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Selective synthesis of C3^2- and C20-monoiodinated chlorophyll derivatives

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ABSTRACT

A chlorophyll derivative possessing an iodine atom at the C3-moiety was synthesized from methyl pyropheophorbide-*a* for the first time using phenyliodine bis(trifluoroacetate) and I_2. The use of larger amounts of reagents resulted in additional iodination at the C20-position, thus affording the 3,20-diiodo derivative. The iodine atom at the C3-moiety of the 3,20-diiodo derivative could be removed selectively by treating with NaN_3, thus affording the 3-vinyl-20-iodo derivative.

Chlorophyll-*a* (Chl-*a*) derivatives or chlorins (Fig. 1) are promising lead compounds in the development of novel photosensitizing drugs for photodynamic therapy (PDT).[1–7] Chlorins have several advantages such as light absorption in the near-infrared region, substantial intersystem crossing (resulting in singlet oxygen generation), and natural abundance. An Asp-conjugated chlorin e_6 is in clinical use and 3-devinyl-3-(1-hexyloxy)ethylpyropheophorbide-*a* (HPPH, Fig. 1) is under clinical trials.[4,5] The introduction of a heavy atom such as iodine in chlorin may improve its singlet oxygen generation due to a heavy-atom effect.[8–15] The efficiency of singlet oxygen generation by brominated or iodinated boron-dipyrromethene dyes has been enhanced by internal heavy-atom effect.[8,9] Pt- or Au-doped silica nanoparticles facilitated the singlet oxygen generation of hypocrellin A encapsulated in the nanoparticles.[13] Iodoaryl moieties bound to chitosan enhanced the singlet oxygen generation of chlorin e_6, a pendant group of the same polymer, by an external heavy-atom effect.[14] Chlorins carrying an iodine atom can be used as PET probes[16,17] and synthetic intermediates.[31]

The following reactions of chlorophyll derivatives have been extensively studied: (i) bromination of the C3-moiety and at the C20- and C10-positions,[18–24] (ii) chlorination of the C3-moiety and at the C20-position,[23–27] and (iii) fluorination at the C20-position.[27] Conjugation of an iodophenyl group at the peripheral substituent of a chlorin has also been reported.[16,17] However, the direct introduction of an iodine atom to the macrocycle and/or peripheral substituents of chlorins needs careful examination. Direct iodination of the *meso*-position of chlorophyll derivatives has been reported;[20,28–31] however, iodination of the reactive C3-vinyl group of methyl pyropheophorbide-*a* (**1**) has not yet been reported. Wang et al. reported that **1** (474 μmol) reacted with I_2 (138 μmol) in the presence of phenyliodine bis(trifluoroacetate) (PIFA, 93 μmol) and pyridine in chloroform, affording 20-iodinated pyropheophorbide-*a* methyl ester (**5**, 62%) directly, remaining the C3-vinyl group unaffected.[20] Similarly, a purpurin imide having a vinyl group at the C3-position was served to the reaction (substrate, 172 μmol; I_2, 40 μmol; PIFA, 163 μmol) and the 3-vinyl-20-iodo derivative was obtained in 51% yield.[28] Recently Tamiaki et al. have reported C20-iodination of chlorins (10 μmol) possessing the C3-ethyl, hydroxymethyl, hydroxyethyl, acetyl, or formyl group, using I_2 (10 μmol) and PIFA (12.5 μmol) and achieved good yields (78–92%).[31] They studied self-assemblies of these iodo-chlorins, while the reactivity of the C3-vinyl-chlorin was not examined. In contrast, we found that under similar reaction conditions, the C3-vinyl moiety was iodinated without any change at the C20-position. Further investigations revealed stepwise iodination at the peripheral vinyl group and C20-position of the macrocycle. Moreover, selective deiodination of the C3-iodoethyl moiety could be achieved using NaN_3, thus enabling the recovery of the vinyl group. Herein, we report the selective synthesis of the monoiodinated derivatives of **1**.

