis ($CHCl_3$) λ_{max}: 395 (1.00), 498 (0.12), 523 (0.05), 596 (0.06), 650 (0.05) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ: −2.29 (brs, 1H, NH), −1.48 (brs, 1H, NH), 1.67 (t, J = 7.7 Hz, 3H, 4b-H), 1.77 (d, J = 7.3 Hz, 3H, 8-CH_3), 2.09—2.32 (m, 1H, 7a-H), 2.44—2.84 (m, 1H, 7b-H), 2.83 (d, J = 2.3 Hz, 1H, 2c-H), 3.28, 3.51, 3.53, 3.56 (s, each 3H, OCH_3 + CH_3), 3.70 (q, J = 7.8 Hz, 2H, 4a-H), 4.30—4.63 (m, 6H, 7,8-H + OCH_2CH_2O), 4.97 (d, J = 17 Hz, 1H, 10-H), 5.14 (d, J = 17 Hz, 1H, 10-H), 6.92 (d, J = 2.3 Hz, 1H, 2a-H), 8.81, 9.56, 10.00 (s, each 1H, *meso*-H); IR (KBr) ν: 3301 (C≡C—H), 2974—2883 (C—H), 2268 (C≡C), 1734 (C = O), 1608 (C = C) cm^{-1}. Anal. calcd for $C_{37}H_{40}N_4O_5$: C 71.58, H 6.51, N 9.03; found C 71.77, H 6.52, N 9.22.

2-(1-Hydroxylpropynyl)-2-devinypyropheophorbide-a methyl ester (**6**)

The compound **5** (0.2 mmol) was stirred in a solution of 60% AcOH for 1 h in dark at 40 ℃, and then it was poured into ice-cooled water. The mixture was extracted with methylene chloide, and washed with water. The organic layer was dried over anhydrous Na_2SO_4, and concentrated. The crude product was chromatographed over a silica gel column [eluent: Hex-EA (3:1, *V/V*)] to give **6** in 90% yield. UV-vis ($CHCl_3$) λ_{max}: 318 (0.23), 409 (1.00), 505 (0.12), 536 (0.12), 604 (0.11), 661 (0.44) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ: −2.30 (brs, 1H, NH), −0.42 (brs, 1H, NH), 1.51 (t, J = 7.8 Hz, 3H, 4b-H), 1.63 (d, J = 7.3 Hz, 3H, 8-CH_3), 2.01—2.28 (m, 1H, 7a-H), 2.30—2.57 (m, 1H, 7b-H), 2.85 (d, J = 2.3 Hz, 1H, 2c-H), 3.12, 3.29, 3.41, 3.58, (s, each 3H, OCH_3 + CH_3), 3.62 (q, J = 7.8 Hz, 2H, 4a-H), 3.87 (brs, 1H, 7-H), 4.28 (brs, 1H, 8-H), 4.78 (d, J = 17 Hz, 1H, 10-H), 4.81 (d, J = 17 Hz, 1H, 10-H), 6.81 (d, J = 2.3 Hz, 1H, 2a-H), 8.39, 9.58, 9.67 (s, each 1H, *meso*-H); IR (KBr) ν: 2972—2882 (C—H), 2257 (C≡C), 1734, 1744 (2C = O), 1608 (C = C) cm^{-1}. Anal. calcd for $C_{37}H_{40}N_4O_5$: C 71.58, H 6.51, N 9.03; found C 71.77, H 6.52, N 9.22.

Zinc(II) 2-(1-hydroxylpropynyl)-2-devinylpyropheophorbid-a methyl ester (**7**)

