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Synthesis, modification, and optical properties of C3-ethynylated chlorophyll derivatives

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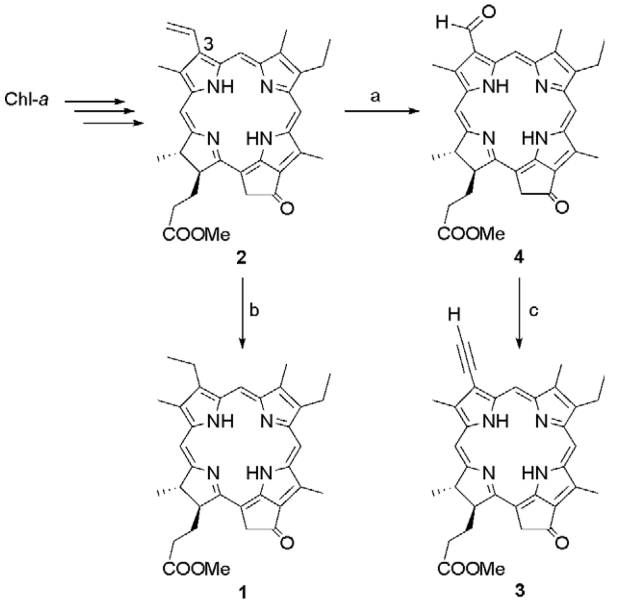
ABSTRACT

3-Ethynyl-chlorin was prepared from methyl pyropheophorbide-*d* using Bestmann-Ohira reagent. The mono-substituted acetylene was subjected to copper-free, Pd-mediated coupling to form chlorin derivatives possessing a series of substituted ethynyl groups at the C3-position. Its 1,3-dipolar cycloadditions with azido compounds were also demonstrated.

Naturally occurring (bacterio)chlorophylls [=(B)Chls] have several kinds of C3-substituents on their tetrapyrrole macrocycles. It is well known that these substituents characterize their structural and spectroscopic properties. For example, Chl-*a* has the C3-vinyl group attached directly to its chlorin π-system, while Chl-*d* has a formyl group at the same position which causes a red shift of the Q_y peak maxima from 662 to 688 nm in ether.[1] To investigate systematically the C3-substituent effects on the (bacterio)chlorin rings, we have developed synthetic routes for transformation of natural moieties to a variety of C3-functional groups.[2] For the basic study of optical properties, Wittig and Knoevenagel reactions to the C3-formyl group were applied to introduce a series of vinyliden units: 3-CHO→3-CH=CXY.[3] In the course of developing chlorophylls with functionalities: a C3-hydroxymethyl group was found to be better than the natural 1-hydroxyethyl unit to form well-ordered self-aggregates,[4,5] 3-trifluoroacetyl-chlorin acted as a visual chemosensor for alcohol/amine detection,[6] and C3-carboxylic acid derivatives have successfully been applied to dye-sensitized solar cells.[7]

Although the oxidation of C3-vinyl to formyl group (**2**→**4**)[4] and the reduction (hydrogenation) to ethyl group (**2**→**1**)[8] were reported, the oxidized (dehydrogenated) state **3** possessing the C3-ethynyl group has not yet been prepared (see Scheme 1). Since many porphyrin derivatives with ethynyl groups have been synthesized to construct artificial models of natural photosynthetic antennae,[9] a chlorophyll-derived ethynyl-chlorin appears to be a more direct and suitable component for developing such supramolecular structures.[10,11] The reactivity of the terminal acetylene is expected to allow versatile reactions such as Sonogashira-coupling



Scheme 1. Reagents and conditions: (a) $NaIO_4$, OsO_4, THF, aq AcOH; (b) 10% Pd–C, H_2, acetone; (c) $(MeO)_2P(O)C(COMe)N_2$, Cs_2CO_3, THF–MeOH, rt, 2 h, 37%.