PIFA (0.5 equiv) and I_2 (1 equiv) was added to compound **1** in 10% aqueous acetone or acetonitrile and stirred for 1 h at room

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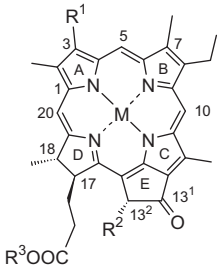


	M	R^1	R^2	R^3
1	H_2	$CH{=}CH_2$	H	CH_3
Chl-*a*	Mg	$CH{=}CH_2$	$COOCH_3$	$C_{20}H_{39}$
MBP-*d*	H_2	$CH(OH)CH_3$	H	CH_3
HPPH	H_2	$CH(OC_6H_{13})CH_3$	H	OH

Figure 1. Molecular structures of chlorophyll derivatives.

temperature (Table 1, Runs 2 and 4). Mass spectrometry of the main product purified by column chromatography revealed an increase of 144 units in molecular weight, corresponding to the addition of one I atom and one OH group to **1**. The ^{1}H NMR spectrum of this product (Fig. 2c) lacked the C3-vinyl proton signals characteristic of **1** (at δ ~8 and 6.2 ppm, Fig. 2a). This product was assigned as the C3-(1-hydroxy-2-iodo)ethyl derivative **3**,[37] because I_2 and PIFA are known to generate electrophilic I+ that reacts with olefin to afford iodoether in the presence of alcohol.[32] The ^{1}H NMR spectrum of iodohydrin **3** showed a multiplet at δ 6.35 ppm, attributed to the C3^1-H, similar to the chemical shift for the C3-(1-hydroxy)ethyl derivative, methyl bacteriopheophorbide-*d* (MBP-*d*, Fig. 1; δ 6.4 ppm).[24,27] The obtained product **3** was a C3^1-racemic mixture, as demonstrated by sets of similar ^{1}H NMR signals with equal areas, for example, the C20-H signals at 8.55 and 8.56 ppm. The UV–visible absorption spectrum of **3** showed the Q_y and Soret absorption peaks at 667 and 411 nm,

Table 1
Composition of the reaction mixture obtained by iodination[a]

Entry	Solvent	H_2O (vol %)	PIFA (equiv)	I_2 (equiv)	**1** (%)	**2** (%)	**3** (%)	**4** (%)
1	Acetone	0	0.5	1	3	50	20	3
2	Acetone	10	0.5	1	18	20	62	0
3	CH_3CN	0	0.5	1	6	63	6	0
4	CH_3CN	10	0.5	1	7	2	77	0
5	$CHCl_3$	0	0.5	1	44	30	1.6	0
6	$CHCl_3$	10	0.5	1	1.4	59	0.4	16
7	$CHCl_3$	20	0.5	1	4	66	1	9
8	$CHCl_3$	10	0	1	100	0	0	0
9	$CHCl_3$	10	1	2	0	25	0.2	44

[a] General reaction conditions: **1** 10–30 μmol in a solvent (10 mL), 1 h at room temperature. Yields were determined from the areas of proton NMR signals specific to respective compounds.