To a saturated solution of $Zn(AcO)_2$ in MeOH (10 mL) was added compound **6** (0.2 mmol) in methylene chloride (20 mL). The mixture was then stirred at 50 ℃ for 3 h before water (20 mL) and methlyene chloride (15 mL) were added. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was chromatographed on silica gel [eluent: Hex-EA (4:1, *V/V*)] to give **7** in 90% yield. UV-vis ($CHCl_3$) λ_{max}: 339 (0.21), 411 (1.00), 524 (0.80), 543 (0.10), 611 (0.09), 667 (0.45) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.43 (t, J = 7.8 Hz, 3H, 4b-H), 1.54 (d, J = 7.3 Hz, 3H, 8-CH_3), 1.92—2.04 (m, 1H, 7a-H), 2.08—2.42 (m, 1H, 7b-H), 2.85 (d, J = 2.3 Hz, 1H, 2c-H), 3.14, 3.25, 3.32, 3.62, (s, each 3H, OCH_3 + CH_3), 3.61 (q , J = 7.8 Hz, 2H, 4a-H), 3.78 (brs, 1H, 7-H), 4.19 (brs, 1H, 8-H), 4.50 (d, J = 18 Hz, 1H, 10-H), 4.61 (d, J = 18Hz, 1H, 10-H), 6.64 (d, 1H, J = 2.3 Hz, 2a-H), 8.10, 9.07, 9.45 (s, each 1H, *meso*-H); IR (KBr) ν: 2972—2882 (C—H), 2260 (C≡C), 1734, 1744 (2C = O), 1608 (C = C) cm^{-1}. FAB-MS calcd for $C_{37}H_{38}N_4O_5Zn$ 685 (M^+ + 1), found 685 (M^+ + 1).

2-(1-*Hydroxyl*-4-*undecenen*-2, 6-*diynyl*)-2-*devinylpyropheophorbid-a methyl ester* (**9a**)

To a solution of terminal alkyne **7** (0.2 mmol) in benzene (10 mL) at room temperature was added $Pd(PPh_3)_4$ (45 mg), *n*-butylamine (0.3 mmol) and (1*Z*)-1-chlorohex-1-en-3-yne (0.3 mmol) under nitrogen rapidly. After 10 min, cuprous iodide (25 mg) was introduced into the stirred solution. After additional 8 h at room temperature, the mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was dissolved in CH_2Cl_2(15 mL), and then treated with 30% aq. TFA (15 mL). The solution was stirred for 4 h at room temperature. The organic layer was washed with water, 5% aq. $NaHCO_3$ and water, dried (Na_2SO_4) and concentrated. Purification by column chromatography [eluent: Hex-EA (4 : 1, *V*/*V*)] afforded **9a** in 62% yield. UV-vis ($CHCl_3$) λ_{max}: 318 (0.25), 411 (1.00), 508 (0.14), 538 (0.13), 610 (0.12), 661 (0.50) nm; ^1H NMR (300 MHz, $CDCl_3$) δ: −2.01 (brs, 1H, NH), −1.76 (brs, 1H, NH), 1.19 (t, J = 7.2 Hz, 3H, 2k-CH_3), 1.43—1.73 (4H, m, 2i + 2j-H), 1.61 (t, J = 7.5 Hz, 3H, 8-CH_3), 1.66 (d, J = 7.2 Hz, 3H, 4b-H), 2.11—2.33 (m, 1H, 7a-H), 2.35—2.71 (4H, 2h + 7b-H), 3.12, 3.19, 3.37, 3.54 (s, each 3H, OCH_3 + CH_3), 3.67 (q, J = 7.8 Hz, 2H, 4a-H), 4.25 (m, 1H, 8-H), 4.41 (m, 1H, 7-H), 5.02 (d, J = 18 Hz, 1H, 10-H), 5.08 (d, J = 18 Hz, 1H, 10-H), 5.82 (1H, br, s, 2e-H), 6.24 (1H, br, s, 2d-H), 7.04 (s, 1H, 2a-H), 8.50, 9.38, 9.78 (s, each 1H, *meso*-H); IR (KBr) ν: 2973 —2881 (C—H), 2255 (C≡C), 1732, 1746 (2C = O), 1608 (C = C) cm^{-1}. Anal. calcd for $C_{43}H_{46}N_4O_4$: C 75.62, H 6.80, N 8.21; found C 75.77, H 6.52, N 8.52.