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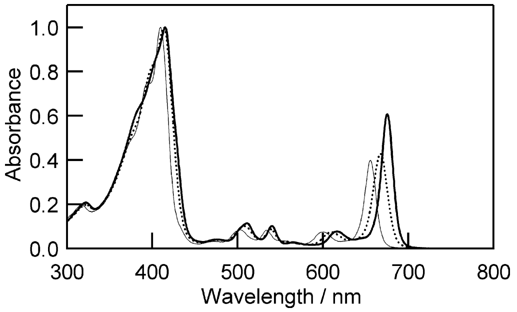
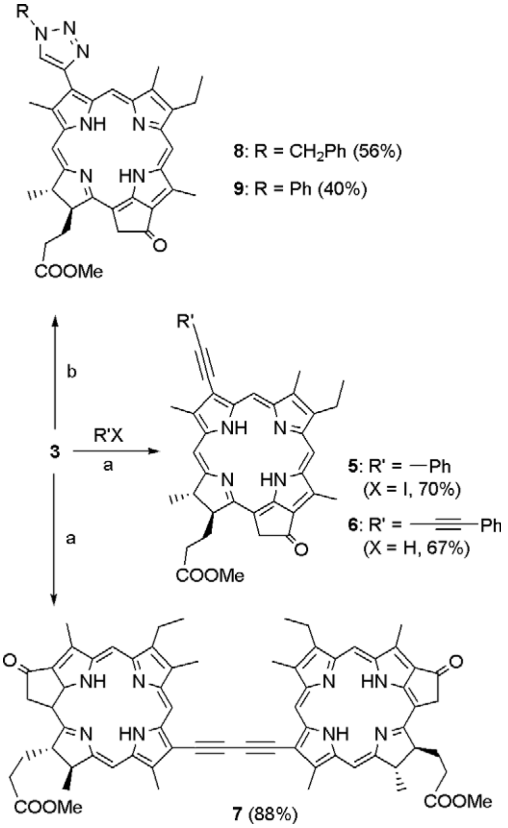


Figure 1. Electronic absorption spectra of 3-ethyl-chlorin **1** (solid thin line), 3-vinyl-chlorin **2** (dotted line), and 3-ethynyl-chlorin **3** (solid thick line) in CH_2Cl_2. All spectra were normalized at their Soret peaks.

with aromatic halides, Glaser-coupling with other ethynylated compounds, and 1,3-dipolar cycloaddition with azido compounds. In this Letter, we report the synthesis and optical properties of 3-ethynyl-chlorin **3** together with some of its chemical modifications.

Methyl pyropheophorbide-*a* (**2**),[4] methyl pyropheophorbide-*d* (**4**),[4] and methyl mesopyropheophorbide-*a* (**1**)[8] were prepared as previously reported. To introduce an ethynyl group at the C3-position, direct transformation of the C3-formyl of **4** to the ethynyl group was examined because recent papers reported the conversion of aromatic aldehydes to the corresponding ethynyl derivatives under mild conditions.[12] Treatment of **4** with commercially available Bestmann-Ohira reagent [$(MeO)_2P(O)C(COMe)N_2$] in the presence of Cs_2CO_3 in THF and MeOH was shown to give 3-ethynyl-chlorin **3** in 37% yield.[13] Figure 1 compares the absorption spectra of three kinds of chlorins **1**–**3** possessing ethyl, vinyl, and ethynyl groups at the C3-position. The Soret, Q_x, and Q_y bands were red-shifted in this order, which were consistent with an increase in the bond order of the substituents (see Table 1). It should be noted that 3-ethynyl-chlorin **3** has a relatively intense Q_y peak [$\mathrm{Int}(Q_y)/\mathrm{Int(Soret)} = 0.61$]. Fluorescence emission peaks excited at the Soret maxima were also shifted to a longer wavelength in the order of **1** < **2** < **3**. The Stokes shift of **3** (40 cm^{-1}) was comparable to that of **1** (50 cm^{-1}), and was much smaller than that of **2** (110 cm^{-1}). Fluorescence quantum yield of **3** (0.26) in an aerated CH_2Cl_2 solution was slightly larger than those of **1** (0.20) and **2** (0.21).



Scheme 2. Reagents and conditions: (a) $Pd_2(dba)_3$, $P(o\text{-tol})_3$, Et_3N, toluene, 60 °C, 12 h; (b) (i) $Zn(OAc)_2 \cdot 2H_2O$, MeOH–CH_2Cl_2; (ii) RN_3, sodium ascorbate, $CuSO_4 \cdot 5H_2O$, acetone–H_2O, 80 °C, 12 h; (iii) aqueous 6 N HCl, CH_2Cl_2.

To explore synthetic routes based on the reactive ethynyl group, several kinds of coupling reactions were investigated. Copper-free Sonogashira coupling[14] of **3** using Pd-catalyst with excess iodobenzene or phenylacetylene gave the expected products in moderate yields (**5**: 70%, **6**: 67%, see Scheme 2).[15] Without additional reactants, homo-coupling of the terminal acetylene of **3** occurred under the same reaction conditions to form dimeric chlorin **7**.[15] Replacement of the terminal hydrogen to phenyl group (**3**→**5**) and π-extension of the phenylethynyl to phenylbutadiyl unit (**5**→**6**) caused slightly red shifts of their electronic absorption maxima. As shown in Figure 2, the Q_y peak maximum of chlorin dimer **7** appeared at a longer-wavelength region (696 nm) with a high intensity [$\mathrm{Int}(Q_y)/\mathrm{Int(Soret)} = 0.95$] compared to those of **6** (686 nm and 0.64), suggesting that two chlorin macrocycles interacted in a molecule through the linear butadiyne spacer along the Q_y axis.