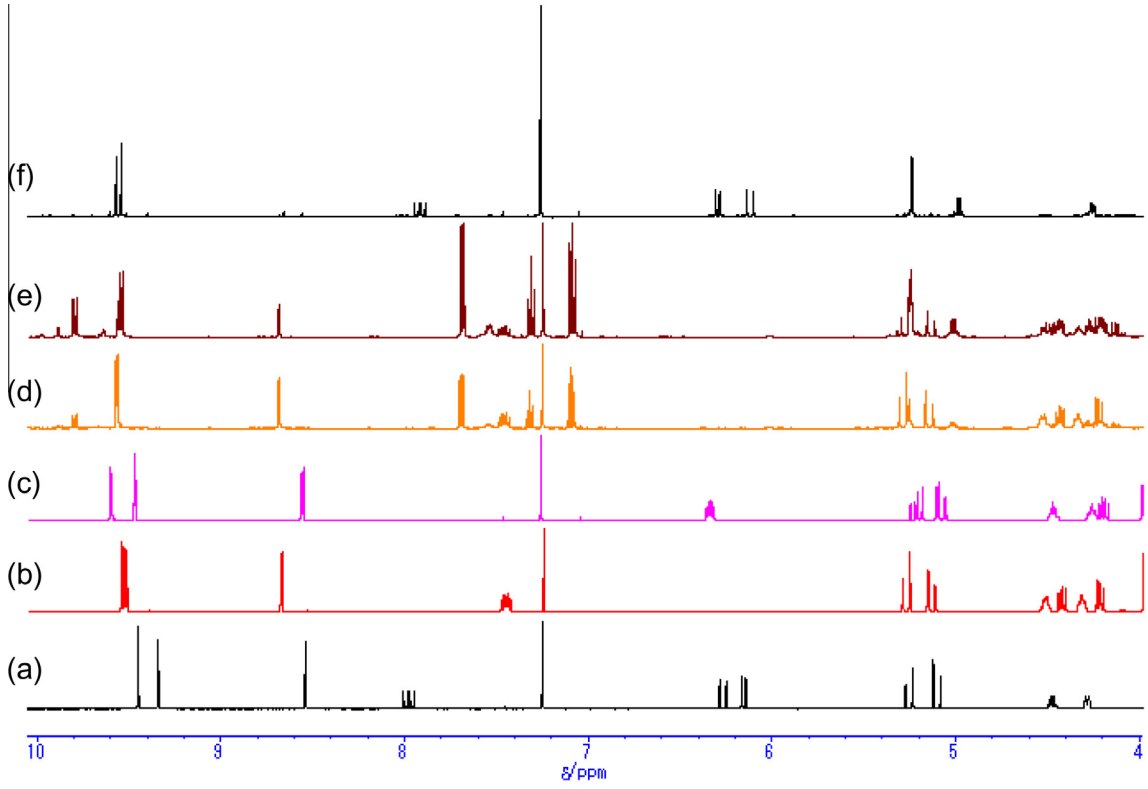


Figure 2. ^{1}H NMR spectra of iodinated chlorins in $CDCl_3$. (a) Compound **1**, (b) compound **2**, (c) compound **3**, (d) a mixture containing compound **4** (obtained by a reaction with 0.5 equiv PIFA and 1 equiv I_2), (e) a mixture containing compound **4** (obtained by a reaction with 1.0 equiv PIFA and 2 equiv I_2), and (f) compound **5**. Signals at δ 7.65, 7.3, and 7.1 ppm in (d) and (e) resulted from the iodobenzene derived from PIFA.

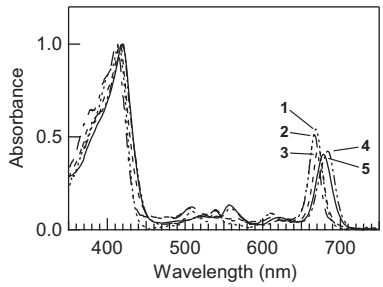


Figure 3. The UV–visible spectra of iodinated chlorins in $CHCl_3$ at room temperature: **1** (···), **2** (––), **3** (–·–), **4** (–···–), and **5** (—). Normalized to the Soret peaks.

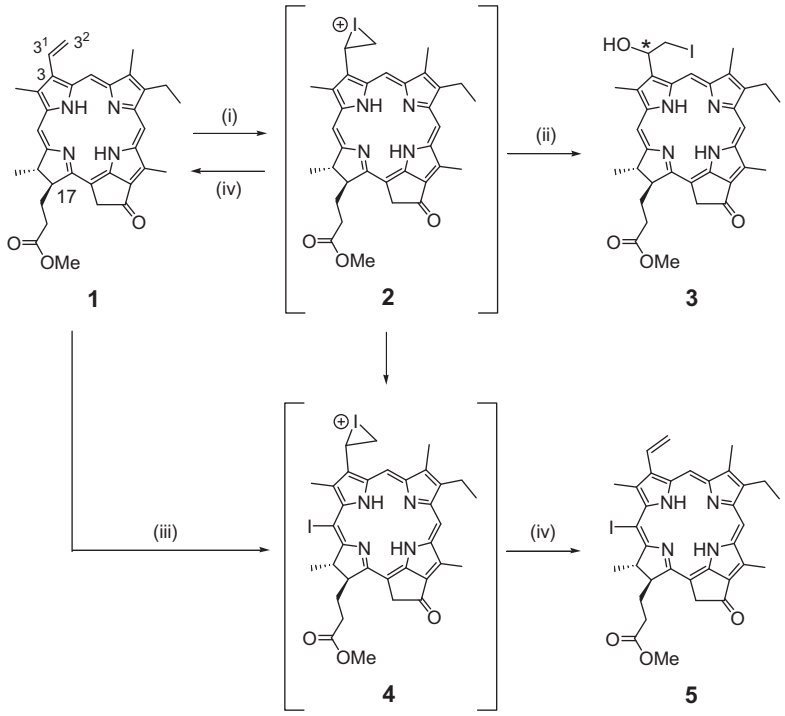
respectively (Fig. 3), slightly red-shifted from those of MBP-*d* (663 and 411 nm, respectively, in $CHCl_3$).[24,27]

Although iodohydrin **3** was obtained in good yields in the aqueous homogeneous solvents containing 10% water (Table 1, Runs 2 and 4; estimated by NMR), **3** was the minor product when the same reaction was conducted in solvents without 10% water. Another new compound, with a characteristic multiplet at δ 7.45 ppm in the ^{1}H NMR spectrum while lacking the C3-vinyl signals, was obtained as the major product (denoted as compound **2**). Compound **2** was also the major product when the reaction was carried out in $CHCl_3$ or 1,2-dichloroethane, while the results were somewhat scattered. The reproducibility was improved by adding water (10–20% v/v) to the solvent system. Increasing the water content in this two-phase system also increased the yield of **2** with a concomitant decrease in residual **1** and by-product **3** (Runs 5–7).[33] Treatment of **2** with water and alcohol afforded iodohydrin (**3**, Scheme 1) and iodoether (see Supplementary data), respectively, indicating that **2** was the intermediate.