2-(1, 9-*Dihydroxyl*-4-*nonnen*-2, 6-*diynyl*)-2-*devinylpyropheophorbid-a methyl ester* (**9b**)

This compound was obtained using the same method as that for preparing **9a** in 59% yield. UV-vis ($CHCl_3$) λ_{max}: 317 (0.21), 411 (1.00), 4.74 (0.05), 506 (0.11), 537 (0.10), 5.57 (0.04), 608 (0.09), 665 (0.53) nm; ^1H NMR (300 MHz, $CDCl_3$) δ: −2.07 (brs, 1H, NH), −0.13 (brs, 1H, NH), 1.60 (t, J = 7.5 Hz, 3H, 8-CH_3), 1.72 (d, J = 7.8 Hz, 3H, 4b-H), 2.05—2.33 (m, 2H, 2g + 7a-H), 2.35—2.66 (m, 2H, 7b-H), 3.51 (q, J = 7.8 Hz, 2H, 4a-H), 3.15 (m, 2H, 2h-H), 3.16, 3.16, 3.43, 3.54 (s, each 3H, OCH_3 + CH_3), 4.12 (m, 1H, 8-H), 4.35 (m, 1H, 7-H), 4,94 (d, J = 18 Hz, 1H, 10-H), 5.09 (d, J = 18 Hz, 1H, 10-H), 5.83 (2H, br, s, 2d, 2e-H), 6.99 (s, 1H, 2a-H), 8.46, 9.17, 9.76 (s, each 1H, *meso*-H); IR (KBr) ν: 2973 —2880 (C—H), 2265 (C≡C), 1733, 1744 (2C = O), 1608 (C = C) cm^{-1}. Anal. calcd for $C_{41}H_{42}N_4O_5$: C 73.40, H 6.32, N 8.35; found C 73.56, H 6.51, N 8.53.

2-(1-*Oxo*-4-*undecenen*-2, 6-*diynyl*)-2-*devinylpyropheophorbid-a methyl ester* (**10**)

A mixture of **9a** (0.2 mmol), *N*-methylmorpholine *N*-oxide (60 mg) in dichloromethane (25 mL) was stirred at room temperature under nitrogen for 10 min. Tetrapropylammonium perruthenate (10 mg) was added, and then the mixture was stirred for 1 h. The mixture was washed with water, dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel, eluting initially with dichloromethane (to remove excess *N*-methylmorpholine *N*-oxide) and then with 1% methanol in dichloromethane. The major fraction was collected to give **10** in 61% yield. UV-vis ($CHCl_3$) λ_{max}: 392 (1.00), 444 (0.75), 525 (0.29), 561 (0.29), 639 (0.24), 698 (0.74) nm; ^1H NMR (300 MHz, $CDCl_3$) δ: −2.11 (brs, 1H, NH), −0.02 (brs, 1H, NH), 1.50—1.80 (m, 4H, 2i + 2j-H), 1.26 (t, J = 7.2 Hz, 3H, 2k-CH_3), 1.68 (d, J = 7.5 Hz, 3H, 8-CH_3), 1.83 (t, J = 7.2Hz, 3H, 4b-H), 2.18—2.40 (m, 2H, 7b-H), 2.49—2.81 (m, 4H, 2h + 7a-H), 3.82, 3.71, 3.62, 3.29 (each s, 3H, CH_3 + OCH_3), 3.80 (q, J = 7.2 Hz, 2H, 4a-H), 4.35 (m, 1H, 8-H), 4.56 (m, 1H, 7-H), 5.20 (d, J = 18 Hz, 1H, 10-H), 5.26 (d, J = 18 Hz, 1H, 10-H), 6.25 (brs, 2H, 2d + 2e H), 8.83, 9.59, 10.54 (each s, 1H, *meso*-H). IR (KBr) ν: 2970 —2878 (C—H), 2255 (C≡C), 1730, 1746, 1678 (3C = O), 1608 (C = C) cm^{-1}. Anal. calcd for $C_{43}H_{44}N_4O_4$: C 75.84, H 6.53, N 8.23; found C 75.65, H 6.51, N 8.45.

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(E0208301 ZHAO, X. J.)