In light of recent trends of click chemistry,[16] Huisgen reactions of **3** with azido compounds were also examined. Since copper ion was requisite for the cycloaddition, free-base chlorin **3** was found to be concomitantly copper-metallated and the desired cycloaddition was also advanced. Thus, chlorin **3** was initially zinc-metallated,[17] and was subjected to the reaction with benzylazide or

Table 1

Visible absorption maxima (λ_{abs}/nm), ratio of absorption peak intensities (Int), fluorescence emission maximum (λ_{em}/nm),[a] and fluorescence quantum yield (Φ_{flu})[a] of chlorophyll derivatives in CH_2Cl_2

Compound	λ_{abs}					$\mathrm{Int}(Q_y)/\mathrm{Int(Soret)}$	λ_{em}	Φ_{flu}
	Soret	Q_x		Q_y				
		(0,1)	(0,0)	(0,1)	(0,0)			
1 ($R^3 = CH_2CH_3$)	410	504	534	600	656	0.40	658	0.20
2 ($R^3 = CH{=}CH_2$)	414	508	539	610	667	0.43	672	0.21
3 ($R^3 = C{\equiv}CH$)	415	511	541	616	675	0.61	677	0.26
5 ($R^3 = C{\equiv}C–Ph$)	419	513	542	620	679	0.56	681	0.26
6 ($R^3 = C{\equiv}C–C{\equiv}C–Ph$)	423	517	546	626	686	0.64	688	0.27
7 ($R^3 = C{\equiv}C–C{\equiv}C\text{-}3'$)	419	519	551	628	696	0.95	700	0.34
8 ($R^3 = C_2HN_3–CH_2Ph$)	413	509	539	610	668	0.51	671	0.26
9 ($R^3 = C_2HN_3\text{-}Ph$)	413	508	539	611	669	0.52	672	0.27

[a] Fluorescence data were recorded by excitation at the Soret peak.

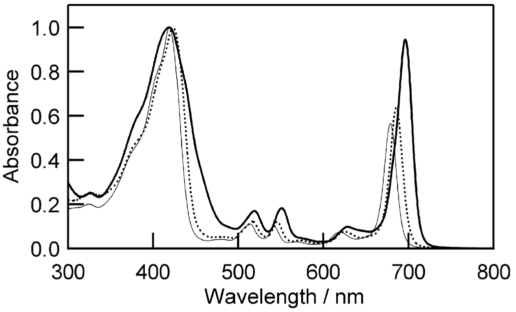


Figure 2. Electronic absorption spectra of 3-(phenyl)ethynyl-chlorin **5** (solid thin line), 3-(phenyl)butadiyl-chlorin **6** (dotted line), and chlorin dimer **7** (solid thick line) in CH_2Cl_2. All spectra were normalized at their Soret peaks.

phenylazide to form a triazole ring followed by acidic demetallation. Two kinds of reaction conditions, $CuSO_4 \cdot 5H_2O$ and sodium ascorbate in aqueous acetone[18] or $Cu(PPh_3)_3Br$ in diisopropylethylamine and THF,[19] gave similar results to afford chlorins **8** and **9** in 56 and 40%, respectively.[15] Less hindered regioisomers as drawn in Figure 2 were the sole products, the stereochemistry of which was confirmed by their NOESY spectra. As summarized in Table 1, optical properties of **8** and **9** were similar to that of 3-vinyl-chlorin **2**, and the benzyl and phenyl substituents on the triazole ring showed no electronic effects on chlorin macrocycles.

In summary, we have shown a facile synthetic route of transforming the C3-formyl to ethynyl group on a chlorin ring. Coupling reactions as well as 1,3-dipolar cycloaddition were demonstrated, which would lead to the construction of chlorin oligomers in artificial photosynthetic systems. Introduction of an ethynyl group to the other positions on a chlorin macrocycle and the synthesis of a chlorin unit possessing multi-acetylene moieties are in progress.