Crude **2** could be isolated by column chromatography.[34] The NMR signal of **2** at δ 7.45 ppm was attributed to the C3^1-H proton based on COSY and NOESY experiments and those at δ 4.3 and 4.5 ppm were attributed to the C3^2-protons (Fig. 2b). Pairs of *meso*-proton signals indicated that **2** is a C3^1-racemic mixture. The MALDI-TOF-MS spectrum of **2** showed *m*/*z* peak at 675, corresponding to **1** + I. The UV–visible absorption spectrum of **2** showed the Q_y and Soret absorption peaks at 672 and 417 nm, more red-shifted than those of **1** and **3** (Fig. 3). Although the precise molecular structure of **2** is not known at this stage, it is believed to be C3-iodonium (Scheme 1).

A mixture of **1** and I_2 did not react in the absence of PIFA (Run 8), while a large excess of PIFA decreased the yield of **2** (data not shown). A mixture of 0.5 equiv PIFA and 1 equiv I_2 was sufficient for the monoiodination of the C3-moiety. Doubling the amounts of PIFA and I_2 (Run 9) resulted in the immediate disappearance of the vinyl proton signals and subsequent decrease in the singlet signal for the 20-H within 30–45 min. The ^{1}H NMR spectrum of the reaction mixture obtained after 1 h of the reaction showed a set of new signals (at δ ~9.8, 7.5, 5.25, and 5.0 ppm, Fig. 2e), while retaining the characteristic signals of **2** (e.g., δ 9.5–8.6, 7.45, 5.3–5.1, and 4.2–4.6 ppm, Fig. 2b). The areas of these new signals increased with increasing contents of iodination reagents (Fig. 2d: 0.5 equiv PIFA and 1 equiv I_2; Fig. 2e: 1 equiv PIFA and 2 equiv I_2), while the NMR signal at δ 8.65 ppm for the C20-H decreased simultaneously. The species responsible for these new signals and lacking the C20-H singlet is assumed to be the C20-iodinated intermediate **4**,[38] because it afforded C20-iodinated chlorin **5** with partial characteristics of **2** and **5**, as described below. The NMR signals at δ 5.0 and 5.25 ppm may be assigned to C13^2-H_2 and C18-H based on the similarity with that of **5**. A broad signal at δ 7.55 ppm could be assigned to the C3^1-H proton of **4** based on the similarity with those of **2** (δ 7.45 ppm). The Q_y absorption band of the mixture containing **4** (684 nm, Fig. 3) was more red-shifted than that of **2** (672 nm), consistent with the distortion of the chlorin macrocycle, induced by the substitution of a large iodine atom at the C20-position.[18,20,21,27]

Compound **2** partially transformed into **1** by incubating in a 1,2-dichloroethane solution, indicating the possibility of deiodination at the C3-moiety. The reaction of **2** with NaN_3 did not afford an



Scheme 1. Iodination of methyl pyropheophorbide-*a* (**1**). Reagents and conditions: (i) PIFA (0.5 equiv), I_2 (1.0 equiv), $CHCl_3$; (ii) H_2O, acetone; (iii) PIFA (1 equiv), I_2 (2.0 equiv), $CHCl_3$; and (iv) NaN_3, CH_3CN. Molecular structures of **2** and **4** are presented as working hypotheses.

Table 2
Composition of the products obtained by the treatment of **4** with NaN_3[a]

Entry	**1** (μmol)	CH_3CN (mL)	NaN_3 (equiv)	**1** (%)	**2** (%)	**5** (%)
1	80	10	1	8	5	25
2	80	10	10	6	6	30
3	80	10	20	12	8	41
4	20	2.5	30	2	2	37
5	20	2.5	40	2	1	41
6	20	2.5	50	2	2	37

[a] Yields were determined from the areas of proton NMR signals specific to the respective compounds.

azide-adduct [C3-(1-azide-2-iodo)ethyl derivative], but compound **1** was obtained, indicating that NaN_3 induced the deiodination of the C3-moiety, regenerating the vinyl group. Then, the effect of NaN_3 on **4** was investigated. Compound **1** was reacted with a mixture of PIFA (1 equiv) and I_2 (2 equiv) at room temperature for 2 h, and the resulting residue containing **4** was redissolved in acetonitrile. Then, 30 equiv NaN_3 was added to the solution, and the resulting mixture was stirred at room temperature for 5 h, affording the desired compound **5** (Table 2).[39] Interestingly, NaN_3 facilitated the selective removal of the iodine atom at the C3-moiety and regenerated the vinyl group, while the C20-iodine atom remained intact. ^{1}H NMR spectrum of the product **5** showed the absence of the C20-proton signal and the presence of the set of double doublets for the C3-vinyl group (δ 7.9 and 6.1–6.3 ppm, Fig. 2f). Notably, some proton signals underwent drastic changes in the syntheses from **1** to **5**. The signals of the C18-H and NH underwent large downfield shifts (δ 4.48 and −1.73 ppm → 4.99 and −1.44 ppm), while the C18-CH_3 doublet underwent an upfield shift (δ 1.81 → 1.53 ppm). Multiplicities of the ^{1}H NMR signals of the C17-H and C18-H changed in the syntheses from **1** to **5** (C17, dt → dd; C18, dq → q). The C13^2-proton signals also changed greatly. UV–visible absorption spectroscopy revealed a large red shift of the Q_y absorption band (Fig. 3; **1**, 662 nm → **5**, 679 nm). The Q_x absorption maximum at 557 nm was also characteristic of **5** (and **4**). These changes can be attributed to the macrocycle distortion.[18,20,21,27] Efficiency of the deiodination increased with increasing NaN_3 content and remained almost unchanged with >20 equiv NaN_3 (Table 2). Product **5** was not obtained by reacting **1**, PIFA, I_2, and NaN_3 simultaneously, or by the treatment of **4** with pyridine.

In conclusion, we developed the selective synthesis of monoiodinated chlorins with an iodine atom at the C3-moiety or C20-position using compound **1** as the starting material. Iodination of the C3-moiety only requires 0.5 equiv PIFA and 1 equiv I_2. Substitution at the C20-position only was accomplished by the iodination of both the C3-moiety and at the C20-position with 1 equiv PIFA and 2 equiv I_2 in the first step, followed by selective deiodination of the C3-moiety by treating with a large excess of NaN_3 in the second step. Thus, we successfully prepared the 3-vinyl-20-iodo derivative of a reactive compound **1**. Detailed mechanistic study is now underway.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.01.057.