Acknowledgments

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References and notes

1. Miyashita, H.; Adachi, K.; Kurano, N.; Ikemoto, H.; Chihara, M.; Miyachi, S. *Plant Cell Physiol.* **1997**, *38*, 274–281.
2. Sasaki, S.; Tamiaki, H. *J. Org. Chem.* **2006**, *71*, 2648–2654.
3. Tamiaki, H.; Kouraba, M. *Tetrahedron* **1997**, *53*, 10677–10688.
4. Tamiaki, H.; Amakawa, M.; Shimono, Y.; Tanikaga, R.; Holzwarth, A. R.; Schaffner, K. *Photochem. Photobiol.* **1996**, *63*, 92–99.
5. Tamiaki, H.; Kitamoto, H.; Watanabe, T.; Shibata, R. *Photochem. Photobiol.* **2005**, *81*, 170–176.
6. Sasaki, S.; Kotegawa, Y.; Tamiaki, H. *Tetrahedron Lett.* **2006**, *47*, 4849–4852.
7. (a) Wang, X.-F.; Xiang, J.; Wang, P.; Koyama, Y.; Yanagida, S.; Wada, Y.; Hamada, K.; Sasaki, S.; Tamiaki, H. *Chem. Phys. Lett.* **2005**, *408*, 409–414; (b) Wang, X.-F.; Matsuda, A.; Koyama, Y.; Nagae, H.; Sasaki, S.; Tamiaki, H.; Wada, Y. *Chem. Phys. Lett.* **2006**, *423*, 470–475; (c) Wang, X.-F.; Koyama, Y.; Nagae, H.; Wada, Y.; Sasaki, S.; Tamiaki, H. *J. Phys. Chem. C* **2008**, *112*, 4418–4426.
8. (a) Smith, K. M.; Goff, D. A.; Simpson, D. J. *J. Am. Chem. Soc.* **1985**, *107*, 4946–4954; (b) Li, G.; Graham, A.; Chen, Y.; Dobhal, M. P.; Morgan, J.; Zheng, G.; Kozyrev, A.; Oseroff, A.; Dougherty, T. J.; Pandey, R. K. *J. Med. Chem.* **2003**, *46*, 5349–5359.
9. (a) Harvey, P. D. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press, 2003; Vol. 18, pp 63–250; (b) Kim, D.; Osuka, A. *Acc. Chem. Res.* **2004**, *37*, 735–745.
10. Chlorophyll oligomers based on acetylene linkage at the C20-position: (a) Kelley, R. F.; Tauber, M. J.; Wasielewski, M. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 7979–7982; (b) Kelly, R. F.; Tauber, M. J.; Wilson, T. M.; Wasielewski, M. R. *Chem. Commun.* **2007**, 4407–4409.
11. Chlorophyll-derived oligomers without acetylene unit: (a) Röder, B.; Ermilov, E. A.; Hackbarth, S.; Helmreich, M.; Jux, N. *Proc. SPIE* **2006**, *6192*, 61920-1-12; (b) Sasaki, S.; Tamiaki, H. *Tetrahedron Lett.* **2006**, *47*, 4965–4968; (c) Campo, M. A.; Gabriel, D.; Kucera, P.; Gurny, R.; Lange, N. *Photochem. Photobiol.* **2007**, *83*, 958–965; (d) Kelley, R. F.; Goldsmith, R. H.; Wasielewski, M. R. *J. Am. Chem. Soc.* **2007**, *129*, 6384–6385.
12. (a) Krämer, C. S.; Zeitler, K.; Muller, T. J. J. *Org. Lett.* **2000**, *2*, 3723–3726; (b) Boydston, A. J.; Bondarenko, L.; Dix, I.; Weakley, T. J. R.; Hopf, H.; Haley, M. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2986–2989; (c) Dai, W.; Petersen, J. L.; Wang, K. K. *Org. Lett.* **2004**, *6*, 4355–4357; (d) Nakamura, Y.; Kiyota, H.; Ueda, R.; Kuwahara, S. *Tetrahedron Lett.* **2005**, *46*, 7107–7109; (e) Ashburn, B. O.; Carter, R. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 6737–6741; (f) Naffziger, M. R.; Ashburn, B. O.; Perkins, J. R.; Carter, R. G. *J. Org. Chem.* **2007**, *72*, 9857–9865.