References and notes

1. Nyman, E. S.; Hynninen, P. H. J. *Photochem. Photobiol. B* **2003**, *73*, 1–28.
2. Oba, T. *Curr. Bioactive Compd.* **2007**, *3*, 239–251.
3. Shibu, E. S.; Hamada, M.; Murase, N.; Biju, V. J. *Photochem. Photobiol. C* **2013**, *15*, 53–72.
4. Pandey, R. K.; Sumlinl, A.; Constantine, S.; Aoudia, M.; Potter, W. R.; Bellnier, D. A.; Henderson, B. W.; Rodgers, M. A.; Smith, K. M.; Dougherty, T. J. *Photochem. Photobiol.* **1996**, *64*, 194–204.
5. Morgan, J.; Jackson, J. D.; Zheng, X.; Pandey, S. K.; Pandey, R. K. *Mol. Pharm.* **2010**, *7*, 1789–1804.
6. Chen, Q.; Huang, Z.; Luck, D.; Beckers, J.; Brun, P.-H.; Wilson, B. C.; Scherz, A.; Salomon, Y.; Hetzel, F. W. *Photochem. Photobiol.* **2002**, *76*, 438–445.
7. Koudinova, N. V.; Pinthus, J. H.; Brandis, A.; Brenner, O.; Bendel, P.; Ramon, J.; Eshhar, Z.; Scherz, A.; Salomon, Y. *Int. J. Cancer* **2003**, *104*, 782–789.
8. Gorman, A.; Killoran, J.; O'Shea, C.; Kenna, T.; Gallagher, W. M.; O'Shea, D. F. *J. Am. Chem. Soc.* **2004**, *126*, 10619–10631.
9. Yogo, T.; Urano, Y.; Ishitsuka, Y.; Maniwa, F.; Nagano, T. *J. Am. Chem. Soc.* **2005**, *127*, 12162–12163.
10. Drzewiecka-Matuszek, A.; Skalna, A.; Karocki, A.; Stochel, G.; Fiedor, L. *J. Biol. Inorg. Chem.* **2005**, *10*, 453–462.
11. Kim, S.; Ohulchanskyy, T. Y.; Bharali, D.; Chen, Y.; Pandey, R. K.; Prasad, P. N. *J. Phys. Chem. C* **2009**, *113*, 12641–12644.
12. Obata, M.; Hirohara, S.; Tanaka, R.; Kinoshita, I.; Ohkubo, K.; Fukuzumi, S.; Tanihara, M.; Yano, S. *J. Med. Chem.* **2009**, *52*, 2747–2753.
13. Zhou, L.; Wei, S.; Ge, Z.; Zhou, J.; Yu, B.; Shen, J. *J. Phys. Chem.* **2012**, *116*, 12744–12749.
14. Lim, C.; Shin, J.; Kwon, I. C.; Jeong, S. Y.; Kim, S. *Bioconjugate Chem.* **2012**, *23*, 1022–1028.
15. Hirohara, S.; Kawasaki, Y.; Funasako, R.; Yasui, N.; Totani, M.; Alitomo, H.; Yuasa, J.; Kawai, T.; Oka, C.; Kawaichi, M.; Obata, M.; Tanihara, M. *Bioconjugate Chem.* **2012**, *23*, 1881–1890.
16. Pandey, S. K.; Gryshuk, A. L.; Sajjad, M.; Zheng, X.; Chen, Y.; Abouzeid, M. M.; Morgan, J.; Charamisinau, I.; Nabi, H. A.; Oseroff, A. R.; Pandey, R. K. *J. Med. Chem.* **2005**, *48*, 6286–6295.
17. Pandey, S. K.; Sajjad, M.; Chen, Y.; Pandey, A.; Missert, J. R.; Batt, C.; Yao, R.; Nabi, H. A.; Oseroff, A. R.; Pandey, R. K. *Bioconjugate Chem.* **2009**, *20*, 274–282.
18. Kureishi, Y.; Tamiaki, H. *J. Porphyrins Phthalocyanines* **1998**, *2*, 159–170.
19. Wang, J.; Han, G.; Wu, X.; Wang, L.; Shim, Y. *Chin. J. Org. Chem.* **2004**, *24*, 537–542.
20. Wang, J.; Li, J.; Yin, J.; Liu, Y. *Chin. J. Org. Chem.* **2008**, *28*, 693–699.