13. *Synthetic procedure and characterization data of compound* **3**: To a solution of **4** (100 mg, 0.18 mmol) in THF (15 ml) and MeOH (15 ml) were added Cs_2CO_3 (100 mg, 0.31 mmol) and $(MeO)_2P(O)C(COMe)N_2$ (168 mg, 0.88 mmol), and the mixture was stirred at room temperature under nitrogen. The reaction was monitored by visible spectrometry for 2 h until the Q_y peak (693 nm) of **4** completely disappeared. The reaction mixture was poured into aqueous saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The extract was washed with H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel chromatography (Et_2O–CH_2Cl_2, 7:93) followed by recrystallization from CH_2Cl_2-hexane to give **3** as a black solid (36 mg, 37%): mp >300 °C; vis (CH_2Cl_2) λ_{max} 675 (ε = 63,000), 616 (8000), 540 (11,000), 511 (12,000), 415 (105,000), 321 nm (22,000); IR (CH_2Cl_2) ν_{max} 3299 (alkyne-C–H), 2967, 2929, 2873, 2110 (alkyne-C≡C), 1734 (ester-C=O), 1693 (keto-C=O), 1620, 1551, 1498, 1222 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 9.53 (1H, s, 5-H), 9.52 (1H, s, 10-H), 8.59 (1H, s, 20-H), 5.33, 5.14 (each 1H, d, J = 19 Hz, 13^1–CH_2), 4.50 (1H, dq, J = 2, 7 Hz, 18-H), 4.32 (1H, dt, J = 8, 2 Hz, 17-H), 3.68 (2H, q, J = 8 Hz, 8-CH_2), 3.68 (3H, s, 12-CH_3), 3.61 (3H, s, 17^2–CO_2CH_3), 3.49 (3H, s, 2–CH_3), 3.26 (3H, s, 7–CH_3), 2.74–2.68 (1H, m, 17–CH), 2.60–2.54 (1H, m, 17^1–CH), 2.33–2.26 (2H, m, 17–CHCH), 1.82 (3H, d, J = 7 Hz, 18–CH_3), 1.69 (3H, t, J = 8 Hz, 8^1–CH_3), 0.19, −1.94 (each 1H, s, NH × 2); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 196.1 ($C13^1$), 173.4 ($C17^3$), 170.8 (C19), 160.5 (C16), 154.7 (C6), 151.1 (C9), 148.8 (C14), 144.9 (C8), 140.3, 138.7 (C1, C2), 138.5, 129.0 (C11, C12), 136.8 (C4), 136.5 (C7), 130.9 (C13), 120.7 (C3), 106.4 (C15), 103.9 (C10), 97.9 (C5), 93.6 (C20), 87.8 ($C3^2$), 77.3 ($C3^1$), 51.9 (C17), 51.7 ($C17^4$), 49.7 (C18), 48.1 ($C13^2$), 30.9 ($C17^2$), 29.8 ($C17^1$), 23.2 ($C18^1$), 19.4 ($C8^1$), 17.4 ($C8^2$), 12.5 ($C2^1$), 12.1 ($C12^1$), 11.1 ($C7^1$); MS (TOF) found: m/z 546.2626. Calcd for $C_{34}H_{34}N_4O_3$: M^+, 546.2631.
14. (a) Wagner, R. W.; Johnson, T. E.; Li, F.; Lindsey, J. S. *J. Org. Chem.* **1995**, *60*, 5266–5273; (b) Laha, J. K.; Muthiah, C.; Taniguchi, M.; McDowell, B. E.; Ptaszek, M.; Lindsey, J. S. *J. Org. Chem.* **2006**, *71*, 4092–4102.
15. Compounds **5–9** were characterized by $^1H/^{13}C$ NMR, visible, fluorescence, and mass spectroscopy. Selected data, **5**: mp 221–223 °C; MS (FAB) m/z 623.3 (MH^+), **6**: mp 122–124 °C; MS (FAB) m/z 647.3 (MH^+), **7**: mp >300 °C; MS (FAB) m/z 1091.3 (MH^+), **8**: mp >300 °C; MS (FAB) m/z 666.4 (MH^+), **9**: mp 286–288 °C; MS (FAB) m/z 680.3 (MH^+).
16. (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599; (b) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064; (c) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51–68.
17. (a) Tamiaki, H.; Takeuchi, S.; Tsuzuki, S.; Miyatake, T.; Tanikaga, R. *Tetrahedron* **1998**, *54*, 6699–6718; (b) Tamiaki, H.; Yagai, S.; Miyatake, T. *Bioorg. Med. Chem.* **1998**, *6*, 2171–2178.
18. Punidha, S.; Sinha, J.; Kumar, A.; Ravikanth, M. *J. Org. Chem.* **2008**, *73*, 323–326.
19. Séverac, M.; Pleux, L. L.; Scarpaci, A.; Blart, E.; Odobel, F. *Tetrahedron Lett.* **2007**, *48*, 6518–6522.