21. Tamiaki, H.; Kotegawa, Y.; Mizutani, K. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6037–6040.
22. Tamiaki, H.; Ariki, N.; Sugiyama, H.; Taira, Y.; Kinoshita, Y.; Miyatake, T. *Tetrahedron Lett.* **2013**, *69*, 8412–8421.
23. Ethirajan, M.; Joshi, P.; William, W. H., III; Ohkubo, K.; Fukuzumi, S.; Pandey, R. K. *Org. Lett.* **2011**, *13*, 1956–1959.
24. Smith, K. M.; Bisset, G. M. F.; Bushell, M. J. *J. Org. Chem.* **1980**, *45*, 2218–2224.
25. Smith, K. M.; Goff, D. A.; Simpson, D. J. *J. Am. Chem. Soc.* **1985**, *107*, 4946–4954.
26. Wang, J.; Zhao, L.; Li, J. *Chin. J. Org. Chem.* **2009**, *29*, 1598–1605.
27. Tamiaki, H.; Takeuchi, S.; Tsudzuki, S.; Miyatake, T.; Tanikaga, R. *Tetrahedron* **1998**, *54*, 6699–6718.
28. Liu, R.; Wanf, L.; Yin, J.; Wu, J.; Liu, C.; Zhang, P.; Wang, J. *Chin. J. Org. Chem.* **2012**, *32*, 318–325.
29. Xu, X.; Yao, N.; Liu, Y.; Yin, J.; Qi, C.; Wang, J. *Chin. J. Org. Chem.* **2014**, *34*, 938–947.
30. Ethirajan, M.; Chen, P.; Ohulchanskyy, T. Y.; Goswami, L. N.; Gupta, A.; Srivatsan, A.; Dobhal, M. P.; Missert, J. R.; Prasad, P. N.; Kadish, K. M.; Pandey, R. K. *Chem. Eur. J.* **2013**, *19*, 6670–6684.
31. Tamiaki, H.; Ariki, N.; Yasuda, S.; Miyatake, T.; Oba, T. *Tetrahedron* **2014**, *70*, 9768–9775.
32. Gottam, H.; Vinod, T. K. *J. Org. Chem.* **2011**, *76*, 974–977.
33. Mixed water in entry 6–9 might control polarity of the solvent to stabilize the iodonium, or change the reactivity of PIFA.
34. Compound **2**. Methyl pyropheophorbide-*a* (**1**) was prepared as described in the literature.[35,36] Compound **1** (43 μmol, 24 mg) was dissolved in a mixture of $CHCl_3$ (10 mL) and water (1 mL). PIFA (22 μmol, 9.5 mg) and I_2 (43 μmol, 11 mg) were added to the solution, and the mixture was stirred at room temperature for 1 h. The reaction mixture was then washed with aqueous $Na_2S_2O_8$ (10 wt%). The organic layer was dried over Na_2SO_4. The solvent was removed in vacuo. The residue was purified by silica gel column chromatography (1,2-dichloroethane/diethyl ether = 9:1), affording **2** as a C3^1-racemic mixture. The product was characterized by NMR (Varian VNMR-500), MS (Bruker Autoflex II), and UV–visible spectroscopy (JASCO V-550). UV–visible ($CHCl_3$) λ_{max} (nm) 672 (relative intensity, 0.44), 613 (0.07), 539 (0.11), 509 (0.13), 417 (1.00); ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 9.538/9.536, 9.52/9.51 (2H, 2s, CH-5, 10), 8.672/8.666 (1H, s, CH-20), 7.45 (1H, m, CH-3^1), 5.27, 5.133/5.129 (2H, 2d, J = 19 Hz, CH_2-13^2), 4.51 (1H, m, CH-18), 4.31 (1H, m, CH-17),

4.45–4.39, 4.24–4.19 (2H, 2m, CH_2-3^2), 3.71, 3.63/3.62, 3.61/3.60, 3.52 (12H, 4s, CH_3-12^1, 17^5, 7^1, 2^1), 3.69 (2H, q, J = 8 Hz, CH_2-8^1), 2.72–2.51, 2.32–2.20 (4H, 2m, CH_2-17^1,17^2), 1.83/1.80 (3H, d, J = 7 Hz, CH_3-18^1), 1.70 (3H, t, J = 8 Hz, CH_3-8^2), 0.08, −1.93 (2H, 2s, NH); MS (MALDI) found: m/z = 675.26, calcd for $C_{34}H_{36}IN_4O_3$: M+, 675.5793. [Some ^{13}C NMR signals were not resolved due to the $C13^2$-racemic mixture. Tentative assignment, see Supplementary data.]

35. Tamiaki, H.; Amakawa, M.; Shimono, Y.; Tanikaga, R.; Holzwarth, A. R.; Schaffner, K. *Photochem. Photobiol.* **1996**, *63*, 92–99.
36. Oba, T.; Masada, Y.; Tamiaki, H. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1905–1909.
37. Methyl 3-devinyl-3-(1-hydroxy-2-iodo)ethylpyropheophorbide-*a* (**3**). Compound **3** can be prepared from **1** by the reaction in 10% aqueous acetone or acetonitrile, or by the treatment of **2** with a mixture of water and acetone. The most efficient procedure is described below: Compound **1** (1.9 mmol, 104 mg) was dissolved in 1,2-dichloroethane (200 mL). PIFA (1.0 mmol, 425 mg) and I_2 (1.9 mmol, 483 mg) were added to the solution and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was washed with aqueous $Na_2S_2O_8$ (10 wt%). Then, morpholine (10 mL) was added to the organic layer and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was washed with water and brine. The organic layer was dried over Na_2SO_4. The solvent was evaporated to dryness. The residue was purified by silica gel column chromatography (1,2-dichloroethane/diethyl ether = 30:1), affording **3** as a $C3^1$-racemic mixture. Black solid (1.4 mmol, 98 mg, isolated yield 73%). Mp >300 °C. HRMS was obtained using Bruker micrOTOF II. UV–visible ($CHCl_3$) λ_{max} (nm) 667 (relative intensity, 0.51), 608 (0.09), 539 (0.10), 505 (0.11), 411 (1.00), 380 (0.64); ^1H NMR ($CDCl_3$, 500 MHz) δ ppm 9.60/9.59, 9.47/9.46 (2H, 2s, CH-5, 10), 8.56/8.55 (1H, s, CH-20), 6.34 (1H, m, CH-3^1), 5.23/5.20, 5.08/5.07 (2H, 2d, 20 Hz, CH_2-13^2), 4.47 (1H, m, CH-18), 4.26 (1H, m, CH-17), 4.23–4.16, 3.99–3.95 (2H, 2m, CH_2-3^2), 3.68 (2H, q, J = 8 Hz, CH_2-8^1), 3.63, 3.622/3.617, 3.417/3.413, 3.24 (12H, 4s, CH_3-12^1, 17^5, 7^1, 2^1), 2.72–2.51, 2.32–2.19 (4H, 2m, CH_2-17^1, 17^2), 1.79/1.78 (3H, d, J = 7 Hz, CH_3-18^1), 1.68 (3H, t, J = 8 Hz, CH_3-8^2), 0.1, −1.97/−1.95 (2H, 2s, NH); MS (MALDI) found : m/z = 693.28; HRMS (APCI) found: m/z 693.1935, calcd for $C_{34}H_{38}IN_4O_4$: MH+, 693.1938. [The OH proton signal was not detected. Some ^{13}C NMR signals were not resolved due to the $C3^1$-racemic mixture. Tentative assignment, see Supplementary data.]
38. Compound **4** could not be isolated. For some spectral characteristics, see Supplementary data.
39. Methyl 20-iodopyropheophorbide-*a* (**5**). Compound **1** (100 μmol, 55 mg) was dissolved in a mixture of $CHCl_3$ (50 mL) and water (5 mL). PIFA (120 μmol, 52 mg) and I_2 (200 μmol, 51 mg) were added to the solution and the mixture was stirred at room temperature for 2 h. The reaction mixture was then washed with aqueous $Na_2S_2O_8$ (10 wt%). The organic layer was dried over Na_2SO_4. The solvent was removed in vacuo. The residue containing intermediate **4** was redissolved in acetonitrile (50 mL). To this solution, sodium azide (3.0 mmol, 195 mg) was added and the resulting mixture was stirred at room temperature for 5 h. The reaction mixture was then washed with water and brine. The organic layer was dried over Na_2SO_4. The solvent was evaporated to dryness. The residue was purified by silica gel column chromatography (1,2-dichloroethane/diethyl ether = 30:1), affording **5**. Black solid (18 μmol, 12 mg, isolated yield 18%). Mp >300 °C. UV–visible ($CHCl_3$) λ_{max} (nm) 679 (relative intensity, 0.41), 623 (0.07), 557 (0.13), 524 (0.08), 420 (1.00); ^1H NMR ($CDCl_3$, 500 MHz) δ ppm 9.57, 9.54 (2H, 2s, CH-5, 10), 7.92 (1H, dd, J = 11.5, 17.7 Hz, CH-3^1), 6.29 (1H, dd, J = 1.7, 11.5 Hz, CH-3^2-*cis*), 6.12 (1H, dd, J = 1.7, 17.7 Hz, CH-3^2-*trans*), 5.26, 5.22 (2H, 2d, J = 20 Hz, CH_2-13^2), 4.99 (1H, q, J = 7.2 Hz, CH-18), 4.26 (1H, dd, J = 3.3, 8.3 Hz, CH-17), 3.66, 3.63, 3.58, 3.25 (12H, 4s, CH_3-2^1, 12^1, 17^5, 7^1), 3.72 (2H, q, J = 7.7 Hz, CH_2-8^1), 2.64–2.46, 2.26–2.17 (4H, 2m, CH_2-17^1, 17^2), 1.70 (3H, t, J = 7.7 Hz, CH_3-8^2), 1.53 (3H, d, J = 7.2 Hz, CH_3-18^1), −1.44 (1H, s, NH) [another NH signal was too broad to be observed]; ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 196.01 ($C13^1$), 173.58, 173.54 (C19, $C17^3$), 161.57 (C16), 153.08 (C6), 151.87 (C9), 148.08 (C14), 144.52 (C8), 140.65, 140.33, 139.89, 136.89, 132.86, 132.34, 131.70, 130.10, 129.89 (C1, C11, C4, C3, C7, C2, C13, $C3^1$, C12), 124.86 ($C3^2$), 106.62 (C15), 104.01 (C10), 99.30 (C5), 65.56 (C20), 55.38 ($C17^5$), 51.77, 51.61 (C17, C18), 48.56 ($C13^2$), 30.92, 29.66 ($C17^1$, $C17^2$), 20.98, 19.99, 19.37, 17.33, 12.11, 11.17 ($C18^1$, $C8^1$, $C8^2$, $C2^1$, $C12^1$, $C7^1$); MS (MALDI) found : m/z = 675.53; HRMS (APCI) found: m/z 675.1826, calcd for $C_{34}H_{36}IN_4O_3$: MH+, 675.1